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TIBBİ GENETİK DERNEĞİ

TÜRK TIBBİ ONKOLOJİ DERNEĞİ
Hayat için bilimin izinde...

TPOG GRUBU
TÜRK PEDİATRİK ONKOLOJİ

ULUSLARARASI JİNEKOLOJİ VE OBSTETRİK DERNEĞİ
UJOD
2020

BİLDİRİ KİTABI

İÇİNDEKİLER

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ORAL PRESENTATIONS

[Abstract:0103]

Somatic Mutational Profile of a 77-Gene Hereditary Cancer Panel in Hepatocellular Carcinoma (HCC): A Signal for Germline Genetic Testing?

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Objective: Approximately 5% of patients with HCC are diagnosed before the age of 50. First-degree family history may be associated with HCC risk. However, germline testing in HCC is not well-defined and not practiced. Somatic involvement of the predisposing cancer genes may give a clue for germline testing.

Materials-Methods: The 77 hereditary cancer genes were selected based on a commercial panel list. Two different cohorts were analyzed (TCGA and CLCA). Mutations annotated as “driver” were analyzed, where variants of unknown significance (VUS) were excluded. Heterozygous (shallow) deletions were reported to interpret copy-number-driven clonal dominance as a cause of high variant allele frequency (VAF).
Results: In 353 patients of the TCGA cohort, 212 (60%) had at least one driver somatic mutation in one of the cancer genes. 34.3% of the mutations had a VAF above 50% [17.3% of the mutations were not associated with shallow deletion]. %70.8% of the mutations had a VAF above 30% (24% of those were not associated with shallow deletion). The most common genes with a driver mutation were TP53 (32%), RB1 (9%), CDKN2A (8%), PTEN (5%), TSC2 (4%), BAP1 (4%), LZTR1 (3%), EGFR (2%), FLNC (2%), MET (2%), TSC1 (2%). Gender and age did not differ between patients with or without mutations. Asian race (51.4% vs 31.9% q=0.011) and East Asian genetic ancestry (51.4% vs 32.6%, q=0.011) were more common in patients with a somatic mutation. Tumors with a mutation had a higher hypoxia score (Ragnum score, $q < 0.001$), higher tumor mutation burden (TMB) (median 3.07 vs 2.67, q=0.011), and higher MSIsensor score (median 0.08 vs. 0.04, q=0.016). Unadjusted disease-free survival [Hazard ratio (HR): 0.60 (95%CI: 0.43-0.85), p=0.005] and progression-free survival [HR:0.67 (95%CI: 0.49-0.90) p=0.012] were worse in patients with a mutation, and overall survival showed a worse trend [HR: 0.70 (95%CI: 0.48-1.00), p=0.058]. In 494 patients of the CLCA cohort, 312 (63%) had at least one driver somatic mutation in one of the genes. The most common genes with a driver mutation were TP53 (51%), RB1 (6%), PTEN (3%), TSC2 (4%), TSC1 (2%), ATM (2%), and CDKN2A (2%). When the two cohorts were combined, BRCA1 or BRCA2 driver somatic mutations were detected in 8 patients (1%), 13 patients had somatic driver mutations in one of MLH1, MSH2, MSH3, or MSH6 (1.5%), and 8 patients had driver mutations in the APC gene (1%).
Conclusion: These preliminary analyses suggest that somatic driver mutations in cancer genes with considerable VAFs (without shallow deletion) may be detected in patients with HCC (~17%). However, uniparental disomy cannot be excluded. The frequency reported here may be considered consistent with a few germline studies in the literature (Mezina et al,2021). Germline analysis, associated clinicopathological factors, and defining the target patient group require further research; however, a possible hereditary predisposition should not be neglected in HCC.

Keywords: hepatocellular carcinoma, hereditary cancer genes, somatic, germline, mutation

[Abstract:0108]

Clinicopathological characteristics and outcomes of non-metastatic breast cancer in germline CHEK2 mutation carriers: a single-center experience

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Objective: CHEK2 is a moderate-penetrance breast cancer susceptibility gene. Although CHEK2 associated breast cancers are typically hormone receptor positive and diagnosed at younger ages, real world data on their clinicopathological features, treatment patterns, and survival outcomes remain limited.Therefore, this study aimed to evaluate the clinicopathological characteristics and survival outcomes of patients with non-metastatic breast cancer harboring germline CHEK2 pathogenic variants in a single center cohort

Materials-Methods: Between 2017-2024, a total of 652 patients diagnosed with breast cancer who underwent germline genetic testing at Trakya University Faculty of Medicine were retrospectively reviewed. Patients harboring pathogenic germline CHEK2 variants were identified, and those with metastatic disease at the time of diagnosis were excluded. The final study cohort consisted of 27 patients with non-metastatic breast cancer. Clinicopathological features, treatment characteristics, and follow-up data were obtained from medical records. Disease-free survival (DFS) and overall survival (OS) analyses were performed using the Kaplan–Meier method.

Results: A total of 27 patients with non-metastatic breast cancer harboring germline CHEK2 pathogenic variants were included in the analysis. The median age at first breast cancer diagnosis was 46 years (range, 30–76), and 66.7% of patients were premenopausal at diagnosis. A family history of cancer was present in 29.6% of patients. Most tumors were invasive ductal carcinoma (81.5%), followed by invasive lobular carcinoma (11.1%). All tumors were estrogen receptor–positive, progesterone receptor positivity was observed in 88.9%, and HER2 positivity in 22.2%. Early-stage disease predominated, with 77.7% of patients diagnosed at stage I–II. Surgical management breast-conserving surgery was the most frequently performed procedure, applied in 17 patients (63.0%) (Table 1).
Concerning systemic treatment, 22 patients (81.5%) received combined chemotherapy and endocrine therapy, whereas 5 patients (18.5%) were treated with endocrine therapy alone. Among patients receiving chemotherapy, neoadjuvant chemotherapy was administered in 7 patients (31.8%), and adjuvant chemotherapy in 15 patients (68.2%), with anthracycline- and taxane-based regimens being the most commonly used (81.8%). Radiotherapy was administered to all patients, predominantly as locoregional irradiation (breast plus axillary lymph nodes) in 81.5% of cases (Table 2).
During follow-up, disease recurrence was observed in 9 patients (33.3%), while 18 patients (66.7%) remained recurrence-free. Local or regional nodal recurrence occurred in 4 patients (14.8%), and distant metastases were detected in 6 patients (22.2%). At the time of last follow-up, 25 patients (92.6%) were alive, and 2 patients (7.4%) had died (Table 2). With a median follow-up duration of 49.2 months, the median DFS was 69.0 months, whereas the median OS was not reached.

Conclusion: In this single-center real-world cohort, patients with non-metastatic breast cancer harboring germline CHEK2 pathogenic variants predominantly exhibited hormone receptor positive tumor biology, consistent with previously published reports, including those by Nizič-Kos et al. Survival outcomes were favorable, with a prolonged median DFS and unreached median OS, supporting prior evidence of a relatively good prognosis in early stage CHEK2-associated breast cancer. These findings add real-world data to the limited literature and may help inform surveillance strategies and clinical decision-making for CHEK2 mutation carriers.

Keywords: CHEK2, germline mutation, early stage breast cancer

Tablo-1. Clinicopathological characteristics of patients with germline CHEK2-mutated breast cancer

		n	%
Age category	<45	12	(44,4)
	≥45	15	(55,6)
Menopausal status	Premenopausal	18	(66,7)
	Postmenopausal	9	(33,3)
Family history of cancer	No	19	(70,4)
	Yes	8	(29,6)
Surgery type	Breast-conserving surgery (BCS)	17	(63,0)
	Mastectomy	10	(37,0)
Histological type of tumor	IDC	22	(81,5)
	ILC	3	(11,1)
	OTHER	2	(7,4)
Type of axillary surgical approach	Sentinel lymph node biopsy (SLNB)	19	(70,4)
	Axillary lymph node dissection (ALND)	8	(29,6)
Anatomical location of the tumor	Left breast	10	(37,0)
	Right breast	15	(55,6)
	Bilateral	2	(7,4)
Tumor quadrant	Inner quadrant	5	(18,5)
	Outer quadrant	18	(66,7)
	Central	2	(7,4)
	Multicentric	2	(7,4)
Tumor size	≤2	8	(29,6)
	2<tm≤5	14	(51,9)
	>5	5	(18,5)
Axillary lymph node involvement status	N0	13	(48,1)
	N1	9	(33,3)
	N2	4	(14,8)
	N3	1	(3,7)
Overall clinical or pathological stage	Stage I	8	(29,6)
	Stage II	13	(48,1)
	Stage III	6	(22,2)
Tumor grade	grade I and II	16	(59,3)
	grade III	11	(40,7)
Lymphovascular invasion	Absent	14	(51,9)
	Present	13	(48,1)
Perineural invasion	Absent	24	(88,9)
	Present	3	(11,1)
Skin involvement	Absent	25	(92,6)
	Present	2	(7,4)
Surgical margin status after tumor resection	Negative	26	(96,3)
	Positive	1	(3,7)
ER status	Negative	0	(0,0)
	Positive	27	(100,0)
PR status	Negative	3	(11,1)
	Positive	24	(88,9)
HER2 receptor status	Negative	21	(77,8)
	Positive	6	(22,2)
KI-67	<15%	9	(33,3)
	≥15%	18	(66,7)
Molecular subtype	Luminal A	6	(22,2)
	Luminal B HER2-negative	16	(59,3)
	Luminal B HER2-positive	5	(18,5)

Tablo-2. Treatment and outcomes of patients with germline CHEK2-mutated breast cancer

		n	%
Type of systemic therapy received	Endocrine therapy alone	5	(18,5)
	Chemotherapy and endocrine therapy	22	(81,5)
Neoadjuvant vs Adjuvant chemotherapy	Neoadjuvant	7	(31,8)
	Adjuvant	15	(68,2)
Type of chemotherapy regimen (if chemotherapy received)	Anthracycline- and taxane-based	18	(81,8)
	Anthracycline-based	1	(4,5)
	Taxane-based	3	(13,6)
Radiotherapy type	Breast only	5	(18,5)
	Locoregional (breast + axiller lymph nodes)	22	(81,5)
Hormone therapy use	Not received	0	(0,0)
	Received	27	(100,0)
Type of hormone therapy agent used	Tamoxifen	7	(25,9)
	Letrozole	3	(11,1)
	Anastrozole	6	(22,2)
	Tamoxifen and AI sequentially	11	(40,7)
Recurrence status	No recurrence	18	(66,7)
	Recurrence present	9	(33,3)
Local nodal recurrence	No	23	(85,2)
	Yes	4	(14,8)
Presence of distant metastasis	No	21	(77,8)
	Yes	6	(22,2)
Vital status	Alive	25	(92,6)
	Died	2	(7,4)

[Abstract:0110]

Olaparib Use in Cancers Other Than Breast and Ovarian Cancer: A Single-Center Experience

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Objective: Advances in molecular genetics have identified several genes, most notably BRCA1/2, as being associated with hereditary susceptibility to breast, ovarian, pancreatic, and prostate cancers, thereby enabling the clinical development and implementation of PARP inhibitors. Olaparib is an oral PARP inhibitor with proven efficacy across multiple tumor types, particularly breast and ovarian cancers, and its therapeutic activity is not limited to BRCA1/2-mutant tumors but also extends to tumors with homologous recombination deficiency (HRD). However, the prevalence of BRCA1/2 mutations in cancers outside classical indications is relatively low and heterogeneous, reported to range from 1–17% in pancreatic cancer, approximately 1–2.5% in germ cell tumors, and only rarely in colorectal cancer. In this context, reporting real world experience with olaparib use in solid tumors other than breast and ovarian cancer is of clinical relevance. The aim of this study was to evaluate the effectiveness of olaparib in patients followed at our clinic with solid tumors other than breast and ovarian cancer.

Materials-Methods: In this retrospective study, ten patients with solid tumors other than breast and ovarian cancer who were followed at the Department of Medical Oncology, Gülhane Training and Research Hospital, and treated with olaparib between 2017 and 2025 were evaluated

Results: Among the included patients, diagnoses were testicular germ cell tumor (n=3), pancreatic cancer (n=3), prostate cancer (n=1), malignant meningioma (n=1), sigmoid colon cancer (n=1), and Ewing sarcoma (n=1). Six patients harbored BRCA1/2 mutations, while four patients had homologous recombination deficiency (HRD). Of the patients included in the study, 30% were female and 70% were male. The median age at diagnosis was 44.5 years (range: 21–84). Prior to olaparib treatment, patients had received a median of two lines of systemic therapy. All patients initiated olaparib treatment at a dose of 300 mg twice daily. No dose reductions were required due to treatment-related adverse events. Grade 1 anemia was observed in two patients, grade 2 neutropenia in one patient, and rash in one patient, no grade >=3 toxicities were reported.

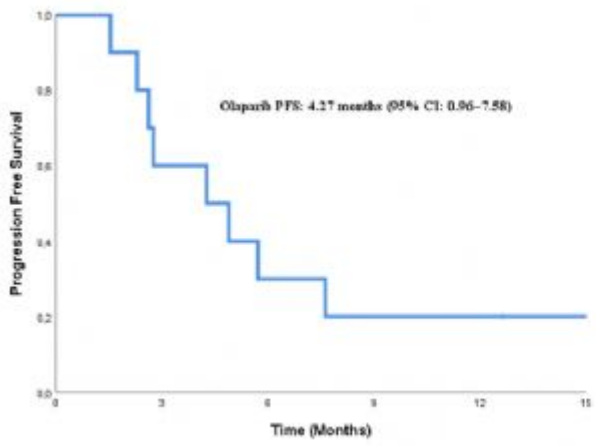
The median progression-free survival (PFS) with olaparib was 4.27 months (95% CI: 0.96–7.58) in the overall study population. The objective response rate (ORR) was 10%, while disease control was achieved in 20% of patients. At the end of the study, six patients were alive.

Discussion: The median PFS of 4.27 months is consistent with real-world PARP inhibitor outcomes in non-traditional malignancies, while the absence of grade >=3 toxicities and exceptional responses in BRCA1-mutant pancreatic cancers suggest clinical benefit in selected populations. Disease control achievement in 20% of heavily pretreated patients underscores the importance of biomarker-driven patient selection in expanding olaparib utilization across solid tumors.

Conclusion: In this small, single-center real-world cohort, olaparib demonstrated modest clinical activity with an acceptable safety profile in selected patients with solid tumors other than breast and ovarian cancer. These findings support the potential role of olaparib beyond classical indications and highlight the need for further prospective studies in larger and molecularly defined populations.

Keywords: PARP inhibitors, Olaparib, BRCA1/2-mutation, homologous recombination deficiency (HRD)

Kaplan–Meier curve for PFS with olaparib



Olaparib Treatment Outcomes- Patient Cohort

Patient	Gender	Age	Diagnosis	Genetic itation	Stage a gnosis	Previous Treatments	Olaparib e of Therap	PFS	Response	Treatment After parib	Current Status
1	Male	30	Testicular ncer-minoma	BRCA2	2	BEP-TIP-GEMPOX-/ASCT	5	5.72	PD	Etoposide	Alive
2	Female	55	Sigmoid ca	HRD EC2	3	FOLFOX – LFIRI+Cetuximab	3	4.90	PD	CAPTEM	Ex
3	Male	60	Pancreas ca	BRCA 1	4	Folfirinox, mcitabine	3	2.63	PD	Gemcitabine+ ecitabine	Alive
4	Male	34	Ewing coma	HRD ECK2	3	Vac/ie- High Dose ICI CT	3	4.27	PD		Ex
5	Male	69	Prostate ca	BRCA1	4	Folfirinox, Xelox, mcitabine	4	2.30	PD		Ex
6	Male	28	Testicular ncer Seminon	HRD P1	1	BEP-TIP- CE/ASCT	4	7.62	PD	Etoposide	Alive
7	Female	33	Anaplastic ningioma	HRD P1 CHECK	Grade	Temozolamide, vacizumab+Irinotecan	3	2.76	PD	Pembrolizumab	Alive
8	Male	84	Prostate ca	BRCA2	4	Enzalutamide, cetaxel	3	1.54	PD		Ex
9	Female	64	Prostate ca	BRCA 1	4	Folfirinox	2	15.05	PR	Etoposide	Alive
10	Male	21	Testicular ncer Mixed rm Tm	BRCA2	1	BEP-TIP-GEMPOX-/ASCT	5	12.65	SD	CAPTEM	Alive

[Abstract:0115]

From Primary Unknown Cancer to Germline Inheritance: The RAD54L Variant and Molecular Tracing of Colorectal Cancer

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Objective: This case report aims to demonstrate the value of Comprehensive Genomic Profiling (CGP) in determining the primary tumor origin at the anatomical and molecular levels in a patient presenting with multiorgan metastases and classified as having Cancer of Unknown Primary (CUP). In addition, the case explores the clinical relevance of an incidentally detected germline RAD54L (p.G160V) variant—an exceptionally rare finding in solid tumor genomics—and discusses its potential contribution to carcinogenesis through partial impairment of DNA double-strand break repair mechanisms, as well as its implications for genetic counseling and family-based risk assessment.
Case: Given the diagnostic ambiguity between a primary ovarian malignancy and metastatic gastrointestinal cancer, CGP was performed. Somatic pathogenic variants were identified in APC (p.Q1429*), KRAS (p.G13D), BRAF (p.G469A), SMAD4 (p.G386V), and PIK3CA (p.K545K). Notably, a RAD54L (c.479G>T; p.G160V) variant was detected at a variant allele frequency of approximately 52%, raising suspicion for a germline origin. This finding was subsequently confirmed through germline DNA analysis. The tumor was microsatellite stable (MSS) and homologous recombination deficiency (HRD) testing was negative.
Discussin and Results: The combination of somatic alterations involving APC, KRAS, and SMAD4, a well-established genomic signature of colorectal carcinogenesis, strongly supported a colorectal origin of the metastatic disease rather than a primary ovarian malignancy. Thus, CGP proved decisive in resolving the anatomical ambiguity characteristic of CUP cases.The detection of a germline RAD54L variant represents a particularly rare finding. RAD54L encodes an ATP-dependent DNA helicase that plays a crucial role in homologous recombination by stabilizing the RAD51 nucleoprotein filament and facilitating chromatin remodeling at sites of DNA double-strand breaks. Although classical HRD metrics were negative in this case, RAD54L is considered a functional modulator rather than a core HR gene, and partial loss of function may not necessarily be reflected in genomic scar–based HRD scores. Therefore, it is biologically plausible that a heterozygous germline alteration in RAD54L could contribute to genomic instability through a mechanism of functional insufficiency rather than complete homologous recombination failure. Importantly, the identification of this germline alteration carries implications beyond the index patient, warranting genetic counseling and consideration of cascade testing in at-risk family members.From a therapeutic standpoint, the presence of a pathogenic KRAS mutation predicted resistance to anti-EGFR therapy. Accordingly, the patient was treated with a FOLFOX and bevacizumab regimen, resulting in marked radiological tumor regression and significant clinical improvement. This case illustrates that genomic profiling can surpass anatomical findings in determining the primary tumor origin in CUP and simultaneously uncover clinically relevant germline alterations. The incidental detection of a rare germline RAD54L variant underscores the importance of integrating somatic and germline data in oncologic practice. Such findings may contribute to genetic risk assessment and family-based preventive approaches in addition to diagnosis and treatment.

Keywords: Cancer of Unknown Primary (CUP), RAD54L, Comprehensive Genomic Profiling, Molecular Diagnostics

[Abstract:0124]

From Cancer to Pregnancy: Experience with Embryonic Genetic Screening in a BRCA2-Mutated Breast Cancer Patient

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Objective: Detecting BRCA risk in patients planning pregnancy with BRCA-mutated cancer.

Case: A 31-year-old premenopausal woman with one healthy male child conceived via IVF was diagnosed in February 2022 with invasive ductal carcinoma (pT2N1M0, grade 2; ER+, PR+; HER2 negative; Ki-67 40%). Neoadjuvant chemotherapy was planned. After 4 cycles of dose-dense AC followed by 4 cycles of docetaxel, she underwent breast-conserving surgery with axillary lymph node dissection (ALND).

She was diagnosed with ypT1N1M0 and received adjuvant radiotherapy, followed by ovarian suppression (LHRH) plus tamoxifen.

On hereditary cancer panel testing, a heterozygous BRCA2 variant was identified. Because the patient wished to become pregnant again, pregnancy was permitted 2 years after treatment initiation. Repeat IVF was planned using oocytes collected during the patient's first pregnancy. As recommended by the treating medical oncologist, BRCA analysis was performed on the embryo planned for transfer. Testing revealed a BRCA2 mutation (c.7660del). At the patient's request, embryo transfer was not performed.

Conclusion: In patients with BRCA mutations planning IVF, genetic testing of embryos before transfer may help reduce potential risks. Further studies are needed.

Keywords: Breast cancer, BRCA2 mutation, Preimplantation genetic testing (PGT-M), IVF / embryo selection

[Abstract:0132]

Identification of a de novo 9q22.32–q22.33 Microdeletion in a Child with Wilms Tumor: Implications for Cancer Predisposition

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Background:
Wilms tumor is the most common pediatric renal malignancy and is frequently associated with underlying genetic and chromosomal abnormalities. In addition to well-established cancer predisposition syndromes, rare genomic imbalances are increasingly recognized as contributors to tumor susceptibility. Microdeletions involving chromosome 9q22 have been associated with developmental delay, congenital anomalies, overgrowth phenotypes, and an increased risk of embryonal tumors, including Wilms tumor.
Methods: Clinical and pathological data were retrospectively reviewed. Cytogenetic analysis was performed using conventional karyotyping, followed by high-resolution chromosomal microarray analysis (CMA) interpreted according to ACMG guidelines. Parental studies were conducted to determine the inheritance of the detected genomic alteration.
Case Presentation:
A 9-year-old girl presented with prenatal findings of increased nuchal translucency and polyhydramnios, while non-invasive prenatal testing (NIPT) was reported as normal. She was born at term with macrosomia and macrocephaly. Postnatal findings included hypotonia, ventricular septal defect, dysmorphic facial features, and global developmental delay. At four years of age, imaging revealed a renal mass, and histopathological examination confirmed Wilms tumor. The patient was treated with neoadjuvant chemotherapy followed by partial nephrectomy. Conventional karyotyping revealed a normal female karyotype (46,XX). Chromosomal microarray analysis identified a de novo 4.5 Mb microdeletion at chromosome region 9q22.32–q22.33.
The deleted region encompasses approximately 27 genes, including PTCH1 and FANCC, which are involved in tumor suppression, genomic stability, and growth regulation. PTCH1, a key component of the Hedgehog signaling pathway, has been associated with overgrowth phenotypes and embryonal tumor development, while FANCC plays a critical role in DNA repair and cancer susceptibility. Consistent with previous reports, among 44 individuals with 9q22.3 microdeletion, 7 (16%) developed Wilms tumor at a mean age of 45 months, frequently in association with dysmorphic features, macrocephaly, developmental delay, and overgrowth. Together, these findings indicate a genotype–phenotype correlation between haploinsufficiency of genes within the 9q22.3 region and predisposition to embryonal tumors, including Wilms tumor.
Conclusion:
This case further supports the association between 9q22.32–q22.33 microdeletion and Wilms tumor and highlights the importance of gene content within this region in cancer predisposition. Chromosomal microarray analysis is an essential diagnostic tool in pediatric cancer patients with congenital anomalies and developmental delay, enabling the detection of clinically significant genomic imbalances that may be missed by NIPT and conventional karyotyping. These findings have important implications for tumor surveillance and genetic counseling.

Keywords: Wilms tumor, 9q22 microdeletion, chromosomal microarray, pediatric cancer, cancer predisposition

Identification of a de novo 9q22.32–q22.33 Microdeletion in a Child with Wilms Tumor: Implications for Cancer Predisposition

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Introduction

Wilms tumor is the most common pediatric renal malignancy and is frequently associated with genetic and chromosomal abnormalities. While well-known cancer predisposition syndromes account for a subset of cases, rare chromosomal microdeletions are increasingly recognized as contributors to tumor susceptibility. Microdeletions involving chromosome 9q22.3 have been associated with developmental delay, congenital anomalies, overgrowth phenotypes, and an increased risk of embryonal tumors, including Wilms tumor. The tumor risk in this region is thought to be related to haploinsufficiency of dosage-sensitive genes involved in growth regulation and genomic stability.

Case Presentation

The patient is a 9-year-old girl with a prenatal history of increased nuchal translucency and polyhydramnios, while non-invasive prenatal testing was reported as normal. She was born at term with macrosomia and macrocephaly. Postnatal findings included hypotonia, ventricular septal defect, dysmorphic facial features, and global developmental delay. At four years of age, abdominal imaging revealed a renal mass, and histopathological examination confirmed Wilms tumor. The patient was treated with neoadjuvant chemotherapy followed by partial nephrectomy, with favorable clinical outcome. Conventional cytogenetic analysis revealed a normal female karyotype (46,XX).

Subsequent chromosomal microarray analysis identified a de novo 4.5 Mb microdeletion at chromosome region 9q22.32–q22.33. Parental studies confirmed the de novo origin of the deletion.

Discussion

The deleted region encompasses approximately 27 genes, including *PTCH1* and *FANCC*, which are known to play roles in tumor suppression, genomic stability, and growth regulation. *PTCH1* is a key component of the Hedgehog signaling pathway and has been associated with overgrowth phenotypes and embryonal tumor development. *FANCC* is involved in DNA repair pathways, and its disruption has been linked to increased cancer susceptibility. Previous studies have reported an elevated risk of Wilms tumor among individuals with 9q22.3 microdeletion. In a cohort of 44 reported patients with this deletion, 7 (16%) developed Wilms tumor at a mean age of 45 months, often accompanied by macrocephaly, dysmorphic features, developmental delay, and overgrowth. These findings support a genotype–phenotype correlation between haploinsufficiency of genes within the 9q22.3 region and predisposition to embryonal tumors.

Conclusion

This case further supports the association between 9q22.3 microdeletion and Wilms tumor and highlights the importance of chromosomal microarray analysis in pediatric cancer patients with congenital anomalies and developmental delay. Identification of such genomic alterations is critical for accurate cancer risk assessment, surveillance strategies, and genetic counseling. Given the potential tumor predisposition associated with this microdeletion, long-term follow-up and individualized monitoring should be considered in affected patients.

[Abstract:0141]

Genotype–Phenotype Associations and Real World Clinical Outcomes in Von Hippel–Lindau Disease: A Single Center Turkish Cohort

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Objective: Von Hippel–Lindau (VHL) disease is a hereditary tumor syndrome characterized by hemangioblastomas of the central nervous system (CNS) and retina, renal cell carcinomas (RCC), and pheochromocytomas. While genotype-phenotype correlations guide surveillance, real-world data on novel systemic therapies like belzutifan remain limited. We aimed to evaluate the clinical characteristics, genotype-phenotype patterns, and early treatment outcomes in a single-center Turkish cohort.
Materials-Methods: The cohort included 12 patients (7 females, 5 males) with a median age at diagnosis of 33 years. Comorbidities were frequent, including hypertension (n=5), diabetes mellitus (n=3), and chronic kidney disease (n=2). Multi-organ involvement was present in 91.7% of patients. The most frequent manifestations were CNS hemangioblastoma (91.7%), followed by RCC (66.7%) and retinal hemangioblastoma (25%). Genetic analysis revealed significant familial clustering among carriers of the c.481C>T (p.Arg161Ter) nonsense mutation. All patients with this variant presented with a Type 1 phenotype (exclusive occurrence of CNS/retinal hemangioblastomas and RCC, with complete absence of pheochromocytoma). Conversely, the single patient with pheochromocytoma harbored a distinct missense mutation (c.499C>T), consistent with the Type 2 phenotype. Regarding systemic therapy, belzutifan was initiated in 3 patients with progressive disease. One patient, followed for 16 months, achieved significant radiological regression in target lesions. Although this patient developed Grade 3 anemia requiring a dose reduction from 120 mg to 80 mg, the treatment was subsequently well-tolerated with sustained disease control.
Conclusion: Our study documents a distinct genotype-phenotype correlation, where the p.Arg161Ter nonsense variant is strongly associated with a Type 1 phenotype, sparing patients from pheochromocytoma risk. Furthermore, our real-world experience highlights the importance of integrating clinical history in variant interpretation and supports belzutifan as an effective therapeutic option with a manageable safety profile in VHL patients.

Keywords: Von Hippel–Lindau disease, genotype-phenotype correlation, belzutifan, real-world data

[Abstract:0147]

In Silico Investigation of Potential Splicing Effects of *NF1* Variants in Hereditary Cancer Cases Without Classical NF1 Clinical Features

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Introduction and Objective

Although Neurofibromatosis Type 1 (NF1) is traditionally diagnosed based on clinical phenotype, the *NF1* gene encodes neurofibromin, a critical negative regulator of the Ras–MAPK pathway. Accumulating evidence suggests that pathogenic *NF1* variants may be detected in the setting of isolated hereditary cancer risk, even in the absence of classical syndromic features (e.g., café-au-lait macules). Moreover, exonic "missense" or "synonymous-appearing" variants may affect splicing regulation, for example through cryptic splice site usage or disruption of auxiliary splicing motif balance. This study explores two hypotheses: (1) *NF1* variants in phenotype-free cases may be relevant to isolated cancer risk; and (2) some exonic *NF1* variants classified as variants of uncertain significance (VUS) may harbor under-recognized splicing effects.

Materials and Methods

Six index cases who underwent NGS-based hereditary cancer panel testing but did not meet clinical diagnostic criteria for NF1 were retrospectively evaluated. The potential impact of the detected variants on splicing was assessed using in silico tools with different algorithmic approaches (HSF 3.1 and SpliceAI), focusing on cryptic splice site predictions, ESE/ESS motif alterations, and—when applicable—comparison with protein-focused pathogenicity predictors.

Results

A pathogenic *NF1* variant (c.2033dup) was identified in a 65 year old asymptomatic female with a dense family history of cancer (pancreatic, prostate, breast), providing an observational example that NF1 findings may become relevant in hereditary cancer assessment even without syndromic manifestations.

Within the VUS group, c.753C>G, detected in two independent cases (early onset breast cancer and bilateral multiple breast masses), showed marked discordance between prediction tools. While SpliceAI produced only low-level/borderline signal (Δ≈0.07), HSF 3.1 predicted activation of both a cryptic acceptor (Δ score: 63.78%) and a cryptic donor (Δ score: 64.96%) site. Notably, HSF also indicated a pronounced auxiliary motif shift, reflected by a decrease in the ESE/ESS motif ratio (-6), which is compatible with impaired exon definition and potential splicing inefficiency. Similarly, for variants such as c.2951G>A, which tended to be classified as benign by protein centric predictors, HSF suggested potential cryptic acceptor activation (Δ score: 67.61%), generating hypotheses for splicing-mediated effects independent of amino acid-level predictions.

Conclusion and Discussion

These observations suggest that, in hereditary cancer cases lacking classical NF1 phenotype, it may be useful to review exonic *NF1* VUS not only for protein impact but also for potential splicing consequences. Tool discordance (HSF vs SpliceAI) highlights that variants appearing benign in protein focused filters may still carry a plausible splicing risk. However, in silico results are hypothesis-generating rather than confirmatory; RNA-based functional validation (e.g., targeted transcript analysis and/or minigene assays) would strengthen interpretation for variants with consistent splicing-related signals.

Keywords: Hereditary cancer predisposition, Human Splicing Finder (HSF 3.1), In silico splicing prediction, Neurofibromatosis type 1 (NF1), SpliceAI

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ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumor predisposition syndrome caused by loss-of-function variants in the *NF1* gene and characterized by a broad phenotypic spectrum. Although diagnosis has traditionally been phenotype-driven, large genotype-first studies suggest that pathogenic *NF1* variants are more prevalent than previously appreciated, leaving many carriers clinically unrecognized. The widespread adoption of NGS-based multigene panels has created an interpretive challenge: how to evaluate *NF1* variants in individuals who do not meet established clinical diagnostic criteria for NF1.

In this study, we assessed the potential impact of *NF1* variants on pre-mRNA splicing using *in silico* tools (HSF Pro and SpliceAI) in six index cases lacking phenotypic features of NF1. For several exonic variants predicted to have low impact by protein-based predictors, splicing analyses indicated cryptic acceptor/donor activation and altered ESE/ESS motif balance. These findings suggest that a splicing-focused approach may help refine variant classification. As *in silico* results are hypothesis-generating, RNA/cDNA-based assays should be considered where feasible to validate predicted splicing effects and support potential variant reclassification.

Keywords: Hereditary cancer predisposition, Human Splicing Finder (HSF Pro), In silico splicing prediction, Neurofibromatosis type 1 (NF1), SpliceAI

1. INTRODUCTION

Neurofibromatosis type 1 (*NF1*) is a clinically heterogeneous tumor predisposition syndrome caused by heterozygous loss-of-function variants in the *NF1* gene (1). Diagnosis has traditionally relied on cardinal features such as café au lait macules, neurofibromas, and Lisch nodules. However, given the disorder's variable expressivity, age-dependent onset, and postzygotic mosaicism, some individuals may not meet established clinical diagnostic criteria, underscoring the limitations of a purely phenotype-based approach (2, 3).

Genotype-first studies indicate that pathogenic *NF1* variants (PVs) are more common than phenotype-based estimates suggest, with carriers lacking classic phenotypic findings representing a substantial subset. In an analysis of over one million individuals, Safonov et al. (4) reported an *NF1* PV prevalence of approximately 1 in 1,286, showing that many carriers were identified without a prior clinical diagnosis or typical features of NF1. These findings prompt a reappraisal of incidentally identified *NF1* variants detected on hereditary cancer panels. In particular, identifying an *NF1* variant in individuals evaluated for malignancies such as breast cancer may warrant consideration of targeted phenotyping and risk counseling, particularly when the personal and/or family history raises suspicion. Even in the absence of overt NF1 features, genotype-driven detection may prompt targeted phenotyping for subtle or atypical manifestations and support individualized counseling based on the overall clinical context and family history.

Growing evidence links *NF1* to an elevated breast cancer risk, particularly in women under 50, with recent work suggesting that this risk may be modulated by the specific mutation type (5). Studies have also begun to clarify the subtype distribution, clinical presentation, and molecular spectrum of *NF1*-associated breast cancers (6). Despite these insights, interpreting variants of uncertain significance (VUS) in large genes such as *NF1* remains challenging. Exonic missense or synonymous variants may appear benign in protein-based predictors yet still alter splicing regulation, leading to loss of function. Reports showing that splice-altering variants can be supported by *in silico* predictions and subsequently confirmed by functional assays highlight the value of splicing-focused analyses for variant classification (7).

In this study, we reevaluated the potential splicing effects of *NF1* variants identified in individuals without phenotypic features of NF1 who underwent testing for suspected hereditary cancer, using complementary *in silico* approaches.

2. MATERIALS AND METHODS

Hereditary cancer panel data from Aydın Adnan Menderes University were retrospectively reviewed to identify six index cases harboring *NF1* (NM_000267/3) variants who did not meet established clinical diagnostic criteria for NF1 at the time of referral. Clinical records were reviewed to extract personal and family cancer histories. Potential splicing impact was assessed using HSF Pro (to predict cryptic splice-site and ESE/ESS motif changes) and SpliceAI (to calculate donor/acceptor gain/loss probability scores). Findings were interpreted alongside protein-based predictors (SIFT and PolyPhen-2) and were considered hypothesis-generating to prioritize variants for future functional follow-up.

3. RESULTS

3.1. Pathogenic Finding

Among the six index cases, one harbored a pathogenic *NF1* variant, whereas the remaining five carried variants classified as variants of uncertain significance (VUS). The pathogenic variant c.2033dup (p.Ile679Aspfs*21) was identified in a 65-year-old asymptomatic woman with a family history of pancreatic, prostate, and breast cancers but no classic clinical features of NF1.

3.2. Splicing Discordance in the VUS Group

Within the VUS group, discordance was observed between protein-based pathogenicity predictors and *in silico* splicing tools.

• **c.753C>G (p.Asp251Glu):** This variant was identified in two independent index cases: a 39-year-old woman with breast cancer and a 31-year-old woman with bilateral multifocal breast masses. In the latter case, the family history included a paternal brain tumor (diagnosed at age 56; death at 57), prostate cancer in three paternal uncles, and follow-up for a breast mass in the daughter of one uncle with prostate cancer. For this variant, SpliceAI yielded no prominent splicing signal, whereas HSF Pro predicted the creation of a cryptic acceptor site (matrix score 43.70 → 71.57; Δ = 63.78%) and a cryptic donor site (41.78 → 68.92; Δ = 64.96%). In addition, a 6-unit decrease in the ESE/ESS motif ratio suggested impaired exon recognition and supported the possibility of alternative splicing.

• **c.2951G>A (p.Gly984Glu)**: In a 40-year-old patient diagnosed with invasive breast carcinoma and concomitant giant uterine fibroids, HSF Pro showed an increase consistent with activation of a new cryptic acceptor site (41.22 → 69.09; Δ = 67.61%), while SpliceAI did not produce a clear signal.

• **c.134A>G (p.Asn45Ser):** This variant was identified in a 44-year-old patient with invasive breast carcinoma who subsequently developed colon adenocarcinoma. The family history included colon cancer in an aunt, pancreatic cancer in two maternal uncles, and lung cancer in another maternal uncle. HSF Pro predicted the potential formation of a new acceptor (Δ = 55.44%) and a new donor (Δ = 71.05%) site. Multiple skin lesions previously followed as acrochordons (skin tags) were noted to warrant reevaluation during targeted phenotyping, given that such lesions may overlap clinically with minor *NF1*-related cutaneous findings or neurofibromas.

• **c.1763A>T (p.His588Leu):** This variant was identified in a 31-year-old woman with invasive ductal carcinoma and multifocal right breast masses, in the absence of classic NF1 features. The family history included stomach cancer in two aunts, childhood leukemia in a cousin, and skin cancer in another aunt. The patient also carried a concurrent heterozygous pathogenic *MUTYH* variant (c.842C>T; p.Pro281Leu). For *NF1*:c.1763A>T, SpliceAI yielded no prominent splicing signal. In contrast, HSF Pro indicated a shift in the enhancer/silencer balance toward silencer motifs—through disruption of one ESE and creation of three ESS motifs—consistent with the possibility of exon skipping.

4. DISCUSSION AND CONCLUSION

This study underscores the value of a splicing-focused assessment when interpreting *NF1* variants detected on hereditary cancer panels in individuals who do not meet phenotypic diagnostic criteria for NF1. Genotype-first analyses suggest that the frequency of PVs is higher than phenotype-based estimates indicate, and that a significant number of carriers may remain undiagnosed.

(4) Accordingly, the clinical relevance of an NF1 finding should not be dismissed solely due to the absence of overt syndromic features; rather, targeted phenotyping, family history, and evidence supporting the biological impact of the variant should be considered together. (2–4)

The importance of genotype-guided reevaluation of cutaneous findings is supported by prior reports. In a case report describing a splice-altering pathogenic *NF1* variant, multiple lesions initially interpreted as acrochordons/fibroepithelial polyps were reassessed after the genetic result and considered more consistent with cutaneous neurofibromas. (7) In our cohort, the case with multiple lesions followed as acrochordons similarly supported the need for targeted phenotyping with attention to subtle or atypical *NF1*-related cutaneous findings. Dermoscopy-based descriptions of cutaneous neurofibromas have also been reported and may support dermatologic assessment when lesion morphology is ambiguous. (8)

Evidence linking NF1 to breast cancer risk has increased, particularly for women under 50 years of age, and genotype–phenotype correlations have been proposed. (5) Recent studies have further characterized clinical presentation, subtype distribution, and the molecular spectrum of *NF1*-associated breast cancers. (6) In this context, identifying an *NF1* variant in patients presenting with breast cancer despite lacking classic NF1 features may inform individualized risk counseling and surveillance, provided that interpretation is integrated with clinical evaluation and family history. (5,6)

From a splicing standpoint, the discordance observed between HSF Pro and SpliceAI for variants such as c.753C>G and c.2951G>A indicates that reliance on a single *in silico* tool may be insufficient. When splicing-related signals (e.g., predicted cryptic splice site creation and/or ESE/ESS imbalance) are present and the overall context supports biological plausibility, RNA/cDNA-based assays should be considered where feasible for confirmation. This is particularly important because functional validation of splice-altering *NF1* variants can directly inform and refine variant classification. (7)

One individual in our cohort also carried a concurrent heterozygous pathogenic *MUTYH* variant. Given that monoallelic *MUTYH* carrier status has not been consistently associated with an increased breast cancer risk, this finding was considered a concurrent result and should be interpreted in the context of the patient's personal and family history and gene-specific guidance. (9)

In conclusion, exonic *NF1* variants detected in hereditary cancer cases without phenotypic NF1 findings may warrant systematic evaluation for potential splicing effects, and variants with suspected splice disruption should be considered where feasible for RNA/cDNA-based assays for functional validation to support clinical interpretation and management. (7)

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[Abstract:0148]

Identification of Two Novel Homozygous XPC Variants: Genotype-Phenotype Correlations in Xeroderma Pigmentosum

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Objective: Xeroderma pigmentosum (XP) is a rare hereditary disorder clinically characterized by acute sun sensitivity, marked freckle-like pigmentation, and sunlight-induced ocular involvement, with a dramatically increased risk of cutaneous neoplasms, including basalcel lcarcinoma, squamous cell carcinoma, and melanoma, developing within the first decade of life.Definitive diagnosis is established through molecular genetic analysis demonstrating biallelic pathogenic variants in nucleotide excision repair pathway genes, such as XPA, XPC, DDB2, POLH, and the ERCC gene family. Herein, we present two cases harboring distinct homozygous novel variants in the XPC gene.

Case: Proband-1, a 4-year-old male, and Proband-2, an 8-year-old male, were referred for evaluation due to marked freckling in sun-exposed areas. Proband-2 had undergone surgical intervention for an ocular neoplasm and a facial basal cell carcinoma, while neurodevelopmental milestones were age-appropriate in both patients. Physical examination demonstrated profuse freckle-like lesions on the face, neck, and hands. Proband-2 additionally presented with conjunctivitis and ectropion. Anthropometric assessment revealed microcephaly (<-2 SDS) in both individuals. Pedigree analysis disclosed parental consanguinity; fourth-degree relatives in Proband-1's family and first-cousin marriage in Proband-2's family. Clinical exome sequencing (CES) covering 3,332 genes (KAPA HyperCapHeredity Panel) was performed on peripheral blood samples. Analysis identified distinct novel variants in the XPC gene. Proband-1 harbored a homozygous missense variant, c.2051T>G (p.Leu684Arg) (ENST00000285021.12) (PM2, PP3, PP4, PP1), while Proband-2 was identified with a homozygous splice-site variant, c.622-1G>C (ENST00000285021.7) (PVS1, PM2, PP4). Neither variant has been previously reported in the literature. The variants were classified as "likely pathogenic" and "pathogenic", respectively, according to ACMG criteria.

Conclusion: This study expands the mutational spectrum of XPC through the identification of two novel homozygous variants. The early development of ocular malignancy and basal cell carcinoma in Proband-2 highlights the severe cancer predisposition associated with XPC deficiency, emphasizing the need for aggressive surveillance protocols. While XPC-related Xeroderma Pigmentosum is classically distinguished from other complementation groups by the absence of primary neurological findings, the presence of microcephaly observed in both patients suggests a broader phenotypic variability than typically recognized. These findings underscore the critical role of clinical exome sequencing in elucidating genotype-phenotype correlations in consanguineous families. Early molecular diagnosis is paramount for implementing strict UV-protection strategies to minimize malignancy risk and for providing accurate genetic counseling and prenatal diagnosis options for future pregnancies.

Keywords: XPC, Xeroderma pigmentosum, cancer predisposition, microcephaly, novel variant

[Abstract:0151]

Germline Pathogenic Variants in Prostate Cancer: A Single-Center Experience

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Objective: The aim of this study was to evaluate germline genetic testing results in prostate cancer patients who were referred to the Department of Medical Genetics between 2023 and 2025, and to determine the frequency and distribution of pathogenic and likely pathogenic germline variants.

Materials-Methods: This retrospective study included 77 prostate cancer patients who were referred to the Department of Medical Genetics between 2023 and 2025 and had an indication for germline genetic testing. Germline variant analysis was performed using a hereditary cancer multi-gene panel based on the Twist Comprehensive Exome Sequencing (TWIST-CES) kit. Library preparation and sequencing were conducted according to the manufacturer's protocols. Bioinformatic analysis focused on genes included in the hereditary cancer panel. Detected variants were interpreted and classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Pathogenic and likely pathogenic (P/LP) variants were included in the final analysis.

Results: P/LP germline variants were identified in 10 of 77 patients (13%). The most frequently affected gene was *ATM*, with variants detected in three patients. Variants in the *BRCA2* gene were identified in two patients, while single patients harbored pathogenic or likely pathogenic variants in the *XPA*, *FANCA*, *MUTYH*, *MSH3*, and *MAD1L1* genes. The majority of the identified genes were involved in DNA damage response and DNA repair pathways. These findings are consistent with previous reports indicating that germline DNA repair gene variants are present in approximately 10–12% of patients with metastatic prostate cancer.

Conclusion: In this study, germline pathogenic or likely pathogenic variants were detected in a substantial proportion of prostate cancer patients undergoing genetic evaluation. The identification of pathogenic variants in homologous recombination and DNA repair genes, particularly *BRCA2* and *ATM*, has important clinical implications. These alterations may guide genetic counseling, familial risk assessment, and therapeutic decision-making, including the potential use of targeted therapies such as poly(ADP-ribose) polymerase (PARP) inhibitors. Our findings support the clinical utility of germline genetic testing in prostate cancer and its role in personalized treatment strategies.

Keywords: *ATM*, cancer, prostate

[Abstract:0165]

Monoallelic *MUTYH* Pathogenic Variants in a Hereditary Cancer Cohort: Frequency and Association with Breast Cancer

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Objective: The *MUTYH* gene encodes a key enzyme of the base excision repair pathway and plays a critical role in maintaining genomic integrity by correcting oxidative DNA damage. Biallelic pathogenic variants in *MUTYH* are a well-established cause of *MUTYH*-associated polyposis, conferring a markedly increased lifetime risk of colorectal cancer. In contrast, the clinical relevance of monoallelic *MUTYH* pathogenic variants remains uncertain. Although heterozygous *MUTYH* variants are relatively common in the general population, their contribution to cancer susceptibility,particularly breast cancer has not been clearly defined. Previous studies have reported inconsistent and sometimes conflicting results, highlighting the need for further evaluation in large and well-characterized hereditary cancer cohorts.
Materials-Methods: This retrospective study included 1,905 consecutive patients referred to our clinic for hereditary cancer evaluation between 2018 and 2025. All individuals underwent germline genetic testing using a 35 gene hereditary cancer panel based on next-generation sequencing. Detected variants were interpreted and classified according to the American College of Medical Genetics and Genomics (ACMG) criteria. Patients harboring pathogenic or likely pathogenic *MUTYH* variants were identified retrospectively. Demographic and clinical data were reviewed, and patients were stratified according to cancer diagnosis, with a particular focus on breast cancer.
Results: Pathogenic or likely pathogenic *MUTYH* variants were identified in 51 of the 1,905 patients (2.7%). Among these individuals, 9 carried biallelic variants, while 42 were monoallelic carriers, corresponding to a monoallelic carrier frequency of approximately 2.2% in the overall cohort. Breast cancer was the most common malignancy, diagnosed in 1,042 patients. Within this subgroup, 18 individuals were monoallelic *MUTYH* pathogenic variant carriers, yielding a carrier frequency of 1.7% among breast cancer patients. Monoallelic *MUTYH* carriers were also observed across a variety of non-breast tumor types, supporting a broad tumor spectrum.
Discussion: The role of monoallelic *MUTYH* variants in cancer susceptibility remains controversial. While current evidence does not support a strong, independent increase in breast cancer risk attributable to heterozygous *MUTYH* variants, their recurrent identification in patients with diverse malignancies suggests a potential biological relevance beyond colorectal cancer. Notably, the presence of monoallelic *MUTYH* variants in patients with a positive family history of cancer, cancer recurrence, or co-occurrence with other cancer susceptibility genes supports the hypothesis that heterozygous *MUTYH* variants may function as low-penetrance modifiers of cancer risk rather than classical high-penetrance predisposition genes.
Conclusion: These results underscore the importance of cautious interpretation of *MUTYH* findings in multigene panel testing and emphasize the need for large, multicenter, and prospective studies to better define cancer risks and guide clinical management of monoallelic *MUTYH* carriers.

Keywords: ACMG, BREAST, CANCER, MONOALLELIC, *MUTYH*

[Abstract:0167]

Hereditary Cancer Panel Results in Ovarian Cancer Evaluation: Variant Spectrum and Gene Distribution

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Objective: Ovarian cancer has a heterogeneous genetic background, and germline predisposition can be identified in a substantial proportion of patients; this is clinically important for both patient management and family screening. In this study, the distribution of variants detected by a hereditary cancer panel according to pathogenicity classes and the gene spectrum were evaluated in individuals with ovarian cancer and/or a family history of ovarian cancer.

Materials-Methods: Cases referred to the Genetic Diseases Evaluation Center at İstanbul Başakşehir Çam and Sakura City Hospital between 2020 and 2025, in whom a 59-gene hereditary cancer panel had been performed, were retrospectively reviewed. Patients tested due to an indication of ovarian cancer and/or a family history of ovarian cancer were included. Variants were classified according to ACMG/AMP criteria, and the clinical interpretation of findings was performed based on NCCN guidelines. The frequencies of P/LP and VUS findings and the gene distribution of P/LP variants were assessed.

Results: A total of 131 cases were evaluated; the median age was 54 years. A family history of ovarian cancer was present in 26/131 (19.8%) patients. At least one P/LP variant was detected in 55/131 (42.0%) patients, and VUS were reported in 87/131 (66.4%) patients. Among P/LP-positive patients, BRCA1/2 variants were identified in 29/55 (52.7%) (BRCA1: n=20; BRCA2: n=9). P/LP findings outside BRCA1/2 were most frequently observed in MUTYH (n=7) and RAD51C (n=3), and less frequently in RAD51D, RAD50, ATM, and MSH2 (n=2 each). Single cases harbored variants in BRIP1, CHEK2, PTEN, POLE, BAP1, NBN, and RTEL1. VUS were most commonly reported in APC (n=11), ATM (n=8), BRCA2 (n=7), and CHEK2 (n=6).

Conclusion: The fact that a substantial proportion of P/LP findings were located in genes other than BRCA1/2 suggests that a multigene panel strategy broadens the scope of genetic evaluation for ovarian cancer. Conversely, the frequent reporting of VUS underscores the need for uncertainty management in genetic counseling and periodic reclassification at appropriate intervals.

Keywords: BRCA1/BRCA2, Hereditary cancer, Multigene panel, Ovarian cancer

[Abstract:0168]

Molecular Diagnosis of Familial Adenomatous Polyposis in an NGS-Negative Case: The Importance of CNV and MLPA Analysis

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Introduction: Familial Adenomatous Polyposis (FAP) is an autosomal dominant hereditary colorectal cancer syndrome caused by pathogenic germline variants in the *APC* gene. While sequence analysis identifies the majority of causative variants, a subset of patients harbor large genomic rearrangements that may be missed by standard next-generation sequencing (NGS) panels. This highlights the importance of complementary copy number variation (CNV) analysis in clinically suspected FAP cases with negative sequencing results.
Case Presentation: We report the case of a 52-year-old female patient who underwent total colectomy in 2011 due to the presence of more than 100 tubular adenomas, consistent with a clinical diagnosis of FAP. The patient had no significant comorbidities and was not using any chronic medication. Family history was remarkable: two male siblings had been clinically diagnosed with FAP and died from colorectal cancer at the ages of 37 and 49, respectively. There was no reported history of FAP among distant relatives. Additional familial malignancies included thyroid cancer in a maternal aunt and lymphoma in a paternal aunt. Both parents had died suddenly at relatively young ages (54 and 57 years), with no documented cancer diagnosis.
Methods-Results: To establish a molecular diagnosis, a hereditary cancer panel including 41 genes was initially performed using NGS technology. No pathogenic or likely pathogenic variants were detected by sequence analysis. Given the strong clinical suspicion of FAP, CNV analysis was subsequently performed, revealing a deletion encompassing exons 7–11 of the *APC* gene. To confirm this finding, multiplex ligation-dependent probe amplification (MLPA) analysis was requested. MLPA results demonstrated a heterozygous deletion involving *APC* exon 9 through intron 13 (rsA5q22.2), confirming the presence of a large genomic rearrangement.
Conclusion: This case underscores the critical role of CNV analysis and MLPA in the molecular diagnosis of FAP, particularly in patients with strong clinical and familial evidence but negative initial NGS sequencing results. Comprehensive genetic testing strategies that include both sequence and dosage analyses are essential to avoid false-negative results, ensure accurate diagnosis, and enable appropriate genetic counseling and surveillance for affected families.

Keywords: *APC*, CNV, FAP, MLPA, NGS

[Abstract:0169]

Re-evaluation of a Single-Exon Deletion Detected by MLPA in the *MLH1* Gene Using Next-Generation Sequencing: A Case Report

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Introduction: Copy number variants (CNVs) constitute a component of the diagnostic process in hereditary cancer predisposition syndromes. The *MLH1* gene is one of the main mismatch repair genes associated with Lynch syndrome, and exon-level deletions and duplications detected in this gene are of clinical significance. Although Multiplex Ligation-dependent Probe Amplification (MLPA) is a sensitive method for the detection of copy number changes, it may yield false-positive results, particularly in cases involving single-exon deletions. One reason for this limitation is the presence of sequence variants within MLPA probe-binding regions, which may interfere with probe hybridization and ligation to the target sequence. In this study, we present a case of a patient with colon cancer in whom an MLPA-detected deletion of exon 15 in the *MLH1* gene was shown to be associated with a heterozygous variant localized to the probe-binding region identified by Next-Generation Sequencing (NGS), highlighting the complementary roles of MLPA and NGS.

Case: A patient diagnosed with colon cancer and evaluated for hereditary cancer predisposition initially underwent an NGS-based hereditary cancer gene panel. No significant pathogenic or likely pathogenic variants were detected in the NGS analysis. Due to persistent suspicion, MLPA analysis targeting the *MLH1*/*MSH2* genes was subsequently performed, revealing a copy number decrease consistent with a deletion of exon 15 in the *MLH1* gene. Given that this finding involved a single exon, the possibility of a technical artifact was considered, and the patient's NGS data were re-evaluated. Reanalysis identified a heterozygous nucleotide variant, c.1693A>T, localized to the probe-binding region corresponding to the exon in which the deletion had been detected by MLPA. The *MLH1* c.1693A>T heterozygous variant identified by NGS was reported with a population frequency of 0.1294% in the Turkish Variome database. The variant was found to be positioned in a manner likely to disrupt binding of the MLPA probe to its target sequence, leading to the conclusion that the deletion signal observed by MLPA represented a false-positive result caused by a sequence variant within the probe-binding region rather than a true genomic deletion.

Discussion: Single-exon deletions require cautious interpretation in MLPA analyses. While MLPA is a method for detecting exon-level copy number changes, heterozygous nucleotide variants located within probe-binding regions may interfere with probe ligation and generate false deletion signals. As demonstrated in this case, identification of c.1693A>T was crucial in reclassifying the MLPA result from a pathogenic deletion to a technical artifact. This scenario underscores the importance of utilizing NGS data not just for SNV detection, but as a mandatory quality control step for validating isolated MLPA findings. Such a combined approach is vital for preventing the clinical mismanagement of patients suspected of having Lynch syndrome.

Conclusion: Sequence variants within MLPA probe-binding regions represent an analytical pitfall that can mimic true genomic deletions. This report highlights that "single-exon" decreases in MLPA signals require mandatory confirmation to avoid misdiagnosis. The integration of NGS data into the MLPA interpretation process is essential for distinguishing technical artifacts from true copy number variants, ensuring accurate genetic counseling and clinical decision-making.

Keywords: *MLH1*, MLPA, NGS

[Abstract:0170]

Birt-Hogg-Dubé Syndrome: Clinical and Genetic Evaluation of a Patient with Pulmonary Cysts and Cutaneous Findings

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Birt–Hogg–Dubé syndrome (BHD) is a rare inherited autosomal dominant genodermatosis caused by germline mutations in the FLCN tumor suppressor gene, located on chromosome 17p11.2. It is typically characterized by multiple pulmonary cysts, spontaneous pneumothorax, cutaneous fibrofolliculomas, and an increased risk of renal neoplasia. The FLCN gene functions as a tumor suppressor by regulating the AMPK and mTOR signaling pathways, thereby controlling cellular growth, metabolism, and proliferation.

We present a 60-year-old male referred for evaluation of cystic lung disease. Physical examination revealed numerous small facial papules that had been present for more than 20 years, and histopathological examination of a papule obtained from the nasal ala demonstrated sebaceous hyperplasia. High-resolution chest CT revealed dense interlobular septal thickening, which became more pronounced toward the lung bases, accompanied by patchy, mild ground-glass opacities, as well as numerous cysts distributed throughout both lungs. The patient had diabetes mellitus and coronary artery disease; however, there was no family history of similar clinical findings or malignancy. Given the coexistence of cutaneous and pulmonary findings, genetic testing using an expanded hereditary cancer gene panel was performed, which identified a heterozygous pathogenic frameshift variant in the FLCN gene (NM_144997:c.1285dup p.His429Profs*27).

BHD is a rare inherited disorder, and its diagnosis is often challenging due to its clinical rarity and phenotypic variability. Accurate diagnosis requires a comprehensive approach that integrates careful clinical evaluation, radiographic imaging, histopathological assessment of cutaneous lesions, and germline genetic testing for pathogenic FLCN variants. In addition to skin and lung involvement, renal neoplasia occur in approximately 19–35% of individuals with BHD and represent the most life-threatening complication of the syndrome. Given the increased lifetime risk of renal neoplasia, abdominal/pelvic magnetic resonance imaging surveillance is recommended starting from the age of 20 years. Early and accurate genetic diagnosis is also important for identifying at-risk family members. In conclusion, this case highlights the importance of a multidisciplinary and comprehensive approach to genetic syndromes with multisystem involvement.

Keywords: Birt–Hogg–Dubé syndrome, cystic lung disease, FLCN gene

[Abstract:0175]

A Neonatal Case of Fanconi Anemia and Xeroderma Pigmentosum Caused by Concurrent FANCA and XPC Mutations

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Objective: Fanconi anemia (FA) is a rare inherited disorder characterized by congenital anomalies, progressive bone marrow failure, and a high risk of malignancy, particularly acute myeloid leukemia and solid tumors. Physical abnormalities occur in approximately 75% of patients, and hematologic involvement typically begins in childhood.
Xeroderma pigmentosum (XP) is a rare autosomal recessive DNA repair disorder marked by extreme ultraviolet sensitivity, early-onset skin cancers, and, in some cases, progressive neurologic involvement.
This case report describes a patient with coexisting FA and XP, highlighting the overlapping features of inherited DNA repair disorders and their implications for cancer susceptibility.
Case: A male neonate was referred to our clinic due to multiple congenital anomalies, intrauterine growth restriction, polyhydramnios, and limb abnormalities. He was born by caesarean section at 36+6 weeks of gestation to a 23-year-old mother from healthy consanguineous parents, with no relevant family history.
At birth, he weighed 1,900g and required brief respiratory support. Oesophageal atresia, a renal fusion anomaly, and multiple limb anomalies were identified, and surgical intervention was planned; newborn metabolic and hearing screenings were normal.
Physical examination revealed growth retardation and dysmorphic features, including bilateral epicanthal folds, mildly low-set ears, microretrognathia, hypoplasia of the left forearm with medial wrist deviation, bilateral hand oligodactyly with absent thumbs, and an undescended right testis.
Echocardiography showed a patent ductus arteriosus and patent foramen ovale. Cranial ultrasonography demonstrated sequelae of germinal matrix haemorrhage, while abdominal ultrasonography was unremarkable.
Genetic analysis revealed a normal male karyotype (46,XY). Molecular testing identified a homozygous likely pathogenic FANCA (NM_000135.4) variant (c.1361_1374delinsGAG), consistent with FA, and a homozygous pathogenic XPC (NM_004628.5) variant (c.413-9T>A), confirming XP group C.
Conclusion: The coexistence of pathogenic variants in FANCA and XPC has not been previously reported, making this the first description of FANCA–XPC co-occurrence. The homozygous truncating FANCA variant (c.1361_1374delinsGAG) is novel, classified as likely pathogenic, and consistent with the Fanconi anemia phenotype. The homozygous intronic XPC variant (c.413-9T>A) disrupts the acceptor splice site, leading to exon 4 skipping and loss of protein function; its pathogenicity has been confirmed by prior reports and RNA-based studies.
Although the patient is currently in the neonatal period without malignancy, close long-term surveillance is required. Recommended follow-up includes regular hematologic monitoring and bone marrow evaluation for Fanconi anemia, as well as strict photoprotection and routine dermatologic, ophthalmologic, and neurologic assessments due to xeroderma pigmentosum.
FANCA and XPC function in distinct but interconnected DNA repair pathways—interstrand crosslink repair and nucleotide excision repair. Their convergence at the ERCC1–ERCC4 endonuclease complex suggests that combined defects may impair genomic stability more severely than either defect alone. Longitudinal follow-up will be essential to determine the impact of this dual defect on cancer susceptibility and to provide further insight for the literature.

Keywords: Fanconi anemia, Xeroderma pigmentosum, Co-occurrence, Interstrand crosslink repair, Nucleotide excision repair

[Abstract:0176]

Four MINAS Cases and Their Molecular/Phenotypical Evaluations

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Introduction: In a subset of cancer cases, cancer initiation is a consequence of a germline pathogenic variant in a high or moderate penetrance cancer susceptibility gene. Multilocus Inherited Neoplasia Allele Syndrome (MINAS) describes individuals who harbor pathogenic or likely pathogenic (LP/P) germline variants in two or more distinct cancer predisposition genes.
Aim: The coexistence of pathogenic variants in distinct cancer susceptibility genes might affect age of disease onset, phenotypical spectrum, and prognosis. This study aims to present 4 different patients carrying 2 pathogenic and/or likely pathogenic (per ACMG guidelines) cancer predisposition gene variations and evaluate their molecular/phenotypical presentation.
Method: Patients' clinical features, pedigree analysis, histopathologic results and imaging findings were evaluated retrospectively. Genomic DNA was isolated from peripheral blood of the patients. Hereditary cancer gene panel which includes 61 genes related to hereditary cancer disposition syndromes using next-generated sequencing was performed for 3 patients. One patient that had epilepsy, dystonia and dysarthria among 24-year-old onset breast carcinoma was analyzed through whole exome sequencing (WES).
Results: Patient 1 was a 10-year-old girl referred with pheochromocytoma in right adrenal gland. Her genetic analysis revealed heterozygous variations in TP53 (NM_000546.6) c.1010G>A (p.Arg337His) and BLM c.2187del (p.Leu730Trpfs*8). Both variations were inherited from asymptomatic father. Pedigree analysis evaluation was very unlikely for Li-Fraumeni syndrome which is consistent for the TP53 variation since multiple reports and functional studies in literature described it to cause a low function protein but not total loss. Patient 2 was 15-year-old girl who had total thyroidectomy due to massive TI-RADS 2-3 thyroid nodules which made pressure on trachea and esophagus. Histopathological evaluation of the resected tissue revealed cystic nodules and bleeding focuses. Heterozygous pathogenic/likely pathogenic PTEN (NM_000314.8) c.1003C>T (p.Arg335*) and RAD50 (NM_005732.4) c.1615G>T (p.Glu539*) variations found in genetic testing. She only had a family history of breast carcinoma in 1 of her third-degree relatives. Mother did not carry any of the variations, but father couldn't be tested. Patient 3 was 34-year-old woman who had triple negative breast carcinoma. She carried BRCA1 (NM_007294.4) c.66dup (p.Glu23Argfs*18) and BRCA2 c.658_659del (p.Val220Ilefs*4) pathogenic variations. Both were paternally inherited, and pedigree analysis showed no history of BRCA1/BRCA2 related cancers in the family. Patient 4 was a 24-year-old woman who was born from consanguineous parents and found to carry homozygous LP variation in ATM (NM_000051.4) c.77_83dup (p.Lys29Serfs*2) and heterozygous LP variation in CHEK2 (NM_001005735.2) c.921+2T>A. ATM variation had biparental and CHEK2 variation had paternal inheritance. She had epilepsy, dystonia, dysarthria and breast carcinoma. Pedigree analysis showed history of breast carcinoma in 3 of her second-degree relatives and one gastric carcinoma in 1 relative.
Discussion: It could be proposed that the adverse phenotypic consequences of MINAS could be additive or synergistic, although it could be protective through synthetic lethality-theoretically. Low incidence of MINAS makes case reports valuable for understanding the nature of co-occurrences. To provide the best prognostic information for individuals with MINAS, long-term follow up and molecular genetic analysis of any MINAS-related cancers should be undertaken.

Keywords: MINAS, cancer, cancer disposition, hereditary

[Abstract:0182]

Germline Cancer Predisposition in Pediatric Solid Tumors

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Objective: Solid tumors constitute a heterogeneous group of malignancies arising from non-hematopoietic tissues, and represent a substantial proportion of childhood cancers. Although pediatric cancers are rare and represent approximately 1-2% of all malignancies, solid tumors constitute nearly 40-50% of childhood cancer cases. Increasing evidence indicates that a approximately 8-12% of unselected pediatric cancer patients harbor pathogenic/likely pathogenic (P/LP) germline variants in cancer predisposition genes. This study aimed to evaluate the contribution of germline cancer predisposition to pediatric solid tumors using clinical exome sequencing (CES) in children and adolescents aged 0-18 years. Germline variants in cancer predisposition genes were systematically analyzed to determine the frequency and molecular spectrum of P/LP variants and to assess their potential clinical relevance for patient management, surveillance, and genetic counseling.

Materials-Methods: A total of 56 pediatric patients diagnosed with solid tumors were included in the study, encompassing a broad spectrum of tumor types, including central nervous system tumors, sarcomas, renal tumors, and other extracranial solid malignancies. Germline analysis was performed using CES on DNA extracted from peripheral blood samples, targeting more than 100 cancer predisposition genes. Rare variants with a minor allele frequency <=0.1% classified as pathogenic, likely pathogenic, or variants of uncertain significance were evaluated, and copy number variation analysis was performed across all genes included in the panel. Identified candidate variants were assessed together with parental segregation analysis.

Results: The cohort included 56 patients with solid tumors, classified as central nervous system tumors (n=18, 32.1%), soft tissue and bone tumors (n=17, 30.4%), renal tumors (n=8, 14.3%), and other solid tumors (n=13, 23.2%). At the time of submission, CES analysis was completed in 26 patients, while analyses in 30 patients were ongoing. Among patients with completed analysis, P/LP germline variants were identified in 11 patients (42.3%). The most frequently affected gene was *NF1* (n=7), and all NF1 patients were diagnosed with central nervous system tumors, especially gliomas. Additional P/LP variants were detected in *RB1* (retinoblastoma, n=2), *PTEN* (glioma, n=1), *DICER1* (ovarian Sertoli-Leydig cell tumor, n=1), *RET* (atypical bronchial carcinoid tumor, n=1), and *TSC2* (glioma and cardiac rhabdomyoma, n=1).

Conclusion: Germline cancer predisposition in pediatric solid tumors remains underexplored despite its potential impact on diagnosis, management, and surveillance. In this study, the identification of P/LP germline variants in a notable subset of children with solid tumors reinforces the relevance of systematic germline evaluation in pediatric cancers. The higher detection rates observed in this cohort likely reflect the inclusion of clinically selected patients, underscoring the importance of heightened awareness in the presence of clinical red flags such as early-onset disease, specific tumor types, or suggestive family histories. These findings emphasize that germline analyses should be considered an integral component of the diagnostic workup in pediatric cancer patients. Completion of the ongoing analyses is expected to further clarify the spectrum and frequency of germline predisposition, and the full results will be presented at the time of the conference presentation.

Keywords: clinical exome sequencing, germline cancer predisposition, pediatric solid tumors

[Abstract:0185]

Multiple Inherited Neoplasia Allele Syndrome Identified in a Hereditary Cancer Testing Cohort: A Single-Center Experience

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Objective: With the increasing use of multigene panel testing in hereditary cancer evaluation, pathogenic variants in more than one cancer predisposition gene are being identified in a subset of patients. This genetic background, referred to as Multiple Inherited Neoplasia Allele Syndrome (MINAS), has been increasingly reported, yet its clinical and molecular characteristics remain incompletely understood. In this study, we aimed to describe MINAS cases detected in our hereditary cancer cohort.

Materials-Methods: A total of 2707 individuals who underwent germline hereditary cancer panel testing were retrospectively reviewed. Pathogenic and likely pathogenic variants were evaluated. MINAS was defined as the presence of pathogenic or likely pathogenic variants in at least two different cancer predisposition genes. Clinical features, cancer type, and age at diagnosis were recorded, and the identified genes were grouped according to their biological pathways.

Results: Fourteen patients (0.52%) met the criteria for MINAS. Breast cancer was the most common malignancy, followed by ovarian, pancreatic, and colorectal cancers. The most frequently affected genes were CHEK2 and ATM, followed by BRCA1, BRCA2, and PALB2. Most pathogenic variants were found in genes involved in DNA damage response and homologous recombination pathways, while a smaller number of patients carried variants affecting different biological pathways. At the time of evaluation, most patients presented with a single primary tumor, even when multiple cancer predisposition genes were involved. Several patients were diagnosed at a young age, suggesting that the clinical spectrum associated with their genetic background may not yet be fully expressed.

Conclusion: MINAS represents a heterogeneous group of patients with variable genetic and clinical features. The findings from our series are consistent with previously reported diversity in MINAS phenotypes, including differences in cancer type, age at onset, and affected biological pathways. These observations underline the importance of individualized interpretation of multigene test results and careful clinical follow-up in patients carrying multiple pathogenic variants.

Keywords: cancer predisposition, germline variants, hereditary cancer, MINAS, multigene panel

[Abstract:0186]

Hereditary Cancer Panel Results in Early-Onset Breast Cancer Patients Aged 30–45: A Single-Center Analysis of 130 Cases

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Objective: Breast cancer diagnosed at a young age is frequently associated with hereditary cancer predisposition syndromes. With the widespread adoption of multigene hereditary cancer panels, pathogenic variants in genes beyond BRCA1 and BRCA2 are increasingly identified. However, the relative contribution of BRCA versus non-BRCA genes in early-onset breast cancer remains incompletely characterized in real-world clinical settings.
Materials-Methods: We retrospectively evaluated hereditary cancer panel results of 130 female patients aged 30–45 years who were diagnosed with breast cancer and referred to Göztepe Prof. Dr. Süleyman Yalçın City Hospital between 2024 and 2025. All patients underwent next-generation sequencing–based multigene hereditary cancer panel testing. Detected variants were classified according to ACMG/AMP guidelines as pathogenic, likely pathogenic, variants of uncertain significance (VUS), or negative. Variant distributions were analyzed descriptively, with particular emphasis on BRCA and non-BRCA gene findings.
Results: Pathogenic or likely pathogenic variants were identified in a considerable proportion of the cohort. BRCA1 and BRCA2 pathogenic variants constituted a substantial proportion of clinically actionable findings, supporting their well-established role in hereditary breast cancer.
Notably, a significant number of pathogenic or likely pathogenic variants were detected in non-BRCA cancer predisposition genes, including CHEK2, PTEN, NF1, ATM, RAD51D, FANCA, MUTYH, and MSH3, demonstrating the added diagnostic value of multigene panel testing beyond BRCA-only analysis.
Variants of uncertain significance were frequently observed across the cohort. The most commonly involved genes included ATM, GALNT12, POLE, POLD1, CDH1, PMS2, MSH6, NF1, APC, and BRIP1, with several patients harboring multiple VUS affecting different cancer susceptibility genes.
A subset of patients showed no reportable pathogenic variants, reflecting the genetic heterogeneity of early-onset breast cancer.
Conclusion: In this single-center cohort of 130 early-onset breast cancer patients, clinically relevant pathogenic variants were identified in both BRCA and non-BRCA genes. While BRCA1/2 mutations remain a major component of actionable findings, non-BRCA pathogenic variants represent a clinically meaningful proportion of hereditary risk, underscoring the limitations of BRCA-focused testing strategies. The high prevalence of VUS highlights the need for continued variant reclassification efforts and careful genetic counseling. These findings support the routine use of comprehensive hereditary cancer panels in young breast cancer patients

Keywords: Early-onset breast cancer, Hereditary cancer panel, BRCA and non-BRCA genes

[Abstract:0190]

Novel Reports and Positional Investigation of BRCA intragenic deletions

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Objective: The BRCAs (BReast CAncer genes, namely BRCA1 and BRCA2) are a couple of tumor suppressor agents, playing a crucial part in maintaining genomic stability via forming mutually exclusive complexes with a number of functional units. Loss-of-function of these genes are associated with a number of neoplasias, such as ovarian cancer (including fallopian tube and primary peritoneal cancers), prostate cancer, pancreatic cancer, and melanoma. The BRCA1 protein contains several important functional domains such as the RING domain (encoded by exons 2–5), and the BRCT domain (encoded by exons 15–23). While sequence changes constitute the major proportion of pathogenic mechanism, 3-11% of disease causing variants are deletions and duplications. Rarity of these CNVs is responsible for the lesser extent of literature in their regard.
Materials-Methods: To detect these large rearragements, BRCA1 MLPA P002 and BRCA2 MLPA P045 were used (MRC Holland). To assess the relationship between BRCA deletions and the clinical course, out of 958 patient cohort, 11 individuals with different intragenic breakpoints were included in the study. MANE select exon numbering was used (1-23). It must be kept it mind that previous exon numbering (a.k.a “classical numbering”) was different, having no exon 4, causing the following exons to be named as 1 greater than they actually are. (Therefore e.g exon 5 in MANE select is exon 6 in classical, and so on).
Results: 9 patients were diagnosed with unilateral breast cancer, and 2 were asymptomatic; the reason for their investigation was family history. Out of 10 samples with BRCA1 deletions, 7 were composed of exons 17-18, 2 were exon 4-18 and finally 1 were 4-6. Exons 17-18 deletions are previously reported, and associated with hereditary cancers. To our knowledge, other BRCA deletions were previosly reported in large cohorts but genotype-phenotype correlation was not detailed. 1 sample with BRCA2 deletion, had its exon 19 deleted, which was previously not reported.Since copy number rearrangements are largely associated with non-allelic homologous recombination events (NAHR) between low-copy-repeats (LCRs), the genomic localization of SINE and LINE elements were analyzed. Breakpoints were found to correlate with the localizations of these elements. In addition, included exons of both BRCA1 and BRCA2 genes harbored functional and critical domains, strenghtening the genotype-phenotype correlations of-especially- previously ill-defined regions
Conclusion: These data can further enhance our understanding of BRCA related pathogenic mechanisms.

Keywords: BRCA1, BRCA2, deletion

Details of samples and respective deletions

Patient No.	Family No.	Age	Sex	Phenotype	Gene	Exons	Correlation
1	1	29	K	Breast Cancer	BRCA1	17-18	Reported
2	2	50	K	Breast Cancer	BRCA1	17-18	Reported
3	3	41	K	Breast Cancer	BRCA1	17-18	Reported
4	3	44	K	Breast Cancer	BRCA1	17-18	Reported
5	4	38	K	Breast Cancer	BRCA1	17-18	Reported
6	5	40	K	Breast Cancer	BRCA1	17-18	Reported
7	6	31	E	-	BRCA1	4-18	Unknown
8	6	56	E	-	BRCA1	4-18	Unknown
9	7	51	K	Breast Cancer	BRCA1	17-18	Reported
10	8	42	K	Breast Cancer	BRCA1	4-6	Unknown
11	9	45	K	Breast Cancer	BRCA2	19	Unknown

[Abstract:0191]

Germline TP53 Variant in a Pediatric Patient with High-Grade Papillary Thyroid Carcinoma: A Case Report

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Objective: Thyroid cancer is one of the most common endocrine malignancies and can occur as part of hereditary cancer predisposition syndromes. Both environmental factors and genetic alterations contribute to thyroid tumorigenesis. Germline mutations in tumor suppressor genes, particularly TP53, are associated with an increased risk of early-onset and multiple cancers, including thyroid malignancies. TP53 plays a crucial role in maintaining genomic stability through regulation of the cell cycle, DNA repair, and apoptosis. This study aims to highlight the clinical significance of a germline TP53 variant in a pediatric patient diagnosed with thyroid cancer.
Case: A 15-year-old female patient with no known prior medical conditions was diagnosed with high-grade papillary thyroid carcinoma (according to WHO criteria). Thyroid ultrasonography revealed a solid–cystic nodule in the left lobe of the thyroid gland. The patient subsequently underwent left thyroid lobectomy, and histopathological examination of the surgical specimen confirmed the diagnosis of high-grade papillary thyroid carcinoma. Next-generation sequencing (NGS) analysis performed on tumor tissue initially identified a TP53 (NM_000546.6) c.472C>T p.(Arg158Cys) variant. Following this finding, germline testing using peripheral blood samples was conducted, which confirmed the presence of the same TP53 variant in the heterozygous state, indicating a germline alteration. The variant was classified as likely pathogenic. There was no reported family history of cancer. Based on the early age of onset and the identification of a germline TP53 variant, a hereditary cancer predisposition syndrome was considered, and appropriate genetic counseling was recommended.
Conclusion: This case highlights the importance of considering germline TP53 variants in pediatric patients diagnosed with high-grade papillary thyroid carcinoma, particularly in the absence of known predisposing medical conditions. The identification of a likely pathogenic TP53 c.472C>T (p.Arg158Cys) variant suggests an underlying hereditary cancer predisposition and underscores the value of genetic testing and early molecular evaluation in young patients with aggressive thyroid malignancies. Early recognition of TP53-associated cancer risk is essential for optimizing long-term management, surveillance, and genetic counseling in pediatric patients and their families. This finding emphasizes that the absence of a family history does not exclude germline TP53 alterations, particularly in pediatric patients with aggressive tumors.

Keywords: Pediatric Thyroid carcinoma, TP53, NGS

[Abstract:0195]

Dynamic Modeling of Familial Risk in Breast Cancer: Integration of Polygenic Risk Scores (PRS), Tyrer-Cuzick, and Biological Interactions

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Objective: Breast cancer is a complex and multifactorial malignancy in which genetic predisposition plays a decisive role in its etiology. High-penetrance genes such as BRCA1/2 account for less than 25% of familial risk; approximately 18% of the remaining 'missing heritability' is predicted to arise from polygenic variants. In this context, Polygenic Risk Scores (PRS) are considered a critical tool for personalized surveillance, offering the potential to refine risk assessment and provide precise risk stratification, particularly in cases where standard genetic tests are 'uninformative.'

Materials-Methods: The study cohort included 20 healthy individuals who presented to the Necmettin Erbakan University Faculty of Medicine, Department of Medical Genetics (2023–2025) with a significant family history of breast cancer, yet tested negative for pathogenic variants in germline targeted next-generation sequencing (NGS) panels. Histopathological and molecular subtype data (Luminal A/B, TNBC, HER2+) from affected family members were integrated into the analysis.
Genomic DNA was genotyped using the CytoScan™ HT-CMA 96F Assay Kit (SNP array). Following raw data quality control via Multi-Sample Viewer (MSV), genotype imputation was performed on the Michigan Imputation Server using the 1000 Genomes (Phase 3) reference panel to maximize variant coverage. To ensure compatibility between the obtained data and PRS models, UCSC chain files and the LiftOver tool were utilized for reference genome (GRCh) conversion. PRS calculations employed models developed for Breast Cancer (PGS000004-Mavaddat) and ER-Positive Breast Cancer (PGS000005). Raw scores were standardized to Z-scores based on European (EUR) population norms. Genotypic risk profiles were then comparatively analyzed against the Tyrer-Cuzick (IBIS v8) phenotypic risk assessment tool. Furthermore, the seven candidate variants contributing most significantly to the PRS in high-risk cases (FGFR2, TOX3, ESR1, MAP3K1, TERT, LSP1, CCND1) were mapped for protein-protein interactions (PPI) using the STRING database.

Results: In the analysis of the 20-case cohort, PRS Z-scores showed a heterogeneous distribution ranging from -0.1 to +2.9 standard deviations (SD). In three cases, the PRS Z-score exceeded the +2.0 SD threshold in at least one of the PRS models and was therefore classified in the 'high-risk/critical case' category. Comparison of the PGS models for Breast Cancer and ER-Positive Breast Cancer revealed that risk scores exhibited subtype-specific dynamic differences. While variants in the FGFR2 and TOX3 genes provided the strongest positive contribution to the cumulative risk in the genotypic profile, the high-confidence protein interaction identified between the CCND1 and ESR1 genes (STRING score: 0.997) confirms the functional alignment of the calculated risk score with biological pathogenesis. Consequently, these three cases, which were under standard follow-up protocols according to traditional clinical risk assessment (Tyrer-Cuzick model), were re-classified into the 'high-risk' category at the molecular level following integrated PRS analysis.
Conclusion: Our study demonstrates that healthy individuals in whom no pathogenic variants are detected via routine genetic panels can be re-classified into high-risk groups through PRS analysis. These preliminary findings highlight the limitations of risk models based solely on family history (such as the Tyrer-Cuzick model) and reveal that PRS integration has significant potential to strengthen personalized preventive surveillance protocols.

Keywords: Polygenic Risk Score (PRS), Familial Breast Cancer, SNP array

Dynamic Modeling of Familial Risk in Breast Cancer: Integration of Polygenic Risk Scores (PRS), Tyrer-Cuzick, and Biological Interactions

Objective: Breast cancer is a complex and multifactorial malignancy in which genetic predisposition plays a decisive role in its etiology. High-penetrance genes such as BRCA1/2 account for less than 25% of familial risk; approximately 18% of the remaining 'missing heritability' is predicted to arise from polygenic variants. In this context, Polygenic Risk Scores (PRS) are considered a critical tool for personalized surveillance, offering the potential to refine risk assessment and provide precise risk stratification, particularly in cases where standard genetic tests are 'uninformative.'

Materials and Methods: The study included 20 healthy individuals who presented to the Necmettin Erbakan University Faculty of Medicine, Department of Medical Genetics between 2023 and 2025 with a family history of breast cancer and in whom no clinically significant pathogenic variants were detected in germline targeted next-generation sequencing (NGS) panels. Histopathological and molecular subtype data (Luminal A/B, TNBC, HER2+) from affected family members were evaluated and included in the analysis. Genomic DNA samples were genotyped using the SNP array (CytoScan™ HT-CMA 96F Assay Kit) method. Raw data quality was controlled using Multi-Sample Viewer (MSV) software. To maximize variant coverage, genotype imputation was performed via the Michigan Imputation Server based on the 1000 Genomes (Phase 3) reference panel. UCSC chain files and the LiftOver tool were utilized to ensure reference genome (GRCh) compatibility between the obtained data and PGS catalog models. Polygenic Risk Scores (PRS) were calculated using polygenic score (PGS) models developed for Breast Cancer (PGS000004-Mavaddat) and ER-Positive Breast Cancer (PGS000005). Raw scores were standardized to Z-scores (Standard Deviation) based on European (EUR) population norms. The resulting genotypic risk profiles were analyzed comparatively with results from the Tyrer-Cuzick (IBIS v8) phenotypic risk assessment tool. In cases identified within the high-risk group, the allelic distributions of 7 candidate variants contributing most significantly to the PRS were examined. The genes harboring these variants (FGFR2, TOX3, ESR1, MAP3K1, TERT, LSP1, CCND1) were mapped for protein-protein interactions (PPI) using the STRING database.

Results: In the analysis of the 20-case cohort, PRS Z-scores showed a heterogeneous distribution ranging from -0.1 to +2.9 standard deviations (SD). In three cases, the PRS Z-score exceeded the +2.0 SD threshold in at least one of the PRS models and was therefore classified in the 'high-risk/critical case' category. Comparison of the PGS models for Breast Cancer and ER-Positive Breast Cancer revealed that risk scores exhibited subtype-specific dynamic differences. While variants in the FGFR2 and TOX3 genes provided the strongest positive contribution to the cumulative risk in the genotypic profile, the high-confidence protein interaction identified between the CCND1 and ESR1 genes (STRING score: 0.997) confirms the functional alignment of the calculated risk score with biological pathogenesis. Consequently, these three cases, which were under standard follow-up protocols according to traditional clinical risk assessment (Tyrer-Cuzick model), were re-classified into the 'high-risk' category at the molecular level following integrated PRS analysis.

Conclusion: Our study demonstrates that healthy individuals in whom no pathogenic variants are detected via routine genetic panels can be re-classified into high-risk groups through PRS analysis. These preliminary findings highlight the limitations of risk models based solely on family history (such as the Tyrer-Cuzick model) and reveal that PRS integration has significant potential to strengthen personalized preventive surveillance protocols.

Keywords: Polygenic Risk Score (PRS), Familial Breast Cancer, SNP array

[Abstract:0198]

Genotype–Phenotype Correlations in Germline Predisposition to Hematologic Malignancies: A Single-Center Retrospective Analysis

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Introduction: The majority of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) cases are considered sporadic. However, the integration of next-generation sequencing (NGS) into diagnostic workflows has demonstrated that inherited forms of MDS and AML are more common than previously recognized. Current data indicate that germline pathogenic variants in cancer predisposition genes are present in approximately 5–15% of adult patients and 4–13% of pediatric patients with MDS or AML. In parallel, numerous novel genes have been identified in recent years that contribute to familial MDS/AML development, either as part of syndromic disorders or as isolated predisposition conditions.

International consensus guidelines are available for certain inherited disorders, including Fanconi anemia, Shwachman–Diamond syndrome, Diamond–Blackfan anemia, and telomere biology disorders. However, standardized international guidelines—particularly for adult patients—are still lacking for many other rare hereditary conditions predisposing to MDS and AML. Germline predisposition syndromes exhibit marked heterogeneity with respect to clinical phenotype, age at onset, penetrance, phenotypic expression, and the somatic cytogenetic and/or molecular alterations that may arise before or during malignant transformation. Moreover, for several conditions associated with germline variants in bone marrow failure syndromes, telomere biology disorders, or genes such as ETV6, the precise risk of malignant transformation remains unclear, largely due to limited long-term data on these rare entities.

Aim and Methods: This study aimed to evaluate genotype–phenotype correlations in individuals carrying pathogenic (P) or likely pathogenic (LP) germline variants in genes associated with hematologic malignancy predisposition. Both patients diagnosed with hematologic malignancies and individuals who had not yet developed malignancy but were identified as carriers of predisposition genes were included. This approach enabled the identification of gene-specific clinical and hematologic features, including phenotypic clues that may emerge prior to malignant transformation and inform clinical surveillance strategies.

Pathogenic or likely pathogenic variants in classical hereditary cancer predisposition genes (BRCA1, BRCA2, NF1, MLH1, MSH2, and MSH6) were included only in individuals with a hematologic malignancy diagnosis or a family history of hematologic malignancies. Molecular multigene sequencing results of individuals referred to the Ege University Department of Medical Genetics between 2021 and 2025 were retrospectively reviewed. Identified germline variants were grouped by gene, and associated clinical phenotypes and hematologic spectra were characterized.

Results: A total of 97 individuals were included; 52 (53.6%) were male and 45 (46.4%) were female, with a mean age of 18.8 years. Pathogenic or likely pathogenic germline variants were most frequently identified in FANCA (n=15), TP53 (n=10), HAX1 (n=8), and ELANE (n=6). Other variants were predominantly distributed among genes associated with bone marrow failure, immunodeficiency, and myeloid malignancy predisposition.

Conclusion: Identification of gene-specific clinical and hematologic features may facilitate early recognition of individuals at increased risk and support the development of appropriate clinical surveillance strategies. Our findings highlight the predictive and guiding clinical value of germline genetic testing beyond its diagnostic role. Prospective studies in larger cohorts are needed to further clarify the clinical impact of these genotype–phenotype associations.

Keywords: Germline predisposition, Hematologic malignancies, Genotype–phenotype correlation, Myelodysplastic syndrome/Acute myeloid leukemia, Next-generation sequencing

[Abstract:0201]

Clinical and Genetic Spectrum in Neurofibromatosis Type 1: Evaluation of Four Family Cases in Terms of Genotype-Phenotype Correlation

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Introduction: Neurofibromatosis Type 1 (NF1) is an autosomal dominant multisystemic neurocutaneous syndrome caused by germline mutations in the *NF1* tumor suppressor gene located at the 17q11.2 locus. The disease is characterized by a predisposition to benign and malignant tumors, cutaneous findings, skeletal dysplasias, and cognitive dysfunction, showing significant clinical heterogeneity even within the same family. In this study, we present the clinical correlation of novel variants and whole gene deletions detected in four different families followed in our clinic.

Methods: *NF1* gene sequence analysis was performed for four different families followed in our center with a preliminary diagnosis of NF1. The data were analyzed on the SEQ variant analysis platform based on the GRCh38 reference genome. To identify deletions and duplications, MLPA (Multiplex Ligation-dependent Probe Amplification) was performed using SALSA MLPA Probemix P081 (mix 1) and P082 (mix 2) kits.

Results: First case was a 3 year old male with multiple café-au-lait macules. His family history revealed multiple cutaneous neurofibromas and café-au-lait macules in his mother. Sequence analysis identified a heterozygous novel c.2630del (p.Met877ArgfsTer4) frameshift variant in the *NF1* gene (NM_001042492.3). This variant was not present in ClinVar. It was classified as likely pathogenic (PVS1, PM2) according to ACMG criteria. Parental segregation analysis confirmed that the variant was maternally inherited.

Second case was a 15 year old male followed for axillary freckling, multiple café-au-lait macules, and plexiform neurofibroma. Following a suspicion of CNV (Copy Number Variation) in the sequence analysis, MLPA detected a heterozygous deletion in all exons of the *NF1* gene.

Third case was a 7 year old female with multiple café-au-lait macules and significant cognitive impairment. Following the detection of CNV in the sequence analysis, MLPA identified a heterozygous whole gene deletion in the *NF1* gene.

Fourth case was a 1 year old female with multiple café-au-lait macules. Sequence analysis identified a c.4174-786T>C intronic variant in the *NF1* gene (NM_001042492.3). The variant has no record in ClinVar and was classified as a VUS (Variant of Uncertain Significance) based on current data. The father, who carries the same variant, had only two café-au-lait macules. This was associated with the phenotypic variability emphasized in the literature and the potential effects of intronic regions on splicing.

Discussion: Although the diagnosis of NF1 is primarily based on clinical criteria, molecular confirmation is essential in sporadic childhood cases and atypical phenotypes. NF1 is a disease where genotype-phenotype correlation is limited; however, specific conditions like whole gene deletions can lead to a more severe oncological and cognitive course. Combining Next-Generation Sequencing (NGS) with MLPA and CMA methods is critical to achieve high detection rates for deletions/duplications. This case series highlights the importance of a multidisciplinary approach and comprehensive genetic testing strategies in the early diagnosis and management of NF1.

Keywords: *NF1*, Genotype-phenotype correlation, Café-au-lait macules, Neurofibroma

[Abstract:0206]

Is CHEK2 c.593-11_593-7del a Clinically Relevant Splice-Altering Variant? A Case Series with RNA Confirmation of Exon 5 Skipping

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CHEK2 encodes a serine/threonine kinase that plays a key role in the DNA damage response, integrating signals from double-strand breaks to activate cell-cycle arrest and facilitate DNA repair. Germline pathogenic variants in CHEK2 are established cancer-predisposition alleles, most consistently associated with breast cancer and, in some settings, colorectal and prostate cancer. CHEK2 is generally considered a moderate-penetrance gene, with risk estimates influenced by variant type, family history, and ancestry. While protein-truncating variants are often easier to interpret, splice-altering variants can be more challenging because they may produce a mixture of normal and abnormal transcripts, and their functional and clinical consequences can vary. Consequently, careful transcript-level validation is important for splice-region variants to support clinical interpretation.

Objective: We aimed to describe the clinical spectrum of individuals carrying CHEK2 NM_007194.4:c.593-11_593-7del identified at our center and to confirm its splicing effect at the RNA level.

Materials-Methods: Nineteen carriers of CHEK2 c.593-11_593-7del identified across different testing indications/panels were retrospectively reviewed. Sex, age, panel type, and cancer status at the time of genetic evaluation were recorded. RNA analysis was performed in a carrier sample: cDNA was generated and RT-PCR was conducted using primers spanning CHEK2 exons 2–9; splice junctions were confirmed by Sanger sequencing.

Results: Eight of 19 carriers had a cancer diagnosis (6 breast cancer, 1 colorectal cancer, 1 myelodysplastic syndrome), while 11 had no cancer diagnosis at evaluation. Among breast cancer cases, one carrier also harbored a pathogenic RAD51C variant; no additional pathogenic/likely pathogenic variants were detected on the tested panels in the remaining breast cancer carriers. RT-PCR followed by Sanger sequencing confirmed exon 5 skipping in carrier-derived cDNA, supporting a splice-altering effect of CHEK2 c.593-11_593-7del in patient material.

Conclusion: This case series provides patient-derived transcript evidence that CHEK2 c.593-11_593-7del results in exon 5 skipping and is observed in a carrier series with a breast-cancer-predominant phenotype. Larger studies incorporating quantitative splicing assays with non-carrier controls, tumor-based assessment for LOH/second-hit events, and family segregation analyses are warranted to refine its clinical significance.

Keywords: CHEK2, Exon skipping, Variant interpretation, Breast cancer predisposition

[Abstract:0213]

Clinical and Molecular Spectrum of Heterozygous *ATM* Variants in Cancer Patients: A Single-Center Experience

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Objective: The *ATM* (Ataxia Telangiectasia Mutated) gene plays a critical role in the DNA damage response pathway by regulating double-strand break repair, genomic stability, and cell cycle checkpoints. Germline heterozygous pathogenic variants in *ATM* are recognized as moderate-penetrance cancer susceptibility factors and have been associated with breast cancer, pancreatic cancer, colorectal cancer, and hematological malignancies. With the widespread implementation of next-generation sequencing (NGS)–based hereditary cancer panels, the detection of *ATM* variants has increased substantially. However, the broad phenotypic spectrum, variable penetrance, and frequent identification of likely pathogenic or pathogenic variants present challenges in clinical interpretation. This study aimed to evaluate the clinical characteristics, cancer spectrum, and molecular features of patients carrying heterozygous *ATM* gene variants identified through hereditary cancer genetic testing.

Materials-Methods: A retrospective single-center study was conducted at the Ankara Bilkent City Hospital Medical Genetics Clinic between 2019 and 2025. Germline hereditary cancer testing was performed in 1155 patients using targeted NGS-based multigene panels. 16 patients with heterozygous *ATM* variants classified as pathogenic or likely pathogenic according to ACMG criteria were included. Clinical data, including cancer type and the presence of multiple primary tumors, were obtained from medical records. Detected *ATM* variants were evaluated in terms of variant type (frameshift, nonsense, splice-site, missense, synonymous), associated cancer types, and recurrence within the cohort.

Results: In this cohort, pathogenic or likely pathogenic variants were identified in sixteen patients, with breast cancer being the most commonly observed malignancy, either as an isolated diagnosis or in combination with other cancer types. Additional tumor types included colorectal cancer, pancreatic cancer, thyroid carcinoma, osteosarcoma, chronic lymphocytic leukemia, lung carcinoma, and premalignant breast lesions. Several patients presented with multiple primary cancers, including combinations of breast, thyroid, rectal, and pancreatic malignancies. Molecular analysis revealed a heterogeneous spectrum of *ATM* variants, with a predominance of truncating alterations such as nonsense, frameshift, and splice-site variants. Recurrent variants included c.3576G>A (p.Lys1192Lys), detected in multiple patients with different cancer types, and c.6047A>G (p.Asp2016Gly), observed in both breast and colorectal cancer cases. Pathogenic truncating variants such as p.Gln2028*, p.Arg2993*, and frameshift duplications or deletions were frequently associated with breast and pancreatic cancers.

Conclusion: This single-center experience demonstrates the broad clinical and molecular heterogeneity of heterozygous *ATM* variants across diverse cancer types. The predominance of breast cancer supports the established association between *ATM* and hereditary breast cancer susceptibility, while the presence of pancreatic, colorectal, hematological, and rare tumors highlights the expanding tumor spectrum linked to *ATM*. The recurrence of specific variants across different malignancies suggests variable expressivity and incomplete penetrance. These findings underscore the importance of integrating molecular data with detailed clinical evaluation to improve variant interpretation, genetic counseling, and personalized cancer surveillance strategies.

Keywords: *ATM*, cancer susceptibility, heterozygous variants

[Abstract:0215]

Incidental Detection of a Pathogenic SMAD4 Gain of Function Variant Through Hereditary Cancer Panel Sequencing

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Objective: SMAD4 is a central mediator of TGF-β and BMP signaling pathways, playing a key role in regulating cell proliferation, differentiation, apoptosis, and extracellular matrix homeostasis. Germline variants in SMAD4 may lead to two distinct and functionally opposing clinical outcomes. Loss of function (LoF) variants impair tumor-suppressor activity and result in Juvenile Polyposis Syndrome (JPS) and Hereditary Hemorrhagic Telangiectasia (HHT). In contrast, highly specific missense variants affecting codons Arg496 or Ile500 within the MH2 domain cause gain of function (GoF) effects by increasing SMAD4 protein stability and enhancing downstream signaling, leading to Myhre syndrome a fibroproliferative multisystem disorder. This report presents a case in which a GoF SMAD4 pathogenic variant was incidentally identified during hereditary cancer testing, altering the clinical direction from oncologic surveillance to evaluation for a fibrotic connective tissue disorder.
Method: Following genomic DNA isolation from a peripheral blood sample, sequencing was performed for hereditary cancer panel genes using a custom designed panel via the Next-Generation Sequencing (NGS) method. Upon completion of bioinformatics analyses, the detected variant was evaluated in accordance with the American College of Medical Genetics and Genomics (ACMG) criteria.
Results/Case: A 36 year old woman with a history of papillary thyroid carcinoma and a strong paternal family history of lung cancer was referred for hereditary cancer evaluation. Multigene NGS testing identified a heterozygous SMAD4 c.1486C>T (p.Arg496Cys) variant. This well characterized hotspot pathogenic variant is known to impair normal SMAD4 ubiquitination, resulting in increased protein stability and excessive TGF-β pathway activation. The variant is associated with Myhre syndrome and does not exhibit features consistent with LoF mutations seen in JPS/HHT. The patient had no history of gastrointestinal polyposis, further supporting a GoF mechanism. Clinical reassessment was recommended to evaluate potential Myhre-related findings such as joint restriction, reduced mobility, hearing impairment, and possible cardiovascular fibrosis.
Conclusion: This case highlights the importance of distinguishing gain of function from loss-of-function mechanisms when interpreting SMAD4 variants detected through hereditary cancer testing. While LoF variants require gastrointestinal and malignancy surveillance, GoF variants necessitate a different strategy focused on monitoring fibrotic progression and avoiding unnecessary invasive procedures. Reverse phenotyping reassessing subtle clinical findings after the molecular diagnosis is crucial to prevent misclassification and to establish accurate, mechanism based management.

Keywords: SMAD4, gain of function, Myhre syndrome, hereditary cancer panel

[Abstract:0216]

Metastatic Juvenile-Type Granulosa Cell Tumor and Atypical Meningioma in a Patient with a Germline *BAP1* Variant: A Case Report

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Objective:*BAP1* tumor predisposition syndrome is associated with various solid tumors, most notably uveal melanoma, malignant mesothelioma, renal cell carcinoma, and meningioma. In addition, there are reports in the literature suggesting an association between *BAP1* variants and certain rare gynecological tumors, particularly sex cord–stromal tumors. In this report, we present a case referred to the Medical Genetics outpatient clinic due to a history of atypical meningioma and a metastatic juvenile-type granulosa cell tumor exhibiting a more aggressive clinical course than expected, in whom a germline *BAP1* variant was identified.

Case:A 48-year-old woman had a medical history of atypical meningioma treated with surgical resection followed by adjuvant radiotherapy. She had also undergone gynecological surgery in 2019 for an endometrial myoma. During follow-up in 2023, abdominal ultrasonography revealed a solid pelvic mass measuring approximately 14.5 cm, extending toward both ovarian regions. The serum CA-125 level at diagnosis was 58 U/mL. Abdominopelvic magnetic resonance imaging demonstrated a heterogeneous solid mass of approximately 20 cm, extending from the umbilical level to the pelvis and involving the adnexal regions and uterine bed.
The patient underwent cytoreductive (debulking) surgery in November 2023. Intraoperatively, tumoral implants were observed on the omentum, appendix, liver surface, pelvic peritoneum, and diaphragmatic peritoneum, and optimal cytoreduction was achieved at the R1 level. Histopathological evaluation revealed a juvenile-type granulosa cell tumor, supported by immunohistochemical positivity for CD56, calretinin, CD99, and vimentin, focal inhibin positivity, estrogen receptor expression in 60% of tumor cells, and a Ki-67 proliferation index of 15%. The disease was staged as operated metastatic sex cord–stromal tumor (pT4N0M1).

Given the coexistence of atypical meningioma and ovarian sex cord–stromal tumor, the patient was managed by the Oncology Department and received six cycles of paclitaxel–carboplatin chemotherapy. Although the patient remained asymptomatic and serum CA-125 levels decreased to 32 U/mL after treatment, follow-up computed tomography revealed disease progression, including pleura-adjacent pulmonary lesions and progression of hepatic and peritoneal implants. Owing to this unexpectedly aggressive clinical course, a biopsy from progressive lesions was planned.
In light of the early metastatic presentation, aggressive disease behavior, and history of atypical meningioma, the patient was referred to the Medical Genetics outpatient clinic. Family history was notable only for endometrial cancer in her mother. A hereditary cancer panel revealed a heterozygous splicing variant, c.1983+2T>G, in the *BAP1* gene, which was classified as likely pathogenic.

Conclusion: This case suggests that *BAP1* gene variants may be associated not only with the classical tumors well described in the literature but also with rare sex cord–stromal tumors that may exhibit an aggressive clinical course. In cases with atypical histopathological features, unexpectedly rapid progression, and a concomitant history of central nervous system tumors, referral to a genetics clinic and the performance of germline genetic analyses are of critical importance for the evaluation of hereditary cancer predisposition.

Keywords: *BAP1*, Meningioma, Sex cord–stromal tumor

[Abstract:0224]

PALB2 in Real-World Data: Variant Spectrum and Clinical Correlations in 635 Individuals Undergoing Hereditary Cancer Panel Testing

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Introduction: *PALB2* (Partner and Localizer of BRCA2) is a critical gene in the homologous recombination DNA repair pathway, and its role in hereditary cancer predisposition is increasingly recognized. Germline pathogenic or likely pathogenic variants (PV/LPV) in *PALB2* lead to genomic instability and are associated with an increased risk of breast, pancreatic, and ovarian cancers. The reported frequency of pathogenic *PALB2* variants in hereditary cancer cohorts ranges from 0.4% to 1.2%. This study aimed to evaluate the frequency and clinical characteristics of *PALB2* variants detected in individuals undergoing hereditary cancer panel testing.

Methods: A total of 635 individuals who presented to the Department of Medical Genetics at Dokuz Eylül University between 2024 and 2025 were retrospectively analyzed. All participants had a personal and/or family history of cancer and underwent multigene hereditary cancer panel testing. Identified *PALB2* variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria.

Results: PV/LPVs in *PALB2* were identified in 3 of 635 individuals (0.47%). Among these, one patient had breast cancer, one had ovarian cancer, and one had a gastrointestinal stromal tumor (GIST). All three carriers had a positive family history of cancer. Variants of uncertain significance (VUS) were detected in 11 individuals (1.7%), including one novel variant. The VUS group consisted of 10 females and one male, with breast cancer being the most common indication for testing. No biallelic pathogenic variants were identified.

Discussion: Existing literature indicates that *PALB2*-associated breast cancers frequently display invasive ductal carcinoma histology, high tumor grade, and HER2-negative status. While hormone receptor positivity is common, the prevalence of triple-negative breast cancer is higher than in the general population. In our cohort, one breast cancer patient carried the pathogenic c.1684+2T>G variant, presenting with invasive ductal carcinoma, which is consistent with previous reports.

The ovarian cancer patient carried the pathogenic c.932_933insC variant and had a first-degree relative with breast cancer. Although the lifetime risk of ovarian cancer is lower than that of breast cancer in *PALB2* carriers, these cases are typically high-grade serous carcinomas. Our findings align with these clinical characteristics.

Notably, one patient with a pathogenic variant was diagnosed with GIST. As *PALB2* is not currently an established predisposition gene for GIST, this may represent a sporadic occurrence. However, given the patient's family history of breast cancer, segregation analysis is planned to further clarify the association.

The VUS detection rate was 1.7%. Nine of these carriers had breast cancer, while one presented with co-existing renal cell carcinoma and lung cancer. All VUS carriers are undergoing genetic counseling, with variant re-evaluation planned as new evidence emerges.

Emerging data suggests that *PALB2*-associated cancers may show increased sensitivity to platinum-based chemotherapy and PARP inhibitors due to homologous recombination deficiency. Therefore, identifying *PALB2* variants is vital for both surveillance and personalized treatment selection.

Conclusion: The detection of *PALB2* variants is clinically significant for risk assessment, cascade testing in families, and therapeutic decision-making. The VUS rate underscores the ongoing need for population-specific data and functional studies to improve variant interpretation.

Keywords: genetic testing, hereditary cancer, HRD, *PALB2*, VUS

[Abstract:0228]

Incidental Cancer Predisposition in Whole-Exome Sequencing: A Retrospective Analysis

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Background: Germline variants predisposing to hereditary cancer syndromes are commonly identified through targeted genetic testing in oncology patients. With the increasing clinical use of next-generation sequencing, such variants are also detected incidentally in genomic analyses performed for indications unrelated to cancer. This creates challenges in variant interpretation and genetic counseling, particularly for individuals without a cancer diagnosis. Methods: We retrospectively analyzed whole-exome sequencing (WES) data from 70 patients without a cancer diagnosis who underwent genetic testing for indications unrelated to cancer. The cohort included 34 males (48.6%) and 36 females (51.4%). All data were re-evaluated using an 84-gene hereditary cancer predisposition panel, and variants were classified according to ACMG guidelines. Results: Sixteen incidental variants were identified in 16 patients (22.9%). Of these, 43.7% (n=7) were classified as pathogenic or likely pathogenic (P/LP), and 56.3% (n:9) as variants of uncertain significance (VUS). One variant was novel. All variants were located in the *MLH1*, *MUTYH*, *LZTR1*, *APC*, *RAD51D, CTNNA1*, *PALB2*, *BMPR1A*, *BRCA2*, *SDHAF2*, and *PTEN* genes. *MUTYH* was the most frequently affected gene, with variants detected in four patients (one homozygous, three heterozygous). All VUS had been previously reported in cancer-related cohorts, but their clinical relevance remains unclear due to the lack of functional validation. Conclusion: Compared with previous reports, a higher frequency of incidental hereditary cancer predisposition variants was observed. This may be related to the broad gene panel analyzed and the inclusion of VUS in the evaluation. In addition, the absence of several affected genes from the ACMG v3.3 Secondary Findings list suggests that list-based approaches alone may not fully reflect clinical complexity. Overall, exome sequencing performed for indications unrelated to cancer can identify clinically relevant incidental cancer predisposition variants beyond the primary diagnostic purpose, emphasizing the need for cautious interpretation, structured genetic counseling, and long-term follow-up.

Keywords: Whole-exome sequencing, Incidental findings, Hereditary cancer predisposition

[Abstract:0233]

Spectrum of Pathogenic, Likely Pathogenic and Uncertain Variants Identified by Targeted Multigene Sequencing in Hereditary Colorectal Cancer

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Objective: Hereditary colorectal cancer (CRC) represents a clinically important subset of colorectal malignancies, most commonly associated with Lynch syndrome and other inherited cancer predisposition syndromes. The increasing use of targeted multigene next-generation sequencing (NGS) panels has enabled comprehensive evaluation of mismatch repair (MMR) genes alongside non-MMR genes implicated in colorectal cancer susceptibility. While this approach improves diagnostic yield, it also increases the detection of variants of uncertain significance (VUS), which complicates clinical interpretation and genetic counseling. Characterizing the distribution of pathogenic/likely pathogenic (P/LP) variants and VUS across genes and patient characteristics is therefore essential to better understand the strengths and limitations of multigene panel testing in hereditary CRC assessment.

Materials-Methods: This retrospective, laboratory-based cohort study included patients with a confirmed diagnosis of colorectal cancer who were referred to the Acibadem Labgen Genetic Disorder Diagnoses Center for genetic testing due to clinical suspicion of hereditary colorectal cancer. Targeted next-generation sequencing was performed using the QIAseq Targeted DNA Hereditary Panel (QIAGEN, Germany). Library preparation followed the manufacturer's protocol, and sequencing was conducted on an Illumina MiSeq platform. The panel interrogated coding exons and flanking splice-site regions (±20 bp) of genes associated with hereditary cancer predisposition, including mismatch repair (MMR) genes and other colorectal cancer–related genes. Variant interpretation and classification were performed in accordance with ACMG/AMP guidelines. Identified variants were categorized as pathogenic/likely pathogenic (P/LP) or variants of uncertain significance (VUS).

Results: A total of 66 patients were included in the analysis, with a predominance of female individuals (81.8%). The median age at testing was 48 years. Pathogenic or likely pathogenic variants were detected in 22 patients (33.3%), whereas 44 patients (66.7%) were found to carry VUS. Patients in the P/LP group were younger at testing compared with those in the VUS group. Among P/LP cases, MMR genes accounted for the majority of pathogenic findings, with MSH2 being the most frequently affected gene, followed by MSH6, MUTYH, and PMS2. In contrast, the VUS group showed a distinct gene distribution pattern, with MSH6 and MLH1 being the most commonly involved genes, followed by MSH2 and APC. Overall, MMR genes represented the dominant gene category across the entire cohort.

Conclusion: Targeted multigene NGS testing in patients with suspected hereditary colorectal cancer reveals a considerable proportion of pathogenic or likely pathogenic variants, predominantly affecting mismatch repair genes. However, the high frequency of VUS underscores a major challenge in variant interpretation and clinical decision-making. Differences in gene distribution between P/LP and VUS groups highlight the complexity of multigene panel results and emphasize the need for cautious interpretation, systematic variant re-evaluation, and ongoing data accumulation. These findings support the clinical utility of multigene panel testing in hereditary CRC while illustrating its current interpretative limitations.

Keywords: Hereditary colorectal cancer, Lynch syndrome, multigene panel, next-generation sequencing, pathogenic variants

[Abstract:0234]

PTEN Hamartoma Tumor Syndrome Across the Lifespan: Clinical–Genetic Insights from Three Cases

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Objective: The PTEN gene encodes a key tumor suppressor protein that inhibits the PI3K/AKT/mTOR signaling pathway and plays a crucial role in the regulation of cell growth, proliferation, and apoptosis. PTEN hamartoma tumor syndrome (PHTS), caused by pathogenic or likely pathogenic germline variants in the PTEN gene, is an autosomal dominant disorder encompassing Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, and related phenotypes, and is characterized by clinical heterogeneity, cancer predisposition, and overgrowth. The aim of this study is to present three cases with PTEN variants and to discuss the clinical–genetic correlations.

Materials-Methods: Genomic DNA was extracted from peripheral blood samples. In the first case, a whole-exome analysis was performed using the Twıst kit on the MGI system. In the second case, all exons and exon-intron boundaries of the PTEN (NM_000314.8) gene were sequenced. In the third case, which was referred with a diagnosis of breast cancer, a hereditary cancer panel was performed. The identified variants were classified according to ACMG criteria and evaluated using Franklin, HGMD, and ClinVar.

Case: The first case was an 18-year-old male presenting with macrocephaly, neuromotor developmental delay, recurrent infections, obesity, and bilateral hand tremor, accompanied by prominent multisystem involvement including multinodular goiter and surgically treated papillary thyroid carcinoma, pulmonary nodules, fibromas and lipomas, gynecomastia, varicocele, myopia, scrotal tongue, and multiple facial trichilemmomas and papules. Genetic analysis revealed a heterozygous c.209+5G>T novel, de novo likely pathogenic variant in the PTEN gene.
The second case was a 2.5-year-old male with macrocephaly, neuromotor developmental delay, and behavioral problems. Genetic testing identified a heterozygous c.407G>A (p.Cys136Tyr) de novo recurrent pathogenic variant in the PTEN gene.
The third case was a 36-year-old female diagnosed with breast cancer, with a family history of colon cancer in her uncle. Hereditary cancer panel analysis revealed a heterozygous c.1047A>C (p.Lys349Asn) novel VUS in the PTEN gene.

Conclusion: PHTS is characterized by a bimodal age distribution, presenting with neurodevelopmental manifestations in childhood and increased cancer susceptibility in adulthood. The presented cases support this clinical pattern. The novel variants identified in our cases aim to contribute to the expanding PTEN variant spectrum.
The VUS identified in Case 3 is located in an evolutionarily conserved region and results in substitution of a positively charged lysine (Lys) with a polar but uncharged asparagine (Asn), suggesting a potential impact on protein function; however, further functional studies are required to clarify its clinical significance. Overall, our findings highlight that interpretation of genetic results within an age-specific clinical context is critical for accurate diagnosis, surveillance, and genetic counseling in PHTS.

Keywords: PTEN, PTHS, bimodal age distribution, clinical heterogeneity, novel

[Abstract:0235]

Clinical and Molecular Characterization of Three Cases with Large 13q Deletions Including the *RB1* Gene

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Introduction: The *RB1* gene is a tumor suppressor gene located on chromosome 13q14.2 and plays a critical role in hereditary cancer predisposition syndromes, particularly retinoblastoma. Heritable retinoblastoma pathogenic variants in the *RB1* gene are most commonly detected by sequence analysis and are reported in approximately 80–84% of cases. Chromosomal microarray analysis (CMA) can detect approximately 6–8% of genome-wide large deletions and duplications including those including *RB1*. Such chromosomal deletions may lead to complex phenotypes extending beyond tumor development, including congenital anomalies and neurodevelopmental disorders.

Objective: This study aims to present the clinical and molecular findings of three cases harboring 13q deletions of varying sizes and mosaicism including the *RB1* gene.

Materials-Methods: Three cases were evaluated in a pediatric genetics department. CMA was performed following detailed clinical assessment. Clinical features, family history, and molecular findings were reviewed retrospectively.

Results: The first case, a 3.5-year-old child, presented with unilateral retinoblastoma and short stature; chromosomal microarray analysis revealed a 5.2 megabase (Mb) heterozygous deletion at 13q14.11–q14.2. The second patient, a premature newborn, was referred due to congenital heart defects, coloboma, and dysmorphic features and was found to have a 44.3 Mb heterozygous deletion at 13q12.3-q22.1. The third case, a 1-year-old child, was evaluated for unilateral retinoblastoma, micropenis, cryptorchidism, intellectual disability, and microcephaly; a mosaic 44.1 Mb deletion was identified at 13q12.3-q22.1

Conclusion: These cases demonstrate the broad phenotypic spectrum associated with 13q deletions including the *RB1* gene and highlight the impact of deletion size and mosaicism on clinical presentation. Larger deletions were associated with earlier onset and multisystem involvement, whereas a mosaic deletion affecting a similar genomic region was associated with a comparatively later clinical course, possibly due to the presence of unaffected cell populations. Importantly, the coexistence of retinoblastoma and dysmorphic features underscores the diagnostic value of chromosomal microarray analysis, as sequence-based testing alone may fail to detect clinically significant large genomic deletions in such patients.

Keywords: 13q deletion, *RB1*, retinoblastoma, chromosomal microarray

[Abstract:0236]

Juvenile Granulosa Cell Tumor Case with a Pathogenic *BRCA2* Variant: A Case Report

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Introduction: Granulosa cell tumors (GCTs) are rare, indolent ovarian tumors originating from the sex cords and ovarian mesenchyme. Unlike epithelial ovarian cancers, these tumors are often diagnosed at an early stage and may occur in younger women. Although the typical clinical presentation includes abdominal distension and pain, they may rarely present with signs of hyperestrogenism or virilization. Due to the high risk of late recurrence, lifelong follow-up is required.

Granulosa cell tumors account for approximately 5% of all ovarian neoplasms and nearly 70% of all ovarian sex cord–stromal tumors. Based on clinical and pathological characteristics, they are classified into two subtypes: juvenile and adult. The adult type is the most common and is typically observed in peri- or postmenopausal women, whereas the juvenile type constitutes only about 5% of cases and is predominantly seen in prepubertal girls and young women.

Trisomy 12 and deletion of 6q have been reported to be associated with juvenile GCT. Activation of the PI3K/AKT/mTOR signaling pathway has also been implicated in the pathogenesis of juvenile GCT. Nevertheless, the molecular pathogenesis of juvenile GCT has not yet been fully elucidated. Since the association between pathogenic BRCA2 variants and juvenile GCT has not been sufficiently explored in the literature, we aimed to present this case.

Case Presentation: A 30-year-old female patient was referred to our medical genetics outpatient clinic due to a history of juvenile granulosa cell tumor. At the age of 17, she was diagnosed with a unilateral juvenile granulosa cell tumor and underwent right oophorectomy with salpingectomy, followed by three cycles of chemotherapy. During the lactation period, she reported a palpable breast mass; however, breast ultrasonography revealed no pathological findings and was reported as BI-RADS 1. Family history revealed that her maternal grandmother had been diagnosed with a gynecological malignancy at the age of 40 and breast cancer at the age of 78. A hereditary cancer gene panel analysis identified a heterozygous pathogenic variant in the BRCA2 gene c.8168A>G (p.Asp2723Gly).

Discussion and Conclusion: Mutations in BRCA1 and BRCA2 are associated with an increased risk of breast, ovarian, pancreatic, melanoma, and prostate cancers. Ovarian cancers associated with germline pathogenic variants in BRCA1 and BRCA2 are predominantly epithelial in origin, most commonly presenting as serous adenocarcinomas. Previous studies have reported that BRCA1 loss activates the PI3K/AKT signaling pathway in breast cancer. The presence of studies suggesting a role for PI3K/AKT/mTOR pathway activation in the development of juvenile GCT leads us to hypothesize that the pathogenic BRCA2 variant identified in our case may contribute to the etiopathogenesis of juvenile granulosa cell tumor.

Keywords: BRCA2, hereditary cancer, juvenile granulosa cell tumor, ovarian cancer

[Abstract:0241]

Evaluation of low/moderate penetrance CHEK2 variants in cases with suspected hereditary cancer: A single center experience

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Introduction: The CHEK2 (Checkpoint Kinase 2) gene is a tumor suppressor gene that arrests the cell cycle in response to DNA damage and initiates DNA repair. Germline variants in the CHEK2 gene have been associated with an increased risk for primarily breast cancer, as well as colorectal, prostate, and certain other cancer types. However, unlike high-penetrance genes such as BRCA1 or BRCA2, CHEK2 is considered a "moderate-risk" (moderate penetrance) gene with highly variable genotype-phenotype correlation. The difference in risk conferred by various variants within the CHEK2 gene leads to significant uncertainties in clinical management. In this study, the clinical interpretation of low-penetrance variants and management strategies in light of current guidelines are discussed through cases screened with a Hereditary Cancer Panel in our clinic, in whom c.470T>C (p.Ile157Thr) and c.592+3A>T variants were detected.

Objective: The aim of this study is to evaluate the demographic characteristics, cancer types, ages at diagnosis, and family histories of cases who applied to our center with a suspicion of hereditary cancer and were found to carry the c.470T>C (p.Ile157Thr) and c.592+3A>T variants in the CHEK2 gene, known as low/moderate penetrance variants, following hereditary cancer panel testing. Furthermore, it is aimed to discuss the challenges in risk management and genotype-phenotype correlation in light of the literature by demonstrating the diversity in the clinical presentation of these variants.

Methods: Data of patients who applied to our Medical Genetics polyclinic with a suspicion of hereditary cancer and underwent hereditary cancer NGS panel testing after obtaining informed consent were screened retrospectively. Variant interpretation was based on ACMG (American College of Medical Genetics and Genomics) criteria, the ClinVar database, and current literature data.

Discussion and Conclusion: The management of CHEK2 variants shows significant variation depending on the variant type. In the histories of cases with c.470T>C (p.Ile157Thr) and c.592+3A>T variants, known as low/moderate penetrance variants in the CHEK2 gene, clinical presentations of primarily breast cancer, as well as colon cancer and prostate cancer, were detected in the patients themselves and/or their families. Specifically, the p.Ile157Thr variant is defined in the literature as a "risk allele" or "low-penetrance pathogenic variant" and is associated with a more modest risk increase compared to high-risk variants such as BRCA1/2 or CHEK2 c.1100delC. This situation necessitates considering not only the genotype but also the cancer burden in the family history, as suggested by current guidelines such as NCCN, in the management of detected variants. As observed in our cases, the presence of these variants alone usually does not justify aggressive prophylactic approaches; instead, it brings personalized screening protocols with more frequent intervals and earlier onset to the agenda. In conclusion, variants such as c.470T>C and c.592+3A>T in the CHEK2 gene should be evaluated as part of a polygenic risk or as risk-modifying factors rather than a classical Mendelian inheritance model. Genetic counseling provided to these patients should cover the combined risk profile formed by the limited clinical effect of the variant and familial risk, and a multidisciplinary approach should be adopted.

Keywords: CHEK2, Breast Cancer, Hereditary Cancer Panel, c.470T>C (p.Ile157Thr), c.592+3A>T

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Keywords: CHEK2, Breast Cancer, Hereditary Cancer Panel, c.470T>C (p.Ile157Thr), c.592+3A>T

[Abstract:0244]

WAGR Syndrome: A Familial Cancer Predisposition Syndrome-Report of Three Cases

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Objective: The Wilms tumor suppressor (WT1) gene encodes a transcription factor and RNA-binding protein that plays a crucial role in cellular differentiation and survival in several organs, including the kidneys and urinary tract, gonads, heart, and nervous system. WT1 was initially identified as a candidate gene conferring susceptibility to nephroblastoma (Wilms tumor, WT), the most common renal malignancy in childhood. However, accumulating evidence suggests that WT1 may have a broader role in tumorigenesis, functioning either as an oncogene or a tumor suppressor depending on the cellular context.

The WT1 gene is located on chromosome 11p13, in close proximity to the PAX6 gene. Large deletions involving this chromosomal region are associated with WAGR syndrome, a familial cancer predisposition disorder characterized by Wilms tumor, aniridia, genitourinary anomalies, and intellectual disability. The estimated incidence of WAGR syndrome is approximately 1 in 1,000,000 live births. The syndrome follows an autosomal dominant inheritance pattern, with most cases arising de novo. However, individuals with a 46,XX karyotype and no genitourinary anomalies may transmit the deletion to their offspring. In this report, three cases of this very rare syndrome are presented.
Case:
Case 1: A 3.5-year-old female patient diagnosed with Wilms tumor and aniridia.
Case 2: A 6-month-old male patient presenting with growth retardation, aniridia, and penoscrotal hypospadias.
Case 3: A 3-month-old female patient diagnosed with isolated aniridia.
None of the three patients had a family history of malignancy or similar clinical features. Conventional chromosome analysis performed in all cases revealed normal karyotypes, and no sex chromosome abnormalities were detected. Chromosomal microarray analysis identified a 16.6-megabase deletion in the 11p15.1–p13 region in Case 1, an 11.4-megabase deletion in the 11p14.3–p13 region in Case 2, and a 12.8-megabase deletion in the 11p14.1–p11.2 region in Case 3. Based on these findings, all patients were diagnosed with WAGR syndrome and received comprehensive genetic counseling. Regular abdominal ultrasonography was strongly recommended for early detection of Wilms tumor.
Conclusion: WAGR syndrome is a rare familial cancer predisposition syndrome with a reported Wilms tumor risk ranging from 42.5% to 77%. The cumulative probability of developing Wilms tumor is approximately 90% by four years of age and 98% by seven years of age. Aniridia is often the earliest clinical manifestation of the syndrome and may serve as an important diagnostic clue. Consequently, diagnostic algorithms have been developed for patients presenting with aniridia. In individuals with isolated aniridia, chromosomal microarray analysis or targeted copy number variation (CNV) analysis of the PAX6 and WT1 genes should be performed as first-line investigations to detect contiguous gene deletions. If these analyses do not explain the clinical findings, it should be considered that point mutations in the WT1 gene may also be responsible for the disease.

Keywords: WAGR Syndrome, WT1 gene, Aniridia, Wilms Tumor

[Abstract:0245]

An Incidentally Detected Copy Number Loss Variant in FH Tumor Predisposition Syndrome

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Objective: FH Tumor Predisposition Syndrome, also known as Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC), is caused by a heterozygous germline pathogenic variant in the fumarate hydratase (FH) gene. The syndrome is characterized by cutaneous leiomyomata, uterine leiomyomata (fibroids), and an increased risk of aggressive renal cell carcinoma. Cutaneous leiomyomas typically emerge between the second and fourth decades of life and increase in number and size with age. Renal tumors associated with HLRCC are often unilateral and solitary but display aggressive behavior, with early metastasis and poor prognosis even when primary tumors are small. Here we present a case of FH Tumor Predisposition Syndrome incidentally diagnosed by chromosomal microarray analysis.

Case: The patient was a 9-year-old female who was referred to our clinic due to epilepsy and facial dysmorphism. An epilepsy multigene panel test yielded normal results. Subsequently, chromosomal microarray analysis (CMA) was performed to investigate epilepsy and dysmorphic features. CMA incidentally revealed a heterozygous 1.2 megabase copy number loss encompassing the FH gene: arr[GRCh38] 1q43(241,420,118_242,648,682)x1. Following this finding, familial segregation analysis was performed, and the same deletion was identified in the patient's father.

Detailed family history revealed multiple affected individuals. The father presented with multiple cutaneous leiomyomas extending from the wrist to the elbow and involving the dorsal region; surgical excision had been attempted previously but was unsuccessful. Cutaneous leiomyomas were also reported in the paternal uncle and the uncle's son. The paternal grandfather had a history of metastatic renal cell carcinoma. The family history was further notable for colon cancer in the paternal grandmother and breast cancer in a paternal aunt. Additionally, epilepsy was reported in the daughter of the affected uncle.

Conclusion: Renal tumors in HLRCC typically present at a mean age of 36 years (range: 11–79). Childhood-onset surveillance and therapeutic recommendations are provided in the NCCN guidelines. Although the FH gene is not included in the ACMG Secondary Findings v3.3 list, reporting pathogenic variants in FH should be considered based on pretest counseling and the patient's informed consent. Haploinsufficiency of the FH gene is well established, supporting dosage sensitivity as a key disease mechanism. This case highlights the clinical significance of FH deletions detected by chromosomal microarray analysis and underscores the importance of comprehensive family history assessment following incidental genomic findings. Our report expands the phenotypic and molecular spectrum of FH-related tumor predisposition and emphasizes the role of chromosomal microarray analysis in uncovering actionable hereditary cancer syndromes, even when performed for unrelated clinical indications.

Keywords: Chrosomal Microarray, FH Tumor Predisposition Syndrome, Hereditary Renal Cell Carcinoma

[Abstract:0248]

Clinicogenetic Features and Germline Variants in Male Breast Cancer: A Single-Center Experience

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Background: Male breast cancer (MBC) is a rare malignancy, accounting for less than 1% of all breast cancers. Pathogenic variants in cancer susceptibility genes-particularly BRCA2- are detected in up to 32% of cases. However, there is limited knowledge about the genetic background and clinicogenetic profiles of male patients with breast cancer.

Objective: This study aimed to characterize the genetic and clinical features of MBC patients, with a particular emphasis on hereditary predisposition and the results of germline testing performed using either BRCA1/2-specific sequencing or multigene hereditary cancer panels. The ultimate goal was to underscore the importance of comprehensive genetic evaluation in MBC management to support personalized care and surveillance strategies for patients and their families.

Methods: Peripheral blood DNA samples were analyzed using the Sophia Genetics Custom Solution CHCS_C_V2 hereditary cancer panel on the NovaSeq® platform. Variants were interpreted through Sophia DDM software according to ACMG/AMP guidelines. Detailed clinical data, tumor types, and family histories were reviewed to assess correlations between variant type, location, and phenotype.

Results: Seven male patients diagnosed with breast cancer at a single center between 2022 and 2025 were retrospectively analyzed. The median age at diagnosis was 63 years (range: 53–75). All patients underwent germline genetic testing for hereditary cancer susceptibility, utilizing either BRCA1/2-specific sequencing or multigene hereditary cancer panels; MLPA was performed when indicated. Clinically significant germline variants were identified in 3 of 7 patients (42.9%): two with pathogenic BRCA2 alterations [c.5851_5854del, exons 21–23 deletion, detected by MLPA)] and one with a likely pathogenic CHEK2 c.549G>C variant. A variant of uncertain significance in RAD51D (c.202G>A) was detected in one patient. The remaining three patients had no pathogenic variants identified. Histopathologically, six patients had invasive ductal carcinoma, and one had invasive carcinoma with cribriform differentiation. All patients were estrogen receptor-positive, six were progesterone receptor-positive, and HER2 overexpression was observed in one patient. All patients and their families were offered genetic counseling

Conclusion: In this single-center case series, clinically significant germline variants were identified in 42.9% of male breast cancer patients, a rate higher than those reported in large population-based cohorts (15–35% overall; BRCA2: 8–16%, BRCA1: 1–4%). While BRCA2 remains the most frequently altered gene, our findings also highlight the presence of clinically relevant variants in moderate-penetrance genes such as CHEK2. Notably, some patients tested negative for pathogenic variants when only BRCA1/2 analysis was performed, underlining the risk of underdiagnosis with limited testing. These results emphasize the genetic heterogeneity of male breast cancer and demonstrate the added value of multigene panel testing over single-gene approaches. Comprehensive germline evaluation, including both high- and moderate-penetrance genes, is essential for improving risk stratification, optimizing personalized surveillance, and facilitating cascade testing among affected families.

Keywords: Male breast cancer, hereditary breast cancer, BRCA mutations, CHEK2

[Abstract:0252]

Malignancies in Neurofibromatosis Type 1: Breast Cancer and a Rare Co-occurrence with Retinoblastoma in a Small Patient Series

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Neurofibromatosis type 1 is an inherited tumor-predisposition syndrome caused by pathogenic alterations in the NF1 gene, which encodes neurofibromin, a tumor suppressor involved in downregulating the RAS/MAPK signaling pathway. Disruption of this regulatory mechanism promotes uncontrolled cell proliferation and increases susceptibility to tumor formation. Individuals with NF1 are therefore at risk for a broad range of benign and malignant tumors, including malignant peripheral nerve sheath tumors, optic pathway gliomas, pheochromocytomas, hematologic malignancies, and breast cancer, particularly at younger ages.

Clinical and genetic data from nine patients diagnosed with NF1, originating from three unrelated families, were retrospectively reviewed. Five patients had received a clinical diagnosis of NF1 based on established diagnostic criteria, without molecular confirmation. All patients exhibited typical phenotypic features consistent with NF1, including café-au-lait macules, cutaneous neurofibromas, and axillary freckling. Overall, three patients were diagnosed with malignancies. Two female patients developed breast cancer: one was diagnosed at 50 years of age and was found to carry a likely pathogenic NF1 variant (c.1139T>C), while the other was diagnosed with breast cancer at 33 years of age and died at 35 years old. In addition, one male patient was diagnosed with retinoblastoma at three months of age and was found to harbor a pathogenic splice-site variant in NF1 (c.1642-2A>G). Demographic characteristics, age at cancer diagnosis, and NF1-related clinical features were systematically evaluated across the cohort.

This case series highlights the heterogeneity of malignancies that may arise in patients with NF1 and underscores the importance of individualized and risk-based cancer surveillance. Epidemiological data indicate that women with NF1 have a significantly increased risk of developing breast cancer, particularly before the age of 50, with reported risk estimates ranging from approximately two- to five-fold compared with the general population, a finding supported by our observations. Variability in tumor occurrence within our cohort may reflect differences in the underlying NF1 variant spectrum and its impact on tumor susceptibility. The rare coexistence of NF1 and retinoblastoma observed in our series further emphasizes the complexity of tumorigenesis in NF1 and suggests that additional or coincidental oncogenic mechanisms may contribute to malignancy development in selected cases. Larger, molecularly well-characterized cohorts are needed to clarify genotype–phenotype correlations and the clinical significance of such rare tumor associations.

Keywords: Breast cancer, neurofibromatosis, retinoblastoma

[Abstract:0253]

Multilocus Inherited Neoplasia Allele Syndrome and Germline Variant Spectrum Identified by Multigene Panel Testing in Ovarian Cancer: A Single-Center Experience

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Objective: Germline genetic testing plays a pivotal role in the clinical management of ovarian cancer. With the widespread use of multigene panel testing, variants are increasingly identified not only in high-penetrance cancer predisposition genes but also in genes with moderate or low penetrance, or in genes whose association with ovarian cancer remains uncertain. Therefore, reporting real-world data obtained from multigene panels is essential to improve genotype–phenotype correlations. This study aimed to evaluate germline variants detected by hereditary cancer panel testing and BRCA1/BRCA2 deletion–duplication analysis in ovarian cancer patients from a single center.

Case: Peripheral blood samples were obtained from 17 patients diagnosed with ovarian cancer, and genomic DNA was extracted. Next-generation sequencing was performed using the SOPHIA DDM™ Hereditary Cancer Solution (HCS) v2.0, covering 82 cancer-predisposition genes. In addition, multiplex ligation-dependent probe amplification (MLPA) analysis was conducted to detect large genomic rearrangements in the BRCA1 and BRCA2 genes. Pathogenic germline variants in high-penetrance genes were identified in two patients, involving BRCA1 and BRCA2. One patient demonstrated double heterozygosity for pathogenic variants in RAD51D and ATM, consistent with Multilocus Inherited Neoplasia Allele Syndrome (MINAS). Furthermore, heterozygous pathogenic variants were detected in XPC, SEC23B, and NTHL1 in three additional patients.

Conclusion: This study reports pathogenic variants in BRCA1, BRCA2, and a case consistent with MINAS in ovarian cancer patients. Multigene panel testing enables the detection of clinically relevant germline variants beyond classical high-penetrance genes; however, the interpretation of findings in genes with limited or uncertain genotype–phenotype associations remains challenging. These results underscore both the clinical value of comprehensive genetic testing and the need for integration of such data into patient management and genetic counseling.

Keywords: ovarian cancer, multigene panels, MINAS

[Abstract:0254]

Combined NGS and MLPA Approach in the Molecular Diagnosis of Tuberous Sclerosis Complex: A Four-Case Series

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Background/Objectives: Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder caused by germline pathogenic variants in the TSC1 and TSC2 genes. Hamartin and tuberin form a heterodimeric complex that negatively regulates the mTORC1 signaling pathway; loss of function results in dysregulated cellular growth and multisystem hamartoma formation. Clinically, TSC demonstrates a broad phenotypic spectrum, including early-onset epilepsy, neurodevelopmental abnormalities, and tumor predisposition, particularly renal angiomyolipomas and lymphangioleiomyomatosis.

The diagnosis of TSC relies on both clinical criteria and molecular genetic testing, underscoring the importance of integrating phenotypic and genotypic findings. Given the marked phenotypic variability, comprehensive molecular approaches are essential. This study presents a clinically suspected TSC case evaluated using a combined molecular strategy, including next-generation sequencing (NGS) and multiplex ligation-dependent probe amplification (MLPA), to highlight the diagnostic value of integrating complementary techniques in the identification of pathogenic TSC gene alterations.

Methods: Four patients with a preliminary clinical diagnosis of tuberous sclerosis complex (TSC) were subjected to molecular genetic analysis.First, The TSC panel, consisting of TSC1 and TSC2 genes, was analyzed using next generation sequencing (NGS). The raw data was analyzed using the 'SEQ variant analysis software' according to the reference genome of GRCh38. Filtered variants were evaluated according to the ACMG Standards and Guidelines recommendations. Subsequently, MLPA testing was applied to patients who showed no variant detection on NGS analysis.

Results: First patient was 16-year-old male with hypomelanotic macules, subependymal nodules and seizures. We identified frameshift variant TSC2 ENST00000219476.9:c.3944del as heterozygous state. The detected variant had not been previously reported in ClinVar and was classified as likely pathogenic based on ACMG guidelines.

Second patient was 5-month-old male with hypomelanotic macules, cardiac rhabdomyoma and subependymal nodules. We identified splice acceptor variant TSC2 ENST00000219476.9:c.976-2A>G as heterozygous state. The detected variant had not been previously reported in ClinVar and was classified as likely pathogenic based on ACMG guidelines.

Third patient was 20-year-old male with hypomelanotic macules, angiofibromas, shagreen patch, subependymal nodules, renal angiomyolipomas and seizures. No pathogenic variant was detected in the NGS analysis performed in the patient. Subsequent MLPA analysis identified a heterozygous duplication involving exons 16–22 of the TSC2 gene. This alteration has not been previously reported and was classified as likely pathogenic according to ACMG criteria.

Fourth patient was 18-year-old female with renal angiomyolipomas. No pathogenic variant was detected in the NGS analysis performed in the patient. Subsequent MLPA analysis identified a heterozygous duplication involving exon 34 of the TSC2 gene. This alteration has not been previously reported and was classified as likely pathogenic according to ACMG criteria.

Conclusion: In this presentation, we aim to emphasize the tumor suppressor role of the TSC, present oncologically relevant TSC cases in which pathogenic alterations were identified through NGS and MLPA analyses, and discuss the implications of TSC–mTOR pathway dysregulation for tumor development and cancer surveillance in the clinical management of tuberous sclerosis complex.

Keywords: TSC, Molecular Genetics Testing, Hereditary cancer syndrome

[Abstract:0255]

Real-World Patterns of Tumor MMR Immunohistochemistry and Germline Results in Individuals with Suspected Lynch Syndrome

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Background: Lynch syndrome (LS) represents the most common hereditary colorectal cancer syndrome and results from germline pathogenic variants in DNA mismatch repair (MMR) genes, most commonly *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* deletions. Universal MMR immunohistochemistry (IHC) or microsatellite instability (MSI) testing, which has transformed LS detection, for colorectal and endometrial cancers is strongly recommended to identify individuals eligible for confirmatory germline sequencing. However, despite standardized recommendations, tumor-based screening and germline testing each provide only a partial view of the underlying biology. In routine practice, loss of MMR protein expression on IHC triggers germline analysis and guides clinical management, yet the extent to which IHC findings reflect germline variation is not always predictable, as up to 15% of sporadic colorectal cancers also demonstrate MMR deficiency due to somatic epigenetic events such as *MLH1* promoter methylation.

Objective: To evaluate the real-world concordance between tumor mismatch repair immunohistochemistry findings and germline sequencing results in patients undergoing assessment for suspected Lynch syndrome.

Methods: We retrospectively evaluated 127 patients diagnosed between 2024 and 2026 with cancers associated with LS and referred for genetic assessment based on clinical, familial, or tumor-based indicators. Cancer types included endometrial (n=63), colorectal (n=51), gastric (n=9), and pancreatic cancers (n=4). Tumor IHC assessed MLH1, MSH2, MSH6, and PMS2 expression. Germline sequencing analyzed *MLH1*, *MSH2*, *PMS2*, and *MLH3* single-nucleotide variants. Cases demonstrating isolated *MSH6* loss were excluded due to lack of corresponding germline data. Complementary tumor analyses—including *MLH1* promoter methylation, *BRAF* V600E mutation testing, and CNV evaluation—were not routinely performed.

Results: Germline variants were identified in 34/127 individuals (26.8%), comprising 20 pathogenic/likely pathogenic (P/LP) findings and 14 variants of uncertain significance (VUS). P/LP variants involved *MLH1* (n=14), *MSH2* (n=4), or *MLH3* (n=2). Among patients with P/LP variants, 12 cases demonstrated loss of the corresponding MMR protein, predominantly in truncating variants. However, preserved IHC expression was observed in 6 patients with P/LP variants and 5 with VUS, illustrating that MMR protein preservation does not exclude germline disease. In contrast, 93 patients without detected germline variants most frequently exhibited combined MLH1/PMS2 loss (73%), particularly among endometrial cancer diagnoses, suggesting a substantial proportion of presumed sporadic MMR-deficient tumors likely attributable to epigenetic causes.

Conclusion: This cohort provides real-world evidence that IHC and germline sequencing are complementary and

not interchangeable tools for LS assessment. IHC efficiently enriches for patients requiring germline evaluation, yet normal staining patterns may miss clinically relevant variants. Meanwhile, MMR protein loss without identifiable germline alterations is common, particularly in endometrial cancer, underscoring the biological heterogeneity of MMR deficiency. Our findings reinforce that the diagnostic value lies in the relationship between tumor and germline data, rather than either modality alone, and support ongoing incorporation of reflex workflows and ongoing reinterpretation strategies to optimize LS identification and individualized care.

Keywords: Germline sequencing, Immunohistochemistry, Lynch syndrome, Mismatch repair (MMR)

[Abstract:0261]

Clinical Spectrum and Genomic Characterization of MEN1 Gene Variants in Patients with MEN1: A Single-Center Study

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Objective: Multiple Endocrine Neoplasia type 1 (MEN1) is a rare autosomal dominant tumor predisposition syndrome characterized by primary hyperparathyroidism, pancreatic neuroendocrine tumors (pNETs), and pituitary adenomas. This single-center study aimed to evaluate the clinical and genomic characteristics of MEN1 gene variant changes identified in patients referred for genetic analysis with a preliminary diagnosis of MEN1.

Methods: Genomic DNA was isolated from peripheral blood samples of patients evaluated according to MEN1 clinical diagnostic criteria. Targeted next-generation sequencing was performed covering the coding regions and exon–intron boundaries of the MEN1 gene. Bioinformatic analyses were conducted using the hg19/GRCh37 reference genome. Identified variant changes were annotated according to HGVS nomenclature and interpreted based on ClinVar, OMIM, gnomAD databases, and relevant literature. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Clinical and genetic data were retrospectively analyzed.

Results: A total of 7 patients with identified MEN1 gene variant changes were included. Of these, 3 were female and 4 were male, with a mean age of 34.6 ± 13.6 years (range: 19–60 years). According to ACMG classification, 5 variants were pathogenic, 1 was likely pathogenic, and 1 was classified as a variant of uncertain significance (VUS). Most variant changes were frameshift, one was a splice-site variant, and the VUS was a missense variant. Clinically, the majority of patients exhibited primary hyperparathyroidism accompanied by pNETs and/or pituitary adenomas, consistent with MEN1 diagnostic criteria.

Conclusion: This single-center case series demonstrates a strong clinical correlation between pathogenic and likely pathogenic MEN1 gene variant changes and the MEN1 phenotype. The predominance of protein-disrupting variant changes supports loss of MEN1 gene function as a key pathogenic mechanism. Variants of uncertain significance should be interpreted cautiously in conjunction with clinical findings and long-term follow-up data.

Keywords: Multiple Endocrine Neoplasia type 1; MEN1 variants; next-generation sequencing

[Abstract:0266]

Germline Genetic Analysis Results in Patients with Pancreatic Cancer: A Single-Center Experience

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Objective: Pancreatic cancer is associated with high mortality and limited treatment options. Germline genetic alterations play an important role not only in familial risk assessment but also in clinical management. This study aimed to evaluate germline variants detected in patients with pancreatic cancer and to assess the clinical contribution of genes beyond *BRCA1/2*.

Methods: This retrospective study included 32 patients who were diagnosed with pancreatic cancer and underwent germline genetic evaluation between 2023 and 2025. According to clinical indication, patients received either *BRCA1/2* germline analysis or a 36-gene hereditary cancer panel. Variants were classified according to ACMG criteria and categorized as pathogenic (P), likely pathogenic (LP), or variants of uncertain significance (VUS). Germline findings were evaluated descriptively according to variant classification. MLPA analysis was performed in selected cases to assess large genomic rearrangements.

Results: Seventeen patients (53.1%) were male and 15 (46.9%) were female. Histopathological evaluation revealed pancreatic adenocarcinoma in 27 patients, while other histological subtypes were rare or unavailable. Among patients with pancreatic adenocarcinoma, those with detected P/LP germline variants had a mean age at diagnosis of 63.0 years, compared with 57.2 years in patients without P/LP variants. The distribution of germline genetic findings according to test type is summarized in Table 1. Five patients had a history of two primary malignancies, and germline P/LP or VUS variants were identified in two of these patients. MLPA analysis was performed in 10 patients for *BRCA1/2* and in 2 patients for *MLH1* deletion screening, with no deletions or duplications detected.

Conclusion: Germline genetic testing identifies clinically relevant germline variants in a substantial proportion of patients with pancreatic cancer. Compared with *BRCA1/2* testing alone, broader hereditary cancer panels yield additional germline findings across a wider range of genes. Family history and age at diagnosis alone are insufficient to exclude hereditary genetic predisposition, supporting the complementary role of germline genetic evaluation in patient management.

Keywords: pancreatic carcinoma, hereditary, BRCA1/2

Table 1. Summary of Germline NGS Testing Results in Patients with Pancreatic Cancer

Test type	Number of patients (n)	Total variants detected (n)	P/LP variants detected, n (%)	Genes with P/LP variant	VUS detected, n (%)	Genes with VUS
BRCA1/2 NGS ana	10	1	1 (10%)	BRCA1/2	0	-
Hereditary cancer panel (36 genes)	22	12	7 (31.8%)	BRCA2 (n=2), MUTYH (n=2), CHEK2, NBN, BARD1	5 (22.7%)	PRSS1, MSH6, ATM, NBN, BRIP1

P, pathogenic; LP, likely pathogenic; VUS, variant of uncertain significance; NGS, next-generation sequencing.

[Abstract:0268]

MLH1/PMS2 Loss as a Marker of Germline MLH1 Pathogenicity: A Clinical Cohort Study

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Objective: Lynch syndrome is an autosomal dominant cancer predisposition syndrome caused by defects in DNA mismatch repair. Loss of DNA mismatch repair (MMR) proteins in tumor tissue is considered an important indicator of Lynch syndrome. In the literature, concurrent loss of MLH1 and PMS2 is reported as the most frequent pattern observed in tumor samples. In this study, we aimed to characterize the genetic and clinical features of patients exhibiting MLH1 and PMS2 expression loss in tumor tissue.
Materials-Methods: A total of 39 cases with loss of MLH1 and/or PMS2 expression in tumor tissue were included in the study. Following DNA extraction from peripheral blood, the MMR genes (MLH1, MSH2, MSH6, and PMS2) were analyzed using next-generation sequencing (NGS), and the findings were evaluated in relation to clinical features.
Results: A total of 39 patients (26 females and 13 males) were included in the study. The age of the cohort ranged from 31 to 78 years, with a median age of 45 years. Among the female patients, 8 (30.8%) had isolated colorectal cancer, 17 (65.4%) had endometrial cancer,and 1 (3.8%) had synchronous endometrial and colorectal cancer. All male patients presented with colorectal cancer arising in the setting of adenomatous lesions. A positive family history was documented in 16 patients (41%).
Pathogenic/likely pathogenic (P/LP) variants in the MLH1 gene were identified in 14 patients (23%), while no clinically relevant P/LP variants were detected in the remaining 23 individuals. Among the three cases with isolated loss of MLH1 protein expression,one (33.3%) harbored a P/LP variant. In contrast, P/LP variants were detected in 13 of the 36 cases (66.7%) with concurrent loss of MLH1 and PMS2 expression. Of the patients carrying P/LP variants, 13 (92%) exhibited combined MLH1 and PMS2 loss, whereas isolated MLH1 loss was observed in a single case (8%). Additionally, early-onset malignancies (<=50 years) were observed in 12/14 (85%) of variant-positive cases, whereas only 10% of variant-negative cases presented before the age of 50.
Conclusion: Our findings demonstrate a strong association between dual MLH1/PMS2 loss on immunohistochemistry and the presence of germline MLH1 pathogenic variants, consistent with the known molecular architecture of the DNA mismatch repair (MMR) system. MLH1 and PMS2 form the MutLα heterodimer, and MLH1 ensures its stability during mismatch repair. Pathogenic variants in MLH1 disrupt this heterodimer, leading to secondary both proteins are lost on immunohistochemistry. Consequently, dual protein loss represents a meaningful surrogate marker for germline MLH1 pathogenicity once somatic mechanisms such as MLH1 promoter hypermethylation are excluded. Higher germline variant rates are in line with expectations, as germline alterations are more frequently identified in younger patients, whereas cancers arising at older ages in variant-negative individuals are more likely to be sporadic and driven by somatic events. These observations align with previous reports indicating that approximately previous reports showing that 10–25% of tumors with MLH1/PMS2 loss harbor germline mutations once somatic events are excluded. Overall, integration of immunohistochemistry with germline genetic testing remains essential for accurate Lynch syndrome diagnosis and management of at risk family members.

Keywords: Immunohistochemistry loss, Lynch Syndrome, *MLH1*

[Abstract:0269]

The Role of Syndromic and Developmental Features in the Diagnosis of Pediatric Hereditary Cancer Syndromes: A Case Series

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Hereditary Cancer Syndromes are inherited genetic disorders that elevate cancer susceptibility throughout life and typically manifest with diverse clinical features affecting multiple systems. The heterogeneous clinical manifestation, combined with the absence of cancer development in younger patients, creates significant diagnostic challenges.
This case series presents three pediatric patients with distinct hereditary cancer syndromes involving different cellular and molecular pathways, all exhibiting complex and multisystemic phenotypes in the pediatric period, and to emphasizes the decisive role of non-oncological findings in the early diagnosis process.
Our patients have shown multiple systemic involvements such as congenital anomalies, endocrine and metabolic system disorders growth failure and developmental delay were noteworthy. In molecular analyses; A 6-year-3-month-old girl referred for evaluation of Hirschsprung syndrome and poor growth was found to have Multiple Endocrine Neoplasia type 2B syndrome caused by a heterozygous in-frame variant (c.1894_1899del) in the *RET* gene; a 12-year-and-9-month-old boy presenting with cleft lip/palate and speech absence carried a 5.89 Mb heterozygous deletion in the 16q22.1-16q23.1 region including the *CDH1* gene, linked to Diffuse Gastric and Lobular Breast Cancer syndrome; and an 11-year-and-6-month-old girl presenting with microcephaly, short stature and hypogonadotropic hypogonadism had a homozygous frameshift insertion (c.800-801insG) in the *NBN* gene, associated with Nijmegen Breakage syndrome.
This case series highlights the importance of early, accurate, and comprehensive evaluation of syndromic/developmental phenotypic findings before cancer onset in hereditary cancer syndrome diagnosis. The management of hereditary cancer syndromes extends far beyond assessing the cancer risk alone. In order to reduce mortality and morbidity, recognizing accompanying non-oncological findings and implementing coordinated multidisciplinary care protocols should be a fundemental approach.

Keywords: Hereditary Cancer Syndromes, NBN, CDH1, RET

[Abstract:0271]

Revisiting NCCN BRCA1/2 Testing Criteria in the Era of Targeted Therapy

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Objective: Pathogenic BRCA1/2 variants are a major cause of hereditary breast, ovarian, prostate, and pancreatic cancers. Clinical practice guidelines, such as those of the National Comprehensive Cancer Network (NCCN), are widely used to identify individuals suitable for BRCA1/2 testing. However, in the era of targeted therapies, including poly(ADP-ribose) polymerase (PARP) inhibitors, the role of these criteria is increasingly being re-evaluated, as genetic testing has transformed from a preventive tool into an integral component of treatment decision-making. The aim of this study was to retrospectively evaluate the performance of NCCN BRCA1/2 testing criteria by examining their association with BRCA-associated cancer phenotypes in patients with identified BRCA1/2 gene variants.

Materials-Methods: We retrospectively analyzed patients evaluated between 2020 and 2025 who were found to have BRCA variants. Current clinical, pathological, and family history data were reviewed, and patients were retrospectively classified as Indicated, May be considered, or Not considered according to the NCCN BRCA1/2 testing criteria. Patients with insufficient clinical or family history information were classified as Indeterminate and excluded from further analysis. The primary outcome was the presence of BRCA-associated cancers, including breast, ovarian, prostate, and pancreatic cancers.

Results: Among 133 patients with identified BRCA1/2 variants, 42 were classified as Indeterminate and excluded due to incomplete data. The remaining 91 patients were included in the evaluation. Of these, 76 were classified as Indicated, and 73 (96.1%) had BRCA-associated cancers. Two patients were classified as May be considered, both of whom had BRCA-associated cancers. Thirteen patients were classified as Not considered, and four of them presented with BRCA-associated cancer phenotypes.

Conclusion: These findings validate the strong performance of the NCCN testing criteria in identifying patients at high risk for BRCA-related cancers. However, a clinically relevant subset of patients with BRCA-related malignancies remained outside the formal testing categories. This suggests that while the criteria are effective, relying heavily on risk-based testing alone may limit sensitivity in the age of genotype-focused therapies. Expanding testing assessments beyond traditional screening frameworks could improve the identification of patients who may benefit from targeted treatment strategies.

Keywords: *BRCA1/2* Associated Cancer, Hereditary Cancer, NCCN Guidelines, Targeted Therapy

[Abstract:0273]

Two Siblings Diagnosed with AML M3

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Introduction: The *BRCA2* gene is a key tumor suppressor involved in the repair of DNA double-strand breaks through the homologous recombination pathway. Heterozygous pathogenic variants in *BRCA2* are associated with hereditary breast and ovarian cancer (HBOC) syndrome. In contrast, the presence of biallelic pathogenic variants in *BRCA2* has been associated with Fanconi anemia, complementation group D1 (FANCD1).
Objective: This study aimed to clinically and genetically evaluate the detection of a homozygous pathogenic *BRCA2*:c.6896dup (p.Asn2299Lysfs*41) variant in one of two siblings who were both 17 years old at diagnosis and diagnosed with acute myeloid leukemia (AML M3) without any additional clinical findings. The other sibling, who received the same diagnosis, was followed within the scope of the case due to clinical similarity, and the genetic analysis process has been planned.
Methods: DNA isolation from peripheral blood samples was performed using the ZeeSan Lab-Aid® 824s Blood DNA Isolation Kit. Molecular analyses were carried out using the SOPHiA Custom Solution CHCS_C_V2 next-generation sequencing panel, which includes *BRCA1, BRCA2* and multiple genes associated with hereditary cancer predisposition. All exons and exon–intron junction regions of the targeted genes were analyzed. Sequencing was performed on the NovaSeq® platform, and the data were analyzed using the SOPHiA DDM™ software. Chromosome breakage tests with diepoxybutane (DEB) were performed to evaluate Fanconi anemia. In addition, carrier testing was conducted for the parents.
Results: The two siblings, both 17 years old at the time of diagnosis, were evaluated with a diagnosis of AML M3 without any additional clinical findings. Neither patient had a history of congenital anomalies characteristic of Fanconi anemia or clinical findings suggestive of bone marrow failure prior to diagnosis. No history of hematologic or solid malignancies was identified in the family history.
Molecular genetic analysis revealed that one sibling was homozygous for the pathogenic BRCA2:c.6896dup variant. Both parents were identified as heterozygous carriers. In this patient, the chromosome breakage test performed for Fanconi anemia yielded a negative DEB result.
In the other sibling, the chromosome breakage test for Fanconi anemia showed a borderline DEB result. Genetic analysis for this sibling has been planned.
Discussion: The literature reports that individuals carrying biallelic pathogenic variants in *BRCA2* may exhibit marked variability in clinical presentation. In such individuals, congenital anomalies characteristic of classic Fanconi anemia or early signs of bone marrow failure may not always be present.
In the presented case, the absence of Fanconi anemia–specific clinical findings, the negative DEB test result, and the detection of a homozygous *BRCA2*:c.6896dup pathogenic variant in a patient diagnosed with AML M3 are consistent with the limited number of atypical clinical presentations reported in the literature in association with biallelic pathogenic variants in *BRCA2*.
These findings indicate that biallelic pathogenic variants in *BRCA2* should be considered in the differential diagnosis of early-onset AML cases, even in the absence of classical Fanconi anemia findings.

Keywords: acute myeloid leukemia, AML M3, *BRCA2*

[Abstract:0274]

Limitations of Current Classification Frameworks in Interpreting *BRCA1/2* Missense Variants

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Objective: The classification of *BRCA1* and *BRCA2* missense variants as variants of uncertain significance(VUS) remains a major barrier in hereditary cancer risk assessment. In this single center cohort, *BRCA* missense VUS variants were frequently identified in individuals with malignant disease, including cancers classically associated with *BRCA* pathogenicity, raising concern that current variant classification frameworks may not fully capture clinically relevant patterns of disease association. The objective of this study was to characterise the clinical context of *BRCA* missense VUS variants in a real world cohort and to highlight the potential need for more clinically informed approaches to variant re-evaluation.

Materials-Methods: As of December 2025, approximately 4,000 patients who presented to Etlik City Hospital between 2024 and 2025 and underwent germline genetic testing were retrospectively evaluated. The analysis focused on missense variants in the *BRCA1* and *BRCA2* genes. Variant annotations and clinical classifications were obtained from ClinVar. Given that the majority of *BRCA* missense variants were classified as variants of uncertain significance, the study examined the clinical context, including cancer phenotypes and family history of cancer, in which these variants were identified.

Results: A total of 151 individuals carrying 111 distinct variants of *BRCA1* or *BRCA2* missense variants were identified. Of these, 101 variants were classified as VUS, while 10 were reported as pathogenic or likely pathogenic. A clinical evaluation revealed that a considerable proportion of individuals carrying a *BRCA* missense VUS variant exhibited a strong family history of cancer and presented with phenotypes classically associated with *BRCA* related malignancies. The recurrent co-occurrence of these clinically relevant hereditary cancer features among VUS variant carriers suggests a potential mismatch between current variant classification frameworks and observed clinical patterns, thereby underscoring the need for systematic and clinically informed re-evaluation of *BRCA* missense VUS variants.

Conclusion: Despite the majority of *BRCA1* and *BRCA2* missense variants identified in this cohort being classified as VUS, the strong concordance between specific VUS variant carriers and significant family histories of cancer suggests that current classification criteria may underestimate the pathogenic potential of certain recurrent missense variants. These findings highlight the critical necessity of integrating comprehensive clinical phenotyping with genomic data to re-evaluate these variants, ensuring that patients with uncertain results receive appropriate risk assessment and clinical management.

Keywords: *BRCA1*, *BRCA2*, Missense Variants, Variant Classification, Variants of Uncertain Significance (VUS)

[Abstract:0281]

Retrospective Evaluation of Multigene Panel Results in Patients at Risk for Hereditary Breast and Ovarian Cancer: A Single-Center Experience

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Introduction: Hereditary breast and ovarian cancer (HBOC) is a genetically heterogeneous cancer predisposition syndrome primarily associated with germline variants in DNA damage repair genes, most notably BRCA1 and BRCA2. Advances in next-generation sequencing (NGS) technologies have enabled the widespread use of multigene panels, leading to the identification of pathogenic variants in both high- and moderate-penetrance genes. However, the increasing detection of variants of uncertain significance (VUS) has introduced new challenges in clinical interpretation and genetic counseling. Evaluating the distribution of genetic variants together with clinical characteristics is essential for improving risk assessment strategies in HBOC.

Objective: The aim of this study was to retrospectively evaluate the clinical characteristics, family history, and multigene panel results of patients referred with suspected hereditary breast and/or ovarian cancer.

Methods

This retrospective study included 163 patients referred to the Medical Genetics Clinic of Erzurum City Hospital with suspicion of hereditary breast and/or ovarian cancer. Demographic characteristics, indications for referral, and personal and familial cancer histories were obtained from medical records. Genetic analyses were performed using NGS-based hereditary cancer gene panels. Detected variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Results: Of the 163 patients included in the study, 92.6% (n=151) were female and 7.4% (n=12) were male. The mean age at referral was 43.1 ± 12.0 years. The most common referral indications were early-onset breast cancer (49.1%, n=80), a family history involving multiple relatives with breast and/or ovarian cancer (35.6%, n=58), and ovarian cancer diagnosis (15.3%, n=25).

Pathogenic or likely pathogenic variants were identified in 30.1% (n=49) of patients. Among these variants, 55.1% (n=27) were located in BRCA1 and 44.9% (n=22) in BRCA2. Variants of uncertain significance (VUS) were detected in 47.9% (n=78) of patients. VUS were most frequently identified in BRCA1 and BRCA2; among non-BRCA2 genes, the most commonly affected genes were ATM, CHEK2, and PALB2. No clinically significant variants were identified in 22.1% (n=36) of cases

Conclusion: This study highlights the genetic and clinical heterogeneity of patients evaluated for hereditary breast and ovarian cancer using multigene panel testing. While BRCA1 and BRCA2 remain the most frequently implicated genes, a substantial proportion of patients harbor VUS in moderate-risk genes, emphasizing the importance of cautious interpretation and long-term variant re-evaluation. These findings underline the value of integrating detailed clinical data with genetic results to optimize genetic counseling and risk management strategies.

Keywords: Hereditary breast and ovarian cancer, BRCA1/BRCA2, Multigene panel testing

Retrospective Evaluation of Multigene Panel Results in Patients at Risk for Hereditary Breast and Ovarian Cancer: A Single-Center Experience

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Abstract

Hereditary Breast and Ovarian Cancer (HBOC) syndrome is a genetically heterogeneous condition associated with germline pathogenic variants in genes involved in DNA repair pathways. Although *BRCA1* and *BRCA2* remain the most well-known high-risk genes, the implementation of multigene panel testing has expanded the spectrum of clinically actionable genes. Detection rates vary significantly depending on patient selection criteria and testing algorithms. This study aimed to evaluate the clinical and molecular findings of a heterogeneous NCCN-based hereditary cancer cohort and compare the results with previously published Turkish cohorts.

A total of 192 individuals who met NCCN Hereditary Cancer Guidelines (v.2023–2025) criteria were retrospectively analyzed between 2023 and 2025 at a tertiary medical genetics center. Multigene panel testing targeting 135 cancer susceptibility genes was performed using hybridization capture-based next-generation sequencing. Variants were classified according to ACMG criteria.

Among 192 individuals (98.4% female), referral indications included breast cancer (65.1%), strong family history (19.8%), ovarian cancer (10.4%), early-onset breast cancer (1.6%), and other hereditary cancer suspicions (3.1%). Pathogenic or likely pathogenic (P/LP) variants were identified in 9.9% of individuals, while 47.9% had variants of uncertain significance (VUS). Among P/LP variants, *BRCA1* accounted for 26.3%, *BRCA2* for 21.1%, *CHEK2* for 15.8%, and *ATM, PALB2, MUTYH* and *TP53* comprised the remainder. Overall, *BRCA1*/2 represented 47.4% of clinically significant findings.

The diagnostic yield in this heterogeneous NCCN-based cohort was consistent with previously reported Turkish multigene panel studies but lower than highly selected breast- or ovarian-only cohorts. The relatively lower proportion of BRCA1/2 variants may reflect pre-panel single-gene testing strategies. High VUS rates highlight the need for improved population representation in global variant databases and the development of national reference datasets.

Introduction

Hereditary Breast and Ovarian Cancer (HBOC) syndrome represents a clinically and molecularly heterogeneous genetic predisposition condition primarily associated with germline pathogenic variants in genes involved in DNA damage repair pathways, particularly homologous recombination (1). Approximately 10% of breast cancers are considered to be associated with hereditary susceptibility, and germline pathogenic variants are identified in nearly 6% of breast cancer patients (2, 3). About half of these variants occur in high-risk genes such as *BRCA1* and *BRCA2*, while the remaining proportion is attributed to moderate-risk genes including *ATM* and *CHEK2* (2, 3). In high-grade serous ovarian cancer, the prevalence of germline pathogenic variants is reported to be approximately 15% (4). Despite well-defined clinical criteria, nearly half of individuals fulfilling HBOC criteria remain without a clearly identified genetic cause (5). The widespread implementation of multigene panel testing has expanded the genetic spectrum of HBOC beyond *BRCA1* and *BRCA2* to include high-risk genes such as *PALB2, TP53, PTEN, CDH1* and *STK11*, as well as moderate-risk genes including *ATM, CHEK2, RAD51C, RAD51D* and *BRIP1*. Each gene differs in cancer risk magnitude, penetrance, and management recommendations, adding complexity to variant interpretation and clinical decision-making (5).

Method

In the present study, we retrospectively analyzed 192 individuals evaluated between 2023 and 2025 at the Medical Genetics Outpatient Clinic of Erzurum City Hospital. All individuals met the National Comprehensive Cancer Network (NCCN) Hereditary Cancer Guidelines (v.2023–2025) criteria for genetic testing. Unlike studies focusing solely on affected individuals, our cohort represents a clinically heterogeneous real-world population that includes breast cancer, ovarian cancer, strong family history, and other hereditary cancer suspicions. Genomic DNA was enriched using the GeneTopia Hybridization Capture Kit, targeting approximately 51 Mb of the human exome, covering more than 99% of coding regions defined in CCDS, RefSeq, and Gencode databases. Sequencing was performed on the GeneMind–SURFSeq 5000 platform. Adequate coverage was achieved in more than 98% of targeted regions, with an average sequencing depth of 20×. Protein-coding exons and ±20 base pair intronic flanking regions were analyzed. Variants with a minimum read depth of 10 were reported. Only variants with a minor allele frequency below 1% in population databases (gnomAD, ExAC, 1000 Genomes, dbSNP) were considered. Variant classification was performed according to ACMG guidelines.

Results

Of the 192 individuals included in the study, 98.4% were female and 1.6% were male. The referral indications were as follows: 65.1% had a diagnosis of breast cancer, 19.8% were referred due to a strong family history of cancer, 10.4% had ovarian cancer, 1.6% had early-onset breast cancer, and 3.1% were evaluated for other hereditary cancer suspicions. This distribution indicates that our cohort included not only affected individuals but also unaffected individuals meeting NCCN testing criteria.

Molecular analysis revealed that 42.2% of individuals had no clinically significant variant identified, 47.9% harbored variants of uncertain significance (VUS), and 9.9% had pathogenic or likely pathogenic (P/LP) variants. Among the 19 individuals with P/LP variants, the distribution by gene was as follows: *BRCA1* accounted for 26.3%, *BRCA2* for 21.1%, *CHEK2* for 15.8%, *ATM* for 10.5%, *PALB2* for 10.5%, heterozygous *MUTYH* variants for 10.5%, and *TP53* for 5.3%. Overall, 47.4% of P/LP variants were detected in *BRCA1/2* genes.

Discussion

When compared with previously published Turkish multigene panel studies, several important observations emerge. Reported P/LP rates in Turkish cohorts range between approximately 11% and 33% (6-17). Studies focusing exclusively on young breast cancer patients or solely ovarian cancer cases generally report higher detection rates. For example, P/LP rates of around 21% have been reported in young breast cancer cohorts, and rates exceeding 20% have been described in ovarian cancer-only cohorts (6-17). In contrast, heterogeneous NCCN-based populations tend to demonstrate P/LP rates in the range of 10–15%. The 9.9% detection rate observed in our study lies at the lower boundary of the national range but is consistent with expectations for a heterogeneous referral population (6-17).

Regarding gene distribution, Turkish cohorts typically report that approximately 60–66% of P/LP variants occur in *BRCA1/2* genes (6-17). In our study, the proportion of *BRCA1*/2 among P/LP variants was 47.4%, which appears comparatively lower. The most plausible explanation for this difference lies in our institutional testing algorithm. In clinical practice, high-risk individuals presenting before treatment are initially tested with targeted *BRCA1/2* sequencing and MLPA analysis. Only those found negative for *BRCA1/2* are subsequently referred for multigene panel testing. Consequently, *BRCA1/2*-positive individuals may have been identified prior to panel testing, resulting in a relative reduction of *BRCA1/2* representation within the panel-tested subgroup. This finding highlights how pre-test strategies and diagnostic algorithms can significantly influence observed gene distributions in panel studies.

One of the most striking differences between Turkish cohorts and large international series is the relatively high VUS rate. International large-scale cohorts generally report VUS frequencies between 20% and 35% (18), whereas Turkish studies often report VUS rates between 30% and 48% (6-17). In our study, the VUS rate was 47.9%, consistent with the upper range reported nationally. Several factors likely contribute to this observation.

First, individuals of Turkish ancestry remain underrepresented in global variant databases such as ClinVar and population databases such as gnomAD. Limited population-specific allele frequency data makes classification of rare variants more challenging and increases uncertainty. Second, the absence of large, well-characterized healthy control datasets specific to the Turkish population hampers accurate interpretation of population-specific variants. Third, regional genetic diversity may introduce rare or private variants that lack sufficient published evidence for classification.

Conclusion

The present study provides real-world data on multigene panel testing in a heterogeneous NCCN-based hereditary cancer cohort. While the diagnostic yield is lower than that observed in highly selected breast- or ovarian-only cohorts, it reflects routine clinical practice in a referral center where both affected and unaffected high-risk individuals are evaluated. The relatively lower proportion of *BRCA1/2* variants among P/LP findings underscores the impact of stepwise testing algorithms. Furthermore, the high VUS rate emphasizes the urgent need for national and regional genetic databases to improve variant interpretation in underrepresented populations.

In conclusion, in this NCCN-based heterogeneous cohort of 192 individuals, the P/LP detection rate was 9.9%, with *BRCA1/2* accounting for nearly half of clinically significant findings. The diagnostic yield aligns with previously reported heterogeneous Turkish cohorts but is lower than that observed in highly selected disease-specific series. The consistently high VUS rates across Turkish studies highlight the need for improved population representation in global databases and the development of national reference datasets. These findings underscore the importance of both patient selection strategies and institutional testing algorithms in shaping the genetic landscape observed in hereditary cancer panel studies.

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[Abstract:0285]

Genotype–Phenotype Correlations in Gorlin Syndrome: A Retrospective Analysis of Six Families

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Objective: Gorlin syndrome, also known as Basal Cell Carcinoma Syndrome or Gorlin–Goltz syndrome, is a rare autosomal dominant cancer predisposition disorder characterized by multiple basal cell carcinomas, craniofacial dysmorphic features, skeletal abnormalities, odontogenic keratocysts, and associated ophthalmological and neurological findings. The estimated prevalence is approximately 1 in 40,000–60,000 individuals. The molecular etiology of the syndrome involves pathogenic variants in genes of the Hedgehog signaling pathway, most commonly PTCH1, while PTCH2 and SUFU variants are reported less frequently. Gorlin syndrome exhibits marked phenotypic variability, even among individuals within the same family, making genotype–phenotype correlation studies important for clinical management.
This study aimed to evaluate the clinical and genetic characteristics of patients with Gorlin syndrome referred to our clinic and to assess genotype–phenotype correlations.

Materials-Methods: A retrospective analysis was performed on six families diagnosed with Gorlin syndrome who were referred to the Medical Genetics Department of Ege University between 2018 and 2025. Demographic data, clinical features, and molecular genetic test results were reviewed. Molecular analyses included the PTCH1, PTCH2, and SUFU genes, and identified variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria. Genotype–phenotype correlations were evaluated by comparing clinical findings with genetic results.
Results: Pathogenic or likely pathogenic variants in the PTCH1 gene were identified in all six families, with a total of six distinct variants detected. The most common clinical manifestations were basal cell carcinoma, craniofacial abnormalities, and skeletal anomalies. No pathogenic or likely pathogenic variants were detected in the PTCH2 or SUFU genes in the study cohort.
Conclusion: Our findings reinforce the central role of PTCH1 in the genetic etiology of Gorlin syndrome and demonstrate substantial phenotypic heterogeneity among affected individuals. Even in the presence of similar genetic variants, clinical presentation varied considerably, emphasizing the need for comprehensive clinical assessment alongside molecular testing. Genotype–phenotype correlation studies are valuable for improving diagnostic accuracy, guiding individualized surveillance strategies, and optimizing long-term patient management. Further studies involving larger cohorts are warranted to better elucidate the relationship between genetic variants and clinical outcomes in Gorlin syndrome.

Keywords: Basal Cell Carcinoma, Genotype–Phenotype Correlation, Gorlin Syndrome, *PTCH1*

[Abstract:0287]

Clinical Spectrum in Patients with Pathogenic DICER1 Variants

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Objective: DICER1 syndrome is a rare, autosomal dominant familial tumor predisposition disorder characterized by a heterozygous germline mutation in the DICER1 gene. Clinically, the most frequently observed tumor is pleuropulmonary blastoma (PPB), a lung neoplasm of early childhood. Family-based studies have demonstrated an association between this condition and various cystic neoplasms. The characterization of DICER1 germline variants has enabled the identification of numerous extrapulmonary neoplasms and non-pulmonary tumor entities—such as Sertoli–Leydig cell tumors, embryonal rhabdomyosarcoma (including cervical involvement), multinodular goiter, differentiated and poorly differentiated thyroid carcinoma, cystic nephroma–anaplastic sarcoma, pineoblastoma, and PPB-like sarcomas—thereby highlighting the extensive phenotypic heterogeneity of DICER1-associated disease.
The aim of this study was to describe the genotypic and phenotypic characteristics of patients with pathogenic DICER1 variants reported by the Medical Genetics Laboratory of Ege University.
Materials-Methods: Genomic DNA was isolated from peripheral blood samples of the patients and sequenced using the TWIST Custom Select Panel on the MGI NextSeq 550 platform. Pathogenic variants identified in the DICER1 gene were retrospectively evaluated.
Results: Four patients harboring pathogenic DICER1 variants were included in this series. One patient was an adult female who had undergone surgery for classic-type papillary thyroid carcinoma and was subsequently followed for follicular nodular thyroid disease; she had no history of PPB, and no additional malignancies were detected on imaging studies. The remaining three patients belonged to the same family and exhibited marked phenotypic variability. Within this family, a 7-year-old girl was diagnosed with PPB following excision of a pulmonary cyst at the age of 4 years, whereas a 36-year-old male relative underwent thyroidectomy for multinodular goiter, with benign histopathological findings.
Conclusion: The coexistence of both malignant and benign manifestations even among members of the same family supports the presence of variable expressivity in DICER1 syndrome. Furthermore, the broad clinical spectrum observed among patients from different families underscores the need for further investigation into potential genotype–phenotype correlations associated with the rare pathogenic DICER1 alleles in the general population.

Keywords: DICER1, familial tumor predisposition disorder, genotype–phenotype correlations, Pleuropulmonary blastoma

[Abstract:0289]

Sarcoma Subtypes and Germline Mutation Spectrum in Türkiye: A Single-Center Experience

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Objective: Sarcomas are rare and biologically heterogeneous malignancies that show regional and ethnic variations in incidence, histological distribution, and molecular characteristics. Sarcomas comprise numerous subtypes with distinct clinical behavior, prognosis, and genetic backgrounds. Recent population-based and international studies have demonstrated that, beyond well-defined hereditary cancer syndromes such as Li–Fraumeni syndrome and neurofibromatosis type 1, germline pathogenic variants in genes including TP53, RB1, NF1, DICER1, SDHx, and DNA damage repair pathway genes contribute to the development of different sarcoma subtypes at varying frequencies. However, real-world data on the prevalence and distribution of germline genetic alterations in unselected sarcoma cohorts, particularly with respect to sarcoma subtypes, remain limited. The aim of this study was to evaluate germline genetic findings in sarcoma patients referred for clinical genetic testing and to investigate their association with sarcoma subtypes.

Materials-Methods: Between 2022 and 2025, 62 patients diagnosed with sarcoma who were referred to the Medical Genetics Outpatient Clinic of Ege University Hospital and underwent germline cancer gene panel testing were retrospectively analyzed. Demographic characteristics, age, pathological diagnoses, and sarcoma subtypes were recorded. In addition, personal history of additional malignancies, family history of cancer, and germline genetic variants identified through genetic testing were evaluated.

Results: Among the 62 patients included in the study, germline genetic testing revealed pathogenic/likely pathogenic (P/LP) variants in 14 patients (22.6%), three of which were deletion-type variants. The most frequently affected genes among patients with P/LP variants were TP53, RB1, BRCA2, MUTYH, and genes involved in DNA damage repair pathways, and these variants were associated with different sarcoma subtypes. Germline RB1 variants were identified in patients with a history of retinoblastoma who subsequently developed leiomyosarcoma or osteosarcoma. TP53 variants were observed in cases of osteosarcoma, myxoid liposarcoma, and high-grade mesenchymal/pleomorphic sarcomas. Additionally, variants in DNA repair genes such as MUTYH, NTHL1, and MSH2 were detected in patients with liposarcoma, osteosarcoma, and angiosarcoma. BRCA2 variants were identified in patients with a history of multiple primary malignancies.

Conclusion: In this study, the distribution of germline genetic variants and their association with sarcoma subtypes were evaluated in patients diagnosed with sarcoma in Türkiye. Our findings demonstrate that different sarcoma subtypes possess distinct genetic backgrounds and that germline pathogenic/likely pathogenic variants are detected at a clinically meaningful frequency. The identification of rare and deletion-type variants, as well as cases with multiple primary malignancies, contributes to the limited existing literature on germline cancer predisposition in sarcoma patients. These results underscore the importance of subtype-specific germline genetic evaluation in sarcoma patients and provide valuable real-world data from Türkiye that add to the current literature.

Keywords: Sarcoma, Germline, Cancer

[Abstract:0290]

BRIP1 Gene in Breast and Ovarian Cancer Cases: A Single-Center Experience

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Introduction: The *BRIP1* (*BRCA1*-Interacting Protein C-terminal Helicase 1) gene, located at 17q23.2, consists of 20 exons and encodes a 1249-amino acid protein. Working in conjunction with the *BRCA1* gene, it plays a pivotal role in regulating replication and homologous recombination, thereby contributing to the maintenance of genomic integrity. Pathogenic variants in the *BRIP1* gene are known to increase the risk of ovarian cancer; however, there is conflicting data in the literature regarding its association with breast cancer. In this study, we aimed to present a case series in which pathogenic and likely pathogenic variants were identified in the *BRIP1* gene through hereditary cancer panel testing performed at our center, and to evaluate the impact of these variants on clinical management.

Materials-Methods: A retrospective analysis was conducted on 4,667 cases referred to the Izmir City Hospital, Department of Medical Genetics, who underwent hereditary cancer panel testing based on individual and/or family history. Following genomic DNA isolation from peripheral blood samples, Next-Generation Sequencing (NGS) was performed for hereditary cancer genes. Following bioinformatic analyses, the identified variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria.

Results: Heterozygous pathogenic/likely pathogenic variants in the *BRIP1* (ENST00000259008.7) gene were identified in 10 out of 4,667 analyzed cases (0.21%). All patients were female, with ages at presentation ranging from 38 to 81 years. Four cases were being followed for breast cancer, three for ovarian cancer, and three cases presented solely due to family history. Among the identified variants, two (c.118del (p.Gln40AsnfsTer15) and c.2623G>T (p.Glu875Ter)) were, to our knowledge, previously undocumented in the literature.

Discussion: Our study underscores the diagnostic yield of multigene panel testing for hereditary cancer syndromes and highlights the clinical significance and contribution to patient management of genes beyond high-penetrance groups in hereditary cancer syndromes. It was demonstrated that performing broad-panel testing in cases with appropriate clinical findings and/or family history increases diagnostic efficiency and is invaluable for preventive medicine approaches. Furthermore, the documentation of these two novel variants is expected to contribute to the expansion of the known *BRIP1* variant spectrum.

Keywords: Ovarian Cancer, Breast Cancer, *BRIP1*

[Abstract:0291]

Heterozygous Pathogenic *NBN* Variants Identified by Hereditary Cancer Panel Testing: Clinical Spectrum and Genotype–Phenotype Correlation

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Objective: The *NBN* gene encodes nibrin, a critical component of the *MRE11–RAD50–NBN* (MRN) complex, which plays an essential role in the early stages of the DNA damage response (DDR). While biallelic pathogenic variants in NBN cause Nijmegen Breakage Syndrome, heterozygous pathogenic variants have been associated with increased susceptibility to various malignancies, particularly breast and prostate cancer. However, the cancer spectrum and genotype–phenotype correlations related to heterozygous NBN variants remain incompletely defined. This study aimed to evaluate the clinical indications, cancer types, and variant spectrum in individuals carrying pathogenic *NBN* variants identified through hereditary cancer panel testing.

Materials-Methods: Targeted next-generation sequencing–based hereditary cancer panel testing was performed on DNA isolated from peripheral blood samples of 2,147 individuals referred to our center for oncogenetic evaluation. Variants were classified according to ACMG/AMP criteria. Clinical indications for testing, personal and family cancer history, and genotype–phenotype correlations were retrospectively analyzed.

Results: Heterozygous pathogenic or likely pathogenic *NBN* variants were identified in 14 patients (14/2147; 0.65%). Of these individuals, 8 patients (8/14; 57.1%) had a personal history of breast cancer. Three patients (3/14; 21.4%) were referred for genetic testing due to a family history of breast cancer without a personal cancer diagnosis. In addition, one patient (1/14; 7.1%) had prostate cancer, one patient (1/14; 7.1%) was diagnosed with gastric cancer, and one patient (1/14; 7.1%) had colorectal polyps.
The recurrent frameshift variant c.657_661delACAAA (p.Lys219AsnfsTer16; rs587776650; chr8:90983441) was detected in 7 patients (7/14; 50.0%), representing the most frequent pathogenic *NBN* variant in this cohort. The remaining patients harbored other rare pathogenic *NBN* variants. Genotype–phenotype correlations were evaluated by comparing these findings with previously reported cases in the literature.

Conclusion: Although heterozygous pathogenic NBN variants—particularly the recurrent c.657_661delACAAA (p.Lys219AsnfsTer16) variant—have been repeatedly reported in individuals with breast and prostate cancer, the strength and clinical significance of this association remain uncertain. Current evidence suggests a possible contribution of NBN to cancer susceptibility; however, penetrance appears to be variable, and causality has not been definitively established. Conflicting results across populations and cancer types, as well as the limited size of most reported cohorts, underscore the need for cautious interpretation. Ongoing functional studies and larger, well-characterized population-based analyses are required to clarify the true cancer risk attributable to heterozygous *NBN* variants and to determine their relevance for clinical risk assessment and management.

Keywords: breast cancer, gastric cancer, genotype-phenotype correlation, *NBN*, prostate cancer

[Abstract:0292]

Spectrum of Germline Cancer Predisposition Variants in Patients With Melanoma: A Retrospective Study

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Objective: Melanoma is one of the most lethal skin cancers and increasing incidence worldwide. Although the majority of melanoma cases are sporadic, a significant porpotion is associated with hereditary cancer predisposition. In individuals with a positive family history, germline variants in melanoma susceptibility genes, are frequently identified. However, melanoma may also arise within the context of broader hereditary cancer syndromes involving non–tumor-specific genes such as PTEN, TP53, BRCA1, BRCA2, and BAP1. Identification of germline pathogenic variants is critical for individual risk stratification, testing of family members to reducing melanoma-related morbidity and mortality. This study aimed to retrospectively evaluate the spectrum and clinical significance of germline variants in patients presenting with melanoma who were referred for hereditary cancer predisposition testing.

Materials-Methods: Patients diagnosed with melanoma between January 2022 and December 2025 and referred to the Department of Medical Genetics at Ege University Hospital were retrospectively reviewed. A total of 43 patients were included in the analysis. Cutaneous melanoma was the primary diagnosis in all cases; additionally, two patients were diagnosed with uveal melanoma and one patient had melanoma originating from the dura mater. Germline genetic testing was performed using either a comprehensive hereditary cancer gene panel (n = 24) or whole-exome sequencing (WES) (n = 18), selected according to clinical features such as age at diagnosis, personal history of multiple malignancies, and family cancer history. Identified variants were classified following the 2015 American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG/AMP).

Results: The mean age at melanoma diagnosis was 45.95 ± 19.32 years. Females comprised 59% of the cohort, while 41% were male. A history of multiple primary malignancies was observed in 56% of patients, whereas 44% presented with melanoma as a single cancer. A positive family history of cancer was reported in 67% of cases. Pathogenic or likely pathogenic (P/LP) germline variants with potential clinical relevance were identified in 18 patients (42%). Variants of uncertain significance were detected in 17 patients, while 8 patients had no reportable variants. P/LP variants were identified in genes involved in melanoma susceptibility including TYR, TERT, CDKN2A, BRCA1, BRCA2, CHEK2, POLH, XPC, ERCC2, SDHB, and SEC23B. Additionally, pathogenic variants were detected in emerging melanoma susceptibility genes, including OCA2 in two patients and the NOTCH gene family in one patient. Two patients carried biallelic pathogenic variants consistent with xeroderma pigmentosum diagnosed prior to melanoma development.

Conclusion: This study highlights the marked genetic heterogeneity underlying hereditary melanoma. The presence of pathogenic variants in both melanoma-specific genes and non–tumor-specific cancer susceptibility genes supports the use of broad multi-gene panel testing or WES, particularly in patients with early-onset disease, multiple primary cancers, or a strong family history. The relatively high detection rate of pathogenic or likely pathogenic variants (42%), compared with unselected melanoma cohorts (10–20%), likely reflects appropriate selection of high-risk individuals. Integration of GWAS, polygenic risk scores, and ongoing gene discovery efforts will be essential to improve diagnostic yield, while comprehensive germline testing remains critical for personalized surveillance and cascade testing to reduce melanoma-related morbidity and mortality.

Keywords: Melanoma, Skin cancers, Hereditary cancer predisposition, Next-generation sequencing (NGS)

[Abstract:0293]

Molecular Characterization of a Deep Intronic *ATM* Variant (c.1899-123A>G) Using PCR and Gel Electrophoresis

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Objective:The *ATM* gene plays a critical role in the DNA damage response and maintenance of genomic stability. Pathogenic variants in this gene are associated with ataxia-telangiectasia and an increased cancer risk in heterozygous carriers. While most reported variants are located in coding regions or canonical splice sites, deep intronic variants remain insufficiently characterized. The clinical significance of the heterozygous deep intronic variant c.1899-123A>G is unclear. The detection of this variant in multiple patients with a history of cancer has raised suspicion regarding its pathogenic potential. Therefore, this study aimed to investigate the potential effect of the heterozygous deep intronic *ATM* variant c.1899-123A>G on RNA splicing using conventional PCR and agarose gel electrophoresis.

Materials-Methods:Fourteen patients carrying the heterozygous c.1899-123A>G variant and presenting with a personal or familial history of cancer were included in the study. Due to technical limitations, RNA analysis was performed in selected patients. Total RNA was isolated from peripheral blood samples and reverse-transcribed into cDNA. Primers flanking the predicted cryptic splice donor site were designed to amplify both normal and aberrant transcripts. PCR products were visualized by agarose gel electrophoresis and compared with healthy controls.

Results:An additional abnormal band, absent in control samples, was detected in the analyzed patients. This fragment was consistent with the activation of a novel cryptic splice donor site created by the variant. The resulting aberrant splicing event is predicted to generate an abnormal transcript that may lead to a frameshift or a premature termination codon. These findings indicate a disruption of normal *ATM* pre-mRNA splicing.

Conclusion:The heterozygous deep intronic *ATM* variant c.1899-123A>G is associated with abnormal splicing and may contribute to cancer development. However, further evidence from expression analyses and advanced functional studies is required to clarify this association. Previous studies involving a limited number of patients demonstrated aberrant transcript formation only at the PCR level. Our study, conducted in a larger cohort, provides further support to the existing evidence. Future studies are planned to quantify aberrant transcript levels using qPCR or RNA sequencing. The integration of transcript-level analyses into routine diagnostics is essential for the accurate classification of non-coding variants in hereditary cancers.

Keywords: *ATM* gene, Deep intronic variant, Hereditary cancer, RNA splicing

[Abstract:0294]

A Rare Coexistence of Pathogenic BRCA1 and Likely Pathogenic FH Variants in a Young Male with Leiomyoma

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Introduction:Hereditary cancer predisposition syndromes may present with early-onset tumors. Pathogenic variants in the BRCA1 gene are classically associated with hereditary breast and ovarian cancer syndrome, whereas variants in the FH (fumarate hydratase) gene cause Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) syndrome. The coexistence of variants in these two genes is extremely rare. Here, we report a young male patient with leiomyoma harboring concurrent pathogenic BRCA1 and likely pathogenic FH variants and discuss the implications for genetic counseling in the context of current literature.

Case:A 25-year-old male patient with no previously known medical conditions was diagnosed with leiomyoma following surgical excision of a mass on his back. It was notable that leiomyoma had been observed in the patient's maternal uncle. Following surgical removal, it was referred to our clinic for evaluation for hereditary cancer predisposition.

Material-Methods:

Genomic DNA was extracted from peripheral blood leukocytes. The targeted hereditary cancer panel was performed using next-generation sequencing. Variant interpretation was performed in accordance with ACMG/AMP guidelines.

Results:Genetic analysis identified a heterozygous pathogenic nonsense variant in the BRCA1 gene (c.3211G>T) and a heterozygous likely pathogenic frameshift variant in the FH gene (c.1352_1353del).

Discussion:The FH variant identified in this patient is consistent with Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) syndrome. The presence of leiomyoma at a young age, together with a supportive family history, aligns with the known clinical spectrum of FH-associated disease, although penetrance and phenotypic variability remain incompletely characterized. The detection of a pathogenic BRCA1 variant, associated with increased risk for multiple malignancies, represents an additional and clinically relevant finding. To our knowledge, the coexistence of pathogenic BRCA1 and likely pathogenic FH variants has not been previously reported, and the FH variant appears to be novel. This case highlights the potential for multiple hereditary cancer predisposition variants to coexist and underscores the importance of individualized genetic counseling and long-term surveillance.

Keywords: BRCA1, FH, hereditary cancer predisposition, leiomyoma/HLRCC

[Abstract:0298]

Clinical Findings, Genetic Characteristics, and Familial Tumor Spectrum in Von Hippel–Lindau Syndrome: A Single-Center Experience

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Objective:Von Hippel–Lindau (VHL) syndrome is a rare inherited cancer predisposition syndrome characterized by a wide spectrum of tumors, including central nervous system hemangioblastomas, pheochromocytoma, renal cell carcinoma (RCC), and pancreatic neuroendocrine tumors. In this study, we aimed to evaluate the age at diagnosis, initial clinical presentations, underlying genetic variants, and intrafamilial phenotypic variability in patients with VHL syndrome.

Methods:A retrospective analysis was performed on twelve genetically confirmed VHL patients from six unrelated families carrying germline VHL variants. Clinical data including demographic characteristics, presenting symptoms, surgical interventions, development of additional tumors during follow-up, and genetic test results were reviewed. Detected variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Results:The age at diagnosis ranged from 4 to 42 years, with most patients diagnosed during childhood and adolescence. Hemangioblastoma and pheochromocytoma were the most common initial clinical findings. During follow-up, several patients developed malignant or premalignant lesions, including bilateral pheochromocytoma, RCC, pancreatic neuroendocrine tumors, and angiomyolipoma. Genetic analysis revealed pathogenic missense variants (c.499C>T [p.Arg157Trp], c.208G>A [p.Glu70Lys], c.482G>A [p.Arg161Gln], c.194C>G [p.Ser65Trp]) as well as heterozygous deletions involving exon 1 or exon 2 of *VHL* gene. Marked intrafamilial phenotypic heterogeneity was observed among individuals carrying the same genetic variant, with differences in age at onset and organ involvement.

Conclusion:VHL syndrome may have onset at different ages and demonstrates substantial intrafamilial phenotypic heterogeneity. Because initial manifestations are frequently indolent or non-specific, delays in genetic confirmation and the lack of structured surveillance protocols may preclude the timely detection of neoplasms, adversely affecting patient outcomes. Early-onset genetic screening, followed by lifelong, organ-specific, and multidisciplinary surveillance, is essential for optimizing clinical outcomes in patients with von Hippel-Lindau (VHL) syndrome.

Keywords: Von Hippel–Lindau syndrome, hereditary cancer syndrome, pheochromocytoma, VHL, hemangioblastoma

[Abstract:0301]

Retrospective Analysis of 465 Cases Undergoing 60-Gene Hereditary Cancer Panel at Marmara University Pendik Training and Research Hospital

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Objective: Hereditary cancer syndromes are critical for early diagnosis and family screening through the identification of genetic predispositions. Advances in Next-Generation Sequencing (NGS) technologies allow for screening a broader mutation spectrum using multi-gene panels. This study aims to evaluate the demographic, clinical, and molecular characteristics of 465 cases tested with a 60-gene hereditary cancer panel at our institution.

Materials-Methods: A total of 465 cases who presented to the Medical Genetics Outpatient Clinic of Marmara University Pendik Training and Research Hospital between 2023 and 2025 were retrospectively analyzed. All patients underwent a 60-gene hereditary cancer panel. Clinical parameters including age at diagnosis, family history, consanguinity, and the presence of multiple primary tumors (MPT) were evaluated.

Results: The cohort included 386 females and 79 males, with a mean diagnosis age of 46.5±16.0 years. The most common malignancies were breast (51.2%), colon (12.0%), and ovarian (9.2%) cancer. Molecular findings potentially associated with the clinical phenotype were identified in approximately one-fourth of the cohort. Additionally, variants with uncertain clinical significance were observed in a small subset of patients. Among the identified variants, those in BRCA2, CHEK2, MUTYH, ATM, and BRCA1 were the most frequent. Although a vast majority (91.4%) had a positive family history, neither consanguinity (p=0.6178) nor diagnosis age (p=0.0532) showed a significant statistical impact on the molecular yield.

Conclusion: The use of comprehensive gene panels facilitates the identification of variants across different risk groups within the hereditary cancer spectrum. These findings provide a representative insight into the hereditary cancer spectrum within our regional population.

Keywords: Hereditary Cancer Panel, NGS, Genetic Predisposition, Turkish population

[Abstract:0302]

Is a High-VAF Truncating *PPM1D* Variant a Distinct Tumor Predisposition Entity? A Lethal Composite Phenotype Beyond JDVS

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Objective: Truncating mutations in the terminal exon of *PPM1D* pose a significant diagnostic challenge. While germline loss-of-function variants cause Jansen-de Vries Syndrome (JDVS), and somatic gain-of-function (GOF) truncating mutations in the same exon are well-established drivers of carcinogenesis mediated by p53 suppression, the clinical significance of mosaic variants remains ambiguous. Specifically, the interpretation of mosaic oncogenic mutations detected in blood is debated: whether they represent a bona fide tumor predisposition or merely secondary therapy-related clonal hematopoiesis (t-CHIP) is often unclear. We present a hypothesis-generating case of a treatment-naive young adult where this distinction carries lethal implications.
Case: A 24-year-old male presented with a lethal multisystem malignancy phenotype. History was notable for a low-grade pontine glioma diagnosed at age 13, which remained radiologically stable for years without oncologic treatment. In early adulthood, the disease course changed abruptly with the development of widespread metastases involving bone, lymph nodes, and liver. Histopathological evaluation of a liver lesion revealed adenocarcinoma, and a pancreatobiliary primary was considered most likely, though the patient expired before the primary site could be definitively assigned. Congenital anomalies included unilateral renal agenesis and retinitis pigmentosa. Whole-exome sequencing revealed a composite etiology: a homozygous PDE6B variant explained the retinal dystrophy, while a de novo truncating *PPM1D* mutation (c.1578delT; p.Ile526Metfs*13) was identified with a variant allele frequency (VAF) of 35.4% in blood.
Conclusion: The patient's pediatric tumor onset and complete absence of prior chemotherapy makes t-CHIP unlikely. Instead, the high VAF and involvement of distinct germ layers (neuroectodermal glioma, endodermal adenocarcinoma, and mesodermal renal agenesis) suggest post-zygotic constitutional mosaicism acquired during early embryogenesis. Mechanistically, this variant localizes to the exon 6 hotspot known to confer oncogenic GOF effects via stabilization of the Wip1 phosphatase and potent p53 suppression. We hypothesize that such biologically intolerable variants are likely embryonically lethal in a widespread germline state, thus becoming observable only in a mosaic context. Confirmatory analysis of a second, non-hematopoietic tissue is currently ongoing to definitively validate the constitutional nature of this mosaicism.
This case highlights the interpretative challenges posed by high-VAF truncating *PPM1D* variants in young, treatment-naive patients. Our findings suggest that such variants may define a distinct, aggressive tumor predisposition entity characterized by multi-organ malignancies. This phenotype warrants consideration beyond the classic frameworks of JDVS and incidental CHIP, underscoring the need for systematic investigation of *PPM1D* mosaicism in hereditary cancer evaluations.

Keywords: *PPM1D*, tumor predisposition, constitutional mosaicism

[Abstract:0307]

Evaluation of Germline Mutations in Patients with Pheochromocytoma/Paraganglioma: A Single-Center Experience

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Objective: Pheochromocytomas and paragangliomas (PGL/PCC) are rare neuroendocrine tumors originating from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. Notably, PGL/PCCs are associated with a relatively high frequency of germline mutations. Previous studies report that approximately 30-40% of the cases carry germline mutations in susceptibility genes such as *SDHA*, *SDHB*, *SDHC*, *SDHD*, *VHL*, *RET*, and *NF1*. Identification of these mutations is crucial for patient management and family screening. Evaluating mutation profiles across different populations facilitates optimization of genetic counseling and testing strategies. This study aimed to describe the frequency and distribution of germline variants in patients diagnosed with PGL/PCC and referred to our institution.

Materials-Methods: This study reviewed 45 patients with pheochromocytoma, paraganglioma, or glomus tumor referred to Gazi University Medical Faculty Department of Medical Genetics between 2019 and 2025. Patient ages ranged from 11 to 71 years (mean:45.9, median:49). Genetic testing strategies varied based on referral timing: whole exome sequencing (n=10, predominantly Twist exome 2.0), clinical exome panels (n=22, predominantly Sophia Genetics CES v2 and v3), custom panels (n=12), and targeted Sanger sequencing (n=1).

Results: Pathogenic or likely pathogenic variants were detected in 11 of 45 patients (24.4%). *SDHD* mutations represented the most prevalent alteration (n=5, 45.5% of positive cases), followed by *VHL* (n=2), with single variants in *SDHC*, *MAX*, *RET*, and *NF1* genes. Seven patients had variants of uncertain significance (VUS) in clinically relevant genes (*SDHA*, *VHL*, *RET*, *NF1*). Three patients had heterozygous variants (VUS) in *TSC1*, *KIF1B* and *FANCA* genes.

Discussion: Our diagnostic rate of 24.4% aligns with international cohorts that report mutation frequencies of 30-40% in PGL/PCC. The high proportion of *SDHD* mutations, accounting for 45.5% of positive cases, is particularly significant. *SDHD* is subject to maternal imprinting, with disease manifestation primarily following paternal inheritance, which has important implications for genetic counseling and interpretation of population database frequencies. When variants of uncertain significance in clinically relevant genes are included, potentially pathogenic variants were identified in 18 of 45 patients (40%). This finding suggests that the actual mutation rate may exceed our confirmed diagnostic yield. A major limitation of this study is the use of heterogeneous testing methodologies, especially the suboptimal coverage of *SDHA* and *SDHD* in Sophia CES_v2, which may have resulted in underascertainment of variants. Nevertheless, our results underscore the importance of comprehensive genetic testing for all patients with PGL/PCC and provide valuable insights into the mutational spectrum within the Turkish population.

Keywords: germline, paraganglioma, pheochromocytoma, variant

[Abstract:0308]

Retrospective Single-Center Analysis of Germline Variants in Prostate Cancer via Hereditary Cancer Panel Testing

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Objective: Prostate cancer (PC, OMIM: # 176807) is one of the most common cancers in men, and approximately 10-15% of cases are known to be associated with a hereditary genetic predisposition. The aim of this study is to retrospectively evaluate the frequency and distribution of germline variants in patients diagnosed with prostate cancer and tested with a hereditary cancer panel at our center.
Materials-Methods: The study included 133 patients diagnosed with prostate cancer who applied to the Department of Medical Genetics at Basaksehir Cam and Sakura City Hospital and had a suspicion of hereditary cancer due to family history or clinical findings. DNA was isolated from peripheral blood samples obtained from the patients, and a multi-gene panel analysis was performed using Next Generation Sequencing (NGS). The detected variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines. The study enrolled 133 patients diagnosed with prostate cancer between 2021 and 2025 who underwent germline genetic testing using a comprehensive hereditary cancer panel (including ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, DICER1, EGFR, EPCAM, FH, FLCN, GALNT12, HMMR, KIT, MEN1, MET, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NQO2, NTHL1, PALB2, PDGFRA, PIK3CA, PMS2, POLD1, POLE, POT1, PTEN, RAD50, RAD51, RAD51C, RAD51D, RAD54L, RB1, RET, RNF43, SMAD4, SMARCA4, STK11, TP53, VHL, and WT1).
Results: Germline variants were identified in 45 of 133 patients (33.8%). Genetic alterations were detected across 15 different genes, with 15 variants (11.2%) classified as pathogenic/likely pathogenic (P/LP) and 30 (22.6%) as variants of uncertain significance (VUS). While no genetic alterations were detected in 88 patients. The most frequently altered gene was BRCA2, followed by CHEK2. Additionally, multiple primary malignancies were observed in a subset of patients, including thyroid cancer (n=4) and pancreatic cancer (n=1). The identification of 45 variants, expands the known mutation spectrum and contributes to a better understanding of potential genotype-phenotype correlations. Comprehensive NGS-based genetic testing facilitates earlier diagnosis and improved management strategies.
Conclusion: The possibility of hereditary cancer should be considered in patients with prostate cancer, even if the absence of a positive family history. The discovery of novel variants underscores the importance of extensive genetic screening in ensuring accurate diagnosis and lifelong surveillance. Further studies involving larger patient cohorts are required to better elucidate the clinical significance of these newly identified variants and the pathogenicity of variants of uncertain significance (VUS). A multidisciplinary approach involving oncologists, surgeons, and geneticists is essential for the optimal management and early detection of prostate cancer.

Keywords: Prostate Cancer, Hereditary Cancer, NGS, Germline Variants

[Abstract:0309]

Beyond *BRCA*: non-*BRCA* P/LP variants and VUS burden in 600 hereditary breast cancer patients

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Introduction: Germline pathogenic and likely pathogenic (P/LP) variants constitute an important component of hereditary breast cancer predisposition. While BRCA1/2 remain the most recognized high-penetrance genes, recent clinical practice has shifted toward multigene hereditary cancer panels that capture broader DNA damage response (DDR), homologous recombination (HR), mismatch repair (MMR) and tumor suppressor pathways. Data regarding the contribution of non-BRCA genes and the burden of variants of uncertain significance (VUS) in real-world cohorts from our region remain limited.

Objective: To characterize the spectrum of germline P/LP and VUS variants in breast cancer patients tested with a 61-gene hereditary cancer panel over a five-year period.

Materials-Methods: We retrospectively reviewed consecutive breast cancer patients who underwent germline testing using a QIAseq custom hereditary cancer panel including 61 predisposition genes (BRCA1/2, PALB2, BARD1, RAD51C/D/B, BRIP1, ATM, CHEK2, TP53, PTEN, CDH1, APC, MUTYH, POLE/POLD1, MSH2, MSH6, MLH1, PMS2 and others) between 2020 and 2025 at a tertiary medical genetics center. Sequencing, bioinformatic analysis and variant interpretation were performed according to ACMG guidelines. Variants were classified as P/LP, VUS or negative. Descriptive statistics were used to summarize findings.

Results: A total of 600 breast cancer patients were analyzed. Germline P/LP variants were identified in 150 patients (25.0%). Approximately one-fifth of P/LP carriers (~30 cases) harbored BRCA1/2 alterations, whereas the majority carried pathogenic variants in non-BRCA genes represented in the 61-gene panel, including HR pathway genes (e.g., PALB2, BARD1, RAD51C/D, BRIP1, ATM, CHEK2) and mismatch-repair genes (e.g., MSH2, MSH6, MLH1, PMS2). VUS were detected in 140 patients (23.3%), reflecting a substantial burden of inconclusive findings, particularly within DDR and HR-associated genes. In contrast, 288 patients (48.0%) had negative results with no reportable variants. Collectively, over half of all patients (312/600, 52.0%) received a non-negative result (P/LP or VUS), highlighting the interpretive complexity of multigene testing in breast cancer.

Conclusion: This five-year single-center experience demonstrates that extended multigene panel testing identifies a considerable proportion of actionable non-BRCA germline variants in breast cancer patients. The significant VUS burden underscores persistent challenges in variant interpretation and the need for population-specific data. Our findings support the integration of broad hereditary cancer panels in routine clinical practice and genetic counseling workflows.These results have direct implications for genetic counseling, risk reduction strategies and eligibility for targeted therapies

Keywords: germline, breast cancer, hereditary cancer, BRCA

Title

Beyond BRCA: Contribution of non-BRCA pathogenic/likely pathogenic variants and VUS-only burden in a 600-patient hereditary breast cancer germline testing cohort

Running title

Non-BRCA P/LP and VUS-only burden in breast cancer

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Keywords
Breast cancer; germline; multigene panel; *BRCA1*; *BRCA2*; variant of uncertain significance; hereditary cancer
Abstract
Introduction: Multigene hereditary cancer panels may identify actionable germline variants beyond *BRCA1/2* but may also increase the burden of variants of uncertain significance (VUS).
Methods: Consecutive breast cancer patients tested between 2020 and 2025 at a tertiary medical genetics center were retrospectively reviewed. Germline testing used a 61-gene hereditary cancer panel. Variant interpretation followed a guideline-based framework. Patients were categorized into mutually exclusive groups: P/LP-positive (≥1 pathogenic/likely pathogenic variant), VUS-only (no P/LP and ≥1 VUS), or negative (no reportable variants).
Results: Among 600 patients, 100 (16.7%) were P/LP-positive, 150 (25.0%) were VUS-only, and 350 (58.3%) were negative. Within P/LP-positive patients (n=100), *BRCA1/2* variants were identified in 46 patients and non-BRCA P/LP variants in 54 patients. The most frequent non-BRCA P/LP genes were *MUTYH* (n=19), *CHEK2* (n=17), and *ATM* (n=7), followed by *PALB2* (n=3) and *TP53* (n=3). In the VUS-only group (n=150), VUS were most common in *ATM* (n=20), *BRCA2* (n=19), *PMS1* (n=11), *CHEK2* (n=8), and *BLM* (n=7), while other genes accounted for 85 patients.
Conclusion: Non-BRCA P/LP variants constituted the majority of actionable findings among P/LP-positive patients, while a substantial VUS-only burden persisted, highlighting the need for structured counseling and systematic variant re-evaluation.
Introduction
Germline predisposition is central to hereditary breast cancer risk assessment, prevention strategies, and cascade testing in relatives. While *BRCA1/2* remain the most widely recognized high-penetrance genes, multigene panel testing has become increasingly integrated into clinical practice to capture actionable variants across broader susceptibility pathways. The 2024 ASCO–Society of Surgical Oncology guideline endorses germline testing strategies that extend beyond *BRCA1/2* in appropriately selected breast cancer patients, reflecting the expanding role of multigene testing in routine care.[1]
However, expanded testing also increases the detection of variants of uncertain significance (VUS), which do not directly guide clinical management. Standardized interpretation is therefore essential. The ACMG/AMP framework provides widely adopted criteria and terminology (pathogenic, likely pathogenic, uncertain significance, likely benign, benign) for clinical sequence variant classification.[2] In real-world settings, VUS results can represent a substantial fraction of reports and necessitate careful counseling, documentation, and periodic re-evaluation. Large clinical cohorts show that variant reclassification occurs over time as evidence accumulates, underscoring the importance of structured recontact and re-interpretation workflows.[3]

In this study, we summarize a five-year single-center experience of germline testing in breast cancer patients using a 61-gene hereditary cancer panel, focusing on patient-level outcomes, the contribution of non-BRCA P/LP variants, and the VUS-only burden.

Materials and Methods

Study design and setting

This was a retrospective, descriptive, single-center cohort study of consecutive breast cancer patients who underwent germline hereditary cancer panel testing between 2020 and 2025 at a tertiary medical genetics center.

Germline panel testing and sequencing

Germline testing was performed using a custom 61-gene hereditary cancer panel covering established breast cancer susceptibility genes and additional hereditary cancer predisposition genes. Sequencing during the study period was performed on Illumina MiSeq and Element AVITI platforms according to manufacturer protocols and institutional standard operating procedures. Run- and sample-level quality metrics (including the proportion of targeted bases achieving >100× coverage and mean depth of coverage) were reviewed; only cases meeting laboratory acceptance criteria proceeded to interpretation and reporting.

Bioinformatic analysis and variant interpretation

Bioinformatic processing and clinical interpretation were performed using CLC Genomics Workbench and Qiagen Clinical Insight (QCI) workflows. Variants were classified as pathogenic, likely pathogenic, VUS, likely benign, or benign using a guideline-based framework consistent with ACMG/AMP recommendations.[2] Only reportable variants (pathogenic/likely pathogenic and VUS) were considered for outcome categorization; benign/likely benign variants were not considered reportable.

Patient-level outcome definitions (mutually exclusive)

Patients were categorized into mutually exclusive groups:

P/LP-positive: at least one pathogenic or likely pathogenic variant detected.

VUS-only: no pathogenic/likely pathogenic variants detected and at least one VUS detected.

Negative: no reportable variants detected (no P/LP and no VUS).

If a patient harbored both a P/LP variant and one or more VUS, the patient was categorized as P/LP-positive; VUS were treated as additional findings and did not alter the primary category.

Statistical analysis

Descriptive statistics were used to summarize findings (counts and percentages).

Ethics and confidentiality

The data were retrospectively compiled from results generated during routine clinical diagnostic testing; no patient identifiers were used at the reporting stage and confidentiality was preserved.

Results

Overall patient-level outcomes

A total of 600 breast cancer patients were included. Patient-level outcomes were:

P/LP-positive: 100 patients (16.7%)

VUS-only: 150 patients (25.0%)

Negative: 350 patients (58.3%)

Thus, 250/600 patients (41.7%) received a non-negative result (P/LP-positive or VUS-only).

BRCA versus non-BRCA contribution among P/LP-positive patients

Within P/LP-positive patients (n=100), BRCA1/2 P/LP variants were found in 46 patients, whereas non-BRCA P/LP variants were found in 54 patients. The most frequent non-BRCA P/LP genes were *MUTYH* (n=19), *CHEK2* (n=17), and *ATM* (n=7), followed by *PALB2* (n=3) and *TP53* (n=3). The remaining non-BRCA P/LP findings were distributed across additional panel genes at lower frequencies.

VUS-only gene distribution

In the VUS-only group (n=150), VUS were most commonly observed in *ATM* (n=20), *BRCA2* (n=19), *PMS1* (n=11), *CHEK2* (n=8), and *BLM* (n=7). Other genes collectively accounted for 85 patients. These counts represent patient-level frequencies rather than variant-level counts.

Tables and Figures (callouts)

Table 1. Patient-level outcomes and key distributions in the cohort (n=600).

Figure 1. Overall outcomes (P/LP-positive, VUS-only, negative).

Figure 2. BRCA1/2 vs non-BRCA among P/LP-positive patients.

Figure 3. Top non-BRCA P/LP genes + closed-system “Other”.

Figure 4. Top VUS-only genes + closed-system “Other”.

Discussion

This real-world cohort demonstrates two clinically relevant themes in multigene germline testing for breast cancer. First, among P/LP-positive patients, non-BRCA genes accounted for the majority (54%) of actionable findings. This supports the rationale for moving beyond *BRCA*-restricted testing strategies in appropriate clinical contexts and aligns with contemporary guidance endorsing expanded germline testing approaches.[1]

Second, the VUS-only burden (25%) was substantial. Under ACMG/AMP standards, VUS findings represent uncertain evidence and should not be used as the basis for major clinical management decisions.[2] Instead, they require structured counseling, documentation of uncertainty, and processes for periodic re-evaluation. In large clinical datasets, variant reclassification occurs over time and is driven by accumulating evidence, reinforcing the need for systematic re-interpretation and communication workflows.[3] In practice, this means the operational impact of multigene testing extends beyond “positive” cases—VUS-only results generate substantial counseling workload and follow-up expectations.

Conflict of interest: The authors declare no conflicts of interest.

This study has limitations. It is retrospective and single-center, which may limit generalizability. Detailed clinical phenotype, family history stratification, and downstream clinical actions (e.g., cascade testing uptake, surveillance changes) were not assessed in this report. In addition, platform-specific quantitative sequencing performance metrics were not provided numerically here, although all samples met laboratory acceptance criteria.

Despite these limitations, the use of mutually exclusive, patient-level outcome definitions ensures numerical clarity and provides a pragmatic snapshot of actionable yield beyond *BRCA* and the magnitude of VUS-only results in routine care.

Conclusion

In a 600-patient breast cancer cohort tested with a 61-gene germline panel, non-BRCA P/LP variants constituted the majority of actionable findings among P/LP-positive patients, while a considerable VUS-only burden persisted. These findings support broad panel testing within appropriate clinical pathways, accompanied by robust genetic counseling and structured variant re-evaluation processes.

Declarations

Funding: None declared.

Category / Gene	n	Notes
Overall outcomes (mutually exclusive)		
P/LP-positive	100	16.7%
VUS-only	150	25.0%
Negative	350	58.3%
Non-negative total (P/LP-positive + VUS-only)	250	41.7%
Within P/LP-positive (n=100)		
BRCA1/2 (P/LP)	46	46.0% of P/LP-positive
Non-BRCA (P/LP)	54	54.0% of P/LP-positive
Top non-BRCA P/LP genes (patient-level; n=54)		
MUTYH	19	
CHEK2	17	
ATM	7	
PALB2	3	
TP53	3	
Other non-BRCA genes	5	
Top VUS-only genes (patient-level; n=150)		
ATM	20	
BRCA2	19	
PMS1	11	
CHEK2	8	
BLM	7	
Other genes	85	

Data availability: Data are available from the corresponding author upon reasonable request, subject to institutional and privacy restrictions.

Author contributions: SOE: study conception, data interpretation, drafting; BS: data acquisition, clinical interpretation; DA: data curation and review; AT: supervision, critical revision. All authors approved the final manuscript.

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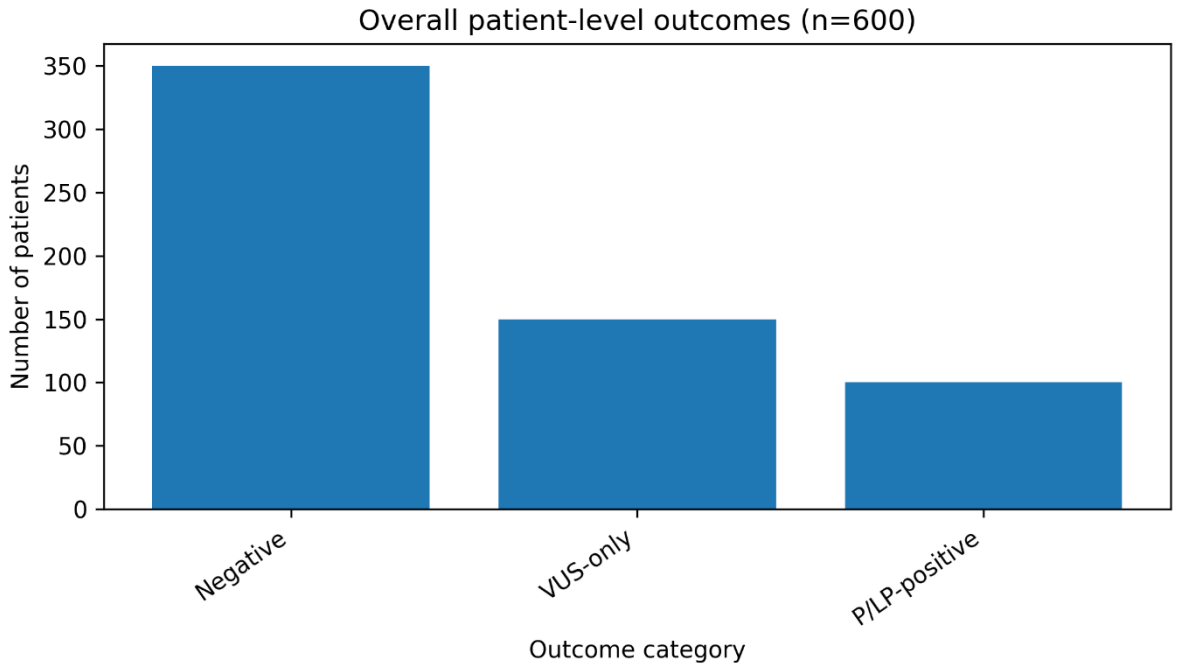
1. Bedrosian I, Somerfield MR, Achatz MI, et al. Germline Testing in Patients With Breast Cancer: ASCO–Society of Surgical Oncology Guideline. J Clin Oncol. 2024;42(5):584-604. doi:10.1200/JCO.23.02225.

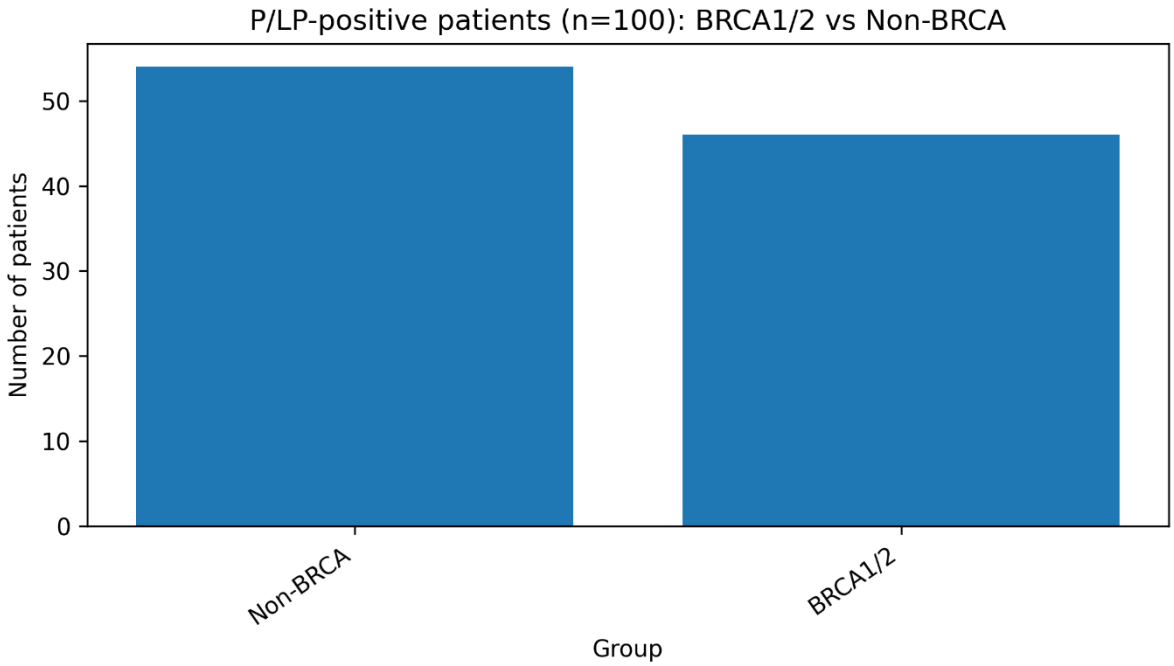
2. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424. doi:10.1038/gim.2015.30.

3. Kobayashi Y, Chen E, Facio FM, et al. Clinical Variant Reclassification in Hereditary Disease Genetic Testing. JAMA Netw Open. 2024;7(11):e2444526. doi:10.1001/jamanetworkopen.2024.44526.

4. **Table 1. Patient-level outcomes and key distributions in the cohort (n=600)**
5.
6. **Figure 1. Overall outcomes.**



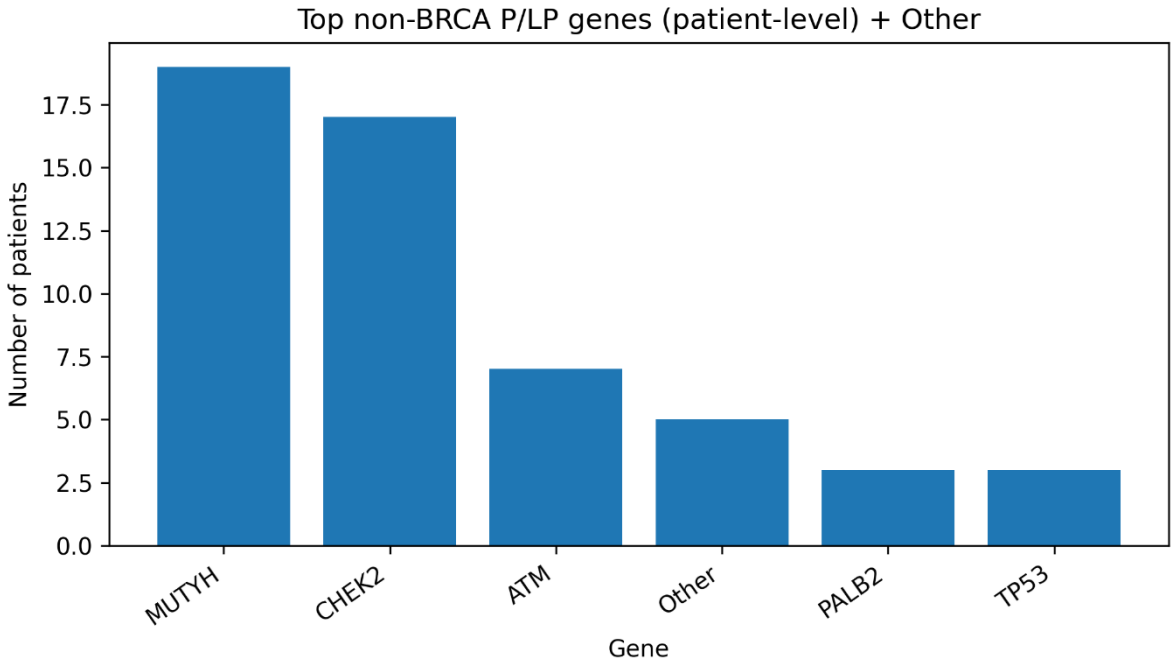
7.
8. *Overall patient-level outcomes: P/LP-positive (n=100), VUS-only (n=150), Negative (n=350).*
9. **Figure 2. BRCA1/2 vs non-BRCA among P/LP-positive patients.**



10.

11. *Distribution within P/LP-positive patients (n=100): BRCA1/2 (n=46) vs Non-BRCA (n=54).*

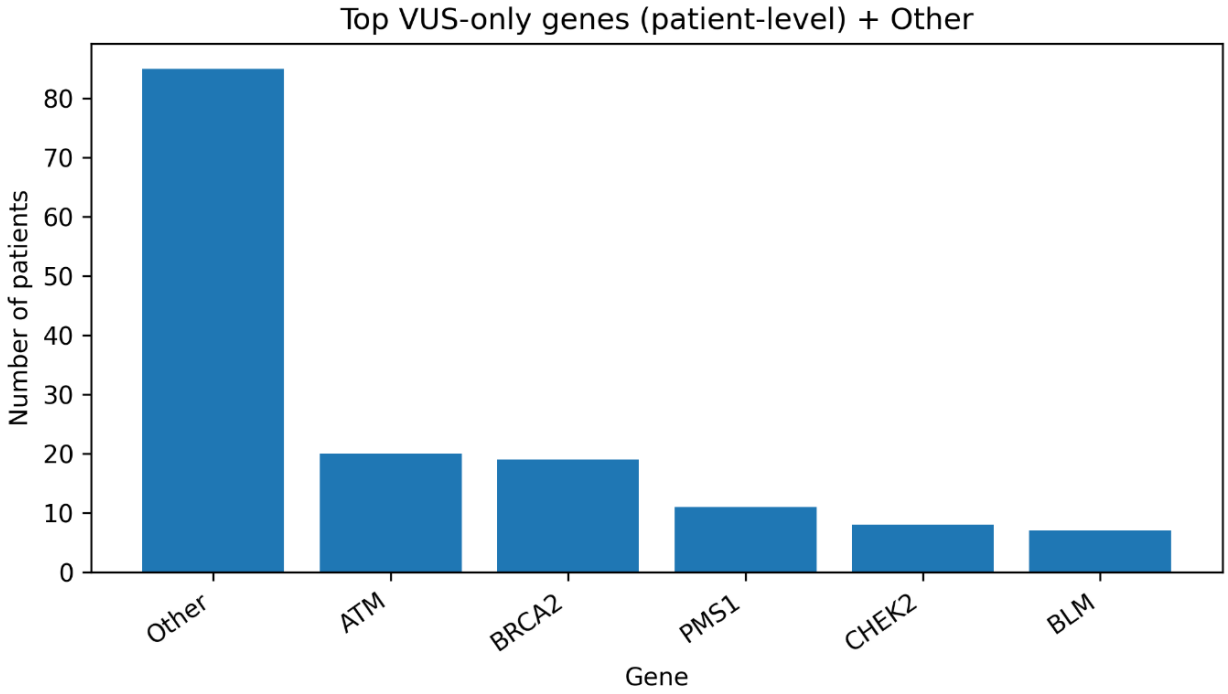
12. Figure 3. Top non-BRCA P/LP genes.



13.

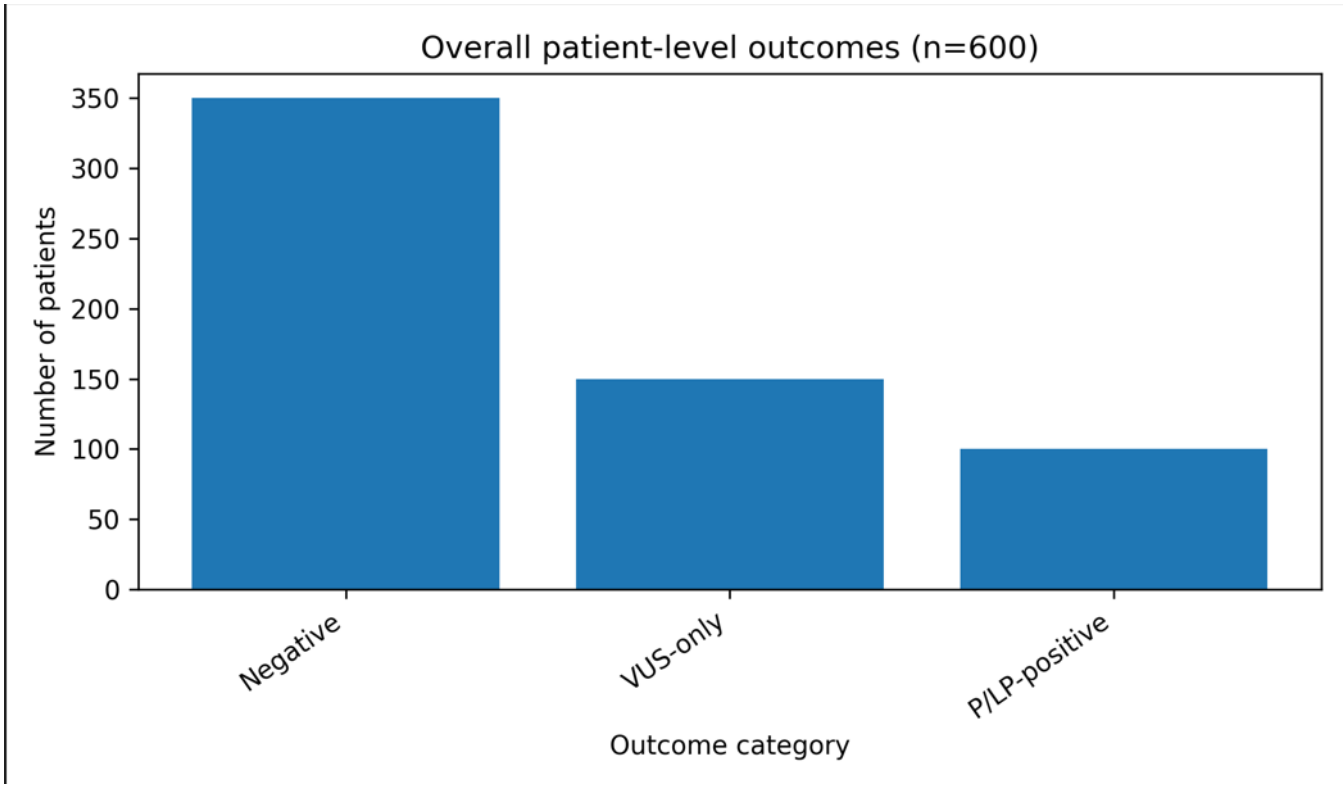
14. *Top non-BRCA P/LP genes (patient-level; total non-BRCA P/LP n=54) with closed-system 'Other' (n=5).*

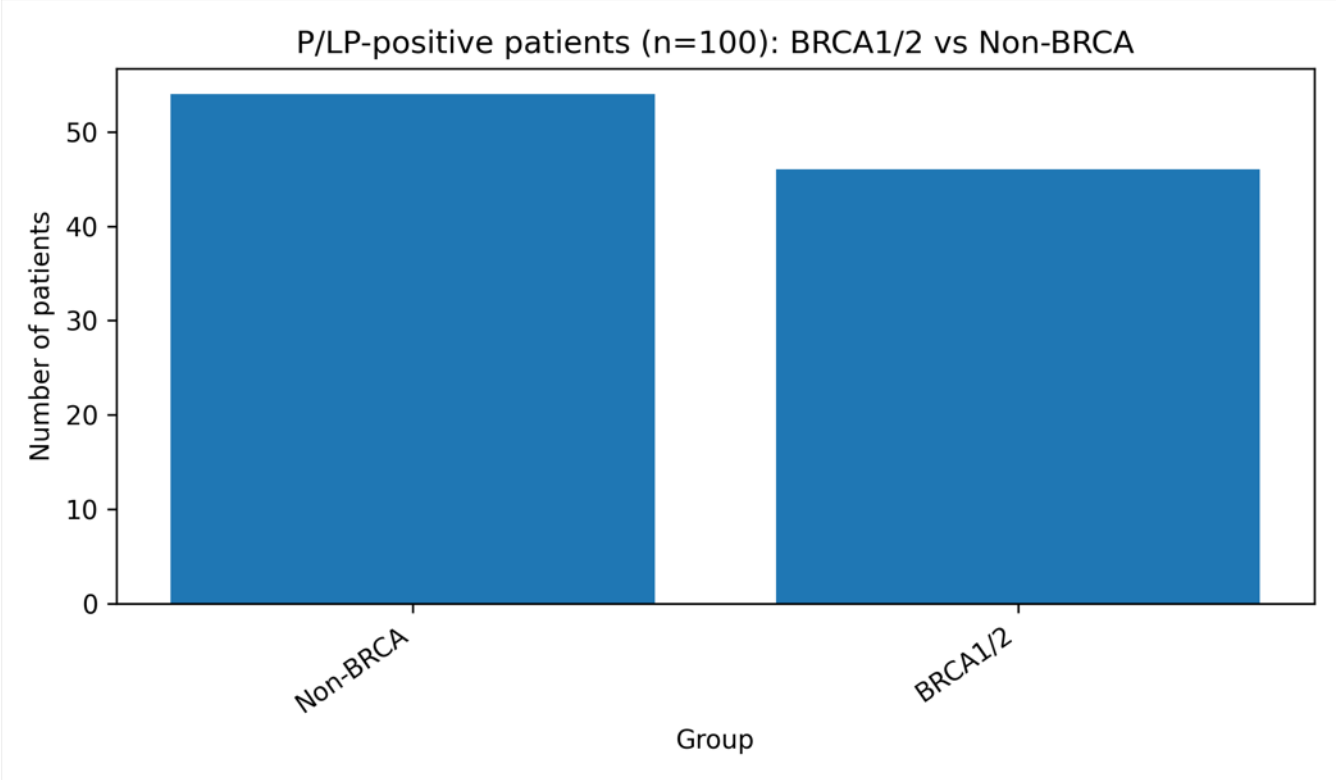
15. Figure 4. Top genes in the VUS-only group.

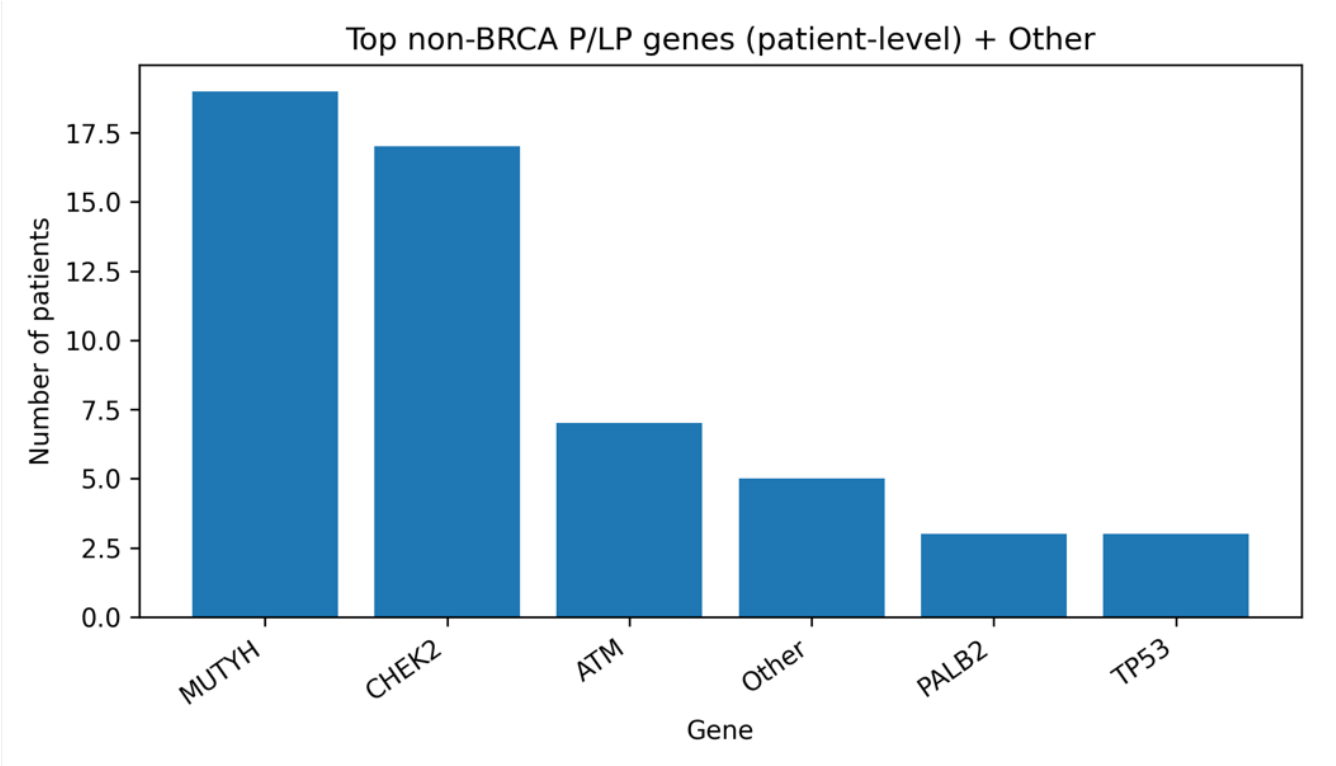


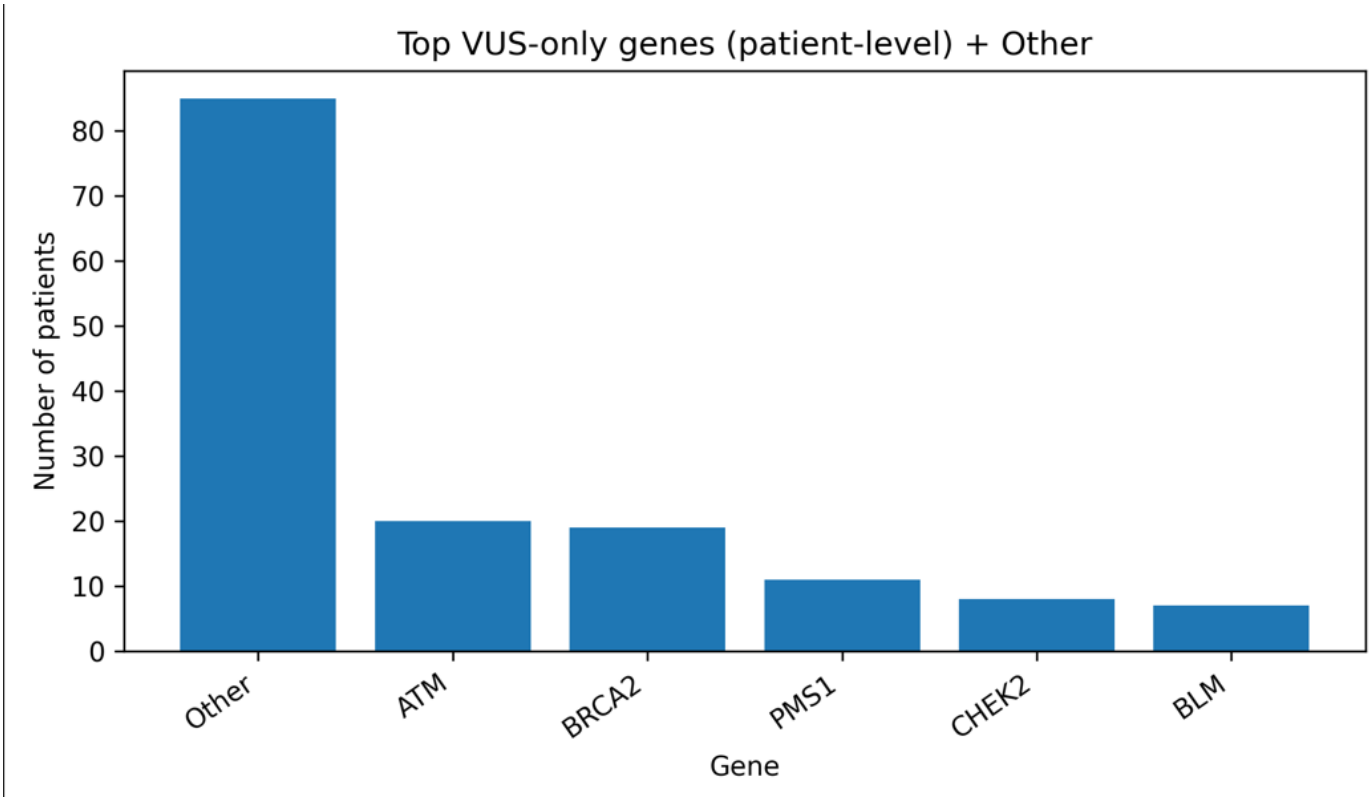
16.

17. *Top genes in the VUS-only group (patient-level; n=150) with closed-system 'Other' (n=85).*




P/LP-positive patients (n=100): BRCA1/2 vs Non-BRCA
Number of patients
0
10
20
30
40
50
Non-BRCA
BRCA1/2
Group


Top non-BRCA P/LP genes (patient-level) + Other
Number of patients
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
MUTYH
CHEK2
ATM
Other
PALB2
TP53
Gene


Top VUS-only genes (patient-level) + Other
Number of patients
0
10
20
30
40
50
60
70
80
Other
ATM
BRCA2
PMS1
CHEK2
BLM
Gene

[Abstract:0311]

Molecular Findings and Clinical Course of Patients With RAD51C/D Mutations

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Introduction: Accurate DNA repair and replication are essential for maintaining genomic stability and preventing carcinogenesis. RAD51 and its gene family play central roles in preserving DNA integrity through their involvement in homologous recombination (HR). As RAD51 paralogs, RAD51C and RAD51D function as key mediators of DNA double-strand break repair, and pathogenic alterations in these genes predispose individuals to hereditary breast and ovarian cancers. The aim of this study was to evaluate the molecular characteristics and clinical course of patients with RAD51C/D mutations.

Materials-Methods: In this retrospective study, 1,050 patients who presented to our clinic and underwent hereditary cancer panel testing between 2022 and 2026 were reviewed. Individuals carrying pathogenic/likely pathogenic variants and variants of uncertain significance (VUS) in the RAD51C and/or RAD51D genes were identified. Clinical characteristics were evaluated after genetic diagnosis using imaging modalities and oncological follow-up data.

Results: The study included 10 patients evaluated for hereditary breast and ovarian cancer (HBOC) who were found to have RAD51C and/or RAD51D variants. Among these patients, 6 were diagnosed with breast cancer and 4 with ovarian cancer. The mean age at diagnosis was 55 years. All patients were female, had a family history of various cancer types, and presented with metastatic disease at diagnosis.The most common histopathological subtype of breast cancer was invasive breast carcinoma of no special type (NST). All ovarian cancer cases were diagnosed as high-grade serous ovarian carcinoma.

Genetic analysis revealed RAD51D variants in 6 patients and RAD51C variants in 3 patients, while 1 patient carried variants in both RAD51C and RAD51D genes. Of the identified variants, 5 were classified as pathogenic or likely pathogenic, and 5 were categorized as variants of uncertain significance (VUS). The most frequent variant types were missense and nonsense mutations, followed by frameshift and synonymous variants.

Conclusion: This study highlights the clinical relevance of low-to-moderate penetrance non-BRCA mutations and supports the need for closer surveillance strategies in individuals with an increased predisposition to cancer. Moreover, as patients with RAD51C/D mutations may benefit from PARP inhibitor–based therapies, a better understanding of genotype–phenotype associations is likely to play an increasingly important role in the management of hereditary breast and ovarian cancers.

Keywords: Homologous Recombination (HR), PARP inhibitors, RAD51C, RAD51D

[Abstract:0312]

Spectrum of Malignancies Associated with Germline *MSH2* Variants: Clinical and Molecular Findings from a Single Center

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Background: Germline *MSH2* variants are a well-established cause of Lynch syndrome and are associated with a broad tumor spectrum, predominantly colorectal and endometrial carcinomas. This study aimed to describe the clinical, pathological, and molecular characteristics of patients carrying pathogenic *MSH2* variants identified over an eight-year period.
Methods: This retrospective study included 20 patients with germline *MSH2* variants identified between 2017 and 2025. All molecular genetic analyses had been previously performed as part of routine diagnostic workflows. Genomic DNA had been isolated using the ZeeSan Lab-Aid 824s Blood DNA Isolation Kit, followed by next-generation sequencing with the SOPHIA Custom Solution CHCS_C_V2 panel on the Illumina NovaSeq platform. Bioinformatic analyses had been completed using SOPHIA DDM software. For the purpose of this study, existing molecular results, immunohistochemical findings, and clinical data were retrospectively reviewed, and variant classifications were reassessed according to ACMG guidelines and ClinVar annotations.
Results: Among the cohort, 12 patients (60%) were diagnosed with colorectal carcinoma (CRC), including 8 males (67%) and 4 females (33%). The age at diagnosis ranged from 20 to 52 years. Immunohistochemical (IHC) analysis demonstrated combined loss of MSH2 and MSH6 expression in 9 of 12 tumors (75%), isolated MSH2 loss in 1 tumor (8%), while IHC was not performed in 2 cases (17%). All CRC patients harbored pathogenic *MSH2* variants previously reported in ClinVar, including frameshift (33%), nonsense (25%), and splice site (42%) variants. Notably, 80% of splice site variants corresponded to the recurrent c.942+3A>T alteration. Three patients (15%) were diagnosed with endometrial carcinoma at ages ranging from 42 to 55 years. All tumors showed combined loss of MSH2 and MSH6 expression. Two patients carried frameshift variants (67%) and one carried a missense variant (33%), all classified as pathogenic in ClinVar.
One female patient developed both colorectal and endometrial carcinomas at the age of 51; tumor IHC was unavailable, and a nonsense *MSH2* variant was identified. Another female patient was diagnosed with renal carcinoma at 57 years and signet ring cell CRC at 67 years; the colonic tumor demonstrated loss of MSH2 expression, and a germline frameshift *MSH2* variant was detected. Additionally, one patient with endometrioid ovarian carcinoma and one patient with pancreatic adenocarcinoma harbored pathogenic *MSH2* variants; both showed combined loss of MSH2 and MSH6 expression in tumor tissue. Finally, one patient was diagnosed with invasive lobular breast carcinoma at 56 years and carried a nonsense *MSH2* variant with conflicting ClinVar interpretations.
Conclusions: This cohort highlights the phenotypic diversity associated with pathogenic *MSH2* variants and underscores the importance of integrated clinical, immunohistochemical, and molecular evaluation in hereditary cancer syndromes. The presence of recurrent *MSH2* variants further suggests potential genotype-phenotype correlations and emphasizes the value of systematic variant aggregation in hereditary cancer diagnostics.
Keywords: IHC, Lynch, MMRd, MSH2

[Abstract:0316]

Evaluation of *BRIP1* Gene Variants in Hereditary Cancer Panel: A Single-Center Retrospective Study

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Objective: The *BRIP1* gene encodes a DNA helicase belonging to the DEAH-box helicase family (also known as *FANCJ*). It plays a critical role in maintaining genomic stability through DNA repair and chromosomal maintenance. *BRIP1* interacts directly with *BRCA1* and participates in the repair of double-strand DNA breaks via homologous recombination, thereby preventing the accumulation of DNA damage. Pathogenic variants in *BRIP1* impair these repair mechanisms, leading to genomic instability and an increased risk of cancer, particularly ovarian cancer and, to a lesser extent, breast cancer. As a DNA helicase, *BRIP1* is functionally related to other helicases involved in DNA replication, repair, and genome maintenance, highlighting its broader role in preserving cellular integrity. Evaluation of *BRIP1* in hereditary cancer panels is clinically important, as identification of pathogenic variants enables personalized risk assessment, targeted surveillance, and informed genetic counseling.

Materials and Methods: This study included patients referred for hereditary cancer screening to the Department of Medical Genetics at Basaksehir Cam and Sakura City Hospital between 2021 and 2025. Genomic DNA was isolated from peripheral blood samples, and patients underwent hereditary cancer panel testing using Next-Generation Sequencing (NGS). Variant interpretation and classification were performed according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Results: A total of 50 patients in the cohort were found to carry *BRIP1* variants. Among these, 11 variants were classified as pathogenic, 1 as likely pathogenic, and 38 as variants of uncertain significance (VUS). Of the 11 patients with pathogenic variants, 8 had breast cancer, 2 had pancreatic cancer, and 1 had ovarian cancer. The patient carrying a likely pathogenic variant had prostate cancer.

Conclusion: Our study presents five-year data on ***BRIP1*** variants detected in patients who underwent hereditary cancer panel testing at our center, aiming to contribute to the existing literature on the role of the ***BRIP1*** gene in hereditary cancer predisposition.
Keywords: *BRIP1*, Hereditary Cancer, NGS

[Abstract:0320]

Clinical Significance of MUTYH Variants, Zygosity and Genotype-Phenothype Relationship

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Objective: To define the zygosity distribution of germline MUTYH variants identified by multigene panel testing (MGPT) in a large hereditary cancer cohort and to compare clinical features between biallelic and monoallelic variant carriers, with particular attention to referral cancer types.

Materials-Methods: To define the zygosity distribution of germline MUTYH variants identified by multigene panel testing (MGPT) in a large hereditary cancer cohort and to compare clinical features between biallelic and monoallelic variant carriers, with particular attention to referral cancer types.

Results: Germline MUTYH variants were detected in 98 of the 3,207 patients (3.06%), including 77 pathogenic/likely pathogenic (P/LP) variants (78.6%) and 21 variants of uncertain significance (VUS) (21.4%). Biallelic MUTYH variants were identified in 13 patients (9 homozygous, 4 compound heterozygous) (13.3%), and most exhibited a phenotype consistent with MUTYH-associated polyposis (MAP) (colorectal polyposis and/or early-onset colorectal carcinoma). The remaining 85 individuals (86.7%) were monoallelic carriers. Among monoallelic carriers, the most common referral diagnosis with 41 patient was breast cancer (48.2%), followed by 17 patient with colorectal cancer (20.0%) and 12 patient with ovarian cancer (14.1%). Ten monoallelic carriers (11.8%) were unaffected at the time of testing and underwent evaluation due to family history hereditary malignancy; the remainder had diverse malignancies (e.g., gastric, pancreatic, renal).

Conclusion: Our cohort demonstrates two clinically distinct contexts for MUTYH findings in MGPT. Biallelic carriers showed a highly penetrant colorectal polyposis/CRC phenotype consistent with MAP. In contrast, monoallelic findings were frequently observed in individuals tested for non-colorectal indications, particularly breast cancer. The clinical management of monoallelic carriers should avoid overemphasizing causality for breast cancer, but it should be considered, and prioritize colorectal risk assessment and tailored screening based on personal/family history and existing guidelines.

Keywords: MUTYH, MUTYH-associated polyposis, multigene panel testing, zygosity

[Abstract:0323]

Reclassification of Variants in a Hereditary Cancer Gene Panel: A Three-Year Follow-Up Study of 100 Patients

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Background:
Genetic variant classification is a dynamic process that evolves with the accumulation of new functional, population, and clinical evidence. Variants detected in hereditary cancer gene panels may be reclassified over time, potentially impacting clinical interpretation and patient management.
Methods: We retrospectively reviewed genetic test results from 100 patients who underwent hereditary cancer multigene panel testing. All variants were initially classified according to the American College of Medical Genetics and Genomics (ACMG) criteria at the time of testing. After approximately three years, variants were re-evaluated using updated databases, current literature, and revised ACMG guidelines. Changes in variant classification were recorded and analyzed.
Results: Among the 100 patients who underwent hereditary cancer multigene panel testing, variant re-evaluation after approximately three years revealed classification changes in 16 patients. All reclassified variants had initially been reported as Variants of Uncertain Significance (VUS). Of these, 10 variants were downgraded from VUS to likely benign, while 6 variants were upgraded to likely pathogenic/pathogenic based on updated population data, functional evidence, and revised ACMG criteria. Variants downgraded to likely benign were mainly synonymous or intronic changes and included APC c.3012T>C (p.Tyr1004=), MLH1 c.775T>C (p.Leu259=), PMS2 c.1170G>A (p.Ala390=) identified in two patients, STK11 c.42G>A (p.Glu14=), MSH6 c.4001+11_4001+15dup, POLH c.273-5C>T, and POLH c.2007A>G (p.Ser669=). In contrast, variants upgraded to likely pathogenic/pathogenic were predominantly missense variants, including CHEK2 c.1556C>T (p.Thr519Met) and c.678G>C (p.Leu226Phe), TP53 c.745A>G (p.Arg249Gly), ERCC2 c.2047C>T (p.Arg683Trp), PTEN c.409G>T (p.Ala137Ser), and XPA c.731A>G (p.His244Arg) identified in two patients. Additionally, one splice-site variant in GALNT12 (c.1035+1G>A) was reclassified from likely pathogenic to VUS due to conflicting evidence in updated databases. Overall, although variant reclassification affected a minority of the cohort, these changes had potential implications for clinical management, surveillance strategies, and family counseling.
Conclusion: Our findings highlight the clinical importance of periodic re-analysis of hereditary cancer panel results. Variant reclassification over time is not uncommon and may significantly influence patient management. Systematic follow-up and re-evaluation should be integrated into routine genetic counseling and clinical genetics practice to ensure accurate and up-to-date interpretation of genomic data.

Keywords: Hereditary cancer, variant reclassification, ACMG guidelines, multigene panel, VUS

AWARD-NOMINATED ORAL PRESENTATIONS

[Abstract:0106]

Applying the 2025 ACMG Clinical Practice Resource to RAD51C, RAD51D, and BRIP1: Insights from a Real-World Cohort

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Objective: *RAD51C, RAD51D*, and *BRIP1* are components of the homologous recombination DNA repair pathway and are classified as moderate-penetrance cancer susceptibility genes. Heterozygous pathogenic variants in these genes are primarily associated with ovarian cancer risk, while associations with other malignancies, particularly breast cancer, vary by gene and remain incompletely defined. In October 2025, the American College of Medical Genetics and Genomics (ACMG) published updated clinical practice recommendations for cancer risk assessment and genetic counselling for carriers of pathogenic variants in these genes. Real-world data applying these recommendations are limited. The objective of this study was to describe the clinical and genetic characteristics of patients with pathogenic or likely pathogenic variants in *RAD51C, RAD51D,* and *BRIP1*, and to assess the implications of the 2025 ACMG guidelines on genetic counselling.
Materials-Methods: We retrospectively identified carriers of pathogenic or likely pathogenic variants in *RAD51C, RAD51D*, and *BRIP1* from a cohort of approximately 8,000 individuals referred for hereditary cancer multigene panel testing between October 2022 and October 2025. Genomic DNA from peripheral blood samples was analysed using next-generation sequencing on the Illumina NextSeq 2000 platform with a targeted hereditary cancer panel (SOPHiA Genetics). Variant interpretation was performed using the SOPHiA DDM platform in accordance with ACMG/AMP 2015 criteria and ClinGen recommendations. Clinical data including cancer diagnosis, age at diagnosis, sex, and family history were collected. Individuals with variants of uncertain significance were excluded. The 2025 ACMG clinical practice resource was used to reassess genetic counselling recommendations.
Results: A total of 45 unrelated individuals (40 females and 5 males) carrying pathogenic or likely pathogenic variants in *RAD51C, RAD51D*, or *BRIP1* were included. Variants were identified in *RAD51C* (n = 13), *RAD51D* (n = 15), and *BRIP1* (n = 17). Genetic testing was performed due to a personal history of cancer in 39 individuals, while 6 were tested based on family history alone. Individuals tested solely for family history were excluded from age calculations, yielding a mean age at cancer diagnosis of 56 years. Ovarian cancer was the most frequent malignancy (n = 21), followed by breast cancer (n = 13). Other malignancies included colorectal cancer (n = 2), cholangiocellular carcinoma (n = 1), pancreatic cancer (n = 1), and prostate cancer (n = 1). An additional pathogenic variant in a different hereditary cancer predisposition gene was identified in 5 patients.
Conclusion: Pathogenic variants in *RAD51C, RAD51D*, and *BRIP1* were predominantly associated with ovarian cancer, supporting their classification as moderate-penetrance ovarian cancer susceptibility genes. Breast cancer was observed across all gene groups, including *BRIP1* carriers; however, in accordance with the 2025 ACMG recommendations, this finding should not be interpreted as evidence of a causal association. These results emphasize the importance of distinguishing cohort-level cancer frequencies from evidence-based gene–cancer associations in genetic counselling. Identification of additional pathogenic variants highlights the complexity of hereditary cancer risk assessment and the value of multigene panel testing. Overall, application of the updated

ACMG recommendations enabled more precise and conservative genetic counselling, supporting individualized risk assessment while minimizing the risk of overtreatment.

Keywords: *BRIP1*, cancer predisposition, genetic counselling, *RAD51C*, *RAD51D*

Applying the 2025 ACMG Clinical Practice Resource to RAD51C, RAD51D, and BRIP1: Insights from a Real-World Cohort Introduction RAD51C, RAD51D, and BRIP1 encode proteins involved in the homologous recombination DNA repair pathway and are classified as moderate-penetrance cancer susceptibility genes. Heterozygous pathogenic variants in these genes are primarily associated with increased ovarian cancer risk, while associations with other malignancies-particularly breast cancer- vary by gene and remain incompletely defined. In contrast to high-penetrance genes like BRCA1 and BRCA2, these genes exhibit difficulties for clinical interpretation due to their intermediate risk levels and varied cancer patterns. In October 2025, the American College of Medical Genetics and Genomics (ACMG) published updated clinical practice recommendations focusing on cancer risk assessment and genetic counselling for carriers of pathogenic variants in RAD51C, RAD51D, and BRIP1. These guidelines stress the importance of gene-specific risk attribution based on evidence and warn against using management strategies from hereditary cancer syndromes with high penetrance. However, data illustrating how these recommendations translate into real-world clinical cohorts remain limited. Materials and Methods We retrospectively identified carriers of pathogenic or likely pathogenic variants in RAD51C, RAD51D, and BRIP1 from a cohort of approximately 8,000 individuals referred for hereditary cancer multigene panel testing between October 2022 and October 2025. Genomic DNA extracted from peripheral blood samples was analysed using next-generation sequencing on the Illumina NextSeq 2000 platform with a targeted hereditary cancer panel (SOPHiA Genetics). Variant interpretation was performed using the SOPHiA DDM platform in accordance with ACMG/AMP 2015 criteria and ClinGen gene-specific recommendations. Clinical data, including cancer diagnosis, age at diagnosis, sex, and family history, were collected retrospectively from medical records. Individuals with variants of uncertain significance were excluded. The 2025 ACMG clinical practice resource provided the foundation for reevaluating genetic counselling and management guidelines. To avoid over-representation of familial variants, only unrelated individuals were included in the final analysis. Results A total of 45 unrelated individuals carrying pathogenic or likely pathogenic variants in RAD51C, RAD51D, or BRIP1 were included in this study. The cohort comprised 40 females and 5 males. Variants were identified in RAD51C in 13 individuals, RAD51D in 15, and BRIP1 in 17. Genetic testing was performed due to a personal cancer history in 39 individuals, whereas 6 were tested exclusively based on familial history. Individuals tested due to family history alone were excluded from age calculations. Among patients with a cancer diagnosis, the mean age at diagnosis was 56 years. Ovarian cancer was the most frequent malignancy, observed in 21 individuals, followed by breast cancer in 13. Less common malignancies included colorectal cancer (2), cholangiocellular carcinoma (1), pancreatic cancer (1), and prostate cancer (1). Ovarian cancer represented the dominant phenotype across all three gene groups. Family history of cancer was absent in 10 individuals, unavailable in 14, and present in the remaining 21 patients. Multigene panel testing identified an additional pathogenic variant in a different hereditary cancer predisposition gene in 5 individuals, underscoring the genetic complexity within this population. Among RAD51C carriers (n = 13), ovarian cancer was observed in 7 individuals with a mean age at diagnosis of 60 years, while breast cancer was observed in 3 individuals with a mean age of 51 years. One individual was diagnosed with pancreatic cancer at 41 years of age, and one male individual with prostate cancer at 58 years; the latter also harboured a pathogenic variant in ATM. Most variants identified in this gene were loss-of-function variants, with 9 null variants and 4 missense variants observed. Also, two novel variants are detected in RAD51C gene: c.83del and c.763del. Among RAD51D carriers (n = 15), ovarian cancer was observed in 8 individuals with a mean age at diagnosis of 63 years; one of these individuals was also diagnosed with melanoma. Breast cancer was observed

in 4 individuals with a mean age at diagnosis of 41 years. One individual was diagnosed with cholangiocellular carcinoma at 49 years of age. Two individuals had no personal history of cancer and were tested based on family history; one of these also carried a pathogenic variant in BRCA1 and had a maternal history of ovarian cancer diagnosed at 45 years. All variants identified in RAD51D were predicted loss-of-function variants. The c.423del variant was identified in 4 unrelated individuals, 2 of whom originated from the Hatay region, 1 from Azerbaijan, and 1 from Istanbul. The c.540+1G>A variant was observed in 3 unrelated individuals, 2 of whom were from the Central Black Sea region. The c.616C>T variant was identified in 2 unrelated individuals from Ankara. We also detect four novel variants in RAD51D gene: c.323+1G>T, c.43del, c.404dup, and c.201del. Among BRIP1 carriers (n = 17), 14 individuals had a personal history of cancer, with a mean age at diagnosis of 59 years. Ovarian cancer was observed in 6 individuals with a mean age at diagnosis of 69 years; one of these individuals was also diagnosed with endometrial cancer. Breast cancer was observed in 6 individuals with a mean age at diagnosis of 43.8 years. Two male individuals were diagnosed with colorectal cancer, both of whom also had a family history of colorectal cancer. Sixteen variants identified in this gene were predicted loss-of-function variants, and interestingly one was an exonic deletion consistent with a copy number variant (CNV). We also detect a novel BRIP1:c.2576-1G>C variant. Discussion: In this real-world cohort, pathogenic variants in RAD51C, RAD51D, and BRIP1 were predominantly associated with ovarian cancer, supporting their classification as moderate penetrance ovarian cancer susceptibility genes. The observed age distribution, indicating that the majority of ovarian cancer diagnoses occur post-50 years, aligns with current penetrance estimates and endorses guideline-recommended timing for risk-reducing salpingo oophorectomy. Breast cancer was observed across all three gene groups, including among BRIP1 carriers; however, in accordance with the 2025 ACMG clinical practice recommendations, this finding should not be interpreted as evidence of a causal association, particularly for BRIP1. This emphasizes the importance of distinguishing cohort-level cancer frequencies from evidence based gene–cancer associations in genetic counselling and clinical decision-making. The predominance of loss-of-function variants across all three genes, together with the identification of recurrent variants in unrelated individuals and regional clustering of certain RAD51D variants, highlights the genetic heterogeneity and potential population-specific patterns within this cohort, while highlighting the need for cautious interpretation in the absence of formal founder analyses. The discovery of additional pathogenic variants in a subset of patients highlights the complexities of hereditary cancer risk assessment and underscores the importance of multigene panel testing combined with structured, guideline-driven interpretation. Individualised evaluation, as opposed to gene-based risk projection, is further supported by the incidence of colorectal cancer in male BRIP1 carriers with a positive family history. Finally, the observation of non-ovarian malignancies, including colorectal, pancreatic, cholangiocellular, and prostate cancers, reflects the heterogeneity encountered in clinical practice but should be interpreted cautiously in the absence of strong epidemiological evidence for gene-specific associations. Overall, the application of the 2025 ACMG clinical practice resource enabled more precise and conservative genetic counselling by shifting practice from generalization based on high penetrance genes to gene-specific and individualized risk assessment. Further research is needed to refine penetrance estimates, clarify population-specific patterns, and improve personalized risk prediction.

[Abstract:0111]

Real-World Evidence for a Multi-Cancer Early Detection Test Based on Multimodal Analysis of Cell-Free DNA Across Asia

Dang Luu Hong Nguyen[1], Minh Ngoc Phan[1], Thuy Phuong Le[1], Nhu Khanh Huynh[1], Anh Thi Minh Nguyen[1], Nguyen Hong Bao Vu[1], Trinh Viet Ngo[1], Uyen Vu Tran[2], Phong Minh Le[2], Van Thi Phan[3], Tien Chi Thuy Cao[3], Chi Van Thien Nguyen[4], Ho Dac Vo[4], Luyen Thi Vu[4], Dat Thanh Nguyen[5], Nhat Duy Nguyen[5], Hoa Giang[5], Duy Minh Phan[5], Nghia Hoai Nguyen[4], Son Le Tran[4], Sang Hung Tang[1], Sinh Duy Nguyen[1]

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Objective: Multi-cancer early detection (MCED) represents an important shift from single-organ screening toward the simultaneous detection of multiple cancers, including those with and without established standard-of-care (SOC) screening options. We developed the SPOT-MAS assay, which integrates multimodal analyses of circulating tumor DNA (ctDNA) epigenetic, fragmentomic, and genetic features to detect signals from 10 cancer types. The performance of SPOT-MAS was subsequently validated in the multicenter prospective K-DETEK study (Clinical trial identification: NCT05227261). However, translation of this assay into routine clinical practice introduces substantially greater heterogeneity and complexity than controlled clinical trial settings. In this study, we present real-world data (RWD) and clinical experience from six Asian countries to evaluate the robustness and clinical applicability of SPOT-MAS in a diverse, unselected population.

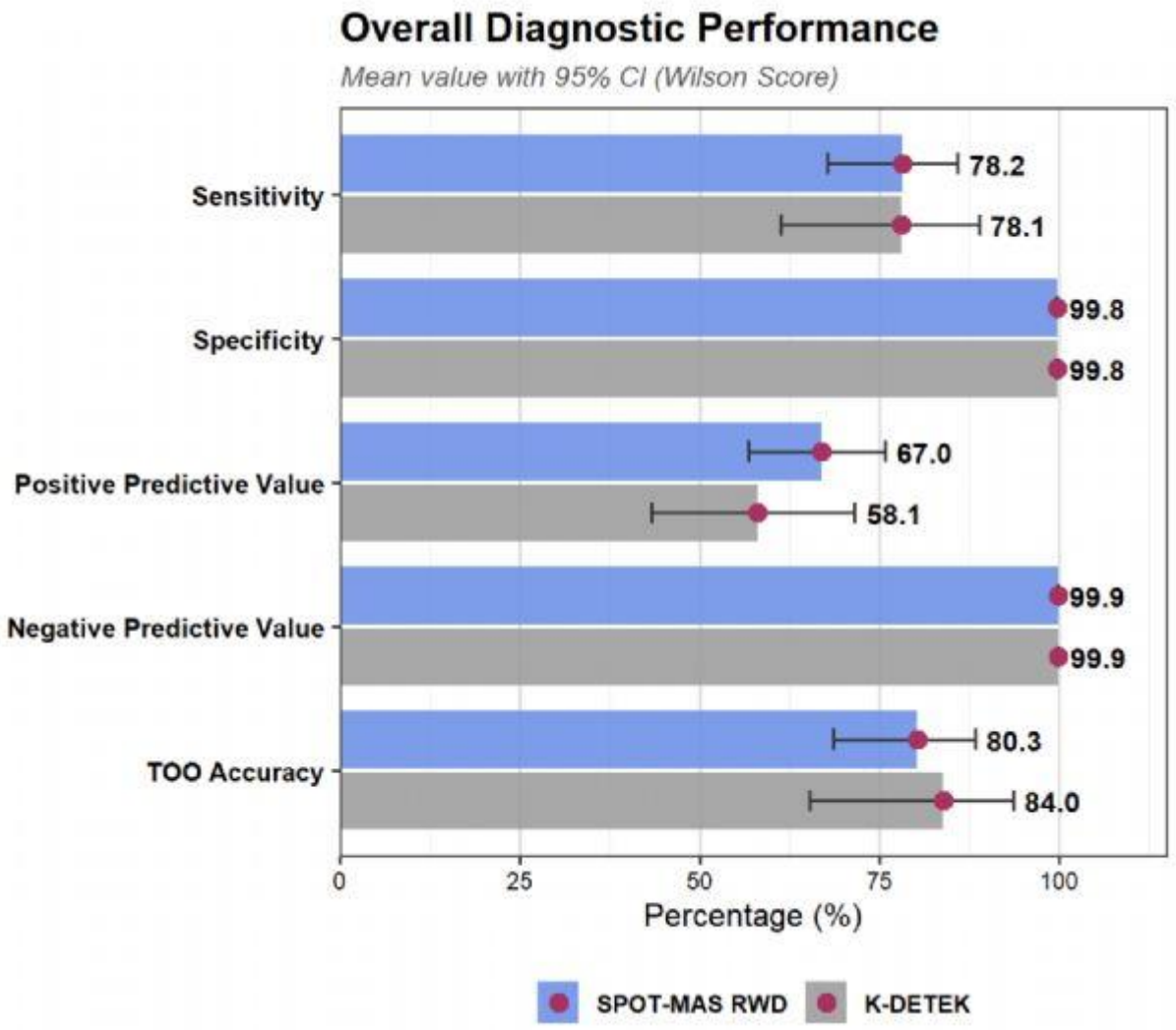
Materials-Methods: From over 36,000 recruited individuals, we analyzed a final cohort of 12,281 asymptomatic participants who completed the mandatory 12-month follow-up. The SPOT-MAS test was administered to all participants to detect cancer signals and predict tumor tissue of origin (TOO). Participants with positive results underwent diagnostic workup in accordance with our previously published post-test consultation protocol. Diagnostic performance and TOO prediction accuracy were evaluated using diagnostic imaging and/or tissue biopsy as the reference standard.

Results: The SPOT-MAS test identified 91 positive cases (0.74%). Among these, 61 participants had precancerous lesions or invasive cancers across nine cancer types, five of which lack SOC screening.. The SPOT-MAS test demonstrated performance comparable to the K-DETEK trial, with a sensitivity of 78.2% (61/78), specificity of 99.8% (12,173/12,203), negative predictive value (NPV) of 99.9% (12,173/12,190), positive predictive value (PPV) of 67.0% (61/90), and TOO prediction accuracy of 80.3%.

Conclusion: To the best of our knowledge, this is the first large-scale real-world study conducted across Asia to consistently demonstrate the clinical utility of a MCED test in a complex clinical setting, distinct from controlled trial environments. By enabling the detection of both precancerous lesions and invasive cancers, including those without SOC screening programs, the SPOT-MAS test may serve as a complementary cancer screening tool.

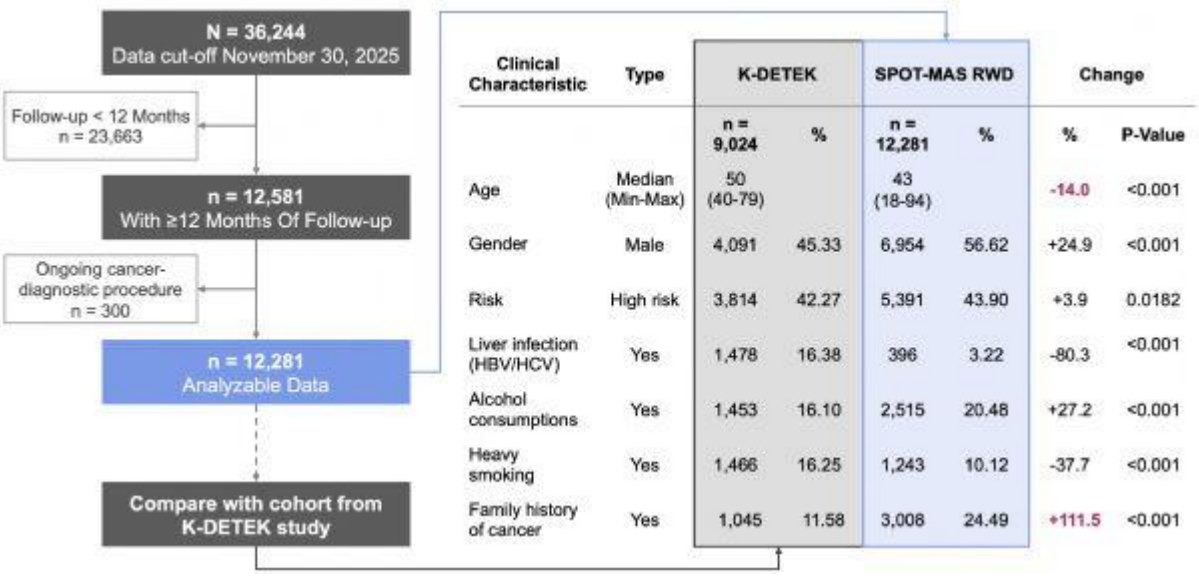
Keywords: Multi-cancer early detection, Liquid biopsy, Cell-free DNA, Real-world evidence, SPOT-MAS

Overall Diagnostic Performance of the SPOT-MAS Assay in a Real-World Setting Compared to the K-DETEK Study



This figure compares key performance metrics between the two cohorts. While sensitivity (78.2%) and specificity (99.8%) remained highly consistent with previous findings, the Positive Predictive Value (PPV) showed a notable increase in the real-world setting, rising to 67.0% compared to 58.1% in the K-DETEK study. This improvement underscores the assay's reliability in a diverse, unselected population.

Participant Selection Flowchart and Comparison of Clinical Characteristics Between the K-DETEK and Real-World Data (RWD) Cohorts



Clinical Characteristic	Type	K-DETEK		SPOT-MAS RWD		Change	
		n = 9,024	%	n = 12,281	%	%	P-Value
Age	Median (Min-Max)	50 (40-79)		43 (18-94)		-14.0	<0.001
Gender	Male	4,091	45.33	6,954	56.62	+24.9	<0.001
Risk	High risk	3,814	42.27	5,391	43.90	+3.9	0.0182
Liver infection (HBV/HCV)	Yes	1,478	16.38	396	3.22	-80.3	<0.001
Alcohol consumptions	Yes	1,453	16.10	2,515	20.48	+27.2	<0.001
Heavy smoking	Yes	1,466	16.25	1,243	10.12	-37.7	<0.001
Family history of cancer	Yes	1,045	11.58	3,008	24.49	+111.5	<0.001

This figure illustrates the data filtering process from N=36,244 recruited individuals down to the final analyzable cohort of n=12,281. It also compares key demographics (Age, Gender) and risk factors (Liver infection, Smoking, Family history) between the retrospective K-DETEK study and the current RWD study.

Real-World Evidence for a Multi-Cancer Early Detection Test Based on Multimodal Analysis of Cell-Free DNA Across Asia Dang Luu Hong Nguyen1, Minh Ngoc Phan1, Thuy Phuong Le1, Nhu Khanh Huynh1, Anh Thi Minh Nguyen1, Nguyen Hong Bao Vu1, Trinh Viet Ngo1, Uyen Vu Tran2, Phong Minh Le2, Van Thi Phan3, Tien Chi Thuy Cao3, Chi Van Thien Nguyen4, Ho Dac Vo4, Luyen Thi Vu4, Dat Thanh Nguyen5, Nhat Duy Nguyen5, Hoa Giang5, Duy Minh Phan5, Nghia Hoai Nguyen4, Son Le Tran4, Sang Hung Tang1, Sinh Duy Nguyen1 1Medical Department, Medical Genetics Institute, Ho Chi Minh City, Vietnam 2Laboratory Department, Medical Genetics Institute, Ho Chi Minh City, Vietnam; Laboratory Department, Gene Solutions, Ho Chi Minh City, Vietnam 3Clinical Trial Department, Medical Genetics Institute, Ho Chi Minh City, Vietnam; Clinical Trial Department, Gene Solutions, Ho Chi Minh City, Vietnam 4R&D Department, Medical Genetics Institute, Ho Chi Minh City, Vietnam; R&D Department, Gene Solutions, Ho Chi Minh City, Vietnam 5Data Department, Medical Genetics Institute, Ho Chi Minh City, Vietnam; Data Department, Gene Solutions, Ho Chi Minh City, Vietnam Objective: Multi-cancer early detection (MCED) represents an important shift from single-organ screening toward the simultaneous detection of multiple cancers, including those with and without established standard-of-care (SOC) screening options. We developed the SPOT-MAS assay, which integrates multimodal analyses of circulating tumor DNA (ctDNA) epigenetic, fragmentomic, and genetic features to detect signals from 10 cancer types. The performance of SPOT-MAS was subsequently validated in the multicenter prospective K-DETEK study (Clinical trial identification: NCT05227261). However, translation of this assay into routine clinical practice introduces substantially greater heterogeneity and complexity than controlled clinical trial settings. In this study, we present real-world data (RWD) and clinical experience from six Asian countries to evaluate the robustness and clinical applicability of SPOT-MAS in a diverse, unselected population. Materials-Methods: From over 36,000 recruited individuals, we analyzed a final cohort of 12,281 asymptomatic participants who completed the mandatory 12-month follow-up. The SPOT-MAS test was administered to all participants to detect cancer signals and predict tumor tissue of origin (TOO). Participants with positive results underwent diagnostic workup in accordance with our previously published post-test consultation protocol. Diagnostic performance and TOO prediction accuracy were evaluated using diagnostic imaging and/or tissue biopsy as the reference standard. Results: The SPOT-MAS test identified 91 positive cases (0.74%). Among these, 61 participants had precancerous lesions or invasive

cancers across nine cancer types, five of which lack SOC screening. The SPOT-MAS test demonstrated performance comparable to the K-DETEK trial, with a sensitivity of 78.2% (61/78), specificity of 99.8% (12,173/12,203), negative predictive value (NPV) of 99.9% (12,173/12,190), positive predictive value (PPV) of 67.0% (61/90), and TOO prediction accuracy of 80.3%. Conclusions: To the best of our knowledge, this is the first large-scale real-world study conducted across Asia to consistently demonstrate the clinical utility of a MCED test in a complex clinical setting, distinct from controlled trial environments. By enabling the detection of both precancerous lesions and invasive cancers, including those without SOC screening programs, the SPOT-MAS test may serve as a complementary cancer screening tool. Keywords: Multi-cancer early detection, Liquid biopsy, Cell-free DNA, Real-world evidence, SPOT-MAS

[Abstract:0112]

Germline Cancer Predisposition in Childhood Solid Tumors: Diagnostic Yield and Clinical Characteristics in a Single-Center Multigene Panel Cohort

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Objective: A significant proportion of pediatric cancers, especially childhood solid tumors, have underlying germline pathogenic/likely pathogenic (P/LP) variants in cancer predisposition genes. Large next-generation sequencing based cohorts generally report detection rates of 7–15%, rising to 18% in some comprehensive genomic approaches. In this context, various referral criteria have been defined, primarily based on Jongmans criteria, with the aim of guiding children toward genetic counseling and germline testing based on tumor type and age, multiple primaries, family history, unusual treatment toxicity and syndromic features. This study aimed to characterize the diagnostic yield and gene spectrum of germline P/LP variants detected by a multigene childhood cancer predisposition panel, and to describe the clinical and familial features of germline variant carriers.

Materials-Methods: Personal and clinical data, family history and genetic test results of 94 pediatric patients evaluated for suspected childhood cancer predisposition and tested using a germline multigene panel were retrospectively reviewed.

Results: P/LP germline variants were identified in 20/94 patients. Clinically significant P/LP variants were detected in 13 patients (13.8%), whereas 7 had findings classified as carrier status/secondary findings. Among clinically significant variant carriers with a confirmed malignancy, the age at first diagnosis ranged from 0–15 years. The distribution of clinically significant P/LP variants was most frequently observed in *TP53* and *APC*, followed by *RB1* and *PMS2*, with single cases observed in *CREBBP*, *MLH1*, *CDKN2A*, *CDC73*, and *SMARCB1*. Two patients harbored germline P/LP variants in two distinct cancer susceptibility genes, one in *MLH1* and *CDKN2A* and the other in *TP53* and *APC*. Family history data were available for 11 of the 13 patients, of whom 9 reported a positive family history of cancer and two reported none. Two of the 20 P/LP variant carriers were referred based solely on a positive family history and had no personal history of malignancy; therefore, they were not eligible for assessment using the Jongmans criteria. All remaining carriers with confirmed cancer fulfilled at least one Jongmans criterion.

Conclusion: The detection yield of germline testing in our cohort appears broadly consistent with rates reported in comparable pediatric solid tumor series; however, the limited sample size and referral bias warrant cautious interpretation. Molecular diagnosis of germline cancer predisposition in a child with a solid tumor is essential to guide individualized management, including risk-adapted surveillance and avoidance of syndrome-associated treatment toxicity; while enabling accurate risk assessment and cascade testing for family members, particularly when biallelic conditions are identified. Notably, identification of P/LP-positive individuals referred solely on family history despite no personal cancer diagnosis in our cohort highlights a limitation of diagnosis-based referral tools, such as the Jongmans criteria. Moreover, the high prevalence of consanguineous marriages in Türkiye may limit the specificity of family history when these tools are used for referral decision. Published data from our country on germline cancer predisposition in pediatric cancers are largely limited to case reports and

tumor- or syndrome-focused series. Therefore, this study contributes to the literature by providing additional cohort-level evidence.

Keywords: Genetic counselling, Germline cancer predisposition, Jongmans criteria, Pediatric solid tumors
Germline Cancer Predisposition in Childhood Solid Tumors: Diagnostic Yield and Clinical Characteristics in a Single-Center Multigene Panel Cohort Ezgi Çevik Demir1, Şule Yeşil2, Fatma Tuba Yıldırım2, Afife Büke1, Abdullah Sezer1, Elifcan Taşdelen1, Haktan Bağış Erdem1 1Ankara Etlik City Hospital, Department of Medical Genetics, Ankara, Türkiye 2Ankara Etlik City Hospital, Department of Pediatric Oncology, Ankara, Türkiye Short Abstract Pediatric solid tumors frequently reflect an underlying germline cancer predisposition. We retrospectively analyzed 94 children evaluated for suspected predisposition who underwent multigene germline panel testing. P/LP variants were detected in 20/94 patients, including 13/94 (13.8%) clinically significant findings relevant to phenotype and management; seven were recorded as carrier status/secondary findings. Clinically significant variants most frequently observed in TP53 and APC, followed by RB1 and PMS2, with single cases in CREBBP, MLH1, CDKN2A, CDC73, and SMARCB1. Two patients harbored P/LP variants in two distinct susceptibility genes: MLH1 and CDKN2A, TP53 and APC. Two P/LP-positive individuals were referred solely due to family history without personal malignancy and were not assessable by Jongmans criteria, while all remaining carriers with cancer met at least one criterion. Overall yield was comparable to pediatric solid-tumor series, supporting the clinical utility of germline diagnosis for individualized management, risk-adapted surveillance, and cascade testing. Diagnosis-based referral tools can under-ascertain P/LP-positive individuals without a defining cancer diagnosis; conversely, in high-consanguinity populations such as Türkiye, reliance on family history may reduce specificity and increase unnecessary referrals. Keywords: pediatric solid tumors; germline cancer predisposition; Jongmans criteria; genetic counselling Introduction A significant proportion of pediatric cancers, especially childhood solid tumors, have underlying germline pathogenic/likely pathogenic (P/LP) variants in cancer predisposition genes. Large next-generation sequencing based cohorts generally report detection rates of 7 15%, rising to 18% in some comprehensive genomic approaches (1, 2). Identifying these germline variants can guide tailored therapy, enable syndrome-specific surveillance for second primary malignancies, and support risk management and reproductive counseling for affected individuals and at-risk family members (3). Therefore, the SIOPE Host Genome Working Group recommends structured screening for hereditary predisposition in all pediatric cancer patients, with targeted germline testing when indicated (1). In this context, several clinical screening tools have been proposed to identify children at increased risk for a cancer predisposition syndrome, including the Jongmans criteria (3), the modified Jongmans criteria (4), the Childhood Cancer Screening Checklist (5, 6), and the McGill Interactive Pediatric Oncogenetic Guidelines (7), which are based on tumor type and age, multiple primaries, family history, and syndromic features, with unusual treatment toxicity additionally included in both the original and modified Jongmans criteria (8). However, studies have shown that clinical screening checklists, despite their high sensitivity, can fail to identify a subset of germline predisposition carriers without distinct phenotypic features, underscoring the limitations of purely phenotype-driven ascertainment (9). This study aimed to characterize the diagnostic yield and gene spectrum of germline P/LP variants identified through panel-based multigene germline testing in children evaluated for suspected cancer predisposition, and to describe the clinical and familial features of variant carriers, including the applicability and limitations of diagnosis-based referral criteria. Materials and Methods Personal and clinical data, family history, and genetic test results were retrospectively reviewed for 94 pediatric patients evaluated for suspected childhood cancer predisposition at the Department of Medical Genetics, Ankara Etlik City Hospital, between October 2022 and November 2025. All clinical variables and genetic test results were obtained from digital medical archive records. Written informed consent for genetic testing was obtained from all patients' parents/legal guardians as part of routine clinical practice prior to testing. The study was approved by the Ankara Etlik City Hospital's ethical

committee (AEŞH-BADEK1-2026 022). Next-generation sequencing was performed using the Sophia DDM Hereditary Cancer Solution (HCS) v2.0 and the Sophia DDM™ Clinical Exome Solution (CES) v3 (Sophia Genetics, Saint-Sulpice, Switzerland). Sequencing was carried out using the Illumina MiSeq system for HCS v2.0 and the Illumina NextSeq system for CES v3 (Illumina Inc., San Diego, CA, USA). Sequencing data were analyzed using the Sophia DDM™ Platform (Sophia Genetics, Saint-Sulpice, Switzerland). For CES v3, a predefined gene list was used to construct a custom Pediatric Cancer Predisposition Panel, and analyses and reporting were limited to the genes included in this panel. The gene content of HCS v2.0 and the Pediatric Cancer Predisposition Panel is provided in Table 1. Table 1. Gene content of the multigene panels used for germline testing in this study Hereditary Cancer Panel (Sophia DDM HCS v2.0) ATM, APC, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, DDB2, ERCC2, ERCC3, ERCC4, ERCC5, FANCA, FANCC, FH, FLCN, GALNT12, HDAC2, HOXB13, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PMS2, PMS2CL, POLD1, POLE, POLH, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, SMAD4, STK11, TP53, TSC1, TSC2, VHL, WT1, XPA, XPC Pediatric Cancer Predisposition Panel (Sophia DDM CES v3) AIP, ALK, ANKRD26, APC, ASXL1, ATM, ATR, ATRIP, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRIP1, BUB1B, CASP10, CASP8, CBL, CDC73, CDH1, CDK4, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CEBPA, CHEK2, CREBBP, CTC1, CTNNA1, DDB2, DICER1, DIS3L2, DKC1, DOCK8, ELANE, ELP1, EP300, EPCAM, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ETV6, EXT1, EXT2, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FBXW7, FH, FLCN, FOXE1, GATA1, GATA2, GBA, GPC3, GREM1, HAX1, HRAS, IKZF1, ITK, KIT, KRAS, LIG4, LZTR1, MAP2K1, MAP2K2, MAX, MBD4, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MTAP, MUTYH, NBN, NF1, NF2, NOP10, NRAS, NSD1, NTHL1, PALB2, PARN, PAX5, PDGFRA, PDGFRB, PHOX2B, PMS1, PMS2, POLD1, POLH, POT1, PPP1CB, PRF1, PRKAR1A, PRSS1, PTCH1, PTEN, PTPN11, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAF1, RB1, RECQL4, RET, RIT1, RNF43, RPL11, RPL35A, RPL36, RPL5, RPS17, RPS19, RPS24, RPS26, RPS7, RTEL1, RUNX1, SBDS, SDHA, SDHAF2, SDHB, SDHC, SDHD, SH2B3, SH2D1A, SHOC2, SLC5A5, SLX4, SMAD4, SMARCA4, SMARCB1, SOS1, SOS2, SPRED1, SQSTM1, STAT3, STK11, STN1, STX11, STXBP2, SUFU, TERC, TERT, TINF2, TMEM127, TP53, TRIM37, TRIP13, TSC1, TSC2, UNC13D, VHL, WAS, WRAP53, WRN, WT1, XPA, XPC, XRCC2 Variant interpretation was performed according to the ACMG/AMP 2015 guidelines (10). Detected P/LP variants were classified as clinically significant when considered relevant to the patient's phenotype and cancer predisposition management, whereas variants interpreted as carrier status or secondary findings were recorded separately. For variant carriers with confirmed cancer, eligibility for evaluation using the Jongmans criteria (3) was assessed when applicable; patients referred solely on family history without a personal malignancy history were considered not eligible for diagnosis-based Jongmans assessment. Individual Jongmans criteria were summarized descriptively. Associations between Jongmans criteria fulfillment and detection of clinically significant germline P/LP variants were tested using two-sided Fisher's exact test. In addition, a subgroup comparison using the same test evaluated patients meeting only the consanguinity component of Jongmans criterion 1 versus those fulfilling other Jongmans criteria. Two-sided pG p.(Tyr1417*) 20.7 P No 4 3 5 yr Mediastinal T-cell lymphoma high grade diffuse glioma, medulloblastoma MLH1 (NM_000249) CDKN2A (NM_000077) c.1690_1693del p.(Leu564Phefs*26) c.9_32dup p.(Ala4_Pro11dup) 100 54.3 P LP Yes 1,2,3 4 8 mo Retinoblastoma RB1 (NM_000321) c.265-2A>C 41.9 LP Yes 2 5 10 mo Retinoblastoma RB1 (NM_000321) c.2359C>T p.(Arg787*) 49.3 P N/A 2 6 4 yr Neuroblastoma TP53 (NM_000546) APC (NM_000038) c.742C>T p.(Arg248Trp) c.1958+1G>A 43.5 35.7 P P Yes 1 7 3 yr Medulloblastoma PMS2 (NM_000535) c.182del p.(Tyr61Leufs*15) 100 P Yes 1,2 8 1 yr Hepatoblastoma APC (NM_000038) c.2802_2805del p.(Tyr935Ilefs*19) 41.1 P Yes 2 9 16 yr Family history TP53 (NM_000546) c.542G>A p.(Arg181His) 45.7 LP Yes N/A 10 15 yr Parathyroid adenoma CDC73 (NM_024529) c.561delinsAA p.(Ile189Asnfs*4) 29.2 P Yes 2 11 7 yr Diffuse leptomeningeal tumor(suspected) TP53 (NM_000546) c.248del p.(Ala83Glyfs*40) 52.1 LP No N/A 12 9 mo Malignant rhabdoid tumor SMARCB1 (NM_003073) c.601C>T p.(Arg201*) 41.7 P N/A 2,3 13 3 yr

Hepatoblastoma APC (NM_000038) c.2802_2805del p.(Tyr935Ilefs*19) 48.6 P Yes 1,2 VAF: Variant allele fraction, yr: years, mo: months, P: Pathogenic, LP: Likely pathogenic, N/A: Not available Discussion and Conclusion The detection yield of germline testing in our cohort appears broadly consistent with rates reported in comparable pediatric solid tumor series; however, the limited sample size and referral bias warrant cautious interpretation (1). A limitation of our study is the use of more than one multigene panel platform, which may have introduced heterogeneity in gene coverage and could lead to underestimation of diagnostic yield for genes not captured on the smaller panel. Nevertheless, the testing strategy reflects real-world clinical practice and allowed identification of clinically actionable predisposition diagnoses in a pediatric referral cohort. In the pediatric setting, syndromic physical findings can be informative for an underlying cancer predisposition and may warrant genetics referral even when family history is uninformative (11). Multigene panels may also reveal pathogenic variants in adult-onset cancer genes as an incidental finding (12). This underscores the importance of informed consent, comprehensive pre-test and post-test counseling. Molecular diagnosis of germline cancer predisposition in a child with a solid tumor is essential to guide individualized management, including risk-adapted surveillance and avoidance of syndrome-associated treatment toxicity; while enabling accurate risk assessment and cascade testing for family members, particularly when biallelic conditions are identified (11, 13). Notably, identification of P/LP-positive individuals referred solely on family history despite no personal cancer diagnosis in our cohort highlights a limitation of diagnosis-based referral tools. Moreover, the high prevalence of consanguineous marriages in Türkiye may limit the specificity of family history when these tools are used for referral decision. While this difference did not reach statistical significance, the lack of clinically significant P/LP variants among patients meeting only the consanguinity component of criterion 1 may indicate that parental consanguinity alone is not a strong discriminator in our cohort; however, this observation should be interpreted cautiously given the small subgroup size. Several cohort studies from our country have recently provided complementary insights, ranging from referral-tool–based pediatric solid-tumor series to sequencing-based analyses in selected high-risk childhood leukemia/lymphoma families (14, 15). Nevertheless, published data from our country on germline cancer predisposition in pediatric cancers remain limited, with much of the literature focusing on individual cases or tumor-specific cohorts rather than reporting cohort-level outcomes from multigene germline testing in a clinically evaluated pediatric referral population. Therefore, our study contributes to the literature by providing additional cohort level evidence. References 1. Bakhuizen JJ, Bourdeaut F, Wadt KAW, Kratz CP, Jongmans MCJ, Waespe N. Genetic testing for childhood cancer predisposition syndromes: Controversies and recommendations from the SIOPE Host Genome Working Group meeting 2022. EJC Paediatric Oncology. 2024;4:100176. 2. Schroeder C, Faust U, Krausse L, Liebmann A, Abele M, Demidov G, et al. Clinical trio genome sequencing facilitates the interpretation of variants in cancer predisposition genes in paediatric tumour patients. European Journal of Human Genetics. 2023;31(10):1139-46. 3. Jongmans MC, Loeffen JL, Waanders E, Hoogerbrugge PM, Ligtenberg MJ, Kuiper RP, et al. Recognition of genetic predisposition in pediatric cancer patients: An easy-to-use selection tool. Eur J Med Genet. 2016;59(3):116-25. 4. Ripperger T, Bielack SS, Borkhardt A, Brecht IB, Burkhardt B, Calaminus G, et al. Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. Am J Med Genet A. 2017;173(4):1017-37. 5. Postema FA, Hopman SM, de Borgie CA, Hammond P, Hennekam RC, Merks JH, et al. Validation of a clinical screening instrument for tumour predisposition syndromes in patients with childhood cancer (TuPS): protocol for a prospective, observational, multicentre study. BMJ Open. 2017;7(1):e013237. 6. Postema FAM, Hopman SMJ, de Borgie C, Aalfs CM, Anninga JK, Berger LPV, et al. Clinical value of a screening tool for tumor predisposition syndromes in childhood cancer patients (TuPS): a prospective, observational, multi-center study. Fam Cancer. 2021;20(4):263 71. 7. Goudie C, Coltin H, Witkowski L, Mourad S, Malkin D, Foulkes WD. The McGill Interactive Pediatric OncoGenetic Guidelines: An approach to identifying pediatric oncology patients most likely to benefit from a genetic

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[Abstract:0129]

Is Cancer Risk of the *NTHL1* p.(Gln90*) Variant Zygosity-Dependent? Evidence From A Large Single-Center Turkish Cohort

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Objective
The *NTHL1* gene plays a role in the base excision repair pathway, and biallelic loss-of-function variants are associated with a rare autosomal recessive cancer predisposition syndrome. *NTHL1*-associated cancer susceptibility has been historically defined by the p.(Gln90*) variant, which results in loss of protein function and is associated with adenomatous polyposis, colorectal cancer, and breast cancer.
In contrast, the cancer risk associated with monoallelic *NTHL1* variants remains controversial, with no consistent evidence of a significant risk increase in the literature. The recurrent p.(Gln90*) variant is frequently detected in heterozygous state in population databases and diagnostic gene panels, posing challenges for the clinical interpretation of cancer risk despite its pathogenic classification according to the ACMG 2015 criteria.
This study aims to highlight the importance of a zygosity-based risk stratification in the clinical interpretation of the *NTHL1* p.(Gln90*) variant and to contribute to the clinical management of monoallelic carriers. It represents one of the first analyses from Türkiye to statistically evaluate these findings using a large diagnostic cohort with an internal control, integrated with population and literature data.

Materials-Methods
We retrospectively evaluated 8,100 individuals who underwent hereditary cancer panel testing (HCS) for hereditary cancer predisposition and 10,000 individuals who underwent clinical exome sequencing (CES) for non-oncologic rare genetic disorders at Ankara Etlik City Hospital between October 2022 and December 2025. Individuals harboring the *NTHL1* c.268C>T (p.Gln90*) (rs150766139) variant were assessed for zygosity status and clinical characteristics. Carrier-rate–based statistical analyses were performed between the HCS and CES cohorts and compared with population-based and published literature data.

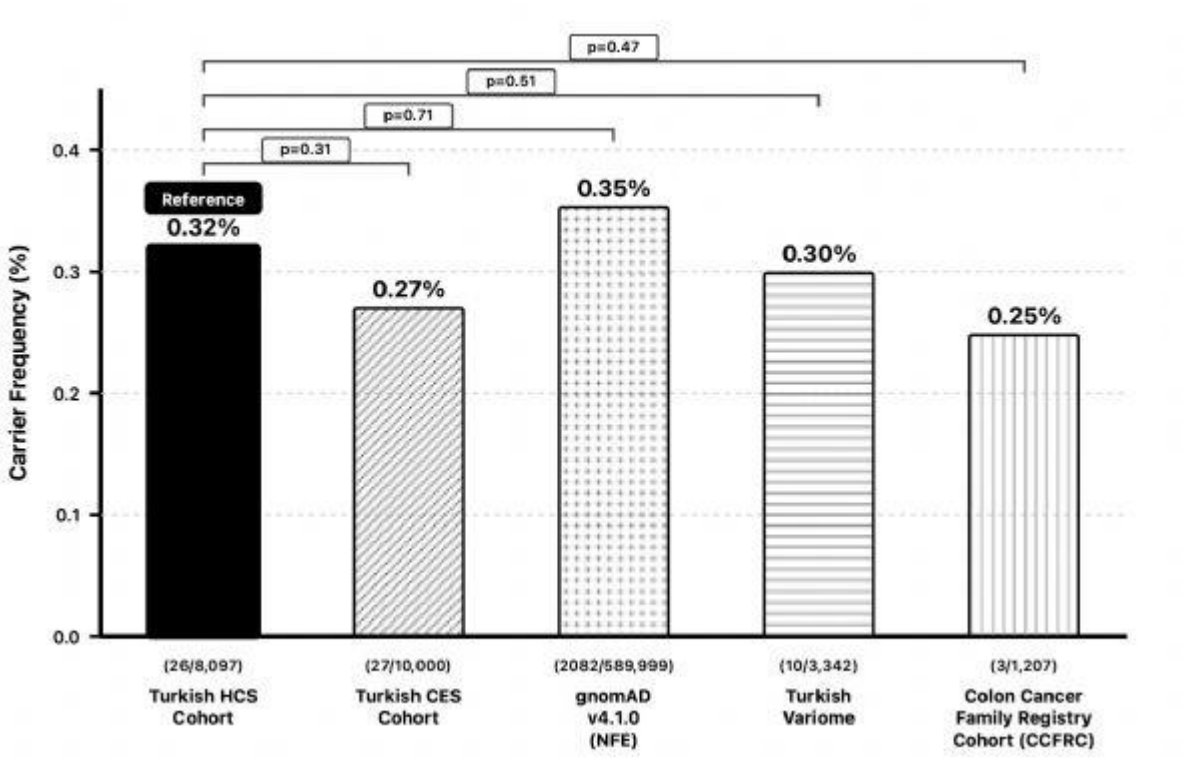
Results
The *NTHL1* p.(Gln90*) variant was identified in 29 individuals in the HCS cohort (26 monoallelic and 3 biallelic; 0.36%) and in 27 monoallelic individuals in the CES cohort (0.27%); no significant difference in carrier frequency was observed between the two cohorts (p=0.31). Using a carrier-rate–based analytical approach, monoallelic *NTHL1* p.(Gln90*) was not enriched in the HCS cohort, with consistent findings observed in comparisons with gnomAD v4.1.0 (p=0.71), Turkish Variome (p=0.51), and CCFRC (p=0.47) (Figure 1).
All three individuals with homozygous p.(Gln90*) identified in the HCS cohort had colorectal and/or breast cancer. Cancer phenotypes within the HCS cohort were heterogeneous, with breast cancer being the most frequent diagnosis (55.2%). Notably, secondary heterozygous pathogenic variants in another cancer susceptibility gene were identified in 5 individuals (17.2%). In the CES cohort, carriers of the p.(Gln90*) variant did not have documented personal/family histories of cancer.

Conclusion
Our findings suggest that the clinical cancer risk associated with the *NTHL1* p.(Gln90*) variant is strongly dependent on zygosity. Monoallelic carriage was not associated with a significant increase in cancer risk when compared with internal control cohorts and global population data, whereas biallelic carriage was consistent

with *NTHL1*-associated tumor syndrome. These results support the interpreting monoallelic *NTHL1* p.(Gln90*) variants as secondary findings in most cases and emphasize that clinical surveillance strategies should be guided by zygosity and family history. Further studies incorporating large clinical cohorts and complementary somatic analyses are also warranted, particularly to assess the risk of extracolonic tumors in monoallelic *NTHL1* carriers.

Keywords: *NTHL1*, p.(Gln90*), base excision repair, monoallelic carriers, variant frequency

Figure 1. Carrier frequency of monoallelic NTHL1 p.(Gln90*) across population-based cohorts



Bars show carrier frequencies (%) calculated as n/N (shown below bars), with the Turkish HCS cohort as the reference. One-sided Fisher exact tests were used to compare HCS cohort with each population-based control cohort; p values are shown above the bars. No significant differences were observed, indicating no enrichment of NTHL1 p.(Gln90) in the Turkish HCS cohort. HCS, hereditary cancer panel cohort; CES, clinical exome sequencing cohort; gnomAD, Genome Aggregation Database; NFE, non-Finnish European; CCFRC, Colon Cancer Family Registry Cohort.*

Is Cancer Risk of the NTHL1 p.(Gln90*) Variant Zygosity-Dependent? Evidence From A Large Single-Center Turkish Cohort Objective The NTHL1 gene encodes a DNA glycosylase involved in the base excision repair pathway, and biallelic loss-of-function (LoF) variants are associated with a rare autosomal recessive cancer predisposition syndrome. NTHL1-associated tumor susceptibility has historically been defined by the recurrent truncating variant p.(Gln90*), which results in complete loss of protein function and is associated with adenomatous polyposis, colorectal cancer (CRC), and breast cancer 1–4. In contrast, the p.(Gln90*) variant is frequently detected in the monoallelic state in population databases and diagnostic multigene panels, creating a clinical challenge in cancer risk interpretation. Clarifying the cancer risk associated with monoallelic NTHL1 variants is therefore essential to inform evidence-based screening and surveillance recommendations. Recent

studies in predominantly European cohorts have demonstrated that monoallelic NTHL1 LoF variants are not enriched in individuals with polyposis or CRC compared with population based controls, and that tumors from monoallelic carriers lack somatic second hits and the SBS30 mutational signature 5,6. In parallel, the role of monoallelic NTHL1 variants in extracolonic cancer susceptibility has been investigated, with the most consistent signal reported for breast cancer. A large case–control study suggest a modest association between heterozygous NTHL1 LoF variants and breast cancer risk; however, effect sizes are small and do not currently support changes in clinical management 7,8. For other extracolonic tumor types, available evidence remains limited and inconclusive. Notably, these studies were conducted predominantly in European-ancestry cohorts. Here, we provide complementary evidence from a large Turkish cohort, contributing data from a population that remains underrepresented in the current literature. Materials-Methods We retrospectively evaluated 8,100 individuals who underwent hereditary cancer panel testing (HCS) based on established guideline-recommended criteria for hereditary cancer predisposition, and 10,000 individuals analyzed by exome sequencing (ES) for diverse non-oncologic rare genetic disorders at Ankara Etlik City Hospital between October 2022 and December 2025. Individuals harboring the NTHL1 c.268C>T (p.Gln90*) (rs150766139) variant were assessed for zygosity status and associated clinical characteristics. The association between monoallelic NTHL1 p.(Gln90*) and hereditary cancer predisposition was assessed using carrier-rate–based statistical analyses. The HCS cohort was defined as the reference, while the ES cohort served as an internal control. Carrier frequencies were compared between the HCS cohort, the ES cohort, and three independent population-based data sets , including the non-Finnish European (NFE) subset of gnomAD v4.1.0, the Turkish Variome dataset, and the Colon Cancer Family Registry Cohort (CCFRC), using one-sided Fisher exact tests. Biallelic carriers were excluded from the carrier-frequency–based analyses and were evaluated descriptively. Results The NTHL1 p.(Gln90*) variant was identified in 29 of 8,100 individuals (0.36%) in the HCS cohort, including 26 monoallelic and 3 biallelic carriers, and in 27 of 10,000 individuals (0.27%), all monoallelic, in the ES cohort. No significant difference in carrier frequency was observed between the two cohorts (OR, 1.19; 95% CI, 0.69–2.04; p=0.31). Using a carrier-rate–based analytical approach, the p.(Gln90*) variant was not enriched in the HCS cohort when compared with population-based control datasets, including gnomAD v4.1.0 NFE (2,082/589,999; OR, 0.91; 95% CI, 0.62–1.34; p=0.71), the Turkish Variome (10/3,342; OR, 1.07; 95% CI, 0.52 2.23; p=0.51), and the CCFRC (3/1,207; OR, 1.29; 95% CI, 0.39–4.28; p=0.47) (Figure 1). All three biallelic carriers in the HCS cohort presented with colorectal and/or breast cancer, consistent with established phenotypes. Cancer phenotypes within the HCS cohort were heterogeneous, with breast cancer being the most frequent diagnosis (55.2%). Clinical indications within the HCS cohort were heterogeneous, with breast cancer being the most frequent diagnosis (55.2%), followed by individuals tested based on a familial cancer history (17.2%), gynecologic malignancies (10.3%), and pancreatic cancer (6.9%). In the ES cohort, carriers of the NTHL1 p.(Gln90*) variant did not have documented personal or family histories of cancer. Notably, in the HCS cohort, secondary heterozygous pathogenic or likely pathogenic variants in established cancer susceptibility genes were identified in 5 of 26 monoallelic NTHL1 p.(Gln90*) carriers (19.2%). These included RAD51C in a patient with endometrial cancer, ATM and BRCA1 in two patients with breast cancer, BRCA1 in a patient with ovarian cancer, and TP53 in a patient with lung squamous cell carcinoma and a strong family history. The presence of secondary pathogenic/likely pathogenic variants in moderate- to high-penetrance cancer susceptibility genes in a substantial proportion of monoallelic carriers underscores the importance of comprehensive variant interpretation and suggests that the primary genetic basis of cancer risk in these individuals may often be better explained by coexisting etiologies rather than by NTHL1 haploinsufficiency. Conclusion In conclusion, our findings from a large Turkish cohort support and extend prior observations from predominantly European-ancestry populations, indicating that the monoallelic NTHL1 p.(Gln90*) variant does not confer an increased risk of colorectal cancer or polyposis. By using an unselected hereditary cancer testing cohort rather than a CRC- or polyposis-enriched population, our study allowed a

broader assessment of cancer risk. The absence of enrichment among monoallelic carriers compared with population-based control and HCS cohorts, together with the frequent detection of co-occurring pathogenic variants in established cancer susceptibility genes, supports a zygosity-dependent interpretation of the NTHL1 p.(Gln90*) variant. These findings suggest that monoallelic NTHL1 variants may represent secondary findings and emphasize that surveillance decisions should be guided by zygosity and family history. Further studies incorporating large and diverse cohorts with integrated somatic analyses are warranted, particularly to clarify the risk of extracolonic tumors in monoallelic NTHL1 carriers. Figure 1. Carrier frequency–based enrichment analysis of the monoallelic NTHL1 p.(Gln90*) variant across diagnostic and population-based cohorts. Bar plots show carrier frequencies (%) of the monoallelic NTHL1 p.(Gln90*) variant, with values displayed above each bar. Sample sizes (carriers/total) are shown in parentheses below each cohort name. The Turkish HCS cohort was used as the reference group (black bar) and compared with population-based cohorts. Pairwise comparisons between the Turkish HCS cohort and each comparison cohort were performed using one-sided Fisher exact tests, with corresponding P values shown above the brackets. No statistically significant differences in carrier frequencies were observed across all comparisons, indicating no enrichment of the NTHL1 p.(Gln90*) variant in the Turkish HCS cohort. HCS, hereditary cancer panel testing cohort; ES, exome sequencing testing cohort; gnomAD, Genome Aggregation Database; NFE, non-Finnish European; CCFRC, Colon Cancer Family Registry Cohort. References 1. 2. 3. 4. 5. 6. 7. 8. Krokan HE, et al. Cold Spring Harb Perspect Biol 2013;5:a012583. Weren RDA, et al. Nat Genet 2015;47:668–671. Grolleman JE, et al. Cancer Cell 2019;35:256–266.e5. Belhadj S, et al. Clin Gastroenterol Hepatol 2017;15:461–462. Elsayed FA, et al. Gastroenterology 2020;159:2241–2243.e6. Mahmood K, et al. Gastroenterology 2023;165:1070–1076.e3. Nurmi AK, et al. Sci Rep 2023;13:21127. Li N, et al. NPJ Breast Cancer 2021;7:76.

[Abstract:0134]

Prognostic Significance Of The Neutrophil-To-Lymphocyte Ratio And Brca/Hrd-Mutational Status In High-Grade Ovarian Cancer

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Objectives:
We aimed to evaluate the prognostic impact of clinicopathological characteristics and BRCA/HRD status, together with serum inflammatory markers, on progression-free survival (PFS) in patients with locally advanced ovarian cancer.

Material-Methods:
This retrospective, single-center, observational study included patients diagnosed with locally advanced ovarian cancer who were treated at the Department of Medical Oncology, Başakşehir Çam and Sakura City Hospital, between 2020 and 2025. Patients were retrospectively analyzed for clinicopathological characteristics, germline and somatic BRCA/HRD status, and serum inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR) and monocyte counts. Inflammatory parameters were recorded at baseline (at initial diagnosis prior to primary treatment) and at the time of first recurrence. The impact of these variables on progression-free survival (PFS) was evaluated.

Results:
A total of 110 patients with locally advanced ovarian cancer were included in the analysis. The median follow-up duration for the entire cohort was 56 months. During follow-up, the median progression-free survival (PFS) for the overall study population was 18.0 months (95% confidence interval [CI], 17.8–23.8 months). BRCA mutations and/or homologous recombination deficiency (HRD) were identified in 27 patients (24.5%). Of these, 13 patients (48%) had germline mutations, whereas 14 patients (52%) had somatic mutations. In contrast, 83 patients (75.5%) had wild-type BRCA/HRD status. Based on the median neutrophil-to-lymphocyte ratio (NLR), patients were classified as having high (>=2.83) or low (<2.83) NLR. Similarly, based on the median monocyte count, patients were classified as having high (>=0.6) or low (<0.6) monocyte levels. Postoperative residual disease was present in 42 patients (38.5%), while complete cytoreduction was achieved in 67 patients (61.5%). Univariate Cox proportional hazards regression analysis was performed to identify clinicopathological and inflammatory parameters associated with progression-free survival (PFS). Age (>=60 vs. <60 years; HR 1.01, 95% CI 0.62–1.63), BRCA and HRD status (mutant vs. wild-type; HR 0.84, 95% CI 0.47–1.50), presence of postoperative residual disease (present vs. absent; HR 1.24, 95% CI 0.76–2.02), neutrophil-to-lymphocyte ratio (high vs. low; HR 1.14, 95% CI 0.70–1.86), and monocyte count (high vs. low; HR 0.88, 95% CI 0.54–1.43) were not significantly associated with PFS in univariate analysis.

Conclusion:
Survival analysis revealed neither BRCA/HRD status nor baseline serum inflammatory markers, including NLR and monocyte count, demonstrated a significant prognostic impact on progression-free survival. Similarly, no clinicopathological parameter evaluated in univariate analysis was significantly associated with PFS. These findings suggest that the prognostic value of inflammatory markers and BRCA/HRD status in this patient population may be limited and warrants further investigation in larger, prospective studies.

Keywords: Ovarian Cancer, Neutrophil-to-Lymphocyte Ratio, BRCA Mutation, Homologous Recombination Deficiency, Prognosis

Univariate and multivariate analysis of characteristic parameters related to progression free survival.

PFS	PFS	Univariate Analysis	Univariate Analysis	Multivariate Analysis	Multivariate Analysis
Characteristics	Category	HR(95% CI)	P	HR(95% CI)	P
Age	>=60 vs. <60	1.01(0.62-1.63)	0.979	N/A	-
BRCA and HRD Status	Mutant vs. Wild-type	0.84(0.47-1.50)	0.550	N/A	-
Residual Disease	Present vs. Absent	1.24(0.76-2.02)	0.391	N/A	-
NLR	High vs. Low	1.14(0.70-1.86)	0.588	N/A	-
Monocyte count	High vs. Low	0.88(0.54-1.43)	0.593	N/A	-

BRCA, breast cancer gene; HRD, homologous recombination deficiency; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival.

PROGNOSTIC SIGNIFICANCE OF THE NEUTROPHIL-TO-LYMPHOCYTE RATIO AND BRCA/HRD-MUTATIONAL STATUS IN HIGH-GRADE OVARIAN CANCER Vedat Bugra Erol1, Tanju Kapagan2, Nilufer Bulut1 1Basaksehir Cam and Sakura City Hospital, Medical Oncology, 2Corlu State Hospital, Medical Oncology ABSTRACT Objectives: This study is intended to assess the prognostic impact of clinicopathological characteristics and BRCA/HRD status, together with serum inflammatory biomarkers, on progression-free survival (PFS) in patients with locally advanced ovarian cancer. Material and Methods: This retrospective, single-center, observational study included patients diagnosed with locally advanced ovarian cancer who were treated at the Department of Medical Oncology, Başakşehir Çam and Sakura City Hospital, between 2020 and 2025. Patients were retrospectively analyzed for clinicopathological characteristics, BRCA/HRD status, and serum inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR) and monocyte counts. Inflammatory parameters were recorded at baseline (at initial diagnosis prior to primary treatment) and at the time of first recurrence. The impact of these variables on PFS was evaluated. Results: A total of 110 patients with locally advanced ovarian cancer (FIGO 3) were included in the analysis. The median follow-up duration for the entire cohort was 56 months. During follow up, the median PFS for the overall study population was 18.0 months (95% confidence interval [CI], 17.8–23.8 months). BRCA mutation and/or homologous recombination deficiency (HRD) was identified in 27 patients (24.5%), whereas 83 patients (75.5%) had wild-type BRCA/HRD status. Based on the median NLR, patients were classified as having high (≥2.83) or low (< 0.05. RESULTS The main objective of this study was to assess the potential association between BRCA status and NLR values in a patients group with high-grade serous ovarian cancer. Additionally, we examined the relationship between NLR values and clinicopathological characteristics, as well as PFS outcomes, in patients with advanced high-grade serous ovarian cancer. A total of 110 patients with Figo stage 3 ovarian cancer were evaluated. The median surveillance period for the cohort was 56 months, and the median PFS for the entire population was 18.0 months (95% confidence interval [CI], 17.8–23.8 months). BRCA mutation and/or homologous recombination deficiency (HRD) was detected in 27 patients (24.5%), whereas 83 patients (75.5%) exhibited wild-type BRCA/HRD status. Using median values as cut-off points, patients were stratified into groups of high versus low according to NLR (≥2.83 vs. < 4) was associated with less

extensive disease, higher rates of primary debulking surgery, lower surgical complexity, and significantly prolonged PFS. Importantly, these favorable outcomes were observed irrespective of BRCA mutational status, and multivariate analysis identified BRCA mutation status, complete cytoreduction, and low NLR as independent predictors of PFS, while also representing the strongest determinants of overall survival, suggesting that NLR acts as an independent prognostic marker largely unrelated to BRCA status (3). Consistent with these findings, a retrospective study in early-stage epithelial ovarian cancer demonstrated that elevated baseline inflammatory markers, particularly NLR ≥ 3 were associated with inferior 3-year disease-free survival. Although BRCA-mutated patients with higher inflammatory marker levels experienced worse outcomes, FIGO stage greater than I remained the only independent predictor of recurrence in multivariate analysis (4). By contrast data from the RECLAMO cohort focusing on high-grade serous ovarian carcinoma in early-stage ovarian cancer, suggested that prognosis was more strongly influenced by immune-related tumor characteristics than by genomic alterations. In this study, neither BRCA1/2 mutation status nor tumor mutation burden was associated with immune infiltration or survival, underscoring potential stage-dependent differences in prognostic determinants between early and advanced disease (5). Despite these observations, the prognostic impact of BRCA mutations on survival in ovarian cancer remains controversial. A large systematic review and meta-analysis including 34 observational studies and 18,396 patients demonstrated that BRCA1/2 mutations were associated with significant improvements in both overall survival and PFS compared with BRCA wild-type disease (6). As apposed to this, a multicenter retrospective study of 378 patients with epithelial ovarian, peritoneal, or fallopian tube cancer reported no significant differences in overall survival or PFS according to BRCA status, although short-term PFS was improved in BRCA-mutated patients, particularly in those with high-grade serous histology and advanced-stage disease (7). Additional evidence from a broader systematic review and meta-analysis of 135 studies across multiple tumor types further supports a tumor-specific prognostic role of BRCA mutations, showing a significant overall survival benefit in ovarian cancer patients with BRCA1/2 mutations, while no such association was observed in breast cancer (8). Moreover, a large single-institution study examining age-related differences demonstrated that although the prevalence of BRCA mutations declined with increasing age, their favorable prognostic impact on disease-free and cancer-specific survival was preserved in elderly ovarian cancer patients, with BRCA mutation status and upfront surgery remaining independent predictors of improved outcomes (9). These apparently conflicting findings may, at least in part, be explained by differences in BRCA mutation location. A recent systematic review and meta-analysis highlighted the prognostic relevance of mutation site, demonstrating that BRCA2 exon 11 mutations were associated with significantly improved PFS, whereas no comparable effect was observed for BRCA1 exon 11 mutations, emphasizing the clinical importance of mutation localization within BRCA genes (10). In our survival analysis, no significant prognostic impact of BRCA/HRD status or baseline systemic inflammatory markers, including NLR and monocyte count, was observed for PFS. Overall survival analysis was not performed due to insufficient event numbers. Furthermore, none of the clinicopathological parameters evaluated in univariate analysis were significantly associated with PFS. Variability in NLR cut-off values across studies may partly explain the heterogeneity reported in the literature. The absence of significance may reflect limited statistical power rather than true biological absence. Importantly, the originality of the present study lies in the simultaneous evaluation of BRCA/HRD status and baseline systemic inflammatory markers within a well-defined cohort of patients with locally advanced ovarian cancer treated in a uniform clinical setting. Unlike previous studies that primarily focused on either early-stage disease or highly selected molecular subgroups, our analysis reflects real-world clinical practice and provides evidence that neither BRCA/HRD status nor routinely used inflammatory indices confer independent prognostic value for PFS in this specific population. These findings underscore the complexity of prognostic stratification in locally advanced ovarian cancer and suggest that the predictive utility of inflammatory markers and BRCA-related biology may be highly context-dependent, varying according to disease stage, treatment strategy, and tumor

burden. By highlighting these limitations, our study contributes to a more nuanced understanding of prognostic heterogeneity and supports the need for integrative, stage-specific biomarker models in future prospective research. FIGURES Table 2. Univariate analysis of characteristic parameters related to progression free survival. PFS Univariate Analysis Characteristics Category HR (95% CI) P Age ≥60 vs.

[Abstract:0139]

Comparison of Clinical Outcomes in Germline and Somatic BRCA-Mutated Ovarian Cancer Patients Treated with PARP Inhibitors

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Objective: Epithelial ovarian cancer is an aggressive gynecologic malignancy with high mortality rates. Defects in DNA damage repair pathways, particularly germline and somatic mutations in the Breast Cancer Gene 1 (BRCA1) and BRCA2, play a major role in tumor biology and therapeutic response. Poly(adenosine diphosphate ribose) polymerase (PARP) inhibitors have improved outcomes in BRCA-mutated ovarian cancer and are widely used as maintenance therapy. However, real-world data comparing outcomes according to BRCA mutation origin and PARP inhibitor type remain limited. This study aimed to compare survival outcomes in patients with germline and somatic BRCA mutations treated with PARP inhibitors and to assess the impact of PARP inhibitor selection on progression-free survival(PFS) and overall survival(OS).

Materials-Methods: This retrospective cohort study included 34 patients diagnosed with epithelial ovarian cancer who received PARP inhibitor therapy. Patients were classified as germline BRCA or somatic BRCA mutation carriers based on genetic testing results. Clinical variables including age, performance status, FIGO stage, histological subtype, residual disease status after surgery, neoadjuvant chemotherapy use, treatment setting (first-line or recurrent), and number of prior chemotherapy lines were collected. Survival analyses were performed using the Kaplan–Meier method, with comparisons using the log-rank test. Cox proportional hazards regression analysis was applied to assess progression risk.

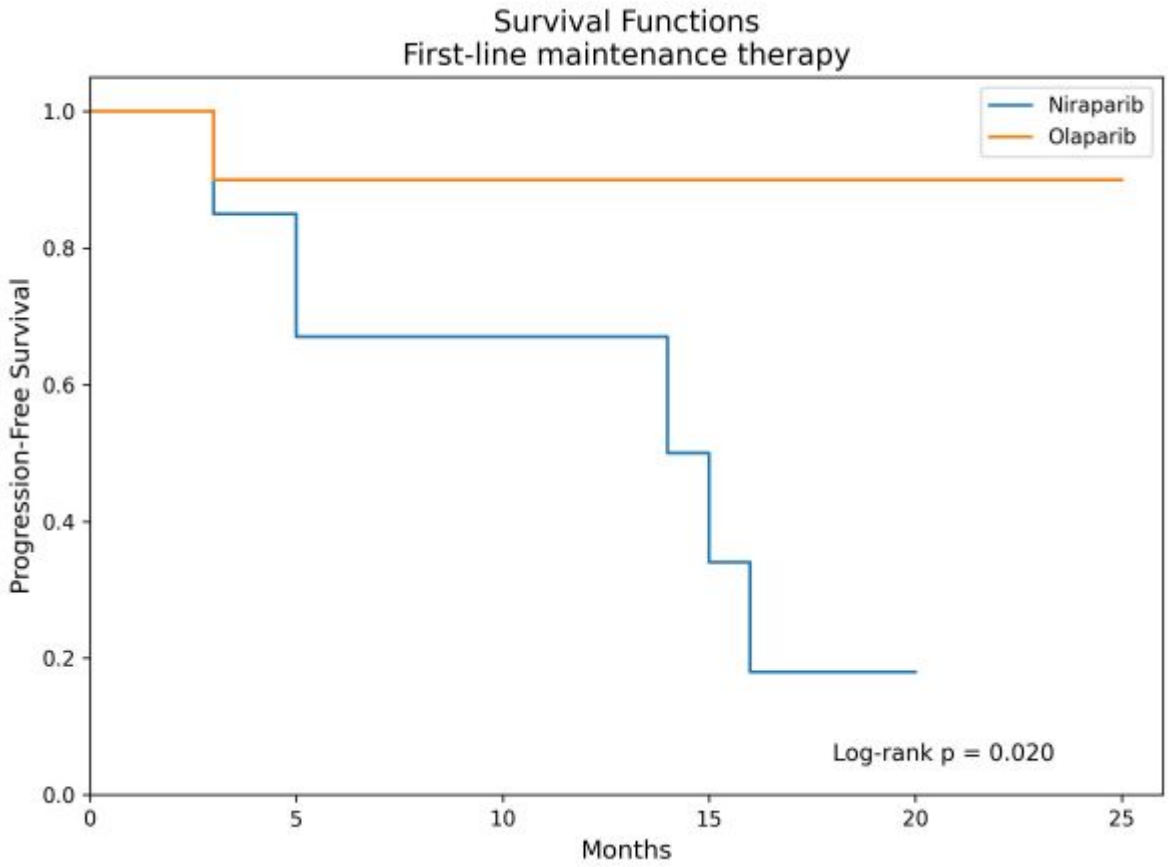
Results: Among the 34 patients included, 10 (29.4%) had germline BRCA mutations(6 patients BRCA1, 3 patients BRCA2, 1 patient BRCA1 and BRCA2) and 24 (70.6%) had somatic BRCA mutations(10 patients BRCA1, 10 patients BRCA2, 4 patients BRCA1 and BRCA2). Baseline clinicopathological characteristics were well balanced between groups.
No statistically significant differences were observed between germline and somatic BRCA groups in terms of PFS or OS. Median PFS was 15 months in the germline BRCA group, while it was not reached in the somatic BRCA group ($p>0.05$). Progression events occurred in 40.0% of germline BRCA patients and 37.5% of somatic BRCA patients. Cox regression analysis demonstrated a numerically lower progression risk in germline BRCA carriers compared with somatic BRCA carriers, although this difference did not reach statistical significance (HR 0.79; 95% CI 0.24–2.59).
In patients first-line and recurrent treatment group, no statistically significant difference in PFS was found between germline and somatic BRCA groups (log-rank $p>0.05$)
In contrast, PARP inhibitor selection emerged as a strong determinant of PFS. Median PFS was 13.0 months in the niraparib group, whereas the median was not reached in the olaparib group (log-rank $p=0.004$). Univariable Cox regression analysis revealed that niraparib use was associated with a markedly increased risk of progression compared with olaparib (HR 5.40; 95% CI 1.48–19.73; $p=0.011$). Importantly, subgroup analysis showed that this benefit was particularly pronounced in the first-line maintenance treatment setting, where olaparib was associated with significantly longer PFS compared with niraparib (log-rank $p=0.020$).

Conclusion: BRCA mutation origin did not significantly influence survival outcomes. In contrast, PARP inhibitor

selection had a clinically meaningful impact on PFS, with olaparib demonstrating superior efficacy compared with niraparib, particularly in the first-line maintenance setting.

Keywords: *BRCA mutation, PARP inhibitors, epithelial ovarian cancer, progression-free survival*

Progression-Free Survival According to First-Line Maintenance Therapy



Clinicopathological Characteristics of the Study Population

Characteristic	Total (n=34)	Germline BRCA (n=10)	Somatic BRCA (n=24)
Age, median (min–max)	61.5 (44–75)	61.0 (51–75)	62.0 (44–75)
ECOG PS, n (%)			
0-1	32 (94.1%)	10 (100%)	22 (91.7%)
>=2	2 (5.9%)	0 (0%)	2(8.3%)
FIGO stage, n (%)			
IIIA	2 (5.9%)	2 (20.0%)	0 (0%)
IIIB	4 (11.8%)	0 (0%)	4 (16.7%)
IIIC	17 (50.0%)	4 (40.0%)	13 (54.2%)
IV	11 (32.4%)	4 (40.0%)	7 (29.2%)

Received neoadjuvant chemotherapy, n (%)	20 (58.8%)	3 (30.0%)	17 (70.8%)
BRCA status, n (%)			
BRCA1 positive	16 (47.1%)	6 (60.0%)	10 (41.7%)
BRCA2 positive	13 (38.2%)	3 (30.0%)	10 (41.7%)
BRCA1 and BRCA2 positive	5 (14.7%)	1 (10.0%)	4 (16.7%)
PARPi, n (%)			
Olaparib	21 (61.8%)	5 (50.0%)	16 (66.7%)
Niraparib	13 (38.2%)	5 (50.0%)	8 (33.3%)
Treatment setting			
First line-maintenance, n (%)	17 (50.0%)	4 (40.0%)	13 (54.2%)
Recurrent-maintenance, n (%)	17 (50.0%)	6 (60.0%)	11 (45.8%)

Values are presented as n (%) unless otherwise stated. Continuous variables are expressed as median (minimum–maximum). ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; PARP: Poly (ADP-ribose) polymerase inhibitor.

Comparison of Clinical Outcomes in Germline and Somatic BRCA-Mutated Ovarian Cancer Patients Treated with PARP Inhibitors Ahmet Baklacı, Meltem Demirtaş Gülmez, Mehmet Nuri Başer, Merve Turan Aydin Adnan Menderes University Faculty of Medicine,Depatment Of Medical Oncology, Aydin, Türkiye Introduction: Epithelial ovarian cancer is an aggressive gynecologic malignancy with high mortality rates. Defects in DNA damage repair pathways, particularly germline and somatic mutations in the Breast Cancer Gene 1 (BRCA1) and BRCA2, play a major role in tumor biology and therapeutic response. Poly(adenosine diphosphate ribose) polymerase (PARP) inhibitors have improved outcomes in BRCA-mutated ovarian cancer and are widely used as maintenance therapy. However, real-world data comparing outcomes according to BRCA mutation origin and PARP inhibitor type remain limited. Objective: This study aimed to compare survival outcomes in patients with germline and somatic BRCA mutations treated with PARP inhibitors and to assess the impact of PARP inhibitor selection on progression-free survival (PFS) and overall survival (OS). Materials and Methods: This retrospective cohort study included 34 patients diagnosed with epithelial ovarian cancer who received PARP inhibitor therapy. Patients were classified as germline BRCA or somatic BRCA mutation carriers based on genetic testing results. Clinical variables including age, performance status, FIGO stage, histological subtype, residual disease status after surgery, neoadjuvant chemotherapy use, treatment setting (first-line or recurrent), and number of prior chemotherapy lines were collected. Survival analyses were performed using the Kaplan–Meier method, with comparisons using the log-rank test. Cox proportional hazards regression analysis was applied to assess progression risk. Results: Among the 34 patients included, 10 (29.4%) had germline BRCA mutations (6 patients BRCA1, 3 patients BRCA2, 1 patient BRCA1 and BRCA2) and 24 (70.6%) had somatic BRCA mutations (10 patients BRCA1, 10 patients BRCA2, 4 patients BRCA1 and BRCA2). Baseline clinicopathological characteristics were well balanced between groups (Table 1). No statistically significant differences were observed between germline and somatic BRCA groups in terms of PFS or OS. Median PFS was 15 months in the germline BRCA group, while it was not reached in the somatic BRCA group ($p>0.05$). Progression events occurred in 40.0% of germline BRCA patients and 37.5% of somatic BRCA patients. Cox regression analysis demonstrated a numerically lower progression risk in germline BRCA carriers compared with somatic BRCA carriers, although this difference did not reach statistical significance (HR 0.79; 95% CI 0.24–2.59). In patients first-line and recurrent treatment group, no

statistically significant difference in PFS was found between germline and somatic BRCA groups (log-rank p>0.05) Table1.Clinicopathological Characteristics of the Study Population Characteristic Total (n=34) Germline BRCA (n=10) Somatic BRCA (n=24) Age, median (min–max) 61.5 (44–75) 61.0 (51–75) 62.0 (44–75) ECOG PS, n (%) 0–1 32 (94.1%) 10 (100%) 22 (91.7%) >=2 2 (5.9%) 0 (0%) 2 (8.3%) FIGO stage, n (%) IIIA 2 (5.9%) 2 (20.0%) 0 (0%) IIIB 4 (11.8%) 0 (0%) 4 (16.7%) IIIC 17 (50.0%) 4 (40.0%) 13 (54.2%) IV 11 (32.4%) 4 (40.0%) 7 (29.2%) Received neoadjuvant chemotherapy, n (%) 20 (58.8%) 3 (30.0%) 17 (70.8%) BRCA status, n (%) BRCA1 positive 16 (47.1%) 6 (60.0%) 10 (41.7%) BRCA2 positive 13 (38.2%) 3 (30.0%) 10 (41.7%) BRCA1 and BRCA2 positive 5 (14.7%) 1 (10.0%) 4 (16.7%) PARPi, n (%) Olaparib 21 (61.8%) 5 (50.0%) 16 (66.7%) Niraparib 13 (38.2%) 5 (50.0%) 8 (33.3%) Treatment setting First line-maintenance, n (%) 17 (50.0%) 4 (40.0%) 13 (54.2%) Recurrent-maintenance, n (%) 17 (50.0%) 6 (60.0%) 11 (45.8%) In contrast, PARP inhibitor selection emerged as a strong determinant of PFS. Median PFS was 13.0 months in the niraparib group, whereas the median was not reached in the olaparib group (log-rank p=0.004). Univariable Cox regression analysis revealed that niraparib use was associated with a markedly increased risk of progression compared with olaparib (HR 5.40; 95% CI 1.48–19.73; p=0.011). Importantly, subgroup analysis showed that this benefit was particularly pronounced in the first-line maintenance treatment setting, where olaparib was associated with significantly longer PFS compared with niraparib (log rank p=0.020) (Figure 1). Figure1. Progression-Free Survival according to first-line maintenance therapy Conclusion: BRCA mutation origin did not significantly influence survival outcomes. In contrast, PARP inhibitor selection had a clinically meaningful impact on PFS, with olaparib demonstrating superior efficacy compared with niraparib, particularly in the first-line maintenance setting. Keywords: BRCA mutation, PARP inhibitors, epithelial ovarian cancer, progression-free survival

[Abstract:0140]

Neuroblastoma and Hereditary Cancer Predisposition: Two Case Reports

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Objective: Neuroblastoma is a common childhood solid tumor and a major cause of pediatric cancer mortality. Although usually sporadic, approximately 1–2% of cases are familial. In addition, about 13% of patients with neuroblastoma harbor pathogenic/likely pathogenic germline variants in cancer predisposition genes. With the increasing use of molecular testing, associations between neuroblastoma and hereditary cancer predisposition syndromes are being recognized more frequently. Here, we present two rare cases with variants in hereditary cancer susceptibility genes.

Case: Case 1: Diagnosed with neuroblastoma at 3 months, the patient received five chemotherapy cycles and surgery. Findings included plagiocephaly, strabismus, broad thumbs/toes, and cryptorchidism. ES showed a mosaic pathogenic CREBBP variant (c.4251C>G; p.Tyr1417*).
Case 2: A one-year-old patient treated with autologous stem-cell transplantation for neuroblastoma had numerous colorectal polyps. Family history included colorectal and breast cancer. ES revealed pathogenic variants in TP53 (c.742C>T;p.Arg248Trp) and APC (c.1958+1G>A).

Conclusion: In familial neuroblastoma, ALK and PHOX2B are the best-known germline susceptibility genes; however, increasing case-based evidence suggests that pathogenic variants in other hereditary cancer predisposition genes may also contribute. In case 1, a mosaic pathogenic CREBBP variant was identified, consistent with mosaic Rubinstein–Taybi syndrome. This case indicates that, particularly in patients with dysmorphic features, a comprehensive clinical evaluation beyond a tumor-focused approach may be essential for identifying hereditary cancer predispositions. In the second case, concurrent pathogenic germline variants in TP53 and APC were detected, raising the possibility of Multilocus Inherited Neoplasia Allele Syndrome (MINAS). Although MINAS has predominantly been described with adult-onset malignancies, this case suggests that it should also be considered in the differential diagnosis in pediatric oncology. In Türkiye, studies investigating the molecular etiology of childhood cancers, including neuroblastoma, are limited. Case-based observations are useful for hypothesis generation but do not establish causality; large cohort studies are required to clarify these associations.
Neuroblastoma and Hereditary Cancer Predisposition: Two Case Reports Elifcan Taşdelen, Hanife Saat, Abdullah Sezer, Umut Can Tekbaş, Ezgi Çevik, Haktan Bağış Erdem Introduction: Neuroblastoma is a common childhood solid tumor and a major cause of pediatric cancer mortality. Although usually sporadic, approximately 1–2% of cases are familial. In addition, about 13% of patients with neuroblastoma harbor pathogenic/likely pathogenic germline variants in cancer predisposition genes. With the increasing use of molecular testing, associations between neuroblastoma and hereditary cancer predisposition syndromes are being recognized more frequently. Here, we present two rare cases with variants in hereditary cancer susceptibility genes. Case presentations: Case 1: Diagnosed with neuroblastoma at 3 months, the patient received five chemotherapy cycles and surgery. Findings included plagiocephaly, strabismus, broad thumbs/toes, and cryptorchidism. ES showed a mosaic pathogenic CREBBP variant (c.4251C>G; p.Tyr1417*). Case 2: A one-year-old patient treated with autologous stem-cell transplantation for neuroblastoma had numerous colorectal polyps. Family history included colorectal and breast cancer. ES revealed pathogenic variants in TP53 (c.742C>T;p.Arg248Trp) and APC (c.1958+1G>A). Conclusion: In familial neuroblastoma, ALK and PHOX2B represent the principal and best-established germline

susceptibility genes, and pathogenic variants in these genes are widely recognized as key contributors to hereditary neuroblastoma pathogenesis. Nevertheless, accumulating case-based evidence suggests that pathogenic variants in additional genes associated with hereditary cancer predisposition syndromes may also confer an increased risk for neuroblastoma and other malignancies in childhood. Within this framework, the two cases presented in this report are of particular interest. In Case 1, a mosaic pathogenic variant in CREBBP was identified, consistent with mosaic Rubinstein–Taybi syndrome (RTS). Although neuroblastoma has rarely been reported in a limited number of patients with RTS carrying germline CREBBP pathogenic variants, to the best of our knowledge, the co occurrence of neuroblastoma with mosaic RTS has not been previously documented. This case underscores the importance of a comprehensive, phenotype-driven clinical evaluation particularly in children presenting with dysmorphic features rather than a solely tumor-centered approach, as such holistic assessment may be decisive for identifying underlying hereditary cancer predispositions. In Case 2, concurrent pathogenic germline variants in TP53 and APC were detected. While neuroblastoma occurring in association with germline TP53 pathogenic variants has been reported, such cases remain rare. In contrast, there is currently no evidence supporting an association between APC pathogenic variants and neuroblastoma. The presence of pathogenic variants in two distinct cancer predisposition genes in a single individual raises the possibility of Multilocus Inherited Neoplasia Allele Syndrome (MINAS). Although MINAS has predominantly been described in the context of adult-onset malignancies, this case suggests that MINAS should also be considered in the differential diagnosis in pediatric oncology, particularly in patients with complex phenotypes or atypical tumor presentations. In Türkiye, studies investigating the molecular etiology of childhood cancers including neuroblastoma remain limited. While case-based observations are valuable for hypothesis generation, they do not establish causality. Therefore, large-scale and systematic cohort studies are required to clarify these potential genotype–phenotype associations. Expanding genetic investigations in pediatric cancer populations may also contribute substantially to identifying novel therapeutic targets, improving risk stratification, and defining prognostic biomarkers.
Keywords: Neuroblastoma, CREBBP, TP53, APC, hereditary cancer predisposition

[Abstract:0150]

Clinical and Molecular Characteristics of Hereditary Cancer–Associated Germline Mutations in Patients with Glioblastoma Multiforme: A Single-Center Retrospective Analysis

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Objective: Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults and remains associated with poor clinical outcomes despite advances in multimodal therapy. Emerging evidence suggests that hereditary cancer–associated germline mutations may contribute to GBM development in a subset of patients, particularly those diagnosed at a younger age or with a positive family history of cancer. This study aimed
to evaluate the prevalence, gene-specific distribution, and clinical relevance of pathogenic germline mutations in patients with GBM.

Materials-Methods: In this single-center retrospective analysis, 29 patients with histologically confirmed GBM were included. Clinical and demographic data were retrieved from medical records. All patients underwent germline genetic testing using a comprehensive hereditary cancer gene panel. Genetic variants were interpreted and classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Only pathogenic
and likely pathogenic variants were considered for analysis.

Results: Pathogenic or likely pathogenic germline mutations were identified in 4 patients (15%). The detected mutations involved TP53, BRCA2, CHEK2, and ATM, genes that play central roles in DNA damage response, cell cycle regulation, and maintenance of genomic stability. Patients harboring germline mutations were diagnosed at a younger median age and more frequently had a family history of cancer compared with mutation-negative patients.
These findings indicate that germline alterations may define a biologically and clinically distinct subgroup within the GBM population.

Conclusion: Hereditary cancer–associated germline mutations represent a clinically meaningful subset of GBM patients. Identification of these mutations may have important implications for genetic counseling, familial risk stratification, and future personalized therapeutic approaches. Germline genetic testing should be considered, particularly in patients with early-onset disease or a suggestive family history.

Keywords: Glioblastoma multiforme, Germline mutations, Hereditary cancer, DNA damage response, Genetic counseling

Table 1. Demographic and Clinical Characteristics of Patients with Glioblastoma Multiforme

Table 1. Demographic and Clinical Characteristics of Patients with Glioblastom

Characteristic	All Patients (n=29)	Germline Mutation (+) (n=4)	Germline Mutation (−) (n=25
Median age, years	56	42	59
Male sex, n (%)	17 (58.6)	2 (50.0)	15 (60.0)
Family history of cancer, n (%)	8 (27.6)	3 (75.0)	5 (20.0)
Multiple primary malignancies, n (%)	3 (10.3)	2 (50.0)	1 (4.0)

Table 2. Detailed Distribution of Identified Germline Genetic Mutations

Table 2. Detailed Distribution of Identified Germline Genetic Mutations

Patient	Gene	Variant Type	ACMG Classification	Molecular Pathway	Clinical Interpretation
1	TP53	Missense	Pathogenic	Cell cycle control	Early-onset GBM, positive family history
2	BRCA2	Frameshift	Pathogenic	Homologous recombination	Family history of breast cancer
3	CHEK2	Nonsense	Likely pathogenic	DNA damage checkpoint	Multiple primary malignancies
4	ATM	Missense	Likely pathogenic	DNA double-strand break repair	Diagnosis at a young age

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[Abstract:0152]

Clinical Characteristics and Therapeutic Outcomes of Patients with Germline BRCA1/2 Mutations Treated with PARP Inhibitors

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Objective: Germline mutations in BRCA1 and BRCA2 genes are central to hereditary cancer syndromes and lead to defective homologous recombination DNA repair. This biological vulnerability provides the rationale for the use of poly(ADP-ribose) polymerase (PARP) inhibitors across a spectrum of BRCA-associated malignancies.This study aimed to evaluate the clinical characteristics, tumor spectrum, and treatment outcomes of patients with germline BRCA1/2 mutations who received PARP inhibitor therapy.
Materials-Methods: In this retrospective study, 40 patients with pathogenic or likely pathogenic germline BRCA1/2 mutations treated with PARP inhibitors were analyzed. Demographic features, cancer types, family history, treatment duration, response rates, and progression-free survival (PFS) were assessed. Germline variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria.
Results: The median age at diagnosis was 49 years (range: 32–71), and 67.5% of patients were female. BRCA2 mutations were more frequent than BRCA1 mutations (65% vs. 35%). A positive family history of cancer was present in 65% of patients, and 22.5% developed multiple primary malignancies. The median duration of PARP inhibitor therapy was 11.2 months. The overall response rate was 57.5%, and the disease control rate was 80%. Median PFS was 13.4 months, with longer PFS observed in patients harboring BRCA2 mutations compared with BRCA1 mutations.
Conclusion: Patients with germline BRCA1/2 mutations represent a distinct hereditary cancer subgroup that derives substantial clinical benefit from PARP inhibitor therapy. Early identification of BRCA mutation carriers enables personalized treatment strategies and optimized oncologic outcomes.

Keywords: BRCA1, BRCA2, hereditary cancer, PARP inhibitors, germline mutation

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Table 1. Clinical Characteristics and Treatment Outcomes of Patients with Germline BRCA1/2 Mutations Treated with PARP Inhibitors (n = 40)

Table. Clinical Characteristics and Outcomes of BRC

Variable	Total (n=40)	BRCA1 (n=14)	BRCA2 (n=26)
Median age at diagnosis, years	49	47	51
Female sex, n (%)	27 (67.5)	12 (85.7)	15 (57.7)
Positive family history, n (%)	26 (65.0)	10 (71.4)	16 (61.5)
Multiple primary malignancies, n (%)	9 (22.5)	3 (21.4)	6 (23.1)
Breast cancer, n (%)	18 (45.0)	9 (64.3)	9 (34.6)
Ovarian cancer, n (%)	9 (22.5)	4 (28.6)	5 (19.2)
Prostate cancer, n (%)	6 (15.0)	0 (0)	6 (23.1)
Pancreatic cancer, n (%)	4 (10.0)	1 (7.1)	3 (11.5)
Median PARP duration (months)	11.2	9.4	13.6
Overall response rate (%)	57.5	42.9	65.4
Median PFS (months)	13.4	10.2	15.6

Glioblastoma Multiforme Hastalarında Herediter Kanserle İlişkili Germline Mutasyonların Klinik ve Moleküler Özellikleri: Tek Merkezli Retrospektif Analiz Özet Amaç: Glioblastoma multiforme (GBM), agresif biyolojik davranışı ve sınırlı sağkalımı ile bilinen primer beyin tümörlerinin en sık görülen alt tipidir. Son yıllarda herediter kanserle ilişkili germline mutasyonların GBM gelişimindeki rolü giderek daha fazla önem kazanmaktadır. Bu çalışmada, GBM tanılı hastalarda germline genetik mutasyonların sıklığını ve klinik özelliklerle ilişkisini değerlendirmeyi amaçladık. Gereç ve Yöntem: Çalışmaya GBM tanısı almış 29 hasta dâhil edildi. Hastaların demografik ve klinik verileri retrospektif olarak incelendi. Tüm hastalara herediter kanser gen paneli kullanılarak germline genetik analiz uygulandı. Varyantlar ACMG kriterlerine göre sınıflandırıldı. Bulgular: Toplam 29 hastanın 4'ünde (%15) patojenik veya olası patojenik germline mutasyon saptandı. Saptanan mutasyonlar; DNA hasar yanıtı, hücre döngüsü düzenlenmesi ve genomik stabilitenin korunmasında merkezi rollere sahip olan TP53, BRCA2, CHEK2 ve ATM genlerini içermekteydi. Mutasyon pozitif hastalar daha genç yaşta tanı almış olup, ailesel kanser öyküsü bu grupta daha sıktı. Saptanan mutasyonların tamamı DNA hasar yanıtı ve hücre döngüsü regülasyonu ile ilişkili genlerde yoğunlaşmaktaydı. Sonuç: GBM hastalarında herediter kanserle ilişkili germline mutasyonlar klinik açıdan anlamlı bir alt grubu temsil etmektedir. Özellikle genç yaşta tanı alan ve ailesel kanser öyküsü bulunan hastalarda genetik danışmanlık ve germline genetik testlerin değerlendirilmesi önerilmelidir. Giriş Glioblastoma multiforme (GBM), Dünya Sağlık Örgütü 2021 sınıflamasına göre derece 4 astrositik tümörler arasında yer almakta olup erişkinlerde en sık görülen malign primer beyin tümörüdür. Standart cerrahi, radyoterapi ve temozolomid bazlı tedavi yaklaşımlarına rağmen prognoz halen kötüdür. GBM olgularının büyük çoğunluğu sporadik olarak kabul edilmekle birlikte, son yıllarda yapılan genetik çalışmalar herediter kanser sendromları ile ilişkili germline mutasyonların GBM gelişiminde rol oynayabileceğini göstermektedir. Özellikle DNA onarım mekanizmalarında görev alan genlerdeki kalıtsal bozukluklar, genomik instabiliteyi artırarak tümör

gelişimine zemin hazırlayabilmektedir. Gereç ve Yöntem Bu retrospektif çalışmaya, merkezimizde GBM tanısı almış 29 hasta dâhil edildi. Hastaların yaş, cinsiyet, tanı anındaki klinik özellikleri ve ailesel kanser öyküleri hasta kayıtlarından elde edildi. Tüm hastalara herediter kanser gen paneli ile germline genetik analiz yapıldı. Saptanan varyantlar American College of Medical Genetics and Genomics (ACMG) kriterlerine göre patojenik, olası patojenik veya benign olarak sınıflandırıldı. Bulgular Hasta Özellikleri Çalışmaya dâhil edilen hastaların medyan tanı yaşı 56 yıl (aralık: 32–74) idi. Hastaların %58,6'sı erkekti. Tüm hastalar standart cerrahi ve adjuvan tedavilerle izlenmişti. Germline genetik analiz sonucunda 4 hastada (%15) patojenik veya olası patojenik mutasyon saptandı. Mutasyon pozitif hastaların tamamında etkilenen genler DNA hasar yanıtı, genomik stabilite ve hücre döngüsü regülasyonu ile ilişkiliydi. Mutasyon pozitif grupta tanı yaşı daha genç olup, ailesel kanser öyküsü ve çoklu primer malignite varlığı daha sık gözlendi. Tablo 1. GBM Hastalarının Demografik ve Klinik Özellikleri Özellik Medyan yaş, yıl Erkek cinsiyet, n (%) Ailesel kanser öyküsü, n (%) Çoklu primer malignite, n (%) Tüm Hastalar (n=29) 56 17 (58,6) 8 (27,6) 3 (10,3) Germline Mutasyon (+) (n=4) 42 2 (50) Germline Mutasyon (–) (n=25) 59 15 (60) 3 (75) 2 (50) 5 (20) 1 (4) Tablo 2. Saptanan Germline Genetik Mutasyonların Ayrıntılı Dağılımı Hasta Gen 1 Varyant Türü TP53 Missense 2 ACMG Sınıfı Patojenik BRCA2 Frameshift Patojenik 3 4 CHEK2 Nonsense ATM Missense Olası patojenik Olası patojenik Moleküler Yolak Klinik Yorum Hücre döngüsü kontrolü Erken yaş GBM, ailesel kanser öyküsü Homolog rekombinasyon DNA hasar kontrol noktası DNA çift zincir kırık onarımı Ailede meme kanseri öyküsü Çoklu primer malignite Genç yaşta tanı Tablo 3. Germline Mutasyonların Moleküler Yolaklara Göre Dağılımı Moleküler Yolak DNA hasar yanıtı İlgili Genler Hasta Sayısı (n) Oran (%) BRCA2, ATM, CHEK2 4 Hücre döngüsü regülasyonu TP53, CHEK2 Homolog rekombinasyon BRCA2, ATM 3 2 Şekil 1. GBM Hastalarında Germline Mutasyon Dağılımı 100 75 50 Glioblastoma multiforme tanılı 29 hastanın germline genetik analiz sonuçlarına göre 4 hastada (%15) patojenik veya olası patojenik germline mutasyon saptanırken, 25 hastada (%85) mutasyon saptanmadı. Tartışma Bu çalışmada glioblastoma multiforme (GBM) tanılı hastaların %15'inde herediter kanserle ilişkili patojenik veya olası patojenik germline mutasyon saptanmıştır. Bu oran, GBM'nin yalnızca sporadik bir tümör olmadığını gösteren güncel literatürle uyumlu olup herediter genetik yatkınlığın klinik pratikte göz ardı edilmemesi gerektiğini desteklemektedir. Literatürde GBM hastalarında bildirilen germline mutasyon sıklığı çalışmalara göre değişkenlik göstermektedir. Zhang ve arkadaşları, pediatrik ve erişkin GBM olgularını içeren çalışmalarında predispozisyon genlerinde germline mutasyon oranını yaklaşık %8–10 olarak bildirmiştir. Mandelker ve arkadaşları ise tümör-odaklı sekanslama yapılan hastalarda germline varyantların %10–18 oranında saptanabildiğini göstermiştir. Çalışmamızda elde edilen %15'lik oran, bu aralıkla uyumlu olup herediter yatkınlığın azımsanmayacak bir hasta grubunda mevcut olduğunu ortaya koymaktadır. Saptanan mutasyonların tamamının DNA hasar yanıtı ve hücre döngüsü regülasyonu ile ilişkili genlerde yoğunlaşması, literatürde bildirilen moleküler mekanizmalarla paralellik göstermektedir. Kinnersley ve Houlston tarafından yayımlanan kapsamlı derlemede, GBM ve diğer gliomaların gelişiminde özellikle TP53, ATM, BRCA2 ve CHEK2 gibi genlerin kritik rol oynadığı vurgulanmıştır. Çalışmamızda aynı genlerin ön planda olması, herediter genomik instabilitenin GBM patogenezindeki önemini desteklemektedir. Özellikle TP53 germline mutasyonları, Li-Fraumeni sendromu kapsamında GBM ile güçlü şekilde ilişkilendirilmiştir. Literatürde TP53 mutasyonu taşıyan bireylerde GBM'nin daha genç yaşta ortaya çıktığı ve agresif klinik seyir gösterebildiği bildirilmiştir. Çalışmamızda TP53 mutasyonu saptanan hastanın genç yaşta tanı alması ve ailesel kanser öyküsünün bulunması, bu literatür bilgileriyle birebir örtüşmektedir. BRCA2 ve ATM gibi DNA çift zincir kırık onarımında görev alan genlerdeki germline mutasyonlar, GBM ile daha nadir ilişkilendirilmiş olmakla birlikte son yıllarda artan sayıda çalışmada rapor edilmektedir. Bu genlerdeki bozuklukların, tümör hücrelerinde artmış genomik instabiliteye ve potansiyel olarak tedavi direncine katkıda bulunabileceği öne sürülmektedir. Çalışmamızda bu genlerin saptanması, GBM'nin moleküler heterojenitesine herediter faktörlerin de katkıda bulunduğunu düşündürmektedir. Klinik açıdan değerlendirildiğinde, mutasyon pozitif hastalarda tanı yaşının daha genç olması ve ailesel kanser öyküsünün daha sık görülmesi, literatürde tanımlanan klinik ipuçlarıyla uyumludur. Birçok çalışmada, genç yaşta

GBM tanısı alan veya birden fazla primer malignite öyküsü bulunan hastalarda germline genetik testlerin daha yüksek tanısal verim sağladığı bildirilmiştir. Bu bağlamda çalışmamız, genetik test için hasta seçiminde klinik belirteçlerin önemini desteklemektedir. Çalışmamızın en önemli katkılarından biri, herediter kanser gen paneli ile sistematik germline tarama yapılan sınırlı sayıda GBM serilerinden biri olmasıdır. Bununla birlikte, hasta sayısının görece düşük olması ve sağkalım analizlerinin sınırlı kalması çalışmanın başlıca kısıtlılıklarıdır. Daha geniş hasta serileri ve prospektif çalışmalar, germline mutasyonların prognoz ve tedavi yanıtı üzerindeki etkisini daha net ortaya koyacaktır. Sonuç GBM hastalarında herediter kanserle ilişkili germline mutasyonlar klinik açıdan anlamlı bir alt grubu temsil etmektedir. Genç yaşta tanı alan ve ailesel kanser öyküsü bulunan GBM hastalarında genetik danışmanlık ve germline genetik testlerin değerlendirilmesi önerilmelidir. Bu yaklaşım, hem hastaya hem de aile bireylerine yönelik kişiselleştirilmiş sağlık stratejilerine katkı sağlayabilir. Kaynaklar 1. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23(8):1231–1251. doi:10.1093/neuonc/noab106. PMID: 34185076. 2. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–996. doi:10.1056/NEJMoa043330. PMID: 15758009. 3. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2015–2019. Neuro Oncol. 2022;24(Suppl 5):v1–v95. doi:10.1093/neuonc/noac202. PMID: 36191255. 4. Scheurer ME, Bondy ML, Aldape KD, et al. Familial aggregation of glioma: a pooled analysis. Am J Epidemiol. 2010;172(10):1099–1107. doi:10.1093/aje/kwq261. PMID: 20858744. 5. Kyritsis AP, Bondy ML, Rao JS, Sioka C. Inherited predisposition to glioma. Neuro Oncol. 2010;12(1):104–113. doi:10.1093/neuonc/nop011. PMID: 20150373. 6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–424. doi:10.1038/gim.2015.30. PMID: 25741868. 7. Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, et al. Germline mutations in predisposition genes in pediatric cancer. N Engl J Med. 2015;373(24):2336–2346. doi:10.1056/NEJMoa1508054. PMID: 26580448. 8. Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, et al. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. Cancer. 2008;113(7 Suppl):1953–1968. PMID: 18798534. 9. Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med. 2015;372(26):2499–2508. doi:10.1056/NEJMoa1407279. PMID: 26061753. 10. Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol. 2015;33(21):2345–2352. PMID: 26014290. 11. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321(5897):1807–1812. doi:10.1126/science.1164382. PMID: 18772396.

[Abstract:0160]

A Rare Association in a BRCA1 Positive Case: Esophageal Squamous Cell Carcinoma and Management of Metachronous Ovarian Cancer

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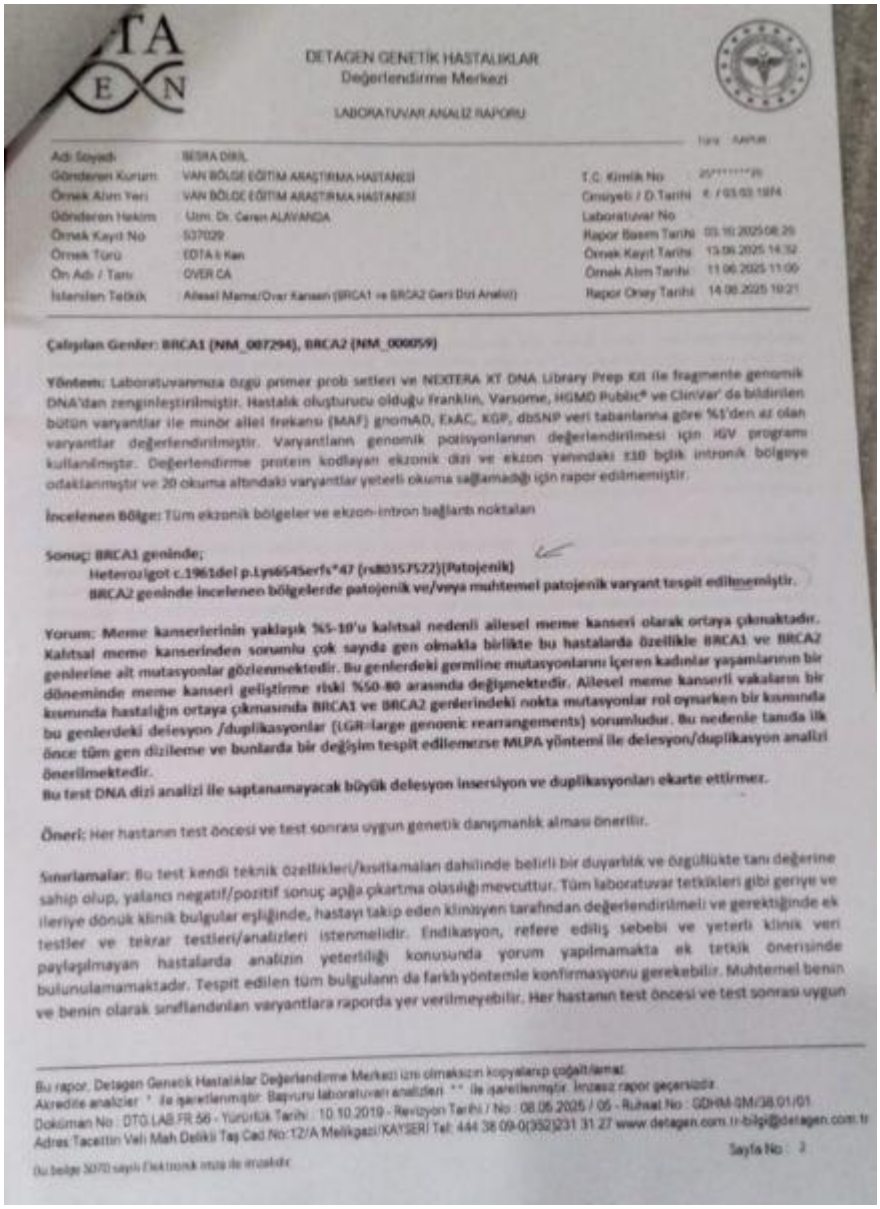
Objective: BRCA1/2 mutations trigger malignant transformation by impairing the cellular ability to repair damaged DNA. Consequently, this damage significantly increases the risk of primarily breast and ovarian cancers, as well as pancreatic and prostate cancers. Although rare, it may also lead to melanoma, endometrial, and digestive system malignancies. While cases of BRCA2-associated esophageal cancer exist in the literature, the relationship between BRCA1 and esophageal cancer is not clearly defined and remains controversial. The aim of this study is to discuss the potential association of a BRCA1 mutation detected during esophageal cancer treatment and to emphasize the importance of prophylactic oophorectomy.
Case: A 51-year-old female patient presented in September 2020 with abdominal pain and dysphagia. Endoscopy revealed a malignant-appearing lesion in the proximal esophagus. Following a biopsy confirming esophageal squamous cell carcinoma (SCC), a systemic PET scan was performed. Uptake was observed starting from the C6 level of the proximal esophagus, extending for a 7.5 cm segment. Additionally, FDG uptake was noted in the bilateral adnexal region. Since the ovarian biopsy was consistent with inflammation, definitive chemoradiotherapy with concurrent carboplatin and paclitaxel was administered. Upon achieving a complete response on post-treatment imaging, the patient was placed under surveillance. Due to a family history of prostate cancer in her brother and father, germline BRCA1/2 testing was performed during this period. The patient, found to be a BRCA1 carrier, was offered prophylactic oophorectomy and mastectomy options; however, as she declined surgery, she was followed up with intermittent surveillance. In 2025, due to worsening abdominal pain, a CT scan was performed, revealing a 27x13 mm lesion in liver segment 7 indistinguishable between hemangioma and metastasis; thus, a dynamic liver MRI was obtained. As metastasis could still not be ruled out, a liver biopsy was performed. The patient, primarily suspected of having metastatic ovarian cancer, underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH+BSO), and metastasectomy in October 2025 following 3 cycles of neoadjuvant chemotherapy. Following an additional 3 cycles of adjuvant carboplatin and paclitaxel, maintenance olaparib therapy was initiated. The patient is currently being followed in remission.
Conclusion: Data regarding the relationship between BRCA mutations and esophageal SCC are limited in the literature. Whether the esophageal tumor in our case was sporadic or mutation-associated remains a matter of debate. However, the effectiveness of the platinum-based chemotherapy administered in achieving long-term remission for both cancers supports the concept of platinum sensitivity in the presence of a BRCA mutation. Furthermore, this case underscores that recommending risk-reducing oophorectomy in individuals with BRCA mutations is of paramount importance.

Keywords: BRCA1 Mutation, Esophageal Squamous Cell Carcinoma, Platinum Sensitivity

BRCA1 MUTASYON SONUCU



DETAGEN GENETİK HASTALIKLAR
Değerlendirme Merkezi

LABORATUVAR ANALİZ RAPORU

Adı Soyadı	BESRA DİRİL		
Gönderen Kurum	VAN BÖLGE EĞİTİM ARAŞTIRMA HASTANESİ	T.C. Kimlik No	[redacted]
Örnek Alım Yeri	VAN BÖLGE EĞİTİM ARAŞTIRMA HASTANESİ	Cinsiyeti / D.Tarihi	K / 03.03.1974
Gönderen Hekim	Uzm. Dr. Ceren ALAVANDA	Laboratuvar No	
Örnek Kayıt No	537029	Rapor Basım Tarihi	03.10.2025 08:20
Örnek Türü	EDTA li Kan	Örnek Kayıt Tarihi	13.06.2025 14:32
Ön Adı / Tanı	OVER CA	Örnek Alım Tarihi	11.06.2025 11:00
İstenilen Tetkik	Ailesel Meme/Over Kanseri (BRCA1 ve BRCA2 Geni Dizi Analizi)	Rapor Onay Tarihi	14.06.2025 10:21

Çalışılan Genler: BRCA1 (NM_007294), BRCA2 (NM_000059)

Yöntem: Laboratuvarımıza özgü primer prob setleri ve NEXTERA XT DNA Library Prep Kit ile fragmente genomik DNA'dan zenginleştirilmiştir. Hastalık oluşturucu olduğu franklin, Varsome, HGMD Public® ve ClinVar' da bildirilen bütün varyantlar ile minör allel frekansı (MAF) gnomAD, ExAC, KGP, dbSNP veri tabanlarına göre %1'den az olan varyantlar değerlendirilmiştir. Varyantların genomik pozisyonlarının değerlendirilmesi için IGV programı kullanılmıştır. Değerlendirme protein kodlayan ekzonik dizi ve ekzon yanındaki ±10 bçtlk intronik bölgeye odaklanmıştır ve 20 okuma altındaki varyantlar yeterli okuma sağlamadığı için rapor edilmemiştir.

İncelenen Bölge: Tüm ekzonik bölgeler ve ekzon-intron bağlantı noktaları

Sonuç: BRCA1 geninde;
Heterozigot c.1961del p.Lys654erfs*47 (rs80357522)(Patojenik)
BRCA2 geninde incelenen bölgelerde patojenik ve/veya muhtemel patojenik varyant tespit edilmemiştir.

Yorum: Meme kanserlerinin yaklaşık %5-10'u kalıtsal nedenli ailesel meme kanseri olarak ortaya çıkmaktadır. Kalıtsal meme kanserinden sorumlu çok sayıda gen olmakla birlikte bu hastalarda özellikle BRCA1 ve BRCA2 genlerine ait mutasyonlar gözlenmektedir. Bu genlerdeki germline mutasyonlarını içeren kadınlar yaşamlarının bir döneminde meme kanseri geliştirme riski %50-80 arasında değişmektedir. Ailesel meme kanserli vakaların bir kısmında hastalığın ortaya çıkmasında BRCA1 ve BRCA2 genlerindeki nokta mutasyonlar rol oynarken bir kısmında bu genlerdeki delesyon /duplikasyonlar (LGR:large genomic rearrangements) sorumludur. Bu nedenle tanıda ilk önce tüm gen dizileme ve bunlarda bir değişim tespit edilmezse MLPA yöntemi ile delesyon/duplikasyon analizi önerilmektedir.
Bu test DNA dizi analizi ile saptanamayacak büyük delesyon insersiyon ve duplikasyonları ekarte ettirmez.

Öneri: Her hastanın test öncesi ve test sonrası uygun genetik danışmanlık alması önerilir.

Sınırlamalar: Bu test kendi teknik özellikleri/kısıtlamaları dahilinde belirli bir duyarlılık ve özgüllükte tanı değerine sahip olup, yalancı negatif/pozitif sonuç açığa çıkarma olasılığı mevcuttur. Tüm laboratuvar tetkikleri gibi geriye ve ileriye dönük klinik bulgular eşliğinde, hastayı takip eden klinisyen tarafından değerlendirilmeli ve gerektiğinde ek testler ve tekrar testleri/analizleri istenmelidir. Endikasyon, refere ediliş sebebi ve yeterli klinik veri paylaşılmayan hastalarda analizin yeterliliği konusunda yorum yapılmamakta ek tetkik önerisinde bulunulamamaktadır. Tespit edilen tüm bulguların da farklı yöntemle konfirmasyonu gerekebilir. Muhtemel benin ve benin olarak sınıflandırılan varyantlara raporda yer verilmeyebilir. Her hastanın test öncesi ve test sonrası uygun

Akredite analizler * ile işaretlenmiştir. Başvuru laboratuvarı analizleri ** ile işaretlenmiştir. İmzasız rapor geçersizdir.

*BRCA1 genindeki mutasyon: heterozigot c.1961del p.Lys654erfs*47(rs80357522) (patojenik)*

Title: Co-occurrence of Esophageal SCC and Metachronous Ovarian Cancer in a BRCA1 Carrier: Etiological Uncertainty and Platinum Sensitivity Introduction and Objective: BRCA1/2 mutations trigger malignant transformation by impairing the cellular ability to repair damaged DNA. Consequently, this damage significantly increases the risk of primarily breast and ovarian cancers, as well as pancreatic and prostate cancers (1). Although rare, it may also lead to melanoma, endometrial, and digestive system malignancies (2). While cases of BRCA2-associated esophageal cancer exist in the literature, the relationship between BRCA1 and esophageal cancer is not clearly defined and remains controversial (3). The aim of this study is to discuss the potential association of a BRCA1 mutation detected during esophageal cancer treatment and to emphasize the importance of prophylactic oophorectomy. Case: A 51-year-old female patient presented in September 2020 with abdominal pain and dysphagia. Endoscopy revealed a malignant appearing lesion in the proximal esophagus. Following a biopsy confirming esophageal squamous cell carcinoma (SCC), a systemic PET scan was performed. Uptake was observed starting from the C6 level of the proximal esophagus, extending for a 7.5 cm segment. Additionally, FDG uptake was noted in the bilateral adnexal region. Since the ovarian biopsy was

consistent with inflammation, definitive chemoradiotherapy with concurrent carboplatin and paclitaxel was administered. Upon achieving a complete response on post-treatment imaging, the patient was placed under surveillance. Due to a family history of prostate cancer in her brother and father, germline BRCA1/2 testing was performed during this period. The patient, found to be a BRCA1 carrier [heterozigot c.1961del p.Lys654erfs*47(rs80357522)], was offered prophylactic oophorectomy and mastectomy options; however, as she declined surgery, she was followed up with intermittent surveillance. In 2025, due to worsening abdominal pain, a CT scan was performed, revealing a 27x13 mm lesion in liver segment 7 indistinguishable between hemangioma and metastasis; thus, a dynamic liver MRI was obtained. As metastasis could still not be ruled out, a liver biopsy was performed. The patient, primarily suspected of having metastatic ovarian cancer, underwent total abdominal hysterectomy, bilateral salpingo oophorectomy (TAH+BSO), and metastasectomy in October 2025 following 3 cycles of neoadjuvant chemotherapy. Following an additional 3 cycles of adjuvant carboplatin and paclitaxel, maintenance olaparib therapy was initiated. The patient is currently being followed in remission. Discussion Previous studies have reported that BRCA2 mutations may play a role in the etiology of various gastrointestinal malignancies. However, data regarding BRCA1 mutations remain limited. In this context, the co occurrence of a BRCA1 mutation and esophageal cancer in our patient warrants evaluation (2). It is well established that BRCA mutations are most frequently associated with breast and ovarian cancers. Consistent with the literature, our case also presents with a concurrent BRCA1 mutation and ovarian cancer (1). BRCA and other homologous recombination genes function by repairing DNA double-strand breaks. In the presence of a mutation, this repair mechanism is compromised, leading the cell to undergo apoptosis. Platinum-based agents exert their cytotoxic effects by inducing DNA damage. Consequently, the therapeutic effect resulting from platinum-induced DNA damage is more pronounced in patients harboring BRCA mutations. In our case, a complete response to platinum-based therapy was achieved and long term remission was observed, findings that are consistent with the literature (4). Conclusion: Data regarding the relationship between BRCA mutations and esophageal SCC are limited in the literature. Whether the esophageal tumor in our case was sporadic or mutation-associated remains a matter of debate. However, the effectiveness of the platinum based chemotherapy administered in achieving long-term remission for both cancers supports the concept of platinum sensitivity in the presence of a BRCA mutation. Furthermore, this case underscores that recommending risk-reducing oophorectomy in individuals with BRCA mutations is of paramount importance. References 1- Yoshida R. (2021). Hereditary breast and ovarian cancer (HBOC): review of its molecular characteristics, screening, treatment, and prognosis. Breast cancer (Tokyo, Japan), 28(6), 1167–1180. https://doi.org/10.1007/s12282-020-01148-2 2- Breast Cancer Linkage Consortium (1999). Cancer risks in BRCA2 mutation carriers. Journal of the National Cancer Institute, 91(15), 1310–1316. https://doi.org/10.1093/jnci/91.15.1310 3- Akbari, M. R., Malekzadeh, R., Nasrollahzadeh, D., Amanian, D., Islami, F., Li, S., Zandvakili, I., Shakeri, R., Sotoudeh, M., Aghcheli, K., Salahi, R., Pourshams, A., Semnani, S., Boffetta, P., Dawsey, S. M., Ghadirian, P., & Narod, S. A. (2008). Germline BRCA2 mutations and the risk of esophageal squamous cell carcinoma. Oncogene, 27(9), 1290–1296. https://doi.org/10.1038/sj.onc.1210739 4- Pennington, K. P., Walsh, T., Harrell, M. I., Lee, M. K., Pennil, C. C., Rendi, M. H., Thornton, A., Norquist, B. M., Casadei, S., Nord, A. S., Agnew, K. J., Pritchard, C. C., Scroggins, S., Garcia, R. L., King, M. C., & Swisher, E. M. (2014). Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clinical cancer research : an official journal of the American Association for Cancer Research, 20(3), 764–775. https://doi.org/10.1158/1078-0432.CCR-13-2287 Figure 5-

[Abstract:0163]

Prediction of the functional impact of variants of uncertain significance in BRCA1 and BRCA2 with Machine Learning

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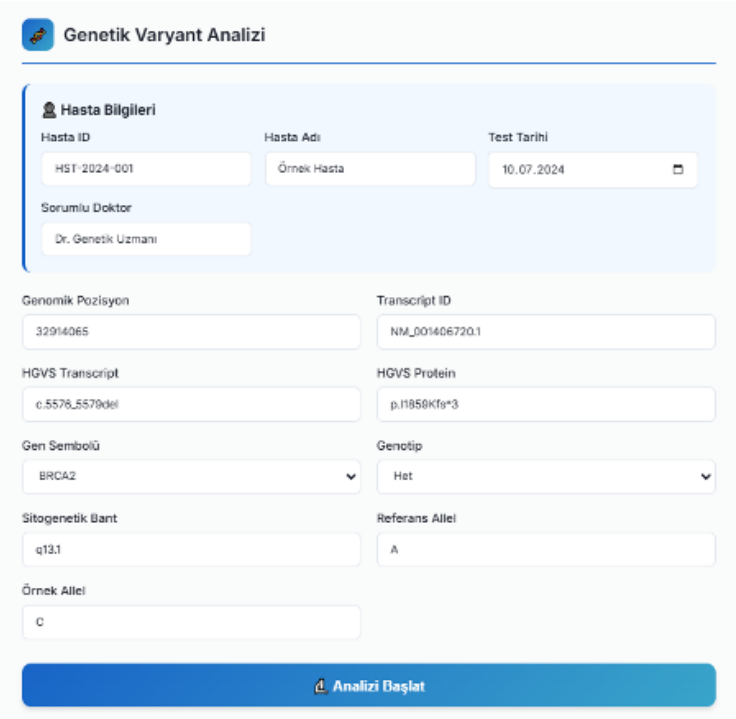
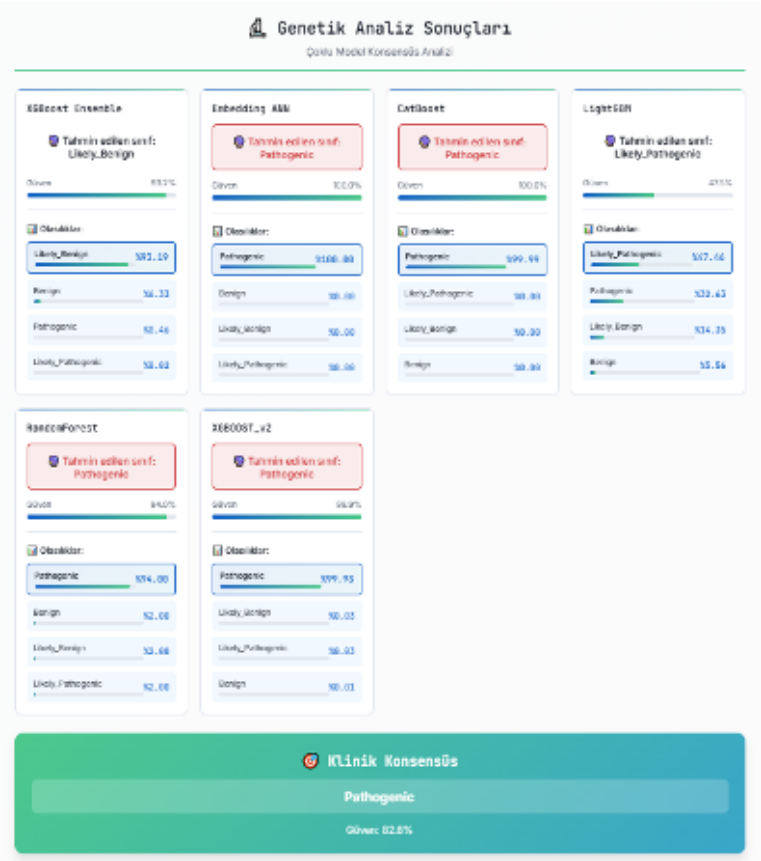
Objective: The implementation of next-generation sequencing (NGS) for the genetic analysis of hereditary diseases has dramatically increased the volume of genomic data, creating both opportunities for precise diagnosis and challenges related to variant classification and clinical interpretation. In silico predictions of missense variants are a significant factor in the interpretation of variants of uncertain significance (VUS) in the context of the BRCA1 and BRCA2 genes.
Materials-Methods: This study analyzed a large-scale retrospective dataset of 202,535 records obtained from the Pamukkale University Genetic Diagnosis Laboratory, spanning the last two years (including 2023). The dataset was categorized into four distinct classes (Benign, Likely Benign, Likely Pathogenic, and Pathogenic) according to ACMG-AMP guidelines. To evaluate model generalization, the data was partitioned into 80% training and 20% testing sets using stratified sampling. Input features were rigorously selected from the NGS pipeline, including genomic coordinates (POS, Cytoband), gene identifiers (GENE_SYMBOL, TRANSCRIPT_ID), molecular variant descriptions (HGVS_TRANSCRIPT, HGVS_PROTEIN), and genotype details (Genotype, Reference Allele, Sample Allele), with ING_CLASSIFICATION serving as the target variable. Reflecting the inherent scarcity of confirmed pathogenic variants in clinical populations—a primary factor contributing to the VUS interpretation challenge—the raw dataset exhibited a severe class imbalance. To overcome this domain-specific limitation, a multi-faceted strategy was implemented: Cost-Sensitive Learning (Class Weights) was computed to impose heavier penalties for misclassifying rare but critical cases, while SMOTE and SMOTENC were utilized to generate synthetic representations for numerical and mixed feature spaces. Furthermore, advanced regularization techniques—including L1 (Lasso) and L2 (Ridge) penalties for XGBoost models and Dropout layers for the Deep Neural Network (ANN)—were applied. Specifically, XGBoost (v1 baseline and v2 optimized), CatBoost, LightGBM, Random Forest, and a Deep Neural Network (ANN) with Entity Embeddings were trained and validated using 5-fold stratified cross-validation on the balanced training split.
Results: The developed models successfully automated the ACMG-AMP classification criteria. On the independent test set, CatBoost and LightGBM demonstrated superior performance. As evidenced by the confusion matrix analysis, the model exhibited exceptional sensitivity for high-risk classes: CatBoost correctly identified 391 out of 392 Pathogenic cases (99.7% Recall) and 70 out of 70 Likely Pathogenic cases (100% Recall). For the Benign class, the model achieved high precision, correctly classifying 39,699 out of 39,725 records. Crucially, the system missed only a single pathogenic case, ensuring near-zero false negatives in clinical risk assessment. A consensus mechanism based on majority voting was implemented to synthesize model outputs, further enhancing prediction reliability.
Conclusion: The findings of this study suggest that the utilization of gene- and disease-specific automated ML models, trained with local population data and advanced feature engineering, has the potential to significantly reduce conflicting interpretations and serve as a robust decision support tool for clinical evaluation.

Keywords: BRCA1, BRCA2, variants of uncertain significance (VUS), Artificial İntelligence

Genetic Variant Analysis



Genetic Variant Results



Prediction of the functional impact of variants of uncertain significance in BRCA1 and BRCA2 with Machine Learning Aydın Demiray1, Şinasi Ege Karataş2, Ömer Güleç2, Ege Rıza Karagür1, Hakan Akça1 1Deparment of Medical Genetics, School of Medicine, Pamukkale University, Denizli and Turkey 2Department of Management Information Systems, Faculty of Economics and Administrative Sciences, Pamukkale University, Denizli and Turkey Objective: The implementation of next-generation sequencing (NGS) for the genetic analysis of hereditary diseases has dramatically increased the volume of genomic data, creating both opportunities for precise diagnosis and challenges related to variant classification and clinical interpretation. In silico predictions of missense variants are a significant factor in the interpretation of variants of uncertain significance (VUS) in the context of the BRCA1 and BRCA2 genes. Materials-Methods: This study analyzed a large-scale retrospective dataset of 202,535 variant-level records obtained from the Pamukkale University Genetic Diagnosis Laboratory, spanning the last two years (including 2023). The dataset was categorized into four distinct classes (Benign, Likely Benign, Likely Pathogenic, and Pathogenic) according to ACMG-AMP guidelines. To maximize label reliability for supervised learning, variants labeled as Uncertain Significance (VUS) or Unknown were excluded due to their intrinsic clinical ambiguity. Prior to model development, rule-based quality control was applied to improve data consistency by filtering records with missing essential HGVS fields, inconsistent allele notation, and duplicated entries. To evaluate model generalization, the data was partitioned into 80% training and 20% testing sets using stratified sampling. Input features were rigorously selected from the NGS pipeline, including genomic coordinates (POS, Cytoband), gene identifiers (GENE_SYMBOL, TRANSCRIPT_ID), molecular variant descriptions (HGVS_TRANSCRIPT, HGVS_PROTEIN), and genotype details (Genotype, Reference Allele, Sample Allele), with ING_CLASSIFICATION serving as the target variable. Reflecting the inherent scarcity of confirmed pathogenic variants in clinical populations—a primary factor contributing to the VUS interpretation challenge—the raw dataset exhibited a severe class imbalance. Given the asymmetric clinical risk of false-negative predictions for pathogenic variants, cost-sensitive learning and macro-averaged evaluation were prioritized. Accordingly, Class Weights were computed to impose heavier penalties for misclassifying rare but clinically critical cases, while SMOTE and SMOTENC were used to generate synthetic representations for numerical and mixed feature spaces. To ensure a leakage-safe and clinically realistic evaluation, resampling procedures were applied strictly within the training folds during cross-validation, while validation and test partitions were kept free of synthetic samples. Furthermore, advanced regularization techniques—including L1 (Lasso) and L2 (Ridge) penalties for XGBoost models and Dropout layers for the Deep Neural Network (ANN)— were applied. Specifically, XGBoost (v1 baseline and v2 optimized), CatBoost, LightGBM, Random Forest, and a Deep Neural Network (ANN) with Entity Embeddings were trained and validated using 5-fold stratified cross-validation on the balanced training split. All records were de-identified prior to analysis and processed in accordance with institutional data governance policies. Results: The developed models successfully automated the ACMG-AMP classification criteria. On the independent test set, CatBoost and LightGBM demonstrated superior performance. As evidenced by the confusion matrix analysis, the model exhibited exceptional sensitivity for high-risk classes: CatBoost correctly identified 391 out of 392 Pathogenic cases (99.7% Recall) and 70 out of 70 Likely Pathogenic cases (100% Recall). For the Benign class, the model achieved high precision, correctly classifying 39,699 out of 39,725 records. Crucially, the system missed only a single pathogenic case, ensuring near-zero false negatives in clinical risk assessment. A consensus mechanism based on majority voting was implemented to synthesize model outputs, further enhancing prediction reliability. Conclusion: The findings of this study suggest that the utilization of gene- and disease-specific automated ML models, trained with local population data and advanced feature engineering, has the potential to significantly reduce conflicting interpretations and serve as a robust decision support tool for clinical evaluation. Keywords: BRCA1, BRCA2, variants of uncertain significance (VUS), Artificial İntelligence

[Abstract:0164]

Clinical Implications of Comprehensive Genetic Panels in Male Breast Cancer: From Pathogenic Mutations to Variants of Uncertain Significance (VUS)

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Male breast cancer (MBC) accounts for less than 1% of all breast cancers but represents a patient population with a high likelihood of hereditary cancer predisposition. Germline BRCA2 mutations are the most frequently identified hereditary alterations in MBC, and international guidelines recommend germline genetic testing for all men diagnosed with breast cancer. Recently, multigene panel testing has increasingly replaced BRCA1/2-only analyses in clinical practice

Objective: This study aimed to evaluate the distribution of comprehensive genetic panel results in male breast cancer patients and to assess the clinical relevance of variants of uncertain significance (VUS) in routine oncologic management.

Materials-Methods: Clinical and molecular data of six male breast cancer patients who underwent next-generation sequencing–based multigene hereditary cancer panel testing due to suspected genetic predisposition were retrospectively analyzed. Genetic findings were categorized as pathogenic variants with clinical implications, VUS, or negative results.

Results: The median age at diagnosis was 58 years (range: 34–69), and the majority of patients were diagnosed with invasive ductal carcinoma. Based on genetic analysis, the results were categorized as follows:
•Clinically actionable group (16.7%):
A pathogenic BRCA2 variant was identified in only one patient. This finding represented the sole actionable result, enabling cascade family screening and consideration of targeted treatment options such as PARP inhibitors.
•Clinical uncertainty (VUS) group (50%):
Variants of uncertain significance (VUS) were detected in half of the patients (3/6). According to current clinical guidelines, these findings did not lead to any changes in treatment or surveillance strategies. The identified variants involved DNA repair genes (e.g., ERCC2, POLE, MSH6); however, no recommendations for risk-reducing surgery or modification of systemic therapy were indicated in routine oncologic practice.
•Negative group (33.3%):

Conclusion: Although BRCA2 remains the key germline determinant influencing clinical management in male breast cancer, the use of comprehensive genetic panels is associated with a high rate of VUS, posing a significant clinical challenge. Based on current evidence, VUS findings in BRCA-negative patients should not alter standard treatment or follow-up strategies. Careful interpretation of multigene panel results within the framework of genetic counseling is essential to avoid unnecessary interventions.

Keywords: BRCA2, Germline genetic testing, Male breast cancer, Variant of uncertain significance (VUS)

Clinical Implications of Comprehensive Genetic Panels in Male Breast Cancer Background Male breast cancer (MBC) is a rare malignancy, accounting for less than 1% of all breast cancer cases. Despite its low incidence, MBC is of particular clinical importance due to its strong association with hereditary cancer predisposition syndromes. Compared with female breast cancer, men diagnosed with breast cancer have a significantly higher probability of harboring germline pathogenic variants, most notably in DNA repair genes. Among these, BRCA2 remains the most frequently identified and clinically relevant mutation. For this reason, international guidelines recommend germline genetic testing for all men diagnosed with breast cancer, regardless of age or family history. In recent years, advances in next-generation sequencing (NGS) technologies have led to the widespread use of comprehensive multigene panel testing, replacing single-gene BRCA1/2 analyses in routine practice. While multigene panels increase the likelihood of detecting hereditary alterations, they also introduce new challenges, particularly the high detection rate of variants of uncertain significance (VUS). The clinical interpretation and management of these variants remain a major concern in daily oncologic practice. Objective The aim of this study was to evaluate the distribution of comprehensive hereditary cancer panel results in male breast cancer patients and to assess the clinical impact of pathogenic variants and VUS findings. Methods Clinical and molecular data of six male breast cancer patients who underwent next-generation sequencing–based multigene hereditary cancer panel testing due to suspected genetic predisposition were retrospectively analyzed. Genetic findings were categorized as pathogenic variants with clinical implications, VUS, or negative results. Results The median age at diagnosis was 58 years, with most patients presenting with invasive ductal carcinoma. Genetic test results were categorized into three groups. A clinically actionable pathogenic variant was identified in only one patient (16.7%), involving a germline BRCA2 mutation. This finding had direct clinical implications, enabling cascade family screening and providing eligibility for targeted therapies such as PARP inhibitors in advanced disease settings. In contrast, variants of uncertain significance were detected in 50% of patients. These VUS involved genes related to DNA repair mechanisms, including ERCC2, POLE, and MSH6. According to current clinical guidelines, none of these variants justified changes in systemic treatment decisions, surveillance strategies, or risk-reducing surgical interventions. This highlights the limited immediate clinical utility of VUS findings and the potential risk of overinterpretation in routine oncology practice. The remaining patients (33.3%) had negative genetic test results, further emphasizing that not all male breast cancer cases are explained by detectable germline pathogenic variants, even with broad panel testing. Conclusion In conclusion, while BRCA2 remains the key germline determinant influencing clinical management in male breast cancer, the use of comprehensive multigene panels is associated with a substantial burden of VUS results. These findings often create uncertainty for both clinicians and patients without providing actionable benefits. Based on current evidence, VUS findings should not alter standard treatment or follow-up strategies, and their interpretation must be performed within the framework of expert genetic counseling. As multigene testing becomes increasingly common, developing standardized approaches for VUS interpretation and patient communication will be essential to optimize clinical decision-making and avoid unnecessary interventions. Keywords BRCA2; Germline genetic testing; Male breast cancer; Multigene panel testing; Variant of uncertain significance (VUS)

[Abstract:0173]

Syndromes with Cancer Predisposition: Three Cases With Werner Syndrome

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Objective: Werner syndrome is a rare autosomal recessive progeroid disorder characterized by multisystem involvement and an increased predisposition to malignancies, including soft tissue sarcomas, osteosarcomas, and thyroid carcinomas. It's caused by biallelic loss-of function variants in the *WRN* gene which encodes a DNA helicase in RecQ family, distrupting its function in DNA stabilization. In this report, we present three patients diagnosed with Werner syndrome who exhibited heterogeneous clinical features, highlighting the broad phenotypic spectrum of the disorder and the importance of systematic surveillance in affected individuals.

Case 1: A 14-year-old female patient was referred due to her myopia, bicuspid aorta and eunuchoid habitus. Her parents were from the same village with no known relation. In physical examination; pinched nose, scoliosis and increased and deep palmar creases were noted. Exom sequencing (ES) revealed a nonsense variant in *WRN* gene (NM_000553.6:c.1105C>T p.Arg369*).

Case 2: A 75-year-old female patient was referred from the rheumatology department because of scleroderma-like skin changes, lower extremity calcifications, and chronic skin ulcers. Her medical history was notable for a 20-year history of diabetes mellitus and bilateral cataract surgery performed at 55 years of age. Physical examination revealed scleroderma-like skin lesions and ulcers, with a pinched nasal appearance as the only additional finding. ES demonstrated a previously described intronic variant in the *WRN* gene (NM_000553.6:c.2089-3024A>G)

Case 3: A 20-year-old male patient was referred from ophthalmology because of bilateral cataracts and a syndromic appearance. He had received special education for 1.5 years due to learning difficulties, and his parents were first-degree cousins. Physical examination revealed a progeroid appearance, gray hair, pinched nose, thin extremities, and central adipose accumulation. ES identified a nonsense variant in the *WRN* gene (NM_000553.6:c.3493C>T; p.Gln1165*). Chromosomal analysis additionally demonstrated mosaic Klinefelter syndrome (mos 47,XXY[19]/46,XY[21]), explaining the patient's hypergonadotropic hypogonadism and establishing a dual genetic diagnosis.

Conclusion: These three distinct cases illustrate the broad phenotypic spectrum of Werner syndrome. All cases, particularly Case 2, demonstrate that individuals with Werner syndrome may be diagnosed at different ages, underscoring the importance of regular surveillance in accordance with published guidelines. These findings further highlight the need for comprehensive, age-spanning surveillance strategies for patients with Werner syndrome, extending from early adulthood through the sixth and seventh decades of life.

Keywords: Werner Syndrome, cancer predisposition, *WRN*

Furkan Baştan1, Abdullah Sezer1, Atakan Deniz1, Öznur Kaya Güneş1, Mehmet Akif Baltacı2, Alper Sarı2, İbrahim Vasi2, Elifcan Taşdelen1 1 Department of Medical Genetics, Ankara Etlik City Hospital, Ankara, Türkiye 2 Department of Rheumatology, Ankara Etlik City Hospital, Ankara, Türkiye Syndromes with Cancer Predisposition: Three Cases With Werner Syndrome Objective: Werner syndrome is a rare autosomal recessive progeroid disorder characterized by multisystem involvement and an increased predisposition to malignancies, including soft tissue sarcomas, osteosarcomas, and thyroid carcinomas. Some populations have a higher prevalence, ranging from 1:20000 to 1:40000 in Japanese population and approximately 1:50000 in Sardinian population. It

is caused by biallelic loss-of-function variants in the WRN gene, encoding a RecQ family DNA helicase essential for DNA stabilization. In this report, we present three patients diagnosed with Werner syndrome who exhibited heterogeneous clinical features, highlighting the broad phenotypic spectrum of the disorder and the importance of systematic surveillance in affected individuals. Case 1: A 14-year-old female patient was referred due to her myopia, bicuspid aorta and eunuchoid habitus. Her parents were from the same village with no known relation. In physical examination; pinched nose, scoliosis and increased and deep palmar creases were noted. Exome sequencing (ES) revealed a nonsense variant in WRN gene (NM_000553.6:c.1105C>T p.Arg369*). Case 2: A 75-year-old female patient was referred from the rheumatology department because of scleroderma-like skin changes, lower extremity calcifications, and chronic skin ulcers. Her medical history was notable for a 20-year history of diabetes mellitus and bilateral cataract surgery performed at 55 years of age. Physical examination revealed scleroderma-like skin lesions and ulcers, with a pinched nasal appearance as the only additional finding. ES demonstrated a previously described intronic variant in the WRN gene (NM_000553.6:c.2089-3024A>G) Case 3: A 20-year-old male patient was referred from ophthalmology because of bilateral cataracts and a syndromic appearance. He had received special education for 1.5 years due to learning difficulties, and his parents were first-degree cousins. Physical examination revealed a progeroid appearance, gray hair, pinched nose, thin extremities, and central adipose accumulation. ES identified a nonsense variant in the WRN gene (NM_000553.6:c.3493C>T; p.Gln1165*). Chromosomal analysis additionally demonstrated mosaic Klinefelter syndrome (mos 47,XXY[19]/46,XY[21]), explaining the patient's hypergonadotropic hypogonadism and establishing a dual genetic diagnosis. Conclusion: These three distinct cases illustrate the broad phenotypic spectrum of Werner syndrome, further emphasizing the value of considering it in differential diagnosis of varying symptoms. All cases, particularly Case 2, demonstrate that individuals with Werner syndrome may be diagnosed at different ages, underscoring the importance of regular surveillance in accordance with published guidelines. These findings further highlight the need for comprehensive, age-spanning surveillance strategies for patients with Werner syndrome, extending from early adulthood through the sixth and seventh decades of life.
Keywords: Werner Syndrome, cancer predisposition, WRN

[Abstract:0177]

Evaluation of the Frequency, Spectrum, and Risk Factors of Genetic Cancer Predisposition in Patients Followed at the Department of Pediatric Oncology, Ankara University Faculty of Medicine Between 2002 and 2024: A Retrospective Cohort Study

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Objective: In the literature, germline alterations associated with cancer predisposition syndromes (CPS) have been reported in approximately 7–10% of pediatric cancer cases. These syndromes may present with clinical clues such as congenital anomalies, dysmorphic features, developmental characteristics, or multiple primary malignancies, along with an increased cancer risk. The primary aim of this study was to determine the frequency and spectrum of CPS in childhood cancers; the secondary aim was to retrospectively evaluate risk markers for CPS according to the modified Jongmans criteria and to determine the predictive value of clinical findings suggestive of cancer predisposition.

Materials-Methods: This single-center retrospective cohort study included 888 patients with childhood cancer who were followed at the Department of Pediatric Oncology, Ankara University Faculty of Medicine, between January 2002 and December 2024. Diagnoses were grouped according to the International Classification of Childhood Cancer. Patients were evaluated for CPS using the modified Jongmans criteria. The diagnosis of CPS was established based on available clinical and genetic data, and the sensitivity and specificity of the screening criteria in discriminating the presence of CPS were analyzed.

Results: Among the 888 patients included in the study, the proportion of males was 56.6%, and the median age at diagnosis was 84 months (IQR: 26–150). The most common diagnostic groups were lymphomas and reticuloendothelial neoplasms (18.2%), central nervous system tumors (15.4%), and malignant bone tumors (15.3%). A family history of cancer was identified in 239 patients (26.9%), and parental consanguinity was detected in 163 patients (18.4%). CPS was identified in 61 patients (6.9%), with neurofibromatosis type 1 being the most frequently observed CPS.

Among CPS-positive patients, at least one Jongmans criterion was positive in 58 patients (95.1%), two or more criteria were positive in 41 patients (67.2%), and three or more criteria were positive in 5 patients (8.2%) ($p<0.001$). For at least one positive criterion, sensitivity was found to be 67.2%. A family history of early-onset cancer (OR: 9.34), parental consanguinity (OR: 2.53), the presence of rare or CPS-associated signature tumors (OR: 3.68), multiple primary malignancies (OR: 8.50), and accompanying congenital anomalies or syndromic clinical findings (OR: 35.62) were found to be significantly associated with CPS ($p<0.001$). Genetic testing was performed in 95 patients (10.7%), and these patients had a younger age at diagnosis. In CPS-positive patients, the rates of genetic testing, targeted therapy, and treatment modifications were significantly higher ($p<0.05$).

Conclusion: The CPS frequency of 6.9% identified in this study is consistent with the literature. The findings demonstrate that family history, consanguinity, rare tumors, and congenital anomalies are strong risk markers for CPS. The modified Jongmans criteria appear to provide a meaningful threshold for genetic referral, particularly

when two or more criteria are positive. Systematic evaluation of all pediatric cancer patients is of critical importance for the early identification of individuals with hereditary predisposition and appropriate referral for genetic counseling.

Keywords: cancer predisposition syndromes, genetic susceptibility, pediatric cancer
Evaluation of the Frequency, Spectrum, and Risk Factors of Genetic Cancer Predisposition in Patients Followed at the Department of Pediatric Oncology, Ankara University Faculty of Medicine Between 2002 and 2024: A Retrospective Cohort Study Introduction and Objectives In the literature, germline alterations associated with cancer predisposition syndromes (CPS) have been reported in approximately 7–10% of pediatric cancer cases. These syndromes may present with clinical clues such as congenital anomalies, dysmorphic features, developmental characteristics, or multiple primary malignancies, along with an increased cancer risk. The primary aim of this study was to determine the frequency and spectrum of CPS in childhood cancers; the secondary aim was to retrospectively evaluate risk markers for CPS according to the modified Jongmans criteria and to determine the predictive value of clinical findings suggestive of cancer predisposition. Methods This single-center retrospective cohort study included 888 patients with childhood cancer who were followed at the Department of Pediatric Oncology, Ankara University Faculty of Medicine, between January 2002 and December 2024. Diagnoses were grouped according to the International Classification of Childhood Cancer. Patients were evaluated for CPS using the modified Jongmans criteria. The diagnosis of CPS was established based on available clinical and genetic data, and the sensitivity and specificity of the screening criteria in discriminating the presence of CPS were analyzed. Results Among the 888 patients included in the study, the proportion of males was 56.6%, and the median age at diagnosis was 84 months (IQR: 26–150). The most common diagnostic groups were lymphomas and reticuloendothelial neoplasms (18.2%), central nervous system tumors (15.4%), and malignant bone tumors (15.3%). A family history of cancer was identified in 239 patients (26.9%), and parental consanguinity was detected in 163 patients (18.4%). CPS was identified in 61 patients (6.9%), with neurofibromatosis type 1 being the most frequently observed CPS. Among CPS-positive patients, at least one Jongmans criterion was positive in 58 patients (95.1%), two or more criteria were positive in 41 patients (67.2%), and three or more criteria were positive in 5 patients (8.2%) (p

[Abstract:0200]

Case Report Of Neurofibromatosis Type 1 Treated With Selumetinib

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Introduction: Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder characterized by tumor development in multiple tissues, including the skin, soft tissue, and central nervous system. Clinical manifestations of NF1 may emerge gradually over time. Patients with NF1 have an increased lifetime risk of developing both benign and malignant tumors. Peripheral neurofibromas (PNs) are the hallmark of NF1 and represent the most common tumor type. Historically, surgery was the standard treatment for PNs; however, due to postoperative complications, selumetinib, which is an oral selective MEK inhibitor, has emerged as an alternative therapeutic option.

Case Presentation:A 23-year-old female patient presented with a family history of neurofibromatosis. A cranial MRI performed in 2008 revealed "multiple hamartomatous foci located in the bilateral globus pallidus, bilateral mesencephalon, and infratentorial regions at the level of the bilateral nuclei." The patient was placed under follow-up by the Department of Pediatric Neurology. A biopsy performed on the left eyelid was reported as a neurofibroma. Physical examination revealed ptosis of the left eye and widespread café-au-lait macules. Based on the family history, clinical findings, and genetic testing results, the patient was diagnosed with Neurofibromatosis Type 1 (NF1) and was followed up in the pediatric clinic. During follow-up, multiple masses were detected in the neck, and a Fine Needle Aspiration Biopsy (FNAB) was performed on June 19, 2020. The pathology result was reported as plexiform neurofibroma, and the case was considered inoperable. Upon the detection of progression in the neurofibromas during follow-up imaging, the patient presented to our clinic. Examinations conducted in November 2023 revealed: a 4x3 cm neurofibroma in the left paravertebral area with a connection to the spinal canal; a 7x5.5 cm neurofibroma in the left adrenal gland; appearances consistent with multiple neurofibromas at the left skull base; and a 3.5 cm neurofibroma at the level of the T1-T2 vertebral bodies. Due to the presence of unresectable multiple neurofibromas, selumetinib therapy was initiated on April 30, 2024, at a dose of 50 mg/day. During follow-up, the selumetinib dosage was reduced to 25 mg/day due to the development of Grade 2 dermatitis as a side effect. Under the current treatment, no new lesions were detected, and the existing lesions remained stable. The patient is currently under follow-up at our clinic.

Discussion and Conclusion :Selumetinib has demonstrated efficacy in reducing plexiform neurofibroma size in pediatric NF1 patients. Although adult data are limited, disease stabilization without new lesion development supports selumetinib as a safe and continuous treatment option in unresectable NF1 cases.

References

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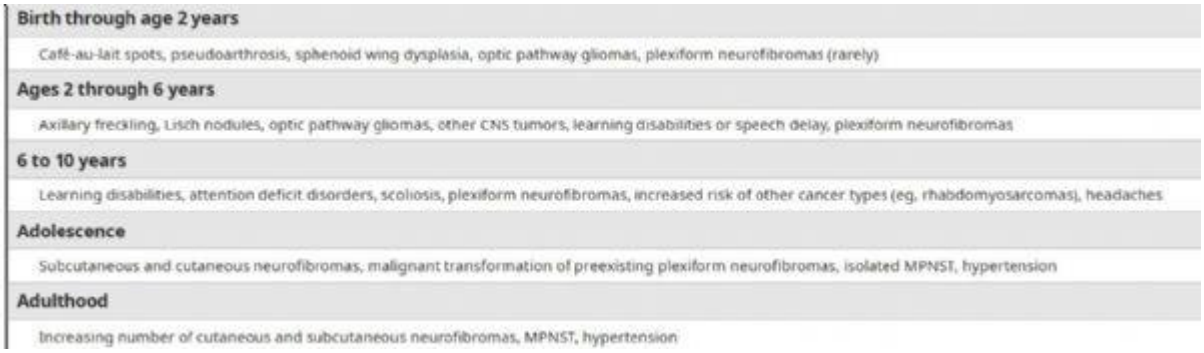
2. Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. N Engl J Med. 2020;382(15):1430–1442.
3. Kim H, Yoon HM, et al. Safety and efficacy of selumetinib in pediatric and adult patients with neurofibromatosis type 1.

Keywords: Neurofibromatosis, Selumetinib, Peripheral neurofibromas

Tablo 1



Features of neurofibromatosis type 1 as a function of the age when they may first be apparent

Case Report Of Neurofibromatosis Type 1 Treated With Selumetinib Gamze Serin Özel[1] [1] Pamukkale University, Department of Medical Oncology, Introduction Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder characterized by tumor development in multiple tissues, including the skin, soft tissue, and central nervous system. Clinical manifestations of NF1 may emerge gradually over time. Patients with NF1 have an increased lifetime risk of developing both benign and malignant tumors. Peripheral neurofibromas (PNs) are the hallmark of NF1 and represent the most common tumor type. Historically, surgery was the standard treatment for PNs; however, due to postoperative complications, selumetinib, which is an oral selective MEK inhibitor, has emerged as an alternative therapeutic option. Case Presentation A 23-year-old female patient presented with a family history of neurofibromatosis. A cranial MRI performed in 2008 revealed "multiple hamartomatous foci located in the bilateral globus pallidus, bilateral mesencephalon, and infratentorial regions at the level of the bilateral nuclei." The patient was placed under follow-up by the Department of Pediatric Neurology. A biopsy performed on the left eyelid was reported as a neurofibroma. Physical examination revealed ptosis of the left eye and widespread café-au-lait macules. Based on the family history, clinical findings, and genetic testing results, the patient was diagnosed with Neurofibromatosis Type 1 (NF1) and was followed up in the pediatric clinic. During follow-up, multiple masses were detected in the neck, and a Fine Needle Aspiration Biopsy (FNAB) was performed on June 19, 2020. The pathology result was reported as plexiform neurofibroma, and the case was considered inoperable. Upon the detection of progression in the neurofibromas during follow-up imaging, the patient presented to our clinic. Examinations conducted in November 2023 revealed: a 4x3 cm neurofibroma in the left paravertebral area with a connection to the spinal canal; a 7x5.5 cm neurofibroma in the left adrenal gland; appearances consistent with multiple neurofibromas at the left skull base; and a 3.5 cm neurofibroma at the level of the T1-T2 vertebral bodies. Due to the presence of unresectable multiple neurofibromas, selumetinib therapy was initiated on April 30, 2024, at a dose of 50 mg/day. During follow-up, the selumetinib dosage was reduced to 25 mg/day due to the development of Grade 2 dermatitis as a side effect. Under the current treatment, no new lesions were detected, and the existing lesions remained stable. The patient is currently under follow-up at our clinic. Discussion and Conclusion Selumetinib has demonstrated efficacy in reducing plexiform neurofibroma size in pediatric NF1 patients. Although adult data are limited, disease stabilization without new lesion development supports selumetinib as a safe and continuous treatment option in unresectable NF1 cases. Tablo 1.NF1'nin Yaşa Bağlı Olarak Ilk Kez Çıkabilecek Klinik Bulgular References 1. Dombi E, Baldwin A, Marcus LJ, et al. Activity of selumetinib in neurofibromatosis type 1 related plexiform neurofibromas. N Engl J Med. 2016;375(26):2550–2560. 2. Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. N Engl J Med. 2020;382(15):1430–1442. 3. Kim H, Yoon HM, et al. Safety and efficacy of selumetinib in pediatric and adult patients with neurofibromatosis type 1.

[Abstract:0205]

Familial Myelodysplastic Syndrome Associated with Emberger Syndrome Caused by a Novel Germline GATA2 Pathogenic Variant

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Objective: Myelodysplastic syndromes (MDS) are heterogeneous clonal disorders of hematopoietic stem cells, most commonly occurring sporadically. However, in patients presenting at an early age and/or with a positive family history, inherited predisposition syndromes should be strongly considered. In this context, the GATA2 gene encodes a transcription factor critical for hematopoietic stem cell homeostasis and the development of monocytes, dendritic cells, B cells, and NK cells. Germline pathogenic variants in the GATA2 gene are recognized as an important cause of familial MDS and acute myeloid leukemia (AML), often accompanied by immunodeficiency and syndromic features such as lymphedema, known as Emberger syndrome. Due to variable penetrance and phenotypic heterogeneity, these cases may be underdiagnosed. The objective of this report is to emphasize the importance of germline genetic evaluation in early-onset familial MDS and to contribute to the literature by presenting a fatal case of GATA2-related Emberger syndrome with familial hematological malignancy history.

Case: We report a 20-year-old patient with a long-standing history of hematological abnormalities. Pancytopenia was first detected at the age of 6, and a bone marrow biopsy performed at 9 years of age revealed myelofibrosis. The patient was later diagnosed with hypocellular MDS. Cytogenetic analysis of bone marrow samples demonstrated monosomy 7. In addition to hematological findings, the patient exhibited lower-extremity lymphedema and recurrent spontaneous pneumothorax. To our knowledge, recurrent spontaneous pneumothorax has not previously been reported as part of the clinical spectrum of Emberger syndrome. Dermatological examination revealed papulopustular lesions with facial telangiectasia, interpreted as rosacea. The disease course was aggressive, and the patient eventually progressed from MDS to AML, resulting in death despite supportive management. Family history was remarkable for the patient's mother, who had died at the age of 34 from AML secondary to MDS, raising suspicion of a hereditary predisposition. Germline genetic analysis using the SOPHIA™ Clinical Exome Solution next generation sequencing kit identified a novel pathogenic frameshift variant in the GATA2 gene (c.301_302insT; p.Gly101Valfs*84).

Conclusion: To date, only 10 families with Emberger syndrome have been reported
in the literature; this case highlights the critical importance of germline variant analysis in patients with early-onset MDS and a suggestive family history. Comprehensive clinical evaluation, including non-hematological findings, may provide important clues for underlying germline predisposition syndromes such as GATA2-related Emberger syndrome and have significant implications for diagnosis, management, and genetic counseling.

Keywords: Emberger syndrome, Familial MDS, GATA2

Familial Myelodysplastic Syndrome Associated with Emberger Syndrome Caused by a Novel Germline GATA2 Pathogenic Variant Çekdar Kapazan, Bilgen Bilge Geçkinli Department of Medical Genetics, Marmara University Faculty of Medicine, Istanbul, Turkey Objective: Myelodysplastic syndromes (MDS) are heterogeneous clonal disorders of hematopoietic stem cells, most commonly occurring sporadically. However, in patients presenting at an early age and/or with a positive family history, inherited predisposition syndromes should be strongly considered. In this context, the GATA2 gene encodes a transcription factor critical for hematopoietic stem cell

homeostasis and the development of monocytes, dendritic cells, B cells, and NK cells. Germline pathogenic variants in the GATA2 gene are recognized as an important cause of familial MDS and acute myeloid leukemia (AML), often accompanied by immunodeficiency and syndromic features such as lymphedema, known as Emberger syndrome. Due to variable penetrance and phenotypic heterogeneity, these cases may be underdiagnosed. The objective of this report is to emphasize the importance of germline genetic evaluation in early-onset familial MDS and to contribute to the literature by presenting a fatal case of GATA2-related Emberger syndrome with familial hematological malignancy history. Case: We report a 20-year-old patient with a long-standing history of hematological abnormalities. Pancytopenia was first detected at the age of 6, and a bone marrow biopsy performed at 9 years of age revealed myelofibrosis. The patient was later diagnosed with hypocellular MDS. Cytogenetic analysis of bone marrow samples demonstrated monosomy 7. In addition to hematological findings, the patient exhibited lower-extremity lymphedema and recurrent spontaneous pneumothorax. To our knowledge, recurrent spontaneous pneumothorax has not previously been reported as part of the clinical spectrum of Emberger syndrome. Dermatological examination revealed papulopustular lesions with facial telangiectasia, interpreted as rosacea. The disease course was aggressive, and the patient progressed from myelodysplastic syndrome (MDS) to acute myeloid leukemia (AML), ultimately resulting in death despite supportive care. Family history was remarkable: the patient's mother had died at the age of 34 from AML secondary to MDS, raising suspicion of an inherited predisposition, and the patient's sister presented with isolated lymphedema. Germline genetic analysis of the patient, performed using the SOPHIA™ Clinical Exome Solution next-generation sequencing panel, identified a novel pathogenic frameshift variant in the GATA2 gene (c.301_302insT; p.Gly101Valfs*84). The same variant was confirmed in the patient and the patient's sister by Sanger sequencing. Conclusion: To date, only ten families with Emberger syndrome have been reported in the literature. This case highlights the critical importance of germline variant analysis in patients with early-onset MDS and a suggestive family history. Comprehensive clinical evaluation, including non-hematological manifestations in families with MDS, may provide important clues to underlying germline predisposition syndromes such as GATA2-related Emberger syndrome and has significant implications for diagnosis, management, and genetic counseling. As additional familial MDS cases are reported, the penetrance and clinical spectrum of hereditary MDS syndromes will be further elucidated.

[Abstract:0210]

Clinical Spectrum and Management Challenges of Multilocus Inherited Neoplasia Allele Syndrome (MINAS): Nine Carriers from Six Families with Distinct Variant Combinations

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Ankara University, School of Medicine, Department of Medical Genetics

Introduction: Multilocus Inherited Neoplasia Allele Syndrome (MINAS) is defined as people who have germline pathogenic or likely pathogenic variants at least two known cancer susceptibility genes. Because multiple gene panels are commonly used, more people are being identified with multilocus genotypes. Having multiple alleles, especially in genes involved in the same DNA damage response and homologous recombination pathways, may affect how severe the clinical features are in these people. In this study, we present the clinical and biological features of individuals with MINAS in our database.

Method: Between 2022 and 2025, inherited cancer panel testing was performed on 652 patients from 513 families referred to our center. Nine cases from six families were found to have heterozygous pathogenic or likely pathogenic variants in two or more cancer susceptibility genes. Variant assessment was performed according to the ACMG Guidelines, using information from ClinVar.

Results: The age of cancer diagnosis in the patients ranged from 29 to 77 years. The cancer types were colorectal, pancreatic, cervical, lung, and prostate cancers. Three patients had no cancer at the time of testing: one was the daughter of a patient with cervical cancer also in the patient group, and the other two were daughter and son of a 56-year-old man with prostate cancer who died at age 60. All cases are summarized in **Table 1**, including cancer types, age at diagnosis, pathogenicity, effect of different gene combinations, and demographic information.

Six different gene combinations were found: *NBN/ATM, BRCA2/CHEK2, BRCA1/MLH1, ATM/PALB2, MLH1/CHEK2,* and *CHEK2/BRIP1.* In all six combinations, the genes are involved in DNA damage response and repair pathways. For all cancers observed, the clinical findings were consistent with the known cancer spectrum of at least one of the genes. However, an atypical manifestation of rectal neuroendocrine carcinoma was noted in a *CHEK2/BRIP1* carrier.

Conclusion: MINAS carriers show a wide range of clinical features. Although the types of tumors generally match the known functions of the genes, having multiple cancer predisposing variants at the same time makes individual risk assessment difficult. These results show that traditional single-gene risk models are limited for MINAS. Furthermore, broader assessments of different gene combinations are needed to improve risk assessment and interpretation.

Keywords: MINAS, Multilocus Inherited Neoplasia Allele Syndrome, Cancer susceptibility genes, Multigene variant carriers, Risk surveillance

Table 1

Family number	Case number	Sex	Age	Age on set	Cancer type	Gene	Variant	Pathogenicity	Effect
1	1	F	33	31	Pancreas ca	ATM (nm_000051.4)	c.2251-4A>G	P	Additive/Synergistic
						NBN (nm_002485.5)	c.247dup p.M1fs*23	P	
1	2	F	37	33	Cervical ca	ATM (nm_000051.4)	c.2251-4A>G	P	Additive/Synergistic
						NBN (nm_002485.5)	c.247dup p.M1fs*23	P	
1	3	F	21	*	Cervical ca in mother	ATM (nm_000051.4)	c.2251-4A>G	P	Additive/Synergistic
						NBN (nm_002485.5)	c.247dup p.M1fs*23	P	
2	4	M	77	60/77	Pancreatic/Lung ca	BRCA2 (nm_0000594)	c.9097dup p.T3033Nfs*11	P	Additive
						CHEK2 (nm_007194.4)	c.893_897del p.Y298Cfs*12	P	
3	5	M	35	29	Colon ca	BRCA1 (nm_007294.4)	c.5236C>A p.H1746N	LP	Synergistic
						MLH1 (nm_000249.4)	c.1042_1043delTT p.L348fs*13	LP	
4	6	M	31	*	Prostate ca in father	ATM (nm_000051.4)	c.7788G>A p.E2596E	P	Additive/Synergistic
						PALB2 (024675.4)	c.2257C>T p.R753*	P	
4	7	F	26	*	Prostate ca in father	ATM (nm_000051.4)	c.7788G>A p.E2596E	P	Additive/Synergistic
						PALB2 (024675.4)	c.2257C>T p.R753*	P	
5	8	F	45	40	Colon ca	CHEK2 (nm_007194.4)	c.1556C>T p.T519M	P	Additive
						MLH1 (nm_000249.4)	c.883A>G p.Ser295Gly	P	
6	9	F	51	50	Rectum NET	BRIP1 (nm_032043.3)	c.608del p.N203Tfs*71	P	Additive
						CHEK2 (nm_007194.4)	c.846+4_846+7del	P	

* 3rd case Mothers age on set 33
5th and 6th case Fathers age on set 56y

All cases are summarized in Table 1, including cancer types, age at diagnosis, pathogenicity, effect of different gene combinations, and demographic information.

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1	2	F	37	33	Cervical ca	ATM (nm_000051.4)	c.2251-4A>G	P	Additive/Synergistic
						NBN (nm_002485.5)	c.247dup p.M1fs*23	P	
1	3	F	21	*	Cervical ca in mothe	ATM (nm_000051.4)	c.2251-4A>G	P	Additive/Synergistic
						NBN (nm_002485.5)	c.247dup p.M1fs*23	P	
2	4	M	77	60/77	Pancreatic/Lung ca	BRCA2 (nm_0000594)	c.9097dup p.T3033Nfs*11	P	Additive
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3	5	M	35	29	Colon ca	BRCA1 (nm_007294.4)	c.5236C>A p.H1746N	LP	Synergistic
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6	9	F	51	50	Rectum NET	BRIP1 (nm_032043.3)	c.608del p.N203Tfs*71	P	Additive
						CHEK2 (nm_007194.4)	c.846+4_846+7del	P	

*All cases are summarized in Table 1, including cancer types, age at diagnosis, pathogenicity, effect of different gene combinations, and demographic information. *3rd case Mothers age on set 33 *5th and 6th case Fathers age on set 56y*

Clinical Spectrum and Management Challenges of Multilocus Inherited Neoplasia Allele Syndrome (MINAS): Nine Carriers from Six Families with Distinct Variant Combinations Batuhan Ergin[1], Sadiye Ekinci[1], Şule Altıner[1], Timur Tuncalı[1], Hatice Ilgın Ruhi[1 1] Ankara University, School of Medicine, Department of Medical Genetics Introduction Before, hereditary cancer research mostly followed the concept of "one gene, one syndrome", one germline mutation being responsible for a single cancer syndrome [1]. After the broader use of Next Generation Sequencing and multigene panel testing, the traditional model was therefore questioned [2]. Thanks to these technical advances, doctors can now discover that a person may have pathogenic variants in multiple cancer, predisposition genes simultaneously [3]. Since there was a need for a term to label and characterize the situation, the researchers Whitworth and coauthors 2016 study has coined the phrase "Multilocus Inherited Neoplasia Allele Syndrome" (MINAS) [4]. The authors referred to the term MINAS by defining it as two or more germline mutations at cancer susceptibility genes each of which can lead to cancer [4]. Their research went to the extent of analyzing a large group of 4833 cases and revealed that the frequency of MINAS among hereditary cancer patients was far greater than previously expected [4]. Nowadays, MINAS cases present major clinical challenges such as a more severe phenotype, an earlier age of cancer diagnosis, or synergistic cases that exhibit characteristics of two different syndromes. Due to this complex situation, it becomes a challenge to estimate the risks during genetic counseling. Therefore, patient specific screening plans have to be developed [5]. MINAS has emerged as an essential idea to grasp the polygenic aspect of hereditary cancers and has played a role in the transition from single gene testing to broader panel testing [6]. Materials and methods This research was a retrospective study of patients who were referred to the Ankara University School of Medicine, Medical Genetics Polyclinic from 2022 to 2025. A total of 652 individuals from 513 unrelated families underwent genetic testing for suspected hereditary cancer syndromes during the study period (The study population included 534 patients with a cancer diagnosis and 118 individuals who presented with a significant family history of malignancy but were asymptomatic at the time of testing). These patients had been referred based on clinical criteria, such as cancer diagnosis at an early age, a strong family history of cancer, or the existence of multiple primary tumors. DNA was purified from peripheral blood samples of all study subjects. A genetic screening of a multigene panel for hereditary cancer predisposition was carried out. This panel consisted of the following 36 genes: APC, ATM, BARD1, BLM, BMPR1A, BRCA1, BRCA2, PMS2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FH, FLCN, MLH1, MRE11, MSH2, MSH6, MUTYH, NBN, NTHL1, PALB2, POLD1, POLE, PRSS1, PTEN, RAD50, RAD51C, RAD51D, SLX4, SMAD4, STK11, TP53, VHL. All variants were comprehensively evaluated detected to standards and guidelines of ACMG.[7] To make certain that our genetic conclusions were of clinical relevance, they were cross checked at the ClinVar database and were confirmed each gene variant's pathogenicity using multiple in-silico prediction algorithms. Only those variants that were classified as pathogenic or likely pathogenic were kept for the final analysis. To retain the clinical emphasis of the research, Variants of Uncertain Significance (VUS) were discarded from the study. In this case series we located the patients with the features of Multilocus Inherited Neoplasia Allele Syndrome. MINAS inclusion criteria consisted of the presence of heterozygous pathogenic or likely pathogenic variants in at least two independent cancer, predisposition genes. Consequently, our final study group consists of nine individuals from six distinct families, and their clinical findings and genetic profiles are analyzed in detail throughout this article. Results General Overview In this study, the individuals diagnosed with cancer were identified as MINAS carriers, with an age range at diagnosis between 29 and 77 years. The types of cancers detected in the study included colorectal, pancreatic, cervical, lung, and prostate. Three out of nine patients were non-cancer cases at the time of testing: one of them was the daughter of a patient diagnosed with cervical cancer whereas the other two were children of a patient who had died of prostate cancer. We have found six different gene combinations: NBN/ATM, BRCA2/CHEK2, BRCA1/MLH1, ATM/PALB2, MLH1/CHEK2, and CHEK2/BRIP1. These are all genes that participate in the pathways of DNA damage response and repair. Based on clinical observations, the majority of cases are consistent with the gene involved; however, a case of rectal

neuroendocrine carcinoma was recorded in a CHEK2/BRIP1 carrier. Detailed information regarding the clinical and molecular profiles of all cases is provided in Table 1. Family number Case number Sex Age Age onset Cancer type Gene Variant Pathogenicity Effect 1 1 F 33 31 Pancreas ca ATM (NM_000051.4) c.2251-4A>G P Additive/Synergistic NBN (NM_002485.5) c.247dup p.M1fs*23 P 1 2 F 37 33 Cervical ca ATM (NM_000051.4) c.2251-4A>G P Additive/Synergistic NBN (NM_002485.5) c.247dup p.M1fs*23 P 1 3 F 21 * Cervical ca in mother ATM (NM_000051.4) c.2251-4A>G P Additive/Synergistic NBN (NM_002485.5) c.247dup p.M1fs*23 P 2 4 M 77 60/77 Pancreatic/Lung ca BRCA2 (NM_000059.3) c.9097dup p.T3033Nfs*11 P Additive CHEK2 (NM_007194.4) c.893_897del p.Y298Cfs*12 P 3 5 M 35 29 Colon ca BRCA1 (NM_007294.4) c.5236C>A p.H1746N LP Synergistic MLH1 (NM_000249.4) c.1042_1043delTT p.L348fs*13 LP 4 6 M 31 * Prostate ca in father ATM (NM_000051.4) c.7788G>A p.E2596E P Additive/Synergistic PALB2 (NM_024675.4) c.2257C>T p.R753* P 4 7 F 26 * Prostate ca in father ATM (NM_000051.4) c.7788G>A p.E2596E P Additive/Synergistic PALB2 (NM_024675.4) c.2257C>T p.R753* P 5 8 F 45 40 Colon ca CHEK2 (NM_007194.4) c.1556C>T p.T519M P Additive MLH1 (NM_000249.4) c.883A>G p.Ser295Gly P 6 9 F 51 50 Rectum NET BRIP1 (NM_032043.3) c.608del p.N203Tfs*71 P Additive CHEK2 (NM_007194.4) c.846+4_846+7del P * 3rd case Mothers age onset 33y 5th and 6th case Fathers age onset 56y Sarı değil Table 1: Clinical and Genetic Profiles of MINAS Cases *3rd case Mothers age onset 33y *5th and 6th case Fathers age onset 56y Family 1: ATM/NBN Combination The proband is a young woman, 31 years old (Case 1), who initially came in with abdominal discomfort and was later found to have Solid Pseudopapillary Neoplasm (SPEN) of the pancreas. There is a strong history of cancer in her family (Figure 1): her sister, now 37, got cervical cancer at 33, and her brother died of leukemia when he was only 10. Genetic testing has shown that the patient has dual heterozygosity for ATM (c. 2251, 4A>G) and NBN (c. 247dup p. M1fs*23). Further testing showed that her sister (III-2) with cervical cancer and her niece (IV-2) are carrying both the variants. The coexistence of the ATM and NBN variant in Family 1 demonstrates both additive and possible synergistic gene interaction effects within the DNA damage response system. An additive effect means that the independent cancer risks from each gene are combined, whereas a synergistic effect comes about because these proteins operate in the same linear biochemical pathway. As a crucial member of the MRN complex, the NBN protein guides the sensing of double strand breaks and the activation of ATM kinase. We can theorize that this biological synergy is probably responsible for the very early onset and aggressive nature of the clinical phenotype observed in this family, including pancreatic cancer at age 31 and leukemia at age 10 [4]. Figure 1 (Family 1 Pedigree) Family 2: BRCA2/CHEK2 Combination A 77 year old man (Case 4) who had been diagnosed with pancreatic adenocarcinoma at age 60 was reexamined when he developed a new primary lung cancer. Genetic testing revealed, both BRCA2 (c. 9097dup p. T3033Nfs*11) and CHEK2 (c. 893_897del p. Y298Cfs*12) variants. Although segregation studies could not be performed for this family, a significant familial burden of cancer was observed (Figure 2). It is particularly noteworthy that the patient is a non-smoker, which increases the clinical suspicion that his lung malignancy is related to a genetic predisposition. The pedigree analysis revealed that the patient's sister (III-3) was diagnosed with breast cancer at age 82, and his brother (III-4), who was a smoker, was diagnosed with lung cancer at age 80. Furthermore, the brother's son (IV-1) was diagnosed with prostate cancer at the age of 55. The double mutation of BRCA2 and CHEK2 in Family 2 seems to indicate that these two genes have a combined cancer, predisposing effect. The BRCA2 gene encodes a protein that plays a critical role in the repair of double strand breaks through homologous recombination, and it is a high penetrance gene. Meanwhile, the protein encoded by CHEK2, a moderate, penetrance gene, is a kinase that helps regulate DNA repair by phosphorylating the substrates, including those involved in the BRCA pathway. Different from synergistic interactions where mutations in the same complex cause very early, onset disease, additive interaction usually leads to a cumulative risk profile. In this scenario, each gene is a separate contributor to the overall stability of the genome. The presence of both mutations probably increases the total "mutational burden" over time, hence our 77 year old patient's occurrence of multiple primary malignancies (pancreatic

adenocarcinoma and lung cancer). This combination is in line with the observation that the CHEK2 gene is a genetic modifier that not only extends the tumor spectrum but also elevates the risk of secondary tumors during one's lifetime [8]. Figure 2 (Family 2 Pedigree) Family 3: BRCA1/MLH1 Combination A 35 year old male (Case 5) was diagnosed with colorectal adenocarcinoma at 29 years old after persistent abdominal pain. He has two likely pathogenic variants: one in BRCA1 (c. 5236C>A p. H1746N) and the other in MLH1 (c. 1042_1043delTT p. L348fs*13). On his father's side, there is a heavy cancer burden of colon, pancreatic, and lymphoma, whereas on his mother's side there are cases of breast, prostate and thyroid cancers (Figure 3). Family 3 is a clear illustration of the synergistic effect of the BRCA1 and MLH1 variants. These genes are responsible for two different but indispensable DNA repair systems: Mismatch Repair for MLH1 and Homologous Recombination for BRCA1. The cell's capacity to keep the genome stable is greatly decreased when both pathways are defective. Synergy arises because the cell is stripped of its "backup" mechanisms. The accumulation of replication errors results in a deficiency of MLH1, but the presence of a BRCA1 mutation prevents the repair of the double strand breaks caused by those errors. Such a "cross pathway" failure results in a fast buildup of mutations, which lead to tumor initiation and progression. This is probably why colorectal adenocarcinoma occurred at such an early age (29 years), much earlier than the average age, even for typical Lynch Syndrome cases [2]. Figure 3 (Family 3 Pedigree) Family 4: ATM/PALB2 Combination A 31 year old male (Case 6) underwent testing because his father had been diagnosed with prostate cancer at the age of 56 (he died at 60). The patient was identified as having ATM (c. 7788G>A p. E2596E) and PALB2 (c. 2257C>T p. R753)* variants. The segregation test revealed that the sibling (III-2) also inherited the same variants (Figure 4). The simultaneous presence of ATM and PALB2 variants in Family 4 is explained as resulting in both additive and synergistic effects within the DNA repair system. In an additive manner, each gene separately raises the risk of developing cancers such as prostate and breast cancer, which accounts for the very strong family history. Nevertheless, a synergistic effect cannot be ruled out since these two proteins are functionally connected in the same homologous recombination pathway. ATM is the main signal that detects DNA damage, while PALB2 is the indispensable link that brings the rest of the repair machinery. Both in the same pathway leads to a more severe defect in DNA maintenance and is very likely to trigger an aggressive disease, such as the prostate cancer of the patients father that was fatal in only four years from diagnosis. However, it is important to note that it is currently unknown whether both mutations were present in the father. It is possible that one of the variants was inherited from the mother; therefore, without performing genetic testing on her, the father's exact genotype cannot be confirmed. This highlights the importance of segregation analysis in MINAS cases to fully understand the inheritance pattern and clinical impact [2][9]. Figure 4 (Family 4 Pedigree) Family 5: CHEK2/MLH1 Combination A 45 year old woman (Case 8) who was diagnosed with moderately differentiated adenocarcinoma of the colon at age 40. She was found with CHEK2 (c. 1556C>T p. T519M) and MLH1 (c. 883A>G p. Ser295Gly). Her family's medical history consists of a sister with endometrial cancer (III-3), a father who passed away from colon cancer at age 45 (II-4), an uncle (II-1) and an aunt (II-3) died from colon cancer at unknown ages (Figure 5). In Family 5, the dual occurrence of MLH1 and CHEK2 gene variants results in an additive effect on cancer susceptibility. MLH1 is considered a high, penetrance gene and the main cause of Lynch Syndrome, leading to a substantial increase in colorectal cancer risk. On the other hand, CHEK2 is a moderate penetrance gene that results in a less significant increase in colorectal risk. Since the two genes are implicated in different biological pathways their risks add up to a higher overall "mutational burden. " [10]. Figure 5 (Family 5 Pedigree) Family 6: BRIP1/CHEK2 Combination A 51 year old woman (Case 9) was found to have a well differentiated rectal neuroendocrine tumor (NET) during a screening colonoscopy. She is a carrier for BRIP1 (c. 608del p. N203Tfs*71) and CHEK2 (c. 846+4_846+7del). Her siblings have had prostate, colon, and breast cancers (Figure 6). The rectal NET is not a typical manifestation, since BRIP1 and CHEK2 are generally related to breast and ovarian cancers. Family 6 shows a remarkably unusual manifestation of MINAS involving the genes BRIP1 and CHEK2. Individually, both genes have been traditionally

linked with risks of breast and ovarian cancers, but our patient developed a rectal NET, a cancer that is not usually associated with both genes. This case exemplifies phenotypic expansion, which means that the combined polygenic load of several variants causes a general deficiency in the DNA Damage Response pathway in all cell types. The overlapping effects of having two mutations may decrease the threshold for cancer development in tissues and can lead to very rare tumor types. This unusual clinical picture is a reminder that single gene screening models have their limitations. It also means that MINAS carriers might need a much wider clinical surveillance to make sure that they detect rare types of cancers [2]. Figure 6 (Family 6 Pedigree) Conclusion In study, it was shown that Multilocus Inherited Neoplasia Allele Syndrome (MINAS) carriers exhibit a very broad and complicated spectrum of clinical features. The tumors found in our six families like colorectal, pancreatic, and breast cancer cases generally represent the biological roles of the genes involved and are borderline with the situation of the presence of multiple pathogenic variants [4] Spotting double heterozygosity particularly in genes such as ATM/NBN or BRCA1/MLH1 gives us an insight into the inadequacy of conventional single gene risk assessment methods. These models are usually not able to factor in the additive or synergistic effects of two or more mutations that may occur, for example, in the same or overlapping DNA repair pathways [11]. Thus, accurately predicting individual risk continues to be a major hurdle for both clinicians and genetic counselors. Moreover, finding unusual symptoms like the rectal NET in a BRIP1/CHEK2 patient indicates that MINAS can be the reason for the extension of the tumor range expected for these genes. To enhance risk evaluation and patient care, it is vital to have wider investigations and bigger global registries that track different gene mixes [5]. One limitation of the study was the inclusion of only pathogenic and likely pathogenic variants. As a result, the study might have missed the possible influence of VUS variants that may act as modifiers. Some studies show that VUS may also be responsible for the diverse clinical manifestations seen in MINAS patients. So, taking these variants into account is essential for a better grasp of personal cancer risks [2]. In the future, strategies for genetic testing will have to change in such a way that they can better reflect the oligogenic nature of hereditary cancer. This will make it possible to design and provide screening and treatment protocols that are more personalized for patients with MINAS [6]. Citations mutations 1-) Ngeow, J., Eng, C. Precision medicine in heritable cancer: when somatic tumour testing and germline meet. npj https://doi.org/10.1038/npjgenmed.2015.6 Genomic Med 1, 15006 (2016). 2-) Tsaousis, G.N., Papadopoulou, E., Apessos, A. et al. Analysis of hereditary cancer syndromes by using a panel of genes: novel and multiple pathogenic mutations. BMC Cancer 19, 535 (2019). https://doi.org/10.1186/s12885-019-5756-4 3-) Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients LaDuca, Holly et al. Genetics in Medicine, Volume 16, Issue 11, 830 – 837 https://doi.org/10.1038/gim.2014.40 4-) Whitworth J, Skytte A, Sunde L, et al. Multilocus Inherited Neoplasia Alleles Syndrome: A Case Series and Review. JAMA Oncol. 2016;2(3):373–379. doi:10.1001/jamaoncol.2015.4771 5-) Yuen, J., Zhou, S., Caeser, R. et al. Multilocus inherited neoplasia alleles syndromes in cancer: implications for clinical practice. Eur J Hum Genet 33, 289–296 (2025). https://doi.org/10.1038/s41431-025-01785-1 6-) Feliubadaló, L., Tonda, R., Gausachs, M. et al. Benchmarking of Whole Exome Sequencing and Ad Hoc Designed Panels for Genetic Testing of Hereditary Cancer. Sci Rep 7, 37984 (2017). https://doi.org/10.1038/srep37984 7-) Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., & Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine, 17(5), 405–423. https://doi.org/10.1038/gim.2015.30 8-) Cybulski, C., Górski, B., Huzarski, T., Masojć, B., Mierzejewski, M., Dębniak, T., Teodorczyk, U., Byrski, T., Gronwald, J., Matyjasik, J., Złowocka, E., Lenner, M., Grabowska, E., Nej, K., Castaneda, J., Mędrek, K., Szymańska, A., Szymańska, J., Kurzawski, G., . . . Lubiński, J. (2004). CHEK2 Is a Multiorgan Cancer Susceptibility Gene. The American Journal of Human Genetics, 75(6), 1131–1135. https://doi.org/10.1086/426403 9-)Holdren, M., Richardson, M., Ritter, D., Young, C., Brannan, T.,

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[Abstract:0211]

APC-Related Familial Adenomatous Polyposis: Clinical Diversity and Molecular Findings from a Single Center

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Objective: Conditions associated with APC pathogenic variants include familial adenomatous polyposis (FAP), which may present as the classic or attenuated form, and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). FAP [MIM #175100] is an autosomal dominant colorectal cancer predisposition syndrome characterized by the development of numerous colorectal adenomatous polyps. The worldwide incidence of FAP is estimated to be 3–10 per 100,000 individuals, accounting for approximately 1% of all colorectal cancers. In addition to colorectal adenomas, extra-colonic manifestations such as desmoid tumors, congenital hypertrophy of the retinal pigment epithelium, osteomas, dental anomalies, epidermoid cysts, lipomas, and upper gastrointestinal tract polyps may also be observed in affected individuals.
Materials-Methods: This study aimed to evaluate the clinical and molecular characteristics of 11 patients diagnosed with Familial Adenomatous Polyposis syndrome between 2021 and 2025 at the Eskisehir Osmangazi University Department of Medical Genetics.
Results: Hereditary mutations in the APC gene were identified in 11 patients, and all of these variants were classified as pathogenic or likely pathogenic according to ACMG criteria. The most frequent alterations were frameshift variants in 54.5% (6/11), five due to small deletions and one to a duplication, all of which resulted in premature stop-codon formation. Of these six frameshift variants, three (50%) represented novel changes that have not been previously reported in the literature. Nonsense mutations accounted for 36.4% (4/11) of the cases, whereas a single splice-site variant was detected in one patient. The majority of the variants were located in exon 16, a functionally critical region of the APC gene that is frequently associated with the classical FAP phenotype. The ages of the patients ranged from 12 to 55 years (median: 27 years). Notably, two patients exhibited predominantly extra-colonic onset: one patient carrying a nonsense variant in exon 16 developed a mandibular desmoid tumor at the age of 12 years prior to the onset of colorectal polyposis,and another patient harboring a nonsense variant in exon 5 developed an ethmoid bone osteoma prior to being diagnosed with FAP at the age of 55 years. In addition, a patient with a frameshift mutation in exon 16 developed an abdominal-wall desmoid tumor after the onset of colorectal polyposis, representing a clinically significant but recognized extracolonic complication of FAP. Apart from these cases, all remaining patients initially presented with multiple colorectal polyps, consistent with the classical FAP presentation. In accordance with current clinical management recommendations, genetic counseling was provided to all patients, and targeted variant testing were recommended for at-risk family members.
Conclusion: In this APC-related FAP cohort, all detected variants were pathogenic or likely pathogenic, with a predominance of truncating mutations and clustering in exon 16. The two patients with extracolonic onset prior to colorectal polyposis illustrate the phenotypic variability of APC-associated disease and highlight the need for early genetic testing and surveillance, particularly in individuals presenting with desmoid tumors or osteomas.

Keywords: APC, FAP, Colorectal polyp, Desmoid tumor

APC-Related Familial Adenomatous Polyposis: Clinical Diversity and Molecular Findings from a Single Center Hilal Gölcür1,Sinem Kocagil1 1.Eskisehir Osmangazi University Department of Medical Genetics Introduction Familial adenomatous polyposis (FAP; OMIM #175100) is an autosomal dominant hereditary colorectal cancer predisposition syndrome caused by pathogenic variants in the APC gene. The disorder is characterized by the

development of hundreds to thousands of colorectal adenomatous polyps, typically beginning in adolescence or early adulthood, with a near-100% lifetime risk of colorectal cancer if left untreated. The estimated worldwide prevalence of FAP ranges between 3 and 10 per 100,000 individuals and accounts for approximately 1% of all colorectal cancer cases.Clinically, FAP can present in a classical or attenuated form, depending on the number of polyps and the age at onset. In addition to colorectal manifestations, affected individuals may develop a variety of extracolonic features, including desmoid tumors, congenital hypertrophy of the retinal pigment epithelium (CHRPE), osteomas, dental anomalies, epidermoid cysts, lipomas, and upper gastrointestinal tract polyps. Another APC associated condition, gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), is characterized by extensive fundic gland polyposis and an increased risk of gastric cancer.Given the clinical heterogeneity of APC-associated disorders, comprehensive genetic testing plays a crucial role in diagnosis, risk assessment, and management of affected individuals and their families.The aim of this study was to evaluate the clinical and molecular characteristics of patients diagnosed with FAP at the Eskişehir Osmangazi University Department of Medical Genetics between 2021 and 2025. Materials and Methods A total of 11 patients diagnosed with FAP between 2021 and 2025 at the Eskişehir Osmangazi University Department of Medical Genetics were included in this retrospective study. Clinical data were obtained from medical records, including age at diagnosis, presenting symptoms, colorectal and extracolonic manifestations, and family history.Genetic testing was performed using next-generation sequencing (NGS)–based hereditary cancer panels covering the APC gene. Detected variants were confirmed by Sanger sequencing when necessary. Variant classification was carried out according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Results Pathogenic or likely pathogenic variants in the APC gene were identified in all 11 patients. The clinical and molecular characteristics of the patients are summarized in Table 1. The most common type of alteration was frameshift variants, detected in 54.5% (6/11) of patients. Five of these resulted from small deletions and one from a duplication, all leading to premature termination codons. Notably, three of the six frameshift variants (50%) (Patient 3,5 and 6) were novel and had not been previously reported in the literature.Nonsense variants accounted for 36.4% (4/11) of cases, while a single splice-site variant was identified in one patient. The majority of variants were located in exon 16, a known mutational hotspot associated with the classical FAP phenotype.The age of patients ranged from 12 to 55 years, with a median age of 27 years. Most patients initially presented with multiple colorectal polyps consistent with classical FAP.Notably, two patients exhibited predominantly extra-colonic onset: one patient carrying a nonsense variant in exon 16 [APC(NM_000038.6):c.4565T>G p.Leu1522*] developed a mandibular desmoid tumor at the age of 12 years prior to the onset of colorectal polyposis,and another patient harboring a nonsense variant in exon 5 [APC(NM_000038.6):c.485C>T p.Gln163*] developed an ethmoid bone osteoma prior to being diagnosed with FAP at the age of 55 years. In addition, a patient with a frameshift mutation in exon 16 [APC(NM_000038.6):c.3927_3931del p.Glu1309Aspfs*] developed an abdominal-wall desmoid tumor after the onset of colorectal polyposis, representing a clinically significant but recognized extracolonic complication of FAP. Apart from these cases, all remaining patients initially presented with colorectal manifestations. In accordance with clinical guidelines, genetic counseling was provided to all patients, and predictive testing was recommended for at-risk relatives. Discussion This study highlights the molecular and clinical spectrum of FAP in a single-center cohort.Consistent with previous reports, truncating variants (frameshift and nonsense) constituted the majority of detected APC mutations, reflecting the critical role of loss-of function mechanisms in FAP pathogenesis. The clustering of variants in exon 16 further supports its importance in classical FAP phenotypes.The identification of three novel frameshift variants expands the mutational spectrum of the APC gene and underscores the importance of ongoing variant documentation. Extracolonic manifestations, particularly desmoid tumors and osteomas, were prominent in a subset of patients and in some cases preceded colorectal polyposis. These findings emphasize that FAP may initially present with non-intestinal features,

potentially delaying diagnosis if genetic testing is not considered.Early recognition of such extracolonic signs is crucial, as timely genetic testing allows for appropriate surveillance and cancer prevention strategies. Our findings reinforce the need for multidisciplinary management of FAP patients, including gastroenterology, surgery, oncology, and genetic counseling services. Conclusions In this cohort of patients with APC-associated FAP, all identified variants were pathogenic or likely pathogenic, with a predominance of truncating mutations and frequent involvement of exon 16. The presence of extracolonic manifestations prior to colorectal polyposis in two patients illustrates the phenotypic variability of FAP and highlights the importance of early genetic evaluation. Genetic testing should be strongly considered in individuals presenting with desmoid tumors or osteomas, even in the absence of colorectal polyposis, to enable timely diagnosis, surveillance, and family screening. Keywords: APC; FAP; Colorectal polyp,Desmoid tumor Table 1. Clinical and Molecular Characteristics of Patients with APC Gene Variants Abbreviations: F, female; M, male. +, positive family history of familial adenomatous polyposis or colorectal cancer; –, negative family history. Patient Sex Age Genetic variant Variant Location Type of mutation Clinical findings Family History 1 F 33 c.532-1G>A Intronic Splice-site Colonic polyps + 2 F 12 c.4565T>G p.Leu1522* Exon 16 Nonsense Mandibular desmoid tumor - 3 M 33 c.1994del p.Leu665Tyrfs*5 Exon 16 Frameshift Gastric polyps - 4 M 26 c.3927_3931del p.Glu1309Aspfs*4 Exon 16 Frameshift Colonic polyps, Abdominal wall desmoid tumor + 5 M 26 c.712del p.Gln238Lysfs*55 Exon 7 Frameshift Colonic polyps - 6 M 27 c.4485_4486dup p.Thr1496Ilefs*12 Exon 16 Frameshift Colonic polyps + 7 M 55 c.487C>T p.Gln163* Exon 5 Nonsense Ethmoid bone osteoma,Colonic polyps + 8 F 22 c.2107dup p.Ala703Glyfs*3 Exon 16 Frameshift Colonic polyps + 9 F 35 c.5990del p.Ser1864Leufs*2 Exon 16 Frameshift Colonic polyps + 10 M 20 c.646C>T p.Arg216* Exon 7 Nonsense Colonic polyps + 11 F 30 c.847C>T p.Arg283* Exon 9 Nonsense Colonic polyps +

[Abstract:0212]

From Prenatal Screening to Maternal Diagnosis: A Case Report of Lynch Syndrome Incidentally Detected via NIPT

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Objective: The noninvasive prenatal test (NIPT) is a screening test for fetal chromosomal aberrations during pregnancy. While the maternal plasma cfDNA pool is predominantly derived from maternal hematopoietic cells, approximately 5–15% originates from placental syncytiotrophoblasts. However, in the presence of maternal malignancy, tumor-derived DNA fragments released via neoplastic cell lysis contribute to this pool, enabling the incidental detection of occult maternal cancers. Atypical genomic profiles characterized by multiple chromosomal aneuploidies or widespread segmental unbalanced rearrangements absent in the fetus are observed in 0.03–0.12% of NIPT series. These findings serve as robust biomarkers for maternal neoplasia, carrying a malignancy risk of approximately 6.4%-73.0%. In this report, we present the diagnostic management of a patient found to have a complex chromosomal anomaly during routine fetal NIPT screening, which ultimately led to the diagnosis of MLH1-associated Lynch syndrome in a large family.

Case: A 29-year-old pregnant woman with no known chronic illness or active symptoms presented at 12 weeks' gestation for routine prenatal screening. NIPT showed a complex genomic profile, including a high-risk result for trisomy 8 and trisomy 13, an approximately 70-Mb duplication involving 7q21.13–q36.3, and a sex chromosome abnormality (XY/X). In light of NIPT findings, patient was referred to perinatology, oncology, and hematology clinics. Further diagnostic imaging was undertaken and revealed a poorly differentiated mucinous adenocarcinoma at the hepatic flexure extending into the proximal transverse colon, radiologically consistent with T3–T4 stage and regional lymphadenopathy. The patient underwent a right hemicolectomy at 20 weeks' gestation, with an uncomplicated perioperative and obstetric course. Concurrently, karyotype analysis and microarray analysis from amniocentesis material done for fetal chromosomal abnormalities revealed normal results as well as maternal peripheral blood karyotyping. In detailed pedigree analysis, it was noted that colorectal carcinoma and endometrial carcinoma was diagnosed in maternal relatives of the proband. A hereditary cancer panel identified a pathogenic variant NM_000249.4:c.790+1G>A in MLH1 gene. Following diagnosis, cascade testing was initiated in the extended family. Segregation analysis in eight relatives with a history of colorectal cancer confirmed that four individuals carried the same heterozygous variant. Accordingly, genetic counseling was provided and tailored surveillance protocols were implemented for all at-risk family members.

Conclusion: NIPT functions as a 'liquid biopsy' that extends beyond fetal screening to facilitate the presymptomatic detection of maternal malignancies. Currently, no guidelines exist to classify a NIPT result as suspicious of an occult malignancy. According to the Maastricht criteria, the presence of more than two chromosomal aberrations, segmental aneuploidies affecting oncogenes or tumor suppressor genes, trisomy 12, trisomy 8, trisomy 9, or monosomies indicates a high-risk category, warranting immediate oncologic evaluation. In such clinical scenarios, a thorough family history is critical for guiding the diagnostic algorithm and elucidating the underlying genetic etiology. As evidenced by this case of Lynch syndrome, a multidisciplinary approach significantly enhances early diagnosis, improves maternal prognostic outcomes, and facilitates the identification of at-risk relatives.

Keywords: Non-invasive prenatal testing (NIPT), Lynch syndrome, Maternal malignancy, MLH1 gene, Colorectal cancer

From Prenatal Screening to Maternal Diagnosis: A Case Report of Lynch Syndrome Incidentally Detected via NIPT

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Introduction and Aim Non-invasive prenatal testing (NIPT) has become an integral component of contemporary prenatal screening for fetal chromosomal abnormalities through the analysis of cell-free DNA (cfDNA) in maternal plasma. In pregnancies at increased risk for common autosomal aneuploidies, NIPT is recommended as a screening test, and positive results should be confirmed by invasive diagnostic procedures. Although the circulating cfDNA pool is derived predominantly from maternal hematopoietic cells, approximately 5–15% originates from placental syncytiotrophoblasts (the fetal fraction). While NIPT is primarily designed to interrogate fetoplacental genetic material, its genome-wide scope can also detect signals originating outside the fetoplacental unit. In pregnant individuals with malignancy, circulating tumor DNA (ctDNA) released through tumor cell apoptosis and/or necrosis may contribute to the maternal cfDNA pool and alter the observed genomic profile. Accordingly, beyond its intended screening indication, NIPT may function as an incidental "liquid biopsy" for otherwise asymptomatic maternal neoplasms. Incidental detection of maternal malignancy through NIPT is uncommon but has been extensively discussed in the literature. Large population-based studies estimate the prevalence of atypical NIPT findings suggestive of malignancy at approximately 0.01–0.03% [1–3]. Although this frequency is low, the risk of maternal malignancy increases substantially when complex genomic patterns such as multiple chromosomal aneuploidies and/or genome-wide segmental copy-number variants (CNVs) are identified. Depending on the platform and the interpretation framework, the reported positive predictive value (PPV) for malignancy in this setting ranges from 6.4% to 73%. In particular, unexplained multiple chromosomal aberrations, rather than an isolated classic aneuploidy, are considered a strong predictor of maternal neoplasia, and several national series have reported PPVs approaching 70% in this subgroup [2,4]. Despite the growing number of published cases, there are currently no standardized international guidelines for the clinical management of pregnant individuals with incidental NIPT findings raising suspicion for maternal malignancy. Nonetheless, current expert opinions and the Maastricht criteria propose that specific patterns such as trisomies associated with hematologic malignancies (e.g., trisomy 8, 9, and 12), complex profiles with more than two aneuploidies, monosomies, or segmental imbalances involving oncogene/tumor-suppressor loci should be regarded as high-risk and prompt urgent multidisciplinary oncologic evaluation [Table 1] [2,4,6]. Here, we report a case that illustrates the diagnostic cascade initiated by incidental NIPT findings. Following the detection of a complex genomic profile on routine NIPT for fetal aneuploidy screening, and further evaluation informed by a positive family history, the patient was diagnosed with colorectal adenocarcinoma and Lynch syndrome. Subsequent family screening identified four additional individuals carrying the same pathogenic variant. Lynch syndrome is an autosomal dominant cancer predisposition syndrome caused by germline pathogenic variants in DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) or EPCAM, and it confers an increased risk of several malignancies—most notably colorectal and endometrial cancer, as well as cancers of the ovary, stomach, small intestine, urinary tract, hepatobiliary system, brain, and skin [7,8]. Through this case, we discuss the management of incidental NIPT findings suggestive of maternal malignancy during pregnancy and emphasize the role of genetic counseling. Case Report A 29-year-old primipara with no known chronic medical conditions and no active symptoms presented to our center at 12 weeks of gestation for routine NIPT for fetal aneuploidy screening. During pre-test genetic counseling, the family history was notable for suspected colon cancer in her mother and one brother; therefore, relatives invited and offered to take next generation sequencing (NGS)-based hereditary cancer panel testing in parallel with the prenatal screening process of the proband. NIPT indicated high-risk results for trisomy 8 and trisomy 13 and revealed a complex genomic profile, including an

approximately 70-Mb duplication spanning 7q21.13–q36.3 and a sex-chromosome abnormality (XY/X, as reported) [Table 2]. When the NIPT findings were scored according to the Maastricht criteria, the total score was 9: 3 points for more than two chromosomal abnormalities; 2 points for an approximately 70-Mb 7q21.13–q36.3 duplication containing multiple cancer-relevant genes; 2 points for monosomy X; 1 point for trisomy 8; and 1 point for the co-occurrence of trisomy 8 and trisomy 13. Because the score was ≥3, the case was classified as high risk for maternal malignancy according to the Maastricht criteria. In line with these findings, the patient received genetic counseling and was referred to Perinatology clinic for invasive prenatal diagnostic testing as well as Medical Oncology and Hematology for evaluation of possible maternal malignancy. In parallel, the hereditary cancer panel workflow was expedited. At 16 weeks of gestation, amniotic fluid was obtained by amniocentesis for prenatal diagnosis, and karyotyping, chromosomal microarray analysis, and QF-PCR were performed. Maternal peripheral blood was also collected for karyotype analysis. All results were normal. Breast ultrasonography, axillary ultrasonography, and neck ultrasonography were unremarkable. Abdominal ultrasonography, however, demonstrated a “pseudokidney” appearance with hypoechoic wall thickening and luminal narrowing (25–30 mm) extending approximately 11–12 cm at the level of the hepatic flexure. Based on these findings, colonoscopy was performed. It revealed a circumferential ulcerated exophytic mass with necrotic exudate, extending approximately 10–12 cm from the mid-ascending colon to the hepatic flexure and proximal transverse colon; multiple biopsies were obtained. Histopathological evaluation revealed a poorly differentiated adenocarcinoma with a mucinous component, consistent with colon adenocarcinoma. Staging CT performed at 19 weeks of gestation showed findings consistent with at least cT3 (possibly cT4) right-sided colonic tumor invasion and mesenteric lymph node enlargement, without evidence of distant organ metastasis. A right hemicolectomy was performed at 20 weeks of gestation, with no perioperative or obstetric complications. Hereditary cancer panel testing identified a heterozygous MLH1 splice-site variant, NM_000249.4:c.790+1G>A, previously reported as pathogenic in ClinVar and classified as pathogenic according to ACMG/AMP criteria (PS4, PS3, PVS1, PM2). The patient was therefore diagnosed with Lynch syndrome [Figure 1]. Following the molecular diagnosis, segregation analysis was performed in eight family members (including individuals with a history of colorectal cancer), and the same heterozygous variant was detected in four relatives. Genetic counseling was provided to all at-risk individuals, and personalized surveillance programs were planned. Other at-risk relatives who could not undergo segregation analysis were also invited to our center for testing upon request [Figure 2] Discussion and Conclusion This case highlights that NIPT may function as an incidental “liquid biopsy” beyond fetal aneuploidy screening, enabling presymptomatic detection of maternal malignancy. At present, no universally accepted guideline exists for classifying NIPT results with respect to the risk of occult maternal malignancy. Nevertheless, this case underscores the clinical utility of the Maastricht criteria as a practical framework informing contemporary diagnostic algorithms. In particular, prompt management of individuals classified as high risk (Maastricht score ≥3) is essential. Such cases should receive timely genetic counseling during pregnancy and undergo multidisciplinary assessment involving Perinatology, Medical Oncology, and Hematology. Although NIPT was performed solely as a screening test in our patient, this case reinforces the importance of obtaining a comprehensive family history during pre-test counseling. Systematic assessment of familial cancer history even at the prenatal screening stage is critical for appropriate management of the diagnostic pathway and for elucidating the underlying genetic etiology. More broadly, careful interpretation of genetic tests in light of the current literature and a multidisciplinary approach can facilitate early diagnosis and improved maternal prognosis, and it may also enable the identification of additional affected relatives beyond the original testing indication, as observed in this family Table 1. Maastricht Criteria [4] Criteria Score Number of aberrations (abnormalities) > 2 3 Monosomy 2 Segmental aneuploidies with presence of an oncogene or tumor suppressor gene 2 Trisomy 12 2 Trisomy 9 2 Trisomy 8 1 Two trisomies in total 1 High significance score of the aberration 1 Probability level Total score No suspicion < 2 Mild suspicion 2 Strong suspicion ≥ 3 Table 2. Z-scores

and ratios of chromosomal abnormalities detected in our patient Finding Risk classification Result Trisomy 13 High risk Z-score: 29.643 (reference: −3 < Z-score < 3) Trisomy 7 High risk Z-score: 7.462 (reference: −3 < Z-score < 3) Finding Risk classification Result Trisomy 8 High risk Z-score: 17.775 (reference: −3 < Z-score < 3) Trisomy 7q32→qter High risk Complex sex chromosome anomaly High risk Ratio: 9.89% (low-risk threshold: < Z score < 3) Figure 1. Integrative Genomics Viewer (IGV) screenshot of the MLH1 splice-site variant (NM_000249.4)c.790+1G>A detected by NGS using a hereditary cancer panel. Fgure 2. Famly members (mother and brother) n whom the heterozygous MLH1 (NM_000249.4):c.790+1G>A varant was dentfed by Sanger sequencng References 1- Banch DW, Chudova D, Sehnert AJ, Bhatt S, Murray K, Prosen TL, Garber JE, Wlkns-Haug L, Vora NL, Warsof S, Goldberg J, Zana T, Halks-Mller M. Nonnvasve Prenatal Testng and Incdental Detecton of Occult Maternal Malgnances. JAMA. 2015 Jul 14;314(2):162-9. do: 10.1001/jama.2015.7120. PMID: 26168314. 2- Heesterbeek CJ, Aukema SM, Galjaard RH, Boon EMJ, Srebnak MI, Bouman K, Faas BHW, Govaerts LCP, Hoffer MJV, den Hollander NS, Lchtenbelt KD, van Maarle MC, van Prooyen Schuurman L, van Rj MC, Schurng-Blom GH, Stevens SJC, Tan Sndhunata G, Zaman Estek M, de De-Smulders CEM, Tjan-Hejnen VCG, Henneman L, Sstermans EA, Macvlle MVE; Dutch NIPT Consortum. Nonnvasve Prenatal Test Results Indcatve of Maternal Malgnances: A Natonwde Genetc and Clncal Follow-Up Study. J Cln Oncol. 2022 Aug 1;40(22):2426-2435. do: 10.1200/JCO.21.02260. Epub 2022 Apr 8. PMID: 35394817. 3- Amant F, Verheecke M, Wlodarska I, Dehaspe L, Brady P, Brson N, Van Den Bogaert K, Derckx D, Vandecaveye V, Tousseyn T, Moerman P, Vanderstchele A, Vergote I, Neven P, Berteloot P, Putseys K, Danneels L, Vandenberghe P, Legus E, Vermeesch JR. Presymptomatc Identfcaton of Cancers n Pregnant Women Durng Nonnvasve Prenatal Testng. JAMA Oncol. 10.1001/jamaoncol.2015.1883. PMID: 26355862. 2015 Sep;1(6):814-9. do: 4- Heesterbeek CJ, Lenaerts L, Tjan-Hejnen VCG, Amant F, van Rj MC, Theuns M, de De-Smulders CEM, Vermeesch JR, Macvlle MVE; Dutch NIPT Consortum. Comprehensve Recommendatons for the Clncal Management of Pregnant Women Wth Nonnvasve Prenatal Test Results Suspcous of a Maternal Malgnancy. JCO Oncol Pract. 2024 Aug;20(8):1027-1034. do: 10.1200/OP.23.00594. Epub 2024 Apr 12. PMID: 38608208. 5- Dharajya NG, Grosu DS, Farkas DH, McCullough RM, Almasr E, Sun Y, Km SK, Jensen TJ, Saldvar JS, Topol EJ, van den Boom D, Ehrch M. Incdental Detecton of Maternal Neoplasa n Nonnvasve Prenatal Testng. Cln Chem. 2018 Feb;64(2):329 335. do: 10.1373/clnchem.2017.277517. Epub 2017 Oct 5. PMID: 28982650. 6- Zhao E, Mller KA, Webster J, Pern J, Coggns A, Jeln AC. Cell-free DNA screenng results by stage of maternal malgnancy. Am J Obstet Gynecol MFM. 2025 Dec;7(12):101804. do: 10.1016/j.ajogmf.2025.101804. Epub 2025 Sep 26. PMID: 41016705. 7- Hodan R, Gupta S, Wess JM, Axell L, Burke CA, Chen LM, Chung DC, Clayback KM, Felder S, Foda Z, Gardello FM, Grady W, Gustafson S, Hagemann A, Hall MJ, Hampel H, Idos G, Joseph N, Kassem N, Katona B, Kelly K, Keber-Emmons A, Kupfer S, Lang K, Llor X, Markowtz AJ, Prats MM, Nell-Swller M, Outlaw D, Przadeh-Mller S, Samadder NJ, Shbata D, Stanch PP, Swanson BJ, Szymanak BM, Welborn J, Wesner GL, Yurgelun MB, Dwyer M, Darlow S, Dwan Z. Genetc/Famlal Hgh-Rsk Assessment: Colorectal, Endometral, and Gastrc, Verson 3.2024, NCCN Clncal Practce Gudelnes In Oncology. J Natl Compr Canc Netw. 2024 Dec;22(10):695-711. do: 10.6004/jnccn.2024.0061. PMID: 39689429. 8- Idos G, Valle L. Lynch Syndrome. 2004 Feb 5 [Updated 2021 Feb 4]. In: Adam MP, Bck S, Mrzaa GM, et al., edtors. GeneRevews® [Internet]. Seattle (WA): Unversty of Washngton, Seattle; https://www.ncb.nlm.nh.gov/books/NBK1211/ 1993-2026. Avalable from: 9- Daz Soto MP, Hakm A, Zerllo JA, Shanker SA, Wolf JL. Nonreportable Cell-Free DNA Prenatal Screenng Test Leads to Colorectal Cancer Dagnoss n the Mother. ACG Case Rep J. 2025 Nov 17;12(11):e01880. do: 10.14309/crj.0000000000001880. PMID: 41262536; PMCID: PMC12626709.

[Abstract:0219]

Spectrum of Malignancies in Individuals with Germline *BRIP1* Variants: A Cohort Suggesting Possible Thyroid and Endometrial Signals

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Introduction: *BRIP1* encodes a DNA repair helicase in the Fanconi anemia/homologous recombination pathway and is considered a moderate-penetrance predisposition gene primarily for tubo-ovarian cancer. However, the broader cancer spectrum and genotype–phenotype correlations remain incompletely defined, and interpretation of variants of uncertain significance (VUS) remains a major barrier to clinical translation. We report our center's experience with germline *BRIP1* variants and highlight potentially non-canonical tumor presentations.

Materials-Methods: This study aimed to evaluate the clinical and molecular characteristics of individuals with germline *BRIP1* variants identified between 2021 and 2025 at the Eskisehir Osmangazi University Department of Medical Genetics. Individuals with *BRIP1* variants detected by NGS-based hereditary cancer multigene panels were retrospectively reviewed; one additional individual was identified by whole-exome sequencing (WES) performed for a non-oncologic indication. Extracted variables included age at diagnosis, cancer type, pathology, treatment, and family history. Variants were categorized as pathogenic (P), likely pathogenic (LP), or VUS using routine laboratory classification.

Results: Sixteen individuals were included (15 panel-based; 1 WES-based). Seven carried P/LP variants and nine carried VUS. The tumor spectrum comprised breast cancer (n=7), tubo-ovarian/peritoneal serous carcinoma (n=4), endometrial cancer (n=2), and thyroid cancer (n=2). One WES-tested individual had no malignancy and was evaluated for hypertrophic cardiomyopathy. Among breast cancers, two were early-onset (age 38) and two individuals had metachronous bilateral cancer. Among tubo-ovarian/peritoneal cases, three carried *BRIP1* VUS and one carried an LP truncating variant; pathology was predominantly serous carcinoma, including high-grade serous.

Conclusion: Current clinical guidance supports *BRIP1* as an actionable gene for tubo-ovarian cancer risk and recommends considering risk-reducing salpingo-oophorectomy close to menopause (approximately 45–50 years) using individualized, age-specific risk estimates. In contrast, large case-control evidence suggests that truncating *BRIP1* variants, including p.Arg798Ter, are not associated with a substantial increase in breast cancer risk; therefore, the high number of breast cancer cases in our cohort should be interpreted carefully, taking into account each patient's family history and other known risk factors. Evidence for a hereditary endometrial cancer role of *BRIP1* is currently limited; nevertheless, germline pathogenic variants in *BRIP1* and other predisposition genes have been reported in endometrial cancer cohorts, supporting continued case-level evaluation and prospective studies. Recent familial thyroid cancer studies implicate DNA damage-repair pathways, suggesting that the apparent thyroid cancer clustering in our cohort is hypothesis-generating rather than definitive. Overall, our cohort underscores that *BRIP1* remains an important but still evolving cancer predisposition gene. Larger, well-designed prospective studies with detailed clinical follow-up are needed to better define the cancer spectrum and to support reclassification of VUS, ultimately improving risk assessment and patient management.

Keywords: *BRIP1*, endometrial cancer, thyroid cancer, tubo-ovarian cancer, variant of uncertain significance (VUS)

Table 1: Clinical, histopathological and genetic findings of the patients

Case	Age	Cancer type	Histopathology	Family history	Variant	Pathogenicity
1	50	Ovarian cancer	Poorly differentiated serous ovarian carcinoma	Lung ca (brother, smoker), ncreatic ca (sister, 48), cousin (smoker); parental same villa	c.2285G>A (het)	VUS
2	63	Breast cancer ateral)	Invasive breast carcinoma,	Uncle lung ca; maternal uncl ynx ca	c.845C>G (het)	VUS
3	54	Breast cancer	Invasive breast carcinoma,	Sister + paternal uncle colon usin <50 breast ca	c.752G>A (het)	LP
4	64	Endometrial cance	Very focal microscopic tum lespread atypical hyperplas (2 focal loss	Sister breast ca (62); anothe er hysterectomy history	c.2119C>T (het)	VUS
5	70	Thyroid cancer	Medullary thyroid carcinon	Father prostate ca; brother c parental same village	c.23A>T (het)	VUS
6	39 / 44	Breast cancer etachronous bilater	Not available	Paternal aunt breast ca (60); tant relative malignant melan	c.2428C>G (het)	VUS
7	Not olicable	No malignancy	Not applicable	Not available	c.608del (het)	P
8	53	Ovarian cancer	Serous carcinoma	Aunt HCC; paternal aunt skir	c.1935+4_1935+7del (he	VUS
9	38	Breast cancer	Invasive ductal carcinoma	Father larynx ca; paternal au known ca), possible thyroid c ternal great-aunts breast ca	c.2392C>T (het)	P
10	57	Endometrial cance	Endometrioid carcinoma	Father colon ca; maternal ndparents first cousins	c.2992_2995del (het)	P
11	65	Ovarian cancer	High-grade serous carcinor	Parental same village; brothe g ca	c.157_159delAGCinsGG t)	LP
12	58	Peritoneal serous cinoma	Low-grade peritoneal serou cinoma	Parental same village; father ostate ca	c.888G>C (het)	VUS
13	38	Breast cancer	Invasive breast carcinoma	Maternal uncle lung ca (38, oker, deceased); parental san age	c.761_764del (het)	P
14	56	Breast cancer	Invasive ductal carcinoma	Mother sigmoid ca (65); fath on ca (45, deceased)	c.139C>G (het)	VUS
15	57	Thyroid cancer	Type not available; RAI eived	Family history positive; mate nts breast ca	c.2992_2995del (het)	P
16	46 / 58	Breast cancer etachronous bilater	High-grade invasive ductal cinoma	Sister breast ca	c.1073T>G (het)	VUS

[BRIP1 (NM_032043.3), LP: Likely pathogenic, P: Pathogenic, VUS: Variant of uncertain significance, NST: No special type, RAI: Radioactive iodine, HCC: Hepatocellular carcinoma, het: heterozygous.]

Spectrum of Malignancies in Individuals with Germline BRIP1 Variants: A Cohort Suggesting Possible Thyroid and Endometrial Signals Emre Akbaş1, Gökçe Koç Çayır1, Sinem Kocagil1 1. Department of Medical Genetics, Eskisehir Osmangazi University, Eskisehir, Türkiye Abstract Introduction: BRIP1 encodes a DNA repair helicase in the Fanconi anemia/homologous recombination pathway and is considered a moderate-penetrance predisposition gene primarily for tubo-ovarian cancer. However, the broader cancer spectrum and genotype-phenotype correlations remain incompletely defined, and interpretation of variants of uncertain significance (VUS) remains a major barrier to clinical translation. We report our center's experience with germline BRIP1 variants and highlight potentially non-canonical tumor presentations. Methods: This study aimed to evaluate the clinical and molecular characteristics of individuals with germline BRIP1 variants identified between 2021 and 2025 at the Eskisehir Osmangazi University Department of Medical Genetics. Individuals with BRIP1 variants detected by NGS (Next Generation Sequencing)-based hereditary cancer multigene panels were retrospectively reviewed; one additional individual was identified by WES (Whole Exome Sequencing) performed for a non-oncologic indication. Extracted variables included age at diagnosis, cancer type, pathology, treatment, and family history. Variants were categorized as pathogenic (P), likely pathogenic (LP), or VUS using routine laboratory classification. Results: Sixteen individuals were included (15 panel-based; 1 WES-based). Seven carried P/LP variants and nine carried VUS. The tumor spectrum comprised breast cancer (n=7), tubo-ovarian/peritoneal serous carcinoma (n=4), endometrial cancer (n=2), and thyroid cancer (n=2). One WES-tested individual had no malignancy and was evaluated for hypertrophic cardiomyopathy. Among breast cancers, two were early-onset (age 38) and two individuals had metachronous bilateral cancer. Among tubo ovarian/peritoneal cases, three carried BRIP1 VUS and one carried an LP truncating variant; pathology was predominantly serous carcinoma, including high-grade serous. Discussion: Current clinical guidance supports BRIP1 as an actionable gene for tubo-ovarian cancer risk and recommends considering risk-reducing salpingo-oophorectomy close to menopause (approximately 45-50 years) using individualized, age-specific risk estimates. In contrast, large case control evidence suggests that truncating BRIP1 variants, including p.Arg798Ter, are not associated with a substantial increase in breast cancer risk; therefore, the high number of breast cancer cases in our cohort should be interpreted carefully, taking into account each patient's family history and other known risk factors. Evidence for a hereditary endometrial cancer role of BRIP1 is currently limited; nevertheless, germline pathogenic variants in BRIP1 and other predisposition genes have been reported in endometrial cancer cohorts, supporting continued case-level evaluation and prospective studies. Recent familial thyroid cancer studies implicate DNA damage-repair pathways, suggesting that the apparent thyroid cancer clustering in our cohort is hypothesis-generating rather than definitive. Overall, our cohort underscores that BRIP1 remains an important but still evolving cancer predisposition gene. Larger, well-designed prospective studies with detailed clinical follow-up are needed to better define the cancer spectrum and to support reclassification of VUS, ultimately improving risk assessment and patient management. Keywords: BRIP1, endometrial cancer, thyroid cancer, tubo-ovarian cancer, variant of uncertain significance (VUS) Introduction BRIP1 (BRCA1 interacting protein 1) is part of the Fanconi anemia/homologous recombination pathway involved in DNA damage repair. This pathway is critical for the cell to accurately repair double-strand DNA breaks in particular. Therefore, inherited, germline disruptions in BRIP1 are thought to increase susceptibility to certain cancer types. The best clinically defined role of BRIP1 is as a moderate penetrance predisposition gene that increases the risk of tubo-ovarian cancer. Various studies have shown that BRIP1 loss-of-function (truncating/frameshift) variants can significantly increase the risk of ovarian cancer. (1, 2) In contrast, BRIP1's place within the "broader cancer spectrum" that is, the degree to which it is associated with which tumors, is not clear. One of the most challenging areas in clinical practice is the frequent VUS (variants of uncertain significance) results in BRIP1; because these variants do not define a clear increase in cancer risk on their own, they complicate patient management. In addition, the genotype-phenotype relationship, namely which variant is more associated with which tumor, is still a maturing field, and in particular

the patient profile and testing indications of different centers can influence this picture. In this article, we present the distribution of malignancies accompanying germline BRIP1 variants identified in our center and we highlight two original points in particular. The first emphasis is the presence in our cohort of tumors such as thyroid and endometrium that are not classically prominent with BRIP1. The role of BRIP1 in endometrial cancer is discussed with limited data; it has been reported that in broad panel screenings, DNA repair genes such as BRIP1 are rarely encountered among non Lynch predisposition genes. (3) For thyroid cancer, studies pointing to DNA repair pathways on a hereditary background are increasing; in this context, we think that repair genes such as BRIP1 should be considered as a “hypothesis-generating” signal. (4) The second emphasis is that, despite the lack of clarity regarding BRIP1’s association with breast cancer, the number of breast cancer cases in our cohort is relatively high and therefore this issue is considered worth discussing. In particular, large case-control data have shown that BRIP1 protein-truncating variants do not “substantially” increase breast cancer risk. (5) For this reason, rather than interpreting the breast cancer clustering in our cohort as BRIP1 being a direct and strong “breast cancer gene,” we consider it carefully together with referral bias, family history, accompanying risk factors, and possible other genetic contributions. Nevertheless, the fact that a considerable proportion of BRIP1 carriers in clinical practice may enter the genetic testing process because of breast cancer is a notable observation in terms of real-world practice and needs to be clarified in larger, well-designed studies. This study aims to make the possible tumor associations of BRIP1 beyond tubo-ovarian cancer visible at the clinical level, to demonstrate the practical impact of the VUS burden, and to contribute our center experience to the literature, especially through the thyroid/endometrium signal and the relative excess of breast cancer cases. Methods Patient Selection: Patients evaluated for hereditary cancer predisposition between 2021 and 2025 at the Eskisehir Osmangazi University Department of Medical Genetics and found to harbor a germline variant in the BRIP1 gene were retrospectively included in the study. In 15 of these patients, a BRIP1 variant was identified using an NGS (Next Generation Sequencing)-based multigene hereditary cancer panel, whereas in one man, a pathogenic BRIP1 variant was incidentally detected on WES (Whole Exome Sequencing) analysis performed for a non-oncologic indication, familial hypertrophic cardiomyopathy. For each patient, data such as demographic information, age at cancer diagnosis, tumor type and histopathology, and family history of cancer were obtained retrospectively from patient files and electronic systems. Genetic Analysis and Variant Interpretation: Panel testing was performed using an NGS panel including 150 genes associated with hereditary cancers in the literature. Sequencing data were aligned and analyzed against the international reference transcript, and variants were annotated. The genomic positions of the detected BRIP1 variants were reported according to the NM_032043.3 reference. The clinical significance of variants was evaluated based on ACMG (American College of Medical Genetics and Genomics) criteria. In this classification, factors such as information from the literature and databases, in silico pathogenicity predictions, the effect of the variant on the protein, and the frequency observed in populations were taken into account. As a result of the evaluation, variants were classified into three categories: Pathogenic, Likely Pathogenic, and VUS. The pathogenic and likely pathogenic groups were collectively considered “clinically significant mutations.” Results Patient Profile: A total of 16 patients (14 women, 2 men) were included in the study. The ages of these individuals ranged from 38 to 70 based on the values at the time of diagnosis. The median age at diagnosis was 54 for breast cancer cases and 56 for tubo-ovarian cancer cases. In fifteen patients, a BRIP1 variant was detected by a hereditary cancer predisposition NGS gene panel test, whereas in one man (56 years) a pathogenic BRIP1 variant was incidentally identified during WES performed for a diagnosis of cardiomyopathy. Of these 16 patients, the BRIP1 variant detected in 7 was in the pathogenic/likely pathogenic category (5 indel variants resulting in frameshift or stop-codon formation, and 2 variants affecting the splice region), while 9 had missense-type VUS. Tumor Diagnoses: The cancer diagnoses of patients carrying BRIP1 variants showed a broad distribution (Table 1). The most frequently observed malignancy was breast cancer: a total of 7 women (43.8%) developed invasive breast carcinoma at some point in their lives.

Ovarian or primary peritoneal cancer was detected in four patients (25%). Two patients (12.5%) had endometrial cancer, and two patients (12.5%) had thyroid cancer. One man had not been diagnosed with any malignancy. Of the 15 patients diagnosed with cancer, 13 were women and 2 were men. While 50% of women carrying a BRIP1 variant had a history of breast cancer, the frequency of ovarian/peritoneal cancer was calculated as 28.6%. Breast Cancer Cases: Of the seven breast cancer patients, five had unilateral disease and two had metachronous bilateral breast cancer. Age at breast cancer development was under 40 in two cases (at 38 and 39 years). Tumor types were generally "No Special Type" (NST) invasive ductal carcinoma, and two patients had multiple primary breast tumors. One had bilateral diagnoses at 39 and 44 years, and the other had metachronous contralateral breast cancer diagnoses at 46 and 58 years. The pathology reports of these patients showed high-grade invasive carcinoma features. In two breast cancer cases (diagnosed at 38 and 48 years), BRIP1 variants were in the pathogenic class (one p.Arg798Ter stop-codon mutation and the other p.Lys998GlufsTer60 frameshift mutation), whereas the others had missense variants classified as VUS. In terms of family history, four of the seven breast cancer patients were found to have a history of breast cancer in first-degree relatives, while the other three had other cancers in the family. Ovarian and Peritoneal Cancer Cases: Serous carcinoma of ovarian or peritoneal origin was identified in four women. Ages at diagnosis were 50, 53, 58, and 65, and three were postmenopausal. Pathological examination results showed high-grade serous carcinoma in three cases (two ovarian, one primary peritoneal) and low-grade serous ovarian carcinoma in one case. The BRIP1 variant detected in three of these patients was VUS (missense or intronic change); in one patient with ovarian cancer at age 65, a frameshift mutation in the BRIP1 gene was detected and reported as "likely pathogenic." Only one of the four ovarian/peritoneal cancer patients (ovarian cancer at age 50) had a family history of ovarian cancer (in a sister); the others had different types in the family history such as lung, liver, or skin cancer. Endometrial Cancer Cases: Endometrial cancer was detected in two women. One patient was diagnosed at age 64, and endometrioid carcinoma was detected only in a microscopic focus, with the lesion observed on a background of widespread atypical endometrial hyperplasia. The other patient was diagnosed at age 57 with stage I endometrioid-type endometrial cancer. Both cases were treated with surgery (hysterectomy + bilateral salpingo-oophorectomy) and did not require radiotherapy or chemotherapy during follow-up. In both of these patients, variants in the BRIP1 gene that had not previously gained clarity in the literature in terms of pathogenicity (p.Arg707Cys and p.Lys998GlufsTer60) were detected. Regarding family history, the 64-year-old patient had a sister with breast cancer at age 62, while the 57-year-old patient's father had died at a young age due to colon cancer; the parents of both patients were distantly related. Thyroid Cancer Cases: Two patients had thyroid cancer. One was a 70-year-old man diagnosed with medullary thyroid carcinoma and treated with total thyroidectomy. In this patient, a p.Tyr8Phe change (VUS) in the BRIP1 gene was detected. Pedigree analysis revealed that the patient's father had prostate cancer and his brother had colon cancer. Notably, this patient also had widespread skin findings, including multiple soft subcutaneous nodules and café-au-lait spots. The second thyroid cancer patient was a 57-year-old woman who underwent thyroidectomy and radioactive iodine therapy for papillary thyroid carcinoma. This patient's BRIP1 variant was the p.Lys998GlufsTer60 frameshift mutation and was classified as pathogenic. In the family history, two maternal aunts had breast cancer and there were no other thyroid cancers. Other Findings and General Assessment: In most cases with a positive family history, the relevant cancers were of types not associated with BRIP1 (e.g., lung and colon cancer), suggesting that carrying a BRIP1 variant alone does not explain the clustering of cancer in these families. Finally, the man, who was evaluated at age 56 for hypertrophic cardiomyopathy and was found to have a pathogenic p.Asn203fs (c.608del) mutation in the BRIP1 gene, has no history of any malignancy to date. This case is noteworthy in terms of suggesting that BRIP1 penetrance may be incomplete and that some carriers may not develop cancer until advanced ages. The clinical and genetic characteristics of patients carrying BRIP1 variants are summarized in Table 1. For each case, age, cancer diagnosis, histopathological features, a summary of family history, the cDNA level notation of the detected BRIP1

variant, and the laboratory pathogenicity classification are provided. Case Age Cancer type Histopathology Family history Variant 1 50 Ovarian cancer Poorly differentiated serous ovarian carcinoma c.2285G>A (het) Pathogenicity VUS Lung ca (brother, smoker), pancreatic ca (sister, 48), cousin lung ca (smoker); parental same village 2 63 Breast (bilateral) cancer Invasive breast carcinoma, NST c.845C>G (het) VUS Uncle lung ca; maternal uncle larynx ca 3 54 Breast cancer Invasive breast carcinoma, NST Sister + paternal uncle colon ca; cousin A (het) LP c.2119C>T (het) VUS PAX2 focal loss 5 70 Thyroid cancer Medullary carcinoma thyroid c.23A>T (het) VUS Father prostate ca; brother colon ca; parental same village 6 39 / 44 Breast cancer (metachronous bilateral) Not available Paternal aunt breast ca (60); distant relative malignant melanoma c.2428C>G (het) VUS 7 Not applicable No malignancy Not applicable Not available c.608del (het) P 8 53 Ovarian cancer Serous carcinoma Aunt HCC; paternal aunt skin ca? c.1935+4_1935 +7del (het) VUS 9 38 Breast cancer Invasive ductal carcinoma Father larynx ca; paternal aunts (unknown ca), possible thyroid ca; maternal great aunts breast ca c.2392C>T (het) P 10 57 Endometrial cancer Endometrioid carcinoma Father colon ca; maternal grandparents first cousins c.2992_2995del (het) P 11 65 Ovarian cancer High-grade serous carcinoma Parental same village; brother lung ca c.157_159delA GCinsGG (het) LP 12 58 Peritoneal serous carcinoma Low-grade peritoneal serous carcinoma Parental same village; father prostate ca c.888G>C (het) VUS 13 38 Breast cancer Invasive breast carcinoma Maternal uncle lung ca (38, smoker, deceased); parental same village c.761_764del (het) P 14 56 Breast cancer Invasive ductal carcinoma Mother sigmoid ca (65); father colon ca (45, deceased) c.139C>G (het) VUS 15 57 Thyroid cancer Type not available; RAI received Family history positive; maternal aunts breast ca c.2992_2995del (het) P 16 46 / 58 Breast cancer (metachronous bilateral) High-grade invasive ductal carcinoma Sister breast ca c.1073T>G (het) VUS Table 1: Clinical, histopathological and genetic findings of the patients [BRIP1 (NM_032043.3), LP: Likely pathogenic, P: Pathogenic, VUS: Variant of uncertain significance, NST: No special type, RAI: Radioactive iodine, HCC: Hepatocellular carcinoma, het: heterozygous.] Discussion In this retrospective cohort of 16 individuals with germline BRIP1 variants, we observed a heterogeneous malignancy profile that included the expected tubo-ovarian spectrum as well as a notable representation of breast cancer, and less classically emphasized tumor types such as endometrial and thyroid cancers. Given the exploratory nature and limited sample size, these observations should be interpreted as hypothesis-generating rather than evidence of causality. From a biological standpoint, BRIP1 is a BRCA1-interacting helicase that contributes to the repair of DNA double-strand breaks through homologous recombination. (6, 7) This role provides a mechanistic rationale for cancer susceptibility, particularly for tumors driven by homologous recombination deficiency. The most established clinical association for heterozygous pathogenic BRIP1 variants is an increased risk of tubo-ovarian cancer, primarily driven by loss-of-function variants, as initially demonstrated in population-based studies and further supported by subsequent series. (8) Consistent with this framework, ovarian/peritoneal cancer cases were present in our cohort. Current clinical management resources generally recommend that risk-reducing salpingo-oophorectomy be considered around the mid-to-late 40s for BRIP1 pathogenic variant carriers, emphasizing individualized decision-making. (9) In contrast, the relationship between BRIP1 and breast cancer remains uncertain. Large case-control analyses have not supported a substantial increase in breast cancer risk for BRIP1 protein-truncating variants, including commonly encountered truncating changes, and clinical-testing-based datasets similarly report no significant association for BRIP1 with breast cancer risk. (10) Findings from familial cohorts are aligned with this interpretation, reporting high ovarian but not familial breast cancer risk for BRIP1 loss-of-function variants. (8) Therefore, the relatively high number of breast cancer cases in our cohort is best discussed in the context of referral/ascertainment patterns, family history structure, and other genetic or non-genetic modifiers, rather than assuming a direct “BRIP1 is a breast cancer gene” conclusion. Endometrial cancer appeared in a small subset of our cohort. The available literature suggests that non Lynch germline pathogenic variants are present in a minority of unselected endometrial cancer cohorts, and BRIP1 can be detected among these rare findings, but the overall strength and direction of association are not yet clear. (3)

Larger endometrial cancer series and tumor-informed analyses will be required before any risk-management implications can be inferred. Thyroid cancer cases in our cohort are similarly intriguing but currently speculative. Recent work in familial nonmedullary thyroid carcinoma supports a possible contribution of rare germline variants in DNA repair genes to susceptibility, reinforcing the plausibility of “DNA repair pathway signals” in thyroid cancer predisposition, although BRIP1 itself is not established as a thyroid cancer predisposition gene. (4) Three variants (c.23A>T; p.Tyr8Phe, c.157_159delAGCinsGG; p.Ser53GlyfsTer2, c.1073T>G; p.Leu358Arg) were noted as candidate novel because no direct records were identified in ClinVar and PubMed searches. Finally, the high burden of VUS in BRIP1 is a practical challenge in hereditary cancer clinics: VUS results should not be used to justify risk-reducing interventions, and periodic reinterpretation as new evidence accumulates remains essential. (11) In this series of 16 cases carrying BRIP1 variants, as expected, tubo-ovarian cancer cases were observed alongside a prominent representation of breast cancer referrals. In addition, less emphasized tumors such as thyroid and endometrial cancers were observed in the cohort. These findings support the need to re-evaluate the clinical spectrum of BRIP1 in larger series across different populations. References 1. Rafnar, T., Gudbjartsson, D. F., Sulem, P., Jonasdottir, A., Sigurdsson, A., Jonasdottir, A., Besenbacher, S., Lundin, P., Stacey, S. N., Gudmundsson, J., Magnusson, O. T., le Roux, L., Orlygsdottir, G., Helgadottir, H. T., Johannsdottir, H., Gylfason, A., Tryggvadottir, L., Jonasson, J. G., de Juan, A., … Stefansson, K. (2011). 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[Abstract:0226]

BRCA1/BRCA2 Double Heterozygosity: A Case Report and Review of the Literature

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Introduction: Breast cancer is the most common cancer among women worldwide. Approximately 5–10% of all breast cancer cases are hereditary, and mutations in the *BRCA1* and *BRCA2* genes are responsible for about half of these hereditary cases. It is well established that *BRCA1/2* mutations predispose individuals to ovarian, pancreatic, and prostate cancers, in addition to breast cancer. Recent studies have also suggested a potential association with gastrointestinal tumors. The presence of pathogenic variants in both *BRCA1* and *BRCA2* genes is extremely rare, with only a limited number of cases reported in the literature.
While comprehensive guidelines exist for surveillance and management for individuals carrying a single pathogenic variant in either *BRCA1* or *BRCA2*, there is no definitive guideline regarding the cancer spectrum, age of onset, or follow-up protocols for double heterozygote individuals due to the rarity of the condition.
In this report, we present a patient with gastric cancer carrying pathogenic variants in both *BRCA1* and *BRCA2*, and discuss the cancer spectrum and clinical implications in double heterozygous carriers.
Method: Germline genetic testing was performed using a next-generation sequencing–based hereditary cancer panel. Identified variants were interpreted and classified according to the ACMG guidelines.
Case Presentation&Results: A 50-year-old female patient was referred to us due to a diagnosis of signet ring cell gastric cancer at the age of 43 and a family history of multiple breast cancers among her first- and second-degree relatives. The patient underwent a gastrectomy followed by chemotherapy.
Germline genetic analysis identified two variants in *BRCA1* (c.4834C>T) [PVS1, PS4, PM2] and *BRCA2* (c.4465A>T) [PVS1, PM2], both classified as pathogenic according to the ACMG guidelines.
Both *BRCA1* and *BRCA2* pathogenic variants were confirmed by Sanger sequencing, and segregation analysis was performed in available family members. Familial segregation studies revealed that one daughter had a single *BRCA2* variant, another daughter had a single *BRCA1* variant, and her son had both *BRCA1* and *BRCA2* variants.
Discussion: Germline double heterozygosity for *BRCA1* and *BRCA2* is exceptionally rare, particularly in non-Ashkenazi individuals, and our patient has no known Ashkenazi ancestry. While pathogenic variants in these genes are classically associated with hereditary breast and ovarian cancer, emerging evidence suggests a broader tumor spectrum in double heterozygotes.
Accordingly, we reviewed previously reported cases to characterize the clinical phenotype and cancer spectrum better. Although the literature suggests a markedly earlier age at diagnosis for breast and particularly ovarian cancer in affected individuals, our patient is 50 years old and has not developed breast or ovarian cancer to date. At the same time, her sister—who carries only the familial *BRCA2* variant—was diagnosed with breast cancer at the age of 55. This presentation within the same family supports variable expressivity and incomplete penetrance, and suggests that additional genetic or non-genetic factors are involved. Additionally, several reports have noted a higher incidence of gastrointestinal malignancies among individuals who are double heterozygous for *BRCA1* and *BRCA2*, which may indicate a possible synergistic effect of dual loss of tumor suppressor genes.

Keywords: BRCA1, BRCA2, breast cancer, double-heterozygosity, gastric cancer
BRCA1/BRCA2 Double Heterozygosity: A Case Report and Review of the Literature Ceren Furtana1, Yusuf Bahap1, Mehmet Ali Ergun1 1Department of Medical Genetics, Gazi University Faculty of Medicine Introduction:

Breast cancer is one of the most significant malignancies affecting women worldwide. Approximately 5–10% of all breast cancers are inherited, and mutations in BRCA1-BRCA2 genes are responsible for the majority of these hereditary cases. The BRCA1 and BRCA2 genes are tumour suppressor genes and they play an important role in DNA repair via homologous recombination[1]. Germline pathogenic variants in these genes are generally associated with Hereditary Breast and Ovarian Cancer syndrome (HBOC), which is inherited in an autosomal dominant manner, and patients with HBOC carry a significantly increased risk of breast and ovarian cancer compared to the general population. In addition, an increased risk of prostate, pancreatic, and other malignancies is also known to be present [2-4]. Double heterozygosity (DH) refers to an individual carrying pathogenic or likely pathogenic variants more than one clinically-relevant gene (in this case, BRCA1 and BRCA2). While this genetic condition is extremely rare in the general population, it is most frequently reported in Ashkenazi Jewish populations. Among all Ashkenazi Jewish breast cancer patients, 12.3% carried a BRCA1 or BRCA2 pathogenic variant, whereas 0.3% carried pathogenic variants in both BRCA1 and BRCA2 due to founder variants[10]. In the non-Ashkenazi population, the estimated prevalence of BRCA1 and BRCA2 mutation carriers is 0.11% and 0.12%, respectively; therefore, DH for pathogenic variants in both genes is expected to be extremely rare, with an estimated frequency of approximately 1 in 190,000. [5] The clinical implications of BRCA1/BRCA2 double heterozygosity are not yet fully understood. It remains unclear whether DH carriers exhibit additive or synergistic cancer risks, earlier age at onset, more aggressive tumor behavior. There are also conclusions about how these patients should optimally be managed in terms of surveillance, risk reducing strategies, and therapeutic decision making. Current international guidelines for hereditary cancer surveillance are largely based on single gene pathogenic variants, and specific recommendations for DH carriers are lacking [6]. In this context, we present a rare case of a non-Ashkenazi individual carrying germline pathogenic variants in both BRCA1 and BRCA2, who developed gastric cancer. By reviewing the clinical features and family history of this patient with previously reported cases, we aim to contribute to a better understanding of the phenotypic consequences and clinical significance of BRCA1/BRCA2 double heterozygosity. Case Presentation&Results: A 50 year old female patient referred to our genetics clinic for evaluation of hereditary cancer predisposition. She was presented with abdominal pain and was diagnosed with gastric signet ring cell carcinoma at the age of 43. The patient underwent total gastrectomy, followed by adjuvant chemotherapy. There was a significant family history of breast cancer; including her sister diagnosed at the age of 55 and three paternal aunts diagnosed in their sixties. A three generation pedigree demonstrating multiple cases of breast cancer on the paternal side is presented in Figure 1. Germline genetic analysis using a hereditary cancer multigene panel identified two pathogenic variants: a BRCA1 (NM_007294.4) nonsense variant, c.4834C>T (p.Gln1612Ter) classified as pathogenic based on ACMG criteria (PVS1, PS4, PM2), and a BRCA2 (NM_000059.4) nonsense variant, c.4465A>T (p.Lys1489Ter) also classified as likely pathogenic according to ACMG guidelines (PVS1, PM2). Both BRCA1 and BRCA2 pathogenic variants were confirmed by Sanger sequencing. These findings established a diagnosis of germline BRCA1/BRCA2 double heterozygosity. After these results, the proband was referred to genetic counseling. The implications of germline BRCA1/BRCA2 double heterozygosity were discussed, and genetic testing was recommended for at risk family members, including her children. Familial segregation analysis revealed intrafamilial variability. While the proband diagnosed with an early onset gastric cancer with double heterozygosity; her sister, who has only the BRCA2 variant, presented with breast cancer at age 55. Additionally, her one daughter carried the single BRCA2 variant, another daughter carried the single BRCA1 variant, and the son carried both BRCA1 and BRCA2 pathogenic variants. All of the offsprings were asymptomatic. Figure 1. Family pedigree. The proband is indicated with an arrow. Discussion: Germline DH for pathogenic variants in BRCA1 and BRCA2 is a rare genetic condition, particularly in non-Ashkenazi populations, and its clinical phenotype is poorly characterized. Most available evidence comes from a limited number of case reports and small case series, and these reports mainly focused on breast and ovarian cancer. This creates

difficulties in understanding the cancer risk, tumor spectrum, and optimal follow-up strategies in DH carriers. [7] Review of the published literature indicates that the majority of reported BRCA1/BRCA2 DH cases present with the classical HBOC phenotype, with breast cancer being the most frequently observed malignancy. Several studies suggest that the clinical phenotype of DH carriers often resembles that of BRCA1 single variant carriers, particularly with respect to tumor pathology, although considerable heterogeneity in age at onset and cancer presentation has been observed [7,8]. Family based studies also demonstrate marked intrafamilial variability, with some DH individuals remaining asymptomatic into later adulthood, while others develop multiple primary malignancies. [9] In this case, familial segregation data allowed us to compare cancer phenotypes within the same family. The proband's sister, who carried only the BRCA2 pathogenic variant, developed breast cancer at the age of 55, consistent with the classical HBOC phenotype. In contrast, the proband, who carries pathogenic variants in both BRCA1 and BRCA2, was diagnosed with gastric signet ring cell carcinoma at age 43 and is now 50 years old. She has not developed breast or ovarian cancer to date. This intrafamilial variability highlights incomplete penetrance and variable expressivity in BRCA-associated cancers and raises the possibility that double heterozygosity may modify tumor spectrum, potentially through additive or synergistic impairment of homologous recombination mediated DNA repair. Recent evidence on digenic inheritance involving homologous recombination genes further supports this complexity [7,10]. In this context, the present case is notable for the development of gastric cancer, a malignancy not classically associated with HBOC. Although gastric cancer has not emerged as a recurrent feature in previously reported DH case series, growing evidence supports an expanded cancer risk profile associated with BRCA1/2 pathogenic variants. A large population based study demonstrated a significantly increased risk of gastric cancer among carriers of pathogenic variants in both genes [11]. In addition, familial and case control studies have suggested a role for BRCA2 pathogenic variants in familial gastric cancer, particularly in individuals without pathogenic variants in classical gastric cancer predisposition genes such as CDH1 [12]. A recent comprehensive review similarly highlighted accumulating evidence linking BRCA1/2 pathogenic variants, especially BRCA2, to gastric cancer susceptibility, while highlighting the absence of standardized gastric cancer surveillance recommendations for BRCA carriers [13]. To date, gastric cancer in the context of BRCA1/BRCA2 double heterozygosity has been reported only exceptionally. Wen et al. described a 50 year old male patient with poorly differentiated gastric adenocarcinoma carrying germline BRCA1 and BRCA2 variants. Similar to our case, the patient had a family history including individuals affected by breast cancer [14]. Additionally, Choi et al. reported a Korean family in which a BRCA1/BRCA2 double heterozygous individual (the mother of one proband) was diagnosed with gastric cancer at the age of 62, further supporting the possibility of a broader tumor spectrum associated with double heterozygosity [15]. However the data about gastric cancer cases associated with DH is very limited. In our literature review of 74 patients with BRCA1/BRCA2 double heterozygosity, 60 patients were diagnosed with breast cancer; age information was available for 57 of them and their average age at diagnosis was 39. Ovarian cancer was reported in 13 patients, with a mean age at diagnosis of 49 years. In addition, 9 individuals developed both breast and ovarian cancer. The distribution of cancer types among DH individuals is summarized in Figure 2. These findings may suggest that DH individuals tend to develop breast cancer at an earlier age compared with single BRCA2 mutation carriers (43.5 ± 9.8 years), while their age at breast cancer diagnosis appears similar to or slightly earlier than that observed in single BRCA1 mutation carriers (41.1 ± 9.2 years). For ovarian cancer, DH individuals were diagnosed at a similar age to those who carry single BRCA1 variant (approximately 49 years), but earlier than those who carry single BRCA2 variant (approximately 58 years) [16]. In line with our findings, Heidemann et al. reported 8 German BRCA1/BRCA2 double heterozygous females and observed a relatively early mean age at first breast cancer diagnosis (approximately 39.6 years), supporting the possibility of earlier disease onset and a potentially more severe phenotype in DH carriers[6]. %2.7 %4.1 %9.5 %12.2 %5.4 Breast only Ovarian only Breast+Ovarian Asymptomatic %66.2 Gastric Other/Mixed Figure 2. Distribution of clinical phenotypes among reported BRCA1/BRCA2 double

heterozygous individuals (n=74). Other /Mixed includes rare non-HBOC malignancies and multiple primary tumors (cholangiocarcinoma, breast+colon, breast+endometrial; total n=3). Furthermore among 68 BRCA1/BRCA2 double heterozygous (DH) individuals with available family history information, 51 patients had a reported family history of breast cancer and 23 patients had a reported family history of gastrointestinal tract malignancies (esophageal, gastric, or colorectal cancers). Notably, gastric cancer was the most frequently reported GI tract malignancy, present in 16 of these 23 families. Consistent with our results, Zuradelli et al. reported that multiple gastrointestinal tumors including gastric cancer, were observed among the relatives of DH carriers in one of the largest DH focused case series [5]. More recently, Wakaki et al. emphasized that, although evidence remains limited, the accumulation of gastrointestinal tumors across reported DH cases and pedigrees supports the concept of an expanded and heterogeneous tumor spectrum, rather than a phenotype restricted to classical HBOC associated cancers [16]. Because of the heterogeneity and incomplete reporting across studies these findings should be interpreted cautiously. Clinically, the lack of DH specific management and surveillance guidelines remains a significant challenge as existing guidelines are largely derived from single gene carrier data and may not represent the complexity observed in DH individuals. Moreover, genetic counseling in DH families may be more complex than in single BRCA carriers, as offspring have a 75% probability of inheriting at least one pathogenic variant (50% for inheriting either variant and 25% for inheriting both), underscoring the importance of cascade testing and individualized risk assessment [17]. Overall, whether double heterozygosity for BRCA1/BRCA2 poses a different risk or a spectrum of malignancy compared to single gene carriers remains uncertain due to the limited number of reported DH cases as well as variability of clinical findings. However, given that our patient had a malignancy outside the classical HBOC spectrum, along with evidence from population based evidence linking BRCA pathogenic variants to gastric cancer, increased clinical awareness may be necessary when counseling and managing DH carriers. Continued reporting of well characterized DH cases; including tumor types, segregation patterns, and long term outcomes, will be essential to better understand the cancer spectrum, improve genetic counseling and inform individualized surveillance strategies. Conclusion: This report describes a rare case of gastric signet ring cell carcinoma in a non Ashkenazi individual with germline BRCA1 and BRCA2 double heterozygosity, contributing to the limited literature with this condition. While BRCA1/BRCA2 double heterozygosity has been predominantly reported in association with breast and ovarian cancers, our findings, together with emerging epidemiological and familial data, support the possibility of an expanded tumor spectrum. The availability of intrafamilial segregation data in this case highlights marked phenotypic variability between single variant and double variant carriers within the same family, underscoring the concepts of incomplete penetrance and variable expressivity in BRCA associated cancers. Given the absence of specific surveillance and management guidelines for BRCA1/BRCA2 double heterozygotes, individualized genetic counseling and clinical follow up are important. Further studies including larger numbers of BRCA1/BRCA2 double heterozygous individuals are needed to better define cancer risk and to establish appropriate clinical surveillance strategies for carriers [18]. References 1. Foulkes WD. Inherited susceptibility to common cancers. N Engl J Med. 2008;359(20):2143 2153. doi:10.1056/NEJMra0802968 2. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017;317(23):2402-2416. doi:10.1001/jama.2017.7112 3. Walsh T, King MC. Ten genes for inherited breast cancer. Cancer Cell. 2007;11(2):103-105. doi:10.1016/j.ccr.2007.01.010 4. Levy-Lahad E, Friedman E. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br J Cancer. 2007;96(1):11-15. doi:10.1038/sj.bjc.6603535 5. Zuradelli M, Peissel B, Manoukian S, et al. Four new cases of double heterozygosity for BRCA1 and BRCA2 gene mutations: clinical, pathological, and family characteristics. Breast Cancer Res Treat. 2010;124(1):251-258. doi:10.1007/s10549-010-0853-8 6. Heidemann S, Fischer C, Engel C, et al. Double heterozygosity for mutations in BRCA1 and BRCA2 in German breast cancer patients: implications on test strategies and clinical management. Breast Cancer Res Treat. 2012;134(3):1229-1239. doi:10.1007/s10549-

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[Abstract:0227]

Tuberous Sclerosis Complex: Clinical Diversity and Molecular Findings from a Single Center

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Objective: Tuberous sclerosis complex (TSC) is a hereditary multisystem disorder caused by pathogenic variants in the TSC1 or TSC2 genes. The disease is characterized by hamartomatous involvement of multiple organs, with clinical findings that may be detected prenatally or may appear later in life. Neurological and renal involvement are frequently encountered, and renal tumors have been reported in individuals with TSC. In routine clinical practice, disease presentation varies considerably among patients. The aim of this study was to describe the clinical diversity and molecular characteristics of patients diagnosed with TSC at a single center.

Materials-Methods: This retrospective study included twelve patients diagnosed with tuberous sclerosis complex between 2022 and 2025 at Eskişehir Osmangazi University, Department of Medical Genetics. Clinical, radiological, and molecular genetic data were reviewed from medical records. Molecular analysis was performed using next-generation sequencing–based gene panel testing of TSC1 and TSC2, together with multiplex ligation-dependent probe amplification (MLPA). Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria.

Results: Age at diagnosis ranged from the prenatal period to adulthood. Pathogenic or likely pathogenic variants, based on ACMG criteria, were identified in TSC1 in five patients and in TSC2 in seven patients. Most variants were loss-of-function changes, including frameshift mutations, nonsense variants, and deletions, observed in ten patients. Missense variants were detected in two patients.
Neurological involvement was common. Epilepsy was present in nine patients, with seizure onset between 4 months and 12 years of age. Brain magnetic resonance imaging showed cortical or subcortical tubers in eleven patients, subependymal nodules in eight patients, and subependymal giant cell astrocytoma in three patients. Neurodevelopmental findings, including developmental delay, learning difficulties, and autism spectrum disorder, were observed in four patients. Renal angiomyolipomas were identified in six patients. Cardiac rhabdomyomas were detected during prenatal or neonatal assessment in three patients. A positive family history was noted in three patients.

Conclusion: This case series presents the clinical diversity of tuberous sclerosis complex, with findings observed across different ages and involving multiple organ systems. Variants in TSC2 and loss-of-function changes constituted a large proportion of the molecular findings in this patient group. Molecular genetic testing was central to the diagnostic process and subsequent clinical follow-up. These findings support the role of early and accurate molecular diagnosis in informing surveillance strategies and genetic counseling in patients with tuberous sclerosis complex.

Keywords: Clinical diversity, Tuberous Sclerosis Complex, TSC1, TSC2

Tuberous Sclerosis Complex: Clinical Diversity and Molecular Findings from a Single Center Gülin Yılmaz1, Ezgi Susam1, Oğuz Çilingir1 Eskişehir Osmangazi University Department of Medical Genetics1 Abstract Background: Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by hamartomatous tumor development in multiple organ systems. This study aims to describe the clinical and molecular spectrum of a Turkish TSC cohort and to report novel pathogenic variants. Methods: A retrospective analysis was performed on

12 patients diagnosed with tuberous sclerosis complex who were followed at the Department of Medical Genetics, Eskişehir Osmangazi University, between 2022 and 2025. Molecular analysis was carried out using a targeted next-generation sequencing panel covering TSC1 and TSC2, followed by multiplex ligation-dependent probe amplification (MLPA) for the detection of exon-level deletions or duplications. Results: The age at diagnosis ranged from the prenatal period to adulthood. Pathogenic or likely pathogenic variants were identified in all patients according to ACMG criteria. Large exon-level deletions detected by MLPA were observed in four patients. Sequence analysis identified two frameshift variants in the TSC1 gene that were not identified in publicly available databases or the literature at the time of analysis. Neurological involvement was prominent, with epilepsy observed in nine patients and subependymal giant cell astrocytoma identified in three patients. Renal angiomyolipomas were a common systemic manifestation. Conclusion: This study expands the mutational spectrum of TSC1 by reporting two novel frameshift variants. The presence of SEGA in pediatric patients highlights the importance of long-term, multidisciplinary surveillance in individuals with tuberous sclerosis complex. Introduction Tuberous sclerosis complex (TSC) is a rare autosomal dominant multisystem disorder characterized by hamartomatous lesions involving multiple organs, most frequently the brain, skin, kidneys, and heart. The disorder is caused by pathogenic variants in the TSC1 or TSC2 genes, which encode hamartin and tuberin, respectively. These proteins form a functional complex that negatively regulates the mammalian target of rapamycin (mTOR) signaling pathway. Loss of function in either gene results in mTOR overactivation, leading to abnormal cellular growth and tumor development. TSC exhibits marked clinical and genetic heterogeneity. Clinical manifestations range from severe early onset epilepsy and neurodevelopmental impairment to milder phenotypes dominated by cutaneous findings diagnosed later in life. Given the complexity of genotype–phenotype correlations, detailed reporting of clinical and molecular data remains essential. This study presents the clinical and molecular features of a single-center TSC cohort, with particular emphasis on two TSC1 frameshift variants considered novel in the current literature. Materials and Methods This retrospective study included 12 patients diagnosed with tuberous sclerosis complex who were followed at the Department of Medical Genetics, Eskişehir Osmangazi University, between 2022 and 2025. Clinical data were obtained from medical records and included age at diagnosis, neurological manifestations, dermatological findings, radiological features, and involvement of other organ systems. Molecular genetic analysis was performed using a targeted next-generation sequencing panel covering the TSC1 and TSC2 genes. To detect large exon-level deletions or duplications not identifiable by sequencing, multiplex ligation-dependent probe amplification (MLPA) analysis was performed using SALSA MLPA probe sets P124 (TSC1) and P337 (TSC2). Variant interpretation and classification were performed according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Written informed consent was obtained from all patients or their legal guardians. Results The age at diagnosis ranged from the prenatal period to 25 years. Prenatal or neonatal diagnosis was established in three patients following the detection of cardiac rhabdomyomas during fetal or early postnatal evaluation. Individual patient characteristics, including age at diagnosis and initial clinical presentation, are summarized in Table 1. Pathogenic or likely pathogenic variants were identified in all patients according to ACMG criteria. Variants affecting the TSC1 gene were detected in five patients, while pathogenic variants in TSC2 were identified in seven patients. Large exon-level deletions detected by MLPA were observed in four patients, involving either TSC1 or TSC2. Sequence-level variants were identified in eight patients; among these, five variants were small deletions resulting in frameshift mutations, while two were missense variants and one was a nonsense variant. Detailed molecular findings, including variant type and gene distribution, are shown in Table 1. Two frameshift variants affecting the TSC1 gene were considered novel, as they were not identified in publicly available variant databases or the available literature at the time of analysis. The first novel variant, TSC1 (NM_000368.4):c.788_791del, was identified in a 25-year-old patient presenting with prominent cutaneous manifestations, including facial angiofibromas and periungual fibromas, as well as bilateral renal

angiomyolipomas. The second novel variant, TSC1 (NM_000368.4):c.2252_2253delAG (p.Lys751Serfs*2), was detected in a neonate diagnosed prenatally with cardiac rhabdomyoma and who later developed epilepsy during infancy. Both variants are predicted to result in premature termination codons and loss of protein function. Neurological involvement was the most prominent clinical feature and was observed in eleven of twelve patients. Epilepsy was present in nine patients, with seizure phenotypes including infantile spasms, focal seizures, and absence seizures, most commonly with onset during infancy or early childhood. Neuroimaging revealed cortical or subcortical tubers in eleven patients and subependymal nodules in nine patients. Subependymal giant cell astrocytoma was identified in three patients during follow-up. Neurodevelopmental manifestations, including developmental delay, intellectual disability, and autism spectrum disorder, were observed in four patients. Cutaneous manifestations were common and were observed in ten patients, most frequently hypomelanotic macules (ash-leaf spots), followed by facial angiofibromas and shagreen patches. Ophthalmological involvement was documented in two patients and consisted of retinal hamartomas identified on ophthalmologic examination. Renal involvement was documented in six patients, all of whom presented with renal angiomyolipomas, including bilateral or multiple lesions detected during radiological surveillance. Cardiac involvement was identified in four patients and consisted primarily of cardiac rhabdomyomas detected during prenatal or neonatal evaluation; left ventricular non compaction was observed in one patient. A positive family history consistent with autosomal dominant inheritance was noted in three patients. Discussion This case series highlights the considerable clinical and molecular heterogeneity of tuberous sclerosis complex and reflects the wide phenotypic spectrum observed in routine clinical practice. The integrated clinical and molecular data summarized in Table 1 demonstrate that disease manifestations may present across different age groups, ranging from prenatal detection to childhood diagnosis, and may involve multiple organ systems with varying degrees of severity. The predominance of neurological manifestations and the frequency of renal and cardiac involvement observed in this cohort are comparable to those reported in previously published TSC case series. Neurological involvement represented the predominant clinical feature in this cohort, consistent with previous reports describing epilepsy and brain structural abnormalities as major contributors to disease burden in TSC. The presence of subependymal giant cell astrocytoma in a subset of pediatric patients further emphasizes the importance of early neuroimaging and longitudinal neurological follow-up, as timely identification of SEGA may have significant implications for clinical management and therapeutic decision-making. Renal and cardiac manifestations were also frequently observed, highlighting the multisystem nature of the disorder and the need for coordinated, multidisciplinary surveillance strategies. The identification of cardiac rhabdomyomas during prenatal or neonatal evaluation in several patients underscores the critical role of early genetic assessment in guiding diagnosis and follow-up from the earliest stages of life. From a molecular perspective, pathogenic variants in TSC2, particularly truncating mutations and large exon-level deletions, appeared to be associated with more extensive multisystem involvement, in line with previously reported genotype–phenotype trends. However, the observed phenotypic variability among patients carrying similar variant types further supports the notion that disease expression in TSC is influenced by additional genetic, epigenetic, and environmental factors. The identification of two previously unreported frameshift variants affecting the TSC1 gene expands the known mutational spectrum of TSC and reinforces the importance of comprehensive molecular characterization. Reporting such variants contributes to the refinement of genotype–phenotype correlations and facilitates more accurate variant interpretation, which is essential for genetic counseling, risk assessment, and long-term patient management. Several limitations of this study should be acknowledged. First, the retrospective design and the relatively small sample size inherent to a single-center cohort may limit the generalizability of the findings. Second, detailed longitudinal outcome data were not uniformly available for all patients, particularly those diagnosed during the prenatal or early neonatal period. Finally, although molecular characterization was comprehensive, functional validation studies were not performed for the identified variants. Despite these

limitations, the detailed clinical and molecular evaluation of this cohort provides valuable insights into the phenotypic variability and mutational spectrum of tuberous sclerosis complex. Conclusion This single-center case series demonstrates the marked clinical and molecular heterogeneity of tuberous sclerosis complex, with manifestations affecting multiple organ systems from the prenatal period through childhood. The predominance of neurological involvement, along with frequent renal, cardiac, and dermatological findings, is consistent with previously reported TSC cohorts and underscores the multisystem nature of the disorder. Comprehensive molecular analysis, including next-generation sequencing and exon-level deletion assessment, was essential for accurate diagnosis and characterization of the cohort. The identification of two previously unreported frameshift variants in the TSC1 gene further expands the mutational spectrum of tuberous sclerosis complex and highlights the value of detailed molecular evaluation in supporting clinical surveillance strategies and genetic counseling. Table 1. Clinical and molecular characteristics of patients with tuberous sclerosis complex Case / Age (Dx) Genotype (Gene, Variant, Type) Key Clinical Manifesta ons P1 / Prenatal TSC2 c.5227C>T (p.Arg1743Trp) (Missense) Cardiac: Fetal rhabdomyoma Neuro: Epilepsy, Cor cal tubers, Thin corpus callosum Skin: Ash-leaf spots P2 / Neonate TSC1 Exon 1-20 dele on (Large Dele on) Neuro: Subcor cal tubers, SEN Skin: Ash-leaf spots, Salmon patch P3 / 25y TSC1 c.788_791del (p.Ser263Trpfs*54) (Frameshi) (Novel) Renal: Bilateral AML Skin: Angiofibromas, Periungual fibromas, Shagreen patch, Ash-leaf spots Other: Ulcera ve coli s P4 / 12y TSC2 c.1852del (p.Leu618Cysfs*80) (Frameshi) Neuro: Epilepsy, Tubers, SEN Renal: Bilateral AML Skin: Angiofibromas, Shagreen patch, Ash-leaf spots Family: Father affected P5 / Neonate TSC1 c.2252_2253delAG (p.Lys751Serfs*2) (Frameshi) (Novel) Neuro: Epilepsy, Tubers, SEN, SEGA, Delayed motor development Cardiac: Fetal rhabdomyoma Skin: Ash-leaf spots Family: Mother affected P6 / 1y TSC2 Exon 4-16 dele on (Large Dele on) Neuro: Epilepsy, SEN, Cor cal tuber, Delayed motor development P7 / 6y TSC1 Exon 1 dele on (Large Dele on) Neuro: Subcor cal tuber Renal: Mul ple AML Eye: Re nal hamartoma Skin: Ash-leaf spots Other: Splenic cyst P8 / 7y Neuro: Focal seizures, Cor cal tubers TSC1 c.1904_1905del (p.Thr635Argfs*52) (Frameshi) Renal: AML Skin: Ash-leaf spots Cardiac: LV non-compac on P9 / 1y TSC2 c.1096G>T (p.Glu366Ter) (Nonsense) Neuro: Infan le spasms, Tubers, SEN Renal: Cor cal fibro c band Skin: Angiofibromas, Shagreen patch, Ash-leaf spots P10 / 3y TSC2 c.1831C>T (p.Arg611Trp) (Missense) Neuro: Epilepsy, ID, Tubers, SEN, SEGA Renal: Mul ple AML Eye: Re nal hamartoma Other: Oral neurinoma P11 / 3y TSC2 Exon 1 & 16 dele on (Large Dele on) Neuro: Epilepsy, ASD, Tubers, SEN Skin: Ash-leaf spots, freckling, hyperpigmented macule Family: Father & sister affected P12 / Neonate TSC2 c.4178_4179delCT (p.Leu1394Alafs*19) (Frameshi) Neuro: Absence seizures, Tubers, SEN, SEGA Cardiac: Cardiac rhabdomyoma Skin: Ash-leaf spots Renal: AML Dx: Age at diagnosis; AML: Angiomyolipoma; SEGA: Subependymal Giant Cell Astrocytoma; SEN: Subependymal Nodule; ID: Intellectual Disability; ASD: Au sm Spectrum Disorder; LV: Le Ventricular. All variants are described according to the canonical transcripts of the TSC1 (NM_000368.5) and TSC2 (NM_000548.5) genes. Nomenclature follows the Human Genome Variation Society (HGVS) recommendations.

[Abstract:0232]

Which Hereditary Cancer Genes Are Edit-Ready? A Bioinformatic Framework for Genome Editing Feasibility

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Objective: The expanding use of germline testing in hereditary cancers has increased the demand for actionable interpretation of genetic findings. Although genome editing technologies offer unprecedented precision, not all hereditary cancer genes or mutations are equally suitable for editing-based intervention. A systematic framework is therefore required to define the feasibility of genome editing across hereditary cancer genes.
Materials-Methods: We developed a genome editing–informed bioinformatic framework to evaluate the editability of major hereditary cancer genes based on functional architecture, pathway dependency, and predicted cellular tolerance to genetic perturbation. Public genomic and transcriptomic datasets were analysed to assess domain essentiality, network redundancy, and variant localisation within critical functional regions. These parameters were integrated to model theoretical genome editing strategies, including gene correction, targeted disruption, and pathway modulation.
Results: Our analysis revealed marked heterogeneity in genome editing feasibility among hereditary cancer genes. Certain genes exhibited discrete, functionally critical domains that may be amenable to precise editing, whereas others displayed broad network dependency, suggesting that indirect pathway modulation may represent a more realistic intervention strategy.
Conclusion: This study provides a rational bioinformatic framework for identifying edit-ready hereditary cancer genes and variants. Such stratification supports realistic translation of genome editing technologies into precision oncology and informs future experimental and clinical prioritisation.

Keywords: Bioinformatics Framework, Genetic Feasibility, Genome Editing, Hereditary Cancer, Precision Oncology

Which Hereditary Cancer Genes Are Edit-Ready? A Bioinformatic Framework for Genome Editing Feasibility The expanding use of germline sequencing in hereditary cancer syndromes has fundamentally altered risk assessment and clinical decision-making; however, the translation of genome editing technologies into this space remains largely conceptual. Despite growing enthusiasm for CRISPR-based interventions, the implicit assumption that all hereditary cancer genes are suitable targets for genome editing is biologically simplistic and potentially unsafe. Critically, no systematic framework currently exists to prioritise which genes are realistically amenable to genome editing and which should be approached with caution or avoided altogether. In this study, we introduce a genome editing–informed bioinformatic framework designed to explicitly address this gap. Using an integrated, multi-dimensional in silico approach, we evaluate the feasibility and risk of editing clinically relevant hereditary cancer genes by combining cellular, systems-level, and technical constraints into a unified decision-support model. A curated panel of hereditary cancer genes was assessed across four key dimensions: cellular essentiality, protein–protein interaction network centrality, tissue expression breadth, and CRISPR guide RNA targetability. Cellular dependency was quantified using CRISPR (Chronos) gene effect scores to estimate tolerance to gene perturbation. Systems-level risk was evaluated through network topology analyses, capturing the extent to which gene disruption may propagate across biological pathways. Tissue expression breadth was

incorporated to reflect organism-level exposure and safety windows, while CRISPR targetability was assessed using CFD-based off-target prediction metrics derived from guide RNA design analyses. Application of this framework revealed striking heterogeneity in genome editing feasibility across hereditary cancer genes. Notably, several genes widely regarded as prime candidates for intervention exhibited unfavourable feasibility profiles due to high network centrality or broad tissue expression, despite limited cellular dependency. Conversely, a subset of DNA repair associated genes demonstrated balanced profiles characterised by moderate dependency, reduced systemic integration, and favourable technical targetability, supporting conditional feasibility for somatic genome editing strategies. Importantly, this integrative assessment consistently outperformed pathogenicity-based prioritisation alone, exposing critical limitations of gene-centric selection approaches. Collectively, these findings redefine genome editing readiness in hereditary cancer as a systems-level property rather than a consequence of pathogenicity or clinical relevance alone. The proposed framework provides a rigorous and transparent method for stratifying genome editing targets, enabling more responsible translational pathways and informed ethical discourse. By aligning genome editing ambitions with biological feasibility, this work establishes a foundational platform for future experimental validation and clinical translation in hereditary cancer research. Keywords: Hereditary cancer; genome editing; CRISPR; bioinformatic framework; network biology; gene essentiality; precision oncology

[Abstract:0240]

Re-evaluation of Variants of Uncertain Significance in the BRCA1 and BRCA2 Genes and Their Clinical Implications

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Objective: The aim of this study was to re-evaluate variants of uncertain significance (VUS) identified in the BRCA1 and BRCA2 genes through hereditary cancer panel testing over the past five years. This was done by integrating current classification criteria and utilizing functional assessment tools driven by machine learning–based approaches. The study sought to delineate the potential clinical implications of pathogenicity prediction models of these variant reclassifications.

Materials-Methods: All cases that underwent hereditary cancer panel testing within the last five years were retrospectively included in the study. Clinical characteristics, family histories, and other variants detected in the panel analyses of cases harboring VUS in the BRCA1 and BRCA2 genes were recorded. Variants were reanalyzed according to the updated ACMG/AMP criteria, and recommendations from ClinGen expert panel curations were also reviewed during the evaluation process. In addition, the functional effects of the variants were reassessed using multiple in silico predictive tools, and the predictive performance of these tools in estimating variant pathogenicity was evaluated.

Results: Among a total of 155 cases re-evaluated over the five-year period, reclassifications performed in accordance with updated ACMG criteria and/or ClinGen recommendations did not result in a statistically significant overall difference. However, analyses based on functional predictive tools demonstrated that a substantial proportion of variants currently classified as VUS could be more distinctly separated into benign or pathogenic categories. In particular, re-evaluation using the MAGPIE tool predicted that BRCA1/BRCA2 missense variants previously reported as VUS in 19 patients were compatible with a “Likely Pathogenic” classification, and in one patient with a “Pathogenic” classification. Notably, these 19 cases exhibited clinical findings consistent with NCCN criteria for homologous recombination deficiency and/or had a significant family history.

Conclusion: This study demonstrates that the dynamic re-evaluation of BRCA1 and BRCA2 missense VUS is of critical clinical importance. The integration of updated ACMG criteria, ClinGen curations, and advanced in silico analyses facilitates the reclassification of VUS and yields clinically meaningful implications for genetic counseling, patient management, and familial screening. The concordance between predictive tool outputs and clinical findings suggests that the integration of functional data with artificial intelligence-based approaches may be promising for variant interpretation and could contribute to the development of follow-up strategies for affected individuals in the future.

Keywords: BRCA1, BRCA2, VUS, reclassification, reanalysis

BRCA1 ve BRCA2 Genlerinin Klinik Önemi Bilinmeyen Varyantlarının Yeniden Değerlendirmeleri Alp Peker, Levent Paralı, Ayça Aykut, Asude Durmaz, Haluk Akın, Aslı Ece Solmaz Ege Üniversitesi Tıp Fakültesi, Tıbbi Genetik Anabilim Dalı Amaç: Bu çalışmanın amacı, son beş yıl içerisinde herediter kanser paneli ile analiz edilmiş ve BRCA1/BRCA2 genlerinde VUS (klinik önemi bilinmeyen) varyantlar saptanmış olguların güncel kriterler ışığında ve çeşitli fonksiyonel araçlar ile yeniden değerlendirilmesi ve olası reklasifikasyonların klinik öneminin ortaya konulmasıdır. Gereç ve Yöntem: Çalışmaya, son beş yıl içinde herediter kanser paneli çalışılmış olan tüm olgular

retrospektif olarak dahil edilmiştir. BRCA1 ve BRCA2 genlerinde VUS varyant saptanan olguların klinik özellikleri, aile öyküleri ve panel analizinde saptanan diğer varyantları kaydedilmiştir. Varyantlar, güncel ACMG/AMP kriterleri kullanılarak yeniden analiz edilmiştir, değerlendirme sürecinde ClinGen expert panel kürasyon önerileri ayrıca incelenmiştir. Ayrıca, varyantların fonksiyonel etkileri çeşitli in-silico prediktif araçlar kullanılarak yeniden gözden geçirilmiş ve bu araçların varyant patojenitesini öngörmedeki prediktif performansları değerlendirilmiştir. Bulgular: Beş yıl içerisinde yeniden değerlendirilen toplam 155 olguda, incelenen varyantların güncel ACMG kriterleri ve/veya ClinGen önerileri doğrultusunda yapılan reklasifikasyonlarının istatistiksel olarak anlamlı bir farklılık oluşturmadığı saptanmıştır. Fakat fonksiyonel prediktif araçların analizlerine bakıldığında günümüzde VUS olarak sınıflandırılan varyantların belirgin bir kısmında benign/patojenik ayrımı açısından keskin sınırlar çizilmektedir. Bunlardan özellikle MAGPIE programı kullanılarak yapılan yeniden değerlendirme sonucunda, daha önce VUS olarak raporlanmış BRCA1/BRCA2 missense varyantlarına sahip 19 hastada varyantların 'Olası Patojenik', 1 hastada ise 'Patojenik' sınıfına uygun olduğu öngörülmüş; bu olguların homolog rekombinasyon eksikliği açısından NCCN kriterleri ile uyumlu klinik bulgulara veya anlamlı aile öyküsüne sahip olmaları dikkat çekmiştir. Sonuç: Bu çalışma, BRCA1 ve BRCA2 missense VUS varyantlarının dinamik bir süreçle yeniden değerlendirilmesinin klinik açıdan kritik önem taşıdığını göstermektedir. Güncel ACMG kriterleri, ClinGen kürasyonları ve gelişmiş in-silico analizlerin entegrasyonu, VUS reklasifikasyonunu mümkün kılmakta ve genetik danışmanlık, hasta yönetimi ve aile taraması açısından anlamlı klinik sonuçlar doğurmaktadır. Prediktif araç sonuçlarının klinik bulgularla uyum göstermesi, fonksiyonel verinin yapay zeka temelli yaklaşımlarla entegrasyonunun varyant değerlendirmesinde umut vadedici olabileceğini ve gelecekte olgular için takip şemalarının oluşturulmasına katkı sağlayabileceğini düşündürmektedir. Bu çalışmada, başlangıçta tamamı önemi bilinmeyen varyant (VUS) olarak raporlanmış olan BRCA1/BRCA2 varyantlarının güncel literatür, popülasyonel veri tabanları ve fonksiyonel çalışmalar ışığında yeniden değerlendirilmesi amaçlanmıştır. İncelenen varyantların bir kısmının zaman içerisinde olasılıkla benign (LB) veya olasılıkla patojenik(LP) sınıflarına doğru yeniden sınıflandırıldığı görülmüştür. Bu durum, BRCA genlerine ait VUS'ların dinamik bir sınıflandırma sürecine sahip olduğunu ve statik raporlamanın klinik açıdan yetersiz kalabileceğini ortaya koymaktadır. VUS'tan LB sınıfına doğru yeniden sınıflandırmada en belirgin katkının gnomAD gibi geniş popülasyonel veri tabanlarında ilgili varyantların beklenenden yüksek allel frekanslarında veya homozigot bireylerde saptanması olduğu izlenmiştir. Bu tür popülasyonel verilerin ClinVar ve benzeri platformlara yansıması sınıflandırma değişikliklerinde temel belirleyicilerden biri olarak öne çıkmaktadır. Buna karşılık, VUS'tan LP/P sınıfına doğru dönüşüm gösteren varyantlarda fonksiyonel çalışmaların kritik rol oynadığı dikkat çekmektedir. Özellikle Homolog Rekombinasyon Eksikliği (HRD) assay gibi BRCA fonksiyonunu doğrudan değerlendiren testlerin sonuçlarının yayımlanması ve ClinVar gibi açık erişimli veritabanlarına entegre edilmesi bu varyantların patojenik lehine yeniden değerlendirilmesine olanak sağlamıştır. Fonksiyonel bozulmayı objektif olarak ortaya koyan bu çalışmalar in silico tahminlerin ötesinde güçlü kanıt sunmaktadır. Son yıllarda geliştirilen MAGPIE ve Alpha-Missense gibi ileri düzey hesaplamalı tahmin araçlarının da patojenik lehine yeniden sınıflandırılan varyantlarda nitelikle tahmin sonuçları verdiği görülmektedir. Bu araçlar tarafından patojenik olarak öngörülen varyantların önemli bir bölümünde ilgili bireylerin kendilerinde veya birinci/ikinci derece akrabalarında NCCN kriterleri ile uyumlu meme kanseri ve/veya BRCA ile ilişkili kanser öyküsü izlenmiştir. Özellikle patojenik lehine tahmin edilen bu varyantların, kohortumuzda birden fazla, birbirinden bağımsız olguda saptanma eğiliminde olması dikkat çekici bir bulgudur. Bu durum söz konusu varyantların rastlantısal olmaktan ziyade, belirli bir popülasyonda daha sık görülen ve klinik olarak anlamlı olabilecek varyantlar olduğunu düşündürmektedir. Bu tekrar eden gözlem, varyantların klinik önemini destekleyen ek bir dolaylı kanıt olarak değerlendirilebilir. Bu bulgular bazı BRCA varyantlarının Türkiye popülasyonunda kurucu varyant özelliği gösterebileceği ihtimalini gündeme getirebilir. Ancak bu hipotezin doğrulanabilmesi için daha geniş popülasyon temelli çalışmalar ve haplotip analizleri gerekmektedir. Alternatif olarak, bu varyantların gerçekten patojenik olmaları durumunda, ilgili bireylerin herediter kanser paneli testi

yaptırma olasılıklarının daha yüksek olması da mantıklı bir açıklama sunmaktadır. Klinik şüphe ve güçlü aile öyküsü test isteme oranlarını artırmakta ve bu durum da patojenik varyantların tanı kohortlarında daha sık yakalanmasına yol açabilmektedir. Dolayısıyla gözlenen tekrar sıklığı hem biyolojik hem de klinik yönlendirme kaynaklı bir seçilim etkisini yansıtıyor olabilir. Re-evaluation of Variants of Uncertain Significance in the BRCA1 and BRCA2 Genes and Their Clinical Implications Alp Peker, Levent Paralı, Aslı Ece Solmaz Objective: The aim of this study was to re-evaluate variants of uncertain significance (VUS) identified in the BRCA1 and BRCA2 genes through hereditary cancer panel testing over the past five years. This was done by integrating current classification criteria and utilizing functional assessment tools driven by machine learning–based approaches. The study sought to delineate the potential clinical implications of pathogenicity prediction models of these variant reclassifications. Materials and Methods: All cases that underwent hereditary cancer panel testing within the last five years were retrospectively included in the study. Clinical characteristics, family histories, and other variants detected in the panel analyses of cases harboring VUS in the BRCA1 and BRCA2 genes were recorded. Variants were reanalyzed according to the updated ACMG/AMP criteria, and recommendations from ClinGen expert panel curations were also reviewed during the evaluation process. In addition, the functional effects of the variants were reassessed using multiple in silico predictive tools, and the predictive performance of these tools in estimating variant pathogenicity was evaluated. Results: Among a total of 155 cases re-evaluated over the five-year period, reclassifications performed in accordance with updated ACMG criteria and/or ClinGen recommendations did not result in a statistically significant overall difference. However, analyses based on functional predictive tools demonstrated that a substantial proportion of variants currently classified as VUS could be more distinctly separated into benign or pathogenic categories. In particular, re-evaluation using the MAGPIE tool predicted that BRCA1/BRCA2 missense variants previously reported as VUS in 19 patients were compatible with a “Likely Pathogenic” classification, and in one patient with a “Pathogenic” classification. Notably, these cases exhibited clinical findings consistent with NCCN criteria for homologous recombination deficiency and/or had a significant family history. Conclusion: This study demonstrates that the dynamic re-evaluation of BRCA1 and BRCA2 missense VUS is of critical clinical importance. The integration of updated ACMG criteria, ClinGen curations, and advanced in silico analyses facilitates the reclassification of VUS and yields clinically meaningful implications for genetic counseling, patient management, and familial screening. The concordance between predictive tool outputs and clinical findings suggests that the integration of functional data with artificial intelligence-based approaches may be promising for variant interpretation and could contribute to the development of follow-up strategies for affected individuals in the future.

[Abstract:0243]

Pseudohypoxia as a Shared Mechanism in Hereditary Cancer Syndromes: A Cohort with Germline VHL, FH, and SDHB Variants

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Objective: The hypoxia-inducible factor pathway is a key regulator of cellular adaptation to hypoxia and plays a central role in tumorigenesis. Germline pathogenic variants in genes involved in oxygen sensing and mitochondrial metabolism, including VHL, FH and SDHB, lead to constitutive activation of HIF-signaling through a pseudohypoxic mechanism and underlie distinct hereditary cancer syndromes.
Materials-Methods: In this study, we retrospectively evaluated a cohort of fifteen patients who underwent hereditary cancer genetic testing and were found to harbor germline pathogenic variants in HIF-pathway related genes. Clinical features, age at diagnosis, and family history were systematically reviewed.
Results: Pathogenic variants were identified in VHL (n = 8), FH (n = 5), and SDHB (n = 2). Patients carrying VHL variants were diagnosed between 14-68 years of age and presented with renal cell carcinoma, pheochromocytoma, cerebellar hemangioblastoma, and pancreatic masses. Four VHL variant carriers were asymptomatic at the time of testing and were identified through cascade-genetic testing following a diagnosis of renal cell carcinoma in a family member. The availability of belzutifan, a HIF-2α inhibitor, highlights the clinical relevance of early genetic diagnosis in this group.
In the FH group, age at diagnosis ranged from 30-69 years. Four patients presented with uterine leiomyomatosis, including one with concomitant cutaneous leiomyomatosis, all with positive family history. One FH variant carrier presented with pancreatic neuroendocrine tumor, papillary thyroid carcinoma, and lung cancer without a family history. Among SDHB variant carriers, one patient presented with pheochromocytoma and paraganglioma, whereas the second carrier was incidentally identified through ACMG-defined secondary findings during genetic testing.
Conclusion: Despite heterogeneous clinical manifestations, pathogenic germline variants in VHL, FH and SDHB converge on dysregulation of the HIF-pathway. These findings highlight pseudohypoxia as a shared molecular mechanism in hereditary cancer syndromes and emphasize the importance of family-based genetic testing for early and presymptomatic identification of at-risk individuals.

Keywords: Pseudohypoxia, Hypoxia-inducible factor (HIF) pathway, Cascade genetic testing, Belzutifan
Pseudohypoxia as a Shared Mechanism in Hereditary Cancer Syndromes: A Cohort with Germline VHL, FH, and SDHB Variants Hatice GÜNDOĞAN, Dilsu Dicle ERKAN, Ceren Damla DURMAZ ÖZDİNÇ, Naz GÜLERAY LAFCI Hacettepe Üniversitesi, Tıbbi Genetik Anabilim Dalı The hypoxia-inducible factor (HIF) pathway is a key regulator of cellular adaptation to hypoxia and plays a central role in tumorigenesis. Germline pathogenic variants in genes involved in oxygen sensing and mitochondrial metabolism, including VHL, FH, and SDHB, lead to constitutive activation of HIF signaling through a pseudohypoxic mechanism and underlie distinct hereditary cancer syndromes. These syndromes are characterized by a broad tumor spectrum and variable age of onset, posing diagnostic challenges and emphasizing the importance of genetic testing and family screening. In this study, we retrospectively evaluated a cohort of fifteen patients who underwent hereditary cancer genetic testing at our center and were found to harbor germline pathogenic variants in HIF pathway–related genes. Clinical characteristics, tumor spectrum, age at diagnosis, and family history were systematically reviewed from medical records. Pathogenic variants were identified in VHL (n = 8), FH (n = 5), and SDHB (n = 2). Among VHL variant carriers, age at diagnosis ranged from 14 to 68 years. Clinical manifestations included renal cell carcinoma (RCC),

pheochromocytoma, cerebellar hemangioblastoma, and pancreatic neuroendocrine tumors. A 35-year-old male patient presented with a combination of pheochromocytoma, pancreatic neuroendocrine tumor, and cerebellar hemangioblastoma. His family history was notable for a VHL diagnosis in his brother and cousin, and pancreatic cancer in his mother. Another female patient, aged 66 years, exhibited pancreatic and renal masses with multiple affected family members carrying VHL variants. In one family, identification of a pathogenic VHL variant in the proband with pheochromocytoma prompted cascade testing, leading to the presymptomatic detection of four additional carriers. The oldest patient was a 68 year-old woman with RCC, whose daughter had previously been diagnosed with VHL after developing renal cell carcinoma and hemangioma. These findings highlight marked intrafamilial variability associated with VHL mutations and underscore the critical value of cascade genetic testing. The recent availability of belzutifan, a HIF-2α inhibitor, further underlines the clinical relevance of early molecular diagnosis in this group. In the FH group, age at diagnosis ranged from 30 to 69 years. Four patients were evaluated due to uterine leiomyomatosis, all with a positive family history of similar findings. One of these patients also had concomitant cutaneous leiomyomatosis, consistent with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. The fifth patient with an FH mutation was a 69-year-old male with a history of pancreatic neuroendocrine tumor, papillary thyroid carcinoma, and lung cancer. His family history revealed ovarian cancer in his sister. This case illustrates the diverse and occasionally atypical tumor spectrum associated with FH variants. Among SDHB variant carriers, one patient was diagnosed with pheochromocytoma and paraganglioma without a known family history, suggesting a de novo or previously unrecognized familial variant. The second SDHB carrier was identified incidentally through ACMG-defined secondary findings at 18 years of age during genetic testing performed for intellectual disability and developmental delay in her child. This incidental finding underscores the importance of secondary findings reporting and its implications for cancer surveillance. Despite heterogeneous clinical manifestations, pathogenic germline variants in VHL, FH, and SDHB converge on dysregulation of the HIF pathway. Our findings support pseudohypoxia as a shared molecular mechanism underlying these hereditary cancer syndromes and emphasize the importance of comprehensive family-based genetic testing. Early identification of at-risk individuals enables timely surveillance, targeted therapies, and improved clinical outcomes.

Pseudohypoxia as a Shared Mechanism in Hereditary Cancer Syndromes: A Cohort with Germline VHL, FH, and SDHB Variants Hatice GÜNDOĞAN, Dilsu Dicle ERKAN, Ceren Damla DURMAZ ÖZDİNÇ, Naz GÜLERAY LAFCI Hacettepe Üniversitesi, Tıbbi Genetik Anabilim Dalı The hypoxia-inducible factor (HIF) pathway is a key regulator of cellular adaptation to hypoxia and plays a central role in tumorigenesis. Germline pathogenic variants in genes involved in oxygen sensing and mitochondrial metabolism, including VHL, FH, and SDHB, lead to constitutive activation of HIF signaling through a pseudohypoxic mechanism and underlie distinct hereditary cancer syndromes. These syndromes are characterized by a broad tumor spectrum and variable age of onset, posing diagnostic challenges and emphasizing the importance of genetic testing and family screening. In this study, we retrospectively evaluated a cohort of fifteen patients who underwent hereditary cancer genetic testing at our center and were found to harbor germline pathogenic variants in HIF pathway–related genes. Clinical characteristics, tumor spectrum, age at diagnosis, and family history were systematically reviewed from medical records. Pathogenic variants were identified in VHL (n = 8), FH (n = 5), and SDHB (n = 2). Among VHL variant carriers, age at diagnosis ranged from 14 to 68 years. Clinical manifestations included renal cell carcinoma (RCC), pheochromocytoma, cerebellar hemangioblastoma, and pancreatic neuroendocrine tumors. A 35-year-old male patient presented with a combination of pheochromocytoma, pancreatic neuroendocrine tumor, and cerebellar hemangioblastoma. His family history was notable for a VHL diagnosis in his brother and cousin, and pancreatic cancer in his mother. Another female patient, aged 66 years, exhibited pancreatic and renal masses with multiple affected family members carrying VHL variants. In one family, identification of a pathogenic VHL variant in the proband with pheochromocytoma prompted cascade testing, leading to the presymptomatic detection of

four additional carriers. The oldest patient was a 68 year-old woman with RCC, whose daughter had previously been diagnosed with VHL after developing renal cell carcinoma and hemangioma. These findings highlight marked intrafamilial variability associated with VHL mutations and underscore the critical value of cascade genetic testing. The recent availability of belzutifan, a HIF-2α inhibitor, further underlines the clinical relevance of early molecular diagnosis in this group. In the FH group, age at diagnosis ranged from 30 to 69 years. Four patients were evaluated due to uterine leiomyomatosis, all with a positive family history of similar findings. One of these patients also had concomitant cutaneous leiomyomatosis, consistent with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. The fifth patient with an FH mutation was a 69-year-old male with a history of pancreatic neuroendocrine tumor, papillary thyroid carcinoma, and lung cancer. His family history revealed ovarian cancer in his sister. This case illustrates the diverse and occasionally atypical tumor spectrum associated with FH variants. Among SDHB variant carriers, one patient was diagnosed with pheochromocytoma and paraganglioma without a known family history, suggesting a de novo or previously unrecognized familial variant. The second SDHB carrier was identified incidentally through ACMG-defined secondary findings at 18 years of age during genetic testing performed for intellectual disability and developmental delay in her child. This incidental finding underscores the importance of secondary findings reporting and its implications for cancer surveillance. Despite heterogeneous clinical manifestations, pathogenic germline variants in VHL, FH, and SDHB converge on dysregulation of the HIF pathway. Our findings support pseudohypoxia as a shared molecular mechanism underlying these hereditary cancer syndromes and emphasize the importance of comprehensive family-based genetic testing. Early identification of at-risk individuals enables timely surveillance, targeted therapies, and improved clinical outcomes.

[Abstract:0247]

Clinicopathological Characteristics of Germline Pathogenic Variants in PALB2, RAD51C and RAD51D in Breast Cancer Patients: A Single-Center Experience

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Introduction and Objective: Hereditary factors account for approximately 8% of breast cancer cases. While *PALB2* germline pathogenic variants (GPV) are detected in roughly 1% of screened women—carrying a 7.2-fold relative risk and a 53% cumulative risk by age 80—prevalence data for *RAD51C* and *RAD51D* remain scarce. Although these genes are frequently linked to triple-negative breast cancer (TNBC), comprehensive data regarding other clinicopathological features like histological subtype and stage are limited. This study aims to characterize the clinicopathological profiles of patients with *PALB2*, *RAD51C*, or *RAD51D* GPVs identified via NGS at our center (2020–2025) and compare these findings with the current literature.
Results: Among 487 breast cancer patients screened, germline pathogenic variants (GPVs) were identified in *PALB2* (n=7; 1.4%), *RAD51C* (n=2), and *RAD51D* (n=2). The age at diagnosis for patients with PALB2 GPVs ranged from 35 to 67 years, with a median age of 51. Genotypically, the c.557dup (p.Asn186LysfsTer4) variant was identified in two unrelated patients, emerging as a recurrent mutation within this group. Analysis of histopathological data revealed a heterogeneous distribution; while the majority of patients presented with hormone receptor-positive (Luminal A and B) tumors, divergent phenotypes were observed among patients harboring the same genotypic alteration: one patient exhibited a HER2-positive phenotype, while the other presented with Triple-Negative Breast Cancer (TNBC). The most prominent shared clinical feature among *RAD51C* GPV carriers was an early age at diagnosis (41 and 45 years, respectively). Patients with *RAD51D* GPVs were of similar ages (54 and 52 years), and both were diagnosed with the Triple-Negative Breast Cancer (TNBC: ER-, PR-, HER2-) histological subtype.
Discussion: Despite our limited cohort (n=11), these findings provide critical clinical insights. While international data report a median diagnosis age of 60–71 for *RAD51C* carriers, local studies suggest a younger onset of 50–55 years in Türkiye. Our notably earlier median of 43 may stem from ascertainment bias in high-risk clinical referrals or the early penetrance of specific variants like c.706-2A>G. Regarding *RAD51D*, the 100% correlation with the TNBC phenotype aligns with its established risk profile. Conversely, the *PALB2* group exhibited significant phenotypic heterogeneity; although Luminal subtypes predominated, the presence of TNBC and HER2-positive cases reflects a broad spectrum similar to *BRCA2*. Finally, the recurrent c.557dup variant reinforces the likelihood of a population-specific founder mutation, highlighting the importance of geographic genetic signatures.
Conclusion: Current guidelines classify *PALB2, RAD51C*, and *RAD51D* as moderate-to-high penetrance genes. Despite our limited cohort, these findings align with existing literature. The identification of population-specific variants, such as *PALB2* c.557dup, underscores the clinical significance of geographic ancestry in genetic counseling. To establish the definitive prevalence of these genes in the Turkish population, larger multicenter studies are warranted.

Keywords: *PALB2, RAD51C, RAD51D*, Breast Cancer

Clinicopathological Characteristics of Germline Pathogenic Variants in PALB2, RAD51C, and RAD51D in Breast Cancer Patients: A Single-Center Experience Introduction Breast cancer is the most common malignancy among women worldwide, with hereditary predisposition playing a pivotal role in approximately 10-15% of cases. For decades, genetic testing was synonymous with BRCA1 and BRCA2 analysis. However, the advent of multigene

panel testing using Next-Generation Sequencing (NGS) has expanded the landscape of hereditary breast and ovarian cancer (HBOC) to include other high- and moderate-penetrance genes involved in the homologous recombination repair (HRR) pathway, specifically PALB2, RAD51C, and RAD51D. PALB2 (Partner and Localizer of BRCA2) is now recognized as a high-risk breast cancer gene. Germline pathogenic variants (GPVs) in PALB2 are detected in approximately 1% of screened women, conferring a 7.2-fold relative risk and a cumulative breast cancer risk of up to 53% by age 80, placing it in a risk category similar to BRCA2. Conversely, RAD51C and RAD51D were initially established as ovarian cancer susceptibility genes. Their association with breast cancer has been more recently solidified, particularly with the Triple-Negative Breast Cancer (TNBC) subtype. Despite establishing these associations, data regarding the specific clinicopathological features—such as histological subtype, hormone receptor status, and age of onset—remain limited, particularly in non-Western populations. Recent studies, such as Spijkervet et al. (2025), have provided data from Dutch cohorts, yet population-specific data for Türkiye is crucial for refining genetic counseling guidelines. This study aims to characterize the clinicopathological profiles of Turkish breast cancer patients harboring PALB2, RAD51C, or RAD51D GPVs identified at our center and to benchmark these findings against global data. Materials and Methods Study Design and Population This retrospective, single-center study included patients diagnosed with breast cancer who underwent multigene panel testing at our institution between 2020 and 2025.Genetic Analysis Genomic DNA was isolated from peripheral blood leukocytes. NGS was performed using a targeted panel covering HRR pathway genes. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) criteria. Only pathogenic or likely pathogenic variants in PALB2, RAD51C, and RAD51D were included in this analysis.Data Collection Clinicopathological data, including age at diagnosis, histological subtype and receptor status were retrieved from electronic medical records. Results Among 487 breast cancer patients screened, germline pathogenic variants(GPVs) were identified in PALB2 (n=7; 1.4%), RAD51C (n=2), and RAD51D (n=2). The age at diagnosis for patients with PALB2 GPVs ranged from 35 to 67 years, with a median age of 51.Genotypically, the c.557dup (p.Asn186LysfsTer4) variant was identified in two unrelated patients, emerging as a recurrent mutation within this group. Analysis of histopathological data revealed a heterogeneous distribution; while the majority of patients presented with hormone receptor-positive (Luminal A and B) tumors, divergent phenotypes were observed among patients harboring the same genotypic alteration: one patient exhibited a HER2-positive phenotype, while the other presented with Triple-Negative Breast Cancer (TNBC).The most prominent shared clinical feature among RAD51C GPV carriers was an early age at diagnosis (41 and 45 years, respectively). Patients with RAD51D GPVs were of similar ages (54 and 52 years), and both were diagnosed with the Triple-Negative Breast Cancer (TNBC:ER-, PR-, HER2-) histological subtype. Discussion Despite the limited cohort size (n=11), these findings provide clinical insights that contribute to the evolving understanding of non-BRCA hereditary breast cancer in the Turkish population.A significant observation in our study is the early onset of breast cancer among RAD51C carriers (median 43 years)(Table 1). This stands in contrast to recent international data, such as the Dutch cohort described by Spijkervet et al. (2025), which reported a median diagnosis age of 71 years, and general literature citing a median onset of approximately 60 years. While our findings align somewhat more closely with local Turkish studies suggesting a younger onset of 50–55 years, the notably earlier median in our cohort may stem from ascertainment bias in high-risk clinical referrals. Alternatively, this discrepancy suggests that specific variants, such as the c.706-2A>G splicing variant detected here, might exhibit higher penetrance or distinct clinical behaviors within the Turkish genetic background.Regarding RAD51D, the presentation of the Triple-Negative Breast Cancer (TNBC) phenotype observed in our cohort aligns with the gene's established risk profile. This mirrors findings from large case-control studies indicating that RAD51D loss-of-function mutations are significantly enriched in TNBC patients.PALB2 group exhibited significant phenotypic heterogeneity, similar to the spectrum seen in BRCA2-associated cancers. Although Luminal subtypes predominated, the presence of both TNBC and HER2-positive

cases reflects a diverse presentation. The identification of the recurrent c.557dup (p.Asn186Lysfs*4) variant in unrelated individuals reinforces the likelihood of a population-specific founder mutation. Furthermore, the observation of discordant tumor subtypes in patients carrying the identical mutation highlights that while germline variants confer susceptibility, somatic events likely play a decisive role in dictating the specific tumor phenotype. Conclusion Current guidelines classify PALB2, RAD51C, and RAD51D as moderate-to-high penetrance genes. Our single-center experience confirms the high risk associated with these genes but highlights population-specific nuances. Specifically, RAD51C carriers in Türkiye may present at a significantly younger age than Western guidelines suggest, necessitating earlier surveillance. The identification of population-specific recurrent variants, such as PALB2 c.557dup, underscores the clinical significance of incorporating geographic ancestry into genetic counseling and panel design. Larger multicenter studies are warranted to establish definitive prevalence rates and modify screening protocols for the Turkish population. TABLE 1 Gene Variant Protein change Rs ID Zygosity ACMG Criteria Mutation Type PATOLOJİ PALB2 c.1008_1010delinsA TA p.Asn336delinsLys * Novel Heterozygous Pathogenic NONSENSE 35 Unknown PALB2 c.172_175del p.Gln60ArgfsTer7 rs180177143 Heterozygous Pathogenic NONSENSE 51 IDC-ER:+ PR:+ HER2:- PALB2 c.2587-1G>C * rs761214886 Heterozygous Pathogenic SPLICE 54 IDC-ER:+ PR:+ HER2:- PALB2 c.3170_3175delCTT CAGinsAATCA p.A1057Efs*18 rs1597073266 Heterozygous Pathogenic NONSENSE 67 IDC-ER:+ PR:- HER2:+ PALB2 c.1647_1648del p.(His549GInfsTer 28) rs786201773 Heterozygous Pathogenic NONSENSE 46 IDC ER:+ PR:+ HER2:- PALB2 c.557dup p.(Asn186LysfsTer 4) rs1555461727 Heterozygous Pathogenic NONSENSE 47 IDC(Carcinoma with Apocrine Differentiation) ER:- PR:- HER2:+ PALB2 c.557_558insA p.Asn186Lysfs*4 rs1555461727 Heterozygous Pathogenic NONSENSE 58 IDC ER:- PR:- HER2:- RAD51 C c.706-2A>G * rs587780259 Heterozygous Pathogenic SPLICE 41 Unknown RAD51 C c.454_455insT p.(Leu152fs) Novel Heterozygous Pathogenic NONSENSE 45 Unknown RAD51 D c.293del p.(Asp98Valfs*25) rs750282687 Heterozygous Pathogenic NONSENSE 54 IDC ER:- PR:- HER2:- RAD51 D c.294del p.(Asp98Glufs*25) Novel Heterozygous Pathogenic NONSENSE 52 IDC ER:- PR:- HER2:-

[Abstract:0250]

Clinical and Molecular Spectrum of Xeroderma Pigmentosum: Insights from a Seven Patient Cohort

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Background: Xeroderma Pigmentosum (XP), is a rare autosomal recessive chronic dermatologic condition resulting from various genetic defects in DNA repair mechanisms related to ultraviolet (UV) induced pyrimidine products. Marked photosensitivity, premature skin aging, increased risk of cutaneous and mucosal cancers characterize the condition. Beyond dermatologic manifestations, progressive neurological degeneration and severe ocular abnormalities are also components of the disease, which makes XP a multisystem disorder.
Methods: Seven patients aged from 1 to 42 were retrospectively reviewed with respect to their detailed medical and family histories as well as clinical features. Five patients out of seven were the offspring of consanguineous parents. The clinical spectrum ranged from early-onset freckling, photosensitivity, neuromotor delay, to squamous cell carcinoma. Clinical exome sequencing (CES) and whole exome sequencing (WES), including copy number variation analysis, were selected based on individual clinical evaluations. Segregation analyses were performed in available family members when applicable. Additional data regarding patient surveillance and follow-up were also collected.
Results: In this cohort, biallelic pathogenic variants were identified in genes of the nucleotide excision repair pathway, including *XPA*, *XPC*, and *ERCC5*, as well as in *POLH*, a gene involved in translesion DNA synthesis, reflecting the known genetic heterogeneity of XP. Two patients had pathogenic variants in the *XPC* (NM_004628.5) gene including one individual with compound heterozygous frameshift variants [c.420_423del p.(Glu141Leufs6), and c.2167del p.(Gln723Serfs44)] and one individual with homozygous intronic variant (c.413-24A>G). A homozygous frameshift variant [c.648_649del p.(Lys217Glufs*3)] was identified in the *XPA* (NM_000380.4) gene in one patient. In addition, homozygous gross exonic deletions were identified in the *ERCC5* (NM_000123.4), including exons 2-5, and in the *POLH* (NM_006502.3) gene, involving exon 10, in one patient each. All identified variants have been previously reported in the literature, with the exception of the exonic deletion in *ERCC5[/I]. Genetic testing is still ongoing for two patients at the time of manuscript preparation for oral presentation.*
Conclusions: *XP exhibits heterogeneity in both clinical presentation and genetic etiology. The previously reported variants in the XPA and XPC genes, as well as the exonic deletion in the POLH gene, together with the novel exonic deletion in ERCC5, contribute to the current body of knowledge. The importance of comprehensive genetic testing, including copy number variation analysis, in patients suspected of having XP is underscored. Early molecular diagnosis is crucial for appropriate surveillance, multidisciplinary management, and genetic counseling, ultimately aiming to reduce morbidity and improve long-term outcomes in affected individuals.*

Keywords: *copy number variation, DNA repair, skin cancer, xeroderma pigmentosum*

CLINICAL AND MOLECULAR SPECTRUM OF XERODERMA PIGMENTOSUM: INSIGHTS FROM A SEVEN-PATIENT COHORT Olida Çeçen1, Tuğba Kalaycı1, Tuğba Atcı2, Can Baykal2 1Department of Medical Genetics, Faculty of Medicine, Istanbul University, Istanbul, Türkiye 2 Department of Dermatology and Venereology, Faculty of Medicine, Istanbul University, Istanbul, Türkiye ABSTRACT Background: Xeroderma Pigmentosum (XP), is a rare autosomal recessive chronic dermatologic condition resulting from various genetic defects in DNA repair mechanisms related to ultraviolet (UV) induced pyrimidine products. Marked photosensitivity, premature skin

*aging, increased risk of cutaneous and mucosal cancers characterize the condition. Beyond dermatologic manifestations, progressive neurological degeneration and severe ocular abnormalities are also components of the disease, which makes XP a multisystem disorder. Methods: Seven patients aged from 1 to 42 were retrospectively reviewed with respect to their detailed medical and family histories as well as clinical features. Five patients out of seven were the offspring of consanguineous parents. The clinical spectrum ranged from early-onset freckling, photosensitivity, neuromotor delay, to squamous cell carcinoma. Clinical exome sequencing (CES) and whole exome sequencing (WES), including copy number variation analysis, were selected based on individual clinical evaluations. Segregation analyses were performed in available family members when applicable. Additional data regarding patient surveillance and follow-up were also collected. Results: In this cohort, biallelic pathogenic variants were identified in genes of the nucleotide excision repair pathway, including XPA, XPC, and ERCC5, as well as in POLH, a gene involved in translesion DNA synthesis, reflecting the known genetic heterogeneity of XP. Two patients had pathogenic variants in the XPC (NM_004628.5) gene including one individual with compound heterozygous frameshift variants [c.420_423del p.(Glu141Leufs6), and c.2167del p.(Gln723Serfs44)] and one individual with homozygous intronic variant (c.413-24A>G). A homozygous frameshift variant [c.648_649del p.(Lys217Glufs*3)] was identified in the XPA (NM_000380.4) gene in one patient. In addition, homozygous gross exonic deletions were identified in the ERCC5 (NM_000123.4), including exons 2-5, and in the POLH (NM_006502.3) gene, involving exon 10, in one patient each. All identified variants have been previously reported in the literature, with the exception of the exonic deletion in ERCC5. Genetic testing is still ongoing for two patients at the time of manuscript preparation for oral presentation. Conclusions: XP exhibits heterogeneity in both clinical presentation and genetic etiology. The previously reported variants in the XPA and XPC genes, as well as the exonic deletion in the POLH gene, together with the novel exonic deletion in ERCC5, contribute to the current body of knowledge. The importance of comprehensive genetic testing, including copy number variation analysis, in patients suspected of having XP is underscored. Early molecular diagnosis is crucial for appropriate surveillance, multidisciplinary management, and genetic counseling, ultimately aiming to reduce morbidity and improve long-term outcomes in affected individuals. Keywords: copy number variation, DNA repair, skin cancer, xeroderma pigmentosum Introduction Xeroderma pigmentosum (XP) is a rare hereditary autosomal recessive genetic disorder that consists of diverse clinical features characterized by photosensitivity, premature aging, and sunlight-induced skin cancers, together with ocular and neurologic manifestations and developmental disorders. The prevalence is estimated as 1/1 million in the USA but in some populations including Türkiye the prevalence is increased up to 1/10 000 due to consanguinity. To date, ten subgroups present based on the genes involved in the condition including DDB2, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, GTF2H4, POLH, XPA and XPC. Molecular defects underlying the condition are defective repair of UV-induced lesions such as pyrimidine photoproducts and pyrimidine dimers, by the nucleotide excision repair (NER) pathway, which surveys the whole genome for damage and restores it (1). In the XP variant patients with normal NER function, the genetic defects in the POLH gene causes the pathologic pyrimidine dimer containing defective DNA strands to continue the replication due to the impaired DNA polymerase function (2). From early childhood, individuals with XP experience significant functional impairment, psychological distress, and social withdrawal as a consequence of repeated biopsies and excisions, often involving mutilating surgery in cosmetically and functionally critical areas, necessitated by their strong predisposition to life-threatening skin cancers; including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma, as well as multiple precancerous lesions (3). In this study, seven patients with xeroderma pigmentosum (XP) were evaluated from both clinical and molecular perspectives, and one patient was identified as harboring a novel pathogenic mechanism involving an exonic deletion in the ERCC5 gene. Material and Methods Four female and three male patients, aged from 1 to 42, were retrospectively examined from the archives of the medical genetics and dermatology departments of Istanbul University Faculty of Medicine. Five of the seven patients were offspring of consanguineous parents.*

Anthropologic measurements and standard deviation (SD) were evaluated according to Kurtoğlu et al. for newborns and Neyzi et al. throughout childhood after the neonatal period (4,5). Clinical exome sequencing (CES) for six patients and whole exome sequencing (WES) for one patient, both tests including the copy number variation (CNV) analysis, were carried out using the Human Core Exome v2 kit (Twist Bioscience, South San Francisco, CA, USA) and/or the Clinical Exome Solution v3 kit (SOPHiA GENETICS SA, Rolle, Switzerland), followed by paired-end sequencing on the Illumina NextSeq 2000 platform (San Diego, CA, USA). Bioinformatic analysis of the sequencing data was conducted using the SOPHiA DDM pipeline (version 4.4.6.0; SOPHiA GENETICS SA, Rolle, Switzerland). Sanger sequencing was additionally performed in selected patients for familial segregation analysis, using PCR amplification followed by bidirectional sequencing on an ABI 3500 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Data were analyzed, and variant pathogenicity was classified in accordance with the practice guidelines of the American College of Medical Genetics and Genomics (ACMG). Results Clinical findings Patient (P)1 was a 1-year-old male whose parents were first-degree cousins presented with delay in the neurodevelopmental milestones and hair loss, bilateral bullous burn scars in his lower legs after minimal sun exposure. He was found to have intrauterine growth restriction, lagging by approximately five weeks starting from the second trimester. He was born with a weight of 2195 grams (-2.25 SD), length of 46 cm (-1.32 SD) and head circumference of 32 cm (−1.61 SD). He achieved head control at 7 months of age, independent sitting at 12 months; independent walking has not yet been attained. Babbling began at 4–5 months of age but subsequently decreased. On physical examination at 1 year of age he had a decreased head circumference of 41 cm (-3.74 SD) and low weight of 6600 grams (-2.96 SD). Height was 69 cm (-1.95 SD). Malar freckling was observed in the physical examination.Thin corpus callosum was demonstrated in brain imaging and his laboratory testing revealed increased levels of alanine aminotransferase and aspartate aminotransferase. P2 was a 3-year-old female evaluated for severe atopy, generalized dryness of skin, and numerous nevi. Her medical history was insignificant other than low birth weight (-2.37 SD). Physical examination revealed generalized freckling in her face, distinct ichthyosis accompanied by hypopigmentation especially in sun exposed areas. P3 was a 16-year-old female born to consanguineous parents who were one and a half removed cousins. She was initially evaluated at the hospital due to the development of bullous lesions and scarring on the face following sun exposure when she was 6 months old. She had been clinically followed with a diagnosis of XP since the age of one year. Clinical evaluation showed strabismus, and review of her medical history revealed delayed neuromotor development, with independent sitting achieved at 12 months of age and independent walking at 2.5 years of age. Severe intellectual disability was also observed. The patient had both an in situ and an invasive melanoma lesion (lentigo maligna and nodular melanoma, respectively) located on the face and neck. In addition, she was diagnosed with basal cell carcinoma (BCC) and keratoacanthoma involving the facial region and had undergone multiple surgical interventions for the pathologically confirmed neoplasms described above. P4 was a 29-year-old female born to first-degree consanguineous parents. She had been clinically followed with a diagnosis of XP, which was first established at 6 months of age based on hypopigmented skin, facial and upper extremity freckling, and marked photosensitivity. She had undergone multiple surgical procedures for pathologically confirmed BCC in her face, as well as three ophthalmologic surgeries for ocular involvement. No other significant medical comorbidities were reported. The patient had previously undergone CES; however, no pathogenic or likely pathogenic variants explaining her clinical phenotype were identified. Therefore, repeat genetic testing (WES) was performed to further investigate the underlying molecular etiology. P5 was a 33-year-old male born to consanguineous parents. His symptoms started when he was 3 years old and he was clinically diagnosed with XP at seven years of age. The first melanoma lesion was identified at 19 years of age, with subsequent lesions developing thereafter. Over the course of follow-up, he developed extensive cutaneous malignancies, including 11 BCC lesions on the face and 4 on the scalp, basosquamous carcinoma involving the face and scalp, and 8 SCC lesions on the face. In addition, he had multiple melanomas, including one on the face, two on the scalp, and one on the upper

*extremity, as well as actinic keratoses affecting the facial region. The melanoma subtypes were primary dermal melanoma and lentigo maligna. He was also suffering from xerophthalmia. P6 was a 41-year-old male whose parents were second-degree cousins. He was initially evaluated for multiple cutaneous lesions involving the face. These lesions were subsequently diagnosed as multiple basal cell carcinomas and melanomas affecting the face, neck, and scalp. Marked photosensitivity was also elicited during clinical evaluation. P7 was a 42-year-old female with a previously established diagnosis of XP. Although parental consanguinity was not reported, her sister was similarly affected and was also being followed with a diagnosis of XP; however, she was not included in the present cohort at the time of this manuscript being conducted. The patient was evaluated for cutaneous manifestations comparable to those observed in the other patients described in this series, including sun-exposure-related skin lesions. Molecular findings Even though the evaluated patients had similar clinical features, the molecular background varied from patient to patient. P1 was the most significant. With the critical advantage of genetic tests applied to patients were including CNV analysis, he was found to harbor a homozygous 4.1 kb deletion, at the location Chr13:102852108-102856249, encompassing exons 2–5 of the ERCC5 gene (NM_000123.4), consistent with XP group G (XP-G), XP Cockayne Syndrome overlap (XP-CS) and cerebro-oculo-facio-skeletal syndrome (COFS). A search of the Human Gene Mutation Database (HGMD) revealed no prior reports of this variant, indicating a novel pathogenic alteration. P2 was identified as compound heterozygous for variants in the XPC gene (NM_004628.5). She carried frameshift variants c.420_423del p.(Glu141Leufs6)(rs1330667099), classified as pathogenic, and c.2167del p.(Gln723Serfs44), classified as likely pathogenic. Segregation analysis of parents confirmed the compound heterozygous state. P3 carried a homozygous frameshift pathogenic variant in XPA (NM_000380.4) gene as c.648_649del p.(Lys217Glufs*3) rs1057519018. P6 carried c. 413-24A>G rs794729657 homozygous intronic pathogenic variant in XPC (NM_004628.5) gene. Lastly P7 had a homozygous deletion in exon 10 of POLH (NM_006502.3) gene. The genetic test results of patients 4 and 5 had not yet been finalized at the time this manuscript was written and were planned to be shared at the time of presentation. Discussion XP exhibits marked heterogeneity at both the clinical and molecular levels, which can result in phenotypes that deviate from the classic presentation of the disease. Beyond the markedly increased risk of cutaneous malignancies, XP has also been associated with internal tumors, including hematologic neoplasms and malignancies of the central nervous system (CNS), gynecologic tract, and thyroid, often with an unusually early age of onset which encompasses the importance of screening, early detection and monitorization of the condition (6). Specific genotype-phenotype correlations have been described for different clinical types of XP: XPA is generally related with neurodevelopmental abnormalities in addition to skin manifestation other than known hotspot mutation c.555+8A>G; hearing loss may be apparent in XPB; XPC patients experience ocular vulnerability; XPD, XPE, XPF, XPV patients are generally reported with cutaneous photosensivity and different types of skin cancers whereas XPG demonstrates the broadest phenotypic spectrum, ranging from classic XP to severe XP CS and even (COFS) (7). When evaluating this cohort's aforementioned genomic changes in XPA, XPC and POLH; homozygous exonic deletion through exon 2 to exon 5 in the ERCC5 in P1 signifies as a new pathogenic molecular mechanism for XP group G and XP-CS phenotypes as emphasized in OMIM database. As this phenotype being extremely rare, UV related skin irritation and malignancies along with features of Cockayne Syndrome like microcephaly, hydrocephaly, cachexia, sensorineural hearing loss, optic atrophy, cognitive defects, dysmyelination and basal ganglia calcification has been reported with a missense homozygous variant by Stehnach et al. (8). In a systematic review concluded by Zhang et al., abnormal live function tests similar to those observed in P1 were reported in association with ERCC5 mutations and it has been highlighted that defective NER mediated responses to oxidative damage elicited by hepatotoxic agents render these patients vulnerable to impaired liver function, cirrhosis and hepatocellular carcinoma; however the specific exonic deletion identified in our patient was not described in that review (7). The genes investigated in this study include ERCC5, POLH, XPA, and XPC. Review of the GeneReviews XP entry and the*

existing literature demonstrates that a wide spectrum of pathogenic, mostly truncating variants such as missense, nonsense, frameshift, splice-site have been reported in association with these genes (9, 10). However, this cohort shows more exonic deletions, in POLH and ERCC5, than previous literature up to our knowledge highlighting not to underestimate the deletion analysis. Cells derived from the XP patients exhibit increased UV induced mutagenesis correlating with the genetic defects in DNA repair pathways resulting in heightened cellular mutational burden which are the fundamental drivers of carcinogenesis (11). Rather than second hit mutations in the tumoral tissue, germline mutations play a more profound role resulting 3.6 fold increased tumor mutational burden higher than sporadic skin cancers with characteristic signature mutations like single base substitutions and CC>TT tandem mutations (12). Limitations Familial segregation analysis for the entire cohort had not been performed at the time this manuscript was prepared. As this paper was prepared for the oral presentation the ethical approval procedures have not been completed yet. Conclusion In conclusion, this paper emphasizes the clinical and molecular heterogeneity of XP through detailed examination of seven patients with diverse phenotypes and genetic alterations. Our novel homozygous multi exonic deletion in ERCC5 expands the spectrum of known variants associated with XP group G and further related phenotypes. For disorders such as XP, which predispose affected individuals to cancer imposing a lifelong burden and significantly reduce life expectancy, it is essential that genetic testing to be performed in a comprehensive manner, including mandatory CNV analysis. Whenever feasible, timely initiation of familial screening is also crucial. In addition, clinical findings beyond the classic phenotype, such as the hepatic dysfunction described in this study, should not be overlooked. Such an approach is critical not only for accurate diagnosis and optimal long-term follow-up of patients but also for advancing the existing literature and improving our understanding of the full disease spectrum. References

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[Abstract:0257]

Evaluation of the Epidemiological, Clinical, and Survival Characteristics of Patients Followed with a Diagnosis of Rare Childhood Tumors at the Department of Pediatric Oncology, Ankara University Faculty of Medicine, Between 2002 and 2022

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Objective: This study aimed to evaluate the epidemiological, clinical, molecular, and survival characteristics of patients diagnosed with rare childhood tumors who were admitted to the Department of Pediatric Oncology, Ankara University Faculty of Medicine, between 2002 and 2022; to assess changes over time; and to compare the data with national cancer registries conducted by the Turkish Pediatric Oncology Group and Turkish Pediatric Hematology Association, as well as international cancer registry data, to inform future healthcare planning.
Materials-Methods: Patients were retrospectively reviewed, and demographic data, presenting complaints, comorbidities, family history, clinical, laboratory, and imaging findings, identified risk factors, treatments, relapse status, and survival were recorded.
Results: A total of 135 rare tumors were analyzed in 131 patients. Of the patients, 60.3% were female, and the most common age at diagnosis was 10–14 years. Consanguinity was present in 14.5% of cases, and a family history of cancer was found in 25.2%. Comorbidities were observed in 29%, most frequently endocrine disorders (19.1%). The most common presenting symptom was swelling (44.4%), followed by thyroid nodules (14.1%) and pain (12.6%). Primary tumor sites were most often located in the head and neck region (63.0%), followed by abdominopelvic (15.6%) and extremity (14.8%) locations. The most frequent diagnosis was thyroid carcinoma (33.3%), followed by rare soft tissue sarcomas (27.4%) and other rare epithelial carcinomas/melanomas (22.2%). Molecular analyses in 21 patients revealed pathogenic alterations including RET, BRAF, NTRK, and ALK mutations/fusions, mutations in TP53, PTEN, CTNNB1, DICER1, and POLE, and PD-1/PD-L1 positivity. Germline genetic testing identified cancer predisposition syndromes or pathogenic variants in 14 patients, including MEN2A (n=4), xeroderma pigmentosum (n=3), Li-Fraumeni syndrome (n=2), Lynch syndrome (n=1), MEN2B (n=1), and DICER1, PTEN, CHEK2, CTNNB1 mutations (n=3).
Surgery was performed in 89.6% of tumors, with surgery alone sufficient in 39.3% of cases. Radiotherapy, chemotherapy, and targeted therapy/immunotherapy were applied in 20.0%, 28.8%, and 18.5% of patients, respectively. Radioactive iodine therapy was used in 57.8% of thyroid carcinoma cases. Treatment-related late effects were observed in 11.1% of patients, most commonly hypocalcemia due to hypoparathyroidism. Localized disease was present in 71.9% and metastatic disease in 28.1% of tumors. The relapse rate was 6.9%, and both metastatic disease and relapse were associated with significantly shorter survival. Median follow-up was 69 months, and 5- and 10-year overall survival was 83.3%.
Conclusion: Rare childhood tumors exhibit heterogeneous clinical, histopathological, and molecular features, with higher prevalence in females and adolescents. The broad molecular diversity and notable frequency of germline pathogenic mutations underscore the importance of cancer predisposition syndromes and the critical role of molecular analyses in guiding targeted therapies. Metastatic disease and relapse negatively impact survival, highlighting the prognostic importance of early diagnosis, risk-adapted, and molecularly guided treatment strategies with long-term follow-up.

Keywords: *Childhood cancers, Epidemiology, Pediatric rare tumors, Prognosis, Survival*

Evaluation of the Epidemiological, Clinical, and Survival Characteristics of Patients Followed with a Diagnosis of Rare Childhood Tumors at the Department of Pediatric Oncology, Ankara University Faculty of Medicine, Between 2002 and 2022 *Ceren Kılınç[1], Sonay İncesoy Özdemir[2], Handan Dinçaslan[2], Melda Berber Hamamcı[2], Nihal Ekin Dağ[2], Cem Çanakçı[2], Vafa Maharramova[2], Nubar Mustafayeva[2], Nur Ayça Çelik[2], Dilara Doğan[2], Nurdan Taçyıldız[2]*
[1] Ankara Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları AD [2] Ankara Üniversitesi Tıp Fakültesi, Çocuk Onkoloji BD, Ankara, Türkiye *Introduction: Although significant improvements in survival rates have been achieved in pediatric oncology over the past 50 years, these gains have largely been limited to malignancies that are common in childhood. In recent years, awareness of pediatric rare tumors has increased through international consortia and registry systems; however, there remains a need for a better understanding of the clinical, molecular, and genetic characteristics of these tumors. Aim: The aim of this study was to evaluate the epidemiological, clinical, molecular, and survival characteristics of patients with rare childhood tumors followed at the Department of Pediatric Oncology, Ankara University Faculty of Medicine, and to determine the frequency of hereditary cancer predisposition syndromes. Materials and Methods: This study was designed as a single-center, retrospective, and descriptive study. Patients aged 0–18 years who were followed with a diagnosis of rare childhood tumors between 2002 and 2022 were included. Demographic, clinical, histopathological, genetic, treatment, and survival data were obtained from patient files and electronic medical records. Descriptive statistics were presented as numbers and percentages; survival analyses were performed using the Kaplan–Meier method, and prognostic factors were evaluated with multivariate analyses. A p value*

[Abstract:0258]

Clinical Spectrum and Management Implications of Germline TP53 Variants Identified Through Broad-Based Genetic Testing: A Real-World Case Series

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Objective: Inherited cancer predisposition syndromes account for a substantial proportion of cancer risk, and identification of pathogenic germline variants has important implications for oncologic management, cancer surveillance, risk-reducing strategies, and cascade testing of at-risk relatives. Estimates of germline cancer susceptibility have largely been derived from registry-based cohorts, high-risk clinics, or testing-company databases, introducing ascertainment bias. With the increasing integration of tumor next-generation sequencing and multigene panel testing into routine oncology practice, germline variants are increasingly identified in patients outside traditional guideline-based testing indications. The clinical interpretation and management relevance of such findings, particularly for TP53, remain incompletely characterized.
Materials-Methods: We conducted a retrospective review of patients in whom germline TP53 variants were identified through multigene hereditary cancer testing at a tertiary referral center. Clinical characteristics, age at cancer diagnosis, tumor spectrum, family history, co-occurring germline variants, and downstream clinical implications were evaluated. Variant classification followed ACMG criteria and ClinVar annotations. Clinical relevance was assessed in the context of modified Chompret criteria and contemporary surveillance recommendations.
Results: Case 1 was a 31-year-old woman diagnosed with breast cancer and no reported family history of malignancy. Germline testing identified a heterozygous TP53 c.824G>A (p.Cys275Tyr) variant, classified as pathogenic (P) according to ACMG criteria and reported in ClinVar as pathogenic/likely pathogenic in association with Li-Fraumeni syndrome.
Case 2 was a 47-year-old man with metastatic cholangiocarcinoma and a reported family history of lung cancer. Germline analysis revealed a heterozygous TP53 c.473G>A (p.Arg158His) variant, classified as pathogenic/likely pathogenic (P/LP). This case represents a non-core tumor type identified in the context of a germline TP53 alteration.
Case 3 involved a woman diagnosed with breast cancer at 40 years of age with a complex multigenerational family history including colorectal, cervical, and brain malignancies. Germline testing demonstrated a heterozygous TP53 c.542G>A (p.Arg181His) variant, classified as likely pathogenic (LP). Her affected sibling with colorectal cancer carried the same TP53 variant in addition to MLH1, ATM variants and a RAD51C variant of uncertain significance (VUS), consistent with a blended hereditary cancer predisposition.
Case 4 was a 31-year-old woman with locally advanced HER2-positive breast cancer and a striking family history of very early-onset malignancies, including maternal breast cancer diagnosed at 22 years of age and a sibling with a childhood brain tumor. Germline testing identified a heterozygous TP53 c.374C>G (p.Thr125Arg) variant, classified as pathogenic/likely pathogenic (P/LP). Based on clinical and family history, this case fulfilled modified Chompret criteria for Li-Fraumeni syndrome.
Case 5 was a 56-year-old woman diagnosed with high-grade serous ovarian carcinoma with no reported family history of cancer. Germline testing revealed a heterozygous TP53 c.524G>A (p.Arg175His) variant, classified as pathogenic (P), despite prior negative germline BRCA1/2 testing.
Conclusion: This case series underscores the phenotypic and clinical heterogeneity associated with germline TP53 variants identified through broad-based genetic testing. Our findings highlight limitations of guideline-restricted

testing approaches and emphasize the need for careful contextual interpretation of TP53 variants. Recognition of germline TP53 alterations has meaningful implications for patient management and familial risk assessment beyond formal syndrome classification.

Keywords: *germline TP53, Li-Fraumeni syndrome, hereditary cancer, variant interpretation*
Clinical Spectrum and Management Implications of Germline TP53 Variants Identified Through Broad-Based Genetic Testing: A Real-World Case Series Feyza Arslan Tan1, Olçun Ümit Ünal1, Altuğ Koç2, Taha Reşid Özdemir2 1 İzmir Şehir Hastanesi Tıbbi Onkoloji 2 İzmir Şehir Hastanesi Tıbbi Genetik Objective The objective of this case series is to characterize the clinical spectrum and management implications of germline TP53 pathogenic variants identified through broad-based multigene testing in routine oncology practice. Specifically, we aim to illustrate how expanded germline testing beyond traditional, phenotype-driven criteria reveals TP53 alterations across diverse tumor types, ages at onset, and clinical contexts, including presentations that fall outside classical Li-Fraumeni syndrome (LFS) definitions. By describing real-world cases, this study seeks to highlight the epidemiologic heterogeneity, diagnostic challenges and downstream clinical consequences of germline TP53 identification, with particular emphasis on implications for treatment decision making, cancer surveillance and cascade testing. Through this approach, we aim to underscore the limitations of guideline-restricted germline testing strategies and to position TP53 as a paradigmatic gene supporting the clinical relevance of broader germline testing frameworks in contemporary oncology. Introduction Inherited cancer predisposition syndromes constitute a significant component of oncologic risk and identification of pathogenic germline variants has far-reaching implications for cancer management, surveillance strategies, risk-reducing interventions and cascade testing of at-risk relatives. Over the past decade, advances in next-generation sequencing (NGS) technologies and the routine incorporation of multigene panel testing into clinical oncology practice have fundamentally reshaped the landscape of hereditary cancer detection, extending germline assessment beyond conventionally defined high-risk populations. Accumulating evidence from large cohort studies and prospective analyses has demonstrated that the prevalence of pathogenic (P) or likely pathogenic (LP) germline cancer susceptibility variants across solid tumors is substantially higher and more heterogeneous than previously recognized. (1,2) In malignancies traditionally associated with hereditary predisposition, most notably breast, prostate, and colorectal cancer, application of broad multigene testing in unselected populations has consistently revealed clinically actionable germline variants that would not have been identified through guideline-restricted or family history-based testing approaches. (3) Comparable observations have been reported across a broader array of tumor types, including ovarian, pancreatic, endometrial, hepatobiliary and other epithelial malignancies, although reported frequencies vary considerably according to cohort composition, testing strategy, and ascertainment methods. Within this evolving paradigm of expanded germline testing, TP53 has emerged as a gene of particular clinical and biological significance. Germline pathogenic variants in TP53 are rare in the general population yet confer among the highest lifetime cancer risks of all known hereditary cancer predisposition genes. (4) Historically, epidemiologic characterization of germline TP53 has relied predominantly on families meeting classical Li-Fraumeni syndrome (LFS) criteria or on referral based cancer genetics cohorts, resulting in an overrepresentation of early-onset, highly penetrant disease. With the widespread adoption of multigene panel testing, however, germline TP53 variants are increasingly identified outside classical LFS pedigrees and in patients with later-onset, apparently sporadic, or non-canonical tumor presentations. (5) The tumor spectrum associated with germline TP53 alterations is exceptionally broad, encompassing soft tissue and bone sarcomas, premenopausal breast cancer, brain tumors, adrenocortical carcinoma, leukemia, and a range of epithelial malignancies. Identification of a germline TP53 pathogenic variant carries immediate and substantial clinical consequences, including implementation of intensive surveillance protocols, avoidance of ionizing radiation when feasible due to heightened radiosensitivity and provision of comprehensive genetic counseling

with cascade testing of at-risk relatives. Concurrently, the increasing detection of TP53 variants through broad-based testing introduces important interpretive challenges, particularly with respect to distinguishing true germline alterations from mosaicism or clonal hematopoiesis and determining clinical relevance in presentations that fall outside classical phenotypic frameworks. Collectively, these developments underscore both the opportunities and complexities inherent to contemporary germline testing strategies and position TP53 as a paradigmatic model for evaluating the limitations of phenotype-driven testing criteria and the necessity of integrating molecular f indings with detailed clinical context to optimize patient care and familial risk assessment. Materials and Methods We conducted a retrospective review of patients in whom germline TP53 variants were identified through multigene hereditary cancer testing at Izmir City Hospital. Clinical characteristics, age at cancer diagnosis, tumor spectrum, family history, co-occurring germline variants, and downstream clinical implications were systematically evaluated. Variant classification was performed in accordance with American College of Medical Genetics and Genomics (ACMG) criteria and annotated using ClinVar. Clinical relevance was assessed in the context of modified Chompret criteria and contemporary TP53-specific surveillance recommendations. Results Five patients with germline TP53 pathogenic or likely pathogenic variants were identified. Case 1 involved a 31-year-old woman diagnosed with triple positive breast cancer, classified as anatomic stage IIA. Notably, she reported no personal or family history of malignancy, and her presentation did not fulfill classical clinical criteria for LFS at the time of diagnosis. Germline testing performed as part of broad based hereditary cancer panel assessment identified a heterozygous TP53 c.824G>A (p.Cys275Tyr) variant, classified as pathogenic according to ACMG criteria and annotated in ClinVar as pathogenic/likely pathogenic in association with LFS. This case exemplifies an atypical TP53 associated presentation, in which early-onset breast cancer served as the sentinel malignancy leading to identification of a germline TP53 pathogenic variant in the absence of a suggestive family history. Detection of the TP53 variant had immediate clinical implications, including modification of local therapy considerations and implementation of TP53 specific cancer surveillance and genetic counseling for the patient and at risk relatives. Case 2 involved a 47-year-old man diagnosed with metastatic cholangiocarcinoma, with a reported family history of lung cancer. Germline genetic testing identified a heterozygous TP53 c.473G>A (p.Arg158His) variant, classified as pathogenic/likely pathogenic. This variant is classified as pathogenic for LFS in ClinVar, with concordant submissions from multiple independent laboratories and no reported conflicts, supporting its established clinical significance. Cholangiocarcinoma is not considered a core tumor type within the classical LFS spectrum, as summarized in GeneReviews (2024 update). Nevertheless, emerging data from large-scale germline testing efforts in hepatobiliary malignancies indicate that pathogenic or likely pathogenic germline variants most commonly involve BRCA1/2, PALB2, BAP1, and mismatch repair genes, whereas TP53 alterations in this disease context have been predominantly reported as somatic events. Case 3 involved a woman diagnosed with stage II luminal B breast cancer at 40 years of age with a complex multigenerational family history including colorectal, cervical, and brain malignancies. Germline hereditary cancer panel testing identified a heterozygous TP53 NM_000546.6:c.542G>A (p.Arg181His) variant, classified as likely pathogenic. Her family history was notable for cervical cancer in her mother and brain and colorectal cancers in maternal relatives. Genetic testing performed in her brother, who was diagnosed with colorectal cancer, revealed multiple germline alterations, including a pathogenic MLH1 variant (exon 17, c.1918delC), a pathogenic ATM variant (exon 26, c.3890_3891insT), and the same TP53 c.542G>A variant, as well as a RAD51C variant of uncertain significance (VUS), consistent with a blended hereditary cancer predisposition within the family. Early-onset breast cancer is a core tumor type within the LFS spectrum and remains the most frequent sentinel malignancy associated with germline TP53 pathogenic variants. The p.Arg181His variant affects the DNA-binding domain of TP53, a region enriched for clinically significant alterations, and is classified as pathogenic/likely pathogenic in public databases, including ClinVar. This case illustrates the phenotypic heterogeneity and intrafamilial genetic complexity increasingly observed with broad-based germline testing and

underscores how clinically actionable TP53 variants may be identified in patients who do not fulfill classical LFS criteria at presentation. Case 4 was a 31-year-old woman diagnosed with locally advanced HER2-positive breast cancer, representing an early-onset malignancy within the TP53 tumor spectrum. Her personal history was notable for aggressive disease requiring multimodal therapy, and her family history was striking for multiple very early-onset malignancies, including maternal breast cancer diagnosed at 22 years of age and a sibling with a childhood-onset brain tumor, raising strong suspicion for an underlying hereditary cancer predisposition syndrome. Germline multigene testing identified a heterozygous TP53 c.374C>G (p.Thr125Arg) variant, which is classified as pathogenic/likely pathogenic according to ACMG criteria and has been previously reported in association with LFS. In the context of the patient's early-onset breast cancer and compelling family history, this presentation fulfilled modified Chompret criteria for LFS. Identification of the TP53 variant had immediate clinical implications, including the need for intensified cancer surveillance, consideration of radiation-sparing therapeutic strategies, and genetic counseling with cascade testing for at-risk relatives. Case 5 was a 56-year-old woman diagnosed with high-grade serous ovarian carcinoma, a tumor type most commonly associated with defects in homologous recombination repair pathways. Notably, she reported no family history of cancer, and prior germline testing limited to BRCA1/2 had yielded negative results. Subsequent broad-based multigene panel testing identified a heterozygous TP53 c.524G>A (p.Arg175His) variant, classified as pathogenic according to ACMG criteria and previously reported in association with LFS. This finding represents an incidental identification of a germline TP53 pathogenic variant in the absence of classical clinical or familial features suggestive of LFS. Identification of the TP53 variant expanded the patient's hereditary risk profile beyond BRCA-associated pathways and prompted consideration of TP53-specific surveillance strategies and genetic counseling, including cascade testing for at-risk relatives. This case highlights the potential for clinically significant germline TP53 variants to be detected in patients with apparently sporadic malignancies and underscores the limitations of gene-restricted testing approaches in contemporary oncology practice. Discussion In this real-world case series, we describe five patients with germline TP53 pathogenic or likely pathogenic variants identified through broad-based multigene testing in routine oncology practice. Collectively, these cases illustrate the expanding clinical spectrum of germline TP53–associated disease and highlight the diagnostic and management challenges that arise when TP53 variants are detected outside classical LFS contexts. Although historically considered a rare and highly penetrant cancer predisposition confined to well-defined familial syndromes, germline TP53 alterations are increasingly encountered across diverse tumor types, ages at diagnosis, and clinical scenarios with the widespread adoption of multigene panel testing. The cases presented encompass early- and later-onset malignancies, classical LFS-associated tumors and non-core tumor types, and both strong and absent family histories of cancer. Notably, several patients would not have fulfilled established phenotype-driven criteria for TP53 testing, yet identification of a germline TP53 variant had direct and meaningful implications for clinical management. A particularly instructive finding in this series is the identification of germline TP53 pathogenic variants in non-classical tumor types and in attenuated or blended hereditary cancer phenotypes, reflecting the evolving landscape of TP53-associated cancer predisposition in contemporary oncology practice. Cases 2 and 5 exemplify non-core tumor presentations, occurring in patients with metastatic cholangiocarcinoma and high-grade serous ovarian carcinoma, respectively. Germline cancer susceptibility variants, including TP53, may be identified across a broader range of epithelial malignancies than previously recognized. In hepatobiliary cancers, germline alterations are increasingly reported most commonly involving homologous recombination repair and DNA damage response genes while TP53 alterations have classically been regarded as somatic events. More recent reviews, including the comprehensive analysis by Chotiprasidhi et al. (1), have highlighted that germline pathogenic variants, including TP53, have been identified across hepatobiliary cancer subtypes, particularly in gallbladder cancer cohorts, underscoring the genetic heterogeneity of these malignancies. In this context, the identification of a germline TP53 pathogenic variant in a patient with cholangiocarcinoma in this series

underscores the importance of not dismissing TP53 findings solely on the basis of tumor type when variants meet stringent pathogenicity criteria. Similarly, case 5 illustrates the incidental detection of a germline TP53 pathogenic variant in a patient with high-grade serous ovarian carcinoma and no reported family history of cancer, despite prior negative BRCA1/2 testing. (2,6) This scenario highlights a key limitation of gene-restricted testing strategies, which may fail to identify clinically significant hereditary cancer predisposition outside canonical pathways. (7) Although TP53 is not a primary driver of homologous recombination deficiency, identification of a germline TP53 variant nonetheless carries substantial implications for long-term cancer risk assessment, surveillance strategies, and cascade testing of at risk relatives. Together, these non-classical cases reinforce the expanding phenotypic spectrum of TP53-associated disease and support a more nuanced, context-aware interpretation of germline TP53 findings beyond rigid tumor-based classifications. Case 3 further illustrates the complexity introduced by attenuated and blended hereditary cancer phenotypes increasingly encountered through multigene panel testing. In this patient, early-onset breast cancer a core LFS-associated tumor occurred in the context of a multigenerational family history marked by diverse malignancies and the coexistence of multiple pathogenic germline variants across different cancer susceptibility genes. The presence of a likely pathogenic TP53 variant alongside pathogenic MLH1 and ATM variants in affected relatives exemplifies the multilocus inheritance patterns that can complicate traditional genotype–phenotype correlations. Such blended genetic architectures challenge the historical paradigm of single-gene syndromic inheritance and underscore the need for individualized risk assessment that integrates the cumulative and potentially interacting effects of multiple germline alterations. Identification of germline TP53 variants in routine oncology practice also raises important interpretive and management challenges. Distinguishing true germline pathogenic variants from clonal hematopoiesis of indeterminate potential or mosaicism is critical, particularly in adult-onset cancers and in tumor types where TP53 alterations are more commonly somatic. Moreover, expanding detection of TP53 variants outside classical clinical contexts complicates penetrance estimation, risk communication, and genetic counseling. These challenges highlight the necessity of integrating molecular findings with detailed clinical evaluation, family history assessment, and expert genetic counseling to guide appropriate surveillance and treatment decisions. Despite these complexities, the clinical implications of identifying a germline TP53 pathogenic variant are substantial. TP53 status directly influences cancer surveillance recommendations, radiotherapy decision-making, and cascade testing of at-risk relatives. In this series, germline TP53 variants were identified in clinical contexts where testing might not have been pursued under guideline-restricted approaches, including non-core tumor presentations and apparently sporadic malignancies. Taken together, these findings underscore the clinical value of broader germline testing frameworks when coupled with rigorous variant interpretation, multidisciplinary management, and adherence to contemporary surveillance guidelines. Limitations This study is limited by its small sample size and retrospective design, which preclude quantitative conclusions regarding prevalence, penetrance, or genotype–phenotype correlations. Ascertainment bias is inherent, as cases were identified through routine multigene testing rather than classical LFS referral pathways, reflecting a different but complementary selection context. Although all variants were classified using ACMG criteria and ClinVar annotations, lack of uniform confirmatory testing from non-hematopoietic tissue means that mosaicism or clonal hematopoiesis cannot be fully excluded. Conclusions In conclusion, this case series demonstrates that germline TP53 pathogenic variants identified through broad-based multigene testing exhibit substantial clinical heterogeneity and are frequently detected outside classical LFS presentations. Although limited by sample size and retrospective design, these real-world cases underscore the clinical relevance of TP53 identification and highlight the limitations of phenotype-driven germline testing strategies in contemporary oncology practice. TP53 emerges as a paradigmatic example of both the opportunities and challenges introduced by expanded germline testing, emphasizing the need for refined interpretive frameworks, multidisciplinary management, and careful integration of molecular and clinical data. To address the knowledge gaps highlighted

by this series, we plan to conduct a multi-center, nationwide study across Türkiye to systematically characterize the prevalence, clinical spectrum, and management implications of germline TP53 variants identified through routine oncologic testing. Such an effort will provide population-specific data, reduce ascertainment bias inherent to single-center reports, and contribute to a more comprehensive understanding of TP53-associated cancer predisposition in real-world settings. Ultimately, larger prospective and collaborative studies will be essential to refine risk stratification, optimize surveillance strategies, and inform evidence based guidelines as germline testing continues to expand in routine cancer care. 1. 2. 3. 4. 5. 6. 7. Chotiprasidhi P, Sato-Espinoza AK, Wangensteen KJ. Germline Genetic Associations for Hepatobiliary Cancers. Cell Mol Gastroenterol Hepatol. 2024;17(4):623-638. doi: 10.1016/j.jcmgh.2023.12.010. Epub 2023 Dec 30. PMID: 38163482; PMCID: PMC10899027. Mandelker D, Donoghue M, Talukdar S, Bandlamudi C, Srinivasan P, Vivek M, Jezdic S, Hanson H, Snape K, Kulkarni A, Hawkes L, Douillard JY, Wallace SE, Rial-Sebbag E, Meric-Bersntam F, George A, Chubb D, Loveday C, Ladanyi M, Berger MF, Taylor BS, Turnbull C. Germline-focussed analysis of tumour-only sequencing: Recommendations from the ESMO Precision Medicine Working Group. Ann Oncol. 2019 Aug 1;30(8):1221-1231. doi: 10.1093/annonc/mdz136. Erratum in: Ann Oncol. 2021 Aug;32(8):1069-1071. doi: 10.1016/j.annonc.2021.05.798. PMID: 31050713; PMCID: PMC6683854. Esplin ED, Nielsen SM, Bristow SL, Garber JE, Hampel H, Rana HQ, Samadder NJ, Shore ND, Nussbaum RL. Universal Germline Genetic Testing for Hereditary Cancer Syndromes in Patients With Solid Tumor Cancer. JCO Precis Oncol. 2022 Sep;6:e2100516. doi: 10.1200/PO.21.00516. PMID: 36108258; PMCID: PMC9489188. Schneider K, Zelley K, Nichols KE, et al. Li-Fraumeni Syndrome. 1999 Jan 19 [Updated 2025 May 1]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026. Villani A, Shore A, Wasserman JD, Stephens D, Kim RH, Druker H, Gallinger B, Naumer A, Kohlmann W, Novokmet A, Tabori U, Tijerin M, Greer ML, Finlay JL, Schiffman JD, Malkin D. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol. 2016 Sep;17(9):1295-305. doi: 10.1016/S1470-2045(16)30249-2. Epub 2016 Aug 5. PMID: 27501770. Samadder NJ, Riegert-Johnson D, Boardman L, Rhodes D, Wick M, Okuno S, Kunze KL, Golafshar M, Uson PLS Jr, Mountjoy L, Ertz-Archambault N, Patel N, Rodriguez EA, Lizaola-Mayo B, Lehrer M, Thorpe CS, Yu NY, Esplin ED, Nussbaum RL, Sharp RR, Azevedo C, Klint M, Hager M, Macklin-Mantia S, Bryce AH, Bekaii Saab TS, Sekulic A, Stewart AK. Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients With Hereditary Cancer Syndrome. JAMA Oncol. 2021 Feb 1;7(2):230-237. doi: 10.1001/ jamaoncol.2020.6252. Erratum in: JAMA Oncol. 2021 Feb 1;7(2):312. doi: 10.1001/jamaoncol.2020.7373. PMID: 33126242; PMCID: PMC7600058. Daly MB, Pal T, Maxwell KN, Churpek J, Kohlmann W, AlHilli Z, Arun B, Buys SS, Cheng H, Domchek SM, Friedman S, Giri V, Goggins M, Hagemann A, Hendrix A, Hutton ML, Karlan BY, Kassem N, Khan S, Khoury K, Kurian AW, Laronga C, Mak JS, Mansour J, McDonnell K, Menendez CS, Merajver SD, Norquist BS, Offit K, Rash D, Reiser G, Senter-Jamieson L, Shannon KM, Visvanathan K, Welborn J, Wick MJ, Wood M, Yurgelun MB, Dwyer MA, Darlow SD. NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2024. J Natl Compr Canc Netw. 2023 Oct;21(10):1000-1010. doi: 10.6004/ jnccn.2023.0051. PMID: 37856201.

[Abstract:0259]

Double Trouble or Not? Clinical Impact of Multiple Cancer Predisposition Gene Variants in a Hereditary Cancer Testing

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Objective: Multigene panel testing has become widespread as part of the evaluation process for hereditary cancers. Patients can be carriers of pathogenic or likely pathogenic (P/LP) variants in more than one cancer predisposition gene; these are called multilocus inherited neoplasia alleles syndromes (MINAS).
Materials-Methods: We retrospectively reviewed results from 4,315 patients who underwent genetic testing for hereditary cancer using NGS panels. We define MINAS as a patient carrying pathogenic or likely pathogenic variants in two or more distinct cancer predisposition genes. Clinical features of MINAS cases were compared with patients who have single-gene pathogenic variants to reveal statistical significant differences.
Results: Among the 4,315 individuals tested, 589 (13.7%) had pathogenic or likely pathogenic variants in at least two cancer predisposition genes. The three most frequent genes were BRCA2 (25.8%), BRCA1 (22.6%), and CHEK2 (11.4%). There were 22 patients (3.7%) classified as MINAS carriers. The median age of diagnosis was significantly lower for MINAS carriers than for patients with a single pathogenic or likely pathogenic variant (43 vs 48 years, p=0.035); also, MINAS carriers had a higher overall rate of cancer (90.9% vs 66.7%, OR=5.0, p=0.018). The proportion of MINAS carriers with multiple primary cancers was no greater than the proportion with such cancers among patients with a single pathogenic or likely pathogenic variant (4.5% vs 5.8%, p=1.0). Additionally, investigations of NCCN guidelines for gene combinations identified in our MINAS cohort revealed surveillance conflicts including timing of risk-reducing surgery, cancer screening frequency within the same organ system, strategies for chemoprevention.
Discussion: Our study found no evidence to suggest a biologic synergistic relationship among these cancer-causing genes. The MINAS mutation carriers had their first cancers at a significantly younger age and also had a significantly higher rate of developing cancer; however, they had the same rate of developing multiple primary cancers as carriers of just one cancer-causing gene. These results suggest that the presence of mutations in more than one cancer-causing gene may affect an individual's likelihood of developing cancer and their time of onset, but it does not appear to increase the likelihood of an individual developing multiple primary cancers. However, these results should be viewed with caution due to the limited number of MINAS mutation carriers. NCCN guidelines do not provide recommendations regarding how to manage patients with multiple cancer-causing gene mutations, leaving physicians to try to follow conflicting guidelines with no clear approach. Therefore, for patients with MINAS mutations, it might be hypothesized that physicians should prioritize the most aggressive surveillance strategy for each site.

Keywords: MINAS, cancer, hereditary cancer, cancer predisposition, NCCN
2. International Hereditary Cancers Congress Double Trouble or Not? Clinical Impact of Multiple Cancer Predisposition Gene Variants in Hereditary Cancer Testing Ali Babazade[1], Yusuf Bahap[1], Mehmet Ali Ergun[1] [1]Gazi University, Department of Medical Genetics Background Multigene panel testing has become widespread as part of the evaluation process for hereditary cancers. Unlike traditional approaches that involve sequential testing of single genes, multigene panels evaluate several cancer susceptibility genes in one simultaneous test to determine an individual's inherited risk of developing cancer. While this method of testing has been very helpful in identifying at-risk patients who may have otherwise gone undetected, it has also identified a new, well recognized clinical entity — individuals who possess a pathogenic or likely pathogenic (P/LP) variant in more than

one cancer predisposition gene; these individuals are classified as Multilocus Inherited Neoplasia Allele Syndrome (MINAS). Despite the increasing recognition of MINAS, the clinical implications of harboring multiple cancer susceptibility variants remain poorly understood. One of the major questions confronting clinicians is whether the interaction of multiple genetic variants leads to a synergistic effect on cancer development that compounds the patient's cancer risk, or if they exist independently without a multiplicative effect on cancer risk. Current clinical practice guidelines, such as those developed by the National Comprehensive Cancer Network (NCCN), address single-gene variant carrier issues but do not address the specific challenges faced by clinicians when managing MINAS patients. Therefore, the purpose of this study was to describe the clinical characteristics of MINAS patients compared to those of patients with a single genetic variant and to identify the existing guideline conflicts that complicate their clinical care. Methods We retrospectively reviewed results from 4,315 patients who underwent genetic testing for hereditary cancer using NGS panels. The P/LP variants used in this study were classified according to American College of Medical Genetics and Genomics (ACMG) and ClinGen ENIGMA (BRCA1/BRCA2) guidelines and only P/LP variants were used in this study. MINAS was defined as patients possessing P/LP variants in two or more different cancer predisposition genes. The comparison group consisted of patients with a single P/LP variant. Data obtained from medical records included clinical information, such as age, sex, cancer diagnoses, age at first cancer diagnosis, number of primary cancers, histopathologic features, and family cancer history. Statistical analyses between MINAS patients and single-gene variant patients used Fisher's Exact Test for categorical data and the Mann-Whitney U test for continuous data. Odds Ratios (OR) with 95% Confidence Intervals (CI) were calculated to assess the strength of association between clinical features and the presence of multiple genetic variants. Systematic analysis of NCCN Guidelines for Genetic/Familial High-Risk Assessment was performed to identify gaps and conflicts in recommendations that apply to the combination of genes seen in our MINAS patients. Results Study Population The study population comprised 641 patients: 18 (2.8%) classified as MINAS and 623 (97.2%) as single-variant carriers. The MINAS cohort demonstrated diverse gene combinations, with BRCA1 and/or BRCA2 present in 50% of cases. No significant differences emerged in baseline characteristics including sex distribution, mean age at diagnosis, family history of cancer, consanguinity, or comorbidity prevalence between groups. Figure 1 | Study Population distribution Breast Cancer Prevalence Analysis Cancer type distribution revealed significantly elevated breast cancer rates in MINAS patients compared to single-variant carriers (77.8% vs. 47.8%; OR=3.82, 95% CI: 1.21-12.05; p=0.015), a finding that remained robust after FDR correction. Gene-stratified subgroup analysis demonstrated particularly striking associations among BRCA carriers. BRCA1-MINAS patients exhibited significantly higher breast cancer prevalence than single BRCA1 carriers (83.3% vs. 30.5%; OR=11.4; p=0.014), and combined BRCA1/2-MINAS patients showed markedly elevated breast cancer rates compared to single BRCA carriers (88.9% vs. 40.1%; OR=11.93; p=0.005), both surviving FDR correction. Figure 2 | Breast Cancer Prevalence: MINAS vs Single-Variant Carrier Driver Gene and Phenotype Concordance Analysis Driver gene analysis in MINAS patients identified a clear phenotype-driving gene in 83.3% of cases. BRCA1/2 served as the primary driver in 44.4% of patients. Phenotype concordance analysis revealed three distinct patterns: "both genes" pattern (22.2%) where patients developed cancers consistent with both genes' expected phenotypes, suggesting additive effects; "single gene dominant" pattern (61.1%) where one gene's phenotype predominated; and "atypical" pattern (16.7%) where observed cancers did not match either gene's expected phenotype. NCCN Guideline Conflicts Among MINAS patients, 13 gene combinations involved two genes with established NCCN surveillance recommendations. Four combinations had conflicting recommendations for the same organ system: BRCA1+BRCA2 and BRCA1+PALB2 showed 5–10 year differences in RRSO timing, ATM+BRCA1 differed in MRI recommendation strength, and MLH1+APC had discordant colonoscopy start ages, upper endoscopy timing/focus, and chemoprevention agents. The remaining nine combinations involved genes affecting different organ systems, for which guidelines provide no framework for managing cumulative cancer risk. Gene 1 Gene 1 Recommendation Gene 2 Gene 2 Recommendation Conflict

BRCA1 RRSO 35-40y; annual breast MRI 30y BRCA2 RRSO 40-45y; annual breast MRI 30y 5-year difference in RRSO timing BRCA1 RRSO 35-40y; discuss RRM PALB2 RRSO 45-50y; discuss RRM 10-year difference in RRSO timing ATM Mammogram 40y; consider MRI 30-35y BRCA1 Annual MRI 30y; RRSO 35-40y Consider vs recommend MRI MLH1 Colonoscopy 20-25y q1-2y; upper endoscopy 30-35y; aspirin APC Colonoscopy late teens q1-2y; upper endoscopy 20-25y; sulindac Colonoscopy start age; upper endoscopy timing; chemoprevention CHEK2 Mammogram 40y; consider MRI 30-35y; thyroid exam RET Thyroid ultrasound; calcitonin; consider thyroidectomy Both have thyroid recommendations; no guidance on combined risk CHEK2 Mammogram 40y; consider MRI 30-35y MLH1 Colonoscopy 20-25y q1-2y; hysterectomy+BSO 40y Different organ focus ATM Mammogram 40y; consider MRI 30-35y PMS2 Colonoscopy 30-35y q1-3y; hysterectomy+BSO 50y Different organ focus BRCA2 RRSO 40-45y; annual breast MRI 30y MITF Annual dermatologic exam; ocular exam Different organ focus BRCA1 RRSO 35-40y; annual breast MRI 30y APC Colonoscopy late teens q1-2y; upper endoscopy 20-25y Different organ focus CHEK2 Mammogram 40y; consider MRI 30-35y APC Colonoscopy late teens q1-2y; upper endoscopy 20-25y Different organ focus BRIP1 RRSO 45-50y APC Colonoscopy late teens q1-2y; upper endoscopy 20-25y Different organ focus BRIP1 RRSO 45-50y CHEK2 Mammogram 40y; consider MRI 30-35y Different organ focus APC Colonoscopy late teens q1-2y; upper endoscopy 20-25y ATM Mammogram 40y; consider MRI 30-35y Different organ focus Table 1 | NCCN Guideline Conflicts in MINAS Patients for Different Gene Combinations RRSO, risk-reducing salpingo-oophorectomy; RRM, risk-reducing mastectomy; MRI, magnetic resonance imaging; BSO, bilateral salpingo-oophorectomy Discussion This study provides comprehensive clinical characterization of MINAS patients compared to single-variant carriers in hereditary cancer syndromes. Our findings demonstrate that MINAS patients exhibit significantly elevated breast cancer risk, particularly among BRCA carriers. The identification of driver genes in the majority of MINAS cases provides preliminary evidence for phenotype prediction in patients with multiple pathogenic variants. These findings underscore the clinical importance of comprehensive genetic testing and individualized risk assessment approaches for MINAS patients, who may face elevated cancer risks not adequately addressed by current single-gene focused guidelines. The study's limitations include small MINAS sample size, retrospective design, warranting prospective validation in larger, multi institutional cohorts to inform development of specific clinical management guidelines for this emerging patient population. The identified NCCN guideline conflicts highlight a significant gap in current clinical practice frameworks. Guidelines do not provide recommendations for managing patients with multiple cancer-causing gene mutations, leaving clinicians to navigate conflicting single-gene recommendations without clear direction. Based on our findings, we hypothesize that physicians managing MINAS patients should prioritize the most aggressive surveillance strategy for each anatomical site, coordinate risk-reducing surgeries to minimize total procedures while respecting gene-specific timing considerations, and consider multidisciplinary tumor board consultation for complex cases. Prospective studies in larger, multi-institutional cohorts are warranted to establish evidence-based management guidelines specifically addressing MINAS patients.

[Abstract:0267]

Diagnostic Pitfalls in CNV Analysis: True and False Positive Findings in Two Breast Cancer Cases

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Objective: The transition from phenotype driven testing to multigene panels in hereditary breast cancer (HBC) has increased the detection of incidental germline variants. Although BRCA1/2 remain the primary targets, variants in other cancer predisposition genes, including Lynch Syndrome associated genes, are increasingly identified. While the association between Lynch Syndrome and breast cancer risk remains debated, accurate variant interpretation is critical for appropriate clinical management. Copy number variation (CNV) analysis of PMS2 is particularly challenging due to high homology with the PMS2CL pseudogene and technical limitations of probe-based assays. In this study we evaluated the concordance of multiple CNV detection methods in two breast cancer cases with suspected PMS2 deletions. Both patients' clinical findings, family history and genetic test results were assessed. The genetic analyses included next-generation sequencing (NGS) for small variants, NGS based CNV algorithms, conventional MLPA, digital MLPA, and visual inspection of NGS read alignments at MLPA probe binding sites.

Case: The first case was a 31-year-old woman diagnosed with unilateral mixed invasive ductal carcinoma and minimal family history. A heterozygous multi-exon PMS2 deletion (exons 1–6) was detected by NGS based CNV analysis and confirmed by both MLPA platforms, supporting a true-positive result. Although the deletion was detected incidentally, its confirmation led to a change in clinical management, including the initiation of Lynch Syndrome specific surveillance.
The second case involved a woman diagnosed with breast cancer at the age of 47, with a strong family history of breast, colorectal, pancreatic, and prostate cancers. NGS analysis did not identify pathogenic single-nucleotide variants or BRCA1/2 CNVs. Both conventional and digital MLPA methods suggested a heterozygous single-exon PMS2 deletion. However, visual NGS read inspection identified a single-nucleotide variant (PMS2 n.26G>C) at the shared probe ligation site, preventing probe ligation and mimicking a deletion. This finding was reclassified as a technical artifact.

Conclusion: While multigene panel testing enables the detection of clinically relevant incidental findings in breast cancer patients, it also increases the risk of false-positive results, particularly in PMS2 CNV analysis. This study underlines that single-probe MLPA deletions should be interpreted with caution, and concordance between MLPA platforms does not exclude ligation-site errors. Visual inspection of NGS data represents a cost effective and essential validation strategy to ensure accurate diagnosis and avoid inappropriate clinical management.

Keywords: Breast Cancer, CNV Analysis, Digital MLPA, PMS2

Diagnostic Pitfalls in CNV Analysis: True and False Positive Findings in Two Breast Cancer Cases Efe Deniz ŞENGÜN, Ceren Damla DURMAZ Hacettepe University Faculty of Medicine The transition from phenotype driven testing to multigene panels in hereditary breast cancer (HBC) has increased the detection of incidental germline variants. Although BRCA1/2 remain the primary targets, variants in other cancer predisposition genes, including Lynch syndrome associated genes, are increasingly identified. While the association between Lynch syndrome and breast cancer risk remains debated, accurate variant interpretation is critical for appropriate clinical management. Copy number variation (CNV) analysis of PMS2 is particularly challenging due to high homology with the PMS2CL pseudogene and technical limitations of probe-based assays. In this study, we assessed clinical

findings, family history and genetic test results of two breast cancer cases with suspected PMS2 deletions and evaluated the concordance of multiple CNV detection methods in these patients. PMS2 is a mismatch repair gene associated with Lynch syndrome, accounting for approximately 5–25% of cases. CNV detection in PMS2 is particularly challenging due to the presence of highly homologous pseudogenes. Because of these challenges, PMS2 CNV analysis frequently depends on probe based techniques such as Multiplex Ligation-Dependent Probe Amplification (MLPA), which have their own technical limitations. MLPA is a gold standard method for detecting CNVs. It uses probe pairs composed of two oligonucleotides that bind to adjacent target DNA sequences, creating a ligation site between them. Successful hybridization allows ligation, enabling subsequent PCR amplification. The resulting amplicons are quantified by capillary electrophoresis in conventional MLPA or by NGS based read counting in digital MLPA. However, a single nucleotide mismatch at the ligation site prevents probe ligation, leading to amplification failure and potentially mimicking a deletion at that locus. The genetic analyses conducted in this study are next-generation sequencing (NGS) for small variants, NGS based CNV algorithms, conventional MLPA, digital MLPA, and visual inspection of NGS read alignments at MLPA probe binding sites. The first case was a 31 year-old woman diagnosed with unilateral mixed invasive ductal carcinoma. Immunohistochemistry showed estrogen receptor positivity, progesterone receptor positivity, and negative HER-2 expression. Her family history was unremarkable except for a malignancy of unknown primary origin in her father. A heterozygous multi exon PMS2 deletion (exons 1–6) was detected by NGS based CNV analysis and confirmed by both conventional and digital MLPA, supporting a true positive result. Although the deletion was detected incidentally, its confirmation led to a change in clinical management, including the initiation of Lynch Syndrome specific surveillance. The second case involved a 70 year-old woman diagnosed with breast cancer at age 47, treated with unilateral mastectomy followed by adjuvant chemotherapy and radiotherapy. Her family history was notable for multiple cancer diagnoses. Her sister, diagnosed with breast cancer at 47 and colorectal cancer at 57, had previously undergone genetic testing revealing a variant of uncertain significance (VUS) in ATM (c.7522G>A, p.Gly2508Arg); which was not present in our patient. One deceased brother had pancreatic cancer, and several relatives were affected by leukemia, lung, prostate, and breast cancers. NGS analysis in our patient identified a VUS in MSH6 (c.3248A>G, p.Glu1038Gly), with no other pathogenic single nucleotide variants or BRCA1/2 CNVs detected. Subsequent digital MLPA suggested a heterozygous single exon PMS2 deletion which was also detected by coventional MLPA. However, visual NGS read inspection identified a single nucleotide variant (PMS2 n.26G>C) at the shared probe ligation site, preventing probe ligation and mimicking a deletion. This finding was reclassified as a technical artifact preventing a false diagnosis of Lynch Syndrome in this patient and avoiding unnecessary testing and surveillance. While multigene panel testing enables the detection of clinically relevant incidental findings in breast cancer patients, it also increases the risk of false-positive results, particularly in PMS2 CNV analysis. This study underlines that single probe MLPA deletions should be interpreted with caution, and concordance between MLPA platforms does not exclude ligation site errors. Visual inspection of NGS data represents a cost effective and essential validation strategy to ensure accurate diagnosis and avoid inappropriate clinical management.

[Abstract:0270]

Immune Checkpoint Inhibitor Therapy in Cutaneous Malignancies Arising from Inherited Genetic Syndromes: A Four-Case Series

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Objective: Cutaneous squamous cell carcinoma (cSCC) is a common non-melanoma skin cancer, most often associated with cumulative ultraviolet exposure in older individuals. In contrast, cSCC developing in the setting of inherited genetic syndromes tends to occur at a younger age and follows a more aggressive clinical course. This case series presents four patients with syndromic cutaneous malignancies, primarily cSCC, highlighting their clinicopathological features and emphasizing the importance of early recognition and multidisciplinary management.

Case-1:A 42-year-old male patient with a diagnosis of xeroderma pigmentosum had been followed for recurrent cSCC involving the scalp and facial regions since 2011. Genetic analysis of the patient revealed a mutation c.155C>G of XB18PF in the XPC gene.During this period, he underwent multiple local excisions with close dermatologic surveillance. In May 2023, disease progression occurred with cervical lymph node and pulmonary metastases.Pembrolizumab was initiated, and after two cycles, radiological assessment according to RECIST version 1.1 demonstrated a near-complete response.Treatment was discontinued due to poor compliance. Despite early cessation, restaging one year later confirmed a sustained response without disease progression.

Case-2:A 23-year-old male patient with a confirmed diagnosis of epidermolysis bullosa was diagnosed with cSCC of the left wrist in October 2023.Following local excision, he was initially followed without evidence of residual or recurrent disease.In May 2025, metastatic recurrence developed, and nivolumab therapy was initiated.Radiological evaluation according to RECIST version 1.1 demonstrated a near-complete response.The patient remains on nivolumab with sustained clinical and radiological disease control.(The patient's mutation test results have been requested and will be added when the patient brings them in.)

Case-3:A 21-year-old female patient with Omenn syndrome had been followed since 2020 for recurrent cSCC of the right eyelid and underwent multiple local excisions.Genetic analysis of the patient revealed the c.256_257delAA mutation in the RAG1 gene. In 2024, metastatic disease developed. Pembrolizumab was initiated; however, disease progression was observed after two cycles.Subsequent treatment with paclitaxel plus carboplatin resulted in further progression after four cycles.The patient later developed intra-abdominal infection complicated by sepsis and died due to infectious complications.

Case-4:A 22-year-old female patient with xeroderma pigmentosum had a history of multiple cutaneous malignancies, including basal cell carcinoma and cSCC, treated with repeated local excisions. Genetic analysis of the patient revealed the mutation C.764C>G(p.S255)(P.Ser255Ter) in the XPC gene.In September 2025, she was diagnosed with metastatic malignant melanoma. Combined nivolumab and ipilimumab therapy was initiated, resulting in a partial response.Treatment was subsequently de-escalated to nivolumab monotherapy, which is ongoing with sustained disease control.*

Conclusion: This four-case series illustrates the aggressive and heterogeneous nature of cutaneous malignancies arising in patients with inherited genetic syndromes. Immune checkpoint inhibitors provided meaningful clinical benefit in several cases, including durable responses despite limited treatment exposure. However, treatment efficacy varied according to the underlying genetic disorder and immune status. These findings underscore the importance of individualized management, early diagnosis, and multidisciplinary care in this high-risk patient population.

Keywords: *Immune checkpoint inhibitors, Inherited genetic syndromes, Malignant cutaneous neoplasms*
Immune Checkpoint Inhibitor Therapy in Cutaneous Malignancies Arising from Inherited Genetic Syndromes: A Four-Case Series Esra Asarkaya, Abdurrahman Aykut, Ertuğrul Bayram, Tolga Köseci, Ismail Oguz Kara Cukurova Univercity Faculty in Medicine Objective: Cutaneous squamous cell carcinoma (cSCC) is a common non-melanoma skin cancer, most often associated with cumulative ultraviolet exposure in older individuals. In contrast, cSCC developing in the setting of inherited genetic syndromes tends to occur at a younger age and follows a more aggressive clinical course. This case series presents four patients with syndromic cutaneous malignancies, primarily cSCC, highlighting their clinicopathological features and emphasizing the importance of early recognition and multidisciplinary management. Case-1:A 42-year-old male patient with a diagnosis of xeroderma pigmentosum had been followed for recurrent cSCC involving the scalp and facial regions since 2011. Genetic analysis of the patient revealed a mutation c.155C>G of XB18PF in the XPC gene.During this period, he underwent multiple local excisions with close dermatologic surveillance. In May 2023, disease progression occurred with cervical lymph node and pulmonary metastases.Pembrolizumab was initiated, and after two cycles, radiological assessment according to RECIST version 1.1 demonstrated a near-complete response.Treatment was discontinued due to poor compliance. Despite early cessation, restaging one year later confirmed a sustained response without disease progression. Case-2:A 23-year-old male patient with a confirmed diagnosis of epidermolysis bullosa was diagnosed with cSCC of the left wrist in October 2023.Following local excision, he was initially followed without evidence of residual or recurrent disease.In May 2025, metastatic recurrence developed, and nivolumab therapy was initiated.Radiological evaluation according to RECIST version 1.1 demonstrated a near-complete response.The patient remains on nivolumab with sustained clinical and radiological disease control.(The patient's mutation test results have been requested and will be added when the patient brings them in.) Case-3:A 21-year-old female patient with Omenn syndrome had been followed since 2020 for recurrent cSCC of the right eyelid and underwent multiple local excisions.Genetic analysis of the patient revealed the c.256_257delAA mutation in the RAG1 gene. In 2024, metastatic disease developed. Pembrolizumab was initiated; however, disease progression was observed after two cycles.Subsequent treatment with paclitaxel plus carboplatin resulted in further progression after four cycles.The patient later developed intra-abdominal infection complicated by sepsis and died due to infectious complications. Case-4:A 22-year-old female patient with xeroderma pigmentosum had a history of multiple cutaneous malignancies, including basal cell carcinoma and cSCC, treated with repeated local excisions. Genetic analysis of the patient revealed the mutation C.764C>G(p.S255)(P.Ser255Ter) in the XPC gene.In September 2025, she was diagnosed with metastatic malignant melanoma. Combined nivolumab and ipilimumab therapy was initiated, resulting in a partial response.Treatment was subsequently de-escalated to nivolumab monotherapy, which is ongoing with sustained disease control. Conclusion: This four-case series illustrates the aggressive and heterogeneous nature of cutaneous malignancies arising in patients with inherited genetic syndromes. Immune checkpoint inhibitors provided meaningful clinical benefit in several cases, including durable responses despite limited treatment exposure. However, treatment efficacy varied according to the underlying genetic disorder and immune status. These findings underscore the importance of individualized management, early diagnosis, and multidisciplinary care in this high-risk patient population. Keywords: Immune checkpoint inhibitors, Inherited genetic syndromes, Malignant cutaneous neoplasms*

[Abstract:0272]

Beyond Classical Lynch Syndrome: Atypical Tumor Spectrum, Novel Variants, and Diagnostic Challenges

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Background: Lynch syndrome (LS) is an inherited cancer predisposition syndrome caused by germline pathogenic variants in DNA mismatch repair (MMR) genes. While LS is classically associated with colorectal cancer (CRC) and cancers of the endometrium, ovary, stomach, small bowel, urinary tract, biliary tract, brain (usually glioblastoma), skin, pancreas, prostate and breast. However clinical spectrum is increasingly recognized as heterogeneous, including atypical tumor presentations and tumor morphology. Therefore, comprehensive evaluation of clinical features, tumor spectrum, and underlying genetic variants in Lynch syndrome is essential to improve diagnosis, surveillance strategies, and personalized management.

Methods: Between 2021 and 2026, 56 individuals from 50 unrelated families who were referred to our department for hereditary cancer susceptibility assessment and identified as carrying pathogenic, likely pathogenic, or variants of uncertain significance (P/LP/VUS) in MMR genes were included. Germline variants in MLH1, MSH2, MSH6, PMS2, and EPCAM were analyzed from peripheral blood samples using next-generation sequencing (NGS) and multiplex ligation-dependent probe amplification (MLPA). Clinical data included gender, age at diagnosis, tumor type, family history and MSI status. Variant classification was performed according to ACMG criteria.

Results: Age at diagnosis was available for 50 patients (mean 43.7; median 45, range 8–80). Among 39 patients with at least one pathogenic or likely pathogenic (P/LP) MMR variant most frequently involving MLH1 (n=28). In 30 patients, P/LP variants were identified by NGS, including nonsense, frameshift, splice-site, in-frame deletion, and missense variants, whereas large deletions or duplications were identified in 10 patients exclusively by MLPA analysis, underscoring its diagnostic importance. Among the 16 patients with variants of uncertain significance (VUS), one harbored a splice-site variant, while the remaining variants were missense. Family studies showed that five variants segregated in respective families, while three variants were recurrent across unrelated families, supporting their clinical relevance. In addition, three variants not previously reported in ClinVar were identified and classified as novel.
Notably, several patients with germline MMR varians presented with atypical malignancies, including testicular seminoma, parotid gland duct carcinoma, medullary rectal carcinoma, thyroid carcinoma, chronic lymphocytic leukemia and cancer of unknown primary.

An 8-year-old patient carrying an MLH1 exon 16–17 deletion exhibited clinical features highly suggestive of constitutional mismatch repair deficiency (CMMRD). Although biallelic pathogenic variants could not be confirmed, alternative explanations cannot be entirely excluded.
Two patients harbored dual germline variants involving MMR and non-MMR cancer predisposition genes, raising important considerations for clinical interpretation and surveillance strategies.
Importantly, in one family diagnosed with LS demonstrated microsatellite-stable (MSS) tumors, underscoring that MSS status alone may be insufficient for excluding hereditary MMR deficiency.

Conclusion: Our findings expand the clinical and molecular spectrum of Lynch syndrome, emphasizing atypical

presentations, early-onset disease, novel and recurrent variants, and molecular discordance. In the patient with suspected constitutional mismatch repair deficiency (CMMRD), MLH1 promoter methylation analysis was planned to further clarify the underlying molecular mechanism. These results support a comprehensive diagnostic approach integrating germline testing, epigenetic analysis, and careful genotype–phenotype correlation to optimize patient management and surveillance.

Keywords: *Lynch syndrome, Atypical presentation, Constitutional mismatch repair deficiency (CMMRD), Microsatellite-stable (MSS) tumors, Multilocus inherited neoplasia allele syndrome (MINAS)*

Beyond Classcal Lynch Syndrome: Atypcal Tumor Spectrum, Novel Varants, and Dagnostc Challenges Sümeyra Özbolat[1], Şule Altıner[1], Halil Gürhan Karabulut[1], Nüket Yürür Kutlay[1], Sadiye Ekinci[1], Timur Tuncalı[1], Ezgi Gökpınar İli[1], Hatice Ilgın Ruhi[1] [1]Department of Medical Genetics, Faculty of Medicine, Ankara University, Ankara, Türkiye

Abstract Background: Lynch syndrome (LS) s an nherted cancer predsposton syndrome caused by germlne pathogenc varants n DNA msmatch repar (MMR) genes. LS s classcally assocated wth colorectal cancer (CRC) and cancers of the endometrum, ovary, stomach, small bowel, urnary tract, blary tract, bran (usually globlastoma), skn, pancreas, prostate and breast. However clncal spectrum s ncreasngly recognzed as heterogeneous, ncludng atypcal tumor presentatons and tumor morphology. Therefore, comprehensve evaluaton of clncal features, tumor spectrum, and underlyng genetc varants n Lynch syndrome s essental to mprove dagnoss, survellance strateges, and personalzed management. Methods: Between 2021 and 2026, 56 ndvduals from 50 unrelated famles who were referred to our department for heredtary cancer susceptbl ty assessment and dentfed as carryng pathogenc, lkely pathogenc, or varants of uncertan sgnfcance (P/LP/VUS) n MMR genes were ncluded. Germlne var ants n MLH1, MSH2, MSH6, PMS2, and EPCAM were analyzed from perpheral blood samples usng next-generaton sequencng (NGS) and multplex lgaton dependent probe amplfcaton (MLPA). Clncal data ncluded gender, age at d agnos s, tumor type, fam ly h story and MSI status. Varant classfcaton was performed accordng to ACMG crtera. Results: Age at dagnoss was avalable for 50 patents (mean 43.7; medan 45, range 8–80). Among 39 patents wth at least one pathogenc or lkely pathogenc (P/LP) MMR varant most frequently nvolvng MLH1 (n=28). In 30 patents, P/LP varants were dentfed by NGS, ncludng nonsense, frameshft, splce-ste, n-frame deleton, and mssense varants, whereas large deletons or duplcatons were dentfed n 10 patents exclusvely by MLPA analyss, underscorng ts dagnostc mportance. Among the 16 patents wth varants of uncertan sgnfcance (VUS), one harbored a splce-ste varant, whle the remanng varants were mssense. Famly studes showed that fve varants segregated n respectve famles, whle three varants were recurrent across unrelated famles, supportng ther clncal relevance. In addton, three var ants not prev ously reported n ClnVar were dentf ed and class f ed as novel. Notably, several patents wth germlne MMR varans presented wth atypcal malgnances, ncludng testcular semnoma, parotd gland duct carcnoma, medullary rectal carcnoma, thyrod carcnoma, chronc lymphocytc leukema and cancer of unknown prmary. An 8-year-old patent carryng an MLH1 exon 16–17 deleton exhbted clncal features hghly suggestve of const tutonal msmatch repar defcency (CMMRD). Although ballelc pathogenc varants could not be confrmed, alternatve explanatons cannot be entrely excluded. cons deratons Two patents harbored dual germlne varants nvolvng MMR and non-MMR cancer predsposton genes, rasng mportant for cln cal nterpretaton and surve llance strateg es. Importantly, n one famly dagnosed wth LS demonstrated mcrosatell te-stable (MSS) tumors, underscorng that MSS status alone may be nsuffcent for excludng heredtary MMR defcency. Concluson: Our fndngs expand the clncal and molecular spectrum of Lynch syndrome, emphaszng atypcal presentatons, early onset dsease, novel and recurrent varants, and molecular dscordance. In the patent wth suspected const tutonal msmatch repar defcency (CMMRD), MLH1 promoter methylaton analyss was planned to further clarfy the underlyng molecular mechansm. These results support a comprehensve dagnostc approach ntegratng germlne testng, ep genetc analys s, and careful genotype–phenotype correlaton to optmze patent management and survellance. Introduction Lynch syndrome (LS) is the

most common hereditary colorectal cancer predisposition syndrome, caused by germline pathogenic variants in DNA mismatch repair (MMR) genes, including MLH1, MSH2, MSH6, PMS2, and deletions involving 1 EPCAM (Lynch et al.). The classical tumor spectrum of LS primarily encompasses colorectal and endometrial cancers, with increased risks for gastric, ovarian, small bowel, hepatobiliary, urinary tract, and certain brain tumors (Dominguez-Valentin et al.; Møller et al.). Despite well-established diagnostic criteria, increasing evidence suggests that the phenotypic spectrum of LS extends beyond these classical malignancies. Rare extracolonic tumors, early-onset presentations, microsatellite-stable (MSS) tumors in confirmed carriers, and complex genotypic patterns such as dual germline variants pose diagnostic and clinical management challenges (Basdhar et al.; Latham et al.; McGuigan et al.; Ferrer-Avargues et al.). In addition, the growing use of next generation sequencing has led to the identification of numerous variants of uncertain significance (VUS) and previously unreported (novel) variants, complicating genotype–phenotype interpretation and genetic counseling (Richards et al.). Furthermore, large deletion and duplications in MMR genes or EPCAM, has been demonstrated in a substantial number of LS patients. Constitutional mismatch repair deficiency (CMMRD), a rare autosomal recessive condition caused by biallelic MMR pathogenic variants, represents another diagnostic challenge, particularly in pediatric patients presenting with early-onset colorectal cancer or brain tumors (Wimmer et al.; Aronson et al.; Colas et al.). Distinguishing between classical LS, suspected CMMRD, and Lynch-like syndromes requires careful integration of molecular, clinical, and family history data (Martínez Roca et al.; Boland et al.). In this study, we present a comprehensive analysis of 56 individuals evaluated for hereditary cancer predisposition, focusing on atypical tumor presentations, novel germline MMR variants, suspected CMMRD, dual germline variant carriers, and the occurrence of MSS tumors in confirmed LS cases. By highlighting these non-classical features, we aim to expand the current understanding of LS-associated tumor heterogeneity and emphasize the importance of nuanced interpretation in hereditary cancer diagnostics. Methods Patients who were referred to our tertiary medical genetics center for hereditary cancer susceptibility assessment between 2021 and 2026 were evaluated. Germline DNA extracted from peripheral blood samples was analyzed using next-generation sequencing (NGS) for single-nucleotide variants and small insertions/deletions (first step), and multiplex ligation-dependent probe amplification (MLPA**) for large deletions and duplications (second step). 56 individuals from 50 unrelated families in which P/LP/VUS variants were detected in the MMR genes constituted the sample group of this study. In addton, segregaton analyss was recommended for frst-degree relatves of patents, partcularly those n whom pathogenc or lkely pathogenc (P/LP) varants were dentfed. Indvduals who provded nformed consent were subsequently enrolled n the study and follow-up program. Variants were classified according to ACMG criteria (Richards et al.). Clinical data included sex, age at diagnosis, tumor type, family history, and microsatellite instability (MSI) status when available. All procedures were conducted in accordance with the Declaration of Helsinki. Genetic testing was performed as part of routine clinical care, and all patients provided informed consent for molecular analyses and the use of anonymized clinical data for research purposes. All data obtained were retrospectively evaluated within the scope of this study. *Genes ncluded n the heredtary cancer NGS panel: APC, ATM, BARD1, BLM, BMPR1A, BRCA1, BRCA2, PMS2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FH, FLCN, MLH1, MRE11, MSH2, MSH6, MUTYH, NBN, NTHL1, PALB2, POLD1, POLE, PRSS1, PTEN, RAD50, RAD51C, RAD51D, SLX4, SMAD4, STK11, TP53, VHL ** Genes ncluded n the MLPA panel: MLH1, MSH2, EPCAM Results 1. Cohort Characteristics The study cohort comprised 50 unrelated probands with total 56 individuals, including 25 males and 31 females. Age at cancer dagnoss ranged from 8 to 80 years, wth a substantal proporton of early-onset cases (≤30 years), accountng for 12 of 56 patents (21.4%). Four patients presented in childhood or young adulthood. The most frequent presenting malignancy was colorectal cancer, followed by breast cancer, endometrial cancer, gastric cancer, and prostate cancer. Less common presentations included rectal cancer, urothelial carcinoma, astrocytoma, testicular seminoma, thyroid carcinoma, parotid gland duct carcinoma, chronic lymphocytic leukemia, and carcinoma of unknown primary. A*

subset of probands presented with synchronous or metachronous tumors, most commonly involving colorectal and endometrial cancer. Family histories were frequently positive for malignancy and showed a broad tumor spectrum. The most commonly reported cancers among relatives were colorectal, endometrial, breast, gastric, prostate and brain tumors, often with early ages of onset. Several pedigrees also included hematologic malignancies, pancreatic cancer, hepatocellular carcinoma, lung and urologic cancers, reflecting marked intrafamilial heterogeneity. 2 Notably, a number of probands lacked a strong family history of cancer despite carrying pathogenic or likely pathogenic MMR variants, highlighting the importance of molecular testing even in the absence of classical pedigree patterns. Conversely, some individuals with extensive cancer histories carried variants of uncertain significance, emphasizing the complexity of genotype phenotype interpretation in clinical practice. 2. Genetic Findings Pathogenic or likely pathogenic (P/LP) germline variants were identified in the majority of probands (n=39), most frequently affecting MLH1, followed by MSH2, MSH6, PMS2, and EPCAM. Addtonally famly studes showed that fve varants segregated n respectve famles, whle three varants were recurrent across unrelated famles, supportng ther clncal relevance. A smaller subset of individuals carried variants of uncertain significance (VUS), predominantly in MSH6 and PMS2 (n=17). Among all detected variants, missense substitutions constituted the most common variant type, particularly within the VUS group. In contrast, nonsense, frameshift, and splice-site variants were predominantly classified as pathogenic or likely pathogenic. Several in-frame deletions were also observed and interpreted as pathogenic based on functional and clinical evidence. Importantly, large copy number variations were detected in multiple probands using MLPA, including heterozygous deletions and duplications involving MLH1(n=9) and EPCAM (n=1). These copy number variants accounted for a substantial proportion of pathogenic findings and would not have been identified by sequencing alone, underscoring the diagnostic value of complementary deletion/duplication analysis in Lynch syndrome testing. Variants in MLH1 represented the largest proportion of P/LP findings, including recurrent missense, nonsense and frameshift variants, as well as multi-exon deletions or duplications. Pathogenic MSH2 variants included missense, truncating and splice site alterations, while MSH6 and PMS2 variants were more frequently missense in nature and often classified as VUS. Overall, most clncally actonable varants n our cohort were truncatng n nature, whle varants of uncertan sgnfcance were predomnantly mssense changes wth lmted functonal or segregaton evdence. Ths pattern reflects the persstent challenges of varant nterpretaton, partcularly for MSH6 and PMS2, where genotype–phenotype correlatons are st ll not clearly establshed. The dstrbuton of germlne MMR varants accordng to gene and varant type, stratfed by pathogencty, s shown n F gure 1. All clinical and genetic data presented in Table 1. Figure 1: Distribution of variants by pathogenicity and variant type in Lynch syndrome–associated genes. This figure illustrates the distribution of variants identified in the MLH1, MSH2, MSH6, PMS2, and EPCAM genes according to pathogenicity and variant type. For each gene, two bars are shown: solid bars represent pathogenic/likely pathogenic (P/LP) variants, and hatched bars represent variants of uncertain significance (VUS). Each bar is stacked by variant type (missense, nonsense, frameshift, splice-site/intronic, in-frame deletion, large deletion, and large duplication). The total number of variants for each gene and pathogenicity group is indicated above the corresponding bar. The color-coded legend at the bottom denotes variant types, while the legend on the right distinguishes pathogenicity groups. Table 1: Clncal and Genetc Characterstcs of the Study Cohort 3 4 Case ID Sex Age at Diagnosis Family History (Tumors / Earliest Age) MSI Status Tumor Type Gene Variant Variant Type ACMG Class Second Gene Second Variant Second ACMG Class* 1 M 20 CRC, prostate, brain tumor / 20y No data Testicular seminoma MLH1 c.848A>G p.Tyr283Cys (rs201931669) Missense Likely pathogenic – – – 2 M 54 CRC / 50y MSI-H, dMMR (MLH1, PMS2 loss) CRC MLH1 c.2059C>T p.Arg687Trp Missense Likely pathogenic – – – 3 M 29 CRC / 29y MSI, PMS2 loss Rectal cancer PMS2 c.2192_2196del p.Leu731Cysfs*3 Frameshift Pathogenic – – – 4 M 67 CRC / 50y MSI-Low CRC MLH1 c.2059C>T p.Arg687Trp Missense Likely pathogenic – – – 5 F 52 Prostate, CRC, breast, leukemia / 7y MSI-H, dMMR CRC MLH1 c.676C>T p.Arg226Ter Nonsense Pathogenic – – – 6 F 16 CRC / 35y No data CRC MLH1 c.1852_1854del*

*p.Lys618del In-frame deletion Pathogenic – – – 7 M 47 No family history MSI-Low, MSH2/MSH 6 loss CRC MSH2 c.942+3A>T Splice-site Pathogenic – – – 8 F 32 CRC / 32y MSS CRC MLH1 c.2059C>T p.Arg687Trp Missense Likely pathogenic – – – 9 F 32 CRC / 32y No data Colonic polyp MSH2 c.210dup p.Gly71Argfs*1 1*** Frameshift Likely pathogenic – – – 10 F 50 Breast, bladder, cervix, Hurthle cell, brain tumors MSI, MSH6 loss Endometrial cancer MSH6 c.3261dup p.Phe1088Leufs* 5 Frameshift Pathogenic – – – 11 F 58 No family history MSI-H CRC PMS2 c.706-2A>T Splice-site Pathogenic – – – 12 M 32 No family history No data; high-grade glial tumor Astrocytom a MSH6 c.1316A>G p.Asp439Gly Missense Likely pathogenic – – – 13 F 28 CRC & endometrial cancer / 27y MSI-H, dMMR CRC + Endometrial cancer MLH1 c.676C>T p.Arg226Ter Nonsense Pathogenic – – – 14 M 43 No family history No data Parotid duct carcinoma PMS2 c.1261C>T p.Arg421Ter Nonsense Pathogenic NTHL1 c.244C> T p.Gln82T er Pathogen ic 15 F 67 Breast cancer / 49y No data Breast cancer MSH2 c.2086C>T p.Pro696Ser Missense Likely pathogenic – – – 16 F 26 CRC, breast / 26y MSI-H, dMMR CRC MLH1 c.1685A>C p.Gln562Pro Missense Pathogenic – – – 17 M 8 Brain tumor at 15y; relatives with gastric cancer MSI-H CRC+ Brain tm MLH1 Exons 16–17 deletion Large deletion Pathogenic – – – 18 M 67 CRC, gastric, bladder / 50y MSS CRC+ Gastric cancer MLH1 Exons 1–19 deletion Large deletion Pathogenic – – – 19 M 62 Breast, endometrial, prostate / 31y MSI-H CRC MLH1 c.1852_1854del p.Lys618del In-frame deletion Pathogenic – – – 20 M 36 Prostate, CRC / 36y MSI-Low CRC MSH2 c.2041C>T p.Gln681Ter Nonsense Pathogenic – – – 21 M 49 Pancreatic, CRC / 46y MSI-H CRC + Urothelial cancer MSH2 c.1667T>C p.Leu556Ser Missense Pathogenic – – – 22 M 51 Prostate, breast, CRC / 51y MSI CRC + Gastric cancer MLH1 c.1154G>A p.Arg385His Missense Likely pathogenic – – – 23 M 49 CRC, brain tumor / 30y MSI-H CRC MLH1 c.676C>T p.Arg226Ter Nonsense Pathogenic – – – 24 F 58 CRC / 58y No data Breast cancer (IDC) MSH2 c.1774A>G p.Met592Val Missense Likely pathogenic – – – 25 M 31 CRC / 31y No data CRC MLH1 c.1649T>C p.Leu550Pro Missense Pathogenic – – – 26 M 52 Breast cancer in family / 52y No data Breast and Lung ca MLH1 Exons 16–17-18 19 duplication Large duplication VUS – – – 27 M 29 Unknown malignancies / 29y MSI CUP MLH1 c.1459C>T p.Arg487Ter Nonsense Pathogenic – – – 28 F 23 CRC, liposarcoma, IPMN, cervix MSI-Low CRC MSH2 c.1165C>T p.Arg389Ter Nonsense Pathogenic – – – 29 F 43 CRC & endometrial / 30y MSI-H CRC MLH1 c.883A>G p.Ser295Gly Missense Pathogenic – – – 30 M 30** Multiple malignancies No data Asymptoma tic MLH1 c.1042_1043delT T p.Leu348fs*13 Frameshift Likely pathogenic BRCA1 c.5236C >A p.His174 6Asn Likely pathogen ic 31 F 63 Rectal & CRC MSI-H Medullary rectal cancer MLH1 c.844G>A p.Ala282Thr Missense VUS – – – 32 M 80 Brain & testicular tumors No data Prostate cancer MLH1 c.116+4C>G*** İntronic VUS – – – 33 F 55 Breast, endometrial, CRC, laryngeal, CLL No data CLL PMS2 c.187G>A p.Val63Met Missense VUS – – – 34 F 37 CRC & brain cancer No data Thyroid cancer PMS2 c.71A>G p.His24Arg Missense VUS – – – 5 Table 1: Ths table summarzes the demographc, clncal, molecular, and genetc features of 56 carryng germlne mutatons n the MMR genes, ncludng sex, age at cancer dagnoss, famly hstory of malgnances, tumor type, mcrosatell te nstabl ty (MSI) status, dentfed germlne varants n msmatch repar (MMR) genes, varant type, and ACMG classfcaton. Large genomc rearrangements detected by MLPA, ncludng deletons and duplcatons, are also reported. Cases wth dual germlne varants and segregaton analyses are ndcated where avalable. ACMG, Amercan College of Medcal Genetcs and Genomcs; CLL, chronc lymphocytc leukema; CRC, colorectal cancer; CUP, cancer of unknown prmary; dMMR, defcent msmatch repar; HCC, hepatocellular carcnoma; IDC, nvasve ductal carcnoma; IPMN, ntraductal papllary mucnous neoplasm; MMR, msmatch repar; MSI, mcrosatell te nstabl ty; MSI-H, microsatellite instability–high; MSI-L, microsatellite instability–low; MSS, mcrosatell te stable; NA, not avalable; VUS, varant of uncertan sgnfcance. *: All variant classifications were based on ACMG criteria applied in the diagnostic laboratory at the time of analysis. **: Age at genetic testing ***: Bolded varants marked ndcate novel varants not prevously reported n ClnVar, HGMD, or populaton databases. 3. Novel Variants Three germline MMR variants identified in this cohort were not previously reported in ClinVar at the time of analysis and were therefore considered novel. These variants were detected in MSH2, MLH1, and PMS2, and exhibited distinct clinical and molecular characteristics (Table 1). The MSH2 frameshift*

*variant, p.Gly71Argfs*11, was identified in Case 9 presenting with a colonic polyp and a strong family history of early-onset colorectal cancer. Given the truncating nature of the variant, its predicted loss-of-function effect, and the concordant clinical phenotype, this variant was classified as likely pathogenic and considered highly consistent with Lynch syndrome. In contrast, the MLH1 splice-region variant (c.116+4C>G) was detected in Case 32 with prostate cancer and a family history of brain and testicular tumors. The late age of onset, atypical tumor spectrum, and lack of tumor molecular data limited 35 F 55 Endometrial, breast, HCC No data Asymptoma tic MSH2 c.2501C>T p.Ala834Val Missense VUS – – – 36 F 50 Breast, gastric, prostate, leukemia No data Breast cancer MSH6 c.3248A>G p.Glu1083Gly Missense VUS – – – 37 F 42 Breast, laryngeal cancer No data Breast cancer (IDC) PMS2 c.1999G>A p.Glu667Lys Missense VUS – – – 38 M 62 No family history MSS CRC PMS2 c.446A>T p.Tyr149Phe*** Missense VUS – – – 39 F 59 Lymphoma, gastric, CRC, prostate No data Endometrial + Breast cancer MSH6 c.1120A>G p.Lys374Glu Missense VUS – – – 40 F 60 No family history No data Breast cancer PMS2 c.1883G>A p.Arg628Gln Missense VUS – – – 41 F 29 Breast, prostate No data Breast cancer MSH6 c.1574G>C p.Ser525Thr Missense VUS – – – 42 F 60 CRC No data CRC MSH6 c.2182A>G p.Lys728Glu Missense VUS – – – 43 F 56 Breast cancer MSS Breast cancer MSH6 c.1857A>C p.Glu619Asp Missense VUS – – – 44 F 65 Breast, colorectal, prostate / 34y No data Gastric cancer MSH2 c.1453A>C p.Met485Leu Missense VUS – – – 45 F 40 Breast, CRC, HCC / 32y No data Breast cancer MSH6 c.3425C>T p.Thr1142Met Missense VUS – – – 46 F 47 Breast, CRC, endometrial, pancreatic, adrenal No data Breast cancer MSH6 c.1069G>A p.Asp357Asn Missense VUS – – – 47 F 45 CRC & breast / 40y MSI-Low CRC EPCAM Exon 9 deletion Large deletion Pathogenic – – – 48 M 36 CRC MSI-H CRC MLH1 Exon 11deletion Large deletion Pathogenic – – – 49 M 43 Multiple cancers / 23y MSI-H CRC MLH1 Exon 11deletion Large deletion Pathogenic – – – 50 M 37 CRC, endometrial / 37y MSI-H CRC MLH1 Exons 3–4–5 deletion Large deletion Pathogenic – – – 51 M 12** Segregation(son of Case 49) No data Asymptoma tic MLH1 Exon 11 deletion Large deletion Pathogenic – – – 52 F 35** Segregation(sibling of Case 28) No data Asymptoma tic MSH2 c.1165C>T p.Arg389Ter Nonsense Pathogenic – – – 53 M 40** Segregation (sibling of Case 16) No data Asymptoma tic MLH1 c.1685A>C p.Gln562Pro Missense Pathogenic – – – 54 F 61** Segregation (sibling of Case 16) No data Asymptoma tic MLH1 c.1685A>C p.Gln562Pro Missense Pathogenic – – – 55 F 33** Segregation (mother of Case 17) No data Asymptoma tic MLH1 Exons 16–17 deletion Large deletion Pathogenic – – – 56 F 13** Segregation (sibling of Case 17) No data Asymptoma tic MLH1 Exons 16–17 deletion Large deletion Pathogenic – – – definitive genotype–phenotype attribution. Consequently, this variant was classified as a variant of uncertain significance, emphasizing the need for functional assays and segregation studies to clarify its clinical relevance. The PMS2 missense variant (c.446A>T, p.Tyr149Phe) was observed in Case 38 with colorectal cancer and microsatellite stable tumor status, without a reported family history of malignancy. The absence of MMR deficiency in the tumor, together with the missense nature of the variant and limited supporting evidence, rendered its association with Lynch syndrome uncertain. 4. Atypical Tumor Spectrum Although Lynch syndrome is most commonly associated with colorectal and endometrial cancers, it is also linked to an expanded set of extracolonic tumors including gastric, urinary tract, pancreatic, and certain brain neoplasms (e.g., glioblastoma) due to germline mismatch repair (MMR) gene defects (MLH1, MSH2, MSH6, PMS2, and EPCAM) (Dominguez-Valentin et al.; Bansdhar et al.; Karamurzin et al.). In clinical practice, however, some malignancies present that lie outside this traditional spectrum, requiring careful interpretation that integrates germline findings with tumor molecular phenotypes and family history. In our cohort, Case 1 carrying a likely pathogenic MLH1 variant developed testicular seminoma. Whle solated cases of testcular sem noma have been descrbed n ndvduals wth Lynch syndrome, ths tumor type s not part of the classcal Lynch spectrum, and current evdence supportng a drect assocaton wth MMR defcency s lmted (Dum et al.; Lobo et al.). Nevertheless, when such atypical presentations occur in carriers of pathogenic MMR variants, evaluating the tumor for microsatellite instability (MSI) and loss of MMR protein expression can help distinguish coincident disease from an MMR driven tumor, given the actionable implications for surveillance and management (Farha et al.; Latham*

*et al.). Case 12 with a likely pathogenic MSH6 variant presented with astrocytoma. CNS tumors, including astrocytomas, have been reported in Lynch syndrome, though they are rare compared to the more frequently observed glioblastomas among mutation carriers (Lynch et al.; Alkhotani et al.). This suggests that while astrocytoma is an uncommon presentation, it should not be dismissed in the context of hereditary MMR deficiency, particularly when clinical history or family patterns raise suspicion. Case 14 with a pathogenic PMS2 variant developed parotid gland duct carcinoma, a salivary gland malignancy. These tumors are not considered part of the Lynch syndrome tumor spectrum. Nonetheless, salivary gland carcinomas have been described sporadically in hereditary cancer contexts, and given the potential clinical relevance of MMR status, performing MSI and/or MMR immunohistochemistry on such tumors may provide insight into whether MMR deficiency contributes to their pathogenesis (Alves et al.). A particularly informative case (Case 27) involved a pathogenic MLH1 truncating variant (p.Arg487Ter) in a proband with carcinoma of unknown primary (CUP). The tumor testing revealed MSI-high status and loss of MLH1 expression, lending strong support to an etiological role for mismatch repair deficiency in the tumor's development. The integration of germline genotype and concordant tumor phenotype in CUP underscores the importance of comprehensive molecular testing when faced with diagnostically ambiguous presentations. In contrast, several probands with atypical tumors such as medullary rectal carcinoma, thyroid carcinoma, and chronic lymphocytic leukemia carried variants of uncertain significance. For instance, thyroid cancer, is not considered part of the classical Lynch spectrum and may occur coincidentally in carriers of MMR variants (Aswath et al.; Stulp et al.). Similarly, hematologic malignancies like CLL remain uncommon in MMR-deficient syndromes and warrant cautious interpretation. These observations indicate that atypical presentations must be interpreted within the broader clinical and molecular context, and that not all rare tumors in carriers of MMR gene variants are necessarily driven by the underlying germline defect (Bochtler et al.). 5. Suspected CMMRD Case Constitutional mismatch repair deficiency (CMMRD) is a rare, autosomal recessive cancer predisposition syndrome caused by biallelic pathogenic variants in the mismatch repair genes (MLH1, MSH2, MSH6, or PMS2). It is characterized by very early-onset malignancies, most commonly colorectal cancer, high-grade brain tumors, hematologic malignancies, and features overlapping with neurofibromatosis type 1 (NF1) (Aronson et al.; Boland et al.; Colas et al.; Wimmer et al.). Unlike classical Lynch syndrome, which follows an autosomal dominant inheritance pattern, CMMRD typically presents in childhood or adolescence and is associated with a markedly aggressive tumor phenotype. In our cohort, Case 17 was diagnosed with colorectal cancer at 8 years, followed by a primary brain tumor at 15 years. Remarkably the age and tumor profiles are highly suggestive of CMMRD. Tumor analysis demonstrated MSI-high status and loss of MLH1 and PMS2 expression, consistent with mismatch repair deficiency. Germline testing revealed a heterozygous MLH1 exon 16–17 deletion. Although biallelic pathogenic variants could not be molecularly confirmed, the clinical presentation strongly supported a CMMRD-like phenotype. Notably, the patient's mother and sister carried the same MLH1 deletion, yet neither had developed malignancy, a pattern more compatible with heterozygous Lynch syndrome carriers rather than classical CMMRD. However, 6 the extremely early onset of cancer in the proband suggested the possible presence of a second, undetected pathogenic event, such as a deep intronic variant, epigenetic alteration, or somatic inactivation affecting the second MLH1 allele. To further investigate this possibility, methylation analysis of the MLH1 promoter was initiated to explore epigenetic silencing as a potential "second hit." Such mechanisms have been reported in suspected CMMRD cases where standard germline sequencing fails to identify biallelic variants (Wimmer et al.). 6. Dual Germline Variants Two probands in our cohort were found to carry dual germline pathogenic or likely pathogenic variants, involving both a mismatch repair (MMR) gene and an additional hereditary cancer predisposition gene. Such multilocus findings complicate risk assessment and challenge traditional single-syndrome surveillance models (Ferrer-Avargues et al.). Case 30 with no personal history of cancer at the time of referral, carried a likely pathogenic MLH1 frameshift variant (p.Leu348fs*13) together with a likely pathogenic BRCA1 missense variant (p.His1746Asn). In addition to the proband being*

asymptomatic, a hereditary predisposition to cancer was suspected due to his family history of various malignancies. The coexistence of MLH1 and BRCA1 variants raises important considerations for cancer surveillance, as the risk profile may extend beyond Lynch-associated tumors to include breast, ovarian, and other BRCA1-related malignancies. Another patient, Case 14, dagnosed wth parotd gland duct carcnoma at 43 years, carred a pathogenc truncatng varant n PMS2 (p.Arg421Ter) together wth a pathogenc NTHL1 nonsense varant (p.Gln82Ter). Interestngly, no strong famly hstory of cancer was documented. Whle NTHL1 s pr mar ly assoc ated w th an autosomal recess ve tumor pred spos ton syndrome, and current evdence does not support a sgnfcantly ncreased cancer rsk n heterozygous carrers, famles should st ll be nformed about the potental r sk for future generatons n whom b allelc mutatons may occur. From a preventve med c ne perspectve, approprate genetc counselng, famly screenng, and long-term follow-up are essental to ensure early detecton and rsk management. As salvary gland carcnomas are not cons dered part of the class cal Lynch spectrum, tumor-based MMR testng may help clarfy whether MMR defcency plays a bologcal role n such cases (Alves et al.). The presence of multiple germline cancer-predisposing variants has been described as multilocus inherited neoplasia allele syndrome (MINAS). Individuals with MINAS often show heterogeneous tumor spectra, variable penetrance, and overlapping cancer risks that cannot be sufficiently addressed by syndrome-specific guidelines alone (McGuigan et al.; Yuen et al.; Whitworth et al.). Instead, surveillance strategies should be individualized, including gene-specific recommendations, personal tumor history, and family context. From a clinical perspective, dual variant carriers require careful counseling, as risk estimates may be additive or synergistic, and management plans should be tailored accordingly. Importantly, these findings also highlight the value of broad multigene panel testing in uncovering complex hereditary cancer profiles that would otherwise remain undetected (Ferrer-Avargues et al.). 7. Microsatellite-Stable Tumors in Lynch Syndrome Although microsatellite instability (MSI) and mismatch repair deficiency are hallmarks of Lynch syndrome associated tumors, a subset of confirmed germline MMR variant carriers in our cohort developed microsatellite-stable (MSS) cancers. This finding is clinically important, as MSS status is often assumed to argue against Lynch syndrome in routine practice (Farha et al.). In our series, two probands with pathogenic or likely pathogenic MMR variants, particularly in MLH1, presented with MSS colorectal or extracolonic tumors. These cases illustrate that MSS status alone does not exclude Lynch syndrome, especially when supported by germline pathogenic variants and compatible family histories. Discussion In this cohort of individuals referred for hereditary cancer evaluation, we observed a wide range of phenotypic and molecular spectrum of mismatch repair (MMR) defcency, many of whch extended beyond the classcal Lynch syndrome phenotype. While colorectal and endometrial cancers remained the most frequent presentations, a consderable number of probands exhibited early-onset disease, atypical tumor types, microsatellite-stable malignancies, and complex germline variant profiles. These real-world observatons hghlght the growng heterogenety of Lynch syndrome and suggest that rgd, tumor-based dagnostc algorthms may not adequately capture all clncally relevant cases. One of the most remarkable features of our cohort was the high proportion of early-onset cancers, including cases diagnosed in childhood and young adulthood. This finding strengthens the importance of considering hereditary cancer syndromes even in pediatric and adolescent patients, particularly when colorectal or brain tumors are involved. The suspected CMMRD case is only one example for the diagnostic challenges in this age group. Although biallelic pathogenic variants could not be confirmed, the combination of colorectal cancer at 8 years, a primary brain tumor at 15 years, and MSI-high tumors with MLH1/PMS2 loss strongly suggested an underlying constitutional MMR defect. Similar scenarios have been described in the literature, where clinical phenotypes precede definitive molecular confirmation, emphasizing the need for extended genetic and epigenetic investigations, including promoter methylation and deep intronic variant analysis (Aronson et al.; Boland et al.; Colas et al.; Wimmer et al.). This case 7 highlights the diagnostic challenges associated with distinguishing early-onset Lynch syndrome from CMMRD. While the molecular criteria for CMMRD require confirmation of biallelic pathogenic variants, real-world cases often present with incomplete

genetic evidence despite a highly suggestive clinical phenotype. In such scenarios, careful longitudinal surveillance, extended molecular testing, and multidisciplinary evaluation remain essential (Aronson et al.; Colas et al.; Wimmer et al.). Another mportant aspect of our fndngs was the presence of novel germlne MMR varants assocated wth heterogeneous clncal presentatons. Whle the MSH2 frameshft varant was lnked to a classcal Lynch syndrome phenotype, the MLH1 splce-regon and PMS2 mssense varants were observed n patents wth later-onset or MSS tumors and lmted famly hstores. In the absence of functonal evdence, tumor-based correlaton, or segregaton data, such newly dentfed varants should be nterpreted wth cauton to avo d over-attrbuton of pathogencty. Overall, these three novel varants demonstrated marked clncal heterogenety, rangng from Lynch-consstent presentatons to atypcal and nconclusve phenotypes. Ths varabl ty underscores that newly dentfed germlne alteratons do not nherently mply clncal causal ty, hghlghtng the need for comprehensve clncal correlaton, tumor molecular proflng, and functonal valdaton to ensure accurate nterpretaton and appropr ate genetc counselng. The observation of atypical tumor types further supports the concept of phenotypic variability in MMR-related cancer predisposition. Seminoma, astrocytoma, parotid duct carcinoma, thyroid cancer, chronic lymphocytic leukemia, and carcinoma of unknown primary are not considered core Lynch-associated malignancies (Farha et al.; Latham et al.; Alkhotani et al.; Alves et al.). Although we have discussed VUS variants separately before, it is extremely important not to overlook Lynch syndromes presenting with atypical clinical features. For tumors such as CUP with concordant MSI-high status and MLH1 loss, the link to MMR deficiency appears biologically reasonable (Cox et al.). In contrast, for parotid gland carcinomas and thyroid cancers, which lack established associations with Lynch syndrome, tumor-based MMR testing may be particularly useful in distinguishing coincidental disease from MMR-driven oncogenesis (Alves et al.). Variants of uncertain significance represented another major interpretive challenge. Most VUS in our cohort were missense variants in MSH6 and PMS2, often accompanied by MSS tumors and incomplete family histories (Richards et al.). These findings highlight the limitations of current classification frameworks for non-truncating variants and support to the need for functional assays and also tumor molecular profiling. Importantly, the coexistence of atypical tumors and VUS should not automatically imply causality, and alternative genetic or environmental explanations must always be considered. The presence of MSS tumors in confirmed MMR variant carriers has important clinical implications. Although MSI is a hallmark of Lynch syndrome–associated cancers, our data confirm that MSS tumors can also occur in this context. Several mechanisms may explain this phenomenon, including biological heterogeneity, technical limitations in MSI testing, or tumorigenesis through MMR-independent pathways (Farha et al.; Dominguez-Valentin et al.). Biological heterogeneity may result in tumors that do not develop classical MMR deficiency despite the presence of a germline variant. In addition, technical factors such as tumor sampling issues, assay sensitivity, or methodological limitations may lead to false-negative MSI results (Dominguez-Valentin et al.). Furthermore, some tumors in MMR variant carriers may arise through alternative oncogenic pathways unrelated to MMR dysfunction. From a clinical perspective, these findings are highly relevant for patient management. Reliance solely on tumor MSI status to guide genetic testing may lead to missed Lynch syndrome diagnoses, particularly in individuals with suggestive personal or family histories. Germline testing should therefore be considered in appropriate clinical contexts, even when tumors are MSS. Overall, our findings underscore the need for a comprehensive diagnostic approach integrating germline genetic testing, tumor molecular characteristics, and pedigree analysis. Such an approach is essential to avoid underdiagnosis, ensure accurate risk assessment, and provide appropriate surveillance for affected individuals and their relatives Finally, the identification of dual germline variant carriers shows the growing complexity of hereditary cancer genetics in the period of multigene panel testing. These patents/famles may beneft from personalzed rsk assessment approaches that ntegrate recommendatons from multple gene-specfc gudelnes, rather than beng managed wthn a sngle heredtary cancer framework (McGuigan et al.; Yuen et al.; Whitworth et al.). Overall, our findings emphasize that Lynch syndrome is not a uniform clinical entity but rather a heterogeneous condition with

variable genetic, molecular, and phenotypic manifestations. Recognizing this diversity is crucial for accurate diagnosis, appropriate surveillance, and effective genetic counseling. In addton, segregaton analyses planned n famles wth dentfed varants were partcularly mportant for rsk stratfcaton of frst-degree relatves, enablng the dentfcaton of asymptomatc carrers who may beneft from ndvdualzed survellance and preventve strateges. From a preventve medcne perspectve, early genetc dentfcaton allows the mplementaton of talored cancer screenng programs, potentally leadng to earler dagnoss, reduced morbdty, and mproved clncal outcomes. Furthermore, ncorporatng genetcally at-rsk ndvduals nto structured survellance protocols facl tates tmely nterventons, nformed reproductve counselng, and long-term r sk management, hghlghtng the crtcal role of famly-based genetc evaluaton n heredtary cancer syndromes. Future studies integrating comprehensive germline testing, tumor sequencing, and functional analyses will be essential to refine genotype phenotype correlations and improve patient care in hereditary cancer syndromes. Conclusion 8 In conclusion, our findings illustrate the broad and heterogeneous clinical spectrum of Lynch syndrome, extending beyond its classical tumor profile. The presence of atypical malignancies, a suspected CMMRD case with childhood-onset cancers, and patients carrying dual germline variants highlight the complexity of hereditary cancer risk assessment and the need for individualized clinical management. Importantly, microsatellite-stable tumors in confirmed MMR variant carriers emphasize that MSS status alone should not be used to exclude Lynch syndrome in clinically suggestive cases. Our cohort also point to the diagnostic value of MLPA in detecting large genomic rearrangements that may be missed by sequencing alone, as well as the importance of cautious interpretation of novel variants. By documenting previously unreported MMR variants and rare tumor presentations, this study contributes to the expanding Lynch syndrome literature. References • Alkhotan, A., Ambus, I., Velsher, L., Rowsell, C., & Keth, J. (2016). IDH1 mutated low grade astrocytoma occurrng n MSH2 mutated Lynch syndrome fam ly. Human Pathology: Case Reports, 6, 45-47. • Alves, G. M. T. T., Sever no-Lazo, R. J. G., do Amaral-Slva, G. K., da Motta Slvera, F. M., & de Vasconcelos Carvalho, M. (2024). DNA msmatch repar system expresson n salvary gland tumors: A Systematc Revew. Medcna Oral, Patología Oral y Crugía Bucal, 29(5), e655. • Aronson, M., et al. (2022). Diagnostic criteria for constitutional mismatch repair deficiency (CMMRD) syndrome. Journal of Medical Genetics. • Aswath, K., Welch, J., Gubb, S., Veeraraghavan, P., Avadhanula, S., Gara, S. K., ... & Klubo-Gwezdznska, J. (2021). Co-Occurrence of Famlal Non-Medullary Thyrod Cancer (FNMTC) and Heredtary Non-Polyposs Colorectal Cancer (HNPCC) Assocated Tumors—A Cohort Study. Fronters n Endocrnology, 12, 653401. • Bochtler, T., Haag, G. M., Schott, S., Kloor, M., Krämer, A., & Müller-Tdow, C. (2018). Hematologcal malgnances n adults w th a fam ly pred spos ton. Deutsches Ärzteblatt Internatonal, 115(50), 848. • Bansdhar, B. J. (2012). Extracolonc manfestatons of lynch syndrome. Clncs n Colon and Rectal Surgery, 25(02), 103-110. • Boland, C. R. (2013). The mystery of mismatch repair deficiency: Lynch or Lynch-like? Gastroenterology. • Colas, C., Guerrini-Rousseau, L., Suerink, M., Gallon, R., Kratz, C. P., Ayuso, É., et al. (2024). ERN GENTURIS guideline on constitutional mismatch repair deficiency: diagnosis, counselling and management. ERN GENTURIS Guideline (PDF). • Cox, R. E., Chakrabart , S., & Cox Jr, R. E. (2022). A Carcnoma of Unknown Prmary (CUP) Patent Treated Successfully Wth Immunotherapy Upon Recognton of Defcent Msmatch Repar Sgnature on Lqud Bopsy: A Case Report. Cureus, 14(7). • Domnguez-Valentn, M., Haupt, S., Seppälä, T. T., Sampson, J. R., Sunde, L., Bernsten, I., ... & Moller, P. (2023). Mortal ty by age, gene and gender n carrers of pathogenc msmatch repar gene varants recevng survellance for early cancer dagnoss and treatment: a report from the prospectve Lynch syndrome database. EClncalMedcne, 58. • Dum, D., Steurer, S., Smon, R., Zmmermann, P. V., Burandt, E., Claudtz, T. S., ... & Fraune, C. (2021). Msmatch repar defcency occurs very rarely n semnomas. Translatonal Andrology and Urology, 10(3), 1048. • Farha, N., et al. (2021). Using immunohistochemistry to expand the spectrum of Lynch syndrome–associated tumors. Cancers (Basel). • Ferrer-Avargues, R., et al. (2021). Co-occurrence of germline pathogenic variants in different cancer predisposition genes. Cancer Reports. • Karamurzin, Y., et al. (2012). Unusual DNA mismatch repair–deficient tumors in Lynch syndrome. Human Pathology. • Latham, A., Srnvasan, P., Kemel, Y., Sha, J., Bandlamud, C., Mandelker, D., ... &

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[Abstract:0277]

Beyond the Breast: Guideline-Based Assessment of Germline Variants in Non-BRCA Cancer Predisposition Genes Identified in Breast Cancer Patients

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Objective: Genetic evaluation of breast cancer patients has traditionally focused on BRCA1 and BRCA2; however, a substantial proportion of patients with personal or familial cancer histories remain BRCA1/2-negative. With the widespread use of next-generation sequencing (NGS) panels, germline variants in non-BRCA cancer predisposition genes are increasingly identified. This study aimed to evaluate the frequency of germline variants detected in selected non-BRCA cancer predisposition genes among breast cancer patients and to assess their potential clinical management implications based on current guideline recommendations

Materials-Methods: A retrospective, single-center study was conducted including breast cancer patients who underwent NGS-based hereditary cancer panel testing between May 2021 and December 2025. A total of 1,166 breast cancer patients were evaluated, and the study cohort was composed of BRCA1/2-negative individuals harboring variants in ATM, CHEK2, PALB2, BARD1, RAD51C, RAD51D, and BRIP1. Variants were classified as pathogenic/likely pathogenic (P/LP) or variants of uncertain significance (VUS). In patients with multiple variants, the presence of at least one P/LP variant was sufficient for classification as P/LP-positive. Clinically meaningful variants were evaluated for their potential clinical management implications according to NCCN Guidelines (version 2.2026). BRCA1/2 copy number analysis (MLPA) was performed when clinically indicated and was not mandatory for study inclusion.

Results: Among the 1,166 breast cancer patients, 208 BRCA1/2-negative individuals were found to carry germline variants in the selected non-BRCA gene set. Of these, 31 patients (14.9%) harbored at least one P/LP variant, while 177 patients (85.1%) carried only VUS. P/LP variants were most frequently identified in ATM, CHEK2, and PALB2. Based on NCCN guideline recommendations, P/LP variants were associated with potential implications for clinical management, primarily related to intensified cancer surveillance strategies. Variants classified as VUS were not considered in the evaluation of potential clinical management implications.

Conclusion: A clinically meaningful proportion of BRCA1/2-negative breast cancer patients carry germline P/LP variants in non-BRCA cancer predisposition genes with guideline-based management relevance. These findings emphasize the importance of distinguishing clinically meaningful variants from VUS and support the integration of expanded gene panels into hereditary cancer evaluation. Importantly, in a breast cancer patient, germline genetic findings guide not only breast-specific surveillance but also comprehensive, patient-centered cancer risk management, highlighting the evolving role of germline genetics beyond the breast.

Keywords: *Breast cancer, Germline variants, NCCN guidelines, Non-BRCA genes*

Beyond the Breast: Gudelne-Based Assessment of Germlne Varants n Non BRCA Cancer Predsposton Genes Identfed n Breast Cancer Patents Süheyla Emre1, Ilker Nihat Okten2, Filiz Özen1 1Istanbul Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Department of Medical Genetics, Istanbul, Turkey 1Istanbul Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Department of Medical Oncology, Istanbul, Turkey Introduction Genetic evaluation of breast cancer patients has historically focused on BRCA1 and BRCA2 genes due to their well-established association with hereditary breast and ovarian cancer syndromes. However, a substantial proportion of patients with personal or familial cancer histories remain BRCA1/2-negative. With the widespread adoption of next-

generation sequencing (NGS)-based multigene panels, germline variants in non-BRCA cancer predisposition genes are increasingly identified. Many of these genes confer moderate to high cancer risk and are associated not only with breast cancer but also with susceptibility to multiple malignancies. Consequently, germline genetic findings may influence broader, patient-centered cancer risk management strategies beyond breast-specific surveillance. Evaluating the clinical relevance of such variants in real-world cohorts is essential to optimize hereditary cancer assessment and guideline-based management. Materials and Methods This retrospective, single-center study included breast cancer patients who underwent NGS based hereditary cancer panel testing between May 2021 and December 2025. A total of 1,166 breast cancer patients were evaluated. The study cohort was composed of BRCA1/2 negative individuals harboring germline variants in selected non-BRCA cancer predisposition genes, including ATM, CHEK2, PALB2, BARD1, RAD51C, RAD51D, and BRIP1. Patients with BRCA1 or BRCA2 variants, those without detectable variants, and those carrying variants in genes outside the predefined target gene set were excluded. Variants were classified as pathogenic/likely pathogenic (P/LP) or variants of uncertain significance (VUS) based on clinical laboratory reports. In patients with multiple variants, the presence of at least one P/LP variant was sufficient for classification as P/LP-positive. Clinically meaningful variants were evaluated for their potential clinical management implications in accordance with NCCN Guidelines version 2.2026. This assessment focused on possible modifications in cancer surveillance strategies, risk-reducing considerations, and cascade genetic testing recommendations. BRCA1/2 copy number analysis using multiplex ligation-dependent probe amplification (MLPA) was performed when clinically indicated and was not mandatory for study inclusion. Results Among the 1,166 breast cancer patients evaluated, 208 BRCA1/2-negative individuals were found to carry germline variants in the selected non-BRCA gene set. Of these, 31 patients (14.9%) harbored at least one P/LP variant, while 177 patients (85.1%) carried only VUS. P/LP variants were most frequently identified in ATM, CHEK2, and PALB2 genes. Variants classified as VUS were observed across multiple genes and were not included in the assessment of potential clinical management implications. According to NCCN guideline recommendations, the identification of P/LP variants was associated with potential implications for clinical management, primarily related to intensified cancer surveillance strategies. These included consideration of earlier initiation of breast cancer screening and the addition of annual breast magnetic resonance imaging in selected patients. In addition, the presence of clinically meaningful germline variants supported recommendations for cascade genetic testing in at-risk family members. No management implications were assigned to VUS findings. Discussion This study demonstrates that a clinically meaningful proportion of BRCA1/2-negative breast cancer patients carry germline P/LP variants in non-BRCA cancer predisposition genes with guideline-based management relevance. While BRCA1/2 mutations remain central to hereditary breast cancer evaluation, variants in genes such as ATM, CHEK2, and PALB2 contribute additional information that may inform personalized cancer risk assessment. Importantly, distinguishing clinically meaningful variants from VUS is essential to avoid inappropriate clinical decision-making. The findings highlight the evolving role of expanded gene panels in hereditary cancer testing and underscore the importance of interpreting genetic results within established guideline frameworks. In breast cancer patients, germline genetic findings guide not only breast-specific surveillance but also comprehensive, patient-centered cancer risk management. Conclusion A significant subset of BRCA1/2-negative breast cancer patients harbor germline P/LP variants in non-BRCA cancer predisposition genes with potential guideline-based management implications. These results support the integration of expanded hereditary cancer panels into routine clinical practice and emphasize the role of germline genetics in shaping holistic cancer risk management beyond the breast.

[Abstract:0282]

Defining informative family history patterns for hereditary cancer panel testing: which features matter most?

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Objective: The identification of eligible individuals for referral to hereditary cancer panel testing remains challenging in clinical practice. Although established family history characteristics that increase the risk for certain hereditary cancer syndromes have been identified, diverse family histories that do not clearly meet the guideline-based criteria are frequently encountered in clinical practice. Identifying family history characteristics that reliably indicate hereditary cancer susceptibility regardless of cancer type is therefore essential to improve test selection and optimize diagnostic yield. The aim of the study was to define family history characteristics associated with hereditary cancer predisposition to determine criteria for NGS-based panel testing, and to identify the factors associated with hereditary cancer-related variant detection.
Materials-Methods: The retrospective study was conducted in 192 patients who presented to the Medical Genetics Department of Gülhane Training and Research Hospital between 2024 and 2025 for NGS-based hereditary cancer panel testing. Three-generation family histories were reviewed. Genetic findings were examined using chi-square or Fisher's exact tests. Independent predictors were assessed by forward conditional logistic regression analysis.
Results: Variants in cancer susceptibility genes consistent with hereditary predisposition were detected in 58 of 192 patients (30.2%). The number of affected relatives was not significantly associated with the detection of hereditary cancer–associated variants, and this lack of association persisted when relatives were stratified by degree of relatedness (all p>0.05).
In contrast, the most important predictive factor was found to be the age at cancer diagnosis within the family. The likelihood of identifying hereditary cancer–associated variants was significantly higher in individuals with a family history of cancer diagnosed before the age of 50 years (p=0.006). The presence of a single first-degree relative with early-onset cancer was associated with an approximately twofold increased risk of identifying associated variants (OR=2.241, 95% CI: 1.047–4.796; p=0.038). When two or more first-degree relatives were affected, this risk increased by up to sevenfold (OR=7.435, 95% CI: 1.357–40.731; p=0.021). This pattern is consistent with a clear dose–response relationship. Early-onset cancer in second-degree relatives was also associated with increased risk, although the magnitude of this effect was more modest (OR=2.836, 95% CI: 1.156–6.959; p=0.023).
Cancers with biological relevance in first-degree relatives were significantly associated with hereditary cancer–related variants (p=0.034), whereas unrelated cancer types were not. Lineage distribution showed no meaningful effect. Cancers limited to second- or third-degree relatives provided limited additional predictive value.
Conclusion: Our study shows that the presence of a relative diagnosed with cancer at an early age—especially among first-degree relatives—is the most significant indicator of hereditary cancer predisposition. The risk of identifying hereditary cancer predisposing variants increases dramatically if one first-degree relative is diagnosed with cancer before age 50 years. This risk rises sharply as the number of early-onset cases increases. By comparison, the total number of affected relatives and lineage distribution alone appear to add little predictive value. An age-focused assessment centered on first-degree relatives therefore offers a practical and clinically relevant framework for guiding referral to NGS-based hereditary cancer panel testing, beyond syndrome-specific considerations.

Keywords: *Family history, Hereditary cancer, NGS-based panel testing*

DEFINING INFORMATIVE FAMILY HISTORY PATTERNS FOR HEREDITARY CANCER PANEL TESTING: WHICH FEATURES MATTER MOST? Oya Demirkaya, Deniz Torun*, Yusuf Tunca* *Department of Medical Genetics, Gülhane Training and Research Hospital, Ankara, Turkey 1. Introduction Hereditary cancer syndromes are defined as clinical conditions in which the risk of cancer development is increased in individuals as a result of germline genetic variants, and this increased risk exhibits inherited patterns among family members.1 With the increasing use of next-generation sequencing (NGS)-based multigene panels in diagnostic processes, an advance in the assessment of genetic predisposition has been provided. However, this technological advance has led to significant complexity in clinical practice regarding decision making processes for selecting suitable patient populations and ensuring accurate clinical indications for genetic tests. Although current guidelines define genetic testing indications for specific hereditary cancer syndromes, they do not adequately consider atypical, non-syndrome-specific, and heterogeneous family history features frequently encountered in clinical practice. For this patient population, evidence-based approaches to guide the genetic evaluation are notably lacking in the literature.2 In addition, a generalizable consensus on the relative importance of family history components such as the number of affected relatives, age at diagnosis, degree of consanguinity, and cancer types has not yet been reached. In light of these uncertainties, identifying family history patterns that can demonstrate common features among different cancer types and reliably indicate hereditary cancer predisposition, beyond specific syndrome criteria, is a fundamental requirement for rationalizing the referral process for genetic testing and improving diagnostic yield.3,4 The aim of this study is to identify family history patterns that can guide referrals for hereditary cancer panel testing, independent of syndrome-specific clinical diagnoses. In this context, the evaluation of predictive familial factors for detecting germline variants associated with hereditary cancer predisposition contributes to filling a critical gap in the literature on the determination of genetic testing indications in clinical practice. 2. Materials and methods This research is a retrospective cohort study encompassing cases who received genetic counseling and underwent NGS-based hereditary cancer panel analysis at the Department of Medical Genetics, Gülhane Training and Research Hospital, between January 2024 and December 2025. The study population consisted of index cases diagnosed with malignancy, as well as asymptomatic individuals who had no personal cancer history but were evaluated for hereditary predisposition due to accumulated familial risk. During the clinical evaluation process, a detailed pedigree analysis covering at least three generations was systematically performed for each case. Family history data were standardized based on four key parameters: number of affected relatives, types of neoplasms, age at diagnosis, and lineage distribution. In evaluating malignancies detected in relatives, biological concordance between tumor types and the index case, and syndrome-specific phenotypic overlap were further classified. The number of affected relatives was categorized according to first, second, and third-degree relatives, and the independent predictive value of each group on the probability of germline variant detection was analyzed. To ensure data integrity, histories of malignancies with an unidentified primary site were excluded from the evaluation, cases without information on age at diagnosis were evaluated within the ≥50 age category in the analyses, and cases without family history information were coded as "cancer history negative." During the molecular analysis phase, genomic DNA isolation was performed from peripheral blood samples using the spin-column method. Target enrichment and library preparation were performed using the SOPHiA Solution Hereditary Cancer (59 genes-IL) panel, and sequencing was carried out on the Illumina NovaSeq platform. The identified germline variants were classified as pathogenic (P), likely pathogenic (LP), and variants of uncertain clinical significance (VUS) in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines. In this study, in addition to pathogenic and likely pathogenic variants, variants of uncertain clinical significance were also considered within the "variant detected" group, as genetic testing in clinical practice is primarily utilized to inform risk assessment and surveillance strategies. Statistical analyses were performed using SPSS v27.0 software.*

Descriptive analyses utilized frequency and percentage distributions; Pearson Chi-square test was applied to compare categorical variables; Fisher's Exact Test was used for 2×2 tables and Fisher-Freeman-Halton Exact Test for higher-dimensional (R×C) tables when expected frequency values did not meet theoretical assumptions. Forward conditional logistic regression analysis was used to identify independent factors predicting germline variant positivity, with a statistical significance level of p

[Abstract:0284]

Clinicopathologic Comparison of Breast Cancer Patients with Germline Pathogenic/Likely Pathogenic Variants: BRCA1, BRCA2, and Non-BRCA1/2

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Objective: This study aimed to describe clinicopathologic characteristics of breast cancer cases with germline pathogenic/likely pathogenic (P/LP) variants detected by hereditary cancer panel testing at our center and to compare findings across BRCA1, BRCA2, and non-BRCA1/2 groups.
Materials-Methods: We retrospectively reviewed 359 breast cancer patients who underwent hereditary cancer panel testing between 2021 and 2025. Sixty-one patients (58 females, 3 males) with germline P/LP variants were included. Cases were grouped by the gene harboring the variant: BRCA1 (n=11), BRCA2 (n=12), and non-BRCA1/2 genes (n=38). The most frequent non-BRCA1/2 genes were CHEK2 (n=13), MUTYH (n=8), MSH6 (n=3), NF1 (n=2), and ATM (n=2). Molecular subtypes were assigned using ER/PR/HER2 and Ki-67 according to a St. Gallen surrogate classification. Analyses were performed on available data per variable. Continuous variables were compared using the Kruskal–Wallis test and categorical variables using the chi-square test; $p<0.05$ was considered significant.
Results: Mean age at diagnosis was 44.9 years in the BRCA1 group (n=11), 47.5 years in the BRCA2 group (n=11), and 44.4 years in the non-BRCA1/2 group (n=38). Triple-negative breast cancer (TNBC) was markedly enriched among BRCA1 carriers (85.7%, 6/7) compared with BRCA2 (12.5%, 1/8) and non-BRCA1/2 cases (15.2%, 5/33). In the BRCA2 group, Luminal B was most common (62.5%, 5/8), while Luminal A and HER2-enriched surrogate each accounted for 12.5% (1/8). In the non-BRCA1/2 group, Luminal B predominated (54.5%, 18/33), followed by Luminal A (27.3%, 9/33) and HER2-enriched (3.0%, 1/33). In BRCA1 carriers, besides TNBC, Luminal B comprised 14.3% (1/7); Luminal A and HER2-enriched were not observed. Family history positivity was high across groups (BRCA1 90.0%, 9/10; BRCA2 81.8%, 9/11; non-BRCA1/2 82.4%, 28/34). Breastfeeding history was reported in BRCA1 85.7% (6/7), BRCA2 100% (4/4), and non-BRCA1/2 87.0% (20/23); breastfeeding duration >=12 months was 85.7% (6/7), 50.0% (2/4), and 69.6% (16/23), respectively. Oral contraceptive use was 37.5% (3/8) in BRCA1, 25.0% (1/4) in BRCA2, and 44.0% (11/25) in non-BRCA1/2; use >=5 years was 12.5% in BRCA1 and non-BRCA1/2 and absent in BRCA2. Mean menarche age was 12.4 (n=7), 14.0 (n=5), and 12.6 (n=26), respectively. Premenopausal diagnosis rates were 37.5% (3/8), 66.7% (4/6), and 79.3% (23/29). BMI >=25 was observed in 50.0% (3/6), 75.0% (6/8), and 62.1% (18/29), respectively. TNBC frequency ($p=0.00031$) and the four-category molecular subtype distribution ($p=0.0053$) differed significantly between groups; other variables were not significantly different.
Conclusion: The main finding of this study is the marked predominance of TNBC among BRCA1 carriers and a significantly different molecular subtype distribution compared with the BRCA2 and non-BRCA1/2 groups. This pattern is in line with the well-described tendency of BRCA1-associated tumors to show basal-like/TNBC features. In contrast, Luminal B was the most frequent subtype in the BRCA2 and non-BRCA1/2 groups, supporting that BRCA2 and several non-BRCA1/2 genes (e.g., CHEK2/ATM) are more often associated with hormone receptor–positive (luminal) disease. The absence of significant differences in reproductive and environmental variables likely reflects the limited sample size (particularly in the BRCA1/BRCA2 subgroups) and missing data. Overall, our findings highlight clinically relevant genotype–phenotype correlations in breast cancer patients carrying germline P/LP variants.

Keywords: *Breast cancer, molecular subtype, multigene panel testing*

Clinicopathologic Comparison of Breast Cancer Patients with Germline Pathogenic/Likely Pathogenic Variants: BRCA1, BRCA2, and Non-BRCA1/2 Aydan Mengübaş Erbaş1, Rıdvan Savaş1, Zehra Manav Yiğit1, Gökay Bozkurt1 Department of Medical Genetics, Adnan Menderes Univesity Faculty of Medicine, Aydın, Türkiye1 Objective: To describe clinicopathologic characteristics of breast cancer patients with germline pathogenic/likely pathogenic (P/LP) variants identified by hereditary cancer panel testing at our center (2021–2025) and to compare BRCA1, BRCA2, and non-BRCA1/2 groups. Materials and Methods: We retrospectively reviewed 359 breast cancer patients tested with a hereditary cancer panel. Sixty-one patients with germline P/LP variants (58 females, 3 males) were included and grouped as BRCA1 (n=11), BRCA2 (n=12), or non-BRCA1/2 (n=38). Molecular subtypes were assigned using ER/PR/HER2 and Ki-67 (St. Gallen surrogate). Available-case analyses were performed; Kruskal–Wallis and chi-square tests were used for continuous and categorical variables, respectively (p

[Abstract:0288]

High-Frequency Detection of PMS2 rs1554294508 in Hereditary Cancer Panels: True Pathogenic Variant or Pseudogene Artifact?

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Objective: The PMS2 protein is a core component of the DNA mismatch repair pathway, and pathogenic variants in PMS2 are associated with "Lynch syndrome type-4" and "Mismatch repair cancer syndrome type-4". An approximately 16 kb inverted duplication of the 3' end of PMS2 has given rise to the PMS2CL pseudogene, located about 700 kb centromeric to PMS2 on the same chromosome. Due to the high sequence homology between PMS2 and PMS2CL, molecular analysis of PMS2 is technically challenging. In this study, we evaluated the interpretation of the PMS2 (NM_000535.7):c.2182_2184delinsG p.(Thr728AlafsTer7) (rs1554294508) variant.

Materials-Methods: Hereditary cancer panel (HCS) was performed with the Sophia Custom Solution CHCS_C_V2 kit and sequenced with Illumina NextSeq 2000, analysed on the Sophia platform. Clinical Exome Sequencing (CES) was performed using the Sophia Clinical Exome Solution V3 kit and sequenced on NextSeq 2000. Analysis was performed on Sophia DDMTM platform. Also, the variant was visualized on Integrative Genomics Viewer (IGV).

Results: In the HCS analysis of 7329 patients, 13 different pathogenic/likely pathogenic variants in the PMS2 gene, classified according to the ACMG-2015 criteria, were identified in 22 patients. Of the thirteen pathogenic variants identified in the PMS2 gene, seven were localized to pseudogene-associated regions exhibiting >99% sequence homology based on segmental duplication annotations from the UCSC Genome Browser. The rs1554294508 variant was detected in six individuals tested with HCS and in three individuals with CES data, performed for various indications other than cancer predisposition. The clinical characteristics of the patients and detected PMS2/PMS2CL variants are summarized in Table-1. The variant is located in a region of PMS2 with high pseudogene homology, with a corresponding PMS2CL variant of NR_002217 n.1122_1124delinsG. According to the ClinVar database, this variant has been reported as pathogenic/likely pathogenic in six submissions and VUS in one submission (ClinVar:231999). IGV visualization of this variant revealed variable allele fractions and locally inconsistent alignment patterns, suggesting that the observed signal may not solely originate from the PMS2. Furthermore, in a single individual for whom immunohistochemistry was available from endometrial tissue, the absence of PMS2 loss supports the possibility that the detected variant may be pseudogene-derived. Review of the literature indicated that this variant has been predominantly reported in African/Brazilian populations. In multiple studies including more than 100 patients, the variant was confirmed to be exclusively pseudogene-derived using long-range PCR and other molecular testing methodology.

Conclusion: Although the rs1554294508 variant is detected at a relatively high frequency in HCS, evaluation of literature data, immunohistochemistry findings, and IGV results from our cohort suggests that this variant is likely pseudogene-associated. Variants detected in highly homologous regions of PMS2 should not be considered clinically pathogenic unless their genomic origin is confirmed using PMS2 spesific PCR or additional confirmatory methods. This study is reported to highlight the technical limitations of PMS2 variant analysis and the critical role of detailed assessment in the analysis and genetic counselling for patients and their families.

Keywords: *PMS2, Pseudogene, rs1554294508, Hereditary Cancer, Lynch Syndrome*

Table 1

Patient	Diagnosis	Age	Family History	Variant Fraction of PMS2 c.2182_2184delinsG	Variant Fraction of PMS2CL 1122_1124delinsG	Immunohistochemistry results
Patient-1	Breast cancer	32	-	22.5%	15.5%	NA
Patient-2	Serous endometrial carcinoma	64	-	20.2%	-	PMS2 IHC: Retained expression
Patient-3	Positive family history of malignancy	51	+ (breast cancer, olorectal cancer)	14.5%	82.8%	NA
Patient-4	Breast cancer	66	-	22.1%	20.0%	NA
Patient-5	Breast cancer	54	-	36.3%	10.8%	NA
Patient-6	Positive family history of malignancy (the offspring of Patient-5)	38	+ (breast cancer)	19.1%	19.2%	-

Clinical characteristics of patients tested with the hereditary cancer panel (HCS) and the detected PMS2/PMS2CL variants

High-Frequency Detection of PMS2 rs1554294508 in Hereditary Cancer Panels: True Pathogenic Variant or Pseudogene Artifact? Öznur Kaya Güneş, Dilsu Dicle Erkan Kolaç, Zeynep Özdemir Pehlivan, Haktan Bağış Erdem Department of Medical Genetics, Etlik City Hospital, Ankara, Türkiye Objective: The PMS2 protein is a core component of the DNA mismatch repair pathway, and pathogenic variants in PMS2 are associated with "Lynch syndrome type-4" and "Mismatch repair cancer syndrome type-4". An approximately 16 kb inverted duplication of the 3' end of PMS2 has given rise to the PMS2CL pseudogene, located about 700 kb centromeric to PMS2 on the same chromosome. Due to the high sequence homology between PMS2 and PMS2CL, molecular analysis of PMS2 is technically challenging. In this study, we evaluated the interpretation of the PMS2 (NM_000535.7):c.2182_2184delinsG p.(Thr728AlafsTer7) (rs1554294508) variant. Materials-Methods: Hereditary cancer panel (HCS) was performed with the Sophia Custom Solution CHCS_C_V2 kit and sequenced with Illumina NextSeq 2000, analysed on the Sophia platform. Clinical Exome Sequencing (CES) was performed using the Sophia Clinical Exome Solution V3 kit and sequenced on NextSeq 2000. Analysis was performed on Sophia DDMTM platform. Also, the variant was visualized on Integrative Genomics Viewer (IGV). Results: In the HCS analysis of 7329 patients, 13 different pathogenic/likely pathogenic variants in the PMS2 gene, classified according to the ACMG-2015 criteria, were identified in 22 patients. Of the thirteen pathogenic variants identified in the PMS2 gene, seven were localized to pseudogene-associated regions exhibiting >99% sequence homology based on segmental duplication annotations from the UCSC Genome Browser. The rs1554294508 variant was detected in six individuals tested with HCS and in three individuals with CES data, performed for various indications other than cancer predisposition. The clinical characteristics of the patients and detected PMS2/PMS2CL variants are summarized in Table-1. The variant is located in a region of PMS2 with high pseudogene homology, with a corresponding PMS2CL variant of NR_002217 n.1122_1124delinsG. According to the ClinVar database, this variant has been reported as pathogenic/likely pathogenic in six submissions and VUS in one submission (ClinVar:231999). IGV visualization of this variant revealed variable allele fractions and locally inconsistent alignment patterns, suggesting that the observed signal may not solely originate from the PMS2. Furthermore, in a single individual for whom immunohistochemistry was available from endometrial tissue, the

absence of PMS2 loss supports the possibility that the detected variant may be pseudogene-derived. Review of the literature indicated that this variant has been predominantly reported in African/Brazilian populations. In multiple studies including more than 100 patients, the variant was confirmed to be exclusively pseudogene-derived using long-range PCR and other molecular testing methodology. Conclusion: Although the rs1554294508 variant is detected at a relatively high frequency in HCS, evaluation of literature data, immunohistochemistry (IHC) findings, and IGV results from our cohort suggests that this variant is likely pseudogene-associated. Variants detected in highly homologous regions of PMS2 should not be considered clinically pathogenic unless their genomic origin is confirmed using PMS2 specific PCR or additional confirmatory methods. This study is reported to highlight the technical limitations of PMS2 variant analysis and the critical role of detailed assessment in the analysis and genetic counselling for patients and their families. Keywords: PMS2, Pseudogene, rs1554294508, Hereditary Cancer, Lynch Syndrome Table 1 Table 1: Clinical characteristics of patients tested with the hereditary cancer panel (HCS) and the detected PMS2/PMS2CL variants Patient Diagnosis Age Family History Variant Fraction of PMS2 c.2182_2184 delinsG Variant Fraction of PMS2CL n.1122_1124 delinsG IHC results Patient-1 Breast cancer 32-22.5% 15.5% NA Patient-2 Serous endometrial carcinoma 64-20.2% PMS2 IHC: Retained expression Patient-3 Positive family history of malignancy 51 + (breast cancer, colorectal cancer) 14.5% 82.8% NA Patient-4 Breast cancer 66-22.1% 20.0% NA Patient-5 Breast cancer 54-36.3% 10.8% NA Patient-6 Positive family history of malignancy (the offspring of Patient-5) 38 + (breast cancer) 19.1% 19.2%

[Abstract:0303]

MINAS Case Series: A Detailed Look into 7 MINAS Patients at a Single Center

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Objective: Multilocus inherited neoplasia allelic syndrome (MINAS) is a newly introduced term to describe individuals harboring two or more pathogenic or likely pathogenic variants in cancer susceptibility genes. MINAS has been reported to occur in approximately 1–5% of all individuals undergoing genetic testing, with the data varying in different studies. However, this estimate may be conservative, as cases involving multiple pathogenic variants are likely to be underdetected and underreported. Although some studies suggest that MINAS carriers develop multiple primary malignancies, diagnosed at an earlier age compared to non-carriers and monoallelic patients, there is still no consensus on the effects of MINAS.
In this retrospective study, patients referred to our clinic between 2022 and 2025 were evaluated. Among 1183, 7 (0,6%) individuals with two or more pathogenic/likely pathogenic variants were included in the study. Patients' data were analyzed using a hereditary cancer panel, a multi-cancer gene panel assessing 53 genes by next-generation sequencing (NGS). NGS analysis was performed using the SOPHIA Custom Solution CHCS_C_V2 kit on the NovaSeq® platform. Variant interpretation was conducted in accordance with the American College of Medical Genetics and Genomics (ACMG) standards and guideline recommendations.

Case: Seven patients were identified as MINAS. All patients were female, with ages ranging from 31 to 50 years. Five (71%) patients were diagnosed with breast cancer, while two (29%) had gynecologic malignancies, including endometrioid ovarian cancer and endometrial cancer.

The first breast cancer case was diagnosed at age 50, and heterozygous pathogenic variants in PALB2, ATM, and MUTYH were detected. The second case was diagnosed with breast cancer at age 48, experienced recurrence at age 58, carried pathogenic variants in BRCA2 and CHEK2. The third case was diagnosed with triple-negative breast cancer at age 38 and carried pathogenic variants in BARD1 and MSH3. The fourth case was diagnosed with breast cancer at age 31 and developed contralateral breast metastasis at age 37; pathogenic variants in ATM and TP53 were identified. The fifth breast cancer case was diagnosed at age 41 with liver metastasis, and pathogenic variants in MUTYH and MLH1 were detected.
The sixth case was diagnosed with ovarian cancer at age 36, and germline pathogenic variants were identified in MSH2 and ERCC2. In the latest case, a 36-year-old woman was diagnosed with endometrial cancer and germline pathogenic variants in PTEN and FANCC.

Conclusion: MINAS is a recently defined entity whose reported frequency is increasing in parallel with growing awareness and broader use of multigene testing. Although its impact on prognosis and cancer behavior remains unclear, available evidence suggests potential clinical relevance, highlighting the need for systematic data collection. This study contributes to the limited literature by evaluating genotype–phenotype associations involving diverse gene combinations and demonstrates a relatively early age at cancer diagnosis in our cohort. Contrary to current reports in which BRCA1/2–based combinations predominate, such patterns were not observed in our cases, suggesting that non-classical variant combinations may be underrecognized. These findings emphasize the importance of comprehensive genetic assessment and data sharing to guide personalized clinical management and familial screening.

Keywords: *MINAS, cancer predisposition genes, hereditary cancer*

*MINAS Case Series: A Detailed Look into 7 MINAS Patients at a Single Center Introduction: Multilocus inherited neoplasia allelic syndrome (MINAS) is a recently introduced term, first described by Whitworth et al. in 2016, to define individuals harboring two or more pathogenic or likely pathogenic variants in cancer susceptibility genes.[1] MINAS has been reported in approximately 1–5% of individuals undergoing genetic testing, although this frequency varies across studies.[1, 2] In the current literature, the majority of reported MINAS patients have been diagnosed with breast cancer, and the most frequently observed genetic combination consists of pathogenic variants in BRCA1 or BRCA2 together with at least one additional cancer susceptibility gene.[3] In a study conducted in Türkiye, 2.14% of the patients who underwent hereditary cancer syndrome (HCS) testing fulfilled the criteria for MINAS, and breast cancer was likewise the most common malignancy observed in this cohort.[4] This estimate may be conservative, as cases involving multiple pathogenic variants are likely to be under detected and underreported. While some studies suggest that MINAS carriers develop multiple primary malignancies at an earlier age compared to non-carriers or monoallelic carriers, there is currently no consensus regarding the clinical impact of MINAS. [3, 5, 6] Methods: In this retrospective study, patients referred to our clinic between 2022 and 2025 were evaluated. Among 1,183 individuals, seven patients harboring two or more pathogenic or likely pathogenic variants were included (%0.59). Genetic data were analyzed using a hereditary cancer panel covering 53 genes via next-generation sequencing (NGS). NGS analysis was performed using the SOPHIA Custom Solution CHCS_C_V2 kit on the NovaSeq® platform. Variant interpretation was conducted in accordance with the American College of Medical Genetics and Genomics (ACMG) standards and guidelines. Results: Seven patients were identified as having MINAS. All patients were female, with ages ranging from 31 to 50 years. Five patients were diagnosed with breast cancer, while two had gynecologic malignancies, including endometrioid ovarian cancer and endometrial cancer. The patient with endometrioid ovarian cancer was diagnosed at the age of 36. Tumor analysis demonstrated loss of MSH2 and MSH6 expression, and germline heterozygous pathogenic variants (PVs) in MSH2 (c.1613del p.Asn538Thrfs*5) and ERCC2 (c.1846C>T p.Arg616Trp) were identified. Her mother had been diagnosed with endometrial and gastric cancer at the age of 55. Her aunt had died from colon cancer at the age of 35. The patient with endometrial cancer was also diagnosed at the age of 36 and had inflammatory pseudopolyps. Her medical history included a prior total thyroidectomy for benign nodules and a cerebellar lesion that had been followed without treatment for more than 10 years. Tumor immunohistochemistry showed loss of MLH1 and PMS2, with estrogen receptor and p53 positivity. Germline heterozygous PVs in PTEN (c.714C>G p.Tyr238Ter) and FANCC (c.456+4A>T) were detected. Her maternal grandmother had died from pancreatic cancer. Among the breast cancer cases, tumor subtypes included ER/PR-negative, ER/PR positive, triple-negative breast cancer, ductal carcinoma in situ, and metastatic disease. Pathogenic variants were identified in the following gene combinations: PALB2/ATM, BRCA2/CHEK2, BARD1/MSH3, ATM/TP53, and MUTYH/MLH1. Several patients had notable family histories of breast, thyroid, colorectal, or gynecologic cancers. The first breast cancer case was diagnosed at the age of 50. Tumor pathology revealed ER and PR positivity, a Ki-67 proliferation index of 20%, and low HER2 (c-erbB2) expression (2+). Genetic analysis identified heterozygous pathogenic variants in PALB2 (c.1159_1162del p.Ser387Leufs*36), ATM (c.6047A>G p.Asp2016Gly), and MUTYH (c.842C>T p.Pro281Leu). The patient's parents originated from the same village, and her family history was notable for breast cancer in a sister (diagnosed at 35), colorectal cancer in her father (diagnosed at 100), brain cancer in another sister (diagnosed at 57), and both gastric and colorectal cancer in her older brother (diagnosed at 67). The second case was diagnosed with invasive ductal breast cancer at the age of 48, with recurrence in the same breast at the age of 58. The initial tumor showed ER/PR negativity, a Ki-67 index of 50%, and HER2 positivity; in contrast, the recurrent tumor demonstrated ER/PR positivity. Genetic analysis revealed heterozygous pathogenic variants in BRCA2 (c.3847_3848del p.Val1283Lysfs*2) and CHEK2 (c.1556C>T p.Thr476Met). Two daughters of her maternal aunts had breast cancer, and another had*

thyroid cancer. One of her maternal aunts had died in her 30s due to an unknown malignancy. Family segregation analysis showed that her daughter also carried the same variants. The third case was diagnosed with triple-negative breast cancer and ductal carcinoma in situ at the age of 38. Tumor pathology revealed a Ki-67 index of 80%. The patient had undergone a polypectomy 10 years earlier. Genetic analysis identified heterozygous pathogenic variants in BARD1 (c.1548T>G p.Tyr516) and MSH3 (c.1897-1G>A). Her paternal grandfather had died from leukemia. The fourth case was diagnosed with left-sided breast cancer at the age of 31 and subsequently developed metastasis to the right breast at the age of 37. Tumor pathology demonstrated ER and PR positivity, HER2 negativity, and a Ki-67 index of 15%. Genetic analysis revealed heterozygous pathogenic variants in ATM (c.2251-4A>G) and TP53 (c.473G>A p.Arg158His). Her paternal grandmother had been diagnosed with renal cancer at the age of 70. The final case was diagnosed with breast cancer with liver metastasis at the age of 41. Tumor pathology revealed ER and PR negativity, HER2 positivity, E-cadherin positivity, S100 positivity, and a Ki-67 index of 35%. Genetic analysis identified heterozygous pathogenic variants in MUTYH (c.1187G>A p.Gly396Asp) and MLH1 (c.184C>A p.Gln62Lys). Her parents were first degree cousins, and her family history was notable for lymphoma in her father and endometrial cancer in her paternal cousin, diagnosed at the age of 53. Discussion: MINAS is a relatively recently defined entity, the reported frequency of which has increased with the expanding use of multigene panel testing and greater awareness of its clinical significance. Although there is currently no consensus regarding the impact of MINAS on prognosis, cancer spectrum, or whether multiple pathogenic variants exert synergistic or additive effects, several studies support these hypotheses. Therefore, the systematic collection, documentation, and analysis of such cases remain crucial. Patients with MINAS may require specialized clinical management strategies, including individualized treatment approaches, closer surveillance, and potentially tailored familial and cancer screening protocols. This study contributes to the limited existing literature by exploring genotype–phenotype correlations involving diverse gene combinations. Consistent with the existing literature, the majority of MINAS patients in our cohort presented with breast cancer.Notably, the mean age at diagnosis in our cohort was relatively young: breast cancer was diagnosed at a mean age of 41 years, ovarian cancer at 36 years, and endometrial cancer at 31 years. These findings suggest a possible association between MINAS and earlier cancer onset. Furthermore, in contrast to the existing literature, the most frequently observed MINAS combination in our cohort was not BRCA1/BRCA2 accompanied by another variant, but rather ATM accompanied by another variant (3/7).This suggests that certain variant combinations may be underrecognized, particularly when they do not conform to classical phenotype-driven expectations, underscoring the importance of comprehensive genetic evaluation independent of clinical presentation. In conclusion, the systematic accumulation and sharing of MINAS-related data are crucial for enhancing prognostic assessment, refining long-term follow-up strategies, and informing familial screening. The present study supports the value of such efforts and underscores the need for broader recognition of diverse gene combinations contributing to MINAS, as well as the importance of further functional studies in this area.*

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[Abstract:0313]

FINDING A TRUE TONE IN CANCER GENETICS: Comparative Performance Analysis Reveals HCSpred as a Superior In Silico Prediction Framework

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Objective: Accurate interpretation of germline variants in hereditary cancer panels remains a major clinical and analytical challenge, primarily driven by the high prevalence of variants of uncertain significance (VOUS). While ensemble machine learning approaches improve discrimination between pathogenic and benign variants, most existing frameworks lack leakage-safe design, structured uncertainty handling, and transparent calibration, limiting their clinical interpretability and generalizability.

Materials-Methods: We developed HCSpred, an adaptive and integrative meta-predictor framework for robust variant interpretation in hereditary cancer genetics. Variant-level in silico scores and metadata were curated from a multi-gene hereditary cancer panel. Pathogenic/likely pathogenic (LP) and benign/likely benign (LB) variants were used for supervised learning, while VOUS were intentionally retained for adaptive downstream inference. To prevent gene-level information leakage, a gene-balanced train/test split was applied, assigning entire genes to either split while preserving LP/LB prevalence.

Four supervised learners—Random Forest, ExtraTrees, XGBoost, and AdaBoost—were trained using group-aware cross-validation and hyperparameter optimization. Each model generated calibrated pathogenicity probabilities, which were combined using three adaptive strategies: AdaptiveStackGLM, probability-weighted triage, and hard-vote VOUS grading. Adaptive triage thresholds (LP >= 0.70; LB <= 0.30) were applied to control decisiveness. VOUS were further stratified into graded subclasses (VOUS-- to VOUS++) reflecting the strength and direction of ensemble agreement. Model behavior was systematically evaluated on an independent test set using call rate, probability distributions, inter-model agreement, calibration curves, score deltas, and gene-level uncertainty analyses.
Results: Adaptive classifiers demonstrated high decisiveness while maintaining robust generalization. The vote-based adaptive classifier achieved a 97% non-VOUS call rate in the test set, compared with 95% for AdaptiveStackGLM and 91% for the conservative probability-weighted strategy, with minimal train–test divergence, indicating stable threshold behavior. VOUS grading showed strong polarization toward benign-leaning (VOUS--) and pathogenic-leaning (VOUS++) categories, whereas the truly unresolved VOUS0 group represented only a small minority, reflecting effective structuring of uncertainty rather than arbitrary exclusion. Predicted pathogenicity probability distributions exhibited clear separation between LP and LB variants across all base learners, with AdaptiveStackGLM and XGBoost showing the sharpest score profiles. Inter-model probability correlations were consistently high (r = 0.92–0.99), indicating coherent and stable scoring behavior.
Conclusion: In ClinVar, only ~10% of variants initially classified as VUS (2017) were resolved to definitive benign or pathogenic categories by 2025, with the majority remaining as VUS or shifting into conflicting interpretations. In contrast, HCSpred adaptive classifiers achieved 91–97% non-VOUS call rates on the independent test set, effectively compressing years of natural reclassification uncertainty into a single, confidence-graded inference step. HCSpred advances variant interpretation beyond binary classification by introducing an adaptive, confidence-aware framework that structures uncertainty, improves decisiveness, and preserves calibration. By integrating ensemble supervised learning with adaptive voting and gene-level robustness analyses, HCSpred

substantially reduces unresolved VOUS while maintaining clinical conservatism. This framework provides a scalable and interpretable foundation for real-world hereditary cancer diagnostics and population-specific variant assessment.

The first in silico application of this model, focusing on the MEFV gene, was presented as a poster at the ASHG 2024 Annual Meeting and subsequently published as a full-length article in Scientific Reports in 2025.

Keywords: *Adaptive classifiers, ensemble machine learning, hereditary cancer, variant interpretation, VOUS reduction*

FINDING A TRUE TONE IN CANCER GENETICS: Comparative Performance Analysis Reveals HCSpred as a Superior In Silico Prediction Framework Mustafa Tarık Alay1, Fahrettin Duymuş2 Ankara Etlik Şehir Hastanesi1 Uşak Eğitim Araştırma Hastanesi2 INTRODUCTION In music, finding a true tone is not about volume or technical virtuosity, but about authenticity, the ability to convey meaning without distortion. Legendary artists such as Cem Karaca were recognized not for perfect pitch, but for an unmistakable tonal truth that resonated beyond surface performance. Cancer genetics faces a strikingly similar challenge. As the number of in silico prediction algorithms continues to grow, technical sophistication has often been mistaken for interpretability and clinical relevance. High scores, like loud notes, may dominate attention, yet fail to capture the underlying biological truth. In this study, we argue that the central problem is not the absence of tools, but the absence of a true tone an integrative, coherent signal that aligns computational prediction with clinical reality. MATERIAL-METHODS Variant cohort and feature representation As of December 2024, ClinVar comprised 3,110,973 variants annotated across 52,815 genes. From this resource, 61 genes were selected using semantic similarity–based algorithms targeting phenotypic associations with hereditary cancer syndromes. To define population-based healthy controls, a total of 730,947 whole-exome and 76,215 whole genome sequences were evaluated from the gnomAD dataset. All selected genes were subsequently categorized and scored using the ALAY classification framework1. Variant interpretation and prediction were performed using the adaptive classifier approach previously described by Alay et al.2, which combines multiple supervised machine-learning models within a hard-voting ensemble and applies adaptive decision thresholds to dynamically resolve pathogenic, benign, and VOUS classifications based on score concordance and model confidence. The real-world clinical test cohort consisted of 7,471 hereditary cancer patients evaluated between 2022 and 2025 at Ankara Etlik City Hospital. Gene-balanced train/test split To minimize gene-specific distribution shift, we performed a gene-balanced train/test split such that variants from each gene were proportionally represented in both partitions. We split the dataset into [e.g., 80/20] train/test, stratifying by gene and, when feasible, by reference label strata. This design preserves gene-level representativeness and reduces the risk of optimistic performance estimates driven by gene leakage. Adaptive supervised ensemble for LB–LP classification We trained an adaptive supervised ensemble composed of four base learners: two boosting models and two bagging models. Each base learner was optimized to discriminate likely benign (LB) versus likely pathogenic (LP) variants on the training set. We retained per-model binary predictions to quantify consensus and support downstream VOUS grading. VOUS grading via 4-model voting and supervised label mapping. VOUS grading was derived from a four-model voting scheme. Let v denote the number of base learners predicting LP among the four models. VOUS grades were assigned as: • v = 4 → VOUS++ • v = 3 → VOUS+ • v = 2 → VOUS0 • v = 1 → VOUS− • v = 0 → VOUS−− We then mapped VOUS grades to supervised labels (S) for downstream analysis: • VOUS++ / VOUS+ → LPs • VOUS0 → VOUSs • VOUS−− / VOUS− → LBs RESULTS Supervised HCSpred models consistently outperformed individual in silico tools across all evaluated metrics. At a probability threshold of 0.5, supervised single models achieved accuracies ranging from 96.7% to 98.1%, while the hard-voting ensemble reached 97.9% accuracy, clearly exceeding the best-performing individual in silico score (~90%) [Figure 1]. Balanced accuracy analyses confirmed this advantage, demonstrating

robust bidirectional discrimination between LP and LB classes that was independent of class imbalance. Effective ROC AUC values were near-perfect for supervised HCSpred models (0.995–0.996), with the hard-voting ensemble maintaining high discriminatory capacity (AUC ≈ 0.986), whereas most individual in silico tools clustered between 0.88 and 0.92 [Figure 2]. Notably, this global performance translated into clinically critical genes, with all 53 BRCA1/2 variants correctly classified, corresponding to 100% prediction accuracy in this subset. Collectively, these findings indicate that the HCSpred framework captures a coherent and clinically meaningful predictive signal that cannot be achieved by isolated in silico scores. DISCUSSION The present study demonstrates that the HCSpred algorithm provides a robust and clinically applicable framework for routine variant classification in hereditary cancer genetics. By integrating multiple supervised machine-learning models within an adaptive hard-voting architecture, HCSpred achieves consistent and high-level discrimination between likely pathogenic and likely benign variants under standard clinical decision thresholds. The observed improvements in accuracy, balanced accuracy, and ROC AUC over individual in silico tools indicate that HCSpred captures a coherent predictive signal that is not attainable through isolated score-based approaches. Importantly, the correct classification of all 53 BRCA1/2 variants underscores the algorithm's reliability in clinically critical genes where accurate classification directly informs patient management and preventive strategies. Collectively, these findings support HCSpred as a practical, scalable, and decision-oriented solution for improving variant interpretation in real-world cancer genetics practice. Keywords: Hereditary Cancers, Adaptive Classifiers, Clinvar, Machine learning Figures Figure 1. Comparison of classification accuracy (threshold = 0.5) between supervised HCSpred models and individual in silico tools. Supervised single models and the hard voting ensemble markedly outperform all individual in silico scores, achieving accuracies approaching 98%. Figure 2. Effective ROC AUC comparison of supervised HCSpred models versus individual in silico tools. Supervised models demonstrate near-perfect discrimination across the full probability space, substantially exceeding the ROC AUC values of standalone in silico predictors.

[Abstract:0319]

Assessment of Patients with Both Breast and Ovarian cancer

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Objective: Hereditary breast and ovarian cancer (HBOC) is most commonly associated with mutations in the BRCA genes. Other implicated genes include ATM, TP53, CHEK2, PTEN, CDH1, and PALB2. Approximately 5–10% of breast and ovarian cancers are hereditary. HBOC is characterized by early onset, a high frequency of bilateral disease, and an increased association with other malignancies.

Among breast cancer patients presenting with adnexal or pelvic masses, pelvic metastasis of breast cancer has been identified in approximately 13% of cases. The lifetime risk of breast cancer is estimated to be 50–80% in BRCA1 mutation carriers and approximately 50% in BRCA2 mutation carriers. BRCA1 mutations increase the lifetime risk of ovarian cancer by 20–50% and are also associated with a moderate increase in prostate and colon cancer risk. BRCA2 mutations increase the risk of ovarian cancer in women by 10–20%. We aimed to investigate the molecular subtypes and prognostic outcomes of patients with both breast and ovarian cancer.
Case: The mean age at diagnosis was 48.7 ± 3 years. A total of 12 patients were included in the study. Eight patients were initially diagnosed with breast malignancy, while four patients were first diagnosed with ovarian malignant neoplasms.

Regarding the histopathological subtypes of breast malignancies, seven patients had invasive ductal carcinoma, two had ductal carcinoma in situ, one had mucinous breast carcinoma, one had metaplastic breast carcinoma, and one had medullary breast carcinoma.

The histological subtypes of ovarian malignancies included one Sertoli cell tumor, two serous papillary ovarian carcinomas, one granulosa cell tumor, one squamous cell carcinoma arising in a mature cystic teratoma, one low-grade serous carcinoma, one serous cystadenocarcinoma, and five high-grade serous carcinomas.

Among breast cancer patients, five were classified as luminal A, one as luminal B, three as triple-negative, one as HER2-positive, and two as ductal carcinoma in situ.

Malignancies were synchronous in two patients, whereas in ten patients the second malignancy was diagnosed after a mean interval of 10 years. Two patients had died, six patients were under follow-up, two patients were receiving adjuvant therapy (one for breast cancer with trastuzumab and one for ovarian cancer with olaparib), and two patients were receiving treatment due to metastatic disease.

Genetic analysis was not performed in three patients. BRCA test results were negative in two patients, one of whom was CHEK2 positive. Three patients were BRCA1 positive and two patients were BRCA2 mutation carriers. In patients with pathogenic BRCA2 variants, heterozygous mutations exon 11 c.1507A>T and exon 11 c.4465A>T were identified. In patients with pathogenic BRCA1 variants, heterozygous variants exon 10 c.928C>T and exons 14–15 c.4675+3A>G were detected. Variant analysis data were unavailable in the medical records of one BRCA1-positive patient. The mean overall survival was 13.9 years.
Conclusion: Our findings are consistent with the existing literature.Further evaluation with a larger patient cohort is required to obtain more reliable and robust conclusions.

Keywords: *brca, both ovarıan and breast cancer, genetic*
Assessment of Patients with Both Breast and Ovarian cancer Bedriye Açıkgöz Yıldız, Gamze Gököz Doğu, Arzu Yaren, Atike Gökçen Demiray, Burcu Yapar Taşköylü Pamukkale Üniversitesi Hastanesi, Tıbbi Onkoloji Objective: Hereditary breast and ovarian cancer (HBOC) is most commonly associated with mutations in the BRCA genes. Other implicated genes include ATM, TP53, CHEK2, PTEN, CDH1, and PALB2. Approximately 5–10% of breast and ovarian cancers are hereditary. HBOC is characterized by early onset, a high frequency of bilateral disease, and an increased association with other malignancies. Among breast cancer patients presenting with adnexal or pelvic masses, pelvic metastasis of breast cancer has been identified in approximately 13% of cases. The lifetime risk of breast cancer is estimated to be 50–80% in BRCA1 mutation carriers and approximately 50% in BRCA2 mutation carriers. BRCA1 mutations increase the lifetime risk of ovarian cancer by 20–50% and are also associated with a moderate increase in prostate and colon cancer risk. BRCA2 mutations increase the risk of ovarian cancer in women by 10–20%. We aimed to investigate the molecular subtypes and prognostic outcomes of patients with both breast and ovarian cancer. Case: The mean age at diagnosis was 48.7 ± 3 years. A total of 12 patients were included in the study. Eight patients were initially diagnosed with breast malignancy, while four patients were first diagnosed with ovarian malignant neoplasms. Regarding the histopathological subtypes of breast malignancies, seven patients had invasive ductal carcinoma, two had ductal carcinoma in situ, one had mucinous breast carcinoma, one had metaplastic breast carcinoma, and one had medullary breast carcinoma. The histological subtypes of ovarian malignancies included one Sertoli cell tumor, two serous papillary ovarian carcinomas, one granulosa cell tumor, one squamous cell carcinoma arising in a mature cystic teratoma, one low-grade serous carcinoma, one serous cystadenocarcinoma, and five high-grade serous carcinomas. Among breast cancer patients, five were classified as luminal A, one as luminal B, three as triple-negative, one as HER2-positive, and two as ductal carcinoma in situ. Malignancies were synchronous in two patients, whereas in ten patients the second malignancy was diagnosed after a mean interval of 10 years. Two patients had died, six patients were under follow-up, two patients were receiving adjuvant therapy (one for breast cancer with trastuzumab and one for ovarian cancer with olaparib), and two patients were receiving treatment due to metastatic disease. Genetic analysis was not performed in three patients. BRCA test results were negative in two patients, one of whom was CHEK2 positive. Three patients were BRCA1 positive and two patients were BRCA2 mutation carriers. In patients with pathogenic BRCA2 variants, heterozygous mutations exon 11 c.1507A>T and exon 11 c.4465A>T were identified. In patients with pathogenic BRCA1 variants, heterozygous variants exon 10 c.928C>T and exons 14–15 c.4675+3A>G were detected. Variant analysis data were unavailable in the medical records of one BRCA1-positive patient. The mean overall survival was 13.9 years. Conclusion: Our findings are consistent with the existing literature.Further evaluation with a larger patient cohort is required to obtain more reliable and robust conclusions. Keywords: brca, both ovarıan and breast cancer, genetic

[Abstract:0321]

Germline BRCA1/2 variant landscape and clinicopathological outcomes in triple-negative breast cancer: a multicenter retrospective study from the Cukurova region

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Objective: Triple-negative breast cancer (TNBC) is characterized by an aggressive clinical course and a lack of targeted hormone or HER2 receptors. Approximately 10–15% of TNBC patients harbor germline BRCA1/2 pathogenic / likely pathogenic variants, which serve as critical biomarkers for familial risk assessment and the utilization of targeted therapies such as PARP inhibitors. This study aimed to evaluate the prevalence of BRCA1/2 variants and their association with clinical outcomes in TNBC patients treated at two tertiary oncology centers in the Cukurova region.

Materials-Methods: This retrospective multicenter study analyzed 120 TNBC patients diagnosed in 2025. Out of the total cohort, 59 patients (49.1%) underwent germline BRCA1/2 analysis. Data regarding age, tumor stage, localization, family history, molecular variants, treatment regimens, and pathological responses were analyzed.

Results: Germline BRCA1/2 variants were detected in 18.6% (n=11) of tested patients. Variants detected in our cohort were classified in nine patients as pathogenic and in two with variants of uncertain significance (VUS). The distribution showed a predominance of BRCA1 (72.7%) over BRCA2 (18.2%), with one patient (9%) harboring variants in both genes. Among the pathogenic BRCA1 (NM_007294.4) variants, the most frequent ones, both identified in 3 unrelated patients, were c.1444_1447del (p.Ile482) and c.5444G>A (p.Trp1815*). Notably, other BRCA1 pathogenic variants, each detected in one patient, included c.2800C>T (p.Gln934*), c.34C>T (p.Gln12*), and c.4485-2A>G. And only one pathogenic BRCA2 (NM_000059.4) variant in our cohort was c.1055dup (p.Tyr352*), detected in a patient carrying pathogenic BRCA1 variant (c.1444_1447del).*
The mean age at diagnosis for BRCA-mutant patients was 40.8 years, and 54.5% had a documented family history of malignancy. Most patients (63.6%) presented with Stage II disease. The majority (91%) received neoadjuvant chemotherapy consisting of doxorubicin/cyclophosphamide followed by paclitaxel. A significant Pathological Complete Response (pCR) rate of 66% was achieved among those undergoing surgery. In the adjuvant setting, targeted approaches included olaparib (11%) and pembrolizumab (18%).
The frequency of BRCA1/2 variants (18.6%) in our Cukurova-based cohort is slightly higher than the globally reported 10–15% average for TNBC, highlighting the regional genetic landscape. The high pCR rates observed in this cohort reinforce the chemosensitivity of BRCA-deficient tumors to standard anthracycline and taxane-based neoadjuvant protocols. Furthermore, the identification of pathogenic variants, including specific splice-site variants, underscores the importance of comprehensive genetic testing in this population to optimize the use of PARP inhibitors and immunotherapy.

Conclusion: Our findings confirm a significant prevalence of germline BRCA variants in TNBC patients in our region, associated with a younger age at diagnosis and favorable response to neoadjuvant therapy. These results support the integration of routine genetic testing into the standard of care to guide both surgical decisions, personalized systemic therapy and also the importance of genetic counselling to the healthy family members to take preventive measurements and early detection.

Keywords: *Breast cancer, BRCA variants, TNBC*

Germline BRCA1/2 variant landscape and clinicopathological outcomes in triple-negative breast cancer: a multicenter retrospective study from the Cukurova region *Müzeyyen Aslı Ergözoğlu1, Burcu Arslan Benli2, İbrahim Kaplan3, Timuçin Çil2, Berksoy Şahin1 1Medical Oncology Department, Faculty of Medicine, Cukurova University, Adana, Turkey 2Medical Oncology Department, Adana City Hospital, Adana, Turkey 3Medical Genetics Department, Adana City Hospital, Adana, Turkey* *Objective: Triple-negative breast cancer (TNBC) is characterized by an aggressive clinical course and a lack of targeted hormone or HER2 receptors. Approximately 10–15% of TNBC patients harbor germline BRCA1/2 pathogenic / likely pathogenic variants, which serve as critical biomarkers for familial risk assessment and the utilization of targeted therapies such as PARP inhibitors. This study aimed to evaluate the prevalence of BRCA1/2 variants and their association with clinical outcomes in TNBC patients treated at two tertiary oncology centers in the Cukurova region. Materials-Methods: This retrospective multicenter study analyzed 120 TNBC patients diagnosed in 2025. Out of the total cohort, 59 patients (49.1%) underwent germline BRCA1/2 analysis. Data regarding age, tumor stage, localization, family history, molecular variants, treatment regimens, and pathological responses were analyzed. Results: Germline BRCA1/2 variants were detected in 18.6% (n=11) of tested patients. Variants detected in our cohort were classified in nine patients as pathogenic and in two with variants of uncertain significance (VUS). The distribution showed a predominance of BRCA1 (72.7%) over BRCA2 (18.2%), with one patient (9%) harboring variants in both genes. Among the pathogenic BRCA1 (NM_007294.4) variants, the most frequent ones, both identified in 3 unrelated patients, were c.1444_1447del (p.Ile482*) and c.5444G>A (p.Trp1815*). Notably, other BRCA1 pathogenic variants, each detected in one patient, included c.2800C>T (p.Gln934*), c.34C>T (p.Gln12*), and c.4485-2A>G. And only one pathogenic BRCA2 (NM_000059.4) variant in our cohort was c.1055dup (p.Tyr352*), detected in a patient carrying pathogenic BRCA1 variant (c.1444_1447del). The mean age at diagnosis for BRCA-mutant patients was 40.8 years, and 54.5% had a documented family history of malignancy. Most patients (63.6%) presented with Stage II disease. The majority (91%) received neoadjuvant chemotherapy consisting of doxorubicin/cyclophosphamide followed by paclitaxel. A significant Pathological Complete Response (pCR) rate of 66% was achieved among those undergoing surgery. In the adjuvant setting, targeted approaches included olaparib (11%) and pembrolizumab (18%). The frequency of BRCA1/2 variants (18.6%) in our Cukurova-based cohort is slightly higher than the globally reported 10–15% average for TNBC, highlighting the regional genetic landscape. The high pCR rates observed in this cohort reinforce the chemosensitivity of BRCA-deficient tumors to standard anthracycline and taxane-based neoadjuvant protocols. Furthermore, the identification of pathogenic variants, including specific splice-site variants, underscores the importance of comprehensive genetic testing in this population to optimize the use of PARP inhibitors and immunotherapy. Conclusion: Our findings confirm a significant prevalence of germline BRCA variants in TNBC patients in our region, associated with a younger age at diagnosis and favorable response to neoadjuvant therapy. These results support the integration of routine genetic testing into the standard of care to guide both surgical decisions, personalized systemic therapy and also the importance of genetic counselling to the healthy family members to take preventive measurements and early detection. Keywords: Breast cancer, BRCA variants, TNBC*

[Abstract:0322]

Outcomes of a Multidisciplinary Hereditary Tumor Board: A Five-Year Single-Center Experience

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Objective: Multidisciplinary hereditary tumor boards play a crucial role in the identification and management of patients with suspected hereditary cancer syndromes. We aimed to evaluate the clinical and genetic outcomes of patients discussed in a hereditary tumor board involving medical genetics and medical oncology specialists.

Materials-Methods: Patients evaluated at the hereditary tumor board between May 2021 and December 2025 were retrospectively analyzed. The tumor board was conducted monthly at Gazi University School of Medicine with the participation of medical genetics and medical oncology specialists. Demographic characteristics, tumor types and stages, family history, genetic testing results, and clinical recommendations were recorded.

Results: A total of 182 patients were discussed during the study period. The majority were female (76.4%), and 11.4% had multiple primary tumors. The median age was 48.2 years (IQR: 39.7–60.1). Most patients were diagnosed at an early stage (stage I–II, 63.3%), while 16.9% had locally advanced disease and 19.9% were metastatic. A positive family history of cancer was present in 63.8% of patients. The most frequently evaluated cancer types were breast (52.2%), colorectal (20.6%), and ovarian cancer (7.8%). Pathogenic variants were detected in 88 patients (48.35%), likely pathogenic variants in 23 patients (12.64%), and variants of uncertain significance (VUS) in 75 patients (41.21%). The most common pathogenic mutations were identified in BRCA2 (n=20), BRCA1 (n=11), CHEK2 (n=9), MUTYH (n=8), and ATM (n=8). CHEK2 was the most frequent likely pathogenic variant (n=6). Among VUS, the most commonly involved genes were ATM, APC, BRCA2, CHEK2, and PALB2. Following board discussions, approximately one-third of patients were referred for cascade family screening, one-third had modifications in surveillance protocols, and prophylactic surgery was recommended for nearly one-fifth of patients.

Conclusion: A multidisciplinary hereditary tumor board provides substantial clinical benefit in hereditary cancer management by guiding personalized surveillance strategies, preventive interventions, and family-based risk assessment.

Keywords: hereditary, cancer, tumor, board, multidisciplinary

Outcomes of a Multidisciplinary Hereditary Tumor Board: A Five-Year Single-Center Experience İmdat Eroğlu1, Mustafa Altay Tekeş1, Ayşe Arslan Kapuci1, Orhun Akdoğan1, Sıla Soylu Koçoğlu1, Tuba Uğur Tuzcu1, Yusuf Bahap2, Osman Sütçüoğlu1, Fatih Gürler1, Gözde Savaş1, Uğur Coşkun1, Aytuğ Üner1, Ozan Yazıcı1, Nuriye Özdemir1, Mehmet Ali Ergün2, Ahmet Özet1 1Gazi University School of Medicine, Department of Medical Oncology, Ankara, Türkiye 2Gazi University School of Medicine, Department of Medical Genetics, Ankara, Türkiye Objective: Multidisciplinary hereditary tumor boards play a crucial role in the identification and management of patients with suspected hereditary cancer syndromes. We aimed to evaluate the clinical and genetic outcomes of patients discussed in a hereditary tumor board involving medical genetics and medical oncology specialists. Materials-Methods: Patients evaluated at the hereditary tumor board between May 2021 and December 2025 were retrospectively analyzed. The tumor board was conducted monthly at Gazi University School of Medicine with the participation of medical genetics and medical oncology specialists. Demographic characteristics, tumor types and stages, family history, genetic testing results, and clinical recommendations were recorded. Results: A

total of 182 patients were discussed during the study period. The majority were female (76.4%), and 11.4% had multiple primary tumors. The median age was 48.2 years (IQR: 39.7–60.1). Most patients were diagnosed at an early stage (stage I–II, 63.3%), while 16.9% had locally advanced disease and 19.9% were metastatic. A positive family history of cancer was present in 63.8% of patients. The most frequently evaluated cancer types were breast (52.2%), colorectal (20.6%), and ovarian cancer (7.8%). Pathogenic variants were detected in 88 patients (48.35%), likely pathogenic variants in 23 patients (12.64%), and variants of uncertain significance (VUS) in 75 patients (41.21%). The most common pathogenic mutations were identified in BRCA2 (n=20), BRCA1 (n=11), CHEK2 (n=9), MUTYH (n=8), and ATM (n=8). CHEK2 was the most frequent likely pathogenic variant (n=6). Among VUS, the most commonly involved genes were ATM, APC, BRCA2, CHEK2, and PALB2. Following board discussions, approximately one-third of patients were referred for cascade family screening, one-third had modifications in surveillance protocols, and prophylactic surgery was recommended for nearly one-fifth of patients. Conclusion: A multidisciplinary hereditary tumor board provides substantial clinical benefit in hereditary cancer management by guiding personalized surveillance strategies, preventive interventions, and family-based risk assessment. Keywords: hereditary, cancer, tumor, board, multidisciplinary Introduction Hereditary cancer syndromes account for approximately 5–10% of all malignancies and are characterized by early disease onset, multiple primary tumors, and strong family aggregation [1,2]. Advances in next-generation sequencing technologies have significantly improved the detection of germline pathogenic variants associated with inherited cancer predisposition [3]. However, the interpretation of genetic results and their integration into clinical practice remain complex, requiring close collaboration among multiple medical disciplines [4]. Multidisciplinary tumor boards have long been recognized as an effective model for optimizing cancer care by improving diagnostic accuracy, treatment planning, and adherence to clinical guidelines [5]. In recent years, hereditary tumor boards specifically focusing on genetic cancer risk assessment have gained increasing importance [6]. These boards typically involve medical oncologists, clinical geneticists, genetic counselors, surgeons, and other specialists, enabling comprehensive evaluation of genetic test indications, variant interpretation, and individualized management strategies [7]. Despite their expanding use, real-world data regarding the clinical and genetic outcomes of hereditary tumor boards remain limited, particularly in middle-income countries [8]. The present study aimed to evaluate the demographic, clinical, and molecular characteristics of patients discussed within a multidisciplinary hereditary tumor board and to assess its impact on patient management and preventive strategies. Materials and Methods This retrospective observational study included patients evaluated at the Hereditary Tumor Board of Gazi University School of Medicine between May 2021 and December 2025. The tumor board was held monthly and involved specialists from the departments of Medical Genetics and Medical Oncology. Patients were referred to the board based on early-onset cancer, multiple primary tumors, rare tumor types, or a strong family history suggestive of hereditary cancer syndromes, in accordance with international testing guidelines [9,10]. Data were extracted from institutional electronic medical records and tumor board documentation. Collected variables included age at diagnosis, sex, personal and family cancer history, tumor types and stages, results of germline genetic testing, and clinical recommendations made following board discussions. Genetic testing was performed using multigene hereditary cancer panels based on individual clinical characteristics. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines as pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign, or benign [11]. Descriptive statistical analyses were conducted to summarize demographic, clinical, and molecular findings. Results A total of 182 patients were discussed during the study period. The majority of patients were female (76.4%), and the median age was 48.2 years (interquartile range [IQR]: 39.7–60.1). Multiple primary tumors were observed in 11.4% of patients. Regarding disease stage at diagnosis, 63.3% of patients had early-stage cancer (stage I–II), 16.9% had locally advanced disease, and 19.9% presented with metastatic cancer. A positive family history of cancer in at least one first- or second-degree relative was present in 63.8% of patients.

Breast cancer was the most frequently evaluated malignancy, accounting for 52.2% of cases, followed by colorectal cancer (20.6%) and ovarian cancer (7.8%). Germline pathogenic variants were identified in 88 patients (48.35%), while 23 patients (12.64%) carried likely pathogenic variants. Variants of uncertain significance were detected in 75 patients (41.21%). The most frequently observed pathogenic mutations involved BRCA2, BRCA1, CHEK2, MUTYH, and ATM. Following tumor board discussions, approximately one-third of patients were referred for cascade family screening. Surveillance protocols were modified in nearly one-third of cases, and prophylactic surgical interventions were recommended for approximately one-fifth of patients. Discussion This study demonstrates the significant clinical value of a multidisciplinary hereditary tumor board in the management of patients with suspected hereditary cancer syndromes. Nearly half of the evaluated individuals were found to carry pathogenic germline variants, underscoring the effectiveness of targeted genetic evaluation strategies [12]. The predominance of breast and colorectal cancers aligns with global epidemiological data, as these malignancies represent the largest proportion of hereditary cancer diagnoses worldwide [1,13]. The substantial contribution of moderate-penetrance genes such as CHEK2 and ATM reflects the increasing use of multigene panel testing and highlights the evolving complexity of hereditary cancer genetics [14]. A notable proportion of patients were diagnosed at early disease stages, emphasizing the role of genetic risk assessment in early detection and cancer prevention [15]. Importantly, tumor board recommendations frequently resulted in clinically actionable decisions, including intensified surveillance, prophylactic surgery, and cascade testing. The high prevalence of VUS findings remains a significant challenge. Multidisciplinary interpretation is critical in avoiding overtreatment while ensuring appropriate follow-up as variant classifications evolve [16]. Conclusion A multidisciplinary hereditary tumor board provides meaningful clinical benefit by integrating genetic data with oncological management. This collaborative model supports personalized surveillance strategies, informed preventive interventions, and systematic family risk assessment. Our findings reinforce the importance of hereditary tumor boards in improving outcomes for patients with inherited cancer predisposition and support their broader implementation in oncology centers. References: 1- Garber JE, Offit K. Hereditary cancer predisposition syndromes. J Clin Oncol. 2005;23:276 292. 2- Rahman N. Realizing the promise of cancer predisposition genes. Nature. 2014;505:302–308. 3- Lincoln SE, et al. Yield and utility of germline testing following tumor sequencing. JAMA Oncol. 2020;6:1–8. 4- Burke W, et al. Genetic testing: ethical, legal, and social implications. Annu Rev Genomics Hum Genet. 2018;19:193–212. 5- Lamb BW, et al. Multidisciplinary cancer team meetings. Lancet Oncol. 2011;12:105–113. 6- Hampel H, et al. A practice guideline from the American College of Medical Genetics. Genet Med. 2015;17:70–87. 7- Weissman SM, et al. Genetic counseling considerations in oncology. CA Cancer J Clin. 2012;62:107–136. 8- Rivera B, et al. Hereditary cancer programs in middle-income countries. Lancet Glob Health. 2020;8:e130–e139. 9- NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment. 10- ESMO Guidelines Committee. Hereditary cancer testing recommendations. Ann Oncol. 2020. 11- Richards S, et al. Standards and guidelines for the interpretation of sequence variants. Genet Med. 2015;17:405–424. 12- Kurian AW, et al. Clinical outcomes of genetic testing. J Clin Oncol. 2017;35:130–137. 13- Stoffel EM, et al. Hereditary colorectal cancer syndromes. Gastroenterology. 2019;156:223 238. 14- Easton DF, et al. Gene-panel sequencing and breast cancer risk. N Engl J Med. 2015;372:2243–2257. 15- Domchek SM, et al. Prevention strategies in hereditary cancer. JAMA. 2020;324:259–270. 16- Mersch J, et al. Cancers associated with VUS interpretation. Genet Med. 2018;20:69–75.

[Abstract:0324]

Gene-Specific Management of Variants of Uncertain Significance in Hereditary Cancer Genes: A ClinVar 2021–2025 Snapshot-Based Re-analysis Model

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Objective: Variants of uncertain significance (VUS) detected in hereditary cancer gene testing remain a major challenge in clinical decision-making. Although current guidelines generally recommend uniform periodic reinterpretation, this approach does not account for gene-specific reclassification dynamics. Therefore, using repeated comparisons of monthly ClinVar snapshots over a long-term period, we aimed to characterize the direction, timing, and determinants of VUS reclassification in hereditary cancer genes and to propose gene-specific reanalysis intervals based on data-driven evidence.

Materials-Methods: Using the GRCh38 ClinVar monthly snapshot archive covering 2021–2025 (60 consecutive releases), successive versions were compared for a hereditary cancer gene panel comprising BRCA1, BRCA2, TP53, POLE, POLD1, PTEN, APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, ATM, CHEK2, PALB2, BARD1, RAD51C, RAD51D, BRIP1, NBN, CDH1, STK11, SMAD4, BMPR1A, VHL, RET, SDHB, SDHD, and MEN1.
Variants were tracked at the ALLELEID level, reduced to unique records, and variants with discordant clinical interpretations were excluded. Reclassification events were defined bidirectionally as VUS→Benign/Likely Benign (B/LB) and VUS→Pathogenic/Likely Pathogenic (P/LP). Time-to-event patterns were summarized using Kaplan–Meier analysis, and determinants of reclassification speed in each direction were evaluated with cause-specific Cox regression. Selected in-silico scores (CADD_phred, REVEL, MVP, AlphaMissense, phyloP, and conservation metrics) were assessed in multivariable and univariable models. Reclassification tendencies were additionally evaluated by variant type.

Results: Across hereditary cancer genes, approximately 87,000 VUS were followed over five years, revealing marked gene-specific heterogeneity in reclassification dynamics. POLE showed the fastest shift toward pathogenic classification, with 1.35% reclassified as P/LP by 12 months and 2.04% by 24 months. In contrast, TP53 demonstrated the most rapid shift toward benign classification, with a median time to B/LB reclassification of 381 days and 2.38% reclassified within the first year. BRCA2, despite a high VUS burden, remained comparatively stable, with rare pathogenic reclassification (0.11% at 24 months) and slower dynamics (median 819 days).
By variant type, deletions and loss-of-function–compatible variants were more likely to be upgraded to pathogenic/likely pathogenic, whereas SNV/missense variants more frequently moved toward benign/likely benign categories. In score-based analyses, CADD_phred showed the most consistent association with pathogenic upgrading, with higher scores corresponding to faster reclassification. Conversely, higher AlphaMissense and phyloP scores were associated with a lower probability of benign reclassification (HR<1).

Conclusion: Previous studies have shown that the majority of VUS reclassifications in hereditary cancer genes tend to occur toward benign categories over time, particularly for missense variants, and our findings are consistent with this general trend while further demonstrating that both the direction and timing of VUS reclassification are strongly gene-specific. Longitudinal ClinVar snapshot comparisons show that VUS

reclassification in hereditary cancer genes follows gene- and variant-specific trajectories in both direction and speed, suggesting that uniform annual reinterpretation may not be optimal for all genes. We propose mandatory 12-month re-analysis for POLE, priority review at 6–12 months for TP53 to reduce early clinical uncertainty, and 12–24-month routine follow-up for lower-risk genes such as BRCA1/2; a gene- and variant-informed re-analysis strategy may improve clinical relevance while optimizing laboratory workload.

Keywords: *gene-specific re-analysis, hereditary cancer genes, POLE, TP53, VUS*

Gene-specific re-analysis intervals based on reclassification frequency

Recommended interval	Genes	Reclassification within follow-up*
6 months	TP53	2.45% within 12 months, 3.32% within 24 months (predominantly B/LB)
12 months	POLE	POLE: 1.35% within 12 months, 2.04% within 24 months edominantly P/LP)
18 months	BRCA2, MUTYH, MSH2, PTEN, BRCA1, RAD51D	~1.0–1.46% within 24 months
24 months	Other panel genes	<1% within 24 months

**Percentage of baseline VUS undergoing any reclassification during follow-up.*

Gene-Specific Management of Variants of Uncertain Significance in Hereditary Cancer Genes: A ClinVar 2021–2025 Snapshot-Based Re-analysis Model Özden Öztürk[1], Ahmet Ünlü[2], Başak Göğüş[1] [1] Directorate General of Public Health, Genetic Diseases Screening Laboratory, Ankara, Türkiye [2] University of Health Sciences Antalya Training and Research Hospital, Division of Medical Oncology, Antalya, Türkiye Abstract Variants of uncertain significance (VUS) identified through hereditary cancer gene testing continue to pose a major challenge for clinical interpretation, patient management, and genetic counseling. Although current practice generally relies on uniform periodic reinterpretation— most commonly at one- to two-year intervals—accumulating evidence suggests that variant reclassification is a dynamic, longitudinal process with substantial heterogeneity across genes and variant types. In this study, we performed a longitudinal re-analysis of baseline VUS using monthly ClinVar GRCh38 snapshot releases from January 2021 through December 2025. Variants were tracked at the ALLELEID level across a broad hereditary cancer gene panel, and bidirectional reclassification events were defined as transitions from VUS to benign/likely benign (B/LB) or pathogenic/likely pathogenic (P/LP). Time-to-event patterns were evaluated using Kaplan Meier analysis, and factors associated with reclassification speed were assessed with cause specific Cox regression. Variant annotation was performed using Ensembl Variant Effect Predictor, with selected in-silico scores extracted from dbNSFP. Marked gene-specific heterogeneity was observed in both the direction and timing of reclassification. TP53 showed the highest early overall reclassification activity, driven predominantly by benign-directed outcomes, whereas POLE demonstrated a distinct pathogenic-enriched trajectory with the fastest pathogenic upgrading observed across the panel. In contrast, genes such as BRCA1 and BRCA2 exhibited slower dynamics with rare pathogenic reclassification within the first two years. These findings support a gene-tailored reinterpretation strategy rather than a uniform schedule. A gene-informed re-analysis framework may reduce prolonged clinical uncertainty, prioritize laboratory resources, and improve the clinical impact of hereditary cancer genetic testing. Keywords: variants of uncertain significance; ClinVar; hereditary cancer; gene-specific reanalysis; variant reclassification Introduction

Variants of uncertain significance (VUS) identified through hereditary cancer gene testing remain a major challenge in clinical genetics and oncology. Advances in high-throughput sequencing have markedly increased the detection of rare germline variants; however, for a substantial proportion of these findings, the available evidence is insufficient to support a definitive pathogenic or benign classification. Consequently, VUS results complicate clinical decision-making, genetic counseling, and risk management for patients and their families. In current clinical practice, VUS are generally reinterpreted at uniform, fixed intervals—most commonly every one to two years. This strategy is largely shaped by guideline recommendations and practical laboratory workflows rather than by gene-specific empirical data. Growing evidence suggests that variant reclassification is not a single, static event but a longitudinal process, with both the direction and timing of reclassification varying across genes, variant types, and evidence accumulation patterns. Longitudinal studies have consistently shown that VUS are frequently reclassified over time and that most changes tend to occur toward benign or likely benign categories, particularly for missense variants, although the pace and frequency of reclassification differ substantially between genes and cohorts (Richards et al., 2015; Landrum et al., 2018; Mersch et al., 2018; Chiang et al., 2021; Chen et al., 2023). ClinVar is a continuously updated public archive of clinical variant interpretations, and its regularly released snapshot versions provide a unique opportunity to study real-world reclassification behavior at scale. Systematic comparisons of consecutive ClinVar releases allow quantification of how rapidly VUS are reclassified, in which direction they evolve, and which factors are associated with faster or slower resolution. Leveraging this longitudinal structure may therefore support the development of more rational, gene-tailored re-analysis strategies. In this study, we used monthly ClinVar GRCh38 snapshot releases from 2021 to 2025 to systematically characterize the direction, timing, and determinants of VUS reclassification across a broad hereditary cancer gene panel. By integrating time-to-event analyses with variant level and gene-level features, we aimed to generate an empirical framework for proposing gene specific re-analysis intervals that may improve clinical relevance while optimizing laboratory workload. Materials and Methods Monthly ClinVar snapshot releases aligned to the GRCh38 reference genome were obtained for the period January 2021 through December 2025, comprising 60 consecutive versions. Analyses were restricted to a predefined hereditary cancer gene panel including BRCA1, BRCA2, TP53, POLE, POLD1, PTEN, APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, ATM, CHEK2, PALB2, BARD1, RAD51C, RAD51D, BRIP1, NBN, CDH1, STK11, SMAD4, BMPR1A, VHL, RET, SDHB, SDHD, and MEN1. Baseline VUS were defined as variants classified as VUS in the January 2021 ClinVar release. Each variant was tracked at the ALLELEID level, resulting in 42,784 unique baseline VUS included in the analysis. For each variant, the baseline time point was defined as the first ClinVar release in which the variant was reported as VUS. Variants were reduced to unique records, and those with discordant or conflicting clinical interpretations were excluded to ensure interpretative consistency. Variant annotation was performed using the Ensembl Variant Effect Predictor (VEP), with additional functional and in-silico prediction scores extracted from dbNSFP. The analyzed scores included CADD_phred, REVEL, MVP, AlphaMissense, phyloP, and selected conservation metrics. For variants with multiple transcript-level annotations, a consistent summarization strategy was applied. Variants were further grouped by type, including missense/SNV, deletions, frameshift, and other loss-of-function–compatible categories. Reclassification events were defined bidirectionally as transitions from VUS to Benign/Likely Benign (B/LB) or to Pathogenic/Likely Pathogenic (P/LP). For each variant, time to first reclassification event was recorded; variants without reclassification were censored at the last available snapshot. Time-to-event patterns were summarized using Kaplan–Meier analysis, and cause-specific Cox regression models were used to evaluate factors associated with reclassification speed in each direction. Analyses were summarized at the gene level to support the derivation of gene-specific re analysis intervals. Results A total of 42,784 baseline VUS identified across the hereditary cancer gene panel were followed longitudinally over a five-year period, using the January 2021 ClinVar snapshot as the baseline and subsequent monthly releases through 2025. Cumulative analyses revealed marked gene specific heterogeneity

in both the direction and timing of VUS reclassification, indicating that reclassification dynamics were not uniform across genes. When cumulative reclassification proportions were examined at predefined time points, TP53 and POLE displayed clearly divergent patterns (Figure 1). Within the first 12 months, TP53 showed the highest overall reclassification activity among the evaluated genes, driven predominantly by transitions toward benign or likely benign categories. Specifically, 2.38% of TP53 VUS shifted to B/LB within the first year, whereas the total TP53 reclassification rate (B/LB + P/LP) reached 3.10% at 12 months; by 24 months, the total reclassification rate increased to 5.41% (Figure 1). By contrast, POLE exhibited a lower overall reclassification frequency at early time points; however, the majority of observed reclassifications were toward pathogenic or likely pathogenic categories. Pathogenic upgrading in POLE reached 1.35% by 12 months and 2.04% by 24 months, representing the fastest shift toward pathogenic classification observed in the panel. In parallel, the total POLE reclassification rate (B/LB + P/LP) was 1.58% at 12 months and 2.73% at 24 months (Figure 1). Overall, the 24-month profiles therefore reflect benign enriched reclassification in TP53 and pathogenic-enriched reclassification in POLE. Figure 1. Gene-specific cumulative reclassification of TP53 and POLE at 12 and 24 months. Across the broader gene panel, both the magnitude and direction of reclassification varied substantially (Figure 2). High-penetrance genes such as BRCA2, BRCA1, MSH2, and MUTYH showed moderate levels of reclassification, largely driven by benign or likely benign outcomes, with relatively infrequent pathogenic upgrading. Notably, BRCA2 remained comparatively stable despite a high baseline VUS burden, with rare pathogenic reclassification events (0.11% at 24 months) and slower overall dynamics (median time to reclassification: 819 days). In contrast, POLE occupied a distinct region characterized by a higher proportion of pathogenic reclassification. Several lower-risk genes clustered near the origin of the direction map, reflecting minimal reclassification activity within 24 months. Although TP53 demonstrated a predominantly benign-directed reclassification pattern, a smaller proportion of variants also underwent pathogenic upgrading, explaining its position away from the vertical axis in the direction map. Figure 2. Reclassification direction map across hereditary cancer genes at 24 months. Time-to-event analyses further highlighted differences in reclassification speed between genes. Kaplan–Meier estimates demonstrated that TP53 variants underwent reclassification earlier and more frequently than BRCA2, consistent with faster benign resolution. In comparison, POLE variants showed delayed but directionally distinct reclassification patterns, with pathogenic upgrading occurring later but at a higher relative frequency. Variant-level characteristics also influenced reclassification behavior. Deletions and variants compatible with loss-of-function mechanisms were more likely to be upgraded to pathogenic or likely pathogenic categories, whereas single-nucleotide variants and missense changes more frequently transitioned toward benign or likely benign interpretations. In score-based analyses, higher CADD_phred values were consistently associated with faster pathogenic upgrading, while higher AlphaMissense and phyloP scores were associated with a reduced probability of benign reclassification (hazard ratio 24 months POLD1, APC, MLH1, MSH6, PMS2, EPCAM, ATM, CHEK2, PALB2, BARD1, RAD51C, BRIP1, NBN, CDH1, STK11, SMAD4, BMPR1A, VHL, RET, SDHB, SDHD, MEN1 24 months) unless new evidence emerges. A gene-informed reanalysis strategy may reduce prolonged uncertainty, better allocate limited laboratory capacity, and improve the clinical impact of hereditary cancer testing, while providing a foundation for future decision-support and dynamic triage approaches. References 1. Richards S, et al. Standards and guidelines for the interpretation of sequence variants. Genetics in Medicine. 2015. 2. Landrum MJ, et al. ClinVar: improving access to variant interpretations. Nucleic Acids Research. 2018. 3. Mersch J, et al. Prevalence of variant reclassification following hereditary cancer genetic testing. Genetics in Medicine. 2018. 4. Chiang T, et al. Reclassification of variants of uncertain significance over time. NPJ Genomic Medicine. 2021. 5. Chen Y, et al. Longitudinal analysis of variant reclassification in clinical sequencing. Genetics in Medicine. 2023. 6. Harrison SM, et al. Using ClinVar as a resource to support variant interpretation. Current Protocols in Human Genetics. 2017. 7. Kang E, et al. Gene-specific machine learning improves pathogenicity prediction for BRCA variants. Genetics in Medicine. 2023. 8.

Nicora G, et al. Machine learning approaches to support variant classification in clinical genomics. Briefings in Bioinformatics. 2022.

POSTER PRESENTATIONS

[Abstract:0088]

Triple Cancer Syndrome Presenting with T-Cell Lymphoblastic Lymphoma

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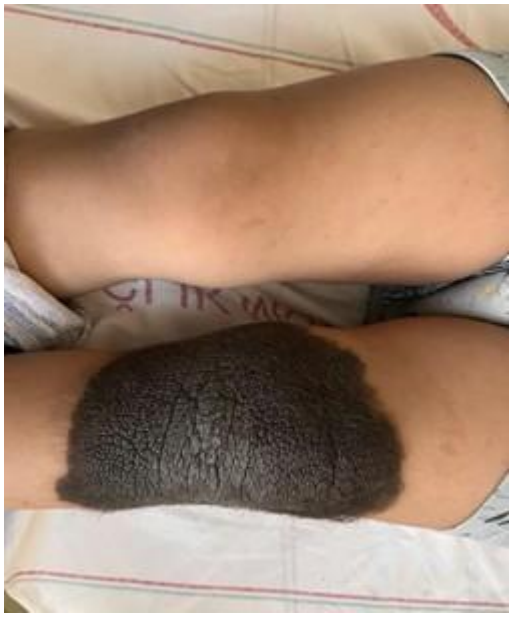
Objective: Mismatch Repair Cancer Syndrome, Lynch Syndrome and Muir Torre Syndrome are rare inherited cancer predisposition characterized by the coexistence of multiple primary malignancies, frequently associated with pathogenic variants in DNA mismatch repair (MMR) genes such as MSH2. The presence of such variants confers an increased risk for Lynch syndrome–related malignancies and hematological neoplasms. We present a pediatric case with a MSH2 pathogenic variant who developed T-cell lymphoblastic lymphoma (T-LBL).
Case: A 2-year-old male presented with progressive respiratory distress and swelling due to a large anterior mediastinal mass (20×10×7 cm) compressing the superior vena cava. Imaging suggested lymphoma. Excisional biopsy initially reported thymoma; however, histopathological reevaluation confirmed T-LBL by flow cytometric evaulation from pleural effusion liquid. Laboratory findings for hemogram and biochemical analysis were normal in range of. Bone marrow aspiration revealed normal cytology compatible with non-infiltrated marrow and Cerebrospinal fluid (CSF) revaeled normal cell morphology and negative flow cytometry.
Treatment was initiated as superior vena cava syndrome (SVC) presented with prednisolone pulse and cyclophosphamide at first. After the diagnosis of T-LBL the patient was started on the ALLIC ESCP protocol with 100% steroid dosing. Molecular genetic testing revealed a homozygous pathogenic variant in the MSH2 gene (c.1571G>C; p.Arg524Pro). Family segregation analysis identified both parents as heterozygous carriers, and the patient's sibling as homozygous, consistent with Lynch syndrome–related hereditary predisposition.

Conclusion: This case represents a rare co-occurrence of T-cell lymphoblastic lymphoma in a pediatric patient with a homozygous MSH2 mutation, fulfilling criteria for Cancer Syndromes.
Mismatch Repair Cancer Syndrome (MMRCS), Lynch Syndrome (LS), and Muir-Torre Syndrome (MTS) represent a clinical continuum of disorders arising from germline pathogenic variants in DNA mismatch repair (MMR) genes, most commonly MSH2, MLH1, MSH6, and PMS2. These genes are essential for the correction of base-pair mismatches and small insertion–deletion loops that occur during DNA replication. Dysfunction of the MMR pathway leads to microsatellite instability (MSI) and accumulation of mutations that predispose to malignancy.Café-au-lait macules (similar to those seen in neurofibromatosis type 1), axillary/inguinal freckling, hypo- or hyperpigmented skin patches and neurofibromas (NF1-like features) are the features of MMRCS and Sebaceous adenomas, or sebaceous carcinomas (face, trunk, or extremities),keratoacanthomas of MTS as LS indivudals are normal in phiscally. Our patient presented a huge 9*4 cm diameter cutanose hyperpigmented skin patch. (Figure 1)
This case emphasizes the importance of integrating molecular genetic testing into the diagnostic process of pediatric lymphoid malignancies, particularly when syndromic features or family history are present.

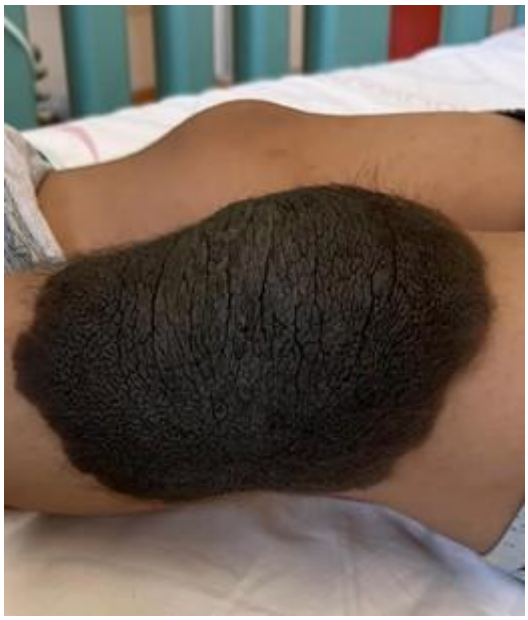
Keywords: T-cell lymphoblastic lymphoma, Mismatch Repair Cancer Syndorme, Lynch syndrome, Muir Torre Syndrome, Familial Genetic predisposition

Figure 1a



The figure depicts a 9 × 4 cm, well-demarcated hyperpigmented cutaneous lesion situated on the left periarticular region

Figure 1b



The figure depicts a 9 × 4 cm, well-demarcated hyperpigmented cutaneous lesion situated on the left periarticular region

[Abstract:0094]

Sequential Breast and Pancreatic Cancer in a Patient with a BRCA2 Mutation: A Rare Case in the Context of Hereditary Cancer

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Objective: BRCA2 gene mutations impair homologous recombination–mediated DNA repair and constitute a major component of the Hereditary Breast and Ovarian Cancer (HBOC) syndrome. In addition to breast and ovarian cancers, BRCA2 carriers have a significantly increased risk of pancreatic adenocarcinoma. The occurrence of sequential primary malignancies in the same individual is uncommon and may pose substantial challenges in clinical management. This case presents the clinical course and treatment outcomes of a patient with a pathogenic BRCA2 mutation who developed sequential breast and pancreatic cancers.
Case: A 69-year-old female patient with a family history of breast cancer in two sisters and one cousin underwent multigene panel testing in 2021, which revealed a pathogenic BRCA2 (c.6174delT) mutation. Her first primary malignancy was estrogen receptor–positive, HER2-positive invasive ductal carcinoma of the right breast diagnosed in 2013. She underwent modified radical mastectomy followed by AC-T plus trastuzumab adjuvant chemotherapy and radiotherapy. She subsequently received approximately 10 years of endocrine therapy, during which no recurrence was observed.

Her second primary malignancy was diagnosed in 2016 when she presented with abdominal pain and weight loss. Imaging revealed pancreatic ductal adenocarcinoma (T3N1M0). She received neoadjuvant FOLFIRINOX, followed by surgical resection. In 2022, liver metastasis developed, and she was treated with FOLFOX, achieving a partial response, after which capecitabine maintenance therapy was administered. Following progression, low-dose carboplatin–paclitaxel resulted in stable disease, although recurrent hematologic toxicities required multiple dose adjustments. A PARP inhibitor was considered due to her BRCA2 status; however, significant hematologic toxicity risk precluded its use. As of 2025, the patient remains on single-agent paclitaxel with stable disease and an ECOG performance status of 1.
Conclusion: This case illustrates the broad clinical spectrum of germline BRCA2 mutations, a central component of the Hereditary Breast and Ovarian Cancer (HBOC) syndrome, and highlights the potential for multiple primary malignancies within the same individual. The patient's long-term remission following multimodality treatment for breast cancer contrasts with the later development of pancreatic adenocarcinoma, reflecting the established elevated pancreatic cancer risk in BRCA2 carriers.

The strong response to platinum-based chemotherapy aligns with the homologous recombination repair deficiency characteristic of BRCA2-associated tumors. However, recurrent hematologic toxicities limited treatment continuity and prevented the use of PARP inhibition despite its proven benefit in BRCA-mutated pancreatic cancer.

Overall, this case underscores the importance of multidisciplinary care, genetic counseling, family screening, and personalized treatment approaches to optimize outcomes in individuals with hereditary cancer syndromes.

Keywords: BRCA2 mutation, Hereditary Breast and Ovarian Cancer (HBOC), Pancreatic ductal adenocarcinoma, Platinum-based chemotherapy, Homologous recombination deficiency (HRD)

[Abstract:0104]

Promising response to PARP inhibitor after multiple lines of chemotherapy: A case of ovarian cancer

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Objective: Ovarian cancer is characterized by a high recurrence rate and the development of resistance to treatment in advanced stages. The standard approach is platinum-based chemotherapy in conjunction with surgery. Additionally, screening for BRCA 1/2 genes, associated with hereditary breast/ovarian cancer syndrome (HBOC), is a critical step in treatment planning and preventive strategies. However, treatment options after multi-line therapy are limited. PARP inhibitors show promising results, particularly in patients with BRCA mutations.
Case: A 44-year-old female patient was diagnosed with FIGO stage IV high-grade serous ovarian cancer in 2020. The patient's family history included ovarian cancer in her aunt's daughter. At the time of diagnosis, she underwent debulking surgery, achieving maximal cytoreduction, and the pathology report indicated pT3aN1bM1b. Adjuvant treatment consisted of six cycles of platinum-taxane combination therapy. Due to recurrence, the patient received multiple lines of treatment (platinum rechallenge, topotecan plus bevacizumab, and pegylated liposomal doxorubicin). In the fourth year of sequential treatments, a somatic BRCA1 mutation was detected. PARP inhibitor therapy (olaparib) was initiated at an external center despite the advanced stage of the disease. She applied to our center for the first time during this period and was followed by manageable grade 1-2 hematological side effects. The patient progressed both radiologically and with an increase in tumor marker levels approximately 12 months of Olaparib treatment. At present, she is undergoing chemotherapy due to progressive disease.
Conclusion: All patients diagnosed with high-grade serous ovarian cancer should undergo BRCA mutation testing, and those with a positive test result should initiate PARP inhibitor therapy. This also offers an opportunity to screen the patient's relatives for HBOC. Our case demonstrates that PARP inhibitors may be beneficial when other treatment options have been exhausted. Furthermore, these agents may be valuable for patients with late-stage disease. However, it is a significant drawback that our patient did not undergo BRCA mutation testing for maintenance PARP inhibition therapy after the initial platinium treatment.

Keywords: Ovarian cancer, BRCA1 mutation, PARP inhibitor therapy

[Abstract:0105]

Gastric cancer and osteosarcoma in a patient with a germline Tp53 mutation: a case suggestive of Li-Fraumeni Syndrome

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Istanbul University Oncology Institute

Objective: Early recognition of hereditary cancer syndromes allows timely initiation of surveillance programs for affected family members.
Case: Personal History:2009 Osteosarcoma,2024 Gastric adenocarcinoma
Family History: Father gastric cancer at age 38 (deceased), Paternal uncle colon cancer at age 68 (deceased), sister osteosarcoma at age 39 (currently under treatment)

A 29-year-old female patient was diagnosed with osteosarcoma in 2009 at the age of 14 after presenting with pain and swelling in the right thigh. Imaging studies revealed a 4 cm mass located at the distal end of the right femur. A biopsy of the lesion confirmed the diagnosis of osteosarcoma.The patient received 4 cycles of neoadjuvant PEI chemotherapy (ifosfamide, cisplatin, etoposide), followed by surgical resection. Postoperative pathological examination demonstrated osteosarcoma with 90% tumor necrosis and negative surgical margins. Subsequently, the patient completed 3 cycles of adjuvant PEI chemotherapy and was placed under routine follow-up. No evidence of recurrence or metastasis was detected during follow-up.In 2024, the patient presented with epigastric pain. Upper gastrointestinal endoscopy revealed a mass involving the esophagogastric junction with extension to the gastric cardia. Gastric biopsy showed adenocarcinoma. Systemic staging with PET-CT demonstrated multiple metastatic lesions in the liver. The patient was diagnosed with metastatic gastric adenocarcinoma and initiated on FLOT chemotherapy (5-fluorouracil, docetaxel, oxaliplatin). Molecular analysis of the tumor revealed microsatellite stability (MSI-S), PD-L1 negativity, and HER2 IHC score of 2+. Subsequent HER2 FISH analysis was positive, and trastuzumab was added to the treatment regimen. After receiving 11 cycles of FLOT and 8 cycles of trastuzumab, interim imaging showed complete response of the primary gastric lesion and marked regression of hepatic metastases, consistent with a partial response. Treatment was therefore continued with FUFA (5-fluorouracil and folinic acid) plus trastuzumab as maintenance therapy.Genetic analysis was performed using next-generation sequencing on DNA isolated from peripheral blood. A heterozygous likely pathogenic variant was identified in the TP53 gene (NM_000546.6). The detected variant was c.783-1G>T, located at chromosome 17 (chr17:7673838).This variant has been previously reported in the literature and is registered in the ClinVar database (ClinVar ID: 634661), where it has been classified once as pathogenic and twice as likely pathogenic. Based on clinical history and genetic findings, the patient was diagnosed with Li-Fraumeni syndrome, and both the patient and her first-degree relatives were referred for genetic counseling. The patient is currently under active treatment and follow-up at our institution.
Conclusion: Li-Fraumeni syndrome is a rare, autosomal dominant hereditary cancer predisposition syndrome characterized by a markedly increased lifetime risk of developing multiple early-onset malignancies. It is most commonly associated with germline mutations in the TP53 tumor suppressor gene. Cancers commonly associated with Li-Fraumeni syndrome include:soft tissue and bone sarcomas,breast cancer (often early-onset),brain tumors, adrenocortical carcinoma, leukemia, gastrointestinal malignancies.
Cancers may occur in childhood, adolescence, or early adulthood, and patients frequently develop more than one primary tumor. This case highlights the importance of considering hereditary cancer syndromes in patients with early-onset malignancies and multiple primary tumors. Long-term surveillance and genetic evaluation are crucial in individuals with a history suggestive of Li-Fraumeni syndrome.

Keywords: Li-Fraumeni Syndrome, Soft tissue and bone sarcomas, Gastrointestinal malignancies, Tp 53, NGS

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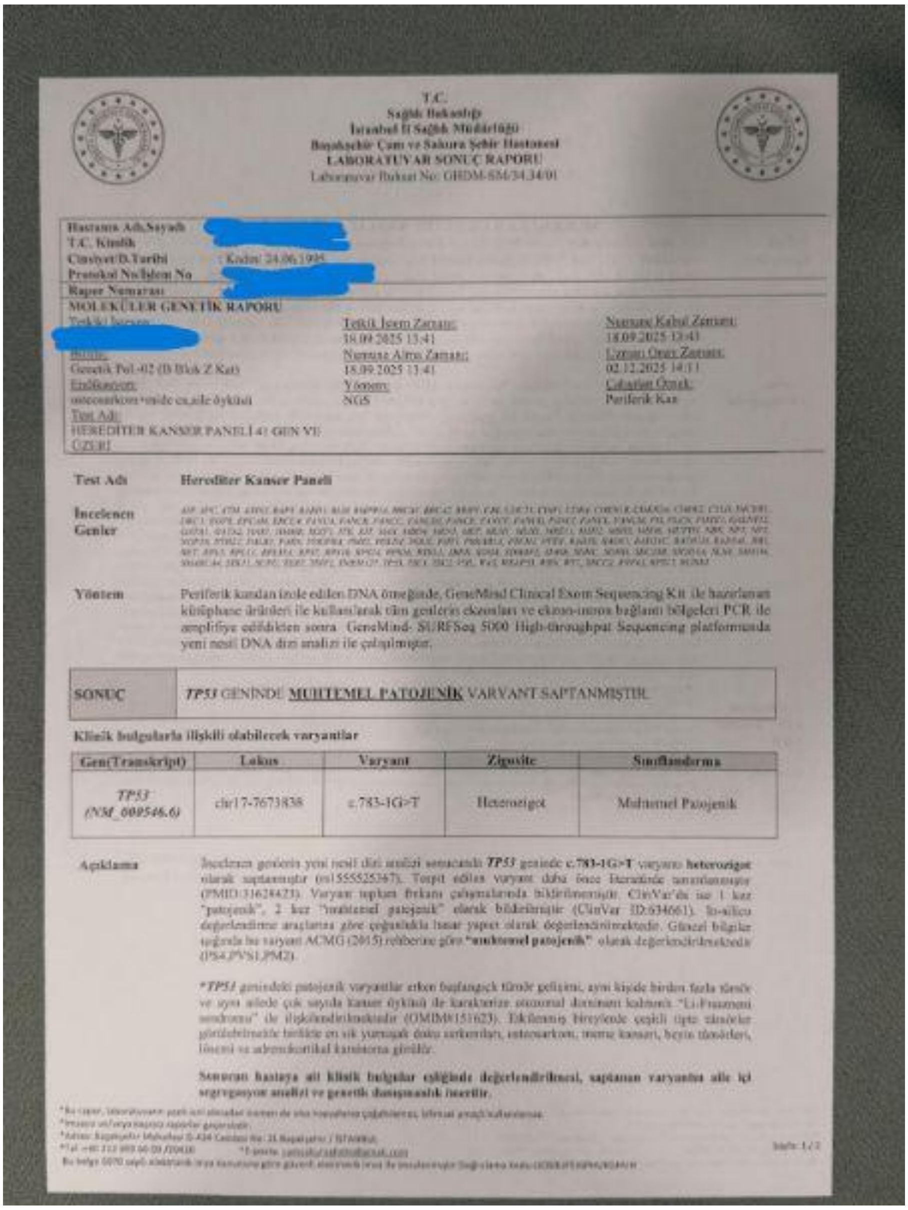
ngs



T.C.
Sağlık Bakanlığı
İstanbul İl Sağlık Müdürlüğü
Başakşehir Çam ve Sakura Şehir Hastanesi
LABORATUVAR SONUÇ RAPORU
Laboratuvar Ruhsat No: GHDM-SM/34.34/01

Hastanın Adı,Soyadı [redacted]
T.C. Kimlik
Cinsiyet/D.Tarihi : Kadın/ 24.06.1995
Protokol No/İşlem No [redacted]
Rapor Numarası

MOLEKÜLER GENETİK RAPORU

Tetkiki İsteyen: [redacted]	Tetkik İstem Zamanı: 18.09.2025 13:41	Numune Kabul Zamanı: 18.09.2025 13:41
Birim: Genetik Pol.-02 (B Blok Z Kat)	Numune Alma Zamanı: 18.09.2025 13:41	Uzman Onay Zamanı: 02.12.2025 14:11
Endikasyon: osteosarkom+mide ca,aile öyküsü	Yöntem: NGS	Çalışılan Örnek: Periferik Kan
Test Adı: HEREDİTER KANSER PANELİ 41 GEN VE ÜZERİ		

Test Adı Herediter Kanser Paneli

İncelenen Genler

Yöntem Periferik kandan izole edilen DNA örneğinde, GeneMind Clinical Exom Sequencing Kit ile hazırlanan kütüphane ürünleri ile kullanılarak tüm genlerin ekzonları ve ekzon-intron bağlantı bölgeleri PCR ile amplifiye edildikten sonra GeneMind- SURFSeq 5000 High-throughput Sequencing platformunda yeni nesil DNA dizi analizi ile çalışılmıştır.

SONUÇ	***TP53*** GENİNDE **MUHTEMEL PATOJENİK** VARYANT SAPTANMIŞTIR.

Klinik bulgularla ilişkili olabilecek varyantlar

Gen(Transkript)	Lokus	Varyant	Zigosite	Sınıflandırma
TP53 (*NM_000546.6*)	chr17-7673838	c.783-1G>T	Heterozigot	Muhtemel Patojenik

Açıklama İncelenen genlerin yeni nesil dizi analizi sonucunda ***TP53*** geninde **c.783-1G>T** varyantı **heterozigot** olarak saptanmıştır (rs1555525367). Tespit edilen varyant daha önce literatürde tanımlanmıştır (PMID:31628423). Varyant toplum frekans çalışmalarında bildirilmemiştir. ClinVar'da ise 1 kez "patojenik", 2 kez "muhtemel patojenik" olarak bildirilmiştir (ClinVar ID:634661). In-silico değerlendirme araçlarına göre çoğunlukla hasar yapıcı olarak değerlendirilmektedir. Güncel bilgiler ışığında bu varyant ACMG (2015) rehberine göre **"muhtemel patojenik"** olarak değerlendirilmektedir (PS4,PVS1,PM2).

**TP53* genindeki patojenik varyantlar erken başlangıçlı tümör gelişimi, aynı kişide birden fazla tümör ve aynı ailede çok sayıda kanser öyküsü ile karakterize otozomal dominant kalıtımlı "Li-Fraumeni sendromu" ile ilişkilendirilmektedir (OMIM#151623). Etkilenmiş bireylerde çeşitli tipte tümörler görülebilmekle birlikte en sık yumuşak doku sarkomları, osteosarkom, meme kanseri, beyin tümörleri, lösemi ve adrenokortikal karsinoma görülür.

Sonucun hastaya ait klinik bulgular eşliğinde değerlendirilmesi, saptanan varyantın aile içi segregasyon analizi ve genetik danışmanlık önerilir.

[Abstract:0113]

Global Trends and Citation Impact of Artificial Intelligence–Based Radiomics in Hereditary Cancer Imaging

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Objective: The objective of this study was to systematically evaluate global research trends in artificial intelligence– and radiomics-based radiological studies focusing on hereditary cancer syndromes and to identify factors associated with citation impact[1,2]. Using a bibliometric approach, we aimed to assess whether publication characteristics—including document type, funding status, international collaboration, and author number—were independently associated
with citation performance[3,4,5].

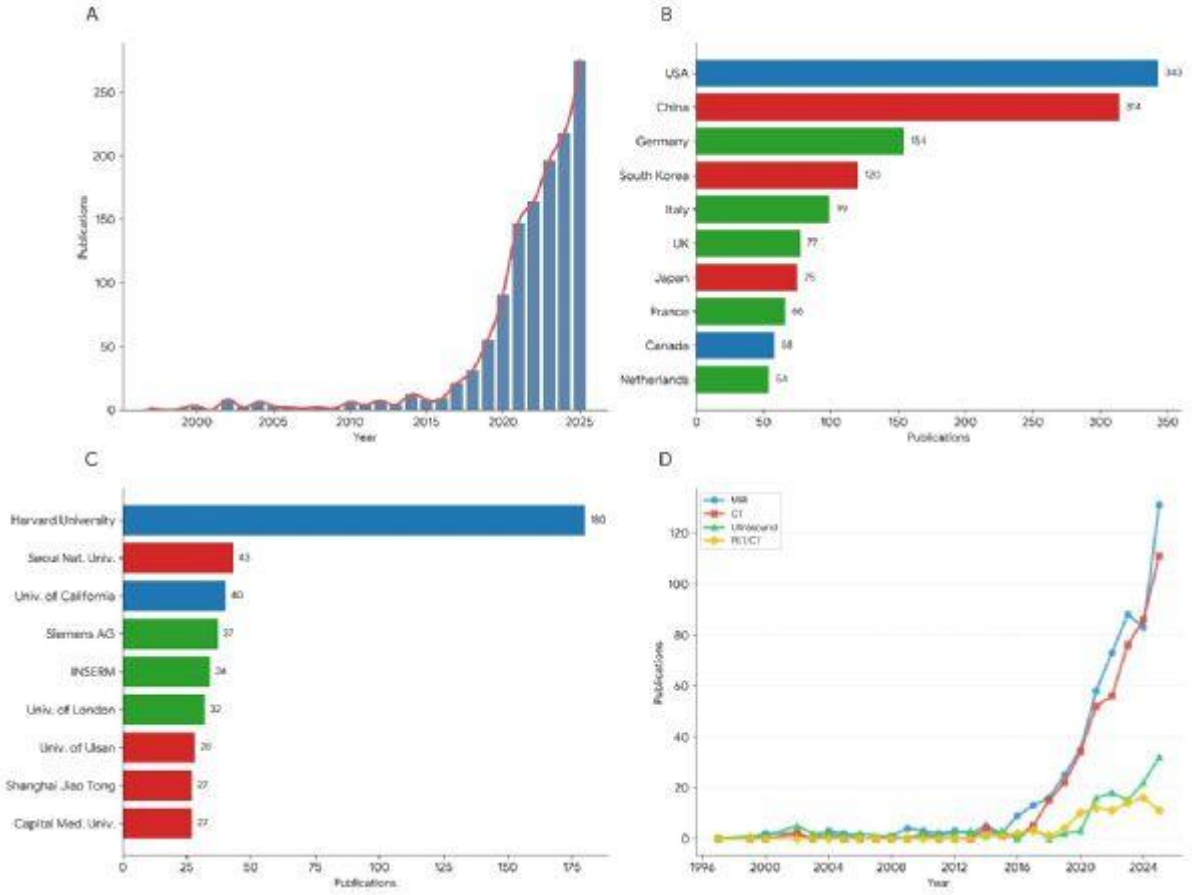
Materials-Methods: A bibliometric analysis was conducted using the Web of Science Core Collection. Publications on artificial intelligence and radiomics in hereditary cancer syndromes were identified through a topic-based search combining hereditary cancer–related, radiological imaging, and AI-related terms. Publications from 1997 to 2025 were included.
Extracted data comprised publication year, document type, author list, institutional affiliations, funding information, and total citation counts. Publications were classified as original articles or review articles. Funding status was defined by the presence of funding information, and international collaboration by authors from more than one country. Author number was calculated per publication. Citation impact was analyzed using non-parametric tests and multivariable negative binomial regression, with statistical significance set at $p < 0.05$.

Results: A total of 1,312 publications related to artificial intelligence and hereditary cancer imaging were included. Annual scientific output remained limited until the mid-2010s, followed by a sharp exponential increase after 2018, reaching a peak of 275 publications in 2025 (Figure 1A). The estimated 10-year compound annual growth rate was 42.4%, indicating rapid expansion of the field.
Geographically, research output was dominated by the United States (n = 343) and China (n = 314), followed by Germany and South Korea, including Turkey (Figure 1B). Europe and East Asia collectively contributed a substantial proportion of publications. At the institutional level, the Harvard University System was the most productive contributor, markedly exceeding other institutions (Figure 1C).
Regarding imaging modalities, MRI (n = 568) and CT (n = 469) accounted for the majority of studies. Temporal analysis demonstrated that MRI- and CT-based publications increased in parallel after 2019, whereas ultrasound and PET/CT showed more modest growth (Figure 1D). These findings highlight the central role of cross-sectional imaging in AI-driven hereditary cancer research.
Keyword co-occurrence (Figure 2A) and overlay network analyses (Figure 2B), with minimum keyword occurrence threshold = 15, revealed tightly connected clusters centered on radiomics, deep learning, machine learning, and artificial intelligence, with recent thematic shifts toward computed tomography, prognosis, and deep learning–based models.
Citation analysis was performed using negative binomial regression (Table 1). Review articles were associated with significantly higher citation counts compared with original articles ($p < 0.05$). International collaboration and author count were independently associated with increased citation impact ($p < 0.001$), while funding status was not. Publication year demonstrated a negative association with total citations, reflecting shorter citation windows for recent studies.

Conclusion: AI-based imaging research in hereditary cancers has grown rapidly, driven by MRI and CT applications[6]. Citation impact is independently influenced by article type, international collaboration, and author count, highlighting the importance of collaborative and synthesis-oriented research in this evolving field.

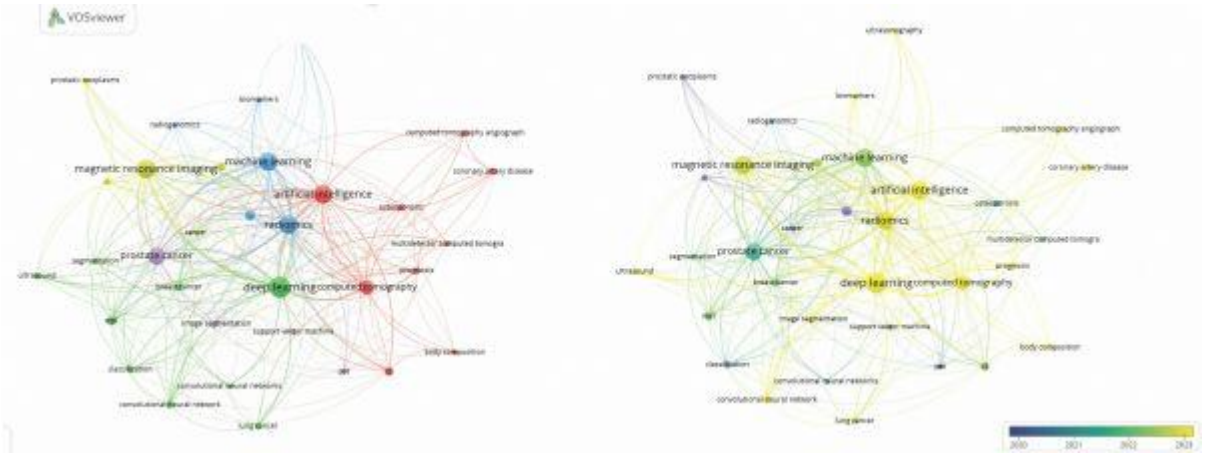
Keywords: Artificial intelligence, Bibliometric analysis, Hereditary cancer, Radiomics

Figure 1



Global publication trends, geographic distribution, and imaging modalities in AI-based radiological research on hereditary cancers.

Figure 2



Keyword co-occurrence and overlay analyses of AI and radiomics research in hereditary cancers.

Table 1.

Variable	Variable	Incidence Rate Ratio (IRR)	95% Confidence Interval	p value
Document type	Review vs Original Article	1.25	1.01–1.54	0.044
Funding status	Funded vs Non-funded	1.01	0.89–1.15	0.832
International collaboration	Yes vs No	1.81	1.37–2.39	<0.001
Author count	Per additional author	1.02	1.01–1.03	<0.001
Publication year	Per year increase	0.72	0.71–0.74	<0.001

Citation impact analysis of publication characteristics. (IRR derived from multivariable negative binomial regression. Values >1 indicate higher citation rates. The model was adjusted for publication year.)

[Abstract:0119]

Lynch Syndrome Associated Pediatric MSI High Colorectal Adenocarcinoma With Subsequent High-Grade Glial Tumor: A Tumor-Agnostic Treatment Experience

Cem Çanakçi[1], Melda Berber Hamamcı[1], Sonay İncesoy Özdemir[1], Handan Dinçaslan[1], Vafa Maharramova[1], Nihal Ekin Dağ[1], Nubar Mustafayeva[1], Nur Ayça Çelik[1], Dilara Doğan[1], Hatice Ilgın Ruhi[2], Berna Savaş[3], Cevriye Cansız Ersöz[3], Seda Kaynak Şahap[4], Suat Fitöz[4], Emel Cabı Ünal[1], Nurdan Taçyıldız[1]

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Objective: Lynch syndrome is an autosomal dominant hereditary cancer predisposition syndrome caused by germline mutations in DNA mismatch repair (MMR) genes. Although colorectal cancer is the most common malignancy associated with Lynch syndrome, central nervous system tumors may also occur, particularly with prolonged survival. Microsatellite instability–high (MSI-H) tumors demonstrate high responsiveness to immune checkpoint inhibitors, forming the basis of tumor-agnostic treatment strategies. Here, we present a pediatric patient with genetically confirmed Lynch syndrome who achieved long-term remission of MSI-H colorectal cancer with nivolumab and subsequently developed a high-grade glial tumor.

Case: A 10-year-old boy presented with a two-month history of weight loss and vomiting, followed by one week of bright red rectal bleeding. Laboratory evaluation revealed microcytic anemia, thrombocytosis, and elevated carcinoembryonic antigen levels. Abdominopelvic computed tomography demonstrated a rectosigmoid mass with invasion of perirectal fat and regional lymphadenopathy.

The patient underwent low anterior resection. Histopathological examination revealed grade 2 adenocarcinoma with perineural invasion and positive lateral surgical margins. Immunohistochemical analysis showed loss of nuclear expression of MLH1 and PMS2, with preserved MSH2 and MSH6 expression. Microsatellite instability testing confirmed MSI-high status. Given the strong family history of gastrointestinal malignancies, comprehensive genetic testing was performed, which demonstrated a heterozygous deletion involving exons 16–17 of the MLH1 gene, confirming the diagnosis of autosomal dominant Lynch syndrome.

Postoperative imaging revealed no residual tumor mass; only minimal residual tissue consistent with postoperative changes was observed. Following surgery, the patient received FOLFOX and FOLFIRI chemotherapy regimens and achieved complete remission. Due to the MSI-H tumor profile and confirmed Lynch syndrome, tumor-agnostic immunotherapy with nivolumab was initiated at a dose of 3 mg/kg every two weeks. The patient remained in complete clinical and radiological remission during long-term follow-up and is currently being monitored in remission.

In December 2024 (6 years after first diagnosis), the patient presented with headache. Brain magnetic resonance imaging revealed a predominantly cystic mass with a contrast-enhancing solid component and thick wall enhancement in the left frontal lobe, causing midline shift and parenchymal compression. Subtotal surgical resection was performed, and histopathological evaluation was consistent with a high-grade glial tumor. Postoperatively, the patient received radiotherapy. Based on molecular findings, targeted therapy with dabrafenib and trametinib was initiated. Nivolumab was discontinued due to unavailability of the drug. After 1 year of diagnosis patient is on remission, with good condition.

Conclusion: This case highlights the potential for multiple primary malignancies in pediatric patients with Lynch

syndrome and underscores the importance of long-term surveillance. Durable remission achieved with nivolumab in MSI-H colorectal cancer supports the efficacy of tumor-agnostic immunotherapy. The subsequent development of a high-grade glial tumor despite ongoing remission further emphasizes the need for vigilant multidisciplinary follow-up in hereditary cancer syndromes.

Keywords: Lynch syndrome, Pediatric colorectal cancer, High-grade glial tumor, Tumor-agnostic therapy, Nivolumab

[Abstract:0121]

Early-Onset Gardner Syndrome in an Adolescent with Delayed Diagnosis Despite Positive Family History

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Objective: Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary cancer syndrome caused by pathogenic variants in the APC gene and is characterized by early-onset colorectal adenomatous polyposis with an almost inevitable risk of colorectal cancer if left untreated. Gardner syndrome is a phenotypic variant of FAP, distinguished by the presence of extracolonic manifestations such as osteomas, thyroid disease, congenital hypertrophy of the retinal pigment epithelium, and soft tissue tumors. Early identification in childhood and adolescence is essential for timely intervention, appropriate surveillance, and family-based risk assessment.
Case: A 15-year-old female presented with a two-year history of intermittent rectal bleeding and abdominal pain. Despite multiple hospital visits, her symptoms had repeatedly been attributed to anal fissures. Five months prior to referral, abdominal ultrasonography performed due to persistent abdominal pain revealed a 2 cm hypoechoic lesion in the liver. Subsequent upper and lower gastrointestinal endoscopy demonstrated diffuse polypoid lesions involving both the upper and lower gastrointestinal tract. Histopathological evaluation of biopsy specimens was consistent with multiple adenomatous polyps.
Given a known maternal history of familial adenomatous polyposis, germline APC testing confirmed the diagnosis, identifying a pathogenic nonsense variant c.4012C>T (p.Gln1338*) (VAF 48%) and a likely pathogenic frameshift variant c.3133_3134del (p.Gln1045Glufs*2) (VAF 35%). The patient underwent prophylactic total colectomy. Further evaluation revealed multiple extra-intestinal manifestations, including a solid–cystic lesion in the right ovary, bilateral solid thyroid nodules, an osteoma in the proximal right tibia, and congenital hypertrophy of the retinal pigment epithelium on ophthalmologic examination, establishing the diagnosis of Gardner syndrome. Fine-needle aspiration biopsy of the thyroid nodules revealed cribriform-morular thyroid carcinoma, and total thyroidectomy was subsequently performed. Cascade genetic testing was offered to first-degree relatives, and genetic analysis was initiated for the patient's siblings.
Conclusion: This case illustrates the broad clinical spectrum of Gardner syndrome in adolescence and underscores the critical importance of early recognition of hereditary cancer syndromes. Notably, despite a positive family history of FAP, the patient experienced a significant delay in diagnosis, with gastrointestinal symptoms misattributed to benign conditions for two years. This highlights the need for increased awareness among healthcare providers regarding family history driven evaluation, early genetic testing, and timely referral to specialized centers to prevent delayed diagnosis and associated morbidity.

Keywords: Hereditary cancer syndrome, Gardner syndrome, Familial adenomatous polyposis

[Abstract:0122]

Importance of the CHEK2 VUS Variant in a Case with Three Primary Cancers and a Dense Family History: A Case Report

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Objective: The use of Next-Generation Sequencing (NGS) technologies in cancer genetics has increased the reporting of "Variants of Uncertain Significance" (VUS) in recent years. CHEK2 is a tumor suppressor gene that leads to a moderate increase in risk. (1,2) While CHEK2 is traditionally known as a moderate-risk tumor suppressor gene, its role in non-classical cancers is still being explored. (3,4) The aim of this study is to discuss the clinical value of the CHEK2 VUS variant identified in a patient with three different primary malignancies—breast, stomach, and pancreas—and a clustering of breast cancer among first-degree relatives, in light of the current literature.
Case: A 66-year-old female with a family history of breast cancer (mother and sister) was diagnosed with locally advanced gastric adenocarcinoma in 2019. Following a perioperative FLOT regimen and surgery (ypT3N1M0), she remained under close follow-up. In 2022, screening mammography—prompted by her family history—detected an 8 mm mass in the right breast. Pathology confirmed invasive breast carcinoma (NST, ER/PR positive, HER2 negative, grade 2), and she underwent breast-conserving surgery (pT1N0) followed by adjuvant radiotherapy and letrozole. In July 2025, the patient presented with pruritus and hyperbilirubinemia; imaging revealed a 38 mm mass in the pancreatic head, diagnosed as poorly differentiated pancreatic adenocarcinoma. Due to vascular involvement, systemic chemotherapy with nab-paclitaxel and gemcitabine was initiated. Genetic testing revealed no mutations in BRCA1, BRCA2, TP53, PALB2, CDH1, or STK11, but identified a c.1312G>T VUS in the CHEK2 gene. The early detection of her breast cancer was attributed to the aggressive monitoring strategy adopted due to her family history and this genetic variant.
Conclusion: This case summarizes the management challenges clinicians face when genetic reports remain "uncertain". CHEK2 mutations are typically linked to breast, colon, and prostate cancers. However, recent large-scale studies suggest that CHEK2 carriers have a 2.3-fold increased risk of gastric cancer and a heightened risk for pancreatic cancer through pathways similar to ATM and BRCA2. (5,6) This reinforces the possibility that the pancreatic involvement in our case is part of a CHEK2-related hereditary spectrum rather than a coincidental occurrence.
While NCCN and ACMG guidelines do not recommend intensive screening based solely on VUS results, this patient's multiple primaries and dense family burden suggest that such variants should be managed with caution, akin to "likely pathogenic" results. (1) This case emphasizes that genetic results must be interpreted alongside clinical history, supporting the need for aggressive follow-up in high-risk VUS carriers.

Keywords: breast cancer, gastric cancer, hereditary cancer, pancreatic cancer, variants of uncertain significance

[Abstract:0125]

Hormone receptor status is associated with BRCA gene type in patients with germline BRCA-mutated breast cancer

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Objective: Breast tumors with distinct biological and pathological characteristics are caused by germline mutations in the tumor suppressor genes Breast Cancer gene (BRCA) 1 and BRCA2, which are associated with a markedly increased risk of breast cancer. According to the literature, BRCA2-associated tumors are usually more heterogeneous and more frequently hormone receptor-positive, while BRCA1-associated breast cancers are often linked to high-grade, basal-like, and hormone receptor (HR)-negative phenotypes. However, using real-world data to evaluate the relationship between HR status and BRCA gene type remains clinically significant.
Materials-Methods: Patients diagnosed with breast cancer between 2001 and 2025 at the Medical Oncology Department of Aydin Adnan Menderes University, with available clinical data, were included in the study. Demographic, clinicopathological, and genomic data were retrospectively collected. Genomic DNA extracted from peripheral blood samples of 28 breast cancer patients was analyzed for BRCA1 and BRCA2 mutations using next-generation sequencing. Identified variants were classified according to the American College of Medical Genetics and Genomics guidelines.
Results: The median age of the patients was 45 years (range: 28–69). 18 patients (64.3%) were premenopausal and 10 (35.7%) were postmenopausal. Most patients (67.9%) had stage II disease at the time of diagnosis. Only 10.7% had stage I disease, 14.3% had stage III disease, and 3.6% had stage IV disease. A palpable mass in the breast or axilla was the most common symptom, seen in 85.7% of patients. Primary tumor localization was the left breast in 50%, the right breast in 46.4%, and bilateral in 3.6%. Invasive ductal carcinoma was the predominant histologic subtype (89.3%). According to HR status, 53.6% of patients were estrogen receptor (ER)-positive and 46.4% were progesterone receptor(PR)-positive. Molecular subtypes included Luminal A (21.4%), Luminal B/Human Epidermal Growth Factor Receptor (HER)2-negative (21.4%), Luminal B/HER2-positive (7.1%), HER2-positive non-luminal (3.6%), and triple-negative breast cancer (39.3%). Surgical treatment with modified radical mastectomy or breast-conserving surgery was performed in 85.7% of patients. BRCA1 mutations were identified in 57.1% and BRCA2 mutations in 42.9% of cases; 78.6% were classified as pathogenic, 10.7% as likely pathogenic, and 10.7% as variants of uncertain significance. Neoadjuvant chemotherapy was administered to 50% of patients, with a pathological complete response rate of 50% among stage I–III patients. A family history of cancer was present in 73.4% of cases. During follow-up, 14.3% developed a second primary malignancy, all ovarian cancer. Mean overall survival was 257.3 ± 29.3 months. BRCA1 mutations were predominant in ER- and PR-negative tumors, whereas BRCA2 mutations were more frequent in hormone receptor–positive tumors, with statistically significant associations for both ER (Fisher's exact test, $p = 0.047$) and PR status ($\chi^2 = 8.429$, $p = 0.004$).
Conclusion: We found a strong correlation between BRCA gene type and HR status in this real-world cohort of breast cancer patients with germline BRCA mutations. While BRCA2 mutations were more commonly found in hormone receptor-positive diseases, BRCA1 mutations were primarily linked to ER- and PR-negative tumors. These results demonstrate the biological distinctions among BRCA-associated breast cancers and imply that combining germline genetic data with tumor biology may enhance clinical judgment.

Keywords: *BRCA1*, *BRCA2*, breast cancer, hereditary cancer

Baseline Clinicopathological Characteristics of Patients (n = 28)

Variable	Category	n (%)
Gene mutation	BRCA1	16 (57.1)
	BRCA2	12 (42.9)
Sex	Female	28 (100)
Menopausal status	Premenopausal	18 (64.3)
	Postmenopausal	10 (35.7)
Family history of cancer	Absent	3 (10.7)
	Present	20 (71.4)
	Unknown	5 (17.9)
History of second cancer	No	24 (85.7)
	Yes	4 (14.3)
Prophylactic TAH + BSO	No	21 (75.0)
	Yes	3 (10.7)
	Unknown	4 (14.3)
Presenting symptom	Palpable breast/axillary mass	24 (85.7)
	Breast pain	2 (7.1)
	Screening	1 (3.6)
Tumor laterality	Right breast	13 (46.4)
	Left breast	14 (50.0)
	Right+Left breast	1 (3.6)
Primary tumor location	Upper outer quadrant	9 (32.1)
	Upper inner quadrant	8 (28.6)
	Lower inner quadrant	3 (10.7)
	Lower outer quadrant	3 (10.7)
	Multicentric	2 (7.1)
	Unknown	3 (10.7)
ER status	Negative	12 (42.9)
	Positive	15 (53.6)
PR status	Negative	14 (50.0)
	Positive	13 (46.4)

Histological subtype	Luminal A	6 (21.4)
	Luminal B / HER2-	6 (21.4)
	Luminal B / HER2+	2 (7.1)
	HER2+ (non-luminal)	1 (3.6)
	Triple-negative	11 (39.3)
Stage at diagnosis	I	3 (10.7)
	II	19 (67.9)
	III	4 (14.3)
	IV	1 (3.6)
Pathological response (neoadjuvant)	pCR	14 (50.0)
	Residual disease	2 (7.1)
Relapse (Stage I–III)	No	27 (96.4)
	Yes	1 (3.6)
Final status	Alive	26 (92.9)
	Exitus	2 (7.1)
Chemotherapy (Stage I–III)	Neoadjuvant	14 (50.0)
	Adjuvant	8 (28.6)
	Neoadjuvant + Adjuvant	2 (7.1)
	None	2 (7.1)

[Abstract:0126]

Li-Fraumeni Syndrome Presenting with Breast Cancer: A Case Report

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Objective: Breast cancer is the most common cancer in women worldwide and the leading cause of cancer-related deaths, and approximately 5-10% of these patients have likely pathogenic/pathogenic variants in predisposing genes. Among hereditary causes, BRCA 1/2 are the main predisposing genes for breast cancer, and Li-Fraumeni Syndrome (LFS) is a rare cause. We aimed to share a case of ours diagnosed with Li-Fraumeni Syndrome because of its rarity and its impact on treatment and follow-up decisions.
Case: A 47-year-old female was investigated for menstrual irregularities. Mammography and breast magnetic resonance imaging (MRI) revealed a 1.5 cm mass in the upper outer quadrant of her left breast. Biopsy revealed hormone receptor (HR) positive, Her-2 negative breast cancer, and she underwent surgery. Postoperative pathology showed pT1cN0, and she received four cycles of adjuvant docetaxel-cyclophosphamide chemotherapy. The affected individual's family history was notable for glioblastoma in a brother, prostate cancer in her father, breast cancer in a paternal aunt, leukemia in the aunt's son, gastric cancer in a paternal uncle, and endometrial cancer in the uncle's daughter. Considering the diagnosis of breast cancer before the age of 50 in the patient and the substantial cancer burden within the family, a multigene panel analysis targeting cancer predisposition–related genes was performed in accordance with NCCN criteria. The panel analysis revealed a heterozygous TP53 gene variant, c.473G>A (p.Arg158His), classified as pathogenic according to ACMG 2015 criteria, with a variant allele frequency (VAF) of 56%. This variant has been previously reported multiple times in association with Li-Fraumeni syndrome. Upon evaluation of the affected individual's phenotype, family history, and genotype, the patient was considered to have Li-Fraumeni syndrome. She was enrolled in a surveillance program and has been followed by a multidisciplinary team with NCCN recommendations.
Conclusion: LFS is a rare, high-penetrance autosomal dominant cancer predisposition syndrome in the TP53. TP53, a key tumor suppressor gene, is widely recognized as the 'guardian of the genome' has important functions such as cellular stress responses, coordination of DNA repair, cell cycle control, and apoptosis. While radiotherapy is an important treatment for preventing local recurrence in breast cancer, there are case reports showing a significant increase in the risk of radio-induced secondary malignancy in these patients. However, due to the rarity of the disease and the fact that the results in the literature are from retrospective case series, the data are not sufficient to definitively say that radiotherapy is contraindicated. Although Petry et al. reported an increased risk of developing soft tissue sarcomas after radiotherapy, it was stated that case-by-case evaluation is important, considering the benefit-risk ratio.
In conclusion, careful questioning of family history during affected indivuals evaluation, thorough assessment of patients for hereditary cancers, and prompt performance of genomic tests when necessary will enable both effective treatment and follow-up planning,and earlier screening of at-risk groups for cancers caused by hereditary factors.

Keywords: Breast cancer, Hereditary cancer, Li-Fraumeni Syndrome

[Abstract:0131]

Multimodal Treatment Experience in SMARCA4-Associated Hereditary Ovarian Small Cell Carcinoma: A Case Report

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Objective: Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is a rare and highly aggressive malignancy predominantly affecting children and young women and is almost universally associated with inactivating SMARCA4 alterations. Owing to its rarity, no standard treatment strategy exists. We present a SMARCA4-associated hereditary SCCOHT case with a prolonged and complex clinical course, highlighting the benefits and limitations of multimodal treatment approaches including surgery, chemotherapy, radiotherapy, and hyperthermic intraperitoneal chemotherapy (HIPEC).

Case: A 15-year-old female underwent left salpingo-oophorectomy for an adnexal mass, with histopathology confirming SCCOHT and loss of SMARCA4 expression.Genetic analysis was performed due to the patient's young age and the aggressive tumor biology. Germline genetic testing using a hereditary cancer panel identified a heterozygous pathogenic variant in the NTHL1 gene (c.433C>T, p.Arg145Ter) and a heterozygous likely pathogenic variant in the SMARCA4 gene (c.2626A>T, p.Lys876Ter). She achieved complete response after adjuvant ifosfamide, cisplatin, and etoposide. Six months later, pelvic recurrence and an isolated brain metastasis developed. The brain lesion was resected and treated with stereotactic radiotherapy. Systemic chemotherapy, cytoreductive surgery, and HIPEC were subsequently administered. Severe grade 4 hematologic toxicity limited further systemic treatment. Germline testing identified a heterozygous SMARCA4 mutation. Despite multiple relapses and treatment-related toxicities, the patient survived nearly five years after diagnosis.

Conclusion: This case highlights the aggressive nature of hereditary SMARCA4-associated SCCOHT and the challenge of balancing intensive multimodal therapy with tolerability. Although cumulative toxicities frequently limit treatment, selected patients may achieve prolonged survival with individualized aggressive approaches. Early recognition of hereditary predisposition is essential for therapeutic decision-making, genetic counseling, and surveillance.

Keywords: SMARCA4, Small cell carcinoma of the ovary, Hereditary cancer

[Abstract:0133]

Clinical Spectrum and Management Challenges in Four Patients with Li-Fraumeni Syndrome: A Single-Center Case Series

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Introduction

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant cancer predisposition syndrome characterized by early-onset and multiple malignancies [1,2].

It is also referred to as SBLA syndrome (Sarcoma, Breast, Leukemia, Adrenal gland) and TP53-related cancer syndrome [3].

LFS is caused by germline pathogenic or likely pathogenic variants in TP53, a critical tumor suppressor gene [1,2].

TP53 plays a central role in DNA damage response, regulating cell-cycle arrest, DNA repair, and apoptosis. Loss of p53 allows survival and proliferation of genetically damaged cells, promoting carcinogenesis [4].

The aim of this poster is to present the clinical spectrum, treatment approaches, and follow-up challenges of four patients diagnosed with LFS at our center.

Results

Four female patients with confirmed Li-Fraumeni syndrome were included. Three patients harbored the TP53 c.743G>A variant, while one patient carried the TP53 c.524G>A variant.

The age at first cancer diagnosis ranged from 25 to 41 years.

Breast cancer was the most common initial malignancy, observed in three patients.

Multiple primary malignancies were detected in three of four patients, with up to five distinct cancers in a single individual. (Table 1)

The tumor spectrum included breast cancer, central nervous system tumors, soft tissue sarcoma, thymic neoplasm, salivary gland carcinoma, and uterine leiomyosarcoma.

One patient developed a radiation-associated soft tissue sarcoma, as Li-Fraumeni syndrome had not been recognized at the time of initial treatment.

A 25-year-old asymptomatic individual, who was a niece of a patient with Li-Fraumeni syndrome, underwent surveillance due to a positive family history. Routine screening led to the detection of an early-stage malignancy, emphasizing the life-saving potential of surveillance in high-risk individuals.

Discussion

This case series illustrates the broad and aggressive tumor spectrum characteristic of Li-Fraumeni syndrome.

The predominance of early-onset breast cancer is consistent with previous reports, emphasizing the need for early genetic evaluation in young patients diagnosed with breast malignancies.

The high incidence of multiple primary tumors highlights the importance of lifelong surveillance.

Notably, the development of a soft tissue sarcoma within a previously irradiated field underscores the potential risks of radiotherapy in TP53 mutation carriers and supports the recommendation to avoid radiation exposure whenever possible.

These findings reinforce the necessity of multidisciplinary management, individualized treatment planning, and comprehensive genetic counseling for both patients and their families.

Conclusion

Li-Fraumeni syndrome presents with early-onset, heterogeneous, and recurrent malignancies, posing significant

diagnostic and therapeutic challenges.
Awareness of this syndrome is critical to optimize treatment strategies, minimize therapy-related risks, and implement appropriate surveillance protocols.
Early identification of TP53 germline mutations enables personalized management and may improve long-term outcomes.

Keywords: Li fraumeni, TP53 mutation, multiple malignancies

Summary of Patients with Li-Fraumeni Syndrome

Patient	Sex	Age at First Diagnosis	Malignancies
1	F	25	Breast cancer
2	F	26	Breast cancer, ymic neoplasm
3	F	25	Breast cancer, ntralateral breast cancer, ft tissue sarcoma oillary carcinoma of the thyroid
4	F	41	Grade 2 astrocytoma, east cancer, aplastic astrocytoma, ivary gland carcinoma, erine leiomyosarcoma

[Abstract:0142]

BRCA2 Mutant Male Breast Cancer: A Case Report

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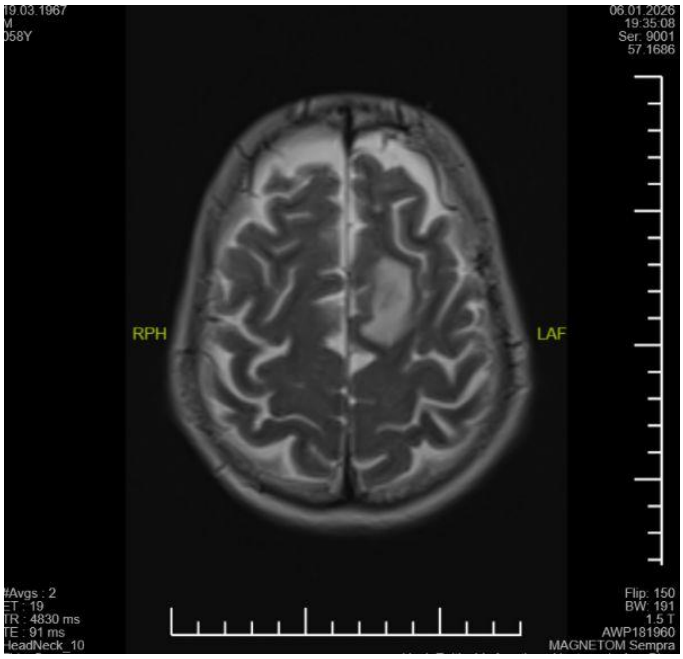
Objective: Male breast cancer is a rare entity, and data regarding its clinical course and biological behavior remain limited. In this report, we present a rare case of BRCA2-associated male breast cancer and emphasize the importance of genetic testing and surveillance in male patients.

Case: A male patient diagnosed in 2015 with hormone receptor–positive, HER2-positive breast cancer harboring a BRCA2 mutation underwent surgical resection followed by adjuvant chemotherapy, trastuzumab, radiotherapy, and five years of endocrine therapy, achieving a complete remission. After a prolonged disease-free interval, in 2025, elevated tumor markers (CEA and CA 15-3) prompted further imaging (whole body ct, endoscopy and colonoscopy) which revealed widespread metastatic disease. Although a biopsy of the metastatic lung lesions was initially planned, histopathological examination of multiple ulcerated lesions detected in the gastric corpus and fundus during endoscopy revealed findings consistent with breast cancer metastasis. The gastric biopsy demonstrated hormone receptor positivity with equivocal HER2 expression (2+); therefore, HER2 FISH analysis was planned, and the lung biopsy was cancelled. While HER2 FISH analysis was pending, cranial imaging performed due to newly developed neurological symptoms revealed brain metastasis.

Conclusion: This case highlights the importance of repeat biopsy and a multidisciplinary approach in the management of late metastatic recurrence in male breast cancer, as it there may be a biological phenotypic discrepancy between primary and metastatic lesions.

Keywords: BRCA mutation, male breast cancer, re-biopsy

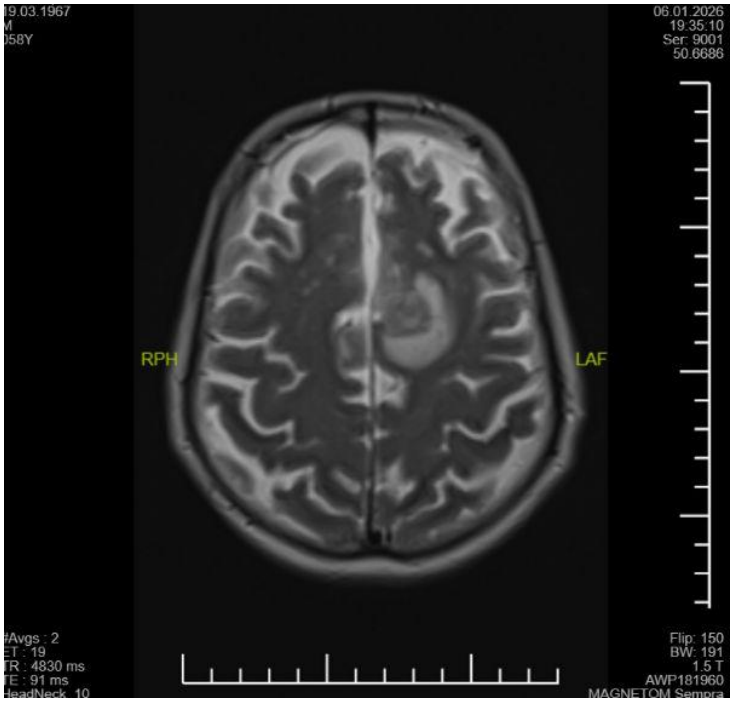
Brain mri



Edematous signal changes measuring approximately 33x21 mm were observed in the subcortical white matter of the left frontal lobe, appearing hyperintense on T2 and T2 flair A images. Images taken after IV contrast

administration revealed a mass lesion of approximately 14 mm at this level (metastatic lesion).

Brain mri



Edematous signal changes measuring approximately 33x21 mm were observed in the subcortical white matter of the left frontal lobe, appearing hyperintense on T2 and T2 flair A images. Images taken after IV contrast administration revealed a mass lesion of approximately 14 mm at this level (metastatic lesion).

[Abstract:0145]

Just a leiomyoma? A Look at HLRCC Syndrome and FH Oncometabolism

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Introduction: The fumarate hydratase (FH) gene encodes a key enzyme that catalyzes the conversion of fumarate to malate, a process known as the Krebs cycle. Germline defects in this gene lead to increased intracellular fumarate levels and activation of the pseudohypoxia pathway of the oncometabolite. Clinically, this results in the "Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)" syndrome, associated with multiple cutaneous leiomyomas, early-onset uterine leiomyomas, and aggressive renal cell carcinoma (RCC).

Aim: This study, based on patients with a history of uterine leiomyoma presenting to our clinic, aims to highlight the need for evaluation of the FH gene in individuals exhibiting characteristic features of Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) Syndrome.

Method: This study investigated FH gene mutations in eight female patients aged 20 to 50 years with leiomyomas exhibiting fumarate hydratase deficiency. DNA obtained from peripheral blood samples was analyzed using Next-Generation Sequencing (NGS) to analyze all exons and exon-intron adjacencies of the FH gene. The identified variants were evaluated against ACMG evidence, and cascade genetic screening was performed on first-degree relatives (a boy and a daughters) of the index case.

Findings: In one of the 8 patients analyzed, a missense variant (NM_000143.4):c.1090G>A, previously undetected in the literature and databases (novel), was detected in the FH gene. In the family study of the index case, the variant was also reported in both of her children.

Results: The mother, who tested positive for the variant, and her two children, a boy and a girl, have been initiated for multidisciplinary follow-up involving genetic, pediatric urology, and dermatology clinics.

Discussion: HLRCC syndrome is a rare condition that can be fatal due to the risk of metastatic kidney cancer if not diagnosed early. The variant we identified (NM_000143.4):c.1090G>A represents a new contribution to the genetic spectrum of the syndrome based on the literature. Screening for FH mutations is vital, especially in patients with characteristic findings at a young age. This approach allows for the inclusion of not only the index case but also other at-risk individuals in the family (such as the two children in our example) in an early surveillance program (annual renal MRI follow-up, etc.). In rare hereditary cancer syndromes like HLRCC syndrome, multidisciplinary follow-up is the most fundamental factor directly affecting survival time and quality of life.

Keywords: HLRCC, FH gene, Leiomyomatosis

[Abstract:0153]

Evidence for a Regional Founder Effect of the BRCA1 c.2884G>T (p.Glu962*) Variant in Southwestern Türkiye

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Objective: Founder effects contribute substantially to population-specific distributions of pathogenic variants in hereditary cancer syndromes. Although numerous BRCA1 founder mutations have been described worldwide, the BRCA1 c.2884G>T (p.Glu962*) nonsense variant is considered globally rare. However, its repeated identification within a limited geographic area in Southwestern Türkiye suggests a possible regional founder effect. This study aimed to investigate whether the recurrent detection of the BRCA1 c.2884G>T (p.Glu962*) variant reflects a regional founder effect by integrating genetic frequency data with geographic and demographic characteristics.

Materials-Methods: Clinical genetic testing data from individuals carrying the BRCA1 c.2884G>T (p.Glu962*) variant were retrospectively reviewed. Variant frequency within the study cohort was calculated and compared with frequencies reported in global population databases. The geographic origin, current place of residence, and generational distribution of affected individuals were analyzed, together with historical and contemporary regional migration patterns.

Results: The BRCA1 c.2884G>T (p.Glu962*) variant was detected at a frequency of 0.00714 in the study cohort, markedly higher than the frequency of <0.0001 reported in global population databases. A total of 23 cases carrying this variant were identified between the Acıpayam and Gölhisar regions. Among these individuals, 11 had breast cancer, 8 had ovarian cancer, and 4 were unaffected carriers. Older carriers predominantly originated from Acıpayam (Denizli) and Burdur, regions historically characterized by semi-isolated rural populations. In contrast, younger carriers were more frequently residing in the Denizli city center, consistent with rural-to-urban migration trends observed in the late 20th century.

Conclusion: The approximately 70-fold regional enrichment of the BRCA1 c.2884G>T (p.Glu962*) variant strongly supports the presence of a regional founder effect originating from the Acıpayam–Burdur region. This founder effect likely emerged following the settlement of Turkish nomadic populations in the region around the 13th century and was reinforced by intergenerational intermarriage, with subsequent dissemination to Denizli through internal migration. These findings emphasize the importance of regional genetic epidemiology and support the consideration of targeted genetic screening strategies for hereditary breast and ovarian cancer syndromes in this population.

Keywords: BRCA1, Founder Effect, Hereditary Cancer

[Abstract:0155]

Clinical Impact of Variant Reanalysis in Hereditary Cancer Panels: Reclassification Patterns of VUS in a Single-Center Cohort

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Introduction: With the routine implementation of next-generation sequencing (NGS) in clinical genetics, variant detection rates have increased substantially; however, this has also intensified the interpretative challenges posed by variants of uncertain significance (VUS). Although the ACMG/AMP 2015 guidelines provide a standardized framework for variant classification, much of the underlying evidence is time-dependent and evolves with accumulating population data, functional studies, and improved genotype–phenotype correlations. Consequently, variant classifications are dynamic rather than static. Importantly, ACMG/AMP standards emphasize that VUS should not guide clinical decision making, making periodic reanalysis and appropriate patient recontact processes critical components of follow-up in clinical practice.
Objective: This study aimed to reassess variants initially reported as VUS in hereditary cancer multigene panel testing at our center, in accordance with updated ACMG/AMP evidence codes, and to evaluate how reclassifications may affect clinical management and genetic counseling.
Methods: We retrospectively reviewed 359 individuals evaluated between 04 July 2024 and 17 October 2025. Germline testing was performed on leukocyte-derived genomic DNA using multigene hereditary cancer panels. 269 cases was sequenced using CHCS_C_v2 (60 genes) on the Illumina MiSeq platform, 90 cases was analyzed using HCS_v2_0_1_hg38 (84 genes) on the Illumina NextSeq platform. Variant analysis was conducted with Sophia DDM v4. For reanalysis, initial report classifications were compared with the most recent classifications recorded during follow-up, and reclassification outcomes were summarized.
Results: Among the 359 individuals, 227 variants had sufficient documentation for meaningful comparison (availability of ACMG-based initial classification and reanalysis data). Within this set, 86 variants initially classified as VUS were identified in 80 patients; six patients carried two distinct VUS in two different genes. In two patients, a VUS co-occurred with a pathogenic (P) or likely pathogenic (LP) variant in another gene. Following reanalysis, 82/86 variants (95.3%) remained VUS, 3/86 (3.5%) were downgraded to likely benign (LB), and 1/86 (1.2%) was upgraded to likely pathogenic (LP). Overall, 4/86 VUS (4.7%) were reclassified. Although most VUS remained unchanged, reclassification necessitated updates in genetic counseling content and, in selected cases, modifications in surveillance strategies.
Discussion: In this cohort, the majority of VUS remained unresolved after reanalysis, reflecting persistent limitations in available functional and population-level evidence for many rare variants. The relatively low reclassification rate may be partly explained by the time required for evidence accumulation and by the fact that a substantial proportion of the cohort was evaluated within the most recent 12 months, limiting follow-up duration. Nevertheless, the reclassification of 4.7% of VUS—particularly upgrades to LP—had clinically meaningful implications for patient monitoring, family screening, and counseling. Conversely, downgrades to LB may help prevent unnecessary surveillance and reduce patient anxiety. These findings underscore the dynamic nature of ACMG/AMP-based variant interpretation and highlight the practical value of structured, periodic reanalysis combined with clear recontact and counseling workflows.

Keywords: Hereditary Cancer, Variant Reanalysis, Variant Reclassification, VUS

[Abstract:0161]

A Case of MEN1 Syndrome Associated Multifocal Pancreatic Neuroendocrine Tumors

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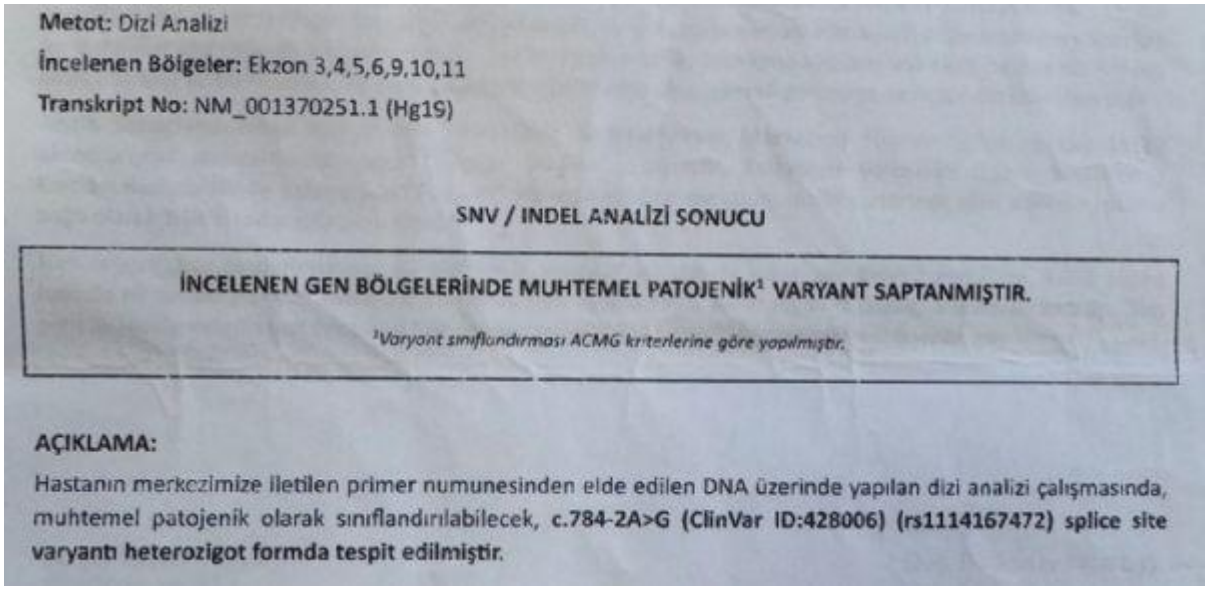
Objective: Introduction: Multiple Endocrine Neoplasia type 1 (MEN1) is a rare autosomal dominant hereditary cancer syndrome caused by pathogenic variants in the MEN1 tumor suppressor gene encoding the menin protein. It is classically characterized by the triad of primary hyperparathyroidism, pancreatic neuroendocrine tumors (pNETs), and pituitary adenomas. Among these, pNETs represent the leading cause of MEN1-related mortality and are frequently multifocal, non-functional, and biologically distinct from sporadic tumors. Optimal management of MEN1-associated pNETs remains challenging and requires an individualized, multidisciplinary approach.

Case: We report the case of a 49-year-old male with a history of primary hyperparathyroidism who underwent total thyroidectomy and subtotal parathyroidectomy in 2016. In 2022, he presented with abdominal pain, and imaging studies revealed a large solid mass in the pancreatic tail measuring 72 × 64 mm. There was no clinical or biochemical evidence of a functional neuroendocrine tumor. The patient underwent distal pancreatectomy and splenectomy. Histopathological evaluation demonstrated three separate well-differentiated pancreatic neuroendocrine tumors (one grade 1 and two grade 2), confirming multifocal disease. The Ki-67 proliferation index ranged from 1% to 4%. No lymph node metastases or lymphovascular or perineural invasion were detected; however, surgical margins were positive, and pathological staging was pT3N0 according to the AJCC 8th edition.
Postoperative Ga-68 DOTATATE PET-CT revealed somatostatin receptor–positive metastatic lesions involving peripancreatic lymph nodes and perihepatic implants. Long-acting octreotide therapy was initiated. Due to radiological disease progression at three months, the patient was referred for peptide receptor radionuclide therapy (PRRT) and received three cycles of 177Lu-DOTATATE while continuing somatostatin analogue treatment. Follow-up imaging demonstrated partial regression and stable disease, indicating a favorable response. The patient remains clinically stable and is currently under follow-up while receiving ongoing octreotide therapy. Next-generation sequencing identified a heterozygous pathogenic splice-site variant in the MEN1 gene (c.784-2A>G), confirming the diagnosis of MEN1 syndrome. Genetic counseling was provided in accordance with the autosomal dominant inheritance pattern.

Conclusion: This case highlights the importance of considering MEN1 syndrome in patients presenting with multifocal pancreatic neuroendocrine tumors. It also underscores the role of somatostatin receptor imaging and PRRT as effective treatment options in selected MEN1-associated pNETs. Given the absence of a standardized treatment algorithm, management should be individualized through a multidisciplinary approach based on tumor grade, disease extent, and molecular characteristics.

Keywords: hereditary, MEN1, neuroendocrine, pancreas

Görüntü 2:MEN1 gen dizi analizi



Metot: Dizi Analizi

İncelenen Bölgeler: Ekzon 3,4,5,6,9,10,11

Transkript No: NM_001370251.1 (Hg19)

SNV / INDEL ANALİZİ SONUCU

İNCELENEN GEN BÖLGELERİNDE MUHTEMEL PATOJENİK[1] VARYANT SAPTANMIŞTIR.

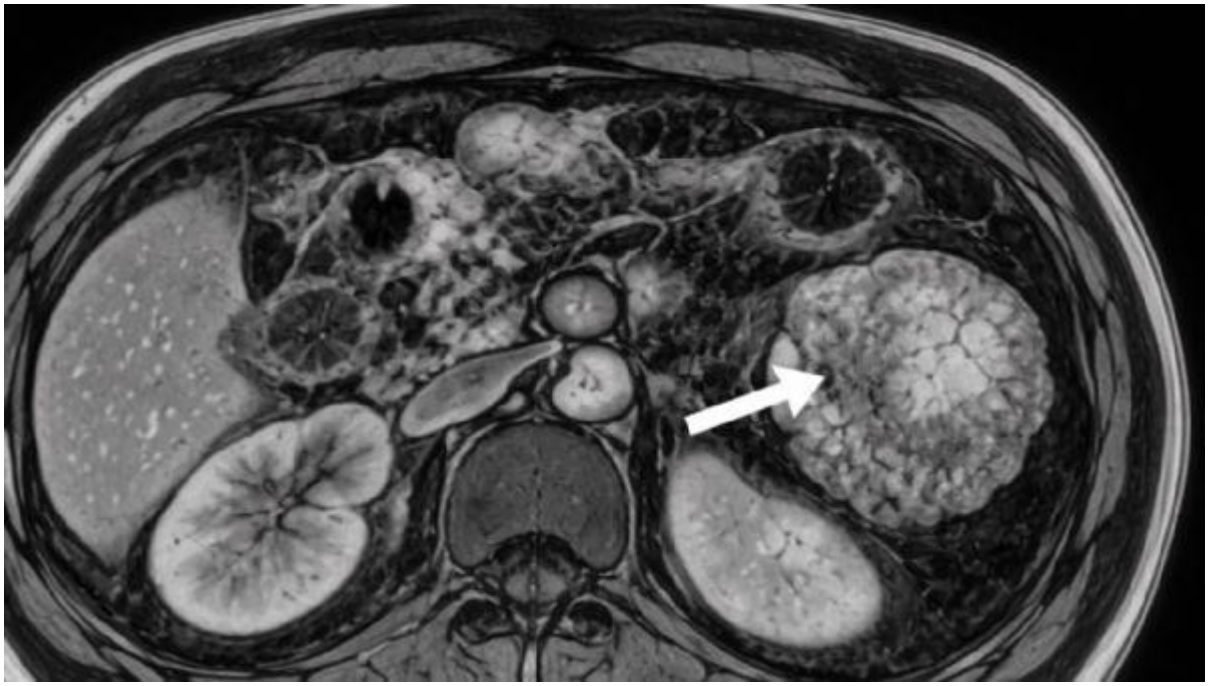
[1]Varyant sınıflandırması ACMG kriterlerine göre yapılmıştır.

AÇIKLAMA:

Hastanın merkezimize iletilen primer numunesinden elde edilen DNA üzerinde yapılan dizi analizi çalışmasında, muhtemel patojenik olarak sınıflandırılabilecek, **c.784-2A>G (ClinVar ID:428006) (rs1114167472) splice site varyantı heterozigot formda tespit edilmiştir.**

MEN1 gen dizi analizi

Görüntü1:Abdomen mr pankreas lezyonu.



Abdomen mr pankreas lezyonu.

[Abstract:0174]

Evaluation of Hereditary Cancer Genes in Gastric Cancer Cases Using Next-Generation Sequencing

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Introduction: Gastric cancer is among the malignancies with high morbidity and mortality, and although a significant portion of cases are considered sporadic, 5–10% have a genetic predisposition associated with hereditary cancer syndromes. With the introduction of next-generation sequencing (NGS) technologies into clinical use, it has become possible to simultaneously evaluate multiple genes in patients diagnosed with gastric cancer; thus, significant gains have been achieved in terms of identifying hereditary cancer genes, individualized patient management, and planning family screenings.

Aim: In this study, the aim was to evaluate hereditary cancer genes in patients diagnosed with gastric cancer who applied to our center using the Next-Generation Sequencing method; to determine the frequency of pathogenic, possibly pathogenic, and clinically undetermined (VUS) variants; and to reveal the relationship of the obtained genetic findings with clinical features.

Method: The study included 7 cases diagnosed with gastric cancer, analyzed using next-generation sequencing (NGS) within the scope of a hereditary cancer panel. 5 cases were sequenced using the CHCS_C_v2 (60 genes) panel on the Illumina MiSeq platform, and data from two cases were sequenced using the HCS_v2_0_1_hg38 (84 genes) panel on the Illumina NextSeq platform. Variant analysis was performed using Sophia DDM v4, and classification was reported according to the ACMG/AMP framework.

Results: Among the seven cases, three were women, and four were men. Ages ranged from 54 to 69 years at diagnosis. All had a family history of cancer. Most cases showed adenocarcinoma on histopathology; gastrointestinal stromal tumors were less frequent. Genetic analysis found a possible pathogenic variant in the *CHEK2* gene in one case. In four cases, clinically significant variants of uncertain significance (VUS) appeared in the *ATM, GALNT12, PMS2,* and *MSH3* genes. In two cases, no clinically significant hereditary cancer variants were detected. Cases without significant variants were diagnosed at a later age than those with variants.

Discussion: In this study, patients diagnosed with gastric cancer and with a family history were evaluated using NGS-based hereditary cancer gene panels. Our findings support the possibility that gastric cancer may be associated with hereditary genetic predisposition in certain patient groups. In particular, the variants detected in the *CHEK2, ATM, PMS2, and MSH3* genes, which are involved in DNA repair pathways, point to the possible role of these genes in the etiology of gastric cancer. However, due to the uncertainty of the clinical significance of VUS variants, the results should be interpreted cautiously. Although the limited number of cases is the main limitation of the study, it is thought that NGS-based multi-gene panels can contribute to the genetic risk assessment in gastric cancer patients with a family history.

Keywords: Gastric Cancer, Hereditary Cancers, Next-Generation Sequencing

Gastric Cancer Cases

Cases	Age	Gender	Pathological Diagnosis	Variant	Variant Type	ACMG Classification	Family History	Age at Diagnosis
Case 1	74	M	Gastrointestinal stromal tumor	ATM NM_000051.3: c.1522C>T p.(Leu508Phe) rs1011518082	Missense	VUS	Yes	67
Case 2	60	M	Adenocarcinoma	GALNT12 NM_024642/4: c.829G>A p.(Gly277Ser) rs200420144	Missense	VUS	Yes	59
Case 3	71	F	Unknown	No clinically significant variants were detected	-	-	Yes	69
Case 4	67	F	Unknown	PMS2 NM_000535/6: c.86G>C p.(Gly29Ala) rs146176004	Missense	VUS	Yes	66
Case 5	50	M	Adenocarcinoma	CHEK2 NM_001005735/1: c.599T>C p.(Ile200Thr) rs17879961	Missense	Likely pathogenic	Yes	40
Case 6	60	F	astrointestinal stromal tumor	MSH3 NM_002439/5: c.178_181delinsCCCCCAGCGCCCCCAGCGCCCCCAGCGCCCC p.(Ala60_Ala61delins11)	Inframe	VUS	Yes	54
Case 7	66	M	Adenocarcinoma	No clinically significant variants were detected	-	-	Yes	64

Demographic and pathological data and analysis results of gastric cancer patients.

[Abstract:0180]

A Case Report of Colon Cancer Diagnosed with Lynch Syndrome

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Objective: Lynch syndrome (hereditary non-polyposis colorectal cancer, HNPCC) is an autosomal dominant cancer predisposition syndrome caused by germline mutations in DNA mismatch repair (MMR) genes. It is most commonly associated with colorectal cancer, increasing the lifetime risk up to 50–80%, and patients typically present at a young age with right-sided colon tumors. Colorectal cancers associated with Lynch syndrome exhibit characteristic molecular features, including microsatellite instability (MSI) and loss of MMR protein expression. In this case report, we aim to present the clinical, pathological, and genetic characteristics of a patient diagnosed with colon cancer associated with Lynch syndrome.

Case: A 24-year-old female patient presented to the hospital with a complaint of rectal bleeding. She had no known history of malignancy. Her family history was remarkable: her mother was diagnosed with ovarian cancer at the age of 40 and was found to be MUTYH-positive. A maternal uncle had colon cancer; one of two maternal aunts had colon cancer, the other had endometrial cancer; and her grandfather had pancreatic cancer. Colonoscopy revealed an ulcerovegetative mass involving a 5cm segment extending distally from the splenic flexure. Biopsy of the lesion was reported as adenocarcinoma. Tumor markers were within normal limits. Contrast-enhanced computed tomography performed for staging demonstrated asymmetric wall thickening involving an approximately 4cm segment in the proximal descending colon, causing luminal narrowing. Additionally, a short segment of wall thickening with contrast enhancement was observed in the rectum. No lymph node involvement or distant organ metastasis was detected.

The patient underwent left hemicolectomy. Postoperative pathological examination revealed a moderately differentiated adenocarcinoma without lymph node metastasis. The tumor was staged as T2N0M0, and no indication for adjuvant chemotherapy was present. Immunohistochemical analysis demonstrated loss of MLH1 expression among the MMR proteins. The tumor was reported as MSI-high. Germline genetic analysis identified a heterozygous pathogenic mutation in the MLH1 gene (NM_000249) c2185dupT(p.Pro730Alafs*3) (frameshift), confirming the diagnosis of Lynch syndrome. Genetic analysis revealed a frameshift variant in the MLH1 gene (NM_000249: c.2185dupT; p.Pro730Alafs*3), resulting in a premature termination codon and subsequent loss of protein function. This variant is classified as a Class 5 pathogenic variant and is consistent with a diagnosis of Lynch syndrome.

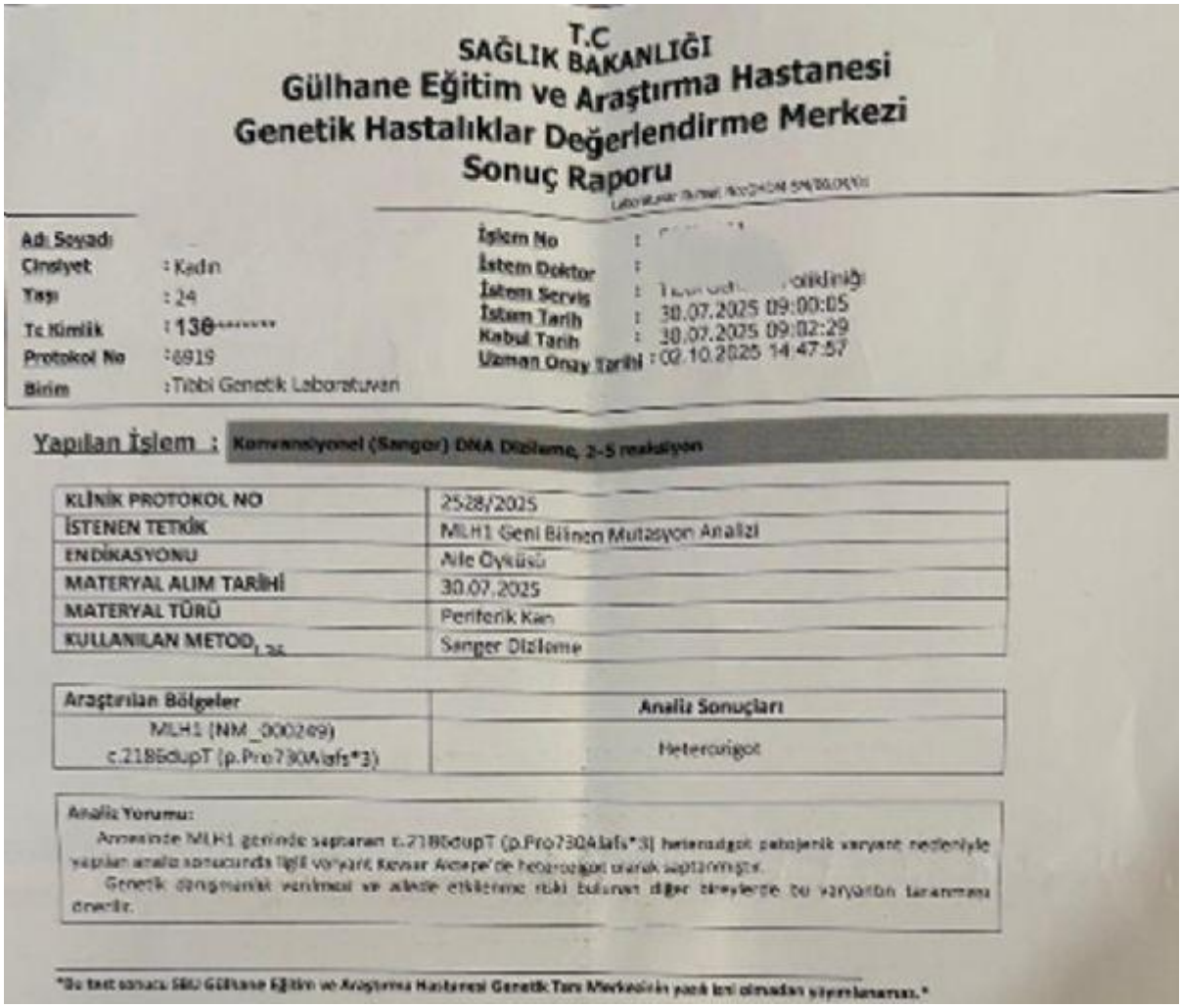
The patient was enrolled in a follow-up program for genetic counseling and surveillance for other Lynch syndrome–associated malignancies. Awareness at an early age was facilitated by the known genetic background in her family.

Conclusion: This case highlights the importance of considering Lynch syndrome in young patients with colorectal cancer and a significant family history. Early diagnosis is crucial not only for patient prognosis but also for appropriate screening and surveillance of at-risk family members.

Colorectal cancers associated with Lynch syndrome exhibit distinct clinical and molecular characteristics compared to sporadic cases. Although MSI-high tumors are generally associated with a more favorable prognosis, the risk of synchronous and metachronous malignancies remains high. Therefore, surgical management, surveillance intervals, and genetic counseling strategies should be individualized. The present case supports the importance of recognizing Lynch syndrome and emphasizes the necessity of family screening and long-term follow-up.

Keywords: Lynch Syndrome, colon cancer, hereditary cancer syndromes

genetic profiling report



T.C
SAĞLIK BAKANLIĞI
Gülhane Eğitim ve Araştırma Hastanesi
Genetik Hastalıklar Değerlendirme Merkezi
Sonuç Raporu

Adı Soyadı
Cinsiyet : Kadın
Yaşı : 24
Tc Kimlik : 138*******
Protokol No : 6819
Birim : Tıbbi Genetik Laboratuvarı

İşlem No :
İstem Doktor :
İstem Servis :
İstem Tarihi : 30.07.2025 09:00:05
Kabul Tarihi : 30.07.2025 09:02:29
Uzman Onay Tarihi : 02.10.2025 14:47:57

Yapılan İşlem : Konvansiyonel (Sanger) DNA Dizileme, 2-5 reaksiyon

KLİNİK PROTOKOL NO	2528/2025
İSTENEN TETKİK	MLH1 Geni Bilinen Mutasyon Analizi
ENDİKASYONU	Aile Öyküsü
MATERYAL ALIM TARİHİ	30.07.2025
MATERYAL TÜRÜ	Periferik Kan
KULLANILAN METOD	Sanger Dizileme

Araştırılan Bölgeler	Analiz Sonuçları
MLH1 (NM_000249) c.2186dupT (p.Pro730Alafs*3)	Heterozigot

Analiz Yorumu:
Annesinde MLH1 geninde saptanan c.2186dupT (p.Pro730Alafs*3) heterozigot patojenik varyant nedeniyle yapılan analiz sonucunda ilgili varyant Kayser Anemi'de heterozigot olarak saptanmıştır.
Genetik danışmanlık verilmesi ve ailede etkilenme riski bulunan diğer bireylerde bu varyantın taranması önerilir.

Bu test sonucu SBÜ Gülhane Eğitim ve Araştırma Hastanesi Genetik Tanı Merkezinin yazılı izni olmadan yayınlanamaz.

[Abstract:0181]

Importance Of Clinic Follow-up:Presentation Of A Family With MUTYH Homozygot Variant Expression

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BASAKSEHİR CAM AND SAKURA CİTY HOSPİTAL

Background: MUTYH-acquired polyposis (MAP) is a rare familial cancer syndrome that is characterized by the autosomal recessive inheritance of an early-onset colorectal adenomatous polyp syndrome. The pathogenesis of this condition involves the repair of DNA base excisions, resulting in a sufficient predisposition to cancer in heterozygous individuals. The presence of biallelic involvement is evident from a relatively early age, manifesting in the form of early adenomatous polyps and young colorectal cancers.

Case Presentation: A 34-year-old male patient was referred for familial cancer surgery for adenomatous colon cancer. The family history was notable for the presence of colorectal polyps in younger male and female patients, and a sister had previously succumbed to colorectal cancer. The family also had a 34-year-old uncle who had been diagnosed with colon cancer, but a thorough assessment of the family history was not yet complete.

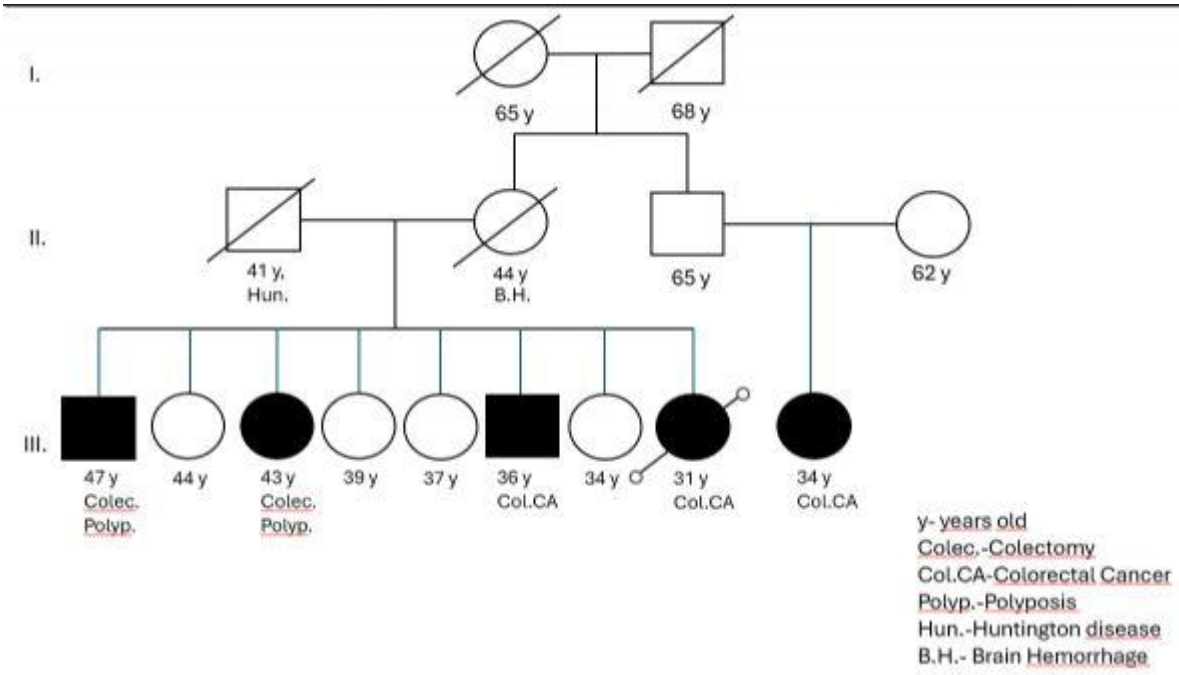
Results: A Hereditary Cancer Panel (ionTorrent) test using Next Generation Sequencing (NGS) was performed, and the identified deficiencies were classified as pathogenic/probably pathogenic according to the ACMG criteria. The presence of homozygous pathogenic characteristics of c.800 C>T was detected in the MUTYH gene. The family segregation process also revealed extra 2 member(2 siblings with colectomy) who were homozygous and the other 3 member revealed as heterozygous for the same variant. The family underwent intensive colorectal surgery, including regular colonoscopic screening, and received genetic counselling regarding the mode of inheritance, recurrence risk, and follow-up recommendations for carriers and affected individuals.

Conclusion: This family case of colorectal polyposis with MUTYH highlights the necessity to expand the consideration of polyposis that can develop in conjunction with MUTYH, thereby emphasizing the pivotal role of familial genetic testing in autosomal recessive cancer predisposition syndromes. The programme has been developed to facilitate early diagnosis of affected and carrier individuals, as well as to implement appropriate surveillance measures and to provide risk reduction recommendations.

The case presented here demonstrates the clinical and genetic heterogeneity of polyposis with MUTYH, emphasising the necessity for further research in this area.

Keywords: MUTYH-associated polyposis, colorectal cancer, family screening

Pedigree



Pedigree

[Abstract:0183]

Clinical and molecular characteristics of *ATM* gene variants in hereditary cancer panel analyses: a single center experience

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Introduction: The *ATM* (Ataxia Telangiectasia Mutated) gene is a key mediator of the DNA damage response and double-strand break repair. Germline pathogenic *ATM* variants are associated with increased susceptibility to several malignancies, most notably breast cancer. However, variants of uncertain significance (VUS), frequently detected in hereditary cancer sequencing, can weaken genotype–phenotype correlations and complicate clinical decision making. This study aimed to characterize the clinical and molecular spectrum of *ATM* variants identified in hereditary cancer panel testing, to present a loss-of-function variant that appeared novel based on the authors' database review at the time of analysis, and to discuss management challenges—particularly when VUS are detected in non-breast cancers.

Methods: Seventeen individuals (14 females, 3 males) with *ATM* variants identified via NGS-based hereditary cancer panel testing at our center were retrospectively evaluated. Clinical variables (diagnosis, age at diagnosis, family history, and associated pathologies) and variant characteristics were reviewed. Variant classification was performed according to ACMG/AMP criteria using up-to-date databases; reanalysis outcomes were recorded when available.

Results: Fifteen individuals had a personal history of malignancy, while two were under follow-up due to family history and/or proliferative breast lesions without a cancer diagnosis. Breast cancer was the most common diagnosis (n=9), followed by ovarian tumors/ovarian cancer (n=4). Additional diagnoses included concomitant gastric gastrointestinal stromal tumor with prostate adenocarcinoma (n=1) and papillary urothelial carcinoma of the bladder (n=1). A positive family history was present in 13/17 cases. Overall, 6/17 variants (35.3%) were classified as Pathogenic/Likely Pathogenic (P/LP) and 11/17 (64.7%) as VUS, predominantly missense. A notable finding was a frameshift variant, *ATM* NM_000051.3:c.975dup p.(Ile326Tyrfs*4), detected in a 43-year-old female without a personal history of cancer but with a family history of breast cancer, including an affected sister; this variant was classified as likely pathogenic (PVS1, PM2) and appeared unreported in major databases at the time of analysis. All *ATM* variants detected in male cases (gastric+prostate cancer, bladder cancer, and one individual with family history only) were missense VUS. Upon reanalysis, one variant was downgraded from VUS to likely benign, while another was upgraded from likely pathogenic to pathogenic.

Discussion: The *ATM* gene is a very large gene, which leads to the detection of numerous rare variants with uncertain clinical significance in the general population. A substantial proportion of these variants are missense in nature, and for most of them, functional studies or reliable segregation data are lacking. While this series contributes to the mutational spectrum of *ATM* by identifying a novel frameshift variant, the high proportion of detected VUS (predominantly missense variants) results in uncertainties in the clinical management process and complicates genetic counseling. In the evaluation of VUS, it is essential to consider family history, perform reanalysis at appropriate intervals, and adopt a comprehensive, integrative assessment approach.

Keywords: ATM, hereditary cancer, VUS

[Abstract:0187]

A Genetic Perspective on a Rare Malignancy: Germline Variants Detected in Male Breast Cancer Cases

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Introduction: Male breast cancer is a rare condition,accounting for approximately 1% of all breast cancers.Due to its low incidence, the clinical and molecular characteristics of this condition have been studied to a limited extent;however, its association with hereditary predisposition is more pronounced.Germline variants,particularly in genes involved in DNA repair pathways,have been shown to increase the risk of the disease.
Aim: The aim of this study is to evaluate the distribution and characteristics of genetic variants detected using hereditary cancer gene panels in cases diagnosed with male breast cancer.The findings aim to contribute to the understanding of genetic predisposition in male breast cancer and to guide clinical-genetic counseling processes.
Method: The study retrospectively evaluated cases that presented to our center between July 2024 and October 2025.Five cases diagnosed with breast cancer, analyzed using next-generation sequencing within the hereditary cancer panel, were included.Data from four of the cases were sequenced using the CHCS_C_v2 (60 genes) panel on the Illumina MiSeq platform,and data from one case were sequenced using the HCS_v2_0_1_hg38 (84 genes) panel on the Illumina NextSeq platform.Variant analysis was performed using Sophia DDM v4,and classification was reported according to the ACMG/AMP framework.
Results: The age at diagnosis of the cases included in the study ranged from 34 to 69 years.Histopathological evaluation revealed invasive ductal carcinoma in three cases, ductal carcinoma in situ in one case,and invasive papillary carcinoma in one case. Molecular analyses revealed variants in the *MSH2* with *ERCC2* genes in one case,and in the *BRCA2* gene in two cases.Two cases showed no clinically relevant variants.In the cases with detected variants,three variants were classified as pathogenic or possibly pathogenic according to the ACMG classification.All cases with clinically relevant variants had a family history of cancer.
Discussion: In this study,the detection of a pathogenic *BRCA2* variant in two cases is consistent with the prominent role of *BRCA2* in male breast cancer and once again highlights the importance of germline predisposition in these patients.In addition to *BRCA2* variants, variants detected in *ERCC2* and *MSH2*, which are involved in DNA repair pathways,may indicate the heterogeneous genetic background of male breast cancer. In a case with a family history of gastric cancer in one parent,the identification of a germline variant in the mismatch repair pathway is noteworthy for hereditary cancer predisposition. This clinical interpretation should,where possible,be strengthened by supportive tumor-based findings and evidence of segregation. The panel-negative results of two cases in the series demonstrate the limitations of hereditary cancer panels and the existence of an "unexplained" subgroup in male breast cancer. In panel-negative cases, rare or as-yet-unidentified genetic alterations outside the gene panel, regulatory variants located in deep intronic regions that cannot be detected by routine NGS analyses,copy number variations, or epigenetic mechanisms may play a role.The presence of a positive family history in all cases with clinically relevant variants emphasizes the importance of genetic testing.However, the limited number of cases is considered a limitation of the study. Studies with larger patient series will contribute to a clearer understanding of genetic risk profiles.

Keywords: *BRCA2*, DNA repair pathways, Male breast cancer

Cases	Age	Gender	Age at Diagnosis	Family History	Pathological Diagnosis	Variant	Variant Type	ACMG Classification
Case 1	36	M	34	Yes	Invasive ductal carcinoma	Not detected	-	-
Case 2	69	M	54	Yes	Invasive ductal carcinoma	BRCA2 NM_000059/3: c.5641_5644del p.(Lys1881Glnfs*27)	Frameshift	Pathogenic
Case 3	70	M	69	Yes	Invasive papillary carcinoma	BRCA2 NM_000059.4: c.8395del p.(Arg2799Aspfs*22) rs80359709	Frameshift	Pathogenic
Case 4	70	M	63	Yes	Ductal carcinoma insitu	MSH2 NM_000251/2: c.1799C>T p.(Ala600Val) NM_000251/2 rs63751236 ERCC2 NM_000400/3: c.1532G>A p.(Arg511Gln) rs772572683	Missense	Pathogenic for MSH2 Likely pathogenic for ERCC2
Case 5	63	M	60	Unknown	Invasive ductal carcinoma	Not detected	-	-

Demographic and pathological data and analysis results of male breast cancers

[Abstract:0188]

A Pediatric Case of Metachondromatosis Caused by a Novel PTPN11 Splicing Variant

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Introduction: Metachondromatosis (OMIM #156250) is a rare, autosomal dominant skeletal dysplasia defined by the coexistence of multiple osteochondromas and enchondromas, particularly affecting the juxta-epiphyseal regions of long bones, iliac crests, and proximal interphalangeal joints of the hands and feet. *PTPN11* is a tumor suppressor gene that encodes the protein tyrosine phosphatase SHP-2, a critical regulator of RAS-MAPK signaling and a key controller of chondrocyte differentiation, cartilage homeostasis, and skeletal development. Distinct molecular mechanisms drive PTPN11-associated disorders: gain-of-function and dominant-negative variants cause Noonan and LEOPARD syndromes, whereas loss-of-function variants cause metachondromatosis. Metachondromatosis is clinically distinct from other exostosis and enchondroma syndromes, including Hereditary Multiple Exostoses, Multiple Enchondromatosis, and overlapping cartilage dysplasias, which may present with progressive lesion growth, bone shortening, angular deformity, or joint instability. In metachondromatosis, exostoses most frequently arise in the juxta-epiphyseal regions of long bones and in the proximal interphalangeal joints of the hands, typically projecting toward the adjacent joint. Lesions may regress spontaneously, and progressive long-bone shortening or deformity is not characteristic. Because the clinical course and management strategy differ from other cartilage tumor-predisposing disorders, genetic confirmation plays a central role in diagnosis, counseling, and the design of a surveillance plan.

Aim: The goal is to demonstrate the value of genetic diagnosis in distinguishing this condition from other multiple-exostosis disorders, defining appropriate management, avoiding unnecessary surgical interventions, and establishing a surveillance strategy.

Methods:A 5.5-year-old male was referred by orthopedics with a preliminary diagnosis of multiple osteochondromatosis. Clinical evaluation showed normal growth parameters (weight: 21 kg, SDS: 0,42; height: 119 cm, SDS: 1,13), joint range of motion, and systemic medical history. No chronic disease, systemic inflammatory symptoms, allergy, or facial dysmorphism were observed. Radiographs and pelvic and long-bone MRI assessed lesion morphology and orientation relative to the physis and screened for synchronous enchondromas. Whole Exome Sequencing was performed, and variant interpretation followed ACMG/AMP standards with additional evidence weighting based on ClinGen recommendations.

Results: The patient exhibited multiple painless, spindle-shaped, cartilage-capped exostotic lesions involving the left second-finger proximal interphalangeal joint, right distal radius and ulna, pelvis, distal femur, and proximal tibia. No limitation of motion, joint subluxation, bone shortening, or progressive deformity was detected. Growth parameters were within expected percentiles for age. Whole Exome Sequencing identified a heterozygous canonical splice-acceptor variant in *PTPN11* (NM_002834.5:c.643-2A>G). The variant is predicted to disrupt splicing and produce a loss-of-function effect. Clinical and molecular findings were consistent with the diagnosis of metachondromatosis.

Discussion: This case underscores the unique position of metachondromatosis within skeletal dysplasia and RAS-MAPK pathway disorders. Molecular results confirm that *PTPN11* loss-of-function variants lead to an isolated skeletal phenotype, distinct from syndromic forms associated with other RASopathy mechanisms. Distinguishing metachondromatosis from progressive cartilage tumor-predisposing disorders changes clinical planning, shifting the approach from surgical prioritization to conservative monitoring due to the potential for spontaneous regression. Genetic confirmation prevented unnecessary orthopedic intervention and reshaped follow-up into a pathway-informed surveillance model, balancing conservative orthopedic management with individualized systemic screening.

Keywords: Metachondromatosis, PTPN11, Whole Exome Sequencing

[Abstract:0196]

Evaluation of Multigene Panel Findings in Hereditary Colorectal Cancer Cases

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Introduction: Colorectal cancer (CRC) is among the most common malignancies worldwide, and hereditary genetic predisposition plays a role in a substantial proportion of cases. In particular, investigating the germline genetic etiology is of critical importance in patients with early-onset disease, multiple primary tumors, or a marked family history, both for diagnostic purposes and for preventive strategies. Hereditary colorectal cancers are associated with numerous genetic mechanisms affecting different biological pathways, resulting in marked clinical and genetic heterogeneity. This heterogeneity limits the diagnostic sensitivity of approaches focused on a single gene or a single syndrome and highlights the need for comprehensive and simultaneous evaluation. Next-generation sequencing (NGS)–based multigene panel analyses enable assessment of a broad genetic spectrum in a single assay in patients with suspected hereditary CRC, thereby increasing diagnostic efficiency and enhancing clinical genetic counseling processes.
Objective: To evaluate the distribution of germline variants identified by hereditary cancer gene panels in patients diagnosed with colon and rectal cancer and to determine their place within the hereditary colorectal cancer spectrum.
Methods: A total of 13 cases who underwent genetic testing with a preliminary diagnosis of hereditary colorectal cancer were retrospectively evaluated. Nine cases were sequenced using the CHCS_C_v2 (60 genes) panel on the Illumina MiSeq platform, three cases using the HCS_v2_0_1_hg38 (84 genes) panel on the Illumina NextSeq platform, and one case using the CES_v3 panel on the Illumina NextSeq platform. Variant analysis was performed using Sophia DDM v4 software, and variant classification was carried out according to ACMG/AMP criteria.
Results: Of the 13 cases, 11 (84.6%) were diagnosed with colon cancer and 2 (15.4%) with rectal cancer. Clinically reportable germline variants associated with hereditary colorectal cancer were identified in 4 cases (30.8%). A heterozygous pathogenic variant in the *APC* gene was detected in one colon cancer case, a homozygous pathogenic variant in the *MUTYH* gene in one colon cancer case, and compound heterozygous pathogenic variants in the *MUTYH* gene in one rectal cancer case. In one rectal cancer case, a heterozygous variant of uncertain significance (VUS) in the *POLE* gene was identified. No clinically significant germline variants were detected in the remaining 9 cases (69.2%).
Conclusion: This single-center study demonstrates that multigene panel analyses are an effective approach for identifying clinically significant germline variants in patients with suspected hereditary colorectal cancer. Multigene panels allow simultaneous evaluation of different hereditary predisposition mechanisms in this genetically heterogeneous patient group. Pathogenic and likely pathogenic variants provide direct clinical benefit by guiding surveillance strategies, risk assessment of family members, and genetic counseling processes. In contrast, variants of uncertain significance require cautious, evidence-based interpretation to avoid unnecessary clinical interventions. Overall, these findings emphasize that multigene panel results in hereditary colorectal cancer cases should be interpreted in a comprehensive manner together with clinical, pathological, and family history data, and they indicate the need for further studies supported by larger patient cohorts and long-term follow-up data.

Keywords: *APC*, Hereditary colorectal cancer, *MUTYH*, *POLE*

[Abstract:0197]

Co-occurrence of Prostate, Colorectal, and Breast Cancer in a Family with a Heterozygous MUTYH Variant: A Large Family-Based Case Report

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Background: The MUTYH gene encodes a DNA repair protein involved in the base excision repair pathway, and biallelic pathogenic variants are known to cause MUTYH-associated polyposis (MAP). Monoallelic MUTYH carrier status is relatively common in the general population and is typically associated with low to moderate cancer risk. However, clustering of different cancer types among carriers of heterozygous MUTYH variants has been reported in certain families.
Objective
The aim of this study was to evaluate the co-occurrence of prostate, colorectal, and early-onset breast cancer in multiple members of a single family carrying a heterozygous MUTYH variant and to discuss its potential clinical significance.
Case: A 72-year-old male patient diagnosed with prostate cancer underwent hereditary cancer panel testing, which identified a heterozygous pathogenic MUTYH variant (c.452A>G, p.Tyr151Cys). Detailed pedigree analysis revealed a history of colorectal cancer in two of the patient's sisters; genetic testing could not be performed in these individuals as they were deceased. Cascade testing within the family identified the same heterozygous MUTYH variant in the granddaughters of two sisters—one with and one without a history of colorectal cancer. Both granddaughters were diagnosed with breast cancer at an early age (30 and 39 years, respectively).
Results: Within this family, carriers of the heterozygous MUTYH variant developed prostate, colorectal, and early-onset breast cancer. Notably, both individuals diagnosed with breast cancer were heterozygous MUTYH carriers, and no pathogenic variants in high-penetrance breast cancer susceptibility genes were identified in the family.
Conclusion: This family-based case report suggests that heterozygous MUTYH variants may be associated with a higher-than-expected cancer burden in certain families. The presence of early-onset breast cancer in addition to colorectal cancer raises the possibility that monoallelic MUTYH variants may act as modifier or contributing factors in cancer susceptibility. Close clinical surveillance of such families and further large-scale, family-based studies are warranted to better define the clinical impact of heterozygous MUTYH variants.

Keywords: Colorectal cancer, Early-onset breast cancer, Hereditary cancer, Monoallelic MUTYH variant, Prostate cancer

[Abstract:0202]

Retrospective analysis of multigene hereditary cancer panel testing performed for family history indication

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Introduction and Objective: Family history is one of the principal clinical indicators guiding the indication for genetic testing in the assessment of hereditary cancer predisposition. Multigene panel testing enables the simultaneous evaluation of high and moderate penetrance susceptibility genes in individuals without a personal history of cancer but considered at increased risk due to familial cancer aggregation. Reporting variants using standardized terminology and classifying them according to current guidelines enhance the clinical interpretability of test results. The objective of this study was to evaluate the distribution of hereditary cancer panel test results and to characterize the gene and variant type profiles of pathogenic/likely pathogenic (P/LP) variants in individuals who presented solely with a family history of cancer and no personal history of malignancy.

Materials and Methods: A total of 50 individuals who underwent multigene panel testing in our clinic between July 4, 2024, and October 17, 2025, with the indication of "family history," and who were not tested for targeted confirmation or cascade testing of a known familial variant, were retrospectively analyzed. Genomic DNA was extracted from peripheral blood leukocytes. A hereditary cancer panel comprising 60 genes was used in 40 cases, while a panel of 84 genes was used in 10 cases. Variant analysis was performed using Sophia DDM v4, and variant classification was reported based on the ACMG/AMP guidelines.

Results: Of the individuals, 37 were female and 13 were male. The distribution of results was as follows: pathogenic/likely pathogenic (P/LP) variants were identified in 13/50 cases (26.0%), variants of uncertain significance (VUS) only were detected in 10/50 cases (20.0%), and no clinically significant germline variants were identified in 27/50 cases (54.0%). The genes harboring P/LP variants included *BRCA1* (n=2), and one case each with variants in *TP53, ATM, CHEK2, PMS2, MSH6, NF1, FLCN, VHL, MUTYH, POLH,* and *RB1*. The distribution of P/LP variant types was as follows: frameshift (n=5; 38.5%), missense (n=4; 30.8%), nonsense (n=1; 7.7%), splice-site (n=1; 7.7%), in-frame indel (n=1; 7.7%), and copy number variation (CNV) (n=1; 7.7%).

Conclusion and Discussion: Previous studies have reported that the prevalence of P/LP variants and VUS in family history–based cohorts varies according to population characteristics, panel size, and selection criteria. The identification of P/LP variants in 26% of this selected cohort presenting solely with a family history of cancer supports the utility of multigene panel testing in detecting clinically meaningful germline variants even in unaffected individuals. As expansion of panel content may increase the burden of VUS, careful selection of panels tailored to the clinical question and effective management of uncertainty during genetic counseling are essential. When a VUS is identified, clinical management should be guided by the individual's personal and family history rather than by the variant itself, as inappropriate reliance on VUS findings may lead to suboptimal clinical decision-making.

Keywords: Hereditary Cancer Predisposition, Family History, Multigene Panel Testing

[Abstract:0203]

Beyond Exons: A Case Report on the Clinical Significance of a Deep Intronic Pathogenic Variant in the ATM Gene

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Background/Objectives: Cancer development and progression are primarily driven by the accumulation of somatic genetic and epigenetic events that trigger oncogenic processes; however, in some cases, cancer initiation results from germline pathogenic variants in high-penetrance (BRCA1, BRCA2, PALB2), moderate-penetrance (ATM, CHEK2, BRIP1), and low-penetrance (RAD51C, BARD1, FANCJ) cancer susceptibility genes. The ATM gene plays a critical role in the sensing of DNA double-strand breaks, cell cycle checkpoint control, and the maintenance of genomic stability. The aim of this study is to highlight the clinical significance of a deep intronic pathogenic variant identified in the ATM gene in a young patient with breast cancer and a remarkable family history, and to emphasize that intronic variants may also exert pathogenic effects through aberrant splicing and consequent loss of gene function.
Method: Patient was evaluated for germline mutations in Hereditary Cancer Syndrome (HCS) genes. The HCS panel, consisting of 47 genes, was analyzed using next generation sequencing (NGS). The raw data was analyzed using the 'SEQ variant analysis software' according to the reference genome of GRCh38. Filtered variants were evaluated according to the ACMG Standards and Guidelines recommendations. The variant identified by NGS analysis was confirmed by Sanger sequencing.
Results: Genetic analysis identified a heterozygous c.3994-159A>G (IVS28-159A>G) variant in intron 26 of the ATM gene (ENST00000675843), which was classified as "Likely Pathogenic" according to ACMG criteria (chr11:108287441, rs864622543, ClinVar ID: 220483). Although this variant does not directly affect the protein-coding region, previously reported RNA-based analyses have demonstrated that it leads to an aberrant splicing event by activating a cryptic splice site. This aberrant splicing mechanism has been shown to result in the production of a nonfunctional protein and/or the introduction of a premature stop codon.
Conclusion: This patient highlights the clinical relevance of a deep intronic germline variant in the ATM gene in a young patient with breast cancer and a significant family history. The findings demonstrate that intronic variants, although not directly affecting protein-coding regions, can be pathogenic through aberrant splicing mechanisms leading to loss of gene function. These results emphasize the importance of including intronic regions in hereditary cancer gene analyses and suggest that RNA-based evidence can substantially contribute to the correct clinical interpretation of intronic variants.

Keywords: ATM, Intronic variant, Hereditary cancer syndrome

[Abstract:0208]

Pediatric Multilocus Inherited Neoplasia Allele Syndrome Associated With Fanconi Anemia

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Objective: To highlight a rare pediatric presentation of Multilocus Inherited Neoplasia Allele Syndrome (MINAS) within the context of hereditary cancer predisposition and to emphasize the importance of comprehensive genomic testing in children presenting with unexplained cytopenias.
Case: A 9-year-old male was referred for evaluation of persistent bicytopenia detected over a three-month period, without any prior transfusion or specific hematologic treatment. His medical history was notable for chronic kidney disease secondary to vesicoureteral reflux diagnosed in infancy. The patient exhibited easy bruising and delayed wound healing, with no additional systemic symptoms. Family history revealed a recent episode of hematemesis in his sibling. Hematologic evaluation confirmed persistent anemia and thrombocytopenia, raising suspicion of an inherited bone marrow failure syndrome. Comprehensive genetic testing revealed a homozygous deletion in the FANCA gene. The patient was ultimately diagnosed with Fanconi anemia caused by a homozygous FANCA deletion; additionally, a pathogenic RET variant was identified as a secondary finding, fulfilling the criteria for Multilocus Inherited Neoplasia Allele Syndrome. The clinical phenotype was predominantly consistent with Fanconi anemia.
Conclusion: This case represents a rare genetic constellation in the pediatric population and underscores the necessity of considering multilocus inheritance in hereditary cancer evaluation. Recognition of MINAS has critical implications for individualized cancer surveillance, long-term follow-up, and genetic counseling for affected patients and their families.

Keywords: Multilocus inherited neoplasia allele syndrome, Inherited bone marrow failure, Fanconi anemia, Bicytopenia

[Abstract:0214]

Clinical Implications of Multilocus Inherited Neoplasia Alleles Syndrome (MINAS): A Case Report of Co-occurring BRCA2 and ATM Pathogenic Variants

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Objective: The widespread implementation of multigene panel testing via Next-Generation Sequencing (NGS) has led to the increased identification of individuals harboring germline pathogenic variants (PVs) in two or more cancer susceptibility genes, a phenomenon termed Multilocus Inherited Neoplasia Alleles Syndromes (MINAS). While MINAS cases involving BRCA1 or BRCA2 genes are relatively well-documented, comprising nearly 80% of reported cases, combinations of other moderate-to-high penetrance genes remain rare and poorly characterized. This study aims to evaluate the clinical impact of co-occurring BRCA2 and ATM variants, highlighting the necessity for personalized risk stratification in the era of pan-cancer genomic profiling.
Case Presentation: A 38-year-old female patient presented to the genetics clinic following a diagnosis of breast cancer at age 37. Her 4-year-old son exhibited multiple congenital cafe-au-lait spots on the abdomen and gluteal region, alongside progressive hypo- and hyperpigmented macules, without any overt skeletal, hematological, or developmental abnormalities. The pedigree was highly suggestive of a hereditary predisposition: a daughter and a nephew had both deceased from medulloblastoma in early childhood, while adult-onset leukemia, prostate, and uterine cancers were reported in first and second-degree relatives. A custom gene panel covering 61 cancer susceptibility genes was sequenced on the DNBSEQ-G400™ platform (MGI Tech Co., Ltd.). Data analysis used the SEQ bioinformatics pipeline (Genomize, version 8.13.0), aligning reads to the GRCh38 genome. NGS results identified the mother as a MINAS patient with a heterozygous pathogenic BRCA2:c.658_659del variant and three changes in ATM: a heterozygous likely pathogenic c.902-2A>T variant, and two novel heterozygous VUS variants (c.7631T>G, c.2441A>G). Remarkably, the son was found to be homozygous for the maternal BRCA2:c.658_659del variant, placing him in the genetic spectrum of biallelic BRCA2-related disorders, which correlates with the family's pediatric medulloblastoma history and his cutaneous findings. The son also inherited the heterozygous likely pathogenic ATM:c.902-2A>T and the ATM:c.2441A>G (VUS) variants. This molecular profile illustrates the transition from a maternal MINAS profile to a high-risk homozygous condition in the offspring, despite the absence of Fanconi Anemia clinical manifestations.
Conclusion: This case underscores that the clinical challenges of MINAS extend far beyond the individual's cancer risk, encompassing complex reproductive and pediatric outcomes. Current literature presents conflicting evidence, with some studies supporting a "synergistic" model of earlier onset and others suggesting an "additive" model of independent tumorigenic pathways. This is particularly critical given that both BRCA2 and ATM genes function within the same homologous recombination repair (HRR) pathway. The detection of a patient with MINAS must trigger immediate consideration for partner testing and prenatal counseling to mitigate the risk of severe autosomal recessive syndromes, even when the classic clinical findings of conditions like Fanconi Anemia is absent. Ultimately, this report emphasizes that standard monoallelic surveillance guidelines are insufficient for MINAS families. Clinicians must integrate detailed pedigree analysis with multi-locus molecular data to provide personalized, high-intensity management frameworks that address the multifaceted risks in both adult and pediatric oncology.

Keywords: MINAS, BRCA2, ATM, Next-Generation Sequencing

[Abstract:0218]

From Spontaneous Pneumothorax to Pleuropulmonary Blastoma Type I Diagnosis: A Pathogenic *DICER1* Splice-Site Variant

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Background: Pleuropulmonary blastoma (PPB) is a rare and highly aggressive primary intrathoracic malignancy of childhood, typically arising from embryonic mesenchymal cells. It is the sentinel manifestation of the DICER1 syndrome, an autosomal dominant disorder caused by germline mutations in the *DICER1* gene. PPB is morphologically classified into three types: Type I (purely cystic), Type II (mixed), and Type III (solid). Early recognition of Type 1 PPB is critical, as it carries a superior prognosis compared to the more advanced types, yet it frequently presents with non-specific symptoms or complications like pneumothorax, which can lead to diagnostic delays.

Objective: The aim of this study is to report the clinical and molecular diagnostic journey of a 1-year-old male patient diagnosed with PPB Type 1 following a spontaneous pneumothorax and to emphasize the importance of applying *DICER1*-specific ClinGen ACMG/AMP specifications in the classification of novel splice-site variants.

Methods: The patient's clinical history, surgical reports, and histopathological data were retrospectively analyzed. Following the pathology report, genetic counseling was provided. Genomic DNA was extracted from peripheral blood, and germline mutation analysis was performed using Next-Generation Sequencing (NGS). The identified variant was evaluated using the *DICER1*-specific ClinGen Sequence Variant Interpretation (SVI) guidelines, incorporating population frequency (gnomAD) and clinical specificity criteria.

Results: A 1-year-old male patient presented with fever and sudden-onset spontaneous pneumothorax. After failing conservative management with a chest tube, the patient underwent surgical excision of pulmonary bullae. Histopathological examination revealed a multiloculated cystic lesion lined with cuboidal epithelium and focal subepithelial clusters of immature spindle cells. Immunohistochemical staining showed positivity for PanCK and EMA in the epithelium, while Vimentin and Desmin were positive in the stroma, confirming PPB Type 1. Clinical examination revealed delayed separation of the umbilical cord (20 days) and curly blonde hair. Germline NGS analysis identified a heterozygous canonical splice acceptor site variant: *DICER1*:c.1377-1G>A. According to the *DICER1*-specific ACMG guidelines, this variant was classified as Pathogenic by meeting the following criteria: PVS1_VeryStrong (canonical splice site affecting exon 9, which is not subject to specific exceptions), PM2 (absent from population databases), and PP4 (highly specific phenotype of PPB).

Conclusion: Spontaneous pneumothorax in early childhood should always be considered a clinical "red flag" for PPB. In this case, the transition from a common clinical complication to a rare genetic diagnosis highlights the necessity of histopathological vigilance in cystic lung lesions. The c.1377-1G>A variant disrupts the highly conserved splice acceptor site, likely leading to exon skipping or intron retention, resulting in a truncated protein and supporting the haploinsufficiency model of *DICER1* syndrome. While the genetic result did not alter the acute surgical management (total resection), it was instrumental in establishing a long-term surveillance protocol. Patients with germline *DICER1* mutations require multi-system screening, including regular thyroid

ultrasounds for multinodular goiter and abdominal imaging for cystic nephroma. This case reinforces that integrating precise molecular classification with clinical findings is essential for the comprehensive management of hereditary cancer syndromes and provides a basis for familial cascade screening.

Keywords: *DICER1*, Pleuropulmonary Blastoma, Pneumothorax

[Abstract:0220]

"BRCA1 Exon 18–19 Deletion Missed by NGS: A Case Highlighting the Value of MLPA"

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Objective: Hereditary breast and ovarian cancer syndrome is primarily driven by pathogenic germline variants in the BRCA1 and BRCA2 genes, which play essential roles in homologous recombination and the stabilization of DNA double-strand breaks. Although next-generation sequencing (NGS) is widely used in hereditary cancer testing, it mainly detects single-nucleotide variants and small indels, and therefore shows limited sensitivity for large genomic rearrangements (LGRs) involving multiple exons. Population based studies have demonstrated that approximately 11–13% of pathogenic BRCA1 variants and 2–3% of BRCA2 variants result from multi-exonic deletions or duplications rather than point mutations. Data from the Turkish population similarly report LGR frequencies ranging from 1% to 3.4%, with the majority occurring in BRCA1. Among these alterations, the BRCA1 exon 18–19 deletion stands out as a recurrent and clinically significant rearrangement, known to disrupt the reading frame and impair gene function. These findings highlight the need to complement NGS with copy-number–sensitive techniques to ensure comprehensive detection of clinically relevant BRCA1/2 variants.

Method: The patient was evaluated for germline mutations using a comprehensive hereditary cancer panel. Genomic DNA extracted from peripheral blood was analyzed by NGS covering multiple cancer susceptibility genes. Raw sequencing data were aligned and interpreted using GRCh38 as a reference genome. Filtering and classification of variants were conducted according to ACMG guidelines. Due to persistent clinical suspicion despite a negative NGS result, MLPA analysis targeting BRCA1/BRCA2 exon-level copy-number alterations was performed using validated probe sets.

Results/Case: A 45-year-old woman diagnosed with ovarian cancer was referred to the medical genetics clinic for hereditary cancer evaluation due to her personal and family history. Although NGS analysis did not reveal any pathogenic or likely pathogenic variants, MLPA identified a heterozygous deletion involving BRCA1 exons 18–19. This multi-exonic deletion is known to cause a frameshift, leading to loss of BRCA1 protein function and homologous recombination deficiency. The variant provided a definitive molecular explanation for the patient's ovarian cancer diagnosis and confirmed that LGRs can remain undetected by sequencing-based methods alone.

Conclusion: This case emphasizes the clinical relevance of incorporating LGR-focused assays, such as MLPA, into hereditary cancer testing workflows. Even when NGS results are negative, large deletions affecting multiple exons can have significant pathogenic consequences. The findings underscore the importance of complementary copy-number analysis for accurate diagnosis, cascade testing of at-risk relatives, and appropriate management decisions involving surveillance strategies and eligibility for PARP inhibitor therapies.

Keywords: BRCA1, MLPA, Hereditary Breast & Ovarian Cancer

[Abstract:0222]

Defining Germline Panel Content in Breast Cancer: A Simulation-Based Comparison with Guideline Recommendations

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Objective: To compare the diagnostic yield and coverage of a real-world germline hereditary cancer panel (HCP) in breast cancer with guideline-based gene sets recommended by the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) using a simulation approach.

Materials-Methods: A total of 165 breast cancer cases evaluated at the Medical Genetics Outpatient Clinic of Aydın Adnan Menderes University Hospital underwent germline NGS-based hereditary cancer panel (HCP) testing: 127 cases were tested with a 60-gene panel and 38 cases with an 84-gene panel. Using a simulation approach, results were reclassified according to breast cancer–related gene sets recommended by NCCN and ESMO, and diagnostic yield (pathogenic/likely pathogenic variant detection rate) was compared across the three approaches (HCP, NCCN, and ESMO). Cochran's Q test was used for comparisons among the three approaches, and pairwise comparisons were performed using McNemar tests with Bonferroni correction; $p<0.05$ was considered statistically significant.

Results: The pathogenic/likely pathogenic (P/LP) detection rate was 18.2% for HCP, 16.4% for the NCCN gene set, and 9.1% for the ESMO core gene set. P/LP variants were identified in ATM, BRCA1, BRCA2, BRIP1, CHEK2, NF1, PTEN, TP53, MUTYH, and NTHL1. There was a significant difference in P/LP detection rates among the three approaches ($p<0.001$). Of the P/LP-positive findings detected by HCP, 90% were captured by the NCCN gene set, whereas the ESMO core gene set captured 50%. Compared with HCP, the ESMO core set showed a significantly lower detection rate ($p<0.001$) and also performed significantly worse than the NCCN gene set ($p<0.001$). In contrast, there was no significant difference between the NCCN gene set and HCP ($p=0.25$).

Conclusion: In this cohort, the ESMO core approach missed half of the P/LP findings detected by the hereditary cancer panel, whereas the NCCN gene set captured the majority of panel-positive results with comparable diagnostic yield. Overall, these results suggest that a panel strategy grounded in NCCN recommendations—covering clinically relevant high- and moderate-penetrance genes and adaptable to individual clinical context—may provide a more rational balance between diagnostic yield and practical feasibility in germline testing for breast cancer.

Keywords: breast cancer, germline multigene panel testing, NCCN, ESMO

[Abstract:0225]

Molecular Diagnosis of Pediatric Hereditary Paraganglioma Caused by a Pathogenic *SDHB* Variant

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Introduction: Paragangliomas are rare neuroendocrine tumors arising from extra-adrenal paraganglia and may present sporadically or as part of hereditary cancer predisposition syndromes. Germline pathogenic variants of genes encoding subunits of the succinate dehydrogenase (SDH) complex are the most frequent genetic causes of hereditary paraganglioma-pheochromocytoma syndromes. Among these genes, SDHB variations are particularly associated with early-onset disease, extra-adrenal localization, and an increased risk of aggressive behavior. In pediatric patients, accurate diagnosis requires an integrated approach combining biochemical and radiological results including functional imaging, and molecular genetic findings.
Aim: The aim of this report is to present a pediatric case of hereditary paraganglioma confirmed by molecular genetic analysis to emphasize the pivotal role of genetic testing in the diagnostic evaluation of suspected hereditary paraganglioma.
Case Presentation: An 11-year-old male patient presented with recurrent vomiting and hypertension (180/100 mmHg), prompting further clinical investigation. The patient had no remarkable prenatal or perinatal history, and family history was negative for hypertension or hereditary tumor syndromes. Anthropometric measurements and physical examination were normal. Biochemical evaluation revealed significantly elevated Pro-BNP levels. Catecholamine and metabolite analyses demonstrated a noradrenergic biochemical phenotype, with markedly elevated urinary normetanephrine levels and increased urinary norepinephrine excretion, while urinary metanephrine levels were within normal ranges. Elevated adrenaline and noradrenaline levels, along with increased plasma normetanephrine concentrations, highly suggestive of a functional paraganglioma. Surgically excised tumor tissue were conisistent with paraganglioma histopathologically.
Urinary ultrasonography and renal Doppler ultrasonography were unremarkable. CT angiography revealed a well-defined, contrast-enhancing mass in the left paraaortic region at the level of the renal pedicle, with imaging features suggestive of a neurogenic tumor. Static renal scintigraphy demonstrated preserved renal function. Oncological PET imaging showed intense uptake in the left paraaortic mass, consistent with paraganglioma. Mild tracer uptake in multiple lymph nodes was interpreted as reactive, with no evidence of distant metastatic disease. In view of the patient's age, tumor localization, and biochemical phenotype, a targeted next-generation sequencing panel comprising 31 genes associated with neuroendocrine tumors was applied. Molecular genetic analysis identified a heterozygous pathogenic variant in the SDHB (NM_003000.3) gene (c.262A>C; p. p.Thr88Pro) which was classified as pathogenic according to ACMG guidelines, based on the PM1, PM2, PP2, and PP3 criteria, confirming the diagnosis of hereditary paraganglioma syndrome.
Discussion: The SDHB gene represents the most frequently implicated gene in hereditary paraganglioma–pheochromocytoma syndromes, accounting for nearly half of all hereditary cases, with most pathogenic variants identifiable through sequence analysis. The majority of germline SDHB pathogenic variants are nucleotide substitutions which approximately 70% of cases. With missense variants representing the most frequent subtype, followed by frameshift variants and less commonly large deletions or duplications. The presence of an extra-adrenal paraaortic tumor, a noradrenergic biochemical phenotype, and early-onset symptomatic presentation reflects the characteristic clinical features associated with pathogenic SDHB variants. This case highlights the central role of genetic testing in the diagnosis of pediatric paraganglioma. Identification of a pathogenic SDHB variant provides definitive etiological clarification and has important implications for prognosis, surveillance, and cascade testing of at-risk family members.

Keywords: hereditary cancer, paraganglioma, *SDHB* gene

[Abstract:0230]

Colorectal Cancer Risk in Patients with Identified MUTYH Variants: A Retrospective Study

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Introduction: MUTYH-associated polyposis (MAP) is an autosomal recessive hereditary polyposis syndrome. Individuals carrying biallelic MUTYH mutations have a significantly increased risk of developing multiple adenomatous polyps and, consequently, colorectal cancer (CRC). Monoallelic MUTYH mutation carriage is detected in approximately 1–2% of the general population; however, its clinical significance and impact on cancer risk remain controversial.

Aim and Methods: This study aimed to evaluate MUTYH gene variants detected among patients who underwent hereditary cancer panel testing in our clinic over the past year due to a personal and/or family history of malignancy. Demographic data including age, sex, and referral indications (personal and/or familial cancer history) were retrospectively analyzed. Detected MUTYH variants were classified according to zygosity as monoallelic heterozygous or biallelic (homozygous/compound heterozygous). Variants were further categorized as pathogenic, likely pathogenic, or variants of uncertain significance (VUS) based on ACMG criteria. Variants within the same category were grouped, and their concordance with clinical findings was evaluated.

Results: A total of 34 patients were included in the study. The mean age was 54.9 years; 58.8% (n=20) were female and 41.2% (n=14) were male. Indications for hereditary cancer panel testing were as follows: family history of malignancy in 35.3% (n=12), breast cancer in 26.5% (n=9), colorectal cancer in 23.5% (n=8), prostate cancer in 5.9% (n=2), ovarian cancer in 2.9% (n=1), concomitant breast and ovarian cancer in 2.9% (n=1), and renal cell carcinoma in 2.9% (n=1).
According to zygosity and ACMG classification, 29.4% (n=10) of variants were VUS, while 70.6% (n=24) were pathogenic or likely pathogenic. Monoallelic (heterozygous) variants were detected in 79.4% (n=27) of cases, whereas biallelic variants (homozygous or compound heterozygous) were identified in 20.6% (n=7).

Discussion: In monoallelic MUTYH carriers, general population screening recommendations are typically applied. However, colonoscopy screening strategies may differ in cases with a personal history of polyps or a first-degree relative with colorectal cancer. According to NCCN guidelines and large meta-analyses in the literature, monoallelic MUTYH carriers may have a mildly increased risk of colorectal cancer. In our study, the presence of personal or familial cancer history among monoallelic MUTYH variant carriers appears to be consistent with these findings. Nevertheless, to establish this association more robustly, segregation analyses in family members and further correlation with clinical data are recommended.

Keywords: Biallelic and monoallelic mutations, Colorectal cancer, MUTYH-associated polyposis

Variant Table

Variant Table	Missense	Frameshift	Inframe	Nonsense	Splice Donor Site	ACMG
c.1187G>A p.Gly396Asp	n=4					VUS
c.884C>T p.Pro295Leu	n=5					Likely Pathogenic
c.800C>T p.(Pro267Leu)	n=9					Likely Pathogenic
c.1103G>A p.(Gly368Asp)	n=2					VUS
c.734G>A p.Arg245His	n=3					Likely Pathogenic
c.559G>A p.(Val187Met)	n=1					VUS
c.1225C>T p.(Arg409Trp)	n=1					VUS
c.643G>A p.Val215Met	n=1					VUS
c.1437_1439del p.Glu480del			n=3			Likely Pathogenic
c.1353_1355del p.(Glu452del)			n=2			Likely Pathogenic
c.369_374dup p.(Trp124_Met125insIleTrp)			n=1			Likely Pathogenic
c.775del p.(Ala259Profs* 32)		n=1				Pathogenic
c.1147del p.Ala385ProfsTer23		n=1				Likely Pathogenic
c.859del p.Ala287ProfsTer32		n=1				Pathogenic
c.1171C>T p.Gln391Ter				n=1		Pathogenic
c.1476+2C>T					n=1	VUS

[Abstract:0231]

A De Novo Germline *MYCN* Variant in an Infant with Hydrocephalus, Macrocephaly, and Limb Anomalies: Expanding the Developmental and Oncogenic Spectrum of *MYCN*

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Objective: The *MYCN* proto-oncogene is a well-established driver of tumorigenesis, particularly in neuroblastoma. Recent evidence, however, indicates that germline *MYCN* variants are also implicated in congenital malformation syndromes such as Feingold syndrome type 1 and megalencephaly–polydactyly syndrome. Here, we report what appears to be the third case worldwide of a de novo germline *MYCN* missense variant associated with severe neurodevelopmental and limb anomalies.
Methods: Whole-exome sequencing was performed because of multiple congenital anomalies. Variant interpretation included population frequency databases, in silico pathogenicity prediction tools, trio-based segregation analysis, and an extensive literature review.
Case Presentation: A one-year-old male infant was prenatally diagnosed with hydrocephalus by fetal ultrasonography and delivered at term. Postnatal evaluation revealed severe hydrocephalus, marked macrocephaly, dysmorphic facial features, and limb anomalies including right-sided postaxial polydactyly, syndactyly of the fourth and fifth digits, and clinodactyly of the left hand. There was no family history of congenital anomalies or cancer. Trio-based analysis identified a heterozygous de novo *MYCN* c.1054A>G (p.Ser352Gly) missense variant. This variant has not been previously reported in population databases or in the literature.
Discussion: *MYCN* encodes a transcription factor that regulates proliferation, differentiation, and neural development. Germline loss-of-function variants are associated with Feingold syndrome type 1, whereas gain-of-function variants have been linked to megalencephaly–polydactyly syndrome. To our knowledge, only two patients with comparable germline *MYCN* missense variants and overlapping phenotypes have been reported to date, making our patient the third such case worldwide.
Conclusion: This case expands the phenotypic spectrum associated with germline *MYCN* variation and underscores the dual developmental and oncogenic roles of *MYCN*. Given its established oncogenic function, long-term clinical surveillance may be warranted, although cancer predisposition associated with germline *MYCN* variants remains unclear.

Keywords: gain of function, megalencephaly, *MYCN*, polydactyly, protooncogene

[Abstract:0237]

Characterization of the Molecular and Clinical Features of Multilocus Inherited Neoplasia Allelic Syndrome (MINAS) Cases in the Turkish Population

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Objective: Multilocus Inherited Neoplasia Allelic Syndrome (MINAS) is a rare genetic syndrome characterized by the presence of multiple pathogenic/likely pathogenic(P/LP) variants in different cancer predisposition genes within the same individual. Patients with MINAS may face early age at onset and multiple primary malignancies. Although it is rare, the detection rate has increased with the use of multigene panels. In our study, we aimed to describe the frequency of MINAS, gene combinations, and clinical associations in a large Turkish hereditary cancer cohort.

Materials-Methods: We retrospectively analyzed HCS panel NGS results of 4,850 individuals who presented to the Medical Genetics Unit of İzmir City Hospital between January 2024 and November 2025 with a preliminary diagnosis of hereditary cancer syndrome due to a personal and/or family history of malignancy. Only patients with variants evaluated as P/LP according to ACMG criteria and/or reported as P/LP in ClinVar were included. Cases carrying variants in two or more different genes were defined as MINAS.

Results: Among 4,850 tested individuals, 38 (0.78%) had P/LP variants in more than one gene. Dual-gene alterations were detected in 37 patients. The most frequent combination was BRCA2–CHEK2 (n=5), followed by ATM–BRCA2, ATM–CHEK2, BRCA1–MUTYH, BRCA1–NTHL1, BRCA2–MSH6, BRCA2–MUTYH, and FH–PALB2 (each n=2). Interestingly, one patient had a triple-gene alteration (BRIP1–CHEK2–MUTYH). Based on inheritance patterns, combinations were distributed as AD/AD: 60.5% (n=23), AD/AR: 36.8% (n=14), and AD/AD/AR: 2.6% (n=1). A malignancy diagnosis was present in 27/38 (%71.1) patients. Clinical phenotypes were mainly driven by the higher-penetrance gene, although overlapping tumor spectra were seen in several cases. The tumor spectrum was clearly dominated by breast cancer.

Conclusion: MINAS represents a rare but clinically important subgroup of hereditary cancer patients. Recognizing these cases is crucial for accurate counseling and personalized surveillance strategies

Keywords: Cancer, Hereditary, MINAS

[Abstract:0238]

Genome Editing–Guided In Silico Functional Prioritisation of Variants of Uncertain Significance in Hereditary Cancer Genes

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Objective: Widespread use of next-generation sequencing in hereditary cancer testing has led to the identification of numerous germline variants, many of which remain classified as variants of uncertain significance (VUS). This uncertainty limits clinical decision-making and genetic counselling. Genome editing technologies offer powerful experimental tools for functional validation; however, experimental testing of all detected variants is impractical. Bioinformatic strategies informed by genome editing principles may help prioritise variants most likely to be functionally relevant.

Materials-Methods: An integrative in silico framework was developed to prioritise VUS in major hereditary cancer genes, including BRCA1, BRCA2, TP53, ATM, and CHEK2. A total of 1,250 VUS were screened across the selected hereditary cancer genes. Publicly available variant datasets were analysed using pathogenicity prediction algorithms, evolutionary conservation metrics, protein domain annotation, and structural impact assessment. Variants were further contextualised within DNA damage response and cell-cycle regulatory pathways to infer their potential functional consequences under genome editing–based perturbation models.

Results: The analysis identified that 14.2% (n=178) of the total VUS analysed localise to evolutionarily constrained and functionally critical protein domains, with predicted disruptive effects on genome maintenance pathways. These variants emerged as a high-priority subgroup for future genome editing–based functional validation.

Conclusion: Genome editing–guided bioinformatic prioritisation represents a scalable and clinically relevant approach to address the VUS challenge in hereditary cancers, supporting improved variant interpretation and personalised risk assessment.

Keywords: Functional Validation, Germline Testing, Hereditary Cancer Genes, In Silico Prioritisation, VUS

[Abstract:0239]

Opportunities and Limitations of Genome Editing in Hereditary Cancer: An In Silico Perspective

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Objective: Genome editing technologies have generated significant enthusiasm for the prevention and treatment of hereditary cancers. However, the clinical translation of these approaches is constrained by biological complexity, gene essentiality, and ethical considerations. Systematic bioinformatic evaluation is required to define where genome editing is plausible, beneficial, or currently unrealistic.
Materials-Methods: An in silico assessment was conducted to evaluate hereditary cancer genes from a genome editing feasibility perspective. Factors including gene essentiality, network centrality, tissue specificity, and potential off-target vulnerability were analysed using publicly available genomic and functional datasets. These parameters were integrated to model theoretical risks and benefits associated with genome editing–based interventions.
Results: The analysis highlighted clear boundaries between theoretically actionable and high-risk genome editing targets. Genes with high network centrality or ubiquitous expression were predicted to carry substantial systemic risk upon perturbation, whereas context-dependent or pathway-modulating targets appeared more amenable to future genome editing strategies.
Conclusion: This study provides a bioinformatic framework for defining the realistic scope and limitations of genome editing in hereditary cancer. Such analyses are essential for guiding responsible translation, informing ethical discourse, and aligning technological promise with biological feasibility.

Keywords: Clinical Translation, Gene Essentiality, Genome Editing, Hereditary Cancer, In Silico Analysis

[Abstract:0246]

Novel Likely Pathogenic *BRCA2* Variants: Clinical and Molecular Findings from Three Cases

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Background: The *BRCA2* gene is an important tumor suppressor gene associated with hereditary cancer predisposition. The routine implementation of next-generation sequencing (NGS) has led to the increasingly frequent identification of novel *BRCA2* variants that are not reported in public databases. Accurate classification of these variants is essential for appropriate clinical management and genetic counseling.
Methods: This study included three patients with a personal history of malignancy. In addition, two relatives of one patient were evaluated due to a family history of malignancy. Genomic DNA isolated from peripheral blood samples was analyzed using an NGS-based hereditary cancer panel. Variant interpretation was performed using ClinVar, population databases (gnomAD), ACMG/AMP classification criteria, and multiple in silico prediction tools. Clinical data were reviewed retrospectively.
Results: Case 1, was a 28 year old woman diagnosed with invasive ductal breast carcinoma at a young age. Genetic analysis revealed a heterozygous novel frameshift variant in exon 11 of the *BRCA2* (NM_000059.4) gene, c.2135dup (p.Gln713AlafsTer6). This variant was not present in ClinVar. Based on ACMG criteria (PVS1, PM2), the variant was classified as likely pathogenic. The null nature of the variant and its localization within a known hotspot region were also considered supporting evidence for pathogenicity. Family screening showed that the same variant was also detected in the patient's father and sister.
Case 2, was an 84 year old patient diagnosed with synchronous gastric and colorectal cancers. Genetic testing identified a heterozygous novel frameshift variant in the *BRCA2* (NM_000059.4) gene, c.80_81dup (p.Ser28Ter). The variant was absent from public databases. Based on ACMG criteria (PVS1, PM2), the variant was classified as likely pathogenic. Genetic counseling was recommended.
Case 3, was a 56 year old patient diagnosed with invasive breast carcinoma. Genetic analysis revealed the same *BRCA2* (NM_000059.4):c.2135dup (p.Gln713AlafsTer6) variant identified in Case 1. No known familial relationship was identified between the two cases. Genetic counseling and family screening were planned.
Conclusion: Although *BRCA2* is a well characterized gene, novel likely pathogenic variants continue to be identified. These cases highlight the importance of standardized variant classification, detailed molecular evaluation, and clinical correlation to support appropriate patient management and genetic counseling.

Keywords: *BRCA2*, hereditary cancer, NGS, novel variant

[Abstract:0249]

A case of Muir–Torre syndrome with a synonymous variant detected in the MSH2 gene

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Introduction: Muir-Torre Syndrome (MTS) is a rare phenotypic variant of Lynch Syndrome and is an autosomal dominant cancer susceptibility syndrome characterized by sebaceous gland neoplasms and visceral malignancies. Germline pathogenic variants in DNA Mismatch Repair (MMR) genes (MSH2, MLH1, MSH6, PMS2) are responsible for the etiology of the syndrome. With the widespread use of Next Generation Sequencing (NGS) technologies, numerous variants are detected; however, the clinical interpretation of these variants presents a complex process. In routine bioinformatic analyses, "synonymous" variants that do not lead to amino acid changes in the protein sequence may be considered benign and filtered out. This report presents a case exhibiting classic MTS clinical features and carrying a variant that appears synonymous at the protein level but exerts a pathogenic effect by disrupting the splicing mechanism in the MSH2 gene.

Objective: The aim of this report is to demonstrate the risks of focusing solely on amino acid changes in the interpretation of genomic variants and to highlight the pathogenicity potential of synonymous variants located at exon-intron boundaries, through the MSH2 c.942G>A variant detected in a patient clinically diagnosed with Muir-Torre Syndrome.

Materials-Methods: A 53-year-old female patient was consulted to the Medical Genetics outpatient clinic due to a history of multiple basal cell carcinomas, sebaceous hyperplasias, actinic keratosis, and keratoacanthomas detected in the dermatology clinic. Family history revealed colorectal cancer in her father, two brothers, and uncles; and early and late-onset endometrial cancer in her sisters. A Hereditary Cancer Panel (NGS) was performed. The obtained data were analyzed using 'SEQ variant analysis software' according to the GRCh38 reference genome. Filtered variants were evaluated according to the ACMG Standards and Guidelines recommendations.

Results: A heterozygous c.942G>A variant was detected in the MSH2 gene (NM_000251.3). This variant converts the CAG sequence coding for the Glutamine (Gln/Q) amino acid at codon 314 of the MSH2 gene to the CAA sequence (p.Gln314=). Although this change appears to be a synonymous variant not altering the amino acid sequence, it was determined that the nucleotide change occurred at the last base (3' end) of exon 5 of the MSH2 gene. This position is of critical importance within the consensus sequence of the "splice donor" site at the exon-intron junction. Literature and database searches (ClinVar ID: 91251) confirmed that this alteration leads to aberrant splicing, causing loss of protein function, and is classified as pathogenic. The molecular diagnosis, combined with the patient's strong family history and dermatological findings, confirmed the diagnosis of Muir-Torre Syndrome.

Discussion and Conclusion: Synonymous variants, particularly those near exon-intron boundaries, can disrupt mRNA splicing processes and cause exon skipping. This case emphasizes that in the interpretation of NGS data, attention should be paid not only to the theoretical effect of the variant on the protein but also to its genomic location and potential impact on splicing signals. In the presence of strong phenotypic suspicion, it is crucial to re-evaluate synonymous variants that might be eliminated during filtering, especially regarding "splice-site" regions, either manually or using specialized algorithms.

Keywords: Muir-Torre Syndrome, MSH2, Synonymous Variant, Splicing Defect, Hereditary Cancer

A case of Muir–Torre syndrome with a synonymous variant detected in the MSH2 gene

Veysel Atasoy, Altuğ Koç, Tuba Sözen Türk, Taha Reşid Özdemir
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Objective: The aim of this report is to demonstrate the risks of focusing solely on amino acid changes in the interpretation of genomic variants and to highlight the pathogenicity potential of synonymous variants located at exon-intron boundaries, through the MSH2 c.942G>A variant detected in a patient clinically diagnosed with Muir-Torre Syndrome.
Materials-Methods: A 53-year-old female patient was consulted to the Medical Genetics outpatient clinic due to a history of multiple basal cell carcinomas, sebaceous hyperplasias, actinic keratosis, and keratoacanthomas detected in the dermatology clinic. Family history revealed colorectal cancer in her father, two brothers, and uncles; and early and late-onset endometrial cancer in her sisters. A Hereditary Cancer Panel (NGS) was performed. The obtained data were analyzed using 'SEQ variant analysis software' according to the GRCh38 reference genome. Filtered variants were evaluated according to the ACMG Standards and Guidelines recommendations.
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Keywords: Muir-Torre Syndrome, MSH2, Synonymous Variant, Splicing Defect, Hereditary Cancer

[Abstract:0251]

Reclassification of BRCA1 and BRCA2 Variants of uncertain significance using ClinGen ENIGMA and CanVIG-UK criteria

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Objective: Accurate classification of germline variants in hereditary cancer genes is critical for the diagnosis, treatment, and follow-up of cancer patients. However, a substantial proportion of variants identified in the BRCA1 and BRCA2 genes are reported as Variants of uncertain significance (VUS), posing significant challenges for clinical interpretation and patient management. The aim of this study was to re-evaluate BRCA1 and BRCA2 variants of uncertain significance using the criteria of the ClinGen ENIGMA BRCA1/2 Variant Curation Expert Panel (VCEP) and the CanVIG-UK gene-specific guidelines, and to assess the impact of these approaches on the VUS burden.
Materials-Methods: A total of 1,308 patients with a personal and/or family history of cancer who underwent hereditary cancer gene panel testing between January 2024 and December 2025 were retrospectively reviewed. Patients with at least one VUS identified in the BRCA1 or BRCA2 genes were included in the study. Overall, 30 distinct variants detected in 39 patients were evaluated. All variants were independently reclassified according to two classification frameworks based on the ClinGen ENIGMA BRCA1/2 VCEP criteria and the CanVIG-UK BRCA1/BRCA2 gene-specific guidelines.
Results: 30 distinct variants analyzed, 9 were located in the BRCA1 gene and 21 in the BRCA2 gene. All BRCA1 variants were missense variants, while BRCA2 variants consisted of 20 missense variants and one in-frame deletion.
Application of the ENIGMA VCEP criteria resulted in reclassification of 27 out of 30 variants (90%) as likely benign, with only three variants remaining classified as VUS.
According to the CanVIG-UK criteria, 23 of the 30 variants (76.7%) were classified as VUS and 7 variants (23.3%) as likely benign. No pathogenic or likely pathogenic variants were identified using either classification system.
Conclusion: The ENIGMA criteria substantially increased the rate of benign-oriented reclassification of BRCA1 and BRCA2 variants, whereas the CanVIG-UK approach adopted a more conservative classification strategy, retaining the majority of variants within the VUS category. These findings highlight fundamental differences in variant interpretation methodologies between the two systems. To achieve more informed and reliable variant interpretation in clinical practice, the identification of population-specific recurrent variants and the development of gene-specific guidelines tailored to our population may significantly contribute to reducing the burden of variants of uncertain significance in hereditary cancer genes.

Keywords: ClinGen ENIGMA, CanVIG-UK, reclassification, variant of uncertain significance (VUS)

SAPTANAN VARYANTLAR

Gen	NM Kodu	Ekzon	Varyant Tipi	cDNA Değişim	Protein Değişi	Zigosite	Klinik Sınıflama	CanVIG-UK	ClinGen ENIGMA (
BRCA1	NM_007294	Ekzon 10	Missense	c.856G>C	p.Glu286Gln	Heterozigot	VUS	VUS	LB
BRCA1	NM_007294	Ekzon 10	Missense	c.884A>G	p.Asp295Gly	Heterozigot	VUS	LB	LB
BRCA1	NM_007294	Ekzon 10	Missense	c.1286T>C	p.Ile429Thr	Heterozigot	VUS	LB	LB
BRCA1	NM_007294	Ekzon 10	Missense	c.1286T>C	p.Ile429Thr	Heterozigot	VUS	LB	LB
BRCA1	NM_007294	Ekzon 10	Missense	c.1286T>C	p.Ile429Thr	Heterozigot	VUS	LB	LB
BRCA1	NM_007294	Ekzon 10	Missense	c.1907G>T	p.Cys636Phe	Heterozigot	VUS	VUS	LB
BRCA1	NM_007294	Ekzon 10	Missense	c.2215A>G	p.Lys739Glu	Heterozigot	VUS	VUS	LB
BRCA1	NM_007294	Ekzon 10	Missense	c.2281G>C	p.Glu761Gln	Heterozigot	VUS	VUS	LB
BRCA1	NM_007294	Ekzon 13	Missense	c.4434G>T	p.Glu1478Asp	Heterozigot	VUS	VUS	LB
BRCA1	NM_007294	Ekzon 15	Missense	c.4730C>A	p.Ser1577Tyr	Heterozigot	VUS	LB	LB
BRCA1	**NM_007294.**	**Ekzon 17**	**Missense**	**c.5186T>A**	**p.Leu1729Gl**	**Heterozigot**	**VUS**	**VUS**	**LB ****
BRCA2	NM_000059	Ekzon 10	Missense	c.1548C>G	p.Phe516Leu	Heterozigot	VUS	**VUS**	**LB ****
BRCA2	NM_000059	Ekzon 11	Missense	c.1939T>C	p.Cys647Arg	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.2798C>A	p.Thr933Lys	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.2798C>A	p.Thr933Lys	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.2951A>G	p.Glu984Gly	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	In-frame del	c.3634_3639	p.Asn1212_G	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.3956A>G	p.Asn1322Ser	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.4159T>A	p.Leu1387Ile	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.4243G>C	p.Glu1415Gln	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.4243G>C	p.Glu1415Gln	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.4766C>A	p.Pro1589Gln	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.5125G>T	p.Asp1709Tyr	Heterozigot	VUS	LB	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.5125 G>T	p.Asp1709Tyr	Heterozigot	VUS	LB	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.5224A>C	p.Asn1742His	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.5378A>G	p.Asn1793Ser	Heterozigot	VUS	LB	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.5590G>A	p.Asp1864Asn	Heterozigot	VUS	LB	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.5590G>A	p.Asp1864Asn	Heterozigot	VUS	LB	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.5590G>A	p.Asp1864Asn	Heterozigot	VUS	LB	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.5975C>T	p.Ser1992Leu	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 11	Missense	c.6562A>C	p.Lys2188Glu	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 13	Missense	c.6966G>T	p.Met2322Ile	Heterozigot	VUS	VUS	LB
BRCA2	NM_000059	Ekzon 13	Missense	c.7005T>G	p.Phe2335Leu	Heterozigot	VUS	VUS	LB
BRCA2	**NM_000059**	**Ekzon 17**	**Missense**	**c.7823C>T**	**p.Pro2608Le**	**Heterozigot**	**VUS**	**VUS**	**VUS**
BRCA2	**NM_000059**	**Ekzon 18**	**Missense**	**c.8236A>G**	**p.Thr2746Ala**	**Heterozigot**	**VUS**	**VUS**	**VUS**
BRCA2	**NM_000059**	**Ekzon 29**	**Missense**	**c.9325C>T**	**p.Leu3109Ph**	**Heterozigot**	**VUS**	**VUS**	**VUS**
BRCA2	**NM_000059**	**Ekzon 29**	**Missense**	**c.9325C>T**	**p.Leu3109Ph**	**Heterozigot**	**VUS**	VUS	**LB**
BRCA2	NM_000059	Ekzon 27	Missense	c.9934A>G	p.Ile3312Val	Heterozigot	VUS	**LB**	**LB**
BRCA2	NM_000059	Ekzon 11	In-frame del	c.3634_3639	p.Asn1212_G	Heterozigot	VUS	VUS	**LB**

[Abstract:0260]

Germline Variant Spectrum in Pancreatic Cancer: A Single-Center Experience

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Objective: Pancreatic cancer is an aggressive malignancy with high mortality and limited therapeutic options. Recent studies have demonstrated that approximately 5–10% of patients with pancreatic cancer harbor germline pathogenic variants, most commonly involving BRCA1/2, ATM, PALB2, and CDKN2A genes. Therefore, the NCCN guidelines recommend germline genetic testing for all patients with pancreatic cancer, regardless of family history.

Materials-Methods: The aim of this study was to evaluate the distribution of germline variants and their association with demographic characteristics in patients with pancreatic cancer who underwent hereditary cancer panel testing. This retrospective, single-center study included patients diagnosed with pancreatic malignant neoplasms who were tested using hereditary cancer panels. Two patients with ongoing genetic analyses were excluded, resulting in a total of 38 patients. Clinical and demographic data were obtained from medical records. Detected variants were classified according to ACMG criteria and interpreted in accordance with NCCN guidelines.

Results: The mean age of the patients was 62.1 ± 9.6 years, with 55% female and 45% male. No germline variants were detected in 15 patients (39.5%). Clinically significant pathogenic or likely pathogenic variants were identified in 3 patients (7.9%), including one pathogenic ATM variant and two likely pathogenic CHEK2 variants. Variants of uncertain significance were detected in 14 patients (36.8%). The most frequently affected genes were BRCA2, TSC2, CDKN2A, MET, POLE, and mismatch repair genes. Patients carrying pathogenic or likely pathogenic variants tended to be younger than those without detected variants.

Conclusion: The frequency of germline pathogenic variants observed in this study is consistent with NCCN and previously published data. The concentration of clinically significant variants in NCCN-associated pancreatic cancer genes supports the clinical utility of universal germline testing in pancreatic cancer. However, the high rate of variants of uncertain significance underscores the importance of genetic counseling and multidisciplinary evaluation in routine clinical practice.

Keywords: Pancreatic Cancer, Hereditary Cancer Panel, NCCN guidelines

[Abstract:0263]

APC Gene Associated Case With Cribriform-Morular Type Thyroid Carcinoma And Colon Polyposis

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Introduction: *APC*-associated polyposis conditions include (classic or attenuated) familial adenomatous polyposis (FAP) and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). FAP is a colorectal cancer (CRC) predisposition syndrome that can manifest in either classic or attenuated form. Classic FAP is characterized by hundreds to thousands of adenomatous colonic polyps, beginning on average at age 16 years (range 7-36 years). GAPPS is characterized by proximal gastric polyposis, increased risk of gastric adenocarcinoma, and no duodenal or colonic involvement in most individuals reported.

Aim: This study aims to present the case of a 27-year-old woman with an APC variant who was referred to the Medical Genetics outpatient clinic after a cribriform-morular variant of papillary thyroid carcinoma was identified on pathological examination of thyroid specimens.

Method: Patient's clinical features, pedigree analysis, histopathologic results and imaging findings were evaluated retrospectively. Genomic DNA was isolated from peripheral blood of the patient. Hereditary cancer gene panel which includes 61 genes related to hereditary cancer disposition syndromes using next-generated sequencing was performed.

Result: 27-year-old woman who had bilateral thyroid nodules applied to Endocrinology outpatient clinic 9 years ago. Fine-needle aspiration biopsy of nodules was reported as malign cytology. She was recommended to have thyroidectomy, but she refused. She applied again this year, and her thyroid nodules were increased by size. Radiology imaging of the nodules was consistent with TI-RADS 4 and 5. Repetition of fine-needle aspiration biopsy resulted as malign cytology again and total thyroidectomy was performed. Histopathologic assessment of the thyroid tissue was consistent with cribriform-morular variant of papillary thyroid carcinoma. Due to high co-occurrences of this rare thyroid carcinoma subtype with FAP, genetic investigation was applied. In her genetic analysis, a heterozygous frameshift c.3471_3474del (p.Glu1157Aspfs*7) (NM_000038.6) variant was detected in *APC* gene. This variation is pathogenic according to ACMG classification. Segregation of the family is planned, and genetic investigation of the family members is still on process. After molecular diagnosis, she was referred to Gastroenterology outpatient clinic for investigation in terms of FAP. Her abdominal tomography and magnetic resonance imaging (MRI) showed multiple polypoid lesions in transverse colon, sigmoid colon and rectum. Colonoscopy was performed and samples were collected from polypoid lesions. Histopathologic investigation of the samples revealed adenocarcinoma.

Discussion: Cribriform-morular variant of papillary thyroid carcinoma is a rare subtype. In this rare type of thyroid cancer, the association with the FAP phenotype should be considered and genetic examinations should be planned. Molecular diagnosis of the FAP is guiding for the patient's symptomatic family member's follow-up and treatment plan.

Keywords: *APC*, cribriform morular, FAP, thyroid cancer

[Abstract:0264]

A Rare Example of Early-Onset Metastatic Gastric Cancer with Germline and Somatic CHEK2: Expanding the Tumor Spectrum of CHEK2

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Pathogenic variants in CHEK2 are well recognized in hereditary breast, prostate, and colorectal cancer predisposition; however, their association with gastric cancer is exceedingly rare and remains poorly characterized. Only a limited number of cases have suggested a possible link between CHEK2 and gastric carcinogenesis. The identification of both germline and somatic alterations in the same gene may provide critical insight into tumor-specific mechanisms.

Case Presentation:

We report a 33-year-old male who presented with massive gastrointestinal bleeding. Upper gastrointestinal endoscopy revealed a gastric ulcer, and histopathological examination confirmed gastric adenocarcinoma with signet ring cell features. At the time of diagnosis, the patient had extensive metastatic disease involving the liver, lungs, retrovesical region, and porta hepatis. Immunohistochemical analysis showed preserved expression of mismatch repair proteins (MLH1, PMS2, MSH2, MSH6), indicating microsatellite stability.Immunohistochemistry revealed no stain for c-ErbB2 and positive stain for PD-L1 (CPS: 60; TPS: 55).

Despite first-line treatment with FOLFOX combined with nivolumab, radiological progression was observed after four cycles, necessitating second-line DCX chemotherapy. Family history revealed a grandfather diagnosed with gastric cancer at the age of 50 who died five years later, further supporting a possible hereditary background.

Genetic Findings:

Comprehensive germline testing using a hereditary cancer panel identified a heterozygous pathogenic splice-site variant in CHEK2 (c.320-2A>G). Tumor-targeted next-generation sequencing demonstrated a somatic alteration involving the same CHEK2 region with a variant allele fraction of approximately 38%. Additional somatic pathogenic variants in TP53 and ARID1A were also detected.

Conclusion:

This case represents a rare and illustrative example of early-onset metastatic gastric cancer associated with CHEK2. The findings expand the phenotypic and tumor spectrum of CHEK2-associated cancers and suggest that CHEK2 may play a contributory role in gastric carcinogenesis. Our report underscores the importance of considering broad germline and somatic genetic testing in early-onset gastric cancer, particularly in cases with aggressive clinical behavior and suggestive family history.

Keywords: CHEK2, gastric adenocarcinoma, somatic mutation

[Abstract:0265]

NF2-Related Schwannomatosis Associated with a Rare Exon 1 Duplication Detected by MLPA: A Case Report

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Objective: The *NF2* gene, located at 22q12.2, encodes an ERM family protein that links the cytoskeleton to the cell membrane and regulates contact-dependent inhibition of cell proliferation, cell–cell adhesion, and transmembrane signaling. This protein interacts with cell-surface components, cytoskeletal regulators, and ion transport–related proteins, and its functional disruption is associated with tumorigenesis and metastatic progression.
Conditions associated with *NF2* include schwannomatosis, vestibular schwannomas, and meningiomas.NF2-related schwannomatosis is characterized by bilateral vestibular schwannomas with associated symptoms of tinnitus, hearing loss, and balance dysfunction. The average age of onset is 18 to 24 years. Almost all affected individuals develop bilateral vestibular schwannomas by age 30 years. Affected individuals may also develop schwannomas of other cranial and peripheral nerves, meningiomas, ependymomas, and (very rarely) low-grade astrocytomas.
NF2 is inherited in an autosomal dominant manner. Approximately 50% of individuals diagnosed with *NF2* have an affected parent.Approximately 50% of individuals diagnosed with NF2 have the disorder as the result of a de novo *NF2* pathogenic variant. Molecular genetic testing for NF2-related schwannomatosis identifies pathogenic *NF2* variants in approximately 75% of probands through sequence analysis, while gene-targeted deletion/duplication analysis or chromosomal microarray analysis (CMA) detects an additional 20% of cases.
Case: A 57-year-old female patient was referred to our clinic due to recurrent multiple meningiomas over a 23-year period accompanied by focal seizures. The patient had no dysmorphic features, but neurological examination revealed right-sided hemiparesis, nystagmus, and vertigo. Cranial imaging demonstrated a 10 × 6 mm extra-axial nodular lesion at the level of the left internal auditory canal, raising suspicion for a vestibular schwannoma.
Based on the clinical and radiological findings, neurofibromatosis was considered as the primary diagnosis. Initial genetic testing using a targeted panel including *NF1, NF2*, *SMARCB1,* and *SPRED1*, but did not cover copy number variation analysis revealed no pathogenic variants. Given the persistent clinical suspicion of *NF2,* multiplex ligation-dependent probe amplification (MLPA) analysis of the NF2 gene was subsequently performed.
MLPA analysis identified a heterozygous duplication involving exon 1 of the *NF2* gene [rsa 22q12.2(NF2exons1)x3].
Conclusion: Despite negative results from the initial sequencing-based panel analysis, the persistent and strong clinical and radiological suspicion of NF2 necessitated further genetic investigation using MLPA analysis. MLPA is of particular importance in this setting, as large intragenic copy number changes of the *NF2* gene may escape detection by conventional sequencing methods.
According to the literature, *NF2* gene alterations most commonly present as point mutations and deletions, whereas duplications are exceedingly rare. The few reported duplication cases predominantly involve exons 2–4 of the *NF2* gene.This observation highlights the diagnostic value of MLPA analysis in patients with ongoing clinical suspicion of NF2 and underscores its role in detecting rare copy number gains that may otherwise remain undiagnosed.

Keywords: MLPA, *NF2*, Vestibular schwannoma

[Abstract:0275]

Detection of CNVs in the MLH1 and EPCAM Genes by an NGS-Based Secondary Analysis Software in Agreement with MLPA

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While next-generation sequencing (NGS) is widely used to detect single-nucleotide variants, the reliable identification of copy number variants (CNVs) using this approach remains limited (Pös et al., 2021). In this study, we investigated the detectability of CNVs in cases with no pathogenic sequence variant identified in routine hereditary cancer panel testing by refining secondary analysis steps in accordance with MLPA data.

The study was conducted using data from thirty-eight patients who had wild type results on routine hereditary cancer panel testing at the Ankara University Faculty of Medicine Genetic Diseases Evaluation Center and subsequently underwent deletion/duplication analysis of the MLH1, MSH2, and EPCAM genes using MLPA. According to MLPA results, five patients harbored heterozygous deletions of varying sizes (MLH1 deletions in four patients and an EPCAM deletion in one patient). In the remaining thirty-three patients, no deletions/duplications were detected in the genes of interest. These thirty-three MLPA-negative cases were designated as “wild type controls” in CLC Genomics Workbench to establish a CNV analysis workflow. The NGS data of the five MLPA-positive cases were then reanalyzed using the same workflow.

The newly constructed secondary analysis workflow yielded results fully concordant with MLPA in all five deletion-positive cases, with exact overlap of the affected exons. No false-positive variants were detected in the MLH1, MSH2, and EPCAM genes for which the algorithm was optimized.

This study contributes to the body of work supporting the hypothesis that, when appropriately trained and calibrated, NGS secondary analysis software can detect CNVs with an accuracy comparable to gold-standard methods such as MLPA. Extending this approach to larger panels and broader patient cohorts may facilitate comprehensive, multi-variant analysis on a single platform in NGS-based testing.

Reference

Pös O, Radvanszky J, Styk J, Pös Z, Buglyó G, Kajsik M, et al. Copy Number Variation: Methods and Clinical Applications. *Appl Sci.* 2021;11(2):819.

Keywords: EPCAM, MLH1, NGS

[Abstract:0278]

Systemic HİF-2a Inhibition with Belzutifan in Von Hippel Lindau Disease

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Objective: To present the clinical course and treatment response of a patient with von Hippel–Lindau disease–associated renal cell carcinoma treated with belzutifan.

Case: The patient has a known family history of Von Hippel–Lindau (VHL) disease on the maternal side. On the maternal side, the mother comes from a family of six siblings, consisting of four sisters and two brothers. VHL was diagnosed in four maternal aunts, one maternal uncle, the maternal grandmother, and the son of an uncle who himself was not affected by VHL.

The maternal uncle underwent surgery due to a brain tumor and died at the age of 36. The middle maternal aunt died at the age of 35 due to cerebrovascular hemorrhage. The maternal grandmother developed vision loss in the right eye, followed by enucleation; she also underwent nephrectomy due to renal cell carcinoma (RCC) and died at the age of 36 due to a pancreatic tumor. Both the eldest and youngest maternal aunts were diagnosed with RCC. In the son of the maternal uncle who did not have VHL, cranial and spinal tumors as well as bilateral RCC were diagnosed.

Due to the high prevalence of VHL in the family, the patient was screened, and in 2007 a heterozygous mutation in exon 3 p.(R161), c.481C>T of the VHL gene was detected, after which the diagnosis of VHL was established and follow-up was initiated.

In 2008, the patient first became symptomatic with sudden bilateral vision loss. Tumors were detected in both eyes, and bilateral ocular cryotherapy was performed. In 2012, when the tumor diameter in the right eye reached 8 cm, enucleation was performed.

In 2016, the patient presented with testicular pain, and imaging revealed cysts in both testes and bilaterally in the kidneys. Bilateral orchiectomy was performed, and the renal cysts were placed under surveillance. In 2018, multiple pancreatic cysts were also detected, and follow-up of the renal and pancreatic cysts was continued.

In August 2025, the patient was diagnosed with RCC in the left kidney and underwent partial nephrectomy, after which Belzutifan was initiated and the patient was placed under follow-up. The patient has been receiving Belzutifan for approximately five months, and apart from multiple pancreatic and renal cysts, no additional pathology has been detected. Since the cysts have shown partial regression in both number and size, Belzutifan treatment has been continued.

Conclusion: Belzutifan provides effective systemic disease control in VHL, with measurable regression of cystic lesions and prevention of new tumor development.

Keywords: BELZUTIFAN, RCC, VHL

[Abstract:0279]

From Sebaceous Neoplasm to Hereditary Cancer Syndrome: A Case of Muir-Torre Syndrome

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Introduction: Muir–Torre syndrome (MTS) is a rare phenotypic variant of Lynch syndrome characterized by sebaceous skin tumors and a broad spectrum of visceral malignancies, particularly colorectal, endometrial, urological, and upper gastrointestinal cancers. Sebaceous neoplasms, rare in the general population, are a distinctive feature of MTS and may precede internal malignancies. The syndrome results from mutations in DNA mismatch repair genes, most commonly *MSH2* and *MLH1*, leading to microsatellite instability.
Case: An 84-year-old woman presented with non-healing lesions on the nasal and malar regions persisting for one month. Histopathological examination of the excised lesions revealed sebaceous adenoma. Her medical history included surgical treatment for a brain tumor 22 years earlier, colorectal cancer 20 years earlier, hysterectomy approximately 8–10 years earlier, and sebaceous carcinoma excised from the lumbar region five years prior. The family history was limited to an unspecified cancer in her mother, and the patient had a solitary kidney. With a preliminary diagnosis of MTS, a hereditary cancer panel was performed, revealing a heterozygous likely pathogenic variant (c.2069A>C) and a heterozygous variant of uncertain significance (c.1783C>G) in the *MSH2* gene (NM_000251.3).
Conclusion: This case highlights the diagnostic value of sebaceous skin lesions as an important clinical clue for hereditary cancer syndromes and underscores the critical role of thorough physical examination and genetic testing in the diagnosis of hereditary cancers.

Keywords: Hereditary Cancer, Lynch Syndrome, Mismatch Repair Deficiency, MSH2, Muir-Torre Syndrome

[Abstract:0283]

Neurofibromatosis Type 1 as a Hereditary Tumor Predisposition Syndrome: Clinical and Genetic Landscape in a Single-Center Cohort

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Background: Neurofibromatosis type 1 (NF1) is a multisystem genetic condition characterized by marked phenotypic variability. Common manifestations include café au lait macules, axillary or inguinal freckling, multiple cutaneous neurofibromas, and neurodevelopmental or behavioral difficulties. NF1 is caused by pathogenic or likely pathogenic variants in the NF1 gene located at chromosome 17q11.2 and is inherited in an autosomal dominant manner. NF1 is a relatively common cause of hereditary cancer disposition with an estimated prevalence of 1 in 2,500 to 1 in 3,000 individuals. It confers an increased lifetime risk of both benign and malignant tumors. Despite its well-established molecular basis, predicting clinical severity and tumor risk remains challenging due to marked interindividual variability.
Methods: We evaluated the clinical and genetic characteristics of patients with suspected NF1 referred to the Department of Medical Genetics, Ankara University School of Medicine, between 06-2021 and 08-2025. A total of 62 individuals from 56 families were included (34 females:28 males). Next-generation sequencing (NGS) was performed on DNA extracted from peripheral blood. NF1 variants were investigated using either single gene testing, a multigene panel including NF1, NF2, and SPRED1 or an 18-gene RASopathy panel. Copy number analysis by MLPA was performed when available. Detailed clinical data were systematically reviewed to assess genotype–phenotype correlations.
Results: Germline pathogenic or likely pathogenic variants in the NF1 gene were identified in 32 of 62 patients (51.6%). Most variants were truncating (nonsense/frameshift) (21/32, 65.6%), followed by missense (8/32, 25.0%), splice-site (2/32, 6.3%), and an intronic variant (1/32, 3.1%). In addition, four NF1 variants were not previously reported in public databases and were considered novel. Furthermore, a variant of uncertain significance (VUS) in NF1 was identified in one patient, presenting with axillary freckling and neurofibromas. One patient harbored a low-level mosaic truncating NF1 variant with an approximate variant allele frequency of 2%. Segregation analysis was performed in 10 patients with pathogenic NF1 variants, of whom 8 were shown to harbor de novo variants. MLPA analysis was performed in 20 patients, with no deletions or duplications detected. In addition, pathogenic SPRED1 variants consistent with Legius syndrome were identified in two siblings evaluated for NF1-like pigmentary features.
Malignant tumors were observed in 6 of 32 patients (18.7%) with pathogenic or likely pathogenic NF1 variants; tumor types included breast cancer(n=2), pheochromocytoma(n=1), esophageal adenocarcinoma(n=1) and malignant peripheral nerve sheath tumor(n=2). Notably, two additional patients with acute myeloid leukemia and NF1 features did not harbor pathogenic NF1 variants.
Conclusion: This single-center cohort highlights the clinical and genetic heterogeneity of NF1 and confirms the predominance of truncating variants among affected individuals. The high malignancy burden observed in adults underscores the importance of long-term clinical follow-up and cancer surveillance. The absence of a molecular diagnosis in a subset of clinically suspected cases may be attributed to limitations of routine testing, including the inability to detect deep intronic and complex structural variants, or low-level mosaicism. This emphasizes the value of integrated clinical and molecular evaluation and encourages the employment of more comprehensive genetic testing in a routine setting.
Keywords: genetic testing, hereditary tumor predisposition, neurofibromatosis type 1 (NF1), variant distribution

[Abstract:0286]

Aggressive early-onset renal cell carcinoma associated with a germline FH variant: a case report

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Objective: Hereditary leiomyomatosis and renal cell cancer (HLRCC; MIM #150800) is an autosomal dominant tumor predisposition syndrome caused by heterozygous pathogenic/likely pathogenic (P/LP) variants in the fumarate hydratase gene (FH; MIM*136850). It is classically associated with cutaneous and uterine leiomyomas and an increased risk of aggressive renal cell carcinoma (RCC). FH-driven renal tumors may metastasize early and behave aggressively despite limited primary tumor burden. In the 2022 WHO classification, renal carcinomas driven by FH inactivation are encompassed under FH-deficient RCC, which may present with or without overt extra-renal stigmata. We describe an early-onset metastatic RCC in a male patient with a germline FH variant, highlighting the diagnostic value and counseling implications of genotype-driven evaluation in aggressive early-onset RCC.

Case: A male patient developed RCC in his early 30s; retrospective review was limited to health-system records available between 2020 and 2023, which documented a predominantly progressive metastatic course. He initially presented with right femoral pain, and biopsy of the femoral lesion demonstrated a malignant epithelial neoplasm compatible with RCC metastasis. Subsequent right nephrectomy with retroperitoneal mass excision confirmed RCC with sarcomatoid differentiation, with bone and lung metastases already present at diagnosis. Serial imaging showed a heterogeneous treatment response with alternating intervals of partial regression and progression. Over time, metastatic disease expanded to additional skeletal sites and pleural involvement, complicated by massive pleural effusion requiring urgent drainage, followed by liver metastases and calvarial metastatic masses on brain MRI. Systemic therapy consisted of multiple lines of VEGF-targeted tyrosine kinase inhibitors and immune checkpoint inhibition, along with bone-directed therapy (intravenous zoledronic acid) and supportive care; however, responses were not durable.

Peripheral-blood clinical exome sequencing identified a heterozygous FH variant NM_000143.4:c.983T>G (p.Met328Arg) in exon 7 with a variant allele fraction of ~48%. The variant was classified as Likely Pathogenic according to ACMG/AMP guidelines (2015), consistent with an FH tumor predisposition/HLRCC-spectrum diagnosis. Available records documented a non-contributory family history.

Conclusion: This case underscores that early-onset, aggressive, multi-organ metastatic RCC should prompt evaluation for hereditary RCC syndromes, including FH tumor predisposition/HLRCC, even in the absence of a suggestive family history or classical extra-renal manifestations. Importantly, lack of family history does not exclude FH-related predisposition due to possible de novo occurrence, reduced penetrance, or variable expressivity. Identification of a likely pathogenic germline FH variant has immediate implications for genetic counseling, including a 50% transmission risk to offspring, cascade testing of at-risk relatives, and syndrome-specific surveillance, most notably annual renal MRI starting at age 8 years, enabling earlier risk management for family members.

Keywords: Fumarate Hydratase, Carcinoma, Renal Cell, Hereditary Leiomyomatosis and Renal Cell Cancer, Neoplasm Metastasis

[Abstract:0295]

A Novel Variant in the *BMPR1A* Gene in a Patient with Colorectal Cancer: Variable Clinical Phenotype and Genotype-Phenotype Correlation

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Introduction: The *BMPR1A* gene is traditionally associated with Juvenile Polyposis Syndrome (JPS) and is a known contributor to colorectal cancer susceptibility. Clinical severity (age of onset, extent of polyposis, etc.) can be highly variable among cases with pathogenic variants in *BMPR1A*, presenting a broad phenotypic spectrum. International guidelines emphasize the necessity of including the *BMPR1A* gene in germline multigene panels used for hereditary colorectal cancer susceptibility syndromes. In this study, we aimed to evaluate the clinical status and variant characteristics of a patient diagnosed with rectal cancer in whom a novel *BMPR1A* variant was identified, and to discuss the genotype-phenotype correlation.
Method: Following genomic DNA isolation from a peripheral blood sample, sequencing was performed for hereditary cancer panel genes using a custom-designed panel via the Next-Generation Sequencing (NGS) method. Following bioinformatic analyses, the variants were evaluated in accordance with the American College of Medical Genetics and Genomics (ACMG) criteria.
Case Presentation: A 41-year-old male patient was diagnosed with rectal adenocarcinoma following biopsies of an ulcerovegetative mass detected during a colonoscopy performed for gastrointestinal complaints. The patient underwent oncological follow-up, surgery, and chemotherapy. During this process, he was referred to the Izmir City Hospital, Department of Medical Genetics, for clinical genetic evaluation. While the patient's personal history was unremarkable, his family history revealed that his mother died of colon cancer at age 50, two brothers died of colon cancer at ages 20 and 40, and a sister died of colon cancer at age 22. Multigene panel testing for hereditary cancer syndromes identified a heterozygous c.678del (p.Gln227SerfsTer34) variant in the *BMPR1A* (ENST00000372037.8) gene. This variant, which has to our knowledge not been previously reported in the literature and is considered novel, was classified as 'likely pathogenic' according to ACMG criteria. Post-test genetic counseling was provided in line with international guidelines, and family screening was planned.

Discussion: This study presents a case diagnosed with rectal cancer at age 41, with the previously undescribed c.678del (p.Gln227SerfsTer34) variant. This case suggests that the clinical spectrum associated with the *BMPR1A* gene is much broader than classical Juvenile Polyposis Syndrome (JPS) and should be considered in early-onset colorectal cancer (CRC) cases where polyposis findings are not prominent.
Although *BMPR1A* variants are typically associated with JPS, the most striking feature in this case is the history of colon cancer at very early ages within the pedigree. This situation highlights once again that the phenotype associated with the *BMPR1A* gene can be highly variable and underscores the importance of a meticulous clinical genetic evaluation and detailed personal and family history in establishing genotype-phenotype correlations.

Keywords: Colorectal Cancer, *BMPR1A*, Genetic Counseling

[Abstract:0300]

Nijmegen Breakage Syndrome Diagnosed During Long Term Follow Up After Acute Lymphoblastic Leukemia

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Objective: Chromosomal breakage syndromes characterized by defects in DNA repair are associated with an increased risk of malignancy, growth and developmental delay, and endocrine dysfunctions. Nijmegen Breakage Syndrome (NBS) is a rare autosomal recessive chromosomal breakage disorder characterized by early-onset malignancies and gonadal failure. Identification of underlying genetic predispositions in patients diagnosed with acute lymphoblastic leukemia (ALL) is crucial for long-term follow-up.
In this case report, we aimed to present a patient who was diagnosed with ALL in childhood and was later found to have Nijmegen Breakage Syndrome during longterm follow up after evaluation for delayed puberty.

Case: The clinical, laboratory, and genetic data of a female patient diagnosed with intermediate-risk B-cell acute lymphoblastic leukemia in 2010 were retrospectively reviewed. The patient completed chemotherapy in 2012 and was referred to our center for follow-up after relocating to another city. At the age of 15, she was referred to pediatric endocrinology due to absence of pubertal development. Endocrinological and genetic evaluation results were analyzed.
Physical examination revealed absence of pubertal development. Pediatric endocrinology evaluation demonstrated hypergonadotropic hypogonadism. The patient was assessed by a medical geneticist, and further investigations were performed for a chromosomal breakage syndrome due to borderline intellectual disability and characteristic facial features. Genetic analyses confirmed the diagnosis of Nijmegen Breakage Syndrome, revealing a homozygous frameshift pathogenic variant (c.665del, p.Phe222Serfs*9) in the *NBN* gene. No relapse of ALL or secondary malignancy was detected during follow up.

Conclusion: Nijmegen Breakage Syndrome is a rare but significant hereditary cancer predisposition syndrome, particularly associated with lymphoid malignancies. This case highlights that underlying genetic syndromes should be considered in childhood ALL survivors presenting with delayed puberty, gonadal failure, and neurodevelopmental findings. Early diagnosis is critical for appropriate malignancy surveillance, prevention of treatment related toxicities, and provision of genetic counseling.

Keywords: Acute Lymphoblastic Leukemia, DNA Repair Defect, Nijmegen Breakage Syndrome

[Abstract:0306]

A Case Series of Four Neurofibromatosis Type 1 Patients Carrying *NF1* Gene Variants

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Introduction: Neurofibromatosis type 1 (*NF1*) is an autosomal dominant neurocutaneous disorder associated with multisystem involvement and an increased risk of benign and malignant tumors. It is caused by pathogenic variants in the *NF1* gene on chromosome 17q11.2, which encodes neurofibromin. Approximately half of *NF1* cases arise from de novo mutations.
Objective: This study presents four cases diagnosed with Neurofibromatosis Type 1 in different age groups, with pathogenic changes detected in the *NF1* gene. The aim of this study is to discuss the clinical findings and molecular genetic findings of these cases.
Method: The clinical findings, family histories and molecular analysis results of four cases with a preliminary diagnosis of *NF1* who underwent next-generation sequencing were retrospectively evaluated. The identified variants were reported and interpreted in accordance with the ACMG variant classification criteria.
Case Description: Case 1: A 8-year-old male patient was referred to us with a history of seizures and the presence of hyperpigmented skin lesions. Upon physical examination, we observed that the patient had an abnormal cervical spine. A brain MRI was performed, which detected the presence of T2 hyperintensities in the cerebellum. Genetic testing revealed a pathogenic c.2842del mutation in the *NF1* gene. There was no family history of similar conditions.
Case 2: A 40-year-old female patient diagnosed with breast cancer was admitted to the clinic. The presence of neurofibromas was detected during the physical examination. Genetic analysis yielded two heterozygous pathogenic variants in the *NF1* gene: c.2560C>T and c.2557C>T. A detailed review of the patient's medical history disclosed that her father and child had also exhibited similar skin lesions.
Case 3: A 26-year-old male patient was evaluated in our clinic with a preliminary diagnosis of neurofibromatosis. Physical examination revealed axillary-inguinal striae, scoliosis, and widespread soft tissue masses in the upper and lower extremities, the largest of which measured 2×3 cm. Brain MRI showed T2 hyperintensities in the posterior corpus callosum and adjacent to the left ventricle. Genetic testing was performed, leading to the identification of a heterozygous pathogenic c.2T>A mutation in the *NF1* gene. Similar cutaneous manifestations were noted in the patient's sibling, father, and maternal grandmother.
Case 4: A 72-year-old male patient referred to our clinic and had been under follow-up with a diagnosis of neurofibromatosis since the age of 20. A physical examination was conducted, which revealed the presence of cutaneous neurofibromas on a wide scale. A review of the patient's family history revealed that he and his daughter, as well as his grandson, exhibited hyperpigmented skin lesions. Genetic testing confirmed the presence of the same heterozygous pathogenic c.7131del mutation in the *NF1* gene in the patient, as well as both the daughter and the grandson, thereby supporting autosomal dominant inheritance across three generations.
Conclusion: This case series demonstrates the marked phenotypic heterogeneity and variable expression within families of *NF1*. Genetic diagnosis, clinical follow-up, and family screening are critical due to the predisposition to benign and malignant tumors in this syndrome and the high frequency of other *NF1*-related complications.

Keywords: Neurocutaneous, Neurofibromatosis, *NF1*

[Abstract:0310]

Two Cases of Hodgkin Lymphoma with CD27 Deficiency

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Objective: CD27 deficiency is an autosomal recessive immunodeficiency characterized by a defect in the CD27-CD70 pathway, susceptibility to Epstein-Barr Virus (EBV), and EBV-related malignancies, including Hodgkin lymphoma (HL). Here, we present the follow-up of two cases with CD27 deficiency from a previously published familial Hodgkin lymphoma case series, diagnosed with advanced-stage, relapsed-refractory EBV-LMP1+ mixed cellularity classic Hodgkin lymphoma, who died due to sepsis and infectious complications during treatment-resistant disease. We aimed to describe the long-term course, treatment responses, and infectious complications of EBV-positive HL in two pediatric patients with CD27 deficiency and to discuss therapeutic implications.
Case: Case 1: The patient was diagnosed with stage 4B HL (EBV-LMP1+). Due to a family history of consanguineous marriage, Hodgkin lymphoma in one sibling before the patient, and a history of intraoperative death in another sibling during surgery for an intra-abdominal mass, the patient was evaluated and found to carry a homozygous c.18del p.Trp7GlyfsTer44 frameshift mutation. Following six cycles of ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) chemotherapy and radiotherapy, the patient was evaluated for hematopoietic stem cell transplantation (HSCT) due to CD27 deficiency; however, treatment was discontinued as no matched sibling donor was available. In July 2022, the patient was admitted to our clinic following a relapse, with a biopsy of a mass lesion in the right lung confirming Hodgkin lymphoma. ICE (ifosfamide, carboplatin, etoposide)-topotecan treatment was initiated. Although significant regression was observed after three cycles, the patient died due to sepsis and septic shock.
Case 2: The patient was diagnosed with stage 4B HL (EBV-LMP1+). Because the patient belonged to the same family as Case 1, further evaluation revealed the same homozygous c.18del p.Trp7GlyfsTer44 frameshift mutation. The patient responded after three cycles of ABVD, but showed progressive disease at the end of six cycles; after being lost to follow-up for five months, the patient presented to our center. Rituximab combined with ICE-topotecan chemotherapy was initiated. Allogeneic stem cell transplantation was planned; however, although one sibling donor was HLA-compatible, it was considered unfavorable because the donor was a heterozygous carrier of the mutation. A search for an unrelated donor was initiated. At the interim evaluation, a partial response was noted, but the patient had progressive disease after six cycles and was switched to the VIT (vincristine, irinotecan, temozolomide) chemotherapy protocol. During treatment, the patient died due to COVID-19 pneumonia and gastrointestinal involvement despite IVIG support and steroid therapy
Conclusion: These two cases demonstrate an aggressive, recurrent/refractory HL phenotype in the context of CD27 deficiency. In pediatric EBV-positive HL cases with a history of consanguinity and recurrent infections, early diagnosis of inborn errors of immunity must be considered. Earlier implementation of immunological management (IVIG, prophylaxis) and timely referral for curative therapies, including the evaluation of allogeneic hematopoietic stem cell transplantation in high-risk cases, may improve outcomes. In our patients, while HSCT was planned, they were lost to relapsed/refractory disease and infectious complications during the unrelated donor search, as there were no suitable matched sibling donors and potential donors were heterozygous carriers.

Keywords: pediatric, hodgkin lymphoma, CD27 deficiency

[Abstract:0314]

Retrospective Evaluation of Multigene Panel Test Results in Hereditary Colorectal Cancer Syndromes

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Introduction: Colorectal cancer (CRC) is the third most common cancer worldwide and is strongly influenced by genetic predisposition. Although most cases are sporadic, approximately 5–10% are associated with hereditary cancer syndromes, most commonly Lynch syndrome, *MUTYH*-associated polyposis (MAP), and familial adenomatous polyposis (FAP). The lack of specific clinical features in the early stages often delays diagnosis, and nearly half of CRC cases are detected at an advanced stage. Advances in molecular genetics have improved the identification of cancer-predisposing genes and have significantly impacted the diagnosis, risk assessment, and management of hereditary CRC. Therefore, genetic testing plays a key role in early diagnosis, personalized surveillance, and the development of preventive strategies.
Objective: In this study, the genetic test results of 61 patients referred to the Department of Medical Genetics, Sivas Cumhuriyet University, for hereditary colorectal cancer syndromes between 2022 and 2025 were retrospectively evaluated. The aim of this study was to present the clinical findings and molecular analysis results of cases with variants detected in genetic analyses.
Materials-Methods: DNA was isolated from peripheral blood samples collected from index cases. Next-generation sequencing (NGS) analysis was performed using primers covering all coding exons and exon-intron junction regions of 71 colon cancer panel genes on the extracted genomic DNA samples. The detected variants were classified according to ACMG criteria. Clinically meaningful variants were reported, taking into account clinical findings and family history.
Results: Of the 61 cases evaluated based on multigene panel results, 27 (44.3%) were male and 34 (55.7%) were female. A total of ten cases had a documented history of primary cancer other than colorectal cancer, and two cases had two separate primary cancer diagnoses. The mean age at the time of cancer diagnosis was calculated to be 54.9 years. The analysis results revealed 27 genetic alterations in 26 patients, of which 8 were classified as pathogenic, 5 as likely pathogenic, and 14 as variants of uncertain clinical significance (VUS). Upon examination of the variant distribution, the most frequent alterations were detected in the *MSH2* gene in 5 patients (representing 18.5% of the study population). This was followed by the *MLH1, MSH6,* and *POLE* genes, each of which was detected in 3 cases (11.1%). A variant was identified in one case in each of the *PMS2, PMS1, APC, POLD1, FLCN, PIK3CA, CHEK2, ATM, BRCA2, EP300, RUNX1, TSC2*, and *RET* genes (3.7%). Pathogenic/Likely pathogenic cases occurred in 69.2% (9/13) of cases in DNA mismatch repair (MMR) genes associated with Lynch syndrome (LS), such as *MLH1, MSH2, MSH6, and PMS2.*
Conclusion: This study aimed to assess the genotype–phenotype relationship in hereditary colorectal cancer syndromes. The findings revealed a heterogeneous distribution of variants, mainly involving DNA mismatch repair (MMR) genes. Follow-up plans were created for patients with cancer in whom genetic alterations were identified. In addition, genetic counseling was provided to mutation-positive family members without a cancer history, including recommendations for screening, surveillance, and preventive strategies.

Keywords: Hereditary Cancer, Colorectal Cancer, Lynch Syndromes

[Abstract:0315]

Expanding the Phenotypic Spectrum of *MSH3*: A Potential Germline Predisposition to Hodgkin Lymphoma Discovered via Secondary WES Findings

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Background: The DNA mismatch repair (MMR) pathway is a fundamental mechanism for maintaining genomic integrity by correcting errors that occur during DNA replication. While germline heterozygous mutations in canonical MMR genes (*MLH1, MSH2, MSH6, and PMS2*) are well-known causes of Lynch syndrome, biallelic mutations in these genes lead to constitutional mismatch repair deficiency (CMMRD) syndrome, which is characterized by an exceptionally high risk of early-onset malignancies. *MSH3*, which encodes a protein that forms the MutSβ complex, has recently emerged as a significant component of this spectrum. Although biallelic *MSH3* deficiency has primarily been associated with adenomatous polyposis, recent literature has begun to describe a broader phenotypic spectrum, including hematological malignancies such as Hodgkin Lymphoma (HL).

Objective: This study aims to report a rare case of a homozygous splice-site deletion in the *MSH3* gene identified as a secondary finding in a patient with a prior history of Classical Hodgkin Lymphoma and to discuss its potential role as a novel germline predisposition factor.

Methods: The medical records of a 20-year-old male patient were retrospectively reviewed. The patient was initially diagnosed with Classical Hodgkin Lymphoma (Mixed Cellularity type) in late 2020 after presenting with B-symptoms and mediastinal lymphadenopathy, confirmed via mediastinoscopy. In 2025, the patient presented with progressive lower extremity weakness. Clinical evaluation showed elevated creatine kinase (CK) levels (777 U/L) and myopathic findings on electromyography (EMG). Whole Exome Sequencing (WES) was performed to investigate the etiology of the progressive myopathy.

Results: WES analysis did not identify a primary genetic cause for the patient's myopathic symptoms. However, a homozygous secondary finding was identified in the *MSH3* gene: c.2253+3_2253+7del. This 5-nucleotide deletion at the donor splice site of exon 15 disrupts the highly conserved consensus sequence required for splicing. In silico analysis via AbSplice (score: 0.296) predicted a significant impact on splicing, particularly in lymphoid tissues. The molecular mechanism involves the skipping of exon 15, leading to a frameshift and premature termination, which triggers nonsense-mediated decay (NMD) and results in a null allele.

Discussion: The identification of a biallelic *MSH3* mutation in a patient with a prior history of Classical HL is highly significant. Recent case reports have documented Classical HL as a presenting feature of biallelic *MSH3* deficiency, suggesting that this gene may be a novel predisposition factor for lymphoid malignancies. This finding highlights the critical clinical utility of reporting secondary findings in WES, as it provides an underlying explanation for the patient's prior oncological history and necessitates immediate proactive surveillance for other associated risks, such as early-onset colorectal cancer. This case reinforces that *MSH3* should be considered in the differential diagnosis of hereditary cancer syndromes presenting with hematological malignancies, expanding the phenotypic landscape of constitutional mismatch repair deficiency.

Keywords: Hodgkin Lymphoma, Mismatch Repair Deficiency, *MSH3*, Secondary Findings

[Abstract:0318]

Clinical management of a family carrying the ATM mutation

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Objective: The ATM gene is a moderate-penetrance gene involved in the repair of DNA double-strand breaks, and germline mutations in this gene increase the risk of breast cancer by approximately 2-3 times.In current oncology practice, the follow-up of healthy individuals with ATM variants and surgical decision-making processes are being reshaped in light of the most up-to-date NCCN and ASCO/SSO guidelines.The aim of this study is to describe the approach of oncology and genetics specialists to ATM Pathogenic/Likely Pathogenic (P/LP) variants detected in healthy individuals using current literature data, and to examine the steps of clinical decision-making thru a specific family. A systematic literature review was conducted in the study based on NCCN and ASCO/SSO guidelines.
Case: As a clinical sample, follow-up data from a family with a history of three breast cancer cases across two generations and the ATM (NM_000051.4:c.8147T>C) variant detected in five healthy individuals thru family screening were used. The guidelines recommend annual contrast-enhanced breast MRI for ATM carriers starting at age 30-35 and annual mammography/tomosynthesis starting at age 40. Prophylactic mastectomy is not a routine recommendation, but it should be personalized in the presence of a strong family history or clinical findings. In the presented family, a carrier with a BIRADS 4 lesion underwent prophylactic surgery, considering genetic risk factors and patient anxiety; the other four carriers with no radiological findings were placed on an intensive screening protocol.
Conclusion: The management of ATM mutations should be based on the balance between the variant's penetrance and the individual's clinical phenotype. Although the presence of mutation alone is considered insufficient for surgery, a strong family history, radiological suspicions such as BIRADS 4, and patient desire and anxiety are critical factors that alter the surgical threshold. As a result, the coordination of oncology and genetics units in the management of these individuals optimizes early diagnosis and primary prevention opportunities while avoiding unnecessary interventions.

Keywords: hereditary cancers, atm mutation carriers, hereditary breast cancers

FULL TEXTS

115- From Cancer of Unknown Primary to Germline Inheritance: The RAD54L Variant and Molecular Tracing of Colorectal Cancer

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Background: Comprehensive Genomic Profiling (CGP) reshapes the diagnostic approach to Cancer of Unknown Primary (CUP) by enabling tissue of origin determination through molecular signatures, extending modern oncology beyond conventional methods. This case demonstrates the multifaceted utility of CGP in both resolving diagnostic ambiguity and uncovering clinically significant germline alterations.

Case: A 68 year old woman with multiorgan metastases and diagnostic uncertainty between ovarian and gastrointestinal primary malignancy is presented. CGP analysis revealed the classic colorectal signature (APC, KRAS, SMAD4, PIK3CA alterations) and a RAD54L c.479G>T (p.G160V) variant detected at 52% variant allele frequency. The tumor was microsatellite stable, HRD negative, with moderately elevated tumor mutational burden. Germline analysis confirmed the RAD54L variant as likely pathogenic. Due to KRAS mutation, anti-EGFR therapy was contraindicated; FOLFOX plus bevacizumab combination achieved marked clinical improvement.

Discussion: RAD54L encodes an ATP dependent helicase essential for homologous recombination. Unlike core HR genes (BRCA1/2), RAD54L functions as an HR modulator; partial loss of function can cause chronic genomic instability without triggering classical HRD signatures. In modern oncogenetic practice, the integrated evaluation of somatic and germline genomic data provides critical information beyond guiding treatment decisions, encompassing both familial risk assessment and preventive strategies.

Conclusion: CGP surpassed anatomical diagnostics in determining tumor origin and revealed a rare germline RAD54L variant with hereditary implications. This case underscores the importance of integrating somatic germline genomic data in oncogenetics.

Keywords: Cancer of Unknown Primary, RAD54L, Germline Variant, Comprehensive Genomic Profiling, Homologous Recombination, Colorectal Cancer

Introduction: Cancer of Unknown Primary (CUP) accounts for 3-5% of all malignancies and poses diagnostic challenges when conventional histopathology and imaging modalities cannot determine the anatomical origin (1). In traditional approaches, the primary site is sought through immunohistochemical panels and morphological assessment; however, these methods frequently prove inadequate due to tumor dedifferentiation and atypical presentations. Comprehensive Genomic Profiling (CGP) has emerged as a powerful tool for tissue of origin determination through identification of tumor specific molecular signatures, while simultaneously uncovering actionable therapeutic targets and hereditary cancer predisposition (2). In recent years, with the integration of next generation sequencing (NGS) technologies into clinical practice, molecular origin can be determined in approximately 80% of CUP cases, a rate significantly higher than that achieved with conventional methods.

RAD54L, a member of the SWI2/SNF2 family, facilitates homologous recombination (HR) by stabilizing RAD51 filaments and enabling chromatin remodeling at DNA double strand break sites (3). Unlike obligate HR genes (BRCA1, BRCA2, PALB2), RAD54L functions as a modulator. In this context, RAD54L

mutations do not abolish HR but reduce its efficiency. Functional characterization of RAD54L demonstrates that this protein is not merely an auxiliary factor in DNA repair but also a critical regulator of chromatin dynamics. Specifically, RAD54L's ATPase activity is required for nucleosome translocation and DNA translocation, and this property plays a central role in fine tuning HR efficiency. Despite its critical role at the molecular level, germline RAD54L variants have been reported in limited numbers in the solid tumor context, and further research is needed to elucidate their clinical significance (4). Here, we present a CUP case in which CGP resolved diagnostic ambiguity and identified a rare germline RAD54L variant with important implications for cancer genetics and family counseling.

Case Presentation:Clinical and Radiological Findings

A 68 year old woman presented with a 10 day history of abdominal pain and vaginal bleeding. Her medical history was unremarkable for chronic illness, prior surgery, or radiotherapy. Family history was negative for malignancy. Physical examination revealed right lower quadrant tenderness. Tumor markers: CEA 29 ng/mL, CA19-9 512 U/mL, CA125 43 U/mL. Routine laboratory tests revealed no pathological findings except mild anemia (Hb: 10.2 g/dL) and hypoalbuminemia (3.1 g/dL). Computed tomography demonstrated extensive metastatic disease including hepatic lesions (largest 22×20 mm), cecal mass, peritoneal carcinomatosis, and osseous metastases (vertebrae, pelvis, ribs). PET-CT showed hypermetabolic activity in the cecum (SUVmax 12.11) and widespread metastases. Additionally, PET-CT noted multiple lymph node involvement (paraaortic, iliac chains) and minimal ascites. Colonoscopy revealed cecal adenocarcinoma invading the ileocecal valve. Elevated CA125 levels and peritoneal involvement raised differential considerations of primary ovarian and gastrointestinal malignancies.

Comprehensive Genomic Profiling

CGP was performed on FFPE tissue using next generation sequencing (Oncomine Comprehensive Assay Plus, 501 genes). Key findings:

Gene/Variant	VAF (%)	TIER	Clinical Significance
RAD54L c.479G>T (p.G160V)	52.5	IIC	Germline confirmed (likely pathogenic)
APC c.4285C>T (p.Q1429*)	41.72	III	Colorectal signature; Wnt pathway
KRAS c.38G>A (p.G13D)	24.86	IIC	Anti-EGFR resistance
SMAD4 c.1157G>T (p.G386V)	9.98	III	Colorectal signature; TGF-β pathway
BRAF c.1406G>C (p.G469A)	28.49	IIC	Non-V600E variant; co-driver
PIK3CA c.1633G>A p.(K545K)	7.05	IIC	PI3K pathway activation

Additional parameters: MSI-stable, TMB 10.41 mut/Mb (moderately elevated), HRD negative (genomic instability score percentile 2%). Copy number variation (CNV) analysis revealed no significant amplifications or deletions. Gene fusion analysis detected no pathological fusion products.

Germline Testing and Treatment

Detection of the RAD54L variant at 52% VAF raised suspicion of germline origin. Germline testing was performed via peripheral blood DNA sequencing (172 gene hereditary cancer panel). The panel encompassed DNA repair genes including BRCA1/2, PALB2, ATM, CHEK2, RAD51C/D, BRIP1, as well as Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2) and other hereditary cancer syndrome associated genes. Heterozygous germline inheritance was confirmed and classified as likely pathogenic according to ACMG criteria (5). Genetic counseling and cascade testing for first degree relatives were recommended.

Due to KRAS mutation, anti-EGFR therapy was contraindicated; the patient was treated with FOLFOX plus bevacizumab combination. Response was achieved: follow up PET-CT demonstrated marked reduction in hepatic and skeletal metastases, CEA decreased to 9 ng/mL, CA19-9 to 123 U/mL, and significant clinical improvement was observed.

Discussion:

Genomic Signature and Tissue of Origin Determination

The APC-KRAS-SMAD4 triad represents the classic molecular signature of colorectal cancer, recapitulating the Fearon-Vogelstein adenoma carcinoma sequence (6). This sequence is a model that defines the molecular pathology of sporadic colorectal carcinogenesis and is accepted as the gold standard for tissue of origin determination in clinical practice. While APC inactivation initiates early adenoma formation, KRAS activation provides proliferative signal amplification, and SMAD4 loss disrupts TGF-β mediated growth suppression, contributing to advanced stage transformation. This genomic profile definitively established colorectal origin despite initial diagnostic uncertainty. Although elevated CA125 and peritoneal involvement suggested ovarian primary, the molecular evidence was conclusive. This case demonstrates CGP's superiority over anatomical diagnostics in CUP cases and validates the principle that the primary address resides not only in anatomy but also in the genome.

The co-occurrence of KRAS and non-V600E BRAF (p.G469A) mutations is noteworthy. Unlike the mutually exclusive KRAS and BRAF V600E mutations, non-V600E BRAF variants exhibit distinct kinase properties and can coexist with RAS mutations. This dual driver configuration may synergistically amplify MAPK signaling and potentially contribute to the aggressive metastatic phenotype observed here.

Role of RAD54L and Clinical Implications

RAD54L is an ATP dependent chromatin remodeler that stabilizes RAD51 filaments, facilitates homology search, and promotes strand invasion during HR (3). Unlike BRCA1/2, which are indispensable for HR, RAD54L functions as an efficiency modulator. This results in an intermediate form of HR capacity that may manifest as chronic, low level genomic instability rather than classical HRD phenotypes.

The HRD negative status in this case despite germline RAD54L alteration is consistent with this functional model. Classical HRD assays detect large scale genomic scars (LOH, TAI, LST) characteristic of BRCA1/2 deficiency (7). Partial RAD54L deficiency may increase point mutation accumulation reflected in moderately elevated TMB without generating the classical structural alteration signatures that define HRD positive tumors, through engagement of error prone repair mechanisms.

Germline RAD54L variants have been reported in limited numbers in solid tumor literature. Moderate level penetrance possibility is discussed in some cases detected in hereditary breast-ovarian cancer families. This patient's negative family history suggests that the variant's penetrance may be variable. Germline variant detection supports genetic counseling and targeted testing approach for first degree relatives. However, due to limited case numbers in the literature, a standard procedure for patient surveillance has not yet been established.

Therapeutic Implications: The KRAS G13D mutation predicted anti-EGFR resistance, guiding selection of FOLFOX plus bevacizumab combination that achieved clinical response. While the therapeutic significance of the detected RAD54L variant remains uncertain, the tumor's HRD negative status indicates insufficient vulnerability to PARP inhibitors. Similarly, the limited neoantigen diversity reflected by moderate TMB (10.41 mut/Mb) and Microsatellite Stable (MSS) phenotype explains why immunotherapy was not considered as initial treatment.

Integration of Somatic Germline Genomics: This case exemplifies how CGP resolves diagnostic ambiguity through molecular signatures and its critical role in uncovering hereditary cancer predisposition through somatic germline data integration (8). In modern oncology practice, integrated evaluation of somatic and germline genomic data guides not only treatment decisions. It simultaneously provides critical information for familial risk assessment and preventive strategies. These genomic data enabled rational treatment planning, paving the way for favorable clinical outcomes. On the other hand, the process revealed the necessity for careful interpretation of rare germline variants detected in accessory DNA repair genes. With the increasing adoption of comprehensive genomic panels, more frequent encounters with such variants will enhance the importance of collaborative efforts toward standardizing cancer risk and treatment management.

Conclusion: Comprehensive Genomic Profiling definitively established colorectal origin in this CUP case through classical molecular signature identification and simultaneously revealed a rare germline RAD54L variant with hereditary implications. The discordance between germline alteration and HRD negative status reflects RAD54L's modulatory role in HR, suggesting subtle functional impairment rather than complete deficiency. This case also highlights the power of molecular diagnostics in clinical practice; genomic data provided diagnostic clarity and positively contributed to clinical management. This case underscores the essential integration of somatic and germline genomic data in precision oncology, enabling both accurate diagnosis and identification of hereditary cancer predisposition. Future research should elucidate RAD54L's cancer risk, functional impact, and potential therapeutic vulnerabilities through large scale epidemiological studies and functional assays.

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147- In Silico Investigation of Potential Splicing Effects of NF1 Variants in Hereditary Cancer Cases Without Classical NF1 Clinical Features

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Abstract:

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumor predisposition syndrome caused by loss-of-function variants in the NF1 gene and characterized by a broad phenotypic spectrum. Although diagnosis has traditionally been phenotype-driven, large genotype-first studies suggest that pathogenic NF1 variants are more prevalent than previously appreciated, leaving many carriers clinically unrecognized. The widespread adoption of NGS-based multigene panels has created an interpretive challenge: how to evaluate NF1 variants in individuals who do not meet established clinical diagnostic criteria for NF1.

In this study, we assessed the potential impact of NF1 variants on pre-mRNA splicing using in silico tools (HSF Pro and SpliceAI) in six index cases lacking phenotypic features of NF1. For several exonic variants predicted to have low impact by protein-based predictors, splicing analyses indicated cryptic acceptor/donor activation and altered ESE/ESS motif balance. These findings suggest that a splicing-focused approach may help refine variant classification. As in silico results are hypothesis-generating, RNA/cDNA-based assays should be considered where feasible to validate predicted splicing effects and support potential variant reclassification.

Keywords: Hereditary cancer predisposition, Human Splicing Finder (HSF Pro), In silico splicing prediction, Neurofibromatosis type 1 (NF1), SpliceAI

Introduction: Neurofibromatosis type 1 (NF1) is a clinically heterogeneous tumor predisposition syndrome caused by heterozygous loss-of-function variants in the NF1 gene (1). Diagnosis has traditionally relied on cardinal features such as café au lait macules, neurofibromas, and Lisch nodules. However, given the disorder's variable expressivity, age-dependent onset, and postzygotic mosaicism, some individuals may not meet established clinical diagnostic criteria, underscoring the limitations of a purely phenotype-based approach (2, 3).

Genotype-first studies indicate that pathogenic NF1 variants (PVs) are more common than phenotype-based estimates suggest, with carriers lacking classic phenotypic findings representing a substantial

subset. In an analysis of over one million individuals, Safonov et al. (4) reported an NF1 PV prevalence of approximately 1 in 1,286, showing that many carriers were identified without a prior clinical diagnosis or typical features of NF1. These findings prompt a reappraisal of incidentally identified NF1 variants detected on hereditary cancer panels. In particular, identifying an NF1 variant in individuals evaluated for malignancies such as breast cancer may warrant consideration of targeted phenotyping and risk counseling, particularly when the personal and/or family history raises suspicion. Even in the absence of overt NF1 features, genotype-driven detection may prompt targeted phenotyping for subtle or atypical manifestations and support individualized counseling based on the overall clinical context and family history.

Growing evidence links NF1 to an elevated breast cancer risk, particularly in women under 50, with recent work suggesting that this risk may be modulated by the specific mutation type (5). Studies have also begun to clarify the subtype distribution, clinical presentation, and molecular spectrum of NF1-associated breast cancers (6). Despite these insights, interpreting variants of uncertain significance (VUS) in large genes such as NF1 remains challenging. Exonic missense or synonymous variants may appear benign in protein-based predictors yet still alter splicing regulation, leading to loss of function. Reports showing that splice-altering variants can be supported by in silico predictions and subsequently confirmed by functional assays highlight the value of splicing-focused analyses for variant classification (7).

In this study, we reevaluated the potential splicing effects of NF1 variants identified in individuals without phenotypic features of NF1 who underwent testing for suspected hereditary cancer, using complementary in silico approaches.

Materıals and Methods: Hereditary cancer panel data from Aydın Adnan Menderes University were retrospectively reviewed to identify six index cases harboring NF1 (NM_000267/3) variants who did not meet established clinical diagnostic criteria for NF1 at the time of referral. Clinical records were reviewed to extract personal and family cancer histories. Potential splicing impact was assessed using HSF Pro (to predict cryptic splice-site and ESE/ESS motif changes) and SpliceAI (to calculate donor/acceptor gain/loss probability scores). Findings were interpreted alongside protein-based predictors (SIFT and PolyPhen-2) and were considered hypothesis-generating to prioritize variants for future functional follow-up.

Results:

Pathogenic Finding

Among the six index cases, one harbored a pathogenic NF1 variant, whereas the remaining five carried variants classified as variants of uncertain significance (VUS). The pathogenic variant c.2033dup (p.Ile679Aspfs*21) was identified in a 65-year-old asymptomatic woman with a family history of pancreatic, prostate, and breast cancers but no classic clinical features of NF1.

Splicing Discordance in the VUS Group

Within the VUS group, discordance was observed between protein-based pathogenicity predictors and in silico splicing tools.

• c.753C>G (p.Asp251Glu): This variant was identified in two independent index cases: a 39-year-old woman with breast cancer and a 31-year-old woman with bilateral multifocal breast masses. In the latter case, the family history included a paternal brain tumor (diagnosed at age 56; death at 57), prostate

cancer in three paternal uncles, and follow-up for a breast mass in the daughter of one uncle with prostate cancer. For this variant, SpliceAI yielded no prominent splicing signal, whereas HSF Pro predicted the creation of a cryptic acceptor site (matrix score 43.70 → 71.57; Δ = 63.78%) and a cryptic donor site (41.78 → 68.92; Δ = 64.96%). In addition, a 6-unit decrease in the ESE/ESS motif ratio suggested impaired exon recognition and supported the possibility of alternative splicing.

• c.2951G>A (p.Gly984Glu): In a 40-year-old patient diagnosed with invasive breast carcinoma and concomitant giant uterine fibroids, HSF Pro showed an increase consistent with activation of a new cryptic acceptor site (41.22 → 69.09; Δ = 67.61%), while SpliceAI did not produce a clear signal.

• c.134A>G (p.Asn45Ser): This variant was identified in a 44-year-old patient with invasive breast carcinoma who subsequently developed colon adenocarcinoma. The family history included colon cancer in an aunt, pancreatic cancer in two maternal uncles, and lung cancer in another maternal uncle. HSF Pro predicted the potential formation of a new acceptor (Δ = 55.44%) and a new donor (Δ = 71.05%) site. Multiple skin lesions previously followed as acrochordons (skin tags) were noted to warrant reevaluation during targeted phenotyping, given that such lesions may overlap clinically with minor NF1-related cutaneous findings or neurofibromas.

• c.1763A>T (p.His588Leu): This variant was identified in a 31-year-old woman with invasive ductal carcinoma and multifocal right breast masses, in the absence of classic NF1 features. The family history included stomach cancer in two aunts, childhood leukemia in a cousin, and skin cancer in another aunt. The patient also carried a concurrent heterozygous pathogenic MUTYH variant (c.842C>T; p.Pro281Leu). For NF1:c.1763A>T, SpliceAI yielded no prominent splicing signal. In contrast, HSF Pro indicated a shift in the enhancer/silencer balance toward silencer motifs—through disruption of one ESE and creation of three ESS motifs—consistent with the possibility of exon skipping.

Discussion and Conclusion: This study underscores the value of a splicing-focused assessment when interpreting NF1 variants detected on hereditary cancer panels in individuals who do not meet phenotypic diagnostic criteria for NF1. Genotype-first analyses suggest that the frequency of PVs is higher than phenotype-based estimates indicate, and that a significant number of carriers may remain undiagnosed.

(4) Accordingly, the clinical relevance of an NF1 finding should not be dismissed solely due to the absence of overt syndromic features; rather, targeted phenotyping, family history, and evidence supporting the biological impact of the variant should be considered together. (2–4)

The importance of genotype-guided reevaluation of cutaneous findings is supported by prior reports. In a case report describing a splice-altering pathogenic NF1 variant, multiple lesions initially interpreted as acrochordons/fibroepithelial polyps were reassessed after the genetic result and considered more consistent with cutaneous neurofibromas. (7) In our cohort, the case with multiple lesions followed as acrochordons similarly supported the need for targeted phenotyping with attention to subtle or atypical NF1-related cutaneous findings. Dermoscopy-based descriptions of cutaneous neurofibromas have also been reported and may support dermatologic assessment when lesion morphology is ambiguous. (8)

Evidence linking NF1 to breast cancer risk has increased, particularly for women under 50 years of age, and genotype–phenotype correlations have been proposed. (5) Recent studies have further characterized clinical presentation, subtype distribution, and the molecular spectrum of NF1-associated breast cancers. (6) In this context, identifying an NF1 variant in patients presenting with breast cancer

despite lacking classic NF1 features may inform individualized risk counseling and surveillance, provided that interpretation is integrated with clinical evaluation and family history. (5,6)

From a splicing standpoint, the discordance observed between HSF Pro and SpliceAI for variants such as c.753C>G and c.2951G>A indicates that reliance on a single in silico tool may be insufficient. When splicing-related signals (e.g., predicted cryptic splice site creation and/or ESE/ESS imbalance) are present and the overall context supports biological plausibility, RNA/cDNA-based assays should be considered where feasible for confirmation. This is particularly important because functional validation of splice-altering NF1 variants can directly inform and refine variant classification. (7)

One individual in our cohort also carried a concurrent heterozygous pathogenic MUTYH variant. Given that monoallelic MUTYH carrier status has not been consistently associated with an increased breast cancer risk, this finding was considered a concurrent result and should be interpreted in the context of the patient's personal and family history and gene-specific guidance. (9)

In conclusion, exonic NF1 variants detected in hereditary cancer cases without phenotypic NF1 findings may warrant systematic evaluation for potential splicing effects, and variants with suspected splice disruption should be considered where feasible for RNA/cDNA-based assays for functional validation to support clinical interpretation and management. (7)

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281- Retrospective Evaluation of Multigene Panel Results in Patients at Risk for Hereditary Breast and Ovarian Cancer: A Single-Center Experience

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Abstract: Hereditary Breast and Ovarian Cancer (HBOC) syndrome is a genetically heterogeneous condition associated with germline pathogenic variants in genes involved in DNA repair pathways. Although BRCA1 and BRCA2 remain the most well-known high-risk genes, the implementation of multigene panel testing has expanded the spectrum of clinically actionable genes. Detection rates vary significantly depending on patient selection criteria and testing algorithms. This study aimed to evaluate the clinical and molecular findings of a heterogeneous NCCN-based hereditary cancer cohort and compare the results with previously published Turkish cohorts.

A total of 192 individuals who met NCCN Hereditary Cancer Guidelines (v.2023–2025) criteria were retrospectively analyzed between 2023 and 2025 at a tertiary medical genetics center. Multigene panel testing targeting 135 cancer susceptibility genes was performed using hybridization capture-based next-generation sequencing. Variants were classified according to ACMG criteria.

Among 192 individuals (98.4% female), referral indications included breast cancer (65.1%), strong family history (19.8%), ovarian cancer (10.4%), early-onset breast cancer (1.6%), and other hereditary cancer suspicions (3.1%). Pathogenic or likely pathogenic (P/LP) variants were identified in 9.9% of individuals, while 47.9% had variants of uncertain significance (VUS). Among P/LP variants, BRCA1 accounted for 26.3%, BRCA2 for 21.1%, CHEK2 for 15.8%, and ATM, PALB2, MUTYH and TP53 comprised the remainder. Overall, BRCA1/2 represented 47.4% of clinically significant findings.

The diagnostic yield in this heterogeneous NCCN-based cohort was consistent with previously reported Turkish multigene panel studies but lower than highly selected breast- or ovarian-only cohorts. The relatively lower proportion of BRCA1/2 variants may reflect pre-panel single-gene testing strategies. High VUS rates highlight the need for improved population representation in global variant databases and the development of national reference datasets.

Introduction: Hereditary Breast and Ovarian Cancer (HBOC) syndrome represents a clinically and molecularly heterogeneous genetic predisposition condition primarily associated with germline pathogenic variants in genes involved in DNA damage repair pathways, particularly homologous recombination (1). Approximately 10% of breast cancers are considered to be associated with hereditary susceptibility, and germline pathogenic variants are identified in nearly 6% of breast cancer patients (2, 3). About half of these variants occur in high-risk genes such as BRCA1 and BRCA2, while the remaining proportion is attributed to moderate-risk genes including ATM and CHEK2 (2, 3). In high-grade serous ovarian cancer, the prevalence of germline pathogenic variants is reported to be approximately 15% (4). Despite well-defined clinical criteria, nearly half of individuals fulfilling HBOC criteria remain without a clearly identified genetic cause (5). The widespread implementation of multigene panel testing has

expanded the genetic spectrum of HBOC beyond BRCA1 and BRCA2 to include high-risk genes such as PALB2, TP53, PTEN, CDH1 and STK11, as well as moderate-risk genes including ATM, CHEK2, RAD51C, RAD51D and BRIP1. Each gene differs in cancer risk magnitude, penetrance, and management recommendations, adding complexity to variant interpretation and clinical decision-making (5).

Method: In the present study, we retrospectively analyzed 192 individuals evaluated between 2023 and 2025 at the Medical Genetics Outpatient Clinic of Erzurum City Hospital. All individuals met the National Comprehensive Cancer Network (NCCN) Hereditary Cancer Guidelines (v.2023–2025) criteria for genetic testing. Unlike studies focusing solely on affected individuals, our cohort represents a clinically heterogeneous real-world population that includes breast cancer, ovarian cancer, strong family history, and other hereditary cancer suspicions.

Genomic DNA was enriched using the GeneTopia Hybridization Capture Kit, targeting approximately 51 Mb of the human exome, covering more than 99% of coding regions defined in CCDS, RefSeq, and Gencode databases. Sequencing was performed on the GeneMind–SURFSeq 5000 platform. Adequate coverage was achieved in more than 98% of targeted regions, with an average sequencing depth of 20×. Protein-coding exons and ±20 base pair intronic flanking regions were analyzed. Variants with a minimum read depth of 10 were reported. Only variants with a minor allele frequency below 1% in population databases (gnomAD, ExAC, 1000 Genomes, dbSNP) were considered. Variant classification was performed according to ACMG guidelines.

Results: Of the 192 individuals included in the study, 98.4% were female and 1.6% were male. The referral indications were as follows: 65.1% had a diagnosis of breast cancer, 19.8% were referred due to a strong family history of cancer, 10.4% had ovarian cancer, 1.6% had early-onset breast cancer, and 3.1% were evaluated for other hereditary cancer suspicions. This distribution indicates that our cohort included not only affected individuals but also unaffected individuals meeting NCCN testing criteria.

Molecular analysis revealed that 42.2% of individuals had no clinically significant variant identified, 47.9% harbored variants of uncertain significance (VUS), and 9.9% had pathogenic or likely pathogenic (P/LP) variants. Among the 19 individuals with P/LP variants, the distribution by gene was as follows: BRCA1 accounted for 26.3%, BRCA2 for 21.1%, CHEK2 for 15.8%, ATM for 10.5%, PALB2 for 10.5%, heterozygous MUTYH variants for 10.5%, and TP53 for 5.3%. Overall, 47.4% of P/LP variants were detected in BRCA1/2 genes.

Discussion: When compared with previously published Turkish multigene panel studies, several important observations emerge. Reported P/LP rates in Turkish cohorts range between approximately 11% and 33% (6-17). Studies focusing exclusively on young breast cancer patients or solely ovarian cancer cases generally report higher detection rates. For example, P/LP rates of around 21% have been reported in young breast cancer cohorts, and rates exceeding 20% have been described in ovarian cancer-only cohorts (6-17). In contrast, heterogeneous NCCN-based populations tend to demonstrate P/LP rates in the range of 10–15%. The 9.9% detection rate observed in our study lies at the lower boundary of the national range but is consistent with expectations for a heterogeneous referral population (6-17).

Regarding gene distribution, Turkish cohorts typically report that approximately 60–66% of P/LP variants occur in BRCA1/2 genes (6-17). In our study, the proportion of BRCA1/2 among P/LP variants was 47.4%, which appears comparatively lower. The most plausible explanation for this difference lies in our institutional testing algorithm. In clinical practice, high-risk individuals presenting before treatment are

initially tested with targeted BRCA1/2 sequencing and MLPA analysis. Only those found negative for BRCA1/2 are subsequently referred for multigene panel testing. Consequently, BRCA1/2-positive individuals may have been identified prior to panel testing, resulting in a relative reduction of BRCA1/2 representation within the panel-tested subgroup. This finding highlights how pre-test strategies and diagnostic algorithms can significantly influence observed gene distributions in panel studies.

One of the most striking differences between Turkish cohorts and large international series is the relatively high VUS rate. International large-scale cohorts generally report VUS frequencies between 20% and 35% (18), whereas Turkish studies often report VUS rates between 30% and 48% (6-17). In our study, the VUS rate was 47.9%, consistent with the upper range reported nationally. Several factors likely contribute to this observation. First, individuals of Turkish ancestry remain underrepresented in global variant databases such as ClinVar and population databases such as gnomAD. Limited population-specific allele frequency data makes classification of rare variants more challenging and increases uncertainty. Second, the absence of large, well-characterized healthy control datasets specific to the Turkish population hampers accurate interpretation of population-specific variants. Third, regional genetic diversity may introduce rare or private variants that lack sufficient published evidence for classification.

Conclusion: The present study provides real-world data on multigene panel testing in a heterogeneous NCCN-based hereditary cancer cohort. While the diagnostic yield is lower than that observed in highly selected breast- or ovarian-only cohorts, it reflects routine clinical practice in a referral center where both affected and unaffected high-risk individuals are evaluated. The relatively lower proportion of BRCA1/2 variants among P/LP findings underscores the impact of stepwise testing algorithms. Furthermore, the high VUS rate emphasizes the urgent need for national and regional genetic databases to improve variant interpretation in underrepresented populations.

In conclusion, in this NCCN-based heterogeneous cohort of 192 individuals, the P/LP detection rate was 9.9%, with BRCA1/2 accounting for nearly half of clinically significant findings. The diagnostic yield aligns with previously reported heterogeneous Turkish cohorts but is lower than that observed in highly selected disease-specific series. The consistently high VUS rates across Turkish studies highlight the need for improved population representation in global databases and the development of national reference datasets. These findings underscore the importance of both patient selection strategies and institutional testing algorithms in shaping the genetic landscape observed in hereditary cancer panel studies.

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