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SÖZEL BİLDİRİLER

[Abstract:0085]

Long-Read Sequencing Technologies in Hereditary Cancer Diagnosis: A Single Centre Study

Behich Koyutourk, Ayla Turgay, Dize Deryalı, Mahmut Çerkez Ergören
Near East University Hospital, Medical Genetics Diagnostic Laboratory, Nicosia, North Cyprus

Objective: This study aimed to demonstrate the clinical utility and diagnostic effectiveness of long-read sequencing technology, particularly the Oxford Nanopore Technology (ONT) platform, in identifying pathogenic genetic variations associated with hereditary cancer syndromes, while highlighting its advantages in resolving complex genomic regions, detecting structural variations, and addressing the limitations of traditional short-read sequencing technologies.

Materials-Methods: This study was conducted at a single centre and employed ONT sequencing of genomic DNA from patients with suspected hereditary cancer predisposition. Library preparation and sequencing were conducted by the HEVA Pro protocol (IVD-CE, 4Bases Switzerland), to ensure optimal quality throughout both processes. Long-read sequencing (LRS) can produce reads of up to 1-2 kilobases in length and be employed for a wide range of genetic changes, including point mutations, repeat expansions, large insertions, and structural variations (SVs). A comparative analysis was conducted with data from other diagnostic laboratories to validate the accuracy and sensitivity of the results. Specific consideration was given to mutations in repetitive and homologous genomic regions, which are difficult to resolve using traditional short-read next-generation sequencing methods.

Results: Since October 2024, the ONT platform has been employed in our medical diagnostic laboratory. The preliminary results of patient sample analysis demonstrate that our process is capable of accurately detecting pathogenic variants, including structural variations, repeat expansions, and other complex variants. The LRS results have been cross-validated with findings from diagnostic testing obtained through other laboratories, confirming both the robustness and accuracy of the centre's workflow. This validation serves to illustrate the efficacy of our laboratory's deployment of ONT sequencing for clinical diagnostics. Moreover, long-read sequencing's capacity to traverse intricate genomic domains has enhanced the identification of variants in genes comprising repetitive sequences, a notable advantage over short-read technologies.

Conclusion: The adoption of ONT long-read sequencing technology at our centre has thus far proven to be a reliable and effective approach for the diagnosis of hereditary cancer syndromes. The capacity to generate reads of 1-2 kilobases in length facilitates the identification of intricate genetic variations, including structural variants (SVs) and repeat expansions, particularly in genomic regions that are challenging to sequence with short-read technologies

Keywords: HereditaryCancerDiagnosis, Genetic, NanoporeSquencing, GeneticVariations

[Abstract:0087]

Clinicopathological Characteristics of Microsatellite Instable Colorectal Cancer from the Lynch Syndrome Perspective; A Single-Center Experience

Ece Ulukal Karancı, Halil Göksel Güzel, Banu Öztürk
Antalya Training and Research Hospital, University of Health Sciences, Antalya,Türkiye

Objective: Lynch Syndrome (LS) is a hereditary cancer predisposition syndrome characterised by a high lifetime risk of developing cancers, primarily endometrial and colorectal cancer (CRC). These cancers exhibit microsatellite instability (MSI) due to cellular mismatch repair (MMR) system defects. In this study, we aimed to reveal real-world data of MSI-high CRC from a single center.

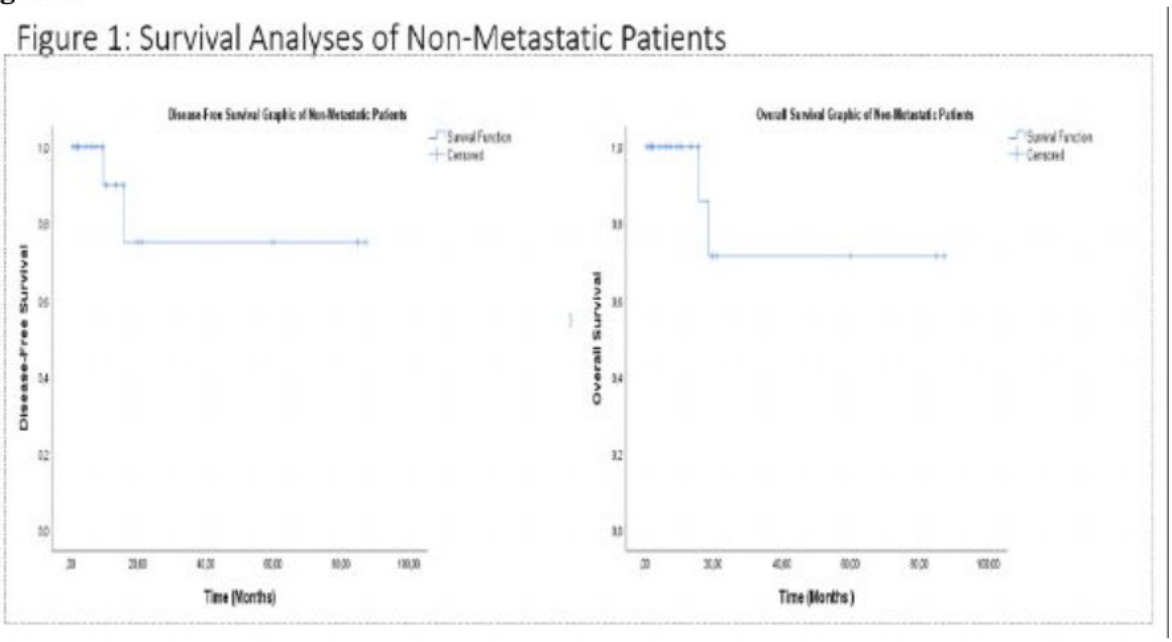
Materials-Methods: We screened dMMR CRC patients presented at Antalya Training and Research Hospital from January 2017 to October 2024. A total of 28 patients were included in the final analyses (n=28).

Results: The median age was 61 (35-84). Seven (25.0) of the patients were female. Nine patients (32.1%) were de-novo metastatic at diagnosis. Sixteen patients (57.1%) had right-sided colon cancer while there were 6 patients (21.4%) patients for left-sided colon cancer and rectum cancer, for each. Ten patients (35.7%) had a first-degree relative diagnosed with colorectal or endometrial cancer. None of the patients had a second primary cancer. RAS and BRAF mutations were detected in 11 (39.3%) and 3 (10.7%) patients, respectively. (Table 1)mAmong 19 patients with non-metastatic disease at diagnosis, 11 (57.9%) had adjuvant chemotherapy (CT). For each, disease recurrence and death without recurrence were observed in 1 patient (5.3%). The median OS was not reached for the non-metastatic patients, while the 5-year OS rate was 71.4%. Also, the median DFS was not reached and the 5-year DFS rate was 75.0%. (Figure 1) Considering the 9 de-novo metastatic patients and 1 patient who had distant disease recurrence in the follow-up period; 1 patient (10.0)% received immunotherapy in the second-line treatment and 1 patient (10.0%) was able to undergo curative surgery. Nine patients (90.0%) received doublet CT. Objective response rate (ORR) was 44.4%. The median PFS was 15.6 months 95% CI (0.0-37.0) AND the median OS was 29.3 months 95% CI
(7.8-59.8). (Figure 2)

Conclusion: We have demonstrated that 89.3% of dMMR patients were BRAF wild who were possibly Lynch syndrome. Moreover, 35.7% of patients had a family history which was compatible with the literature. Lynch syndrome was associated with better CT response than the sporadic dMMR patients.

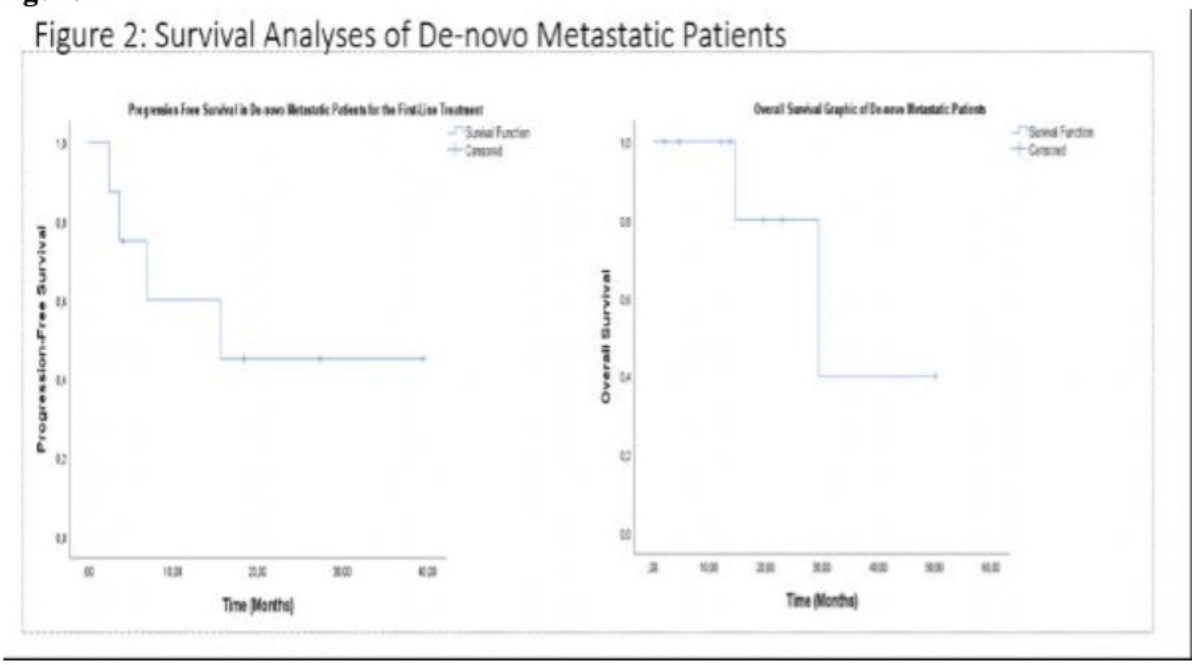
Keywords: MSI-high, Lynch Syndrome, Colorectal Cancer

figure 1



survival analyses of non-metastatic patients

figure 2



survival analyses of De nova-metastatic patients

table 1

		All Patients (n=28) n, (%)
Age	<50 >=50	5 (17.9) 23 (82.1)
Sex	Male Female	21 (75.0) 7 (25.0)
Tumor Location	Right-colon Left-colon Rectum	16 (57.1) 6 (21.4) 6 (21.4)
RAS	Wild Mutant	17 (60.7) 11 (39.3)
BRAF	Wild Mutant	25 (89.3) 3 (10.7)
Family History of CRC or Endometrium Cancer	yes no	10 (35.7) 18 (64.3)
Histological Grade	1 2 3	5 (17.9) 15 (53.6) 8 (28.5)
T stage	1-2 3-4	2 (7.1) 26 (92.9)
N stage	0 1	13 (46.5) 15 (53.5)
M stage	0 1	19 (77.9) 9 (32.1)

Clinicopathological Characteristics of The Study Population

[Abstract:0088]

Attenuated Form of Nijmegen Breakage Syndrome: Case Report

Sultan Kevser Gangal, Abdullah Sezer, Haktan Bağış Erdem
Etlik City Hospital, Ankara, Türkiye

Nijmegen Breakage Syndrome (NBS, MIM #251260) is a rare DNA repair disorder characterized by microcephaly, growth retardation, dysmorphic features, immunodeficiency, and predisposition to cancer. NBS results from biallelic pathogenic variants, predominantly truncating, in the NBN gene. The prognosis of NBS is generally poor and known as a life-limiting disorder. mWe report a case of
69-year-old male diagnosed with prostate cancer six years ago, who was referred to our outpatient clinic to investigate a possible genetic etiology of familial cancer predisposition. He was the fourth live-born child of first-cousin parents. His mother was diagnosed with colorectal cancer at age 60, three of his sisters were diagnosed with malignancies; one with lymphoma at age 50, and the others with thyroid cancer at ages 35 and 55. His father's and three children's medical histories were uneventful. He had severe pneumonia around the age of seven and frequent coughs and sinusitis throughout his adult life. He had never been diagnosed with any other medical issue, his intellectual capabilities were normal. His anthropometric measurement were within normal ranges. He has facial rash, freckling and irregular hyperpigmented macules. His basic biochemistry and blood counts were normal. The next-generation sequencing panel test (Hereditary Cancer Solution v2.0, SOPHiA, Switzerland) identified the c.1894C>T p.(Arg632*) pathogenic variant in the NBN gene (NM_001024682.2) in the homozygous state. Chromosomal analysis was normal.m Although the patient was not diagnosed with a malignancy at an early age and his head circumference was within the normal range, the history of malignancies in his family, along with his skin lesions and mild immunodeficiency, are consistent with NBS. Only three mild cases of NBS have been reported in the literature to date. Based on our knowledge, our patient is the oldest documented individual with NBS. This case is distinct in his fertility, chromosomal analysis, and skin lesions. Several mechanisms could explain this mild clinical presentation, including the location of the variant in the gene and its effect on protein function. Our case might represent an attenuated form of NBS. This report aims to broaden our understanding of this rare phenotype and the clinical spectrum of the syndrome.

Keywords: Nijmegen Breakage Syndrome, atypical presentation, DNA repair disorder

[Abstract:0090]

A Novel Variant in the APC Gene: A Case Report of FAP

Mürsel Hazaloğlu[1], Ahmet Dursun[1], Sevim Karakaş Çelik[1], Güneş Çakmak Gen[ç1], Özgür Ölme[z2]
[1]Department of Medical Geneticsm, Zonguldak Bülent Ecevit University, Zonguldak, Türkiye
[2]Department of Medical Oncology, Zonguldak Bülent Ecevit University, Zonguldak, Türkiye

Objective: FAP (Familial Adenomatous Polyposis) (FAP; OMIM #175100) is an OD hereditary syndrome caused by mutations in APC (OMIM*611731). These mutations in APC lead to the formation of colon polyps at an early age, increasing the risk of developing cancer over time. More than 1000 different disease-causing mutations in APC have been identified. Over 95% of the mutations result in the production of a non-functional truncated protein with variable loss of the C-terminus resulting from nonsense mutations (40%), deletions (41%), insertions (12%), and splice site mutations (7%).
Approximately 60% of mutations in APC are clustered in a small region of exon 15, called the mutation cluster region (MCR).
Case: We present the case of a 39-year-old woman who underwent colonoscopy with a complaint of hematochezia and was found to have hundreds of polyps. Pathological examination revealed carcinomatous transformation of adenomatous polyps, and she was referred to our clinic for evaluation in terms of FAP. The patient's pedigree revealed a history of colon cancer in her mother and two siblings. Based on these findings, APC and MUTYH gene sequence analysis revealed a heterozygous c.2671dup/p.Met891Asnfs*21 variant in APC. Although this variant has not been previously reported in the literature, it was determined that it may have a damaging effect because it causes a frame shift according to the ACMG guidelines. mThe early diagnosis of FAP is critical for preventing the development of cancer. P/LP mutations in APC can increase the number and size of colon polyps and accelerate their progression to cancer. The average age at diagnosis of colorectal cancer (CRC) in untreated individuals (risk-reducing surgery) was 39 years. Therefore, genetic testing and early follow-up are important in patients with FAP. Especially in individuals with a familial history of colon cancer, genetic testing plays a vital role in determining the risk and implementing appropriate treatment strategies.
Conclusion: The identification of this new variant emphasizes the necessity of integrating genetic testing into clinical practice and the importance of genetic counseling. Furthermore, early diagnosis and creation of personalized treatment plans through genetic testing are important steps in cancer prevention.
Keywords: FAP, APC, CRC

[Abstract:0096]

Evaluation of the LINC00958/miR-3619-5p/CTNNB1 pathway in patients with colorectal cancer

Momen Kanjee[1], Çiğdem Yüce Kahraman[1], Esra Dişçi2, Mehmet Hamdi Sakarya[3], Abdulgani Tatar[1]

[1]Depaetment of Medical Genetics, Atatürk University Faculty of Medicine, Erzurum, Türkiye
[2]Department of General Surgery, Atatürk University Faculty of Medicine, Erzurum, Türkiyem
[3]Clinic of General Surgery, University of Health Sciences, Erzurum City Hospital, Erzurum, Türkiye

Objective: Colorectal cancers (CRCs) are the third most common cancer type worldwide and the second leading cause of cancer-related deaths. Investigating the role of non-coding RNAs (ncRNAs) in cancer development and progression provides valuable insights for future research and clinical applications in cancer treatment. In this study, we evaluated the expression levels and correlation of the LINC00958/miR-3619-5p/CTNNB1 pathway between cancerous and adjacent normal tissue samples obtained from CRC patients. To the best of our knowledge, this is the first study to compare the expression of LINC00958/miR-3619-5p/CTNNB1 with the patients' clinicopathological characteristics.
Materials-Methods: Forty patients diagnosed with CRC were included in the study. Total RNA was isolated from CRC and adjacent tissues (with negative surgical margins) obtained during surgery. The expression analysis of the target genes was performed using quantitative real-time PCR (qPCR).
Results: The expression levels of LINC00958 and CTNNB1 were found to be significantly increased in CRC tissue samples, while miR-3619-5p expression was significantly decreased. When the expression levels of these genes were compared with the clinicopathological characteristics of the patients, significant differences were observed in terms of gender and tumor localization. These findings highlight the therapeutic potential of targeting the LINC00958/miR-3619-5p/CTNNB1 pathway and offer novel insights into CRC biology.
Conclusion: These results demonstrate the clinical significance of these pathways and emphasize their potential in the development of new biomarkers and targeted therapies. This study contributes to the growing understanding of the roles of ncRNAs in CRC and sheds light on their applications in personalized medicine.
Keywords: Colorectal Cancer, CTNNB1, Gene Expression, LINC00958, miR-3619-5p

[Abstract:0098]

Retrospective Evaluation of NGS Results in Patients with Colorectal Polyposis

Ziya Bulduk, Momen Kanjee, Çiğdem Yüce Kahraman, Abdulgani Tatar
Department of Medical Genetics, Ataturk University Faculty of Medicine, Erzurum, Türkiye

Objective: Approximately 5% of colorectal cancer (CRC) cases are associated with hereditary predisposition resulting from germline pathogenic variants. Hereditary polyposis syndromes constitute an important part of hereditary causes. They are clinically and genetically heterogeneous and therefore difficult to diagnose. Familial Adenomatous Polyposis (FAP; OMIM #175100) and MUTYH-associated polyposis (MAP; OMIM #608456) account for the majority of cases. In this study, we aimed to share next generation sequencing (NGS) panel results and evaluate genotype-phenotype correlations of patients referred to us with the diagnosis of colorectal polyposis.
Materials-Methods: In this study, we included 53 patients referred to Ataturk University Genetic Diseases Evaluation Center (ATAGEN), Between January 2019 and December 2024, with the diagnosis of colorectal polyposis. Using next generation sequencing (NGS), we performed a hereditary cancer panel test containing 71 genes for each patient's sample. Variants were classified according to the guidelines of ACMG. Pathogenic and likely pathogenic variants were evaluated.
Results: Pathogenic or likely pathogenic variants were detected in 31 patients (58.5%). 20 patients (37.7%) had variants in the MUTYH gene and 9 patients (17%) had variants in the APC gene. The most frequently detected variants were; (NM_001048174.2): MUTYH c.800C>T, p.P267L (30.2%) and MUTYH c.1353_1355del, p.E452del (11.3%). We also reported a novel variant, (NM_000038.6): APC c.3081T>G p.Y1027*, which was not previously reported. 10 patients (18.8%) developed colorectal cancer. Of these patients, 4 had variants in the MUTYH gene and 2 had variants in the APC gene.
Conclusion: In this study, we assume that MUTYH c.800C>T and MUTYH c.1353_1355del variants are common in the eastern part of Türkiye. The number of polyps was very variable in patients with variants in the MUTYH gene. On the other hand, there was a genotype-phenotype correlation consistent with the literature in the patients with APC gene variants. This study once again demonstrated the importance of NGS-based Hereditary Cancer Panel testing in patients with colorectal polyposis. Early diagnosis is of a great importance in preventing cancer with strict colonoscopic follow-up and prophylactic colectomy.
Keywords: APC, colorectal cancer, MUTYH, NGS, polyposis

[Abstract:0102]

Hereditary Cancer Panel in Patients Considered for Hereditary Colorectal Cancer Evaluation of Results

Süheyla Emre[1], Beyza Adaçoğlu[1], Filiz Özen[1], Elif Yılmaz Güleç[2]

[1]Department of Medical Genetics, İstanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul, Türkiye
[2]Department of Medical Genetics, İstanbul Medeniyet University Faculty of Medicine, İstanbul, Türkiye

Objective: Colorectal cancer (CRC) is the third most common cancer globally and a leading cause of cancer-related deaths. While sporadic CRC is often linked to environmental factors, hereditary syndromes arise from genetic mutations and are more aggressive. Hereditary CRC includes polyposis syndromes (e.g., familial adenomatous polyposis [FAP], MUTYH-associated polyposis) and Lynch syndrome, caused by pathogenic variants in DNA mismatch repair (MMR) genes. Other syndromes, such as juvenile polyposis (BMPR1A, SMAD4) and Peutz-Jeghers syndrome (STK11), are also linked to CRC. The aim of this study is to identify genetic variants associated with hereditary colorectal cancer syndromes in our series and to compare our results with the literature to understand the unique characteristics of our population.

Materials-Methods: Between January 2021 and January 2025, a total of 147 patients with a family history of CRC were admitted to our clinic and included in this study. Among these, 87 patients were also diagnosed with CRC.A hereditary cancer panel analyzing 60 genes was performed using next-generation sequencing (NGS), and clinical data were retrospectively reviewed.

Results: Pathogenic or likely pathogenic variants were identified in 50 patients (34%). MUTYH variants were the most common, detected in 25 patients (17%), including 5 pathogenic, 2 likely pathogenic homozygous,15 likely pathogenic heterozygous, and 3 variants of uncertain significance (VUS). APC gene alterations were identified in 6 patients (4%), including 5 pathogenic and 1 likely pathogenic variant.MMR gene variants were identified in 8 patients (5.4%), including MSH2 (3), MLH1 (3), MSH3 (1), and MSH6 (1).Variants in CHEK2 were identified in 2 patients (1.4%). No clinically significant variants were detected in 34 patients (23%).

Conclusion: Our findings revealed a higher-than-expected rate of hereditary CRC (34%) compared to the literature (5–10%). MMR gene variants were detected in 5.4% of patients, exceeding the reported 3%, and MUTYH variants were found in 17%, far surpassing the <1% reported in the literature.These discrepancies may reflect the unique characteristics of our population and the high referral rate for family history. Integrating genetic testing into routine clinical practice is essential for early diagnosis, personalized management, and improved outcomes. Further research is warranted to explore the clinical significance of low-penetrance alleles and emerging genetic markers in refining CRC management strategies.

Keywords: Colorectal cancer, hereditary colorectal cancer syndromes, MUTYH, APC, polyposis syndromes

[Abstract:0107]

ATM Gene Variants in Hereditary Cancer Patients: Single-Center Experience

Bilgesu Ak, Özge Güngör, Haluk Akın, Aslı Ece Solmaz
Clinic of Medical Genetics, Ege University Hospital, İzmir, Türkiye

Objective: The ATM gene is essential for DNA repair and genomic stability. Variants in ATM are associated with hereditary cancers, including breast, ovarian, colorectal, and pancreatic cancers, collectively known as ATM-related cancer predisposition (MONDO:0700270). This study evaluates ATM gene variants in hereditary cancer patients to assess their clinical significance and impact on cancer risk.
Materials-Methods: A total of 2,274 patients suspected of hereditary cancer syndrome were evaluated at Ege University Hospital Medical Genetics, identifying 40 patients with ATM gene variants. Clinical data, including cancer type, age, and variant classification, were collected. The cohort included 29 patients with breast cancer, one with breast and endometrial cancer, one with breast, thyroid, and Hodgkin lymphoma, two with peritoneal cancer, two with colon cancer, one with malignant melanoma, two with ovarian cancer, and one with pancreatic adenocarcinoma. Variants were classified as pathogenic, likely pathogenic, or variants of uncertain significance (VUS) based on ACMG criteria.
Results: The cohort had an average age of 48.6 years. Among the identified 40 variants, there were 5 frameshift, 27 missense, 2 nonsense, 5 splice-site, and 1 synonymous mutation. Eleven variants were classified as pathogenic, 5 as likely pathogenic, and 24 as VUS. Importantly, three of the identified variants were novel. mConclusion: This study contributes to the growing body of literature on ATM gene variants and their association with specific cancer types. By identifying three novel variants and correlating ATM alterations with detailed clinical data, we provide valuable insights into the relationship between ATM variants and cancer risk. These findings enhance our understanding of ATM-related cancer susceptibility and support the development of personalized diagnostic and therapeutic strategies.
Keywords: ATM gene, hereditary cancer syndrome, breast cancer

[Abstract:0110]

Clinical Significance of PALB2 Variants and Genotype-Phenotype Relationship

Özge Güngör, Bilgesu Ak, Haluk Akın, Aslı Ece Solmaz

Clinic of Medical Genetic, Ege University Medical School and Hospital, İzmir, Türkiye

Objective: To investigate the clinical significance of PALB2 variants and examine their genotype-phenotype relationship in patients with hereditary cancer.

Materials-Methods: This study included 51 patients who underwent hereditary cancer panel testing at the Department of Medical Genetics, Ege University Hospital, between 2020 and 2025. The analysis of patient samples was conducted using either the SOPHiA Custom Hereditary Cancer Solution or TWIST CES kits. The identified variants were classified as pathogenic or likely pathogenic (P/LP) based on genetic analysis and a review of the literature. Variant types and their distribution across exons were evaluated.

Results: Out of 51 patients, 26 were found to have pathogenic or likely pathogenic PALB2 variants. 12 P/LP variants were identified, including 6 frameshifts, 3 stop codons, 2 splices, and 1 copy number variation. Of these, 5 variants were located in exon 4 and 2 in exon 5, consistent with the known concentration of variants in these exons reported in the literature.

Conclusion: The study highlights the critical role of PALB2 variants in hereditary cancer, particularly in breast and pancreatic cancers. It emphasizes the importance of understanding the genotype-phenotype relationship of PALB2 variants for cancer susceptibility research and genetic counseling processes. The findings provide new insights into the pathogenic mechanisms of PALB2 variants and their potential clinical implications.

Keywords: Breast cancer, cancer, PALB2, variants

[Abstract:0111]

Prevalence and Clinical Characteristics of Germline BRCA1/2 Mutations in Epithelial Ovarian Cancer Patients

Ayşe Pelin Toker[1], Rahma Eno Hassano[2], Yunus Kasım Terzi[1], Hüseyin Akıllı[2], Esra Kuşçu[2], Zerrin Çelik[1]

[1]Department of Medical Genetics, Başkent University Faculty of Medicine, Ankara, Türkiye
[2]Department of Obstetrics and Gynecology, Başkent University Faculty of Medicine, Ankara, Türkiye

Objective: Ovarian cancer is strongly associated with hereditary predispositions, mainly through mutations in DNA repair genes. Germline mutations in BRCA1 or BRCA2 are found in 10–15% of epithelial ovarian cancer (EOC) patients. This study aims to determine the prevalence of pathogenic and likely pathogenic variants in BRCA1 and BRCA2 in EOC patients and compare these patients based on family cancer history, recurrence rates, and age at diagnosis.

Materials-Methods: Between January 2023 and December 2024, we conducted a retrospective analysis of 130 patients diagnosed with EOC. All patients met the testing criteria for BRCA genes or hereditary cancer panels as defined by the National Comprehensive Cancer Network (NCCN).

Genomic DNA was extracted from peripheral blood samples. Targeted next-generation sequencing for BRCA1 and BRCA2 was performed on 100 patients, while hereditary cancer panels were utilized for the remaining 30 patients. Variants were classified according to the guidelines of the American College of Medical Genetics and Genomics (ACMG).

Results: Among the 130 patients studied, pathogenic or likely pathogenic variants were detected in 24 individuals, representing 18.4% of the cohort. Of these, 19 patients (14.6%) had variants in the BRCA1 gene, while five patients (3.8%) had BRCA2 variants. All but one of the pathogenic variants were found in high-grade serous ovarian cancer cases. The BRCA1 variants were predominantly identified as nonsense and frameshift mutations, primarily located in hotspot regions within exons 10 and 11. Additionally, patients with BRCA1 mutations were diagnosed at a younger age compared to those with BRCA2 mutations. Among the patients with BRCA1 variants, eight had a family history of various cancers, whereas only one patient with a BRCA2 variant reported a similar family history. Recurrence rates were notably higher for BRCA1 variants, with 13 out of 19 patients experiencing recurrence, compared to 2 out of 5 patients with BRCA2 variants.

Conclusion: Our study highlights the clinically relevant prevalence of BRCA1 and BRCA2 mutations in epithelial ovarian cancer, emphasizing their association with younger age at diagnosis, higher recurrence rates, and family cancer history. These findings reinforce the importance of genetic testing, genetic counseling, and personalized treatment strategies for high-risk patients.

Keywords: BRCA1, BRCA2, epithelial ovarian cancer, germline mutations

[Abstract:0112]

Prevalence of germline pathogenic variants in cancer predisposition genes among selected patients with lung adenocarcinoma

Zeynep Özdemir[1], Taha Bahsi2, Hanife Saat[1], Ömür Berna Çakmak Özksüzoğlu[1], Umut Demirci[2], Osman Sütçüoğlu[1], Haktan Bağış Erdem[1]

[1]Ankara Etlik City Hospital, Ankara, Türkiye
[2]Ankara Memorial Hospital, Ankara, Türkiye

Objective: Lung adenocarcinoma is a leading cause of cancer-related mortality worldwide. While smoking and environmental factors are well-established contributors, the role of genetic predisposition remains underexplored. This study investigates the prevalence and characteristics of germline pathogenic variants in cancer predisposition genes. The patients were selected based on specific clinical and familial criteria.
Materials-Methods: This study was conducted at Ankara Etlik City Hospital. A total of 28 patients diagnosed with lung adenocarcinoma were selected using the following criteria: age at diagnosis, smoking history, environmental/occupational exposures, history of a second primary cancer, and strong familial cancer history. Peripheral blood samples were collected, and DNA was analysed using a 58-gene hereditary cancer panel with next-generation sequencing (NGS).
Results: Germline pathogenic variants were identified in 6 out of 28 patients, yielding a prevalence of 21.4%. Notably, all pathogenic variants were found in genes involved in DNA repair pathways. This finding highlights the critical role of genomic stability mechanisms in lung adenocarcinoma predisposition. The high frequency of these variants underscores the importance of screening for hereditary cancer syndromes, even in cancers not traditionally associated with strong genetic predisposition.
Conclusion: This study demonstrates a significant prevalence of germline pathogenic variants in DNA repair pathway genes in lung adenocarcinoma patients, highlighting the effect of impaired genomic maintenance on cancer development. Identifying these variants has profound implications for early detection, risk stratification, and targeted preventive measures. Moreover, identifying the genetic component of lung adenocarcinoma can help develop precision oncology and open the door to new therapeutic strategies, such as the possible use of PARP inhibitors or other drugs that target DNA repair. Few studies have explored genetic susceptibility in lung adenocarcinoma, making our research a significant contribution to this area. Integrating germline testing into clinical care could seriously improve outcomes for patients and their families.
Keywords: dna repair pathways, genetic predisposition, hereditary cancers, lung adenocarcinoma, next generation sequencing

[Abstract:0114]

Breast Cancer: A Novel Variant in HMMR Gene

Hüseyin Saylam, Zeynal Sütkurt, Ali Çiçekli, Hasan Acar, Ebru Marzioğlu Özdemir

Department Of Medical Genetics, , Selçuk University Faculty of Medicine Konya, Türkiye

Objective: Breast cancer is the most commonly diagnosed cancer in women worldwide. Both environmental factors and genetic variations contribute to the development of the disease. Mutations in genes such as BRCA1, BRCA2, ATM, TP53, PALB2, and CHEK2 have been well established as playing significant roles in the onset of breast cancer. Recently, the HMMR gene, which regulates cellular motility and influences how cells respond to external stimuli, has also gained attention. Studies suggest that mutations in HMMR may contribute to the development of various malignancies, including breast cancer. This study aims to investigate the significance of a particular variant in the HMMR gene in a patient diagnosed with triple-negative breast cancer.
Case: A 60-year-old female patient, with a medical history of hypertension, diabetes, and a family history of breast and prostate cancer, was diagnosed with triple-negative breast cancer. The patient underwent mastectomy followed by chemotherapy. In 2021, imaging studies revealed a mass in the left breast, which led to fibrosis, and a biopsy confirmed medullary-type invasive breast carcinoma. Additionally, an abdominal CT scan revealed an adrenal adenoma on the right adrenal gland and a follicular cyst on the left ovary, with recommendations for follow-up. Later, the patient was diagnosed with endometrioid-type endometrial adenocarcinoma. Clinical exome sequencing identified a heterozygous c.1385G>A variant in the HMMR gene (NM_001142556.2), which is currently classified as a VUS (variant of uncertain significance) in the existing literature. The BRCA1-2 MLPA analysis was normal, ruling out mutations in these well-known breast cancer susceptibility genes.
Conclusion: In this case, a heterozygous c.1385G>A variant in the HMMR gene was identified in a patient with triple-negative breast cancer. While research on HMMR's involvement in cancer cell invasion, metastasis, and tumor progression continues to expand, the clinical significance of this particular variant remains uncertain. Further genetic research is essential to better understand the potential role of HMMR in breast cancer development. Clarifying the impact of such variants could improve genetic counseling, risk assessment, and personalized treatment strategies for patients with breast cancer.
Keywords: Breast Cancer, Ngs, HMMR

[Abstract:0116]

Case Report: Early Age of Onset but Delayed Diagnosis Dyskeratosis Congenita with TERT mutation

Maide Korkmaz[1], Alper Özcan[2], Derya Altay[3], Munis Dündar[1]

[1]Department of Medical Genetics, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[2]Department of Pediatric Hematology, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[3]Department of Pediatric Gastroenterology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

Objective: Dyskeratosis congenita (DKC) is a rare, progressive bone marrow failure syndrome caused by mutations in telomere biology-related genes. It is characterized by a clinical triad of reticulated skin hyperpigmentation, nail dystrophy, and oral leukoplakia. These mutations affect critical steps in cell division and maturation, predisposing individuals to malignancies. The spectrum of DC/TBD varies widely: mild cases may show minimal physical findings and normal bone marrow function, while severe cases present with the triad and early-onset bone marrow failure (BMF). The disease's variable presentation and incomplete penetrance complicate diagnosis.
Case: We present a case of a 13-year-old male whose diagnosis was delayed by nine years due to initially mild symptoms. Early signs included dizziness, fatigue, recurrent respiratory infections, and isolated leukopenia. Despite follow-up, he was discharged when no progression was observed. Nine years later, his symptoms worsened, with recurrent respiratory tract infections, bicytopenia, splenomegaly, hepatic fibrosis, and portal hypertension. His family history revealed cirrhosis on the paternal side. Serological tests for infectious causes of cirrhosis and bone marrow failure were negative. A bone marrow biopsy revealed hypocellularity. Whole exome sequencing identified an NM_198253.3 c.1892G>A (R631Q) pathogenic variant in the TERT gene. Relative telomere length, measured via real-time qPCR, was three times shorter than age-matched healthy controls. Family segregation analysis confirmed the same variant in the father.
Conclusion: Dyskeratosis congenita requires early genetic testing, especially in patients at risk for bone marrow failure, malignancies, and solid tumors. Prompt diagnosis allows early intervention and better disease management. Clinicians should consider the variable manifestations of the disease, as even mild findings at a young age can indicate significant underlying pathology. Variability within families further underscores the importance of genetic testing in suspected cases.
Keywords: TERT, bone marrow failure, R631Q, early onset

[Abstract:0118]

Interpretation of Hereditary Cancer Panel Results in Patients with Multiple Primary Malignancies

Dilara Aydemir, Abdulgani Tatar, Çiğdem Yüce Kahraman
Department of Medical Genetics, Ataturk University Faculty of Medicine, Erzurum, Türkiye

Multiple primary malignancies are defined as two or more histopathologically different malignancies in an individual. Although the incidence of multiple primary cancers is rare, it is now reported more frequently due to better diagnostic techniques, prolonged life expectancy and increased long-term survival rates of cancer patients. The incidence varies between 1.6% and 5.2%. In our study, cancer patients admitted to our outpatient clinic between July 2018 and December 2024 were screened and 39 of them had two or more solid tumors. Pathology reports confirmed that the tumors were not metastatic. A hereditary cancer panel including 71 cancer predisposition genes was perfomed in 8 male and 31 female patients. The most common tumor coexistency was breast+ovarian cancer in 9 patients, followed by breast + thyroid cancer in 5 patients. There were synchronous tumors in 4 patients and metachronous tumors in 35 patients. 2 patients had 3 primary tumors. LP/P variant was not detected in 23 (59%) patients. While 2 (25%) of 8 male patients were possesing LP/P variant, 14 (45%) of 31 female patients were possesing LP/P variant. Totally, P/LP variants were detected in 7 different genes. These genes were BRCA2, MLH1, BRCA1, ATM, CHEK2, APC, MUTYH, TP53 genes, respectively. In the literature, the rate of LP/P variant detection in patients with multiple primary malignancies has been reported as 30-55%. Our positivity rate was 41% and this rate can be increased by more comprhensive gene panel and by using additional methods. There is an increased secondary tumor risk for patients who have hereditary cancer gene mutation. For this reason, the risks should be explained to these patients and close follow-up and regular scans for secondary tumors should be recommended. Thus, it will be possible to minimize the possibility of secondary malignancy. Also individuals at risk in their families should be screened and effective genetic counseling should be provided.

Keywords: BRCA2 gene, Hereditary cancers, Multiple Primary Malignancies

[Abstract:0119]

MINAS Case Series:A Single Center Observation

Busra Saruhan, Abdulgani Tatar, Çiğdem Yüce Kahraman

Department of Medical Genetics, Ataturk University Faculty of Medicine, Erzurum, Türkiye

Multiplocus inherited neoplasia allelic syndrome(MINAS) is a recently known term that describes the coexistence of two or patogenic/likely patogenic variants in cancer susceptibility genes(CPGs) in a person. This term is coined in 2016 by Whitworth et al. As next generation sequencing technology advances, increasing usage of large cancer gene panels or whole-exome/genome sequencing provide the opportunity for recognition of more cases of MINAS. According to the literatures, frequency of MINAS is estimated as aproximately 5%. We present six MINAS cases which were selected among a large cancer patients group. 1089 patients were analysed with a comprehensive gene panel that includes almost all hereditary cancer gene described in the literatures. The first of MINAS cases was a 71-year-old man carrying PVs in the mutated CHEK2 and MSH2 genes, with colon cancer. The second was a 24-year-old woman carrying heterozygote PV in the mutated BRCA2 gene and homozygote PVs in the mutated MUTYH gene, with unilateral breast cancer. Also, her mother was diagnosed breast cancer a couple of years ago and she was carrying same patogenic variants as like her daughter. The third one was a 55-year-old woman carrying PVs in the mutated CHEK2 and MSH2 genes, with colon cancer. The fourth patient was a 64-year-old woman carrying PVs in the mutated BRCA2 and PALB2 genes, with HER-2 negative breast cancer. The fifth was a 65-year-old man carrying heterozygote PV in the mutated CHEK2 gene and homozygote PVs in the mutated MUTYH gene, with colon cancer. The last one was a 44-year-old woman carrying PVs in the mutated BRCA1 and CHEK2 genes, with bilateral breast cancer diagnosed 11 years apart. We describe their clinical informations and family histories. All of these patients are compatible with a MINAS diagnosis. Predicting the phenotypic effect of two variants in CGS is challenging. In conclusion, further analyses and prospective follow-up of these MINAS patients are needed to establish specific risks for affected individuals and to develop personalised follow-up guidelines to reduce the associated mortality.

Keywords: MINAS, cancer predisposition genes, hereditary cancer, BRCA1, BRCA2

[Abstract:0124]

Detailed Examination of Patients Diagnosed with Lynch Syndrome: A Single-Center, Descriptive Study

Emre Akbaş[1], Nazlı Sena Şeker[2], Ebru Erzurumluoğlu Gökalp[1], Beyhan Durak Aras[1]

[1]Department of Medical Genetics, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Türkiye
[2]Department of Medical Pathology, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Türkiye

Introduction: Lynch syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is a rare, autosomal dominant hereditary cancer predisposition syndrome resulting from pathogenic variants in MLH1, MSH2, MSH6, PMS2, and EPCAM genes. This condition is characterized by an elevated risk for various cancers, including colorectal, endometrial, ovarian, gastric, small intestinal, urinary tract, biliary tract, brain, skin, pancreatic, and prostate cancers.
Objective: This study aimed to evaluate the clinical and molecular characteristics of 10 patients diagnosed with Lynch syndrome between 2021 and 2024 at the Eskisehir Osmangazi University Department of Medical Genetics.
Results: The patients' clinical, histopathological, and genetic findings are summarized in Table 1. Among the 10 variants identified in the patients, 7 (70%) were sequence variants detected through sequence analysis, while 3 (30%) were exonic deletions detected by MLPA analysis. The most prevalent cancer type was colorectal cancer, accounting for 80% of cases, which aligns with existing literature. Ovarian cancer (20%), endometrial cancer (20%) and periampullary tumor (10%) were observed less frequently. Multiple primary tumors were detected in three patients (30%), and one patient was diagnosed with Muir-Torre syndrome, a rare variant of Lynch syndrome, who had a history of recurrent basal cell carcinoma, endometrial cancer, and colon cancer. The age at diagnosis of the patients ranged from 24 to 69 years, with an average of 47.9 years. Notably, all variants detected in the patients had been previously reported in the literature. Genetic counseling was provided to all patients, and specific variant analysis was recommended for their family members. In three families, pathogenic variants were identified in asymptomatic individuals, and screening and prevention recommendations were subsequently made by current guidelines.
Conclusion: This study aimed to share the findings of the cases diagnosed with rare Lynch syndrome at our center and to highlight the heterogeneity of clinical and genetic findings in patients.
Keywords: Lynch syndrome, hereditary cancer syndromes, colorectal cancer, Muir-Torre syndrome

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

Cases	Age at diagnosis	Cancer	Histopathology	Loss of Nuclear Expression	Variant	Pathogenicity
I	44	Colon ca	Moderately differentiated adenocarcinoma	Loss of nuclear expression of MLH1 + PMS2	MLH1(NM_000249.3):c.1441dupA (Heterozygous)	Pathogenic
II	67	Colon ca + Endometrium ca + Basal cell carcinoma	Not applicable	Not applicable	MSH2(NM_000251.2):c.839_840insT (Heterozygous)	Pathogenic
III	50	Colon ca	Moderately differentiated mucinous adenocarcinoma	Loss of nuclear expression of MSH2 + MSH6	MSH2 whole gene deletion (Heterozygous)	Pathogenic

IV	55	Colon ca + Ovarian ca	Signet ring cell carcinoma	Loss of nuclear expression of MSH2 + MSH6	MSH2(ENST00000233146):c.942+3A>T(Heterozygous)	Pathogenic
V	45	Colon ca	Moderately differentiated mucinous adenocarcinoma	Loss of nuclear expression of MSH2	Heterozygous deletion in exons 1, 3, 5, 6, 7 of the MSH2 gene	Pathogenic
VI	69	Periampullary tumor	Moderately differentiated adenocarcinoma	No loss of nuclear expression	MSH2 (NM_000251.3): c.2038C>T (Heterozygous)	Pathogenic
VII	53	Colon ca	Moderately differentiated adenocarcinoma	Loss of nuclear expression of MSH2 + MSH6	MSH2(ENST00000233146):c.1120C>T (Heterozygous)	Pathogenic

VIII	51	Colon ca	Moderately differentiated mucinous adenocarcinoma	Loss of nuclear expression of MSH2 + MSH6	Heterozygous deletion of exons 1-9 in the MSH2 gene + Heterozygous deletion of exon 9 in the EPCAM gene	Pathogenic
IX	51	Colon ca	Well-differentiated adenocarcinoma	Loss of nuclear expression of MLH1 + PMS2	MLH1(ENST00000231790):c.676C>T (Heterozygous)	Pathogenic
X	36	Endometrium ca + Ovarian ca	Endometrioid carcinoma	Loss of nuclear expression of MSH2 + MSH6	MSH2(NM_000251.3):c.942+3A>T (Heterozygous)	Pathogenic

[Abstract:0127]

Ovarian Small Cell Carcinoma of Hypercalcemic Type: A Rare Case Report Associated with Germline SMARCA4 Mutation

Zeki Sakallı[1], Aslı Ece Solmaz[1], Hüseyin Salih Semiz[2], Erdener Özer[3], Haluk Akın[1]

[1]Department of Medical Genetics, Ege University, Faculty of Medicine, İzmir, Türkiye
[2]Department of Medical Oncology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[3]Department of Pathology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

Introduction: Ovarian cancer is one of the leading causes of cancer-related mortality among gynecological malignancies. Small cell ovarian cancer is a rare and aggressive tumor. To date, only about 300 cases have been reported in the literature. This cancer predominantly affects young women, with a median age of 24 years. Despite the availability of various therapeutic approaches, there is no established guideline for the management and follow-up of this disease.mThe discovery of loss-of-function mutations in the SMARCA4 gene as a causative factor for small cell ovarian cancer represents a significant breakthrough. SMARCA4 encodes the ATPase subunit of the mammalian SWI/SNF chromatin remodeling complex. Dysregulation of the SWI/SNF complex can negatively impact cellular migration, nuclear hormone receptor signaling, embryonic stem cell programs, and cell proliferation.
Case: The patient was referred for genetic evaluation due to recurrent ovarian cancer.
She had a history of type 1 diabetes mellitus diagnosed at age 5. At the age of 15, a tumor was identified in the left ovary. The patient underwent unilateral salpingo-oophorectomy, followed by six cycles of chemotherapy due to postoperative residual disease. After achieving a complete response, radiotherapy was administered to the left paraaortic region, and an additional six months of chemotherapy was planned.Following a six-month treatment-free observation period, disease recurrence was detected, and four cycles of chemotherapy were administered. With a good partial response, the patient subsequently underwent TAH+BSO; however, recurrence occurred seven months later. Family history revealed no prior cancer cases or parental consanguinity. Genetic testing using a hereditary cancer panel identified a heterozygous c.2626A>T (p.Lys876*) (chr19-11132410 A>T) variant in the SMARCA4 gene, previously unreported in databases. Functional analysis indicated the variant results in premature termination of BRG1 protein synthesis. Segregation analysis confirmed the variant was absent in both parents, classifying it as a de novo mutation.mConclusion: The identification of mutations in small cell ovarian cancer using next-generation sequencing technologies provides new insights into the biological mechanisms and potential therapeutic targets of this rare malignancy. These findings highlight the necessity for further research to better understand the underlying pathways and develop targeted treatment strategies in the future.

Keywords: Ovarian cancer, Small cell carcinoma of hypercalcemic type, Germline SMARCA4 mutation

[Abstract:0128]

Different genetic approaches to TP53 variations: heterozygous de novo and homozygous cancer cases

Rahime Laçin, Ayşe Gül Zamani, Mahmut Selman Yıldırım

Department of Medical Genetics, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye

Introduction: Li-Fraumeni Syndrome (LFS) is an inherited cancer predisposition syndrome primarily caused by heterozygous mutations in the TP53 gene. Patients typically present with LFS spectrum tumors at an early age across multiple organs, including breast cancer, sarcoma, brain tumors, adrenocortical carcinoma, leukemia, and germ cell tumors. The risk of developing breast cancer in TP53 mutation carriers is as high as 80-90%, a rate even higher than that observed in BRCA1 or BRCA2 carriers. In the late adulthood phase, pancreatic cancer is one of the most common pathologies, with a median age at diagnosis of 53 years. Additionally, other sarcoma types, including liposarcoma, are also present in this phase, with liposarcoma having a median age at diagnosis of 26 years.
Materials and Methods: Peripheral blood samples from patients analyzed using the Next-Generation Sequencing (NGS) method. The KAPA HyperCap DSHereditary Cancer Research Panel was used in the analyses. Identified germline variants were classified according to the American College of Medical Genetics (ACMG) standards.
Results: Case 1: A 30-year-old female patient was referred from the Medical Oncology outpatient clinic due to recurrent breast cancer. She was diagnosed four years ago and had undergone radical mastectomy. A heterozygous frameshift variant, c.459del (ENST00000269305), was detected in the TP53 gene.
Segregation analysis confirmed that the variation was de novo. MLPA analysis of the BRCA1 and BRCA2 genes was normal.
Case 2: A 56-year-old man was referred with metastatic pancreatic cancer. His family history included prostate cancer, lymphoma, testicular cancer, and brain tumors. A homozygous stop-gain variant, c.574C>T (ENST00000269305), was detected in TP53. Due to the death of the parents, segregation analysis could not be performed, but the variant was confirmed by Sanger sequencing. Genetic screening for siblings was recommended.
Conclusion: The possibility of new germline TP53 mutations or the existence of homozygous patients should be kept in mind. Therefore, the genetic approach should not be the same for every patient.
These cases underscore the importance of individualized genetic testing and clinical monitoring. A deeper understanding of LFS and TP53 mutations will improve patient management.
Keywords: TP53, li-fraumeni, cancer

[Abstract:0129]

Evaluation of the effects of the MUTYH gene heterozygosity in a cancer-family

Betül Okur Altındaş, Mahmut Selman Yıldırım

Department of Medical Genetics, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye

Objective: MUTYH gene encodes a critical component of the base excision repair(BER) pathway and plays an important role in the oxidative DNA damage repair, through excising the mismatched adenine bases from the DNA backbone. Oxidative damage to DNA can lead directly to mutagenesis or programmed cell death. The protein encoded by the MUTYH gene also mediates the apoptosis signaling by the introduction of single-strand breaks following oxidative damage. Individuals with biallelic germline MUTYH mutations develop MUTYH-associated polyposis (MAP) syndrome, an autosomal recessive condition that typically manifests with adenomatous colorectal polyps. Patients with MAP are at 93 folds increased risk of colorectal cancer. However the cancer risk in heterozygous carriers of the MUTYH gene mutations still remains uncertain. Here, we present a cancer-family harbouring a single pathogenic MUTYH gene variation.

Case: A 33-year-old male patient was diagnosed and died with colorectal adenocarcinoma. His family pediagree revealed that one of his aunts and two of his uncles of the maternal side were also diagnosed and deceased due to colon cancer before the age of 50. His maternal grandmother were diagnosed with gastric adenocarcinoma in her late-life. Next-generation sequencing of the family members revealed a heterozygous null MUTYH-gene variation(ENST00000372098.3:c.850del, A284Pfs*32, rs761468459). That was a frameshift change causing a premature termination in exon 10 where loss of function is a known mechanism of disease (PVS1). Alelle frequency was extremely low in population databases (PM2) and ClinVar classifies this variant as Pathogenic (PP5). Considering these criteria, the variation was interpreted as Pathogenic according to the American College of Medical Genetics and Genomics (ACMG).

Conclusion: Defects in base excision repair pathway are associated with both increased mutational burden and carcinogenicity. Monoallelic germline MUTYH carriers have an increased risk for cancer due to the possible explanation of somatic loss of the wild-type allele, which manifests as loss of heterozygosity (LOH). This family was reported to underline the importance of the heterozygous changes in DNA repair pathways, including the MUTYH gene.

Keywords: the MUTYH gene, cancer predisposition, base excision repair

[Abstract:0131]

Retrospective analysis of ACMG Secondary Findings v3.2 cancer-related genes in 2383 patients undergoing clinical exome sequencing

Busra Özgüc Calışkan, Munis Dündar

Erciyes University, Faculty of Medicine, Department of Medical Genetics, Kayseri, Türkiye

Rapid advances in genetic research in recent years have revolutionised the diagnosis and treatment of genetic diseases. Next-generation sequencing (NGS) technologies are increasing the speed and accuracy of genomic analysis and providing a better understanding of genetic variation. Thanks to the large amount of genetic data they provide, these technologies not only shed light on the primary findings that explain a patient's preliminary diagnosis, but also allow the study of genetic information outside the research target, such as incidental or secondary findings. The management of secondary findings is controversial in terms of genetic counselling and ethical approaches. The American College of Medical Genetics and Genomics (ACMG) has published guidelines since 2013 to regulate the role of these findings in clinical practice, with the latest guideline published in 2023 increasing the list of genes to be reported to 81. This study aims to retrospectively evaluate 28 cancer-associated genes in ACMG v3.2 from clinical exome sequencing data of 2383 patients and to determine the rate of secondary cancer gene findings in the Turkish population. Genetic analysis revealed 35 different pathogenic/ likely pathogenic variants in 16 different genes in 54 individuals. The variant detected in 9 patients was consistent with the indication of application and was thus designated as a primary finding, consequently not being included in the secondary finding rate. Furthermore, heterozygous MUTYH variants found in 23 patients were excluded from the calculation due to the recommendation that they should be reported in biallelic status.22 patients had reportable variants, and the rate of secondary findings was calculated to be approximately 1%.

Keywords: ACMG v3.2, Actionable genes, Malignancy, Next generation sequencing, Secondary findings

[Abstract:0132]

Early-Onset CNS Tumors in a Pediatric Patient: A Unique Presentation of the Coexistence of CMMRD and MINAS

Tuğba Afşin Erdoğdu, Naz Güleray Lafcı, Ceren Damla Durmaz Özdinç
Department of Medical Genetics, Hacettepe University Faculty of Medicine, Ankara, Türkiye

Objective: Constitutional Mismatch Repair Deficiency (CMMRD) is a rare hereditary cancer syndrome characterized by early-onset brain tumors and hematological malignancies. CMMRD is caused by biallelic pathogenic variants in MMR genes, which are critical for DNA repair. Multilocus Inherited Neoplasia Allele Syndrome (MINAS) is another rare condition defined by pathogenic variants in multiple hereditary cancer-related genes. In this study, we present a case of multiple primary central nervous system malignancies diagnosed with both CMMRD and MINAS, highlighting the complexity of overlapping cancer predisposition syndromes.
Case: A male proband was diagnosed with mediastinal T-cell ALL at age 4, medulloblastoma and a high-grade glial tumor at age 5. Physical examination revealed multiple café-au-lait spots. The pedigree analysis identified parental consanguinity and history of Lynch syndrome-associated cancers in multiple family members. Comprehensive multigene testing revealed homozygous MLH1 c.1690_1693del, p. (Leu564Phefs*26) and heterozygous CDKN2A c.9_32dup, p.(Ala4_Pro11dup) variants. Segregation analysis confirmed that the father was heterozygous for both variants, while the mother was heterozygous for the MLH1 variant.
Conclusion: MINAS has become increasingly recognized with the broader application of multigene panel testing for inherited cancer syndromes. To the best of our knowledge, no other cases have been reported in the literature where CMMRD and CDKN2A variants coexist. It is important to emphasize that CMMRD, unlike other hereditary cancer syndromes, follows an autosomal recessive inheritance pattern. Furthermore, it can be clinically mistaken for Neurofibromatosis Type 1 due to overlapping features, thus CMMRD should be considered in the differential diagnosis, especially in populations with a high prevalence of consanguinity. Moreover, while malignancies associated with CMMRD typically develop in childhood, the occurrence of two distinct central nervous system tumors by the age of 5 years in this proband may suggest a potential additive effect of the coexisting CMMRD and CDKN2A variants, since CDKN2A mutations are also associated with an increased risk of CNS malignancies. This dual diagnosis of CMMRD and MINAS offers new insights into early-onset malignancy and may reshape genetic risk assessment in hereditary cancer syndromes. Identifying similar cases will improve genetic counseling, risk assessment, and refine treatment strategies in such patients with complex hereditary cancer syndromes.
Keywords: Hereditary cancer syndrome, CMMRD, MINAS

[Abstract:0133]

Exploring Germline Mutations in Hematologic Malignancies: A Case of Pediatric ALL with Unique Phenotypic and Genetic Features

Rumeysa Atasay Ayyıldız[1], Mustafa Mert Aydın[1], Alper Özcan[2], Deniz Koçak Gol[2], Veysel Gök[2], Munis Dündar[1]

[1]Department of Medical Genetics, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[2]Department of Pediatrics, Division of Pediatric Hematology-Oncology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

Objective: Hematologic malignancies may result from both somatic and germline mutations. While advances in next-generation sequencing (NGS) have enhanced personalized diagnostics and therapies, the role of germline mutations has been increasingly recognized for their impact on therapy selection, risk assessment, donor compatibility in hematopoietic stem cell transplantation, and disease surveillance. This study aims to investigate the genetic underpinnings of a childhood acute lymphoblastic leukemia (ALL) case with clinical features suggestive of a predisposition to hematologic malignancies.

Case: We report a 4-year-and-4-month-old girl presenting with clinical manifestations of piebaldism, heterochromia, pancytopenia, and splenomegaly. Whole-exome sequencing (WES) was conducted on DNA isolated from the patient's peripheral blood to uncover potential genetic contributions to her condition. The analysis identified four heterozygous variants: 1. KIT gene: A c.1347-1G>C splice acceptor variant, classified as likely pathogenic (novel), disrupting melanocyte and hematopoietic progenitor cell differentiation. 2. BLM gene: A c.1642C>T p.Gln548Ter stop-gained variant, classified as pathogenic, associated with chromosomal instability and an increased risk of malignancy. 3. RTEL1 gene: A c.1030C>T p.Pro344Ser missense variant, classified as a variant of uncertain significance (novel), potentially affecting telomere maintenance and contributing to bone marrow failure and splenomegaly. 4. KRAS gene: A c.436G>A p.Ala146Thr missense variant, classified as likely pathogenic, impacting cellular signaling pathways and contributing to pancytopenia and hypersplenism. The c.1347-1G>C variant in the KIT gene and the c.1030C>T variant in the RTEL1 gene are novel and were not found in existing genomic databases.

Conclusion: This case highlights the importance of comprehensive genomic analysis, particularly WES, in identifying germline mutations in pediatric patients with atypical hematologic malignancies. The identification of four heterozygous variants, including two novel ones, explains the patient's clinical features and underscores the necessity for further studies, including family segregation and
tissue-specific analyses, to improve the classification of germline and somatic variants and advance personalized care.

Keywords: Acute lymphoblastic leukemia, whole-exome sequencing, germline mutations, KRAS gene, KIT gene

[Abstract:0134]

Identifying CDKN2A Deletion in Melanoma-Neural System Tumor Syndrome Using Digital MLPA: A Game-Changer in Hereditary Cancer Diagnostics

Nesibe Saliha Bulut, Ceren Damla Durmaz Özdinç

Department of Medical Genetics, Hacettepe University Faculty of Medicine, Ankara, Türkiye

Objective: CDKN2A is a pivotal tumor suppressor gene involved in cell cycle regulation, and germline mutations, including point mutations and copy number variations (CNVs), are associated with an increased risk of malignancies such as melanoma, pancreatic cancer, and astrocytomas. Despite the increasing application of next-generation sequencing (NGS) in hereditary cancer syndromes, reliable CNV detection remains a significant challenge. Here, we report a family with "Melanoma-Neural System Tumor Syndrome (MIM: 155755)" in whom a heterozygous CDKN2A deletion was detected using digital MLPA, supporting the utility of this method in hereditary cancer diagnostics.

Case: A 19-year-old male with multiple primary tumors, including glioblastoma multiforme and ameloblastic fibrosarcoma, presented to our clinic. Family history revealed malignant melanoma in the father and central nervous system tumors in multiple paternal relatives. Initial testing with a 60-gene hereditary cancer panel revealed no pathogenic variants. Given the strong cancer predisposition in the family, digital MLPA was utilized to assess CNVs across 28 hereditary cancer-related genes. A heterozygous deletion in CDKN2A was identified, explaining the proband's phenotype and familial cancer history. Retrospective analysis showed the deletion was detectable in the proband by NGS, yet missed in the father due to algorithmic limitations.

Conclusion: CNVs account for approximately 10% of hereditary cancer cases, emphasizing the importance of robust detection methods. While NGS offers a broad diagnostic scope, its CNV detection algorithms are limited by false positives, reliance on gender-matched controls, and sequencing variability. Our findings demonstrate the utility of digital MLPA as a complementary diagnostic tool, particularly for cases with a strong clinical suspicion but negative initial sequencing results. This study highlights the critical role of digital MLPA in uncovering clinically significant CNVs and its potential to refine diagnostic workflows in hereditary cancer syndromes.

Keywords: Digital MLPA, Melanoma-neural system tumor syndrome, CDKN2A deletion

[Abstract:0137]

Integrating Somatic and Germline Variant Analysis for Comprehensive Cancer Management through Tumor DNA Sequencing

Hülya Tarım, Emine Göktaş, Ayşe Gül Zamani, Mahmut Selman Yıldırım
Department of Medical Genetics, Faculty of Medicine, Necmettin Erbakan University, Konya, Türkiye

Objective: DNA sequencing of tumor tissues has become a standard approach in cancer management, enabling the detection of somatic mutations for diagnostic, prognostic, and therapeutic purposes. In addition to somatic alterations, cancer gene panels can identify germline variants, providing insights into genetic predispositions, such as hereditary cancer syndromes. This study examined hereditary cancer panel results in patients suspected of harboring germline variants based on somatic cancer panel findings.

Materials and Methods: This study included 19 solid tumor patients referred to Necmettin Erbakan University Medical Genetics Department in 2024. Tumor tissue samples, formalin-fixed paraffin-embedded (FFPE), were sequenced using the KAPAHyperPETE Pan Cancer Panel. Somatic variants were analyzed according to the guidelines of the AMP/ASCO/CAP. Clinically significant alterations (pathogenic or likely pathogenic based on the American College of Medical Genetics (ACMG) classification) in cancer susceptibility genes were identified. Somatic variants with an allele fraction above 30% for single nucleotide variants or 20% for small insertions/deletions were selected. These variants were then analyzed using a germline-focused panel on the patients' blood samples.

Results: The cohort included 9 male and 10 female patients, with a mean age of 63 at diagnosis. Most tumors originated from the gastrointestinal system (7/19) and ovaries (4/19), while others included lung cancer (3/19), endometrial cancer (2/19), breast cancer (1/19), glioblastoma (1/19), and cancer of unknown primary origin (1/19). Of the somatic variants detected in the APC, BRCA1, BRCA2, CDKN2A, STK11, and TP53 genes, 14% (4/28) were of germline origin. Two cases of breast and colon cancer were diagnosed with BRCA2-associated hereditary breast and ovarian cancer (HBOC), one case with ovarian cancer was diagnosed with BRCA1-associated HBOC, while a patient with lung cancer was diagnosed with Li-Fraumeni Syndrome. Genetic counseling was provided, and family screening was recommended

Conclusion: DNA sequencing of tumor tissues is essential for detecting both somatic mutations and germline alterations. Identifying germline variants offers insights into cancer risk, aids in genetic counseling for relatives, and supports prophylactic strategies. Pathogenic germline variants in DNA repair genes, such as BRCA1 and BRCA2, enable targeted therapy. This study underscores the clinical benefits of integrating germline variant analysis into somatic mutation testing, emphasizing its role in personalized cancer care and management.

Keywords: Tumor sequencing, germline testing, cancer-susceptibility genes, somatic variants, germline variants

[Abstract:0139]

Genetic Insights into Retinoblastoma: Somatic Mosaicism and Clinical Correlations

Muhammed Fatih Mülayım[1], Özge Vural[2], Hatice Tuğba Atalay[3], Gülsüm Kayhan[1]

[1]Department of Medical Genetics, Gazi University Faculty of Medicine, Ankara, Türkiye
[2]Department of Pediatric Hematology and Oncology, Gazi University Faculty of Medicine, Ankara, Türkiye
[3]Department of Ophthalmology, Gazi University Faculty of Medicine, Ankara, Türkiye

Introduction: Retinoblastoma (RB) is a malignant neoplasm of the retina, predominantly affecting pediatric patients. A substantial proportion of cases are hereditary and are caused by heterozygous variants in the RB1 gene.
Objectives: This case study aimed to evaluate the correlation between somatic genetic variants in RB patients and their associated clinical manifestations.
Methods: A 9-month-old boy with trilateral retinoblastoma was evaluated by next-generation sequencing (NGS) technology for the RB1 gene on peripheral blood samples and tumor tissue.
Results: The peripheral blood analysis detected a pathogenic RB1 variant with a very low variant allele frequency (VAF) of 6%. In contrast, analysis of tumor tissue [formalin-fixed paraffin-embedded (FFPE)] demonstrated a significantly higher VAF of 62%, consistent with postzygotic somatic mosaicism. As expected, there was also a second pathogenic variant in the patient's tumor tissue. Segregation analysis revealed that the variants was de novo.
Conclusion: The findings underscore the critical importance of analyzing tumor tissue alongside low-frequency variants in blood samples. The integration of peripheral and tumor tissue analysis is essential to accurately detect mosaic variants, providing valuable insights for tailoring patient care.
Such efforts are crucial for guiding treatment decisions, genetic counseling, and assessing familial risk.
Keywords: RB1, Retinoblastoma, Somatic Mosaicism

[Abstract:0140]

Counseling for Non-Founder CHEK2 Mutations

Ege Baltacı, Ayşe Pelin Toker, Yunus Kasım Terzi, Zerrin Çelik

Clinic of Medical Genetics, Başkent University Hospital, Ankara, Türkiye

Objective: The CHEK2 gene encodes a protein kinase that acts as a tumor suppressor and participates in DNA damage repair. Germline mutations of this gene have been associated with a variety of cancers, including breast, colorectal, gastric, ovarian, kidney, prostate, and thyroid cancers. However, some of these associations are still controversial. The most studied CHEK2 mutations are the founder mutations, including c.1100delC, c.444+1G>A, p.I157T, and Δexon9_10. While these variants have been extensively studied, other mutations of this gene are often overlooked. Literature suggests that different mutations may be linked to distinct cancers and thus require different strategies for genetic counseling and screening. Here, we present two cancer cases with non-founder CHEK2 mutations and discuss the main differences in management compared to founder CHEK2 mutations.

Case: The first patient is a 61-year-old female with a history of bilateral hormone receptor-negative breast cancer. She has a family history of breast and pancreatic cancer. A hereditary cancer panel and BRCA1/2 MLPA were performed, and only a known pathogenic non-founder CHEK2 mutation was identified (c.1427C>T, p.Thr476Met, NM_007194.4). This mutation is in the protein kinase domain, like the c.1100delC founder mutation. The second patient is a 62-year-old female who presented with a personal and family history of colon cancer. She had mucinous adenocarcinoma with perineural invasion in the sigmoid colon. Clinical exome sequencing revealed a previously unreported non-founder CHEK2 mutation (c.1547_1551del, p.Ser516*, NM_007194.4). She also had a history of hysterectomy and bilateral salpingectomy performed 10 years ago for endometrial hyperplasia.

Conclusion: Although CHEK2 is typically seen as a low- to moderate-penetrance gene for cancer susceptibility, its involvement in the ATM-CHK2-p53 double-strand DNA break pathway connects it to several cancers. The c.1100delC allele has long been considered the primary clinically relevant CHEK2 variant linked to breast cancer. However, recent research indicates that this variant is associated with various other cancers and other CHEK2 mutations may be related to various malignancies. Given the inconsistencies in the literature regarding CHEK2 mutations, patients, especially those with non-founder mutations, should be evaluated individually based on their genetic profiles.

Keywords: Breast cancer, CHEK2, Founder mutation, Low penetrance

[Abstract:0142]

CHEK2 variants detected in Single Centre Hereditary Cancer Panels Evaluation according to ACMG classification

Levent Paralı, Aslı Ece Solmaz, Asude Durmaz, Ayça Aykut, Haluk Akın

Department of Medical Genetics, Ege University Faculty of Medicine, İzmir, Türkiye

Objective: CHEK2 gene poses an intermediate risk for hereditary cancer when compared with other hereditary cancer-associated genes. It is especially associated with breast, ovarian and colon cancers. We aimed to evaluate the variants we detected in the HC panels studied in our centre according to the acmg classification and according to the population frequency.
Materials-Methods: 2162 hereditary cancer panels and 2591 other panels studied in our centre were retrospectively screened for CHEK2 variants. Variants found were classified according to ACMG criteria. Clinical histories of positive patients were compiled.
Results: 141 cases (6.9%) in HCS and 15 (0.6%) in other panels, chek2 variants were detected. 104 of them were pathogenic and likely pathogenic. 13 different null variants were identified. 31 different missense variants were identified. 22 of them were evaluated as vus. CHEK2:c.470T>C p.Ile157Thr 1427C>T p.Thr476Met and 592+3A>T (NM_007194.4) pathogenic variants were found to be 0.5%, 0.4% and 0.3%, respectively.
Conclusion: We suggest that a comprehensive study of variant distribution and clinical correlation of such a gene with moderate cancer effect will contribute to hereditary cancer genetics.
Keywords: CHEK2, Hereditary Cancer, variant classification

[Abstract:0143]

Two Patients With Atypical Cancer History And Pathogenic Mutation In The SDHA Gene

Asiye Sevde Can, Aslı Ece Solmaz, Zeynep Nur Paralı, Haluk Akın

Department of Medical Genetics, Ege University Faculty of Medicine, İzmir, Türkiye

Introduction: The SDHA gene encodes one of the four subunits of the succinate dehydrogenase (SDH) complex and functions as a tumor suppressor.Mutations in these complex genes predispose to familial paraganglioma-pheochromocytoma syndrome and gastrointestinal stromal tumors (GIST).Diagnoses reported in patients with germline SDHA pathogenic variants include prostate and colon adenocarcinomas, endometrial carcinoma, urothelial carcinoma, poorly differentiated gastric carcinoma, clear cell renal carcinoma, triple-negative breast cancer, and neuroblastoma.
Case: A 43-year-old female patient was diagnosed with breast cancer at the age of 37 in 2018 and applied to Ege University Medical Genetics Department.Her family history revealed several cancer cases:her father had colon cancer at the age of 70, her paternal aunt had rectal cancer at the age of 75,another aunt had breast cancer at the age of 72,and her grandmother had gastric cancer at the age of 75.In 2018,hereditary cancer panel and BRCA1/2 MLPA were studied and resulted normal.In 2024, the patient's 7.5-year-old son was referred to our clinic with a diagnosis of rhabdomyosarcoma. A hereditary cancer panel performed on the son revealed a heterozygous c.1433-2A>G variant in the SDHA gene and a heterozygous c.3028+3A>G variant in the MET gene.The variant detected in the SDHA gene was classified as likely pathogenic in the ClinVar database and also evaluated as likely pathogenic according to ACMG criteria.The variant identified in the MET gene was reported as VUS in the ClinVar database and similarly evaluated as VUS based on ACMG criteria. Following the identification of these mutations in the son,we included the 43-year-old female patient in a hereditary cancer panel targeting 59 genes associated with cancer.The SDHA and MET gene mutations identified in the son were also observed in the mother.Family members were invited for segregation analysis.
Conclusion: SDHA germline mutations can lead to unexpected cancer spectrums in both pediatric and adult individuals. In our case, we particularly focused on the detection of SDHA mutation in the case of rhabdomyosarcoma.We have previously identified pathogenic/likely pathogenic SDHA variants in patients with breast cancer and hemangioblastoma within our cohort.Further research is needed to investigate the association of germline mutations in both the SDHA and MET genes with atypical cancers.
Keywords: Cancer, MET, rhabdomyosarcoma, SDHA

[Abstract:0145]

Investigation of RAD51C/RAD51D Gene Variants in Patients with Hereditary Breast and Ovarian Cancer: Single Center Experience

Fatma Uğuzdoğan, Aslı Ece Solmaz, Haluk Akın
Department of Medical Genetics, Ege University Faculty of Medicine, İzmir, Türkiye

Introduction: Hereditary breast and ovarian cancer syndrome (HBOC) is primarily linked to germline mutations in BRCA1/BRCA2, which play a critical role in maintaining genomic stability through homologous recombination repair of DNA breaks. Other homologous recombination genes, like RAD51C and RAD51D, are linked to mutations that increase the risk of breast and ovarian cancer.
Method: The mutation spectrum and clinical findings of patients with a preliminary diagnosis of HBOC and germline mutations in RAD51C/D genes who were admitted to Ege University Department of Medical Genetics between 2021 and 2025 were retrospectively evaluated.
Discussion/Conclusion: We evaluated 25 patients who were admitted to Ege University Medical Genetics outpatient clinic with a prediagnosis of HBOC and RAD51C/D variants were detected. Of these patients, 20 had breast cancer and 5 had ovarian cancer. The most common type of breast cancer was ductal carcinoma, which was detected in 45% (9/20) of cases. Less common were lobular (3/20) and mixed (3/20) types. In receptor expression, triple negative type breast cancer was the most common (7/20). The mean age at diagnosis was 50 years (34-64). The majority of the patients were female and there was 1 male patient. This patient had a family history of breast cancer in her older sister and genetic testing revealed a pathogenic RAD51D gene mutation. 11 of 20 patients had a family history of malignancy. Genetic analysis revealed mutations in the RAD51D gene in 13 patients and in the RAD51C gene in 7 patients. Of these mutations, 6 were pathogenic/potentially pathogenic and 14 were VUS. Most mutations were missense (14/20), followed by nonsense (4/20), del/ins (1/20), and splice site (1/20). The most common histologic type of ovarian cancer was serous tumor (3/5). The mean age at diagnosis was: 58.5 (51-67). Genetic analysis revealed mutations in the RAD51C gene in 5 patients. 1 mutation was pathogenic and 4 were VUS. Of the variants, 3 were missense, 1 was nonsense and 1 was splice site. Family history was positive in 4 of 5 patients. With this study, we aimed to present our single center hereditary breast/ovarian cancer experience.
Keywords: Breast and ovarian cancer, RAD51C, RAD51D

[Abstract:0146]

Phenotypic Manifestations of Germline Heterozygous NBN Pathogenic Gene Variants: Single-Center Experience

Elif Bulut, Mehmet Kocabey, Tufan Çankaya, Elçin Bora, Ayfer Ülgenalp, Ahmet Okay Çağlayan

Department of Medical Genetics, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

Objective: Biallelic pathogenic or likely pathogenic variants in NBN cause Nijmegen Breakage Syndrome (NBS), an autosomal recessive disorder characterized by growth retardation, microcephaly, radiosensitivity, immunodeficiency, and a predisposition primarily to lymphoid malignancies. NBN plays a critical role in the early steps of the DNA damage response (DDR) by forming the MRN complex along with MRE11 and RAD50. Previous studies have supported the association of the NBN p.K219fs variant with an increased risk of prostate cancer and lymphoid malignancies, while conflicting evidence exists regarding its association with other cancer types, particularly breast and colorectal cancers, in certain populations.
Materials and Methods: Targeted next-generation sequencing for onco-risk analysis was performed on DNA isolated from the peripheral blood of 1,715 patients evaluated at our center for various indications.
Results: Heterozygous pathogenic NBN variants were identified in eight patients (8/1715; 0.46%). Among these, the c.657_661del (p.Lys219AsnfsTer16, rs587776650) variant was detected in five patients, while the other variants identified in one patient each were c.1399G>T (p.Glu467Ter), c.1496C>G (rs587776650), and c.163_171+3delACCAACCTGGTA (rs1057516772). The cancer types associated with these variants in the patients were gastric, prostate, and breast cancer. This study conducted a detailed genotype-phenotype correlation by comparing these rare NBN pathogenic gene variants, previously described in the literature, with existing data.
Keywords: breast cancer, gastric cancer, genotype-phenotype correlation, NBN, prostate cancer

[Abstract:0147]

Results of Cancer Screening in Unaffected Individuals with a Family History of Hereditary Cancer

Mukaddes Feyza Baltacı[1], Emine Merve Aydın[1], Diyar Sayıt[1], Elif Yılmaz Güleç1, Filiz Özen[2]

[1]Clinic of Medical Genetics, Istanbul Goztepe Prof. Dr. Süleyman Yalcin City Hospital, Istanbul, Türkiye; Department of Medical Genetics, İstanbul Medeniyet University, Faculty of Medicine, Istanbul, Türkiye
[2]Clinic of Medical Genetics, Istanbul Göztepe Prof. Dr. Süleyman Yalcin City Hospital, Istanbul, Türkiye

Objective: Approximately 5-10% of all diagnosed cancer cases are believed to be part of hereditary cancer syndromes. Multigenic panels are currently used to detect responsible variants. In addition to their use for individuals who have already been diagnosed with cancer, these panels are also used to screen unaffected individuals with a strong family history of hereditary cancers. This study aims to evaluate pathogenic and likely pathogenic variants detected in healthy individuals with a family history of hereditary cancer and discuss the results of Hereditary Cancer Sequencing in this population.
Method: HCS results of 340 healthy individuals who were tested at Göztepe Prof Dr Süleyman Yalçın City Hospital, in 2024, due to a family history of cancer were retrospectively screened. The inclusion criterion was based on the National Comprehensive Cancer Network (NCCN) Guidelines version 1.2025 for hereditary cancer testing in unaffected individuals meeting family history criteria.
Individuals with known pathogenic/likely pathogenic variant carrier status in their families were excluded from the study. For sequencing we used the Illumina NextSeq 500 platform with the Mid Output v2 Kit and Hereditary Cancer Panel (Sophia) kit. Hereditary Cancer Panel covers 60 genes associated with hereditary cancer risk. For bioinformatic analyses, we used the Sophia-DDM-V4 software. The hereditary cancer panel results were reviewed for pathogenic and likely pathogenic variants.
Results: In 340 individuals, 56(16.4%) Pathogenic/Likely Pathogenic variants were identified in BRCA1(11), BRCA2(10), ATM(7), CHEK2(6), MUTYH(4), RET(2), CDKN2A(2), XPA(2), FANCC(1), PMS2(1), NBN(1), FANCA(1), RAD51C(1), APC(1), BLM(1), MSH3(1), MLH1(1), PTEN(1), BRIP1(1) and ERCC2(1) genes.
Conclusion: This study highlights the importance of genetic testing for individuals with a significant family history of hereditary cancer. Identifying Pathogenic/Likely Pathogenic variants enables early interventions, personalized risk management, and cascade testing for at-risk relatives.
Future studies with larger cohorts and long-term follow-up are warranted to solidify these findings.
Keywords: Hereditary Cancer Sequencing, Family History, Unaffected Individuals

[Abstract:0148]

A Rare case associated with a pathogenic mutation detected in the SMAD4 gene: Juvenile Polyposis-Hereditary Hemorrhagic Telangiectasia Syndrome

Rashad Abdullayev[1], Muhammed Burak Bereketoğlu[2], Kübra Tuncer[3]

[1]Department of Medical Genetics, Pamukkale University Faculty of Medicine, Denizli, Türkiye
[2]Department of Medical Genetics, Ege University Faculty of Medicine, İzmir, Türkiye
[3]Clinic of Physical Medicine and Rehabilitation, Tunceli State Hospital, Tunceli, Türkiye

Introduction: Juvenile Polyposis-Hereditary Hemorrhagic Telangiectasia Syndrome is a combined phenotype characterized by multiple organ involvement, hemorrhagic telangiectasias, and multiple hamartomatous polyps in the colon, presenting as an overlap clinical entity. Affected individuals have an increased lifetime risk of gastrointestinal tract cancers. The SMAD4 gene encodes proteins involved in the TGFB signaling pathway, which directs signals from the cell surface to the nucleus, playing a critical role in cell growth and proliferation. The severity of the clinical spectrum caused by SMAD4 gene variants varies depending on the specific mutation.
Case: A 21-year-old female patient was referred to the Medical Genetics outpatient clinic for etiological investigation due to findings of hypertrophic osteoarthropathy and intestinal polyposis. A detailed physical examination revealed rectal bleeding, clubbing of the fingers, epistaxis, cyanosis of the lips, swelling and effusion in both knees and ankles, as well as syncopal episodes and swelling in the distal radius of both wrists. Biochemical tests indicated anemia, and radiodiagnostic evaluations showed pulmonary arteriovenous malformations. Based on the clinical findings, a preliminary diagnosis of a clinical spectrum associated with the SMAD4 gene was considered.
Materials and Methods: Next-generation sequencing (NGS) was performed to sequence the entire SMAD4 gene. Bioinformatic analyses were conducted using Franklin by Genoox in accordance with the ACMG guidelines. As a result of these analyses, a heterozygous p.C363R (c.1087T>C) variant in the SMAD4 gene was identified as pathogenic. The patient was provided with genetic counseling and referred to the oncology clinic for further evaluation.
Conclusion: In patients with juvenile polyposis, accompanying vascular dysplasias and physical examination findings should be carefully evaluated for differential diagnosis. Consequently, achieving a definitive diagnosis through whole-gene sequencing, hereditary cancer panels, or whole-exome sequencing using next-generation sequencing methods is crucial for patient survival.
Keywords: Polyposis, SMAD4 gene, next-generation sequencing

[Abstract:0149]

A homozygous case with moderate penetrance RET variant p.Leu790Phe

Oğuzhan Demir[1], İrfan Nuhoğlu[2], Alper Han Çebi[1], Ayberk Türkyılmaz[1]

[1]Department of Medical Genetics, Karadeniz Technical University Faculty of Medicine Trabzon, Türkiye
[2]Division of Internal Diseases, Department of Endocrinology and Metabolism Disorders, Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye

31 years old woman admitted to endocrinology clinic with the complaints of overweight, previously diagnosed insulin resistance and grade 2-3 hepatosteatosis. She also had diagnosis of polycystic ovary syndrome and had insulin resistance since her pregnancy. To exclude all possible endocrine reasons for these complaints, she underwent broad biochemical testing and thyroid ultrasonography which showed 3 mm sized hypoechoic nodule on the right thyroid gland. Upon her biochemical tests, calcitonin levels found to be high, and she was consulted to medical genetics polyclinic for investigation in terms of Multiple Endocrine Neoplasia (MEN) syndromes. Her parents are third-degree relatives (first-cousin marriage). Her mother was learnt to have thyroid nodules also and she was in follow up of endocrinology clinic. Patient's one sister and one aunt of the mother side were in follow up of endocrinology clinic also for hypothyroidism. Patient was tested for RET gene sequence analysis and detected c.2370G>T (p.Leu790Phe) homozygous variant. Her parents, 2 sisters and 1 son were also tested for same variant and all but one sister whose test normal was found to be heterozygous. She underwent bilateral thyroidectomy and pathology reports revealed medullary thyroid carcinoma. Soon after, her mother followed the same path, and her pathology report was concordant with the same carcinoma. Heterozygous germline pathogenic variants of RET gene are known to cause MEN2A and MEN2B syndromes which predispose pheochromocytoma, medullary thyroid carcinoma (MTC), parathyroid adenoma. Genotype-phenotype correlations were found for recurrent variants and The American Thyroid Association Guidelines Task Force has classified pathogenic variants based on their risk for aggressive MTC [Wells et al 2015]. p.Leu790Phe variant was described as moderate penetrance variant and associated with MEN2A, and to be more specific pheochromocytoma and papillary thyroid carcinoma. Homozygous variants are rare and by nature of the proto-oncogenes and expected to cause more severe phenotypes.

Keywords: cancer, hereditary, medullary thyroid cancer, men2a

[Abstract:0150]

Expanding the Mutation Spectrum of ATM: A Case of Ataxia-Telangiectasia with Leukemic Presentation

Sümeyye Şanal[1], Mahmut Selman Yıldırım[1], Hüseyin Tokgöz[2], Sevgi Keleş[3]

[1]Department of Medical Genetics, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye
[2]Department of Pediatric Hematology and Oncology, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye
[3]Department of Pediatric Allergy and Immunology, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye

Objective: Ataxia-telangiectasia (A-T) is an autosomal recessive disorder characterized by the childhood onset of progressive cerebellar ataxia, immunodeficiency, and oculocutaneous telangiectasia. A-T has a high risk of malignancy, particularly of lymphoma and leukemia, and carcinomas. A-T results from germline biallelic pathogenic variants in the ATM gene, which is involved in DNA damage repair. In these cases with null variants have a higher risk for cancer. Also, a partial or complete loss of ATM function is associated with hereditary cancer predisposition in heterozygous individuals. In this report, we present a patient with ataxia-telangiectasia and acute lymphoblastic leukemia (ALL) and aim to highlight a novel variant in the ATM gene.
Case: A 4-year-old patient was referred to our medical genetics clinic for molecular genetic testing because of ataxia and immunodeficiency symptoms. Pedigree analysis showed that the proband's parents are first-degree cousins, and his brother was also diagnosed with ataxia-telangiectasia and passed away at the age of 11 due to ALL. DNA was isolated from the patient's peripheral blood, and next-generation sequencing (NGS) analysis covering the ATM gene and other genes relevant to the differential diagnosis was performed.The data were then evaluated using the SEQ NGS analysis platform. Molecular analysis revealed a homozygous novel variant (c.3746+1G>A, ENST00000675843) in the ATM gene. This sequence change affects a donor splice site in intron 25 of the ATM gene and is expected to disrupt RNA splicing, thereby resulting in a loss of protein function. The variant was classified as pathogenic according to ACMG criteria, supported by the evidence codes PVS1, PM2, and PP5. Since pathogenic variants in the ATM gene confer cancer predisposition in heterozygous individuals, molecular genetic screening was offered to the other family members.
Conclusion: Germline mutations in the ATM gene, which is associated with hereditary cancer syndromes, can lead to ALL, one of the most frequently detected malignancies in childhood. In cases with null variants in the ATM gene, cancer development represents a major risk factor for mortality. Therefore, it should be noted that determining the genotype of these patients may be valuable in predicting prognosis.
Keywords: ATM gene, leukemia, hereditary cancer predisposition

[Abstract:0151]

Role of Liquid Biopsy in Personalized Cancer Management: A Clinical Perspective

Simge Tuana Ay Öner[1], Diyar Sayıt[1], Elif Yilmaz Gülec[2], Filiz Özen[1]

[1]Clinic of Medical Genetics, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul, Türkiye
[2]Department of Medical Genetics, İstanbul Medeniyet University Faculty of Medicine, Istanbul, Türkiye

Objective: Liquid biopsy is a valuable, minimally invasive tool for detecting somatic variants, aiding in diagnosis, prognosis, and therapy selection. This study aims to evaluate its clinical utility by analyzing results from our clinic and comparing them with existing literature.
Materials-Methods: Liquid biopsy results of 40 patients with various cancer types (lung, gastric, ovarian, cervical, melanoma, and tumors of unknown primary origin) were reviewed from March 2021 to June 2022. Cell-free DNA (cfDNA) was isolated from plasma, and targeted gene regions were amplified using the Archer® Reveal ctDNA 28 kit. Sequencing was performed on the Illumina NextSeq® platform, and data were analyzed with Archer Analysis software.
Results: Somatic mutations were detected in 20 patients and categorized by TIER classification: • Tier 1a (Clinically actionable): Detected in 5 patients (EGFR: 3, KRAS: 2), all observed in adenocarcinoma. • Tier 1b (Potentially actionable): Detected in 3 patients (KRAS), all observed in adenocarcinoma. • Tier 2 (Variants of uncertain significance in actionable genes): Detected in 2 patients (TP53, PIK3CA). • Tier 3 (Variants of uncertain significance): Detected in 10 patients (TP53: 9, RET: 1). The majority of mutations were identified in Non-Small Cell Lung Cancer (NSCLC), particularly adenocarcinoma. Germline confirmation was required for two patients due to high Variant Fraction values; one was confirmed as a germline RET mutation, while the other was identified as a highly clonal somatic TP53 mutation. Furthermore, three patients benefited from the findings by directly accessing targeted therapies.
Conclusion: This study highlights the clinical utility of liquid biopsy in identifying actionable variants, consistent with literature findings, particularly for NSCLC patients. Germline testing emphasizes the importance of distinguishing somatic from hereditary mutations, enhancing personalized cancer management.
Keywords: Liquid Biopsy, NGS, actionable variants, TIER classification

[Abstract:0153]

Two separate cases with the same novel variant in the FANCA gene related with gastric cancer

Elif Uzay[1], Sümeyra Oğuz[1], Hilal Keskin Karakoyun[2]

[1]Zeynep Kamil Woman and Children Diseases Hospital, İstanbul, Türkiye
[2] Department of Moleculer Biology and Genetics, Dvision of Sapiens Genetics, Demiroglu Bilim University Faculty of Science, İstanbul, Türkiye

Gastric cancer is an important global health issue. It is the fourth leading cause of cancer deaths and the fifth most commonly diagnosed type of cancer. Risk factors for gastric cancer include Helicobacter pylori infection, eating habits, genetic factors, and age. Approximately 15% to 20% of gastric cancers may be caused by hereditary cancer predisposing syndromes. Monoallelic germline mutations in Fanconi anemia (FA) genes can increase the risk of cancer, unlike biallelic mutations that lead to the typical FA symptoms. Two separate cases from the different regions of the Türkiye, 54 years old male proband diagnosed gastric cancer and 38 years old male with multiple relatives diagnosed with gastric cancer referred to our clinic. Hereditary cancer panel was performed and as a result of the analysis, NM_000135.4, c.1361_1374delinsGAG, p.(Ala454Glyfs*27) heterozygous novel variant was detected in the FANCA gene. This variant was reported as likely pathogenic according to ACMG criterias. In this study, the association of the same novel FANCA mutation detected in two different families with gastric cancer is presented. We emphasize the importance of genetic analysis using expanded panels in the evaluation of gastric cancers, especially in individuals with high familial burden. In addition to being particularly important in identifying other individuals at risk in the family, this will also contribute to a better understanding of pathogenesis and the development of new treatment methods in the future.

Keywords: gastric cancer, FANCA, novel mutation, c.1361_1374delinsGAG

[Abstract:0154]

The role of mitochondrial tumor suppressors in hereditary cancers from a single-center perspective

Ezgi Çevik Demir, Afife Büke, Hanife Saat, Ahmet Kablan, Abdullah Sezer, Haktan Bağış Erdem

Clinic of Medical Genetics, Ankara Etlik City Hospital, Ankara, Türkiye

Objective: Mitochondrial tumor suppressors are proteins encoded in the nuclear genome and involved in the Krebs cycle. These include genes encoding the succinate dehydrogenase enzyme complex (SDHx: SDHA, SDHB, SDHC, SDHD, and SDHAF2) and fumarate hydratase (FH).
Loss-of-function mutations in these genes leading to tumor formation can be explained by activation of the pseudo-hypoxic pathway: the accumulation of metabolites and increased production of reactive oxygen species leads to inappropriate activation of hypoxia-induced factor (HIF). Heterozygous germline pathogenic variants in SDHx genes are associated with hereditary
paraganglioma-pheochromocytoma (PGL/PCC) syndromes, while those in the FH gene cause hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. This study aimed to evaluate genotype-phenotype correlations of rare SDHx and FH mutations.
Materials-Methods: In this study, personal and clinical data, family history and segregation data of patients with a germline pathogenic/likely pathogenic variant in SDHx and FH genes were retrospectively evaluated.
Results: Of 8 patients, SDHA was detected in a patient with a familial history of pheochromocytoma, SDHB in another patient with pheochromocytoma and gastrointestinal stromal tumor, and SDHD variant in 3 patients with paraganglioma. Among the three patients with pathogenic FH variants, one presented with uterine leiomyoma, another with breast cancer, and the third had a familial history of renal carcinoma. Heterozygous FH(NM_000143):c.585G>A variant identified in this study has not been reported previously. Family members of four patients were admitted for segregation. Patient data and the variants identified are summarized in Table 1.
Conclusion: Mitochondrial dysfunction plays an important role in cancer pathogenesis. Heterozygous germline mutations in SDHx and FH genes implicated in the Krebs cycle can lead to hereditary cancer syndromes, while somatic mutations can lead to sporadic cancers. Furthermore, biallelic pathogenic variants of SDHA, SDHB, SDHD and SDHAF2 genes lead to mitochondrial complex II deficiency.
Similarly, biallelic FH variants are known to cause fumaric aciduria, a rare metabolic disease. Therefore, the risk of having affected children should be explained during genetic counselling. Molecular diagnosis is important for personalized surveillance strategies and risk assessment for family members. This case series contributes to the literature and increases awareness for this rare hereditary cancer syndrome.
Keywords: FH, HLRCC, Mitochondrial Tumor Suppressors, PGL/PCC, SDHx

Table 1. Characteristics of patients with a germline pathogenic/likely pathogenic variant in SDHx and FH genes.

Case	Age	Gender	Clinical Indication	Family history	Segregation Data	Gene	Variant	Classification
#1	35	M	Family history	+ (PCC)	+ (2 carriers)	SDHA (NM_004168.4)	c.1765C>T p.(Arg589Trp)	Pathogenic
#2	56	F	PCC+GIST	-	+ (3 carriers)	SDHB (NM_003000.3)	c.422C>T p.(Pro141Leu)	Likely Pathogenic
#3	57	M	HNPGL	+ (HNPGL)	-	SDHD (NM_003002.4)	c.209G>T p.(Arg70Met)	Likely Pathogenic
#4	45	M	HNPGL	+ (HNPGL)	+ (9 carriers)	SDHD (NM_003002.4)	c.209G>T p.(Arg70Met)	Likely Pathogenic
#5	24	F	HNPGL	+ (HNPGL)	-	SDHD (NM_003002.4)	c.166del p.(His56Ilefs*30)	Likely Pathogenic
#6	49	F	Family history	+ (RCC, PC, Leukemia, GC)	+ (4 carriers)	FH (NM_000143.3)	c.1127A>C p.(Gln376Pro)	Pathogenic
#7	46	F	BC	+ (Leukemia)	-	FH (NM_000143.3)	c.585G>A p.(Met195Ile)	Likely Pathogenic
#8	37	F	Uterine leiomyoma	+ (EC, LC)	-	FH (NM_000143.3)	c.701C>T p.(Thr234Ile)	Pathogenic

Abbreviations: BC: Breast cancer, EC: Endometrial cancer, GC: Gastric cancer, GIST: Gastrointestinal stromal tumor, HNPGL: Head and neck paraganglioma, LC: Lung cancer, PC: Pancreatic cancer, PCC: Pheochromocytoma, RCC: Renal cell carcinoma.

[Abstract:0155]

Retrospective Evaluation of Ovarian Cancer Cases Analyzed by Hereditary Cancer Panel

Beyza Adaçoğlu[1], Süheyla Emre1, Filiz Özen[1], Elif Yılmaz Güleç[2]

[1]Clinic of Medical Genetics, İstanbul Göztepe Prof. Dr. Suleyman Yalcin City Hospital, İstanbul, Türkiye
[2]Department of Medical Genetics, İstanbul Medeniyet University Faculty of Medicine, İstanbul, Türkiye

Objective: Ovarian cancer is the second most common gynecologic malignancy and the second leading cause of death from gynecologic cancer. 20% of ovarian cancer cases are hereditary and several associated loci have been identified. While BRCA1 and BRCA2 germline mutations constitute
%65-85 genetic abnormalities in hereditary ovarian cancer, several other suppressor genes and oncogenes have been associated with hereditary ovarian cancer. We evaluated hereditary cancer panel results of 171 patients diagnosed with ovarian cancer who admitted to our clinic between 2022 and 2024.
Materials-Methods: 172 patients diagnosed with ovarian cancer were evaluated. A total of 60 genes were analyzed within the scope of the hereditary panel.The analysis utilized the ClinVar database and current literature.Variants were assessed according to ACMG criteria relevant to the patient's clinical profile being reported.
Results: According to the panel results,pathogenic variants were identified in 30 (17.44%) patients.Among these,14 (8.13%) were BRCA2 mutations, 7 (4.06%) were BRCA1 mutations, 3 (1.74%) were MUTYH, 3 (1.74%) were RAD51C mutations and 2 (1.16%) were FANCC mutations. Likely pathogenic variants were detected in 17 (9.94%) patients,with mutations identified in various genes.In 47 (27.48%) patients, no variants associated with ovarian cancer syndromes were found.
Conclusion: This study provides insight into the genetic factors involved in ovarian cancer and compares our findings with the existing literature. The rate of genetic alterations in our cohort was 26.9%, higher than the typical rate of 20% reported in the literature. This underlines the value of genetic analysis in the diagnosis and treatment of ovarian cancer. In contrast to the literature where BRCA1 mutations are more common, the frequency of BRCA2 mutations was higher in our study. This finding warrants further research on the role of BRCA2 in the pathogenesis of ovarian cancer. In addition, the detection of FANCC mutations in 3 patients is higher than reported, suggesting more common role of FANCC. Our findings emphasize the importance other gene variants in addition to BRCA mutations in the pathogenesis of ovarian cancer underline the importance of considering these genetic factors in clinical management.
Keywords: hereditary ovarian syndromes, ovarian cancer, BRCA1, BRCA2

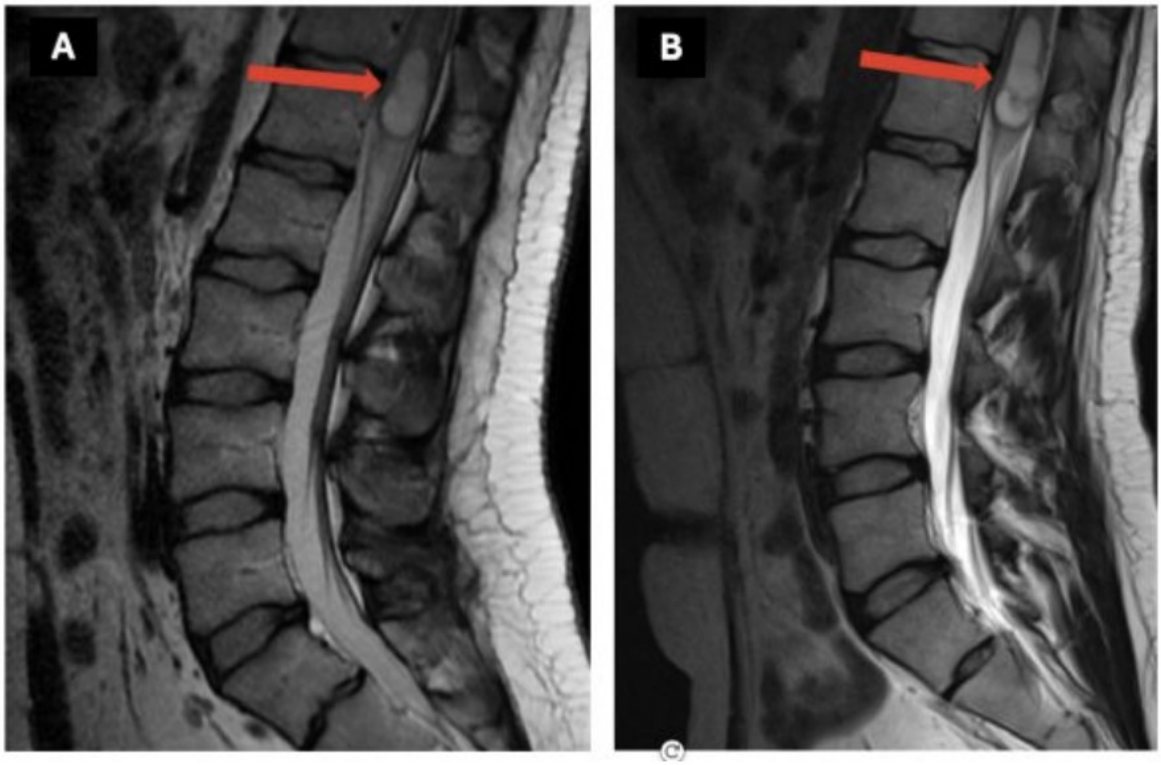
[Abstract:0156]

Belzutifan for VHL Syndrome: Managing RCC and CNS Hemangioblastomas – A Case Report

Hatice Bölek, Yüksel Ürün
Department of Medical Oncology, Ankara University Faculty of Medicine, Ankara, Türkiye

Objective: The Von Hippel-Lindau (VHL) gene, located on chromosome 3p25–26, is a tumor suppressor gene. VHL disease is characterized by the development of renal cell carcinoma, retinal angiomas, central nervous system hemangioblastomas, pheochromocytomas, paragangliomas, pancreatic neuroendocrine tumors, and cysts in the pancreas and kidneys.
Case: A 26-year-old male with a known history of Von Hippel-Lindau (VHL) syndrome and no prior medications was admitted to our clinic. In 2016, the patient underwent nephron-sparing surgery for an incidentally detected mass in the right kidney, which was confirmed as clear cell renal cell carcinoma (ccRCC) on pathology. In 2021, a mass in the contralateral kidney was treated with nephron-sparing surgery, and pathology revealed grade 2 ccRCC.Genetic analysis identified a heterozygous VHL gene mutation (c.481>T, p.R161*), which was also detected in the patient's father.In March 2022, the patient underwent another nephron-sparing surgery for a mass in the right kidney, and pathology again confirmed ccRCC. Magnetic resonance imaging (MRI) in January 2022 revealed multiple spinal cord lesions, including a dominant lesion measuring 1.5x1.5x4 cm at the T11-12 level, suggestive of hemangioblastomas. By January 2023, the lesion at the T11-12 level increased to 30x15 mm (Figure 1), and the patient underwent spinal surgery. Pathology revealed a grade 1 hemangioblastoma.In May 2023, he was admitted to our clinic. At the time of the admission to our department, brain and spinal MRI showed multiple lesions in the cerebellum, with the largest measuring 14x6 mm, and multiple hemangioblastomas in the spinal cord. Abdominal computed tomography (CT) revealed multiple cysts in bilateral kidneys and nodular lesion in the right kidney consistent with RCC. Additionally multiple cysts were identified in pancreas.The patient was started on belzutifan at 120 mg/day in May 2023.
Follow-up imaging in December 2023 demonstrated a partial response in the renal lesions and stability of the hemangioblastomas. The patient continues treatment with belzutifan without any drug-related toxicities.
Conclusion: VHL syndrome is the most well-known and common hereditary form of clear cell renal cell carcinoma. Currently, the HIF-alpha inhibitor belzutifan is the only approved treatment option for these patients.
Keywords: belzutifan, hemangioblastoma, kidney cancer, von hippel lindau disease

Figure 1



Hemangioblastoma at the T11-12 level in January 2022 (A) and January 2023

[Abstract:0158]

Somatic tp53 Mutation Detection and Clonal Hematopoiesis in Hereditary Cancer Panel

Zeynep Nur Paralı, Zeki Sakallı, Haluk Akın, Aslı Ece Solmaz
Department of Medical Genetics, Ege University Faculty of Medicine Hospital, İzmir, Türkiye

Objective: Clonal hematopoiesis of indeterminate potential (CHIP) refers to the presence of at least one driver mutation in hematopoietic cells in peripheral blood without hematologic malignancy. The accumulation of somatic mutations in HSCs occurs in an age-dependent manner. Somatic mutations in blood indicative of clonal hematopoiesis of indeterminate potential (CHIP) are associated with an increased risk of hematologic malignancy, coronary artery disease, and all-cause mortality. It is also common in patients with solid tumors who have received chemotherapy and is associated with poor prognosis.

Case: The first case was a 74-year-old woman, who underwent left partial mastectomy and radiotherapy for breast cancer at the age of 41. The patient was admitted to us at the age of 69 for her second primary myoepithelial metaplastic triple negative breast cancer. In 2019, BRCA1-2 mutation screening and MLPA results were negative. In 2023, the patient represented to us due to a family history of cancer and a hereditary cancer panel was planned. The second case was an
83-year-old male patient, 81 years old with known hypertension, diabetes, renal failure and CLL. The patient presented to our outpatient clinic with multiple polyps in colonoscopy and a hereditary cancer panel was planned.

Conclusion: The first patient had a variant allele fraction of 29% TP53:c.742C>T and the second patient had a variant allele fraction of 28% TP53:c.395A>C. Both patients were referred to the hematology department for frequent follow-up. Somatic mutations found in germline mutation scans performed by NGS method are important in the prognosis and follow-up of patients with hematologic cancers. Therefore, we present this case to emphasize the importance of referring patients to the relevant unit for detailed follow-up by considering the Variant Allele Fraction.

Keywords: CHIP, NGS, Somatic, tP53, VAF

[Abstract:0159]

Frequency of Cancer Predisposition Variants as Secondary Findings in Clinical Exome Sequencing Data: One Center Experience

Emine Merve Aydın[1], Mukaddes Feyza Baltacı[1], Filiz Özen[2], Elif Yılmaz Güleç[1]

[1]Clinic of Medical Genetics, Istanbul Goztepe Prof. Dr. Süleyman Yalcin City Hospital, Istanbul, Türkiye; Department of Medical Genetics, İstanbul Medeniyet University, Faculty of Medicine, Istanbul, Türkiye
[2]Clinic of Medical Genetics, Istanbul Göztepe Prof. Dr. Süleyman Yalcin City Hospital, Istanbul, Türkiye

Objectives: Next generation sequencing (NGS) and multigene panel testing is a common molecular diagnostic test for individuals with multigenic and/or undiagnosed rare genetic disorders. In addition to the primary indication for testing, genetic information about diseases that do not yet cause clinical symptoms or predisposition to multifactorial diseases as hereditary cancers can be detected. In this study, we aimed to infer the prevalence of cancer predisposition in the general population based on the secondary findings of NGS data analyzed patients.
Materials-Methods: Clinical Exome Sequencing data used for multigene panel testing and NGS testing for 3000 patients who were admitted to Istanbul Göztepe Süleyman Yalçın City Hospital Medical Genetics Department during 2023-2024 were reviewed. On the Illumina NextSeq 500 platform, genes covered by the Hereditary Cancer Panel (Sophia) kit panel were screened in NGS analyses as secondary, incidental findings and pathogenic/likely pathogenic variants were documented.
Results: Pathogenic or likely pathogenic variants associated with hereditary cancers were identified as secondary findings in 44 of 3,000 individuals (1.47%).In this study, pathogenic/likely pathogenic variants were identified in the following genes:APC(1), ATM(2), AXIN2(1), BRCA1(6), BRCA2(9), BRIP1(1), CHEK2(2), MLH(3), MSH2(2), MSH6(3), MUTYH(6), NBN(1), NF1(1), PALB2(2), PTEN(1), RAD51D(1), RAD54L(1), RNASEL(1), SEC23B(1), and TP53(1).
Conclusion: This study is the largest cohort conducted in our country and presents the frequency of secondary findings related to cancer in NGS sequencing. In approximately 1% of patients, pathogenic/likely pathogenic variants in genes associated with cancer susceptibility were detected.This rate is similar to previous studies conducted in a smaller group of patients in Türkiye and shows that 1 out of every 100 people in our country has a high risk for hereditary cancers.
Detection of variants that predispose to high cancer risk enables early diagnosis and treatment of patients through appropriate cancer screening programs.
Keywords: Hereditary Cancer, Clinical Exome Sequencing, Secondary Findings

[Abstract:0160]

Non-BRCA High Penetrance Genes in Patients with Breast Cancer: What's the Overall Etiological Rate?

Ayşe Ceren Sağdıç[1], Ahmet Cevdet Ceylan[2], Mustafa Altan[1], Mehmet Ali Nahit Şendur[3], Birol Korukluoğlu[4], Büşranur Çavdarlı[2]

[1]Department of Medical Genetics, Ankara City Hospital, Ankara, Türkiye
[2]Department of Medical Genetics, Ankara City Hospital, Ankara, Türkiye; Faculty of Medicine, Department of Medical Genetics, Ankara Yıldırım Beyazıt University, Ankara, Türkiye
[3]Department of Medical Oncology, Ankara City Hospital, Ankara, Türkiye; Department of Medical Oncology, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye
[4]Clinic of General Surgery, Ankara City Hospital, Ankara, Türkiye

Objective: Hereditary factors are responsible for approximately 20% of breast cancers, and variants in the BRCA1 and BRCA2 genes account for 25% of familial breast cancer cases.In addition to BRCA1-2, other genes such as TP53,PTEN,STK11,CHEK2,ATM,CDH1,BRIP1 and PALB2 also contribute to hereditary breast cancer, but are less common and usually associated with intermediate penetrance.Hereditary breast cancer(HBC) without BRCA1-2 variants are often referred as "non-BRCA" breast cancer and represents a significant proportion of HBC cases. Approximately 25% of hereditary cases are caused by mutations in a rare and highly penetrant gene that increases the risk of developing breast cancer to 80%.Our study aimed to investigate the genes(CDH1,PALB2,PTEN,STK11,TP53) reported as high penetrant for breast cancer in the NCCN Guidelines and for which screening is recommended in patient with breast cancer.

Materials-Methods: Data of 177 patients who were followed up with breast cancer between 2019-2024 years, who underwent normal BRCA1/BRCA2 sequence analysis and MLPA, and who underwent a "Familial Cancer Panel" or "Non-BRCA HBC Panel" due to family history or personal HBC risk indications were retrospectively investigated.Pathogenic/likely pathogenic and clinically uncertain significance variants in CDH1,PALB2,PTEN,STK11,TP53 genes were examined according to family history, age at diagnosis and histopathological features.

Results: No variant was detected in 79 out of 177 patients (44.3%). Variants in a cancer susceptibility gene were detected in 98 patients; 22(12%) had CHEK2 and 15(8%) had ATM variants.While high-penetrance non-BRCA gene variants were detected in only 9 patients(5%),the PALB2 gene variant was detected most frequently in this group.Variants were examined according to ACMG classification, age at diagnosis, family history, pathological features[Table 1].The mean age at diagnosis of the patients was 43.2 years. The most common family history of the patients was breast cancer, followed by lung and hematological malignancies.

Conclusion: Investigating non-BRCA HBC is crucial to developing targeted screening and prevention strategies.Identifying specific genetic mutations can aid in the clinical management of patients and potentially lead to more effective surveillance and treatment options.In conclusion, identifying and characterizing relevant genetic variants will be key to improving diagnosis, treatment,prevention and long term follow up strategies for affected individuals.

Keywords: Breast cancer, hereditery, high penetrance genes, non-BRCA

TABLE 1: Clinical Features and Variant Classification of the Patient with a High Penetrant Gene Variants(CDH1,PALB2,PTEN,STK11,TP53)

PATIENT	VARIANT	ACMG CLASSIFICATION	AGE OF DIAGNOSIS	MEDICAL/ FAMILY HISTORY	PATHOLOGY
1	"PALB2(NM_024675.3):c.932_933insC p.(K311fs*10) Heterozygous "	Pathogenic	40	Second Primary: Malignant Melanoma, Her sister has a history of pancreatic cancer.	Carcinoma Metastasis: ER 90%, PR 5%, Cerb-B2 score:+2
2	"PALB2(NM_024675.4):c.833_834delTAinsAT p.(L278H) Heterozygous "	Variant of Uncertain Significance	42	Her aunt has a history of breast cancer.	Invasive Lobular Carcinoma ER 91-100%, PR 81-90%, Cerb-B2 Score:2 Loss of E-cadherin and Beta Catenin expression
3	"PALB2(NM_024675.4):c.557dup p.(Asn186fs) Heterozygous "	Pathogenic	44	Her aunt has a history of breast cancer.	N/A

4	"PALB2(NM_024675.3):c.3122A>C p.(K1041T) Heterozygous "	Variant of Uncertain Significance	47	Her aunt has a history of breast cancer.	Ductal Carcinom a Insitu ER-, PR 91-100%
5	"PTEN(NM_000314.8):c.209+4_209+7delAGTA Heterozygous "	Pathogenic	45	Her father has a history of thyroid cancer, her cousin(uncle's son) has a history of skin cancer.	Ductal Carcinom a Insitu ER-, PR-, Cerb-B2 Score:0
6	"CDH1(NM_004360.4):c.796G>T p.(Val266Phe) Heterozygous "	Variant of Uncertain Significance	39	Her sister has a history of breast cancer, her brother has a history of leukemia, her cousin(aunt's son) has a history of lung cancer.	N/A
7	"CDH1(NM_004360.5):c.1867A>T p.(T623S) Heterozygous STK11(NM_000455.5):c.694T>A p.(S232T) Heterozygous "	Variant of Uncertain Significance	44	Her mother has a history of leukemia.	N/A

8	"TP53(NM_000546.6):c.455C>A p.(P152Q) Heterozygous "	Likely Pathogenic	53	A sibling has a history of liposarcoma, another sibling has a history of gastric cancer, the mother has a history of pancreatic cancer, two aunts have a history of breast cancer and one cousin(uncle's daughter) and another cousin(aunt's daughter) also have a history of breast cancer.	N/A
9	"TP53(NM_000546.6):c.524G>A p.(R175H) Heterozygous "	Pathogenic	35	Her sister has a history of breast cancer, her father has a history of lung cancer, her aunt has a history of breast cancer and her daughter has a history of B-ALL(B-cell Acute Lymphoblastic Leukemia).	N/A

[Abstract:0162]

PMS2 and PMS2CL: Case report and review of the literature

Semih Aşıkovalı[1], Hilmi Tozkır[1], Bilçağ Akgün[2]

[1]Department of Medical Genetics, Tekirdağ Namik Kemal University, Tekirdağ, Türkiye
[2]John P. Hussman Institute for Human Genomics, University of Miami, Miami, USA

Objective: Heterozygous germline pathogenic variants (gPV) in the PMS2 gene that DNA mismatch repair gene, are responsible for Lynch Syndrome (LS). Carriers are at a higher risk of developing
LS-related cancers, particularly colorectal and endometrial cancers. Molecular diagnosis for PMS2 gPVs is complicated by numerous pseudogenes sharing sequence homology with PMS2, particularly the pseudogene PMS2CL.
Case: A 66-year-old women was diagnosed at 55 with left unilateral triple negative breast cancer. The patient's father was diagnosed with prostate cancer at the age of 62. Due to the hormon-negative breast cancer and family history, the patient was considered molecular testing for the multigene panel was offered. Following the informed consent process, analyzed by Next-Generation Sequencing (NGS) through the DNBSEQ-G400 platform using Twist Clinical Exome v.2 amplification kit. After in-house standard bioinformatic processes, a heterozygous germline variant in PMS2 (NM_000535.7) c.2186_2187del (rs587779335) was detected. Due to pseudogenes of PMS2, gene-specific PCR and Sanger sequencing was performed. It was shown that there was no mutation in the 13th exon of the PMS2 gene with this approach.
Conclusion: This study indicated the significance of implementing specific strategies to prevent misinterpretation of pathogenic PMS2 variants. Considering the limitations of short-read NGS distinguishing between particular regions of PMS2 and PMS2CL, using complementary methodologies are required to provide an accurate diagnosis.
Keywords: PMS2, Pseudogene, PMS2CL

[Abstract:0163]

RET Variants in Cancer Predisposition: Risk Management Lessons from a Single-Center Cohort

Afife Büke, Ezgi Çevik Demir, Hanife Saat, Elifcan Taşdelen, Ahmet Kablan, Haktan Bağış Erdem
Department of Medical Genetics, Etlik City Hospital, Ankara, Türkiye

Objective: The REarranged during Transfection (RET) proto-oncogene encodes a receptor tyrosine kinase. Germline pathogenic/ likely pathogenic(P/LP) gain-of-function variants of the RET proto-oncogene cause multiple endocrine neoplasia type 2 (MEN2), which is associated with an increased risk of medullary thyroid carcinoma (MTC), pheochromocytoma, and other malignancies.
This retrospective study aimed to evaluate the genotype-phenotype correlation of RET proto-oncogene variants, in addition to addressing early diagnosis and clinical management in variant carriers.
Materials-Methods: This study retrospectively analyzed cases in which hereditary cancer panel and RET sequence analysis were performed at the Etlik City Hospital Medical Genetics Department from October 2022 to December 2024. All patients' family history, personal information, and clinical information were collected from the digital medical archive.
Results: RET P/LP variants were detected in 14 cases diagnosed with cancer and in 10 cases by segregation analysis. Mean ages were 49 (27-71) and 33 (6-70) years, respectively. The distribution of the frequency of the detected RET mutations and according to the diagnosis is summarized in Table 1.
Conclusion: The RET genotype provides the basis for MEN2 risk classification. To determine hereditary MTC, the recommended timing of early thyroidectomy, and the follow-up intervals of associated clinics, The American Thyroid Association (ATA) standardized risk categorization based on the codon position of the PV. RET is a key oncogene not only in the development of MEN2, but also in other malignancies. Presence of RET somatic alterations has been documented in PTC, lung and breast cancers, but data on the frequency of RET germline PVs in other cancers not associated with MEN2 are limited. Increasing use of multigene panel testing has also revealed RET PVs in other cancers such as breast carcinoma, colorectal carcinoma, meningioma, gastrointestinal stromal tumor and hepatoma. In this study, the RET p.V804M variant was detected in 2 breast cancer and 1 polyposis coli cases without MEN2-related clinical features or family history. Therefore, further studies are needed to clarify the role of RET germline variants in such cases. In conclusion, molecular diagnosis plays a vital role in guiding risk assessment and management through genotype-phenotype correlation in RET variant carriers.
Keywords: Breast Cancer, Hereditary Medullary Thyroid Carcinoma, Multiple Endocrine Neoplasia, RET

Table 1. Distribution of RET mutations detected in the study cohort by diagnosis and summary of ATA recommendations for variants in the cohort

Variants	Frequency and diagnoses in our cohort	ATA recommendations			
		MTC risk level	Incidence of PHEO	Incidence of HPTH	Age of prophylactic thyroidectomy
Val804Met	2 2 1 3	Moderate	+	+	When calcitonin raise After 5 years
Cys620Arg	1 0	Moderate	+/++	+	When calcitonin raise After 5 years
Cys609Ser	2	Moderate	+/++	+	When calcitonin raise After 5 years
Glu768Asp	0	Moderate	-	-	When calcitonin raise After 5 years
Leu790Phe	1 1	Moderate	+	-	When calcitonin raise After 5 years
Ser891Ala	0	Moderate	+	+	When calcitonin raise After 5 years
Cys634Trp	2	High	+++	++	<5years
Met918Thr	0	Highest	+++	-	As soon as possible

MTC PHEO BREAST CA POLYPOSIS COLI SEGREGATION

Table 1. Distribution of RET mutations detected in the study cohort by diagnosis and summary of ATA recommendations for variants in the cohort (Accardo et al., 2017). Abbrevations: MTC: Medullary Thyroid Cancer, PHEO: Pheochromocytoma, HPTH: Hyperparathyroidism

[Abstract:0164]

The Incidence and Clinical Outcomes Following Prophylactic Risk-Reducing Salpingo-Oophorectomy in BRCA Mutation Carriers: A Single-Center Retrospective Study

Tuğçe Sırma[1], Konul Mehdiyeva[1], Lena Türeyici[1], Gürdeniz Serin[2], Göktuğ Aydoğan[2], Aslı Ece Solmaz[3], Haluk Akın[3], Ahmet Aydın Özsaran1, Mustafa Coşan Terek[1], Levent Akman[1], Nuri Yıldırım[1]

[1]Department of Obstetrics and Gynecology, Division of Gynecological Oncology, Ege University Faculty of Medicine, İzmir, Türkiye
[2]Department of Pathology, Ege University Faculty of Medicine, İzmir, Türkiye
[3]Department of Genetics, Ege University Faculty of Medicine, İzmir, Türkiye

Objective: The aim of this study was to determine the incidence of Secretory cell outgrowth (SCOUT), p53 signature, serous tubal intraepithelial lesion (STIL), serous tubal intraepithelial carcinoma (STIC) and occult invasive cancer (OC) in patients with BRCA1 and/or 2 patogenic variants and to evaluate clinical outcomes and the risk of developing primary peritoneal carcinoma (PPC) in the follow-up period.
Materials-Methods: This study is a single center retrospective clinical study. We evaluated 63 patients with BRCA mutations. The treatment approach was prophylactic risk-reducing salpingo-oophorectomy (RRSO) according to Sectioning and Extensively Examining the Fimbriated end of the fallopian tube (SEE-FIM) protocol and immunohistochemical staining. The patients had proven BRCA1-2 variants, but had no personal history of ovarian, peritoneal, or fallopian tube cancer, and there was no preoperative sign of malignancy.
Results: Out of 63 patients, 29 women were identified as carrying a mutation in the BRCA1 gene, while 33 were identified as carrying a mutation in the BRCA2 gene. One patient had both a BRCA 1 and 2 mutation. The mean age at surgery was 45.9 years (range, 34 to 71 years). In total, 10 (15.8%) SCOUTs, 4 (6.3%) p53 signatures and 3 (4.7%) STILs were observed. One patient with isolated STIC was detected which was identified in both BRCA1 and 2 mutations and did not undergo restaging surgery or adjuvant chemotherapy. After diagnosis of STIC at RRSO, PPC did not develop during 23 months.
Conclusion: Out of 63 patients, 29 women were identified as carrying a mutation in the BRCA1 gene, while 33 were identified as carrying a mutation in the BRCA2 gene. One patient had both a BRCA 1 and 2 mutation. The mean age at surgery was 45.9 years (range, 34 to 71 years). In total, 10 (15.8%) SCOUTs, 4 (6.3%) p53 signatures and 3 (4.7%) STILs were observed. One patient with isolated STIC was detected which was identified in both BRCA1 and 2 mutations and did not undergo restaging surgery or adjuvant chemotherapy. After diagnosis of STIC at RRSO, PPC did not develop during 23 months.
Keywords: BRCA, Risk-reducing salpingo-oophorectomy, Serous tubal intraepithelial carcinoma

[Abstract:0165]

A Novel Integrative Mutli-Class Hereditary Cancer Classifier Performs Outstanding Performance

Mustafa Tarik Alay, Haktan Bagis Erdem, Taha Bahsi, Afife Büke, Hanife Saat

Clinic of Clinical Genetics, Ankara Etlik City Hospital, Ankara, Türkiye

Objective: The majority of hereditary cancer gene missense variants reported in ClinVar remain unclassified as benign or pathogenic. Studies evaluating existing in silico tools have shown that their performance in classifying cancer-related variants is lower compared to their effectiveness in rare diseases. Therefore, there is a need to optimize existing algorithms and develop new approaches to predict the pathogenicity of these variants more accurately. In this study, we aimed to develop a novel method to optimize the classification of hereditary cancer variants using an integrative multi-class classifier.

Materials-Methods: As of December 2024, ClinVar contained 3,110,973 variants from 52,815 genes. Among these, 61 genes were identified as associated with hereditary cancers. The phenotypic relationships between these genes were assessed using semantic similarity algorithms. A total of 114,748 missense germline variants from these genes were included in the analysis. Among these variants, 105, 979 (92.36%) were classified as either variants of uncertain significance (VOUS) or variants with uncertain pathogenicity. The six primary classification categories in ClinVar were revised and harmonized using pairwise comparison. A total of 46 pathogenicity prediction tools were used to retrain these variants using the XGBoostTree algorithm. The newly trained model was then used to predict hereditary cancer panel results for 4,102 patients who were evaluated at Etlik City Hospital between 2022 and 2024.

Results: The XGBoostTree algorithm achieved 98% accuracy and F1-score in the training dataset. When tested on an independent dataset, the model achieved 98% accuracy and F1-score.
Additionally, the algorithm correctly classified all 53 pathogenic variants (100%) that were previously reported in our center. Moreover, it successfully imputed the pathogenicity of 4,000 VUS variants, which were clinically correlated by physicians at our center.

Conclusion: The clinical interpretation of VOUS remains a significant challenge in the field of cancer genetics. Our study aimed to overcome this issue by evaluating gene-to-gene phenotypic relationships and integrating multiple prediction tools.Furthermore, testing our model on a large patient cohort highlights its potential for clinical genetic practice. The proposed model could further enhance its performance when combined with rigid and adaptive classifiers.

Keywords: hereditary cancers, in silico tools, clinvar, XGBTree, Machine learning

AuthorToEditor: Çalışmamız, genetik danışma süreçlerinde belirsiz varyantların yorumlanmasına katkı sunarak klinik genetik pratiğini güçlendirmeyi hedeflemektedir. Proje kapsamında hastaların klinik verileri yalnızca anonimleştirilmiş formatta kullanılacak olup, herhangi bir bireysel kimlik bilgisi paylaşılmayacaktır. Bu bağlamda, çalışmamızın bilimsel açıdan değerlendirilmesi ve etik uygunluk açısından onaylanması hususunda gerekli işlemlerin başlatılmasını saygılarımızla arz ederiz.
Saygılarımla, Dr. Mustafa Tarık Alay

[Abstract:0166]

Evaluation of Cancer Panel Results in Cases Referred to Our Clinic with Suspected Hereditary Colorectal Cancer: Novel Variant

Edanur Bulut1, Zeynep Esener[1], Seray Saray[2], Yakup İriağaç[2], Hilmi Bolat[1]

[1]Department of Medical Genetics, Balıkesir University Faculty of Medicine, Balıkesir, Türkiye
[2]Department of Medical Oncology, Balıkesir Ataturk City Hospital, Balıkesir, Türkiye

Introduction: Colorectal cancers third most commonly diagnosed cancer and the second leading cause of cancer-related deaths in both sexes. This study focuses on the analysis of cancer panel results in cases referred to our Medical Genetics outpatient clinic between 2023 and 2024 with a preliminary diagnosis of hereditary colorectal cancer. We aim to evaluate the distribution and spectrum of detected mutations, including the identification of one novel variant.

Materials and Methods: This study included 23 cases diagnosed with colorectal cancer who were referred to the Medical Genetics Outpatient Clinic of Balıkesir University between between 2023 and 2024, with a preliminary diagnosis of hereditary colorectal cancer. Targeted next-generation sequencing (NGS) analysis was performed using a hereditary cancer panel.

Results: A total of 23 cases diagnosed with colorectal cancer were included in the study. The age range of the cases was 29 to 76 years, with a mean age of 50.4 years. Among these cases, 11 (47.83%) were found to have 15 different variants in genes associated with these syndromes. 5(33.33%) of the variants were classified as pathogenic or likely pathogenic. One was identified as novel. The cases with pathogenic/likely pathogenic variants (P/LP) had a mean age of 47.27 years. The distribution of P/LP variants was as follows: MLH1: 2 variants (40%), ATM: 1 variant (20%), CHEK2: 1 variant (20%),
MUTYH: 1 variant (20%)

Discussion: Our findings show that 21.74% of colorectal cancer cases presented with hereditary cancer syndrome variants, higher than the 10%-16% reported in the general population. The increased prevalence in our cohort can be explained by the fact that all cases were referred by oncology, and were likely selected based on clinical suspicion of a hereditary colorectal cancer syndrome. A novel variant was identified in our study. This emphasizes the importance of continuing research and genetic testing in the discovery of new mutations that could potentially be implicated in hereditary colorectal cancer syndromes.

Keywords: Hereditary cancer panel, hereditary colorectal cancer, novel

[Abstract:0167]

Detection of BRCA and Non-BRCA Variants in Breast Cancer Cases Using Next-Generation Sequencing: The Experience of Balıkesir University

Dilan Genç Akdağ[1], Zeynep Esener[1], Seray Saray[2], Yakup İriağaç[2], Hilmi Bolat[1]

[1]Department of Medical Genetics, Faculty of Medicine, Balıkesir University, Balıkesir, Türkiye
[2]Clinic of Medical Oncology, Balıkesir Ataturk City Hospital, Balıkesir, Türkiye

Objective: According to the Global Cancer Statistics report, breast cancer is the most commonly diagnosed cancer in women and ranks as the fifth leading cause of cancer-related deaths.
Approximately 90% of these cancers are sporadic, while 5-10% of cases show hereditary transmission. Germline causal variants in the BRCA1/2 genes are responsible for about a quarter of hereditary breast cancers. In this study, where we investigate the genetic predisposition of patients presenting with a diagnosis of breast cancer.
Materials-Methods: Between 04.12.2023 and 24.10.2024, 105 female patients who applied to the Balıkesir University Genetic Disorders Evaluation Center were included in the study. Initially, sequencing analysis of the BRCA1 and BRCA2 genes was performed in order. In cases where no mutations were detected through BRCA1/2 whole gene sequencing, a Non-BRCA multi-gene panel associated with cancer susceptibility was studied.
Results: In 33 cases (31.4%), a total of 35 different variants were identified, including 4 novel variants, that could be associated with hereditary breast cancer according to the NCCN guidelines. Of the identified variants, 15(14.29%) were pathogenic/likely pathogenic variants.The P/LP variants were detected as follows: 2 cases(13.33%) in BRCA2, 4 cases (26.67%) in BRCA1, 4 cases (26.67%) in
CHEK2, 1 case(6.67%) in ATM, 2 cases(13.33%) in NTHL1, 1 case (6.67%) in SLX4, and 1 case (6.67%) in MSH6.
Conclusion: The average age of the cases included in the study was 52.5.In our study, which was conducted on a group of cases meeting the NCCN criteria for hereditary breast cancer, we found the frequency of pathogenic/likely pathogenic variants in BRCA1 and BRCA2 to be 5.7%.Non-BRCA variants were detected in 8.5% of the cases. However, in several single-center studies from different geographical regions of Türkiye, the frequency of pathogenic/likely pathogenic variants in BRCA1 and BRCA2 has been reported to range between 8-21%. Due to the relatively small sample size in our study, we anticipate that our findings may be lower compared to the rates reported in the literature. Additionally, multi-gene panels are important for elucidating the molecular mechanisms in non-BRCA breast cancer cases and for assessing the patient and presymptomatic individuals in their family.
Keywords: BRCA, Breast Cancer, Non-BRCA

[Abstract:0168]

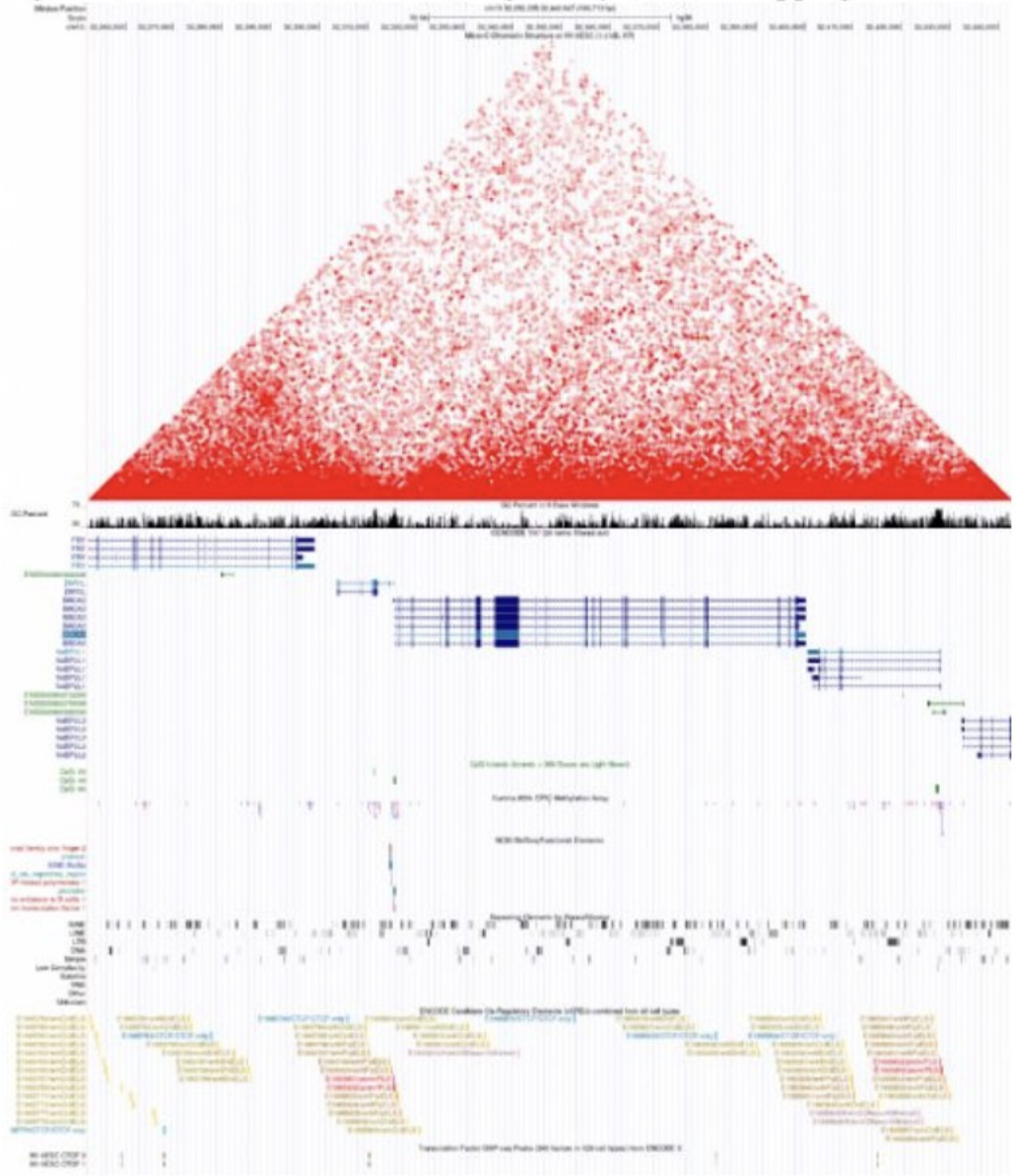
Bringing CTCF Germline Mutations into Focus: A Call to Action for Clinical Implications

Ali Torabi[1], Feyza Mermer[1], Sara Rafiei Gavgani[2], Büşra Göksel Tulgar[1], Burak Aktaş[1], Nadir Koçak[1], Ebru Marzioğlu Özdemir[1]

[1]Department of Medical Genetics, Selçuk University Faculty of Medicine, Konya, Türkiye
[2]Department of Biology, University of Ankara, Faculty of Science, Ankara, Türkiye

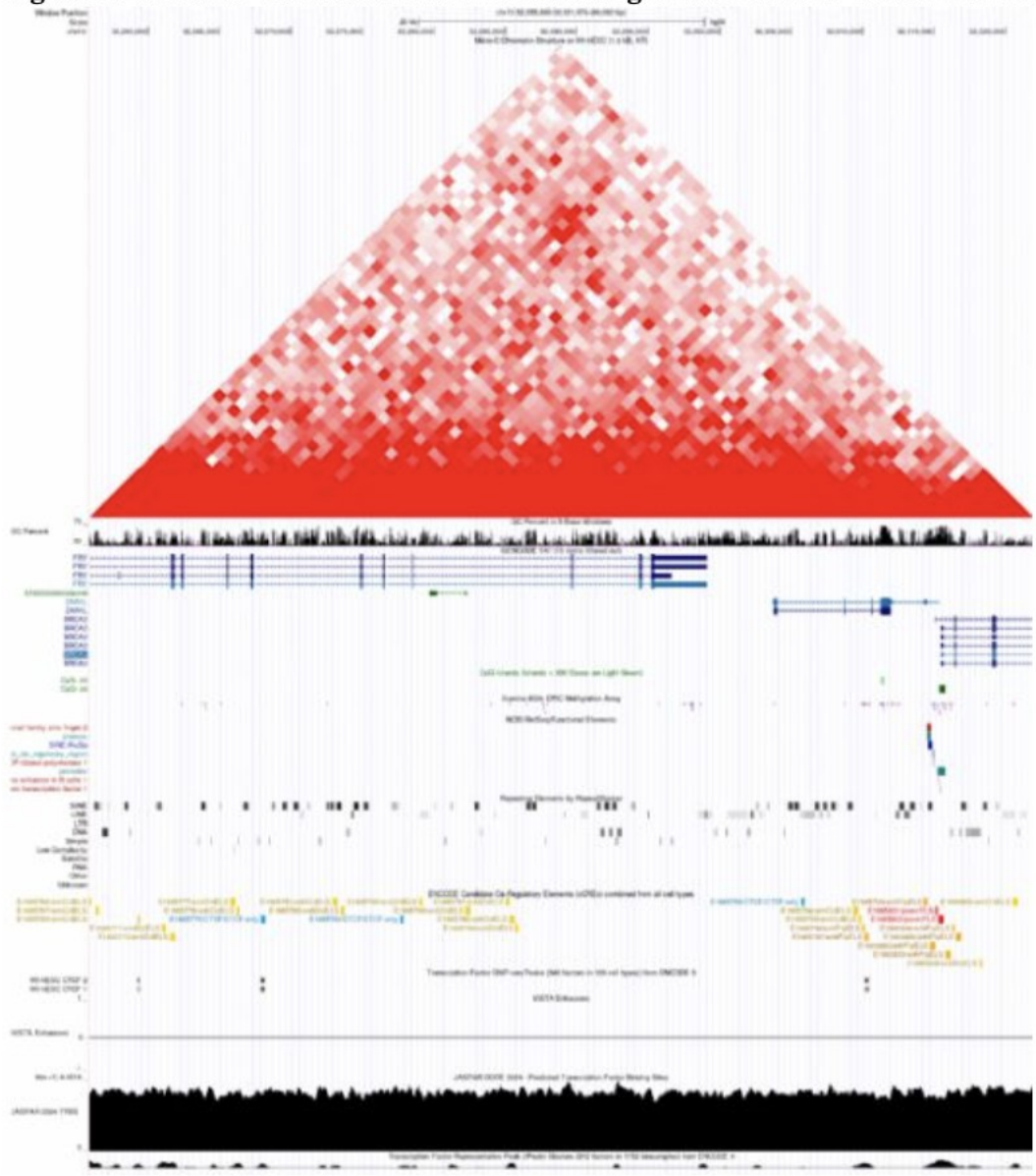
Objective: This study investigates the regulatory effects of CCCTC-binding factor (CTCF) germline mutations, focusing on their role in chromatin organization, DNA methylation, and transcriptional regulation. The research emphasizes CTCF's impact on the BRCA2 promoter and its broader implications for cancer pathogenesis.
Materials-Methods: Between January 2023 and July 2024, 650 patients presenting with suspected genetic conditions underwent clinical exome sequencing (CES) at Selçuk University. DNA samples were sequenced using the Roche CES kit and DNBSEQ-G400™ platform, with variant analysis performed on Genomize.SEQ. Of the 650 patients, 268 harbored CTCF variants. Quality filtering, segregation analysis, and clinical evaluations identified seven cases for detailed study. Multi-track genomic analysis via the UCSC Genome Browser was conducted, integrating data on CpG methylation, chromatin loops, histone modifications, and transcription factor binding sites (TFBS). These analyses aimed to uncover the regulatory mechanisms mediated by CTCF mutations.
Results: A notable case involved a 67-year-old patient with aggressive endometrial adenocarcinoma. Genomic analysis identified two CpG sites upstream of the BRCA2 promoter: a large CpG island (>300 bp) and a smaller CpG shore (<300 bp), with a methylation-sensitive CTCF binding site (CBS) located at the shore. Functional annotations revealed that CTCF, PARP1, and cohesin cooperatively regulated BRCA2 transcription via chromatin looping. High microsatellite instability (MSI-H), caused by MLH1 and PMS2 loss, further disrupted the regulatory landscape.The UCSC analysis uncovered additional regulatory elements, including Zinc Finger 2 and silencer elements, in the BRCA2 para-promoter region. Chromatin looping structures upstream of BRCA2 brought enhancer regions into proximity with its promoter, supporting dynamic transcriptional regulation. Nearby genes such as ZAR1L and FRY, involved in embryogenesis and genomic stability, respectively, were found to interact with BRCA2 through shared TFBS peaks, suggesting a coordinated regulatory network critical for genomic stability.
Conclusion: This study highlights CTCF's pivotal role in epigenetic regulation, emphasizing its influence on BRCA2 expression and cancer susceptibility. The findings underscore the necessity of integrating regulatory element analyses into genetic studies for improved diagnostics and targeted therapies.
Keywords: CTCF germline mutations, epigenetic regulation, BRCA2, chromatin looping, cancer pathogenesis

Figure 1: Chromatin structure and regulatory element mapping at the BRCA2 locus



This figure illustrates chromatin looping interactions at the BRCA2 promoter region using Micro-C chromatin heatmap analysis (top panel). Key regulatory features, including CpG islands, methylation profiles from the Illumina 850K EPIC array, and functional genomic elements (e.g., enhancers, silencers, and transcription factor binding sites), are annotated. CTCF binding sites and associated cis-regulatory elements are highlighted, demonstrating their potential role in transcriptional insulation and promoter activity.

Figure2: Extended chromatin interactions and genomic context of the BRCA2 locus



This figure presents a broader view of chromatin organization at the BRCA2 locus, integrating additional regulatory features from neighboring regions, including ZAR1L and FRY. The Micro-C chromatin heatmap (top panel) reveals long-range looping interactions, emphasizing coordinated regulation across multiple genes. Tracks for CpG methylation, transcription factor binding sites, and enhancer activity further underscore the complex interplay of regulatory elements influencing BRCA2 transcriptional dynamics.

The profile of detected CTCF variants in Endometrial Cancer Patiant

c.1208-212T>C	Intron Variant	chr16:67655133 T->C	rs7191281	Benign	AD | Intellectual developmental disorder, autosomal dominant 21	homozygous
c.*29T>G	3 Prime UTR Variant	chr16:67671804 T->G	rs6499137	Benign	AD | Intellectual developmental disorder, autosomal dominant 21	homozygous
c.1838-101_1838-100dup	Intron Variant	chr16:67670472 G->GTA	rs66893507	Benign	AD | Intellectual developmental disorder, autosomal dominant 21	heterozygous

Author To Editor: The scope and detail of this study are extensive and go far beyond what can be conveyed within the constraints of a 350-word abstract. We believe the findings and the methodology deserve a comprehensive explanation to fully showcase the significance of the work. Therefore, following the acceptance of this oral presentation at the congress, we plan to submit the full version—or at least an expanded version—of this research for publication in the Gazi Medical Journal. This will allow for a more in-depth discussion of the results and their broader implications. with regards Dr.Ali Torabi Main Authorm

[Abstract:0169]

An In Silico Analysis of Gene Co-occurrence Patterns in Colorectal Tumor Samples Using Whole Exome Sequencing

Talha Laçin, Ali Torabi, Batuhan Şanlıtürk, Nadir Koçak, Tülin Çora
Department of Medical Genetics, Selçuk University Faculty of Medicine, Konya, Türkiye

Objective: Colorectal cancer is among the most prevalent malignancies globally, characterized by complex genomic alterations. Understanding gene co-occurrence patterns in colorectal tumors can shed light on tumorigenesis and unveil potential therapeutic targets.
Materials-Methods: In this study, we performed an in silico analysis of gene co-occurrence patterns using publicly available whole exome sequencing (WES) data from the COSMIC database, comprising 80 colorectal adenocarcinoma patients.The analysis process was initiated by evaluating the frequency of co-occurring gene pairs across patients and comparing their observed and expected frequencies to assess the statistical significance of co-occurrence. Gene pairs with significant co-occurrence ($p < 0.05$) were further analyzed for functional and pathway-level annotations using the Reactome database for pathway analysis and the 3D Genome Browser for structural genomic insights. Additionally, STRING and BioGRID databases were used to explore potential functional and protein-protein interactions.
Results: The analysis identified gene pairs with potentially significant co-occurrence in colorectal tumors. Among the notable gene pairs identified were GOLGA5-RABEP1 and JAK2-PML, which exhibited significant co-occurrence. Structural genomic and pathway-level analyses revealed potential functional and regulatory relationships among these gene pairs.
Conclusion: This in silico study demonstrates the power of publicly available WES data in uncovering gene co-occurrence patterns in colorectal tumors. The integration of functional and structural analyses provides a comprehensive understanding of the biological relevance of these co-occurring genes.
These findings provide a foundation for future experimental validation and the discovery of novel biomarkers or therapeutic targets in colorectal cancer.
Keywords: Colorectal cancer, gene co-occurrence, in silico analysis, whole exome sequencing

[Abstract:0171]

RUNX1-related monosomy 7 predisposition syndrome: A case of acute myeloid leukemia

Ekin Alpaslan[1], Serap Kirkiz Kayalı[2], Emine Yılmaz Orulluoğlu[2], Gülsüm Kayhan[1]

[1] Department of Medical Genetics, Gazi University Faculty of Medicine, Ankara, Türkiye
[2] Department of Pediatric Hematology, Gazi University Faculty of Medicine, Ankara, Türkiye

Introduction: Monosomy 7 predisposition syndromes (M7PS) are characterized by bone marrow failure, immunodeficiency and an increased risk for myeloid malignancies. One of these syndromes, "platelet disorder, familial, with associated myeloid malignancy (FPDMM)", results from heterozygous germline pathogenic variants in the RUNX1 gene and has been reported in less than 1% of M7PS patients.
Materials-Methods: A 5-year-old female patient was diagnosed with aplastic anemia at the age of 3. There was no family history. Chromosome analysis, DEB, and NGS-based panel tests were performed on the peripheral blood sample. Sanger sequencing analysis was performed on the parents' blood and the patient's intestinal tissue samples.
Results: Chromosome analysis and DEB test were found to be normal. In NGS analysis, the heterozygous c.280A>C (p.Ser94Arg) variant was detected in the RUNX1 gene and interpreted as likely pathogenic. In addition, the heterozygous c.181C>A (p.Gln61Lys) (Q61K) variant, which is a somatic variant frequently detected in malignant neoplasms, was detected in the NRAS (NM_002524.5) gene. CNV analysis also revealed monosomy 7. In Sanger analysis of intestinal FFPE tissue from the patient's previous intussusception surgery, the RUNX1 variant was heterozygous, while the c.181C region in the NRAS gene was normal. Therefore, the RUNX1 variant was considered germline, and the NRAS variant was a somatic mutation resulting from clonal hematopoiesis. This result was compatible with FPDMM and "monosomy 7 predisposition." The parents' analysis was normal for both variants. Following these results, the patient was diagnosed with acute myeloid leukemia (AML) after examinations for myeloid malignancies.
Conclusion: Somatic variants in the NRAS gene and monosomy 7 have been reported in individuals with germline variants in the RUNX1 gene who developed myeloid malignancy. Germline predisposition rapidly progresses to MDS or AML after the development of monosomy 7. The present patient was evaluated with suspicion of myeloid malignancy after genetic analysis and was diagnosed with AML. As this case exemplifies, with the precise application of genetic test algorithms, it will be possible to rapidly diagnose patients, determine their prognosis, and plan appropriate treatments.
Keywords: Acut myeloid leukemia, Monosomy 7, NRAS, RUNX1

[Abstract:0172]

TP53 Gene Variant Spectrum Screened for Various Cancers

Aydeniz Aydın Gümüş[1], Pelin Ercoşkun[1], Ezgi Gökpınar İli[2], Nazım Can Demircan[3]

[1] Clinic Genetics Department, University of Health Sciences, Başakşehir Çam and Sakura City Hospital, İstanbul, Türkiye
[2] Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Türkiye
[3] Clinic of Medical Oncology, University of Health Sciences, Başakşehir Çam and Sakura City Hospital, İstanbul, Türkiye

Objective: TP53 is a gene located in the chromosomal region 17p13.1, which is famous for coding the tumor suppressor protein called p53 primarily responsible for DNA repair by arresting the cell cycle or, if repair is not achieved, to undergo programmed cell death, preventing tumor growth. Somatic mutations of TP53 are more common, but germline mutations also predispose to a variety of cancers, such as Li-Fraumeni Syndrome. In chronic lymphocytic leukemia (CLL), 4-10% have 17p deletion, which includes the tumor suppressor protein (TP53) gene, at the time of diagnosis. The aim of this study is to examine the TP53 mutation spectrum of patients examined for various cancers in our center.
Materials-Methods: The TP53 gene was studied using next-generation sequencing analysis from DNA isolated from 37 bone marrow, 171 peripheral blood samples sent to the Genetic Diseases Evaluation Center of Başakşehir Çam and Sakura City Hospital between 2021 and 2024.
Results: A total of 28 likely pathogenic/pathogenic variants were detected, 16 of which were from bone marrow/peripheral blood samples of CLL patients and 12 from peripheral blood samples of patients with solid organ tumors.
Conclusion: The mutation rate detected by NGS of CLL patients is 9%. 4 of these mutations are deletions and 14 are missense changes. Of the other 12 patients with pathogenic mutations, 9 had breast cancer, 2 had breast and endometrial cancer, and 1 had breast and ovarian cancer. Knowing the TP53 variant spectrum is an important element in facilitating the follow-up of oncological patients.
Keywords: TP53, leukemia, breast, cancer

[Abstract:0173]

Pathogenic BRCA Mutations and Coexisting Cancer Susceptibility Variants: Highlighting the Importance of Multigene Panel Testing

Esma Kayılıoğlu[1], Gülay Güleç Ceylan[2], Büşranur Çavdarlı[2], Burcu Sağlam Ada[1], Didem Şener Dede[3], Cavidan Nur Semerci Gündüz[2]

[1]Department of Medical Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Medical Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye; Department of Medical Genetics, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye
[3]Department of Medical Oncology, Ankara Bilkent City Hospital, Ankara, Türkiye; Department of Medical Oncology, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye

Objective: Hereditary cancer susceptibility involves a broad spectrum of genetic factors, with various genes contributing to cancer onset and progression. Among these, the BRCA1 and BRCA2 genes are among the best-characterized and most frequently associated with inherited cancer risk, particularly in breast, ovarian, pancreatic, and prostate cancers. The prevalence of pathogenic BRCA mutations in the general population is approximately 1 in 400, which is relatively high. However, even in individuals with a pathogenic BRCA mutation, additional hereditary cancer risks may exist, especially when the family history includes cancers unrelated to BRCA mutations. This highlights the importance of multigene panels in assessing additional susceptibility genes for comprehensive risk evaluation.
Materials-Methods: This study included patients with significant BRCA variants, identified through the Hereditary Cancer Panel conducted at our center between 2019 and 2024. The panel examines 61 cancer susceptibility genes using Next-Generation-Sequencing (NGS) technology. All detected variants were classified according to ACMG guidelines. Variants-of-uncertain-significance (VUS) were further subclassified as VUS-LB(likely benign) or VUS-LP(likely pathogenic) based on their proximity to either classification. For patients with BRCA mutations, additional variants, family histories and segregation analyses were evaluated.
Results: A total of 20 patients with pathogenic or likely pathogenic BRCA mutations were identified through the Hereditary Cancer Panel. In these patients, multigene panels were preferred over BRCA-only testing due to diverse cancer types in their family histories. Of these, 7 had BRCA1 mutations, and 13 had BRCA2 mutations. Among the 20 patients, no additional variants were detected in 10. In the remaining 10 patients, 6 VUS-LP variants were identified in MSH6, RAD51B,
POLD1, CHEK2, ATM, and VHL genes. The personal and family histories of these patients revealed a variety of cancers, including endometrial, gastric, colorectal, and renal malignancies.
Conclusion: This study highlights that multiple genetic variants associated with cancer susceptibility can coexist in a single patient. Furthermore, in patients with a family history of diverse cancer types, using multigene cancer susceptibility panels instead of BRCA gene sequencing alone is crucial to identify additional predispositions. Identifying these variants enables more comprehensive risk assessments, essential for appropriate screening protocols and early interventions for patients and at-risk relatives.
Keywords: BRCA1, BRCA2, hereditary cancer susceptibility, multigene panels

[Abstract:0175]

JAK1: A New Hereditary Cancer Gene? Primary Immunodeficiency and Diffuse Large B-Cell Lymphoma with Cancer and Mycobacterial Susceptibility - The Second Case Worldwide

Rashad Abdullayev[1], Muhammed Burak Bereketoglu[2], Mahir Serbes[3], Ummuhan Cay[4], Ayse Ozkan[5], Ozlem Ozgür Gundeslioglu[4], Gulay Sezgin[5], Dilek Ozcan[3], Derya Alabaz[4], Serhan Kupeli[5]

[1]Department of Medical Genetics, Pamukkale University, Denizli, Türkiye
[2]Department of Medical Genetics, Ege University, İzmir, Türkiye
[3]Department of Pediatrics, Division of Allergy and Immunology, Faculty of Medicine, Çukurova University, Adana, Türkiye
[4]Department of Pediatrics, Division of Infectious Diseases, Faculty of Medicine, Çukurova University, Adana, Türkiye
[5]Department of Pediatrics, Division of Pediatric Oncology and Pediatric Bone Marrow Transplantation Unit, Faculty of Medicine, Çukurova University, Adana, Türkiye

Introduction: JAK1 is a tyrosine kinase that regulates the JAK/STAT signaling pathway through cytokine receptor activation, playing a critical role in immune responses, growth, and cell differentiation. The protein, consisting of four subdomains, mediates these processes via receptor interactions and kinase activity. While gain-of-function mutations in JAK1 are linked to autoimmune diseases and hematological malignancies, loss-of-function (LOF) mutations are rare, with only one germline case reported. This prior case involved susceptibility to mycobacterial infections and metastatic bladder carcinoma. Somatic LOF mutations have been identified in tumors such as endometrial, colorectal, gastric, and prostate cancers. Here, we present the second known case of a compound heterozygous JAK1 LOF mutation associated with cancer and immunodeficiency

Case: A 15-year-old male presented with immunodeficiency at the medical genetics clinic. Born at term with no parental consanguinity, he remained infection-free until six months old but was hospitalized for bronchitis at that time. Following BCG vaccination, multiple lymphadenopathy developed, and antituberculosis treatment was initiated at 12 months. Despite treatment, he experienced repeated hospitalizations for drug-resistant atypical mycobacterial infections. Physical examination revealed right eye edema, developmental delay, and intellectual disability. The patient's immunobiochemical laboratory results are presented in Table 1. Biopsy of a nasal polypoid mass confirmed diffuse large
B-cell lymphoma (DLBCL). Whole-exome sequencing identified a homozygous c.581T>C (p.V194A) variant in JAK1. Microarray analysis revealed a 1p31.3 (64,734,882_65,410,168)x1 deletion, indicating compound heterozygosity. Parental genetic testing confirmed separate inheritance of the variant.

Materials-Methods: Genomic DNA isolated from peripheral blood leukocytes was analyzed by microarray using the Affymetrix Cytoscan Optima 315K system. Whole-exome sequencing was performed on the NextSeq 550 platform using the Twist Bioscience Human Comprehensive Exome Kit.

Conclusion: Our findings highlight that biallelic LOF mutations in JAK1 can lead to primary immunodeficiency with susceptibility to mycobacterial infections and malignancies. While the only other reported germline case involved metastatic bladder carcinoma, our patient was diagnosed with DLBCL. The large deletion identified supports the compound heterozygous effect of the JAK1 variant. This case underscores JAK1 as a potential novel candidate gene for hereditary cancer predisposition, warranting further study.

Keywords: JAK1, Diffuse Large B-cell Lymphoma, Whole Exome Sequencing

Table 1

Parameter	Result	Reference Range	Interpretation	Increase/Decrease Ratio
IgG	1910 mg/dl	822-1070 mg/dl	High	78.50% High
IgM	81 mg/dl	39-79 mg/dl	High	2,53 % High
IgA	40 mg/dl	85-211 mg/dl	Low	52.94 % Low
IL12	13 pg/ml	20-50 pg/ml	Low	35.00 % Low
Burst Test(NBT)	100%	-	Normal	-
CD3	67.6%	62.6-80.4%	Normal	Normal
CD4	38.1%	32.6-51.5%	Normal	Normal
CD8	23.0%	19-29%	Normal	Normal
CD19	25.5%	11.9-21.0%	High	21.43 % High
CD45	100%	-	Normal	-
HLA- DR	34.5%	-	Normal	-
CD16+56	6.3%	4.5-16.2%	Normal	Normal
CD4/CD8	1.66	1.21-2.64	Normal	-

[Abstract:0177]

Unraveling Familial Hemophagocytic Lymphohistiocytosis: The Role of Genetic Testing in Diagnosis and Treatment- A Case Report

Fahrettin Duymuş[1], Ayşe Şimşek[2]

[1]Clinic of Medical Genetics, Konya City Hospital, Konya, Türkiye
[2]Clinic of Pediatric Hematology, Konya City Hospital, Konya, Türkiye

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyper-inflammatory syndrome caused by excessive immune activation. This overactivation triggers a cytokine storm, leading to severe inflammation and multi-organ failure. Familial hemophagocytic lymphohistiocytosis (fHLH), a rare genetic form of HLH, is associated with mutations in the PRF1, UNC13D, STX11, and STXBP2 genes. These mutations impair the cytotoxic functions of T cells and natural killer (NK) cells, resulting in uncontrolled immune activation and the clinical manifestations of HLH. Diagnosing fHLH is particularly challenging due to its overlapping symptoms with secondary HLH and other mimicking conditions.

Comprehensive clinical evaluation and genetic testing are essential for confirming the diagnosis. Genetic testing plays a critical role in identifying pathogenic variants associated with fHLH and guiding appropriate treatment. This report presents the case of a 4-month-old male diagnosed with
UNC13D-related fHLH. The patient was admitted to the pediatric intensive care unit with persistent fever and a deteriorating general condition. Clinical examination revealed splenomegaly, cytopenia, hypertriglyceridemia, and hyperferritinemia. Hemophagocytic cells were identified in a bone marrow aspiration biopsy. Preliminary differential diagnoses included HLH, macrophage activation syndrome, infection/sepsis, liver failure, encephalitis, and autoimmune lymphoproliferative syndrome. The patient's family history revealed parental consanguinity and one healthy sibling. Genetic analysis identified a homozygous c.753+1G>T variant in the UNC13D gene, which leads to a premature termination codon. This variant was classified as pathogenic according to ACMG criteria, confirming the diagnosis of fHLH. The patient was treated with an allogeneic stem cell transplant from the healthy sibling. Genetic counseling was provided to the family, and segregation analysis was planned. This case highlights the critical importance of genetic testing in accurately diagnosing familial hemophagocytic lymphohistiocytosis, guiding treatment decisions, and providing tailored genetic counseling for affected families. Genetic analysis not only confirms the diagnosis but also facilitates effective patient management and supports informed decision-making for the family.

Keywords: Differential diagnosis, familial hemophagocytic lymphohistiocytosis, genetic testing

[Abstract:0178]

Multiple Primary Cancers: Hereditary Cancer Genetic Test Results From Single Center

Hüseyin İlbasmış, Şule Altıner, Timur Tuncalı, Nüket Kutlay, Halil Gürhan Karabulut, Sadiye Ekinci, Ezgi Gökpınar İli, Hatice Ilgın Ruhi

Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Türkiye

Objective: Hereditary cancer syndromes are conditions in which the risk of cancer is increased due to germline genetic mutations. Multiple primary cancers can also be observed in these syndromes. One in six individuals diagnosed with cancer receives a second primary cancer diagnosis during their lifetime. Conducting genetic risk assessments in individuals with multiple primary cancers is a critical step for individualized patient management. In this study, we aimed to investigate the relationship between the genetic data of hereditary cancer susceptibility and cancer types in patients diagnosed with multiple primary malignancies who were referred to our center.

Materials-Methods: This study included 36 patients who presented to the Department of Medical Genetics at Ankara University Faculty of Medicine with multiple primary malignancies, regardless of cancer type, between 2022 and 2024. The cross-sectional study retrospectively analyzed the genetic data of these patients using next-generation sequencing-based hereditary cancer panel comprising 36 genes. Genetic variants and their pathogenicity were analyzed in relation to cancer types.

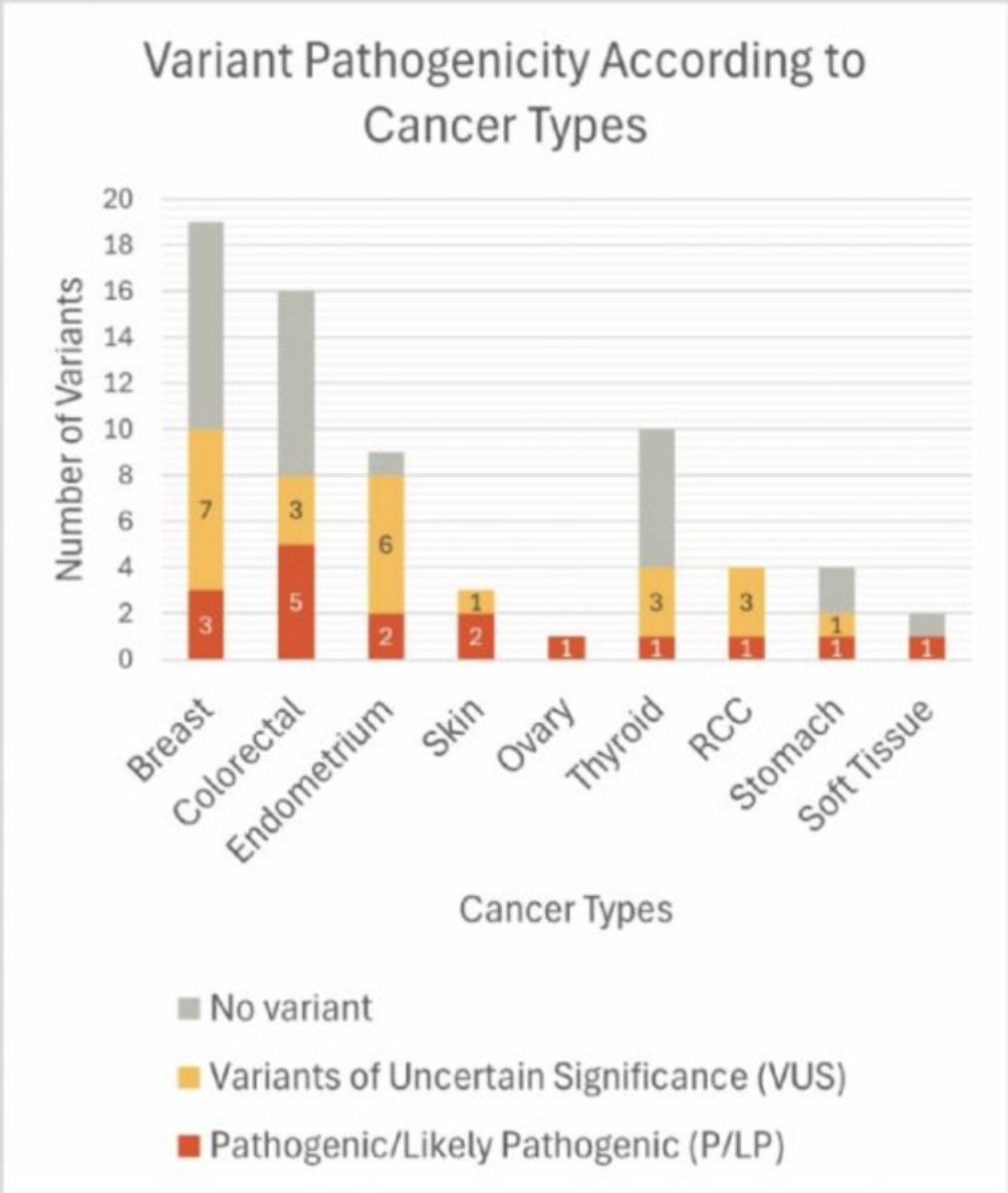
Results: In the cohort of 36 patients, 84 primary cancers were identified. 25 patients (69%) had two primary cancers, 10 patients (28%) had three, and 1 patient (3%) had four primary cancers. The three most common cancer types observed were breast, colorectal, and thyroid cancer, respectively. Among the 36 patients, 28 variants associated with hereditary cancer were identified in 21 patients (58%).

Pathogenic/likely pathogenic (P/LP) variants were detected in 9 patients (25%), and 12 patients (33%) had one or more variants of uncertain significance (VUS).

Conclusion: This study examined the presence and pathogenicity of genetic variants in patients with multiple primary malignancies. In the literature, the reported rate of pathogenic variants in patients with a single primary malignancy is 24.2%. In our study, a similar rate (25%) was found in patients with multiple primary malignancies. Hereditary cancer panels are valuable not only for current malignancy management but also for predicting future malignancies. Hereditary cancer syndromes increase the risk of malignancies in multiple organs or systems. Utilizing genetic tests as an auxiliary tool in risk assessment processes contributes to enhancing opportunities for early diagnosis and the planning of individualized screening protocols.

Keywords: Cancer, hereditary, multiple, NGS

Pathogenicity of Variants in Various Cancer Types



Distribution of patients according to variant pathogenicity

	Percentage	Number
P/LP variant	%25	9
1 or more VUS variant	%33,33	12
wt	%41,67	15
Total	%100	36

[Abstract:0179]

Single Center CHEK2 Experience and Multi-Locus Inherited Neoplasia Allele Syndrome

Ali Duru, Mehmet Berkay Akcan, Altuğ Koç, Berk Özyılmaz, Taha Reşit Özdemir

Department of Medical Genetics, İzmir City Hospital, İzmir, Türkiye

Objectives: The development and progression of cancer are primarily driven by 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 CHEK2 gene on chromosome 22 encodes a protein crucial for DNA damage response, cell cycle regulation, and tumor suppression. Activated by DNA damage, CHEK2 inhibits CDC25C to prevent mitosis, stabilizes p53 for G1 arrest, and interacts with BRCA1 for DNA repair. CHEK2 mutations are linked to elevated risks of various cancers, including breast, prostate, thyroid, colon, kidney, and sarcomas. Multi-locus Inherited Neoplasia Allele Syndrome (MINAS) describes individuals who detected germline pathogenic mutations in two or more cancer susceptibility genes.
Methods: Four patients were 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 GRCh37(hg19). Filtered variants were evaluated according to the ACMG Standards and Guidelines recommendations.
Results: First patient was 31-year-old female with breast carcinoma. We identified missense variant [NM_007194.4(CHEK2):c.499G>A(p.Gly167Arg)] as homozygous state. It was classified as likely pathogenic in ClinVar. Second patient was 60-year-old female with breast cancer. We identified missense variant (NM_007194.4(CHEK2):c.190G>A(p.Glu64Lys)] as heterozygous state. It was classified as conflicting classifications of pathogenicity (submissions:11-likely pathogenic; 18-uncertain significance) in ClinVar. Third patient was 38-year-old female with breast cancer. We identified two missense variants [NM_007294.4(BRCA1):c.2131_2132del(p.Lys711fs)] as heterozygous state, classified as pathogenic in ClinVar and [NM_007194.4(CHEK2):c.499G>A(p.Gly167Arg)] as heterozygous state classified as likely pathogenic in ClinVar. Fourth patient 54-year-old female with endometrium cancer. We identified two missense variants [NM_000251.3(MSH2):c.2038C>T(p.Arg680Ter)] as heterozygous state, classified as pathogenic in ClinVar and [NM_007194.4(CHEK2): c.470T>C(p.Ile157Thr)] as heterozygous state classified as conflicting classifications of pathogenicity(submissions:6-pathogenic; 14-likely pathogenic; 1-pathogenic, low penetrance; 1-established risk allele; 9-uncertain significance) in ClinVar.
Conclusion: In this presentation, we aim to describe the tumor suppressor function of CHEK2, present our cases with pathogenic variants in CHEK2 and evaluate the relationship between CHEK2 gene and MINAS.
Keywords: CHEK2, HEREDITARY CANCER SYNDROMES, MINAS

[Abstract:0180]

MCPH1: A Novel Candidate Gene for Hereditary Breast Cancer

Veysel Atasoy, Altuğ Koç, Kadri Murat Erdoğan, Taha Reşid Özdemir, Berk Özyılmaz

Clinic of Medical Genetics, University of Health Sciences, İzmir City Hospital, İzmir, Türkiye

Breast cancer is the most common type of cancer among women worldwide. It is the second leading cause of cancer-related deaths in women, following lung cancer. Breast cancer, which develops as a result of the interplay between environmental, hormonal, and genetic factors, is a highly heterogeneous cancer both clinically and biologically. It is known that 5-10% of breast cancer cases are hereditary.
Various genes associated with hereditary breast cancer have been identified. Genes with high-penetrance in breast cancer, such as BRCA1, BRCA2, and PALB2, as well as genes with moderate-penetrance like CHEK2, ATM, and BRIP1, are among the most important known genes in hereditary breast cancer. Recent studies have suggested a potential association between the MCPH1 gene and breast cancer, proposing that MCPH1 may be recognized as a novel hereditary breast cancer gene.mIn this study, we aimed to present the MCPH1 variant detected in a patient diagnosed with breast cancer and to discuss its potential relationship with the disease. Our patient, a 69-year-old woman, was diagnosed with breast cancer and referred to our clinic following a breast cancer multidisciplinary council decision. An HBOC NGS panel test was planned for her. The NGS panel revealed a heterozygous variant of MCPH1 c.2145 G>A (p.Trp715Ter) in a non-target region.mSeveral studies have highlighted the connection between the MCPH1 gene, which plays a crucial role in regulating cell cycle checkpoints and chromosome condensation, and breast cancer. Through this case, we aim to emphasize a newly identified gene that should be considered in hereditary breast cancer cases.

Keywords: MCPH1, breast cancer, cancer

[Abstract:0182]

Comprehensive Multigene Panel Testing for Hereditary Cancer Syndromes: Variant Classifications and Clinical Relevance

Tuna Eren Esen[1], Lale Yılmaz Çelik[1], Aynur İslamova[1], Nilüfer Bulut[2]

[1]Department of Medical Genetics, University of Health Sciences, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye
[2]Department of Medical Oncology, University of Health Sciences, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye

Introduction: Hereditary cancer syndromes (HCS) are conditions characterized by inherited pathogenic variants that increase susceptibility to specific cancer types, accounting for approximately 5–10% of all cancers. Advances in next-generation sequencing (NGS) have enabled comprehensive multigene panel testing, allowing the identification of additional genetic variants linked to cancer susceptibility.
Objective: This study aimed to evaluate the results of Hereditary Cancer Panel analyses performed on patients with a cancer diagnosis or a family history of cancer. The goal was to identify genetic variants associated with HCS and assess their clinical significance for early diagnosis, genetic counseling, and targeted treatment strategies.
Materials-Methods: The study included 308 patients evaluated using a multigene panel targeting 81 genes associated with HCS in 2024. Detected variants were classified based on their pathogenicity as pathogenic (P), likely pathogenic (LP), or variants of uncertain significance (VUS). Statistical analyses were conducted to determine the frequency and distribution of identified variants across genes and cancer types.
Results: Among 308 patients, 108 cancer-related variants were identified (35.1%). Of these, 58 were classified as VUS (53.7%), 41 as pathogenic (38.0%), and 9 as likely pathogenic (8.3%). Variants were detected in 14 genes, with BRCA2 (13 cases, 12.0%) and CHEK2 (12 cases, 11.1%) being the most frequently mutated. The distribution of pathogenic and likely pathogenic variants was as follows: ATM (4 cases, 9.8%), BRCA1 (7 cases, 17.1%), BRCA2 (9 cases, 22.0%), CHEK2 (6 cases, 14.6%), MUTYH (8 cases, 19.5%), FH (2 cases, 4.9%), and MSH2 (2 cases, 4.9%). Clinical diagnoses included 28 breast cancer cases (25.9%), 10 ovarian cancer cases (9.3%), 3 endometrial cancer cases (2.8%), 2 colorectal cancer cases (1.9%), 1 renal cell carcinoma case (0.9%), and 6 cases with significant family history (5.6%).
Conclusion: This study underscores the utility of multigene panels in identifying hereditary cancer-related variants, including VUS, which remain a challenge in clinical interpretation and counseling. Further advancements in variant classification and functional studies are essential to enhance the precision of genetic counseling and improve patient care.
Keywords: Hereditary cancer syndromes, NGS, multigene panel

[Abstract:0183]

Co-Occurrence of Pathogenic Mutations in DNA Repair Genes and Their Effects on Genomic Stability

Burak Aktaş, Ali Torabi, Zeynal Sütkurt, Nadir Koçak, Tülün Çora

Department of Medical Genetics, Selçuk University Faculty of Medicine, Konya, Türkiye

Objective: Objective of this studys is research co-occurence of germline variants DNA repair genes.
Materials-Methods: In this study, CES analyses were performed on 857 individuals with various complaints and findings suspected to be of genetic origin at the Department of Medical Genetics, Selcuk University Faculty of Medicine. For bioinformatics analysis, the Genomize Seq platform was used. Variants were aligned to the human reference genome GRCh37 and searched using FreeBayes.
Pathogenicity classification was performed according to ACMG criteria, and variants were filtered using various databases.
Results: According to the analyses, pathogenic or likely pathogenic mutations were detected in at least one gene involved in DNA repair mechanisms in 123 out of 857 individuals who underwent CES analysis for various reasons. Among these, 13 individuals had a P/LP mutation in one DNA repair gene accompanied by a P/LP mutation in another DNA repair gene (10.5%). The top 10 most frequently mutated genes were: MUTYH (13 / 9.49%), CHEK2 (11 / 8.03%), BRCA2 (10 / 7.30%), FANCA (7 / 5.11%), ATM (6 / 4.38%), MSH3 (6 / 4.38%), POLG (6 / 4.38%), BRCA1 (5 / 3.65%), and RAD50 (5 / 3.65%)(figure 2). Among the mentioned 13 individuals who had co-occurrence of the DNA repair gene mutations at LP/P clinical evidence significant level, 6 had the mutation in the MUTYH gene (46.15%), and 2 individuals had the mutation in the ATM gene (15.38%).
Conclusion: In our study, the co-occurrence rate of mutations in DNA repair genes among individuals with P/LP mutations detected through CES analyses was 10.5%. This suggests that mutations in two different DNA repair genes may significantly increase the risk of disease development, aligning with reports of higher cancer risk in individuals with dual mutations. Hi-C analyses revealed the interchromosomal spatial proximity of MUTYH, MSH3, and BRCA1 genes, emphasizing the importance of physical proximity between DNA repair genes in maintaining genomic stability. This study highlights the frequency and clinical implications of co-occurring mutations in DNA repair genes, offering valuable insights for genetic disease and cancer research. It also supports the development of genomic medicine and personalized therapies.
Keywords: Co-Occurrence, DNA repair genes, genomic stability, Hi-C analysis

[Abstract:0184]

Genetic Variants and Neoplastic Features in TSC1 and TSC2: a Single-Center Experience

Miray Zorluer[1], Gülay Güleç Ceylan[2], Esra Kılıç[3], Neriman Sarı[4], Derya Özyörük[4], Büşranur Çavdarlı[2]

[1]Department of Medical Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Medical Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye; Department of Medical Genetics, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye
[3]Department of Pediatric Genetics, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Türkiye
[4]Department of Pediatric Hematology and Oncology, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Türkiye

Objective: Tuberous-sclerosis-complex (TSC) is a rare, autosomal dominant genetic disorder characterized by hamartomas in multiple organ systems, including the brain, skin, heart, kidneys, and lung. TSC is caused by mutations TSC1 or TSC2 genes, which encode the proteins hamartin and tuberin, respectively. These proteins play a critical role in the regulation of cell growth and proliferation. Early diagnosis and regular follow-up are essential due to the treatment and risk of malignancy. TSC is often caused by a de novo variant, but about one third of cases are inherited from an affected parent. The aim of this study is to retrospectively analyse the TSC1, TSC2 variants identified in patients and their genotype-phenotype correlation.
Materials-Methods: This study is a retrospective review of the results of 137 patients referred to our clinic with suspected tuberous sclerosis who underwent Next-Generation-Sequencing (NGS) of the TSC1, TSC2 genes, and patient with deletion in the TSC2 genes detected by microarray analysis between April 2019 and November 2024. The clinical findings of the patients (48 cases) with pathogenic/likely pathogenic (P/LP) and variant of uncertain significance (VUS) in the relevant genes were evaluated.
Results: As a result, disease-associated variants were identified in 47 out of 137 NGS patients; 42 variants were classified as P/LP, 7 variants were VUS. Two patients had two different variants. In addition, a deletion in the TSC2 gene was found in one patient by microarray analysis. While 34 of 48 variants were detected in TSC2 gene, 14 were detected in TSC1 gene. Clinical findings of these patients: 23 had rhabdomyoma (5 TSC1/18 TSC2), 40 had hamartomatous lesions on brain (12 TSC1/28 TSC2), 16 had renal angiomyolipoma (16 TSC2). No malignancy was detected in any patient, but one patient had chronic kidney disease.
Conclusion: If TSC is still suspected despite normal sequence analysis, additional testing for deletions may be considered. If these tests are negative, genetic investigation of the affected tissue may be planned due to potential somatic mosaicism. Despite high penetrance, segregation analysis should be suggested when a variant is detected, given the variability in clinical findings and the inheritance rate in one-third of patients.
Keywords: Genetic variants, genotype-phenotype correlation, TSC1 gene, TSC2 gene, tuberous sclerosis complex

[Abstract:0185]

Clinical and Molecular Evaluation of Patients Diagnosed with Lynch Syndrome Through Hereditary Cancer Panel

Esma Ertürkmen Aru[1], Haktan Bağış Erdem[1], Hanife Saat[1], Taha Bahsi[2]

[1]Department of Medical Genetics, Ankara Etlik City Hospital, Ankara, Türkiye
[2]Department of Medical Genetics, Memorial Healthcare Group, Ankara, Türkiye

Objective: Lynch syndrome (LS) is an autosomal dominant disorder caused primarily by pathogenic germline variants in mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) and deletions in EPCAM, which lead to MSH2 silencing. LS is responsible for 2–3% of both colorectal and endometrial cancers and significantly increases the risk of other malignancies, such as ovarian, gastric, small bowel, and urinary tract cancers. This study aims to present the clinical findings of patients diagnosed with molecular LS in conjunction with their genetic analysis results.
Materials-Methods: In this study, patients referred to the Medical Genetics outpatient clinic of Ankara Etlik City Hospital with various cancer diagnoses between 2022 and 2024, who were diagnosed with LS through hereditary cancer panel testing, were selected. DNA samples were extracted from peripheral blood and analyzed using the NextSeq platform (Illumina, USA) with the Custom Solution (CHCS_C_v2) kit by Sophia Genetics. The sequencing data were analyzed using Sophia DDM, and the identified genomic alterations were classified according to the current ACMG/AMP guidelines.
Results: Among a total of 55 patients diagnosed with LS, pathogenic or likely pathogenic variants were found in 16 patients (29%) in the MSH2, 15 patients (27%) in the MSH6, 13 patients (24%) in the MLH1, and 11 patients (20%) in the PMS2. Of the 55 LS patients, 20 were diagnosed with colorectal cancer, 14 with endometrial cancer, 5 with breast cancer, and 4 with ovarian cancer. Additionally, 9 patients (16%) had a history of multiple primary cancers. Notably, 44% of patients with pathogenic variants in the MSH2 had a history of multiple primary cancers. Furthermore, three patients were found to carry a secondary pathogenic variant in other hereditary cancer genes alongside the pathogenic variant in the MMR genes.
Conclusion: This study is significant as it includes a large cohort of Turkish patients diagnosed with LS, providing valuable insights into the clinical and molecular characteristics of LS within the Turkish population. Early identification of LS patients enables timely intervention and intensive surveillance, which may improve disease prognosis and reduce morbidity and mortality.
Keywords: Hereditary cancer syndromes, HNPCC, lynch syndrome, MMR

[Abstract:0186]

A Case of Late-Diagnosed Neurofibromatosis Type I Presenting with Metastatic Breast Cancer: The Critical Role of Surveillance in Cancer-Prone Syndromes

Freshta Jurat, Esra Arslan Ateş, Mustafa Özen

Department of Medical Genetics, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye

Objective: Neurofibromatosis Type I (NF1) is caused by variants in the NF1 gene, which encodes neurofibromin. This condition is associated with an elevated risk of developing both benign and malignant tumors, including breast cancer. In this case study, we present a 55-year-old woman with a complex medical history, including NF1, pheochromocytoma, and invasive ductal carcinoma (IDC) of the breast, highlighting a potential link between NF1 mutations and breast cancer.

Case: A 55-year-old woman was referred to our clinic due to widespread neurofibromas and café-au-lait spots across her body. At the age of 52, she experienced a hypertensive crisis, which led to a diagnosis of pheochromocytoma following a left adrenalectomy. At 53, she was diagnosed with breast cancer, and histological investigations revealed ER-positive (ER+), HER2-negative (HER2-) invasive ductal carcinoma (IDC). A PET-CT scan identified multiple organ metastases, including those in the calvarium, mandible, and right adrenal gland. She subsequently underwent 15 doses of radiotherapy. The patient's mother appeared to be affected by NF1, although no clinical or molecular data were available to confirm this. Her half-sister was diagnosed with breast cancer (IDC) at the age of 52. Previous genetic testing for BRCA1 and BRCA2 variants in both siblings revealed no causative mutations. However, sequencing of the NF1 gene in our patient revealed a known pathogenic variant (c.1139T>C, p.Leu380Pro).

Conclusion and Discussion: NF1 is a tumor suppressor gene, and its loss or pathogenic variations can lead to uncontrolled cell growth. Women with NF1 under the age of 50 have up to a fivefold increased likelihood of developing breast cancer compared to the general population. The National Comprehensive Cancer Network (NCCN) recommends that women with NF1 begin breast cancer screening at an earlier age than the general population, specifically starting at age 30. Here, we present a case of late-diagnosed NF1 with metastatic breast cancer to underscore the critical importance of cancer surveillance programs for relatively rare cancer-prone disorders.

Keywords: Breast cancer, genetic sequencing, genetic predisposition, İnvasive ductal carcinoma, Neurofibromatosis type 1

[Abstract:0188]

Evaluation of confirmation results of patients with suspected CNV in BRCA1-2 genes analyzed by NGS method using the MLPA method

Onur Hanoğlu[1], Ayşenur Ersoy Karayumak[1], Şenol Demir[2], Zeynep Münteha Başer[1], Esra Dirimekin[1], Ceren Alavanda[2], Ayberk Türkyılmaz[3], Esra Arslan Ateş[4], Ahmet İlter Güney[1]

[1]Department of Medical Genetics, Marmara University Faculty of Medicine, İstanbul, Türkiye
[2]Department of Medical Genetics, University of Health Sciences, Van Training and Research Hospital, Van, Türkiye
[3]Department of Medical Genetics, Karadeniz Technical University Faculty of Meidicine, Trabzon, Türkiye
[4]Department of Medical Genetics, İstanbul University-Cerrahpasa Faculty of Medicine, İstanbul, Türkiye

Introduction: In this study, we evaluated the results of the MLPA (Multiplex Ligation-dependent Probe Amplification) test conducted to confirm the suspected CNV (Copy Number Variation) detected in BRCA1-2 genes during NGS (Next Generation Sequencing) analyses of breast,ovarian and prostate cancer patients who presented to our outpatient clinic.
Materials-Method: Following DNA isolation using the QIAamp DNA Mini Kit®, variations in all exons and exon-intron junctions of the BRCA1 and BRCA2 genes were identified using the Multiplicom BRCA Mastr Dx® next-generation sequencing kit and the Illumina MiSeq® system.For patients tested with the hereditary cancer panel, DNA isolation was performed using the ZeeSan Lab-Aid® 824s Blood DNA isolation kit.Variations in all exons and exon-intron junctions of the panel genes were identified using the SOPHIA Custom Solution CHCS_C_V2 next-generation sequencing kit and the NovaSeq® system.The data were analyzed with Sophia DDM and interpreted in light of relevant databases.
Cases: The MLPA results of a total of 46 patients, 36 with suspected deletions and 10 with suspected duplications, were evaluated.All patients with suspected duplications were reported as normal in the MLPA results.Among the 36 patients with suspected deletions, 9 were confirmed by MLPA (25%).It was determined that 30 of the patients with suspected deletions underwent single-gene sequencing (SGS) and 6 underwent hereditary cancer panel testing. The confirmation rate of suspected deletions in patients who underwent SGS was 3/30 (10%), whereas all suspected deletions in panel patients were confirmed.There were 14 patients with medium confidence CNV suspicion, of whom 11 had suspected deletions and 3 had suspected duplications. All MLPA results for these patients were reported as normal.
Conclusion: In conclusion, it is essential to confirm patients with suspected CNV detected in BRCA1-2 genes through sequencing methods, and based on these results, patients should receive genetic counseling and be referred to relevant departments. This study determined that the reliability of CNV suspicion is lower in SGS, while CNV suspicions in panels are confirmed at a higher rate. Similarly, deletion suspicions are more accurately identified compared to duplications, emphasizing the need to consider this during analyses.We recommend conducting similar studies for other genes to enrich the literature data.
Keywords: BRCA1-2, CNV, confirmation, MLPA

[Abstract:0189]

Evaluation Of Liquid Biopsy Results In HRD-Associated Cancers In Relation To Survival, Clinical Data, And Hereditary Cancer Genetic Test Results

Alp Peker, Ekin Cemre Bayram Tokaç, Aslı Ece Solmaz, Ayça Aykut, Asude Durmaz, Haluk Akın

Department of Medical Genetics, Ege University Faculty of Medicine, İzmir, Türkiye

Objective: Liquid biopsy is a non-invasive diagnostic method that analyzes tumor DNA, RNA, or other biomarkers from blood to detect and monitor cancer. It is advantageous over traditional biopsies as it provides faster results and can be used to track disease progression, and monitor treatment responses. Liquid biopsy is particularly valuable in cancers associated with Homologous Recombination Deficiency (HRD), such as ovarian, breast, and prostate cancers, which are more responsive to targeted therapies like PARP inhibitors.

Materials-Methods: Peripheral blood samples from 119 patients were used to obtain cfDNA, which was sequenced using the AVENIO Tumor Expanded Panel and Illumina NextSeq technology. The variants were analyzed using AVENIO Oncology Software, and reports were generated using the CE-IVD approved "Navify Mutation Profiler" software. Cases with insufficient clinical data were excluded (n:8).

Results: We analyzed 85 breast, 12 ovarian, 11 prostate, and 3 pancreatic cancer cases. The most frequent variants were in TP53 (29%), followed by PIK3CA (25%), ESR1 (12%), and RB1 (8 Survival rates strongly varied based on the number of liquid biopsy variants. 68% of patients with 0 variants, 42% with 1 variant, 37% with 2 variants, and 30% with 3 variants were alive. The survival rate for patients with 4 or more variants was 0%. Patients with higher variant allele frequency (VAF) were diagnosed 5 years earlier (45 vs. 50 years). Those with TP53 variants had the lowest survival (5 years), compared to PIK3CA (7.6 years) and ESR1 (9 years). In 42 cases, hereditary cancer panel (HCP) testing identified pathogenic variants in BRCA1, BRCA2, and PALB2, which were linked to lower 5-year survival compared to non-patients.

Conclusion: The number of variants detected in liquid biopsy is associated with tumor aggressiveness and poor survival, highlighting the need for aggressive treatment in such cases. TP53 variants, in particular, are associated with the lowest survival rates, stressing the importance of developing targeted therapies for these mutations. Stressing the study's small sample size limits, increased patient numbers and better follow-up, and a deeper focus on HCP testing, will enlighten clinical outcomes in cancer management for future studies.

Keywords: Liquid biopsy, hereditary cancer, HRD, breast cancer, ctDNA

[Abstract:0190]

Beyond the genes: Decoding Lynch Syndrome missteps

Fethiye Esenkaya, Merve Saka Güvenç, Özgür Kırbıyık, Ali Duru, Altuğ Koç, Taha Reşid Özdemir, Berk Özyılmaz

Clinic of Genetic Disorders Evaluation Center, İzmir City Hospital, İzmir, Türkiye

Objective: Lynch syndrome (LS) is a hereditary condition that increases the risk of colorectal and endometrial cancers. It accounts for about 5-10% of colorectal cancer cases and has a high lifetime risk for cancer, especially in the colon (80%) and endometrium (60%). Genetic mutations in mismatch repair (MMR) genes, such as MLH1, MSH2, MSH6, and PMS2, cause LS. Early diagnosis is essential, and testing includes microsatellite instability (MSI) analysis and immunohistochemical (IHC) staining of MMR proteins. Germline genetic testing is recommended for those with abnormal MSI or IHC results. Despite criteria like the Amsterdam and Bethesda Guidelines, genetic testing is crucial for accurate diagnosis and management. We present a case of a patient in whom a false positive result was identified during genetic testing for Lynch syndrome.

Case: A 44-year-old male patient with complaints of bloating and no significant personal or family medical history, underwent a colonoscopy, which revealed a mass in the cecum. A right hemicolectomy was performed, and pathological evaluation demonstrated a moderately differentiated pT3N0, stage 2A adenocarcinoma. Immunohistochemistry revealed loss of nuclear expression for MSH2 and MSH6, suggesting Lynch syndrome. Genetic analysis identified an intronic variant of uncertain significance (VUS) in the MSH2 gene. Multiplex ligation-dependent probe amplification (MLPA) analysis revealed a heterozygous deletion of exon 16. However, confirmatory analysis with an alternative probe set did not detect this deletion. Further investigation revealed that the intronic variant interfered with the probe binding region, leading to a false positive result. This case underscores the necessity of confirmatory testing and careful interpretation in genetic diagnostics.

Conclusion: This case highlights the technical limitations of genetic testing methods. Mutations that affect probe binding regions can cause false positive results in MLPA. Therefore, anomalies detected by MLPA should be confirmed. It emphasizes the importance of careful interpretation of genetic tests and the critical role of further analysis for accurate diagnosis.

Keywords: Lynch syndrome, mismatch repair, MLPA, young-onset colorectal cancer

[Abstract:0191]
"MSH2 Gene Deletion: A Family History and Case Report Related to Lynch Syndrome"

Oğuz Dülger, Özlem Anlaş, Altuğ Koç, Mehmet Berkay Akcan, Kadri Murat Erdoğan

Clinic of Genetic Disorders Evaluation Center, İzmir City Hospital, İzmir, Türkiye

Lynch syndrome is an inherited cancer predisposition syndrome caused by mutations in DNA mismatch repair genes, following an autosomal dominant inheritance pattern. This syndrome is commonly associated with an increased risk of colorectal cancer, endometrial cancer, ovarian cancer, as well as cancers in the stomach, small intestine, kidney pelvis/ureter, and other organs.
Approximately 20-40% of Lynch syndrome cases are associated with mutations in the MSH2 gene. While point mutations are frequently observed in Lynch syndrome-related genes, exonic deletions and duplications are also seen in 10-40% of cases. This case report evaluates the clinical features of a patient with a heterozygous deletion in exon 11 of the MSH2 gene. A 33-year-old female patient, who is under oncological follow-up for endometrial and ovarian cancer, was referred to our genetic clinic for evaluation of hereditary cancer risks. A hereditary cancer panel containing 31 genes, including those associated with Lynch syndrome, was tested using Next-Generation Sequencing (NGS), but no pathogenic variants related to the clinical features were identified. Subsequently, an MLPA (Multiplex Ligation-dependent Probe Amplification) test was conducted for the MLH1/MSH2 genes. As a result, a heterozygous deletion in exon 11 of the MSH2 gene was detected and confirmed. Genetic counseling and family screening were recom-mended for the patient, and relatives carrying the deletion were identified. Early screening programs and preventive strategies are crucial for patients with pathogenic variants or deletions/duplications in the MSH2 gene associated with Lynch syndrome. In hereditary cancer research, understanding the molecular mechanisms of the relevant cancers and requesting MLPA tests for deletions and duplications when necessary is essential. This case serves as an important example of how the thorough application of molecular testing algorithms can provide appropriate treatment and follow-up strategies for the patient and other family members.
Keywords: DNA mismatch repair, Lynch syndrome, MLPA, MSH2

[Abstract:0192]

ATM Heterozygous Variant Identified in a Breast Cancer Case Series

Ozge Ozer Kaya[1], Merve Saka Guvenc[1], Sercan On[2]

[1]Clinic of Medical Genetics, İzmir City Training and Research Hospital, Medical Oncology, İzmir, Türkiye

Objective: Clinical manifestations of autosomal recessive Ataxia-telangiectasia are not expected in carriers of ATM heterozygous variants. However, an increased risk of breast cancer in these individuals was first reported in the late 1970s and has since been confirmed by numerous studies. It has been reported that germline pathogenic/likely pathogenic variants in the ATM gene increase the risk of breast cancer by approximately 2-3 times, with certain specific variants associated with even higher risks. This study aims to detail the molecular and clinical characteristics of individuals with pathogenic or likely pathogenic ATM variants identified among those diagnosed with breast cancer and to evaluate the potential phenotypic effects of these variants.

Materials-Methods: Next-Generation Sequencing (NGS)-based Hereditary Cancer Panel analyses of 748 breast cancer patients were retrospectively reviewed. Individuals carrying pathogenic or likely pathogenic variants in the ATM gene were identified and selected for detailed analysis. Clinical data, including age, age at diagnosis, family history, and other accompanying factors, were evaluated.

Results: Pathogenic or likely pathogenic heterozygous variants in the ATM gene were identified in 17 out of 748 patients (2.3%). The age range of these individuals was determined to be between 32 and 74 years. Molecular analyses revealed that missense variants were the most frequently detected type (47%, n=8).

Conclusion: Determining the molecular and clinical spectrum of individuals with pathogenic variants in the ATM gene significantly contributes to understanding genetic predisposition in breast cancer.

These findings provide critical data to improve genetic counseling processes and support personalized risk management approaches.

Keywords: ATM, breast cancer, mutation, moderate risk gene

[Abstract:0194]

A Likely Pathogenic Variant in STK11 Gene Associated with Peutz-Jeghers Syndrome: A Case Report

Haydar Tümkaya, Aydeniz Aydın Gümüş, Alper Gezdirici, Mustafa Doğan

Department of Medical Genetics, University of Health Sciences, Başakşehir Çam and Sakura City Hospital, İstanbul, Türkiye

Objective: Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder characterized by gastrointestinal hamartomatous polyps and mucocutaneous pigmentation. Germline mutations in the serine/threonine kinase 11 (STK11) gene play a key role in its pathogenesis, with a prevalence of approximately 70-90% among individuals diagnosed with PJS. Additionally, specific STK11 variants are observed with varying frequencies; certain hotspot mutations and deletions are more common in affected individuals. This report highlights a 16-year-old boy patient presenting with clinical features of PJS and a likely pathogenic STK11 gene variant.

Case: A 16-year-old boy presented to the emergency department with bilious vomiting. The patient was referred to pediatric surgery after computed tomography(CT) revealed an intussusception.

Multiple polyps were found on colonoscopy. Segmental resection was performed and the polyps were histopathologically confirmed to be hamartomatous and compatible with PJS. The patient was also referred to our center. After isolation of genomic DNA from the patient's peripheral blood sample, next generation sequencing was performed on the NextSeq® 500 System / Illumina System using the Celemiks Hereditary Cancer Panel Kit. Variants identified by SEQ Genomize bioinformatic analysis were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines. A heterozygous c.914A>C (p.Q305P) variant in the STK11 gene was detected and identified likely pathogenic according to the ACMG criteria (PM1, PM2, PP5). This variant was associated with the patient's clinical findings and family history. In the patient's family history, his mother and brother also had hamartomatous polyps. The patient is currently being followed for potential complications, including malignancies associated with PJS.

Conclusion: The c.914A>C (p.Q305P) variant in the STK11 gene alters protein function and contributes to the development of PJS. This case highlights the importance of genetic testing in individuals with a suggestive clinical and family history to facilitate early diagnosis and intervention. Regular surveillance and management are essential to reduce the morbidity and mortality associated with PJS-related malignancies. Further research is needed to understand the full spectrum of genotype-phenotype correlations in PJS.

Keywords: Early diagnosis, Hamartomatous polyps, Genetic testing, Peutz-Jeghers Syndrome (PJS), STK11 gene

[Abstract:0195]

Clinical and Genetic Evaluation of a Variant of Uncertain Significance in the BMPR1A Gene: A Case Report in a Family with a History of Colorectal Cancer

Tuba Uğurlu Er, Rüveyda Nur İz, Taner Durak, Aydın Demiray, Kadri Karaer

Department of Medical Genetics, Pamukkale University Faculty of Medicine, Denizli, İstanbul

Introduction: BMPR1A (Bone Morphogenetic Protein Receptor Type 1A) is a receptor gene that transmits the signals of bone morphogenetic proteins (BMPs) belonging to the TGF-β superfamily from the cell membrane to the nucleus. The protein encoded by this gene binds to BMP ligands and activates SMAD proteins, which regulate cellular growth, differentiation, and apoptosis. Activated SMAD protein complexes are translocated to the nucleus, where they control gene expression. Pathogenic variants in the BMPR1A gene are associated with gastrointestinal polyposis syndromes, particularly Juvenile Polyposis Syndrome (JPS), as well as certain types of cancers.
Therefore, BMPR1A serves as a critical focus of research for understanding both cellular functions and the pathophysiology of genetic diseases. This study aimed to perform the genetic evaluation of a case with a family history of colorectal cancer involving multiple affected individuals and to investigate the potential clinical impact of a variant of uncertain significance (VUS) identified in the BMPR1A gene.
Case: A 36-year-old female patient with a family history of colon cancer presented to our clinic. Her family history includes colon and uterine cancer in one sister, liver, colon cancer, and lymphoma in another sister, colon cancer in her father, and colorectal cancer in her paternal grandfather. The patient herself has no complaints.After obtaining informed consent, DNA was isolated from peripheral blood. Genetic analysis was performed using next-generation sequencing (NGS) with the Qiagen hereditary cancer panel, covering approximately 60 genes.
Conclusion: NGS analysis identified a heterozygous variant, c.264_266del, in the BMPR1A gene. According to the ACMG classification, this variant met the PM2 and PM4 criteria and was classified as a variant of uncertain significance (VUS). The same variant was also detected in the patient's sister, who had been diagnosed with colon and liver cancer at an external center. A review of the literature revealed that the c.264_266del (p.Glu88del) variant in the BMPR1A gene has been associated with colorectal cancer and/or adenomas.However, further functional studies are required to assess the pathogenicity of this variant. The patient received genetic counseling, and screening protocols, as well as risk-reducing strategies, were recommended for the family.
Keywords: BMPR1A mutations, Familial colorectal cancer (FCCX), Hereditary Cancer

[Abstract:0196]

Molecular Alterations in Pediatric Acute Lymphoblastic Leukemia: Potential Role of ENOX2 and LIG4 Gene Variants and Their Clinical Implications

Nurana Mammadova[1], Alper Özcan[2], Munis Dündar[1]

[1]Department of Medical Genetics, Erciyes University, Kayseri, Türkiye
[2]Pediatric Hematology-Oncology Department, Erciyes University, Kayseri, Türkiye

Objective: This study investigates the relationship between monoallelic LIG4 and hemizygous ENOX2 gene variants, identified through Whole Exome Sequencing (WES), and childhood acute lymphoblastic leukemia (ALL) in a patient diagnosed with this condition. A 16-year-old male patient, diagnosed with relapse acute lymphoblastic leukemia (ALL), was included in the study. Peripheral blood samples were collected from the patient, and DNA isolation was performed using automated systems. Whole Exome Sequencing (WES) was conducted using the Twist Human Core Exome Kit on the Genomize SEQ platform, with the hg19 reference genome.
Case: The patient was referred to our clinic by the pediatric hematology-oncology department due to a relapse of acute lymphoblastic leukemia (ALL), diagnosed 11 years ago. Pathological evaluation and immunophenotyping revealed that the patient had the CALLA+ B-ALL phenotype. No significant dysmorphic features were observed during the physical examination. The patient's developmental progress was reported to be appropriate for his age. There was no consanguinity in the family history. Molecular analysis revealed that the patient diagnosed with relapse ALL carries a hemizygous in-frame deletion variant c.60_62del p.(Ser20del) in the ENOX2 gene and a heterozygous missense variant c.2316C>G (p.Asn772Lys) in the LIG4 gene. Both variants have not been previously reported in the literature and are considered novel variants.
Conclusion: Novel variants were identified in the patient, contributing to the variant spectrum. Additionally, these findings may provide further insights into the role of these variants in childhood leukemia.
Keywords: Childhood Acute Lymphoblastic Leukemia (ALL), WES, ENOX2, LIG4

[Abstract:0198]

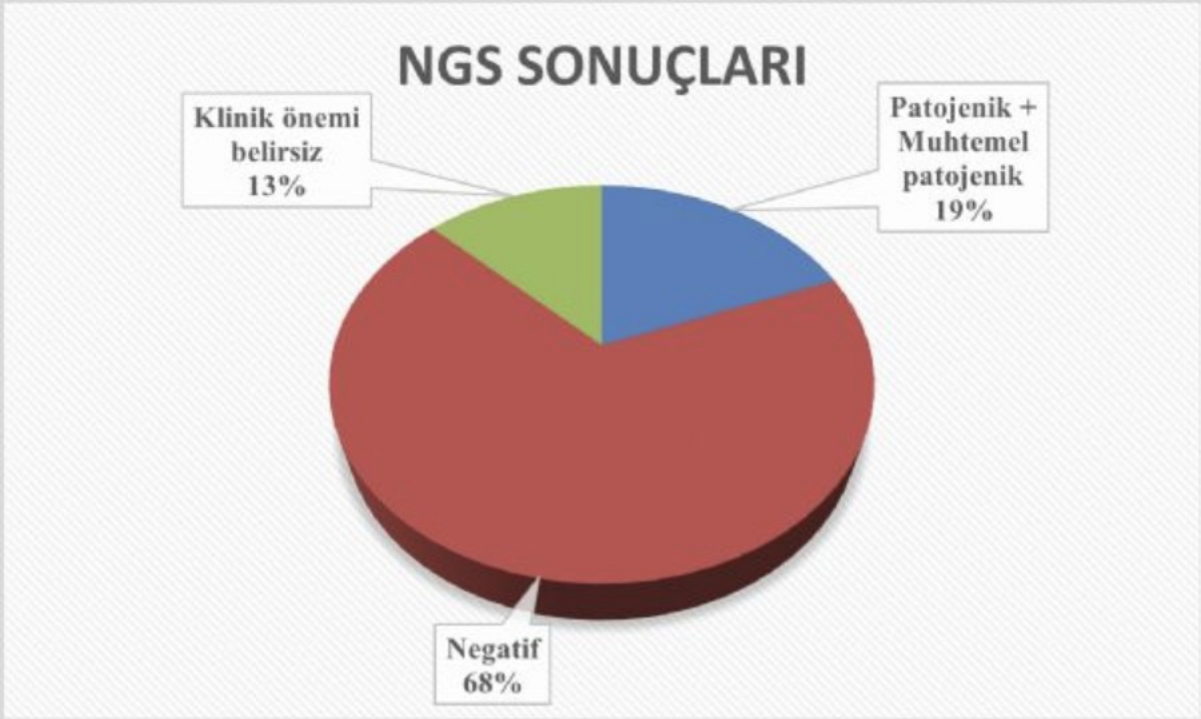
Genetic Screening for Hereditary Cancer Predisposition in a Turkish Cohort: Insights from a Multigene NGS Panel

Kübra Baysal, Uğur Gümüş, Bahtiyar Şahinoğlu

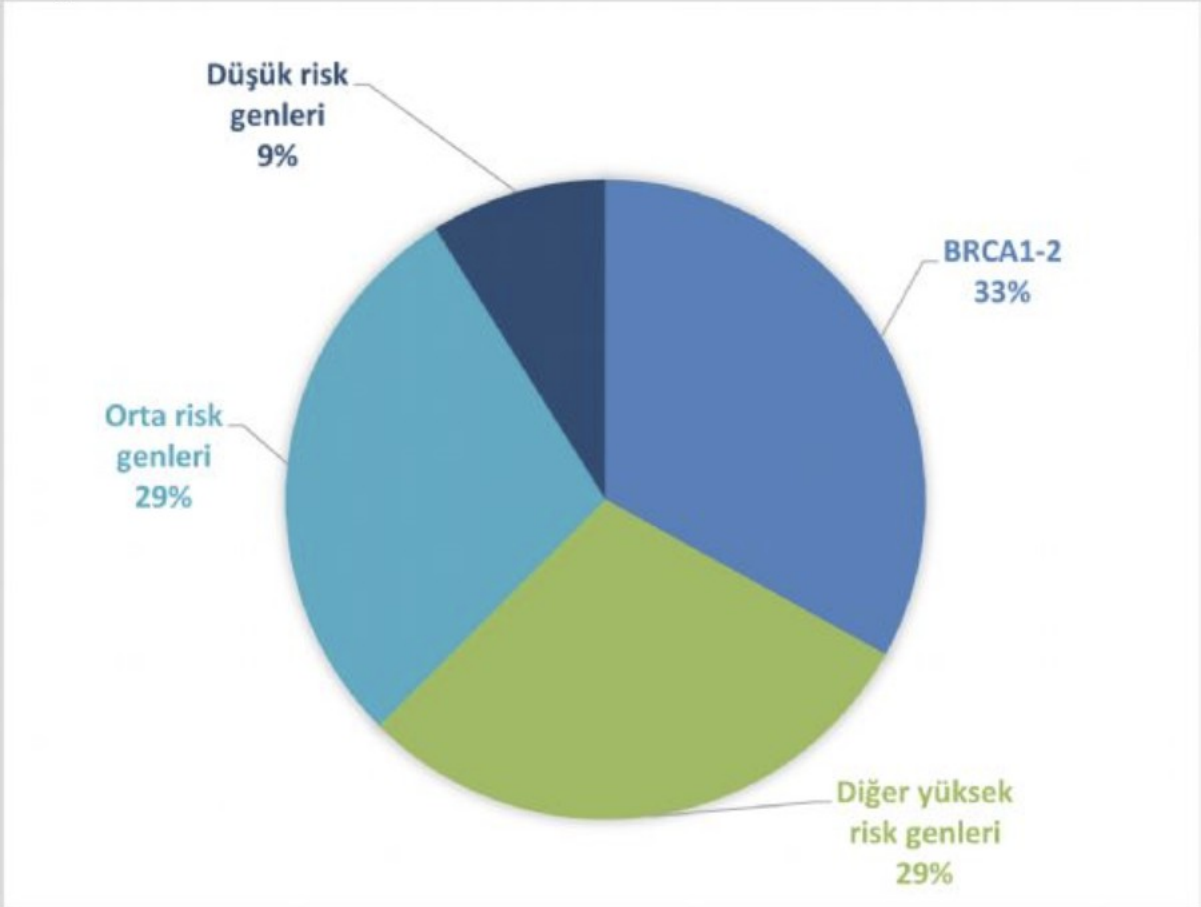
Department of Medical Genetics, Gaziantep City Hospital, Gaziantep, Türkiye

Objective: 5-10% of all cancers are linked to hereditary cancer predisposition syndromes. In the past, individual gene screenings were performed for these syndromes. However, with the efficiency and cost-effectiveness of emerging NGS technologies, screenings are now conducted using multigene panels. The aim of this study is to investigate variants in hereditary cancer predisposition genes in individuals who apply to our clinic.
Materials-Methods: In this study, the molecular and clinical findings of 592 patients who underwent testing through the Hereditary Cancer Panel at Gaziantep City Hospital in 2024 were evaluated retrospectively. The patients, the majority of whom had breast and ovarian cancers as well as unaffected individuals with a family history of cancer, were selected according to the criteria outlined in the NCCN guidelines. A panel of 83 genes was sequenced using NGS technologies on the Aviti platform (Element Biosciences). Detected variants were classified according to ACMG criteria.
Pathogenic and likely pathogenic variants considered clinically significant.
Results: The majority of patients tested (445/592) sought consultation due to breast and ovarian cancers. A clinically significant variant was identified in 19.1% of the patients, while a variant of uncertain clinical significance was detected in 12.8%. Clinically significant variants were found in 27 out of 83 genes. Among the 119 clinically significant variants detected, the most common were found in the BRCA1 (21/119), BRCA2 and CHEK2 (16/119), and ATM (13/119) genes. Clinically significant variants were observed in 15.8% of breast cancer patients, 29.6% of ovarian cancer patients, 11.1% of prostate cancer patients, and 52.7% of colorectal cancer patients. BRCA1/BRCA2 variants were positive in 7.4% of patients with breast and/or ovarian cancer, while clinically significant variants were detected in other genes in 10.9% of BRCA1/2-negative patients.
Conclusion: In our cohort, clinically significant variants would have been detected in 6.2% of patients with BRCA1/2 sequence analysis alone. This rate increased to 11.8% when other high-risk genes were included, and to 19% when medium- and low-risk genes were also considered. Multigene NGS panels have proven to be effective in providing genetic counseling for patients and their families, as well as in supporting decision-making processes in patient management.
Keywords: Hereditary cancer predisposition, multigene panel, cancer, genetic

NGS Results of Screened Patients



Pathogenic/likely pathogenic variants detected in genes according to cancer risk categories



NGS Panel Test Results According to Patients' Clinical Profiles

	Pathogenic + Likely pathogenic n (%)	Negative n (%)	Variant of unknown significance n (%)	Total n (%)
Breast cancer	62 (15,8)	273 (69,9)	56 (14,3)	391 (100)
Ovarian cancer	16 (29,6)	31 (57,4)	7 (13)	54 (100)
Colorectal cancer	19 (52,8)	13 (36,1)	4 (11,1)	36 (100)
Prostate cancer	5 (11,1)	35 (77,8)	5 (11,1)	45 (100)
Other cancer types	7 (14,9)	37 (78,7)	3 (6,4)	47 (100)
Family history of cancer	5 (26,3)	13 (68,4)	1 (5,2)	19 (100)
Total n (%)	113 (19,1)	403 (68,1)	76 (12,8)	592 (100)

[Abstract:0199]

Clinical Significance of Gene-Specific ACMG/AMP Classification: A Single-Center Retrospective Analysis of BRCA1 and BRCA2 Variants of Uncertain Significance Using ClinGen ENIGMA Expert Panel Guideline

Yusuf Bahap, Tarık Düzenli, Ali Babazade, Ozan Vural, Mehmet Ali Ergün

Department of Medical Genetics, Gazi University Faculty of Medicine, Ankara, Türkiye

Introduction: Identifying variants in the hereditary cancer genes is crucial for diagnosis, treatment and follow-up of cancer patients. However, many genetic variants detected in these genes are classified as "variants of uncertain significance (VUS)", which often creates significant challenges for patient management. The study aims to reclassify the VUS reported in BRCA1/2 genes according to the gene-specific guideline, thereby improving clinical interpretation.

Materials-Methods: In this study, we retrospectively analyzed the results of hereditary cancer panel testing conducted on 1,614 patients between December 2022 and December 2023. Among these patients, in the BRCA1 and BRCA2 genes, a total of 132 VUS were identified. These VUS were reclassified in accordance with the ClinGen ENIGMA Expert Panel Guideline.

Results: Following reclassification based on the ClinGen ENIGMA Expert Panel Guideline, 56.8% (n=75) of the 132 VUS were reclassified as likely benign, 10.6% (n=14) benign, 31.8% (n=42) VUS, and 0.8% (n=1) as likely pathogenic.

Discussion: The reclassification of 132 VUS in the BRCA1 and BRCA2 genes, according to the ClinGen ENIGMA Expert Panel Guideline, suggests that standardized and evidence-based criteria may help reduce uncertainty in variant interpretation. A notable proportion of the variants (67.4%) were reclassified as likely benign or benign, consistent with rates reported in the literature. Despite these findings, 31.8% of the variants remained classified as VUS, emphasizing the need for additional functional studies and further data integration to improve classification accuracy. The identification of one likely pathogenic variant illustrates the potential of these guidelines to recognize clinically significant findings. These results highlight how expert-guided approaches could contribute to interpreting BRCA1/BRCA2 variants. However, further validation and research are necessary, alongside the development of population-specific biobank data to incorporate personalized clinical information effectively.

Keywords: BRCA1, BRCA2, VUS, Reclassification, ENIGMA

Author To Editor: Güncel ENIGMA kılavuzu ile yeniden değerlendirdiğimiz hastaları ve kılavuzdaki önerilerin klinik uygulanabilirliğini tartıştığımız çalışmamızı bilgilerinize sunarız. Saygılarımla

[Abstract:0200]

Evaluation of Variants in the BRIP1 Gene in Patients Included in the Hereditary Cancer Panel

Çağlar Arısoy, Aslı Ece Solmaz, Haluk Akın

Clinic of Medical Genetics, Ege University Faculty of Medicine Hospital, İzmir, Türkiye

Objective: The BRIP1 gene encodes a protein belonging to the RecQ DEAH helicase family. Its primary functions include DNA repair and tumor suppression. The BRIP1 protein interacts with BRCA1 to repair double-strand DNA breaks through homologous recombination and contributes to chromosomal stability. Mutations in the BRIP1 gene disrupt these repair mechanisms, thereby increasing the risk of cancer development, particularly breast and ovarian cancer. Studies have shown that individuals with BRIP1 mutations have a significantly higher susceptibility to these cancers compared to those without such mutations.

Materials-Methods: In this study, we retrospectively analyzed cancer patients who were referred to the Department of Medical Genetics at Ege University between 2017 and 2024. These patients underwent hereditary cancer panel testing using next-generation sequencing.

Results: Variants in the BRIP1 gene were reported in a total of 71 patients. Among these, 42 patients exhibited variants exclusively in the BRIP1 gene, while 39 patients had variants in the BRIP1 gene as well as in other genes. Of the reported variants, 12 were pathogenic, 3 were likely pathogenic, and 56 were classified as variants of uncertain significance (VUS).

Conclusion: This study aimed to determine the mutation distribution of the BRIP1 gene within the Turkish population.

Keywords: Cancer, brip1, NGS

[Abstract:0201]

Improving Diagnostic Accuracy in Lynch Syndrome: The Key Role of Deletion-Duplication Analysis After Inconclusive Next-Generation Sequencing

Batuhan Ergin, Okan Kurtçu, Şule Altıner, Nüket Yürür Kutlay, Muhammed Faruk Ürkmez, Hatice Ilgın Ruhi

Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Türkiye

Lynch syndrome, one of the most common hereditary cancer syndromes, is caused by pathogenic variations, deletions/duplications in mismatch repair genes or genomic rearrangements involving the EPCAM gene. This syndrome is characterized mainly by an elevated predisposition to colorectal and endometrial cancers. While next-generation sequencing is more than capable of detecting sequence alterations, it is limited in identifying large deletions or duplications. These limitations highlight the need for complementary methods to ensure a comprehensive genetic evaluation. Multiplex
ligation-dependent probe amplification is a critical tool in cases where NGS fails to identify a clinically significant pathogenic deletion-duplication variant. MLPA is capable of detecting copy number variations and EPCAM deletions that are not recognizable through NGS. Incorporating MLPA into the diagnostic work process bridges critical gaps in genomicmassessment and minimizes blind spots when approaching Lynch syndrome. This presentation will explain how Lynch syndrome is diagnosed, focusing on the strengths and weaknesses of NGS and showing how MLPA can help in certain cases. Giving examples from our clinical practice, such as detecting an MLH1 variation, an MLH1 deletion in exon 11, and an EPCAM deletion, it will show how MLPA can help solve problems when NGS results don't explain the cancer burden in the family history. The presentation will also discuss the importance of an accurate and timely diagnosis, which helps in areas like cancer treatment, assessing family risks, and creating personalized monitoring plans. By offering a clear diagnostic approach that uses both NGS and MLPA, this presentation aims to emphasize this topic for both oncologists and medical geneticists working with Lynch syndrome. It highlights the importance of using multiple methods to make sure patients and their families get the best diagnosis and care.

Keywords: Lynch syndrome, NGS, MLPA, Deletion-duplication analysis

[Abstract:0203]

Genetic Variants in Asymptomatic Individuals with a Family History of Breast and/or Ovarian Cancer: A Retrospective Analysis

Hilal Avcı[1], Aslıhan Kiraz[1], Mevlüde İnanç[2], Munis Dündar[1]

[1] Clinic of Medical Genetics, Erciyes University Medical Faculty Hospital, Kayseri, Türkiye
[2] Clinic of Medical Oncology, Erciyes University Medical Faculty Hospital, Kayseri, Türkiye

Objective: Individuals with a family history of breast and/or ovarian cancer are at an increased risk of carrying germline pathogenic variants associated with hereditary cancer syndromes. Identifying these variants in asymptomatic individuals is crucial for cancer risk assessment, early diagnosis, and the implementation of preventive measures. This study aims to evaluate genetic predisposition in individuals with a family history of breast and/or ovarian cancer who have no personal history of cancer.
Materials-Methods: Between 2021 and 2024, a total of 1,430 hereditary cancer panel tests were conducted in our clinic, of which 346 (24.2%) were performed on individuals with a family history of cancer but no personal diagnosis. Among these, 264 individuals (18.4%) had a family history specifically of breast and/or ovarian cancer. The genetic analysis results of these 264 individuals were retrospectively reviewed. Genetic variants were classified according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP).
Results: Among the 264 individuals analyzed, 132 (50%) were found to carry a total of 177 variants. Of these, 66 (37.2%) were classified as likely pathogenic or pathogenic variants, while 111 (62.8%) were variants of uncertain significance. In the remaining 132 individuals (50%), no genetic variants were detected. Pathogenic variants were predominantly identified in genes associated with hereditary breast and ovarian cancer syndromes.
Conclusion: This study highlights the presence of pathogenic variants associated with hereditary cancer syndromes in individuals with a family history of breast and/or ovarian cancer. The findings underscore the importance of early detection of cancer-predisposing genetic variants in asymptomatic individuals and the integration of genetic counseling into clinical practice. Genetic testing, guided by ACMG/AMP standards, plays a pivotal role in facilitating early diagnosis, implementing preventive strategies, and advancing personalized healthcare approaches for high-risk individuals.
Keywords: Breast-ovarian cancer, Family history, Genetic susceptibility, Hereditary cancer

[Abstract:0204]

Report of a family with homozygous pathogenic variant in CHEK2 gene

Şenol Demir, Ceren Alavanda

Department of Medical Genetics, University of Health Sciences, Van Training and Research Hospital, Van, Türkiye

Objective: Hereditary cancers are a group of cancers in which pathogenic variants in genes predispose individuals to cancer and constitute approximately 5-10% of all cancers. Genes such as BRCA1, BRCA2, TP53, APC, PTEN, and CHEK2, which are commonly mutated in hereditary cancers, are genes involved in cell cycle control, DNA repair, and tumor suppressor functions. Heterozygous pathogenic variants in the CHEK2 gene have been associated with tumor predisposition Type 4 (MIM:# 609265). Our study aimed to evaluate the clinical findings and genetic results of the patient with a homozygous pathogenic variant in the CHEK2 gene and her family members. After anamnesis and detailed clinical examination, DNA was isolated from the peripheral blood sample of the patient. DNA sequencing was performed with the next-generation sequencing (NGS) method. A custom design panel was created and analyzed for cancer-related genes. A segregation study was performed with the NGS method in terms of the detected variant.

Case: A 60-year-old woman was referred to our clinic with a history of papillary thyroid cancer at the age of 50 and bilateral breast cancer at the age of 53. Her family history included papillary thyroid cancer in her sister, colon cancer in another sister, and papillary thyroid cancer in 2 daughters.

Conclusion: The patient's genetic analysis revealed a homozygous c.538C>T p.Arg180* pathogenic variant in the CHEK2(NM:001005735.2) gene. In the segregation study, the same variant was found to be heterozygous in two daughters and homozygous in her sister. As in our study, screening of family members is very significant if the index case has a homozygous CHEK2 variant. Heterozygous germline pathogenic variants in the CHEK2 gene are associated with breast cancer, thyroid cancer, prostate cancer, and colorectal cancer. Therefore, screening and regular controls are important in these patients. Preventive surgery or other risk-reducing strategies may be considered depending on the family history and risk profile.

Keywords: CHEK2, Breast cancer, tumor predisposition syndrome

[Abstract:0205]

Molecular and Clinical Findings of Neurofibromatosis Type-1 Patients: A Single Center Experience

Uğur Olgun Çelik[1], Sinem Kocagil[1], Ezgi Susam[3], Coşkun Yarar[2], Sevilhan Artan[1]

[1]Department of Medical Genetics, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[2] Department of Pediatric Neurology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[3]Sakarya Training and Research Hospital, Sakarya, Türkiye

Neurofibromatosis type 1 (NF1, OMIM #162200) is an autosomal dominant disorder characterized by café-au-lait macules, Lisch nodules, optic pathway gliomas, intertriginous freckling, osseous lesions, and cutaneous neurofibromas with an increased susceptibility to tumor formation. The NF1 gene functions as a tumor suppressor, playing a critical role in regulating cell growth and development. This study presents the molecular and clinical findings of patients diagnosed with Neurofibromatosis type 1 at Eskişehir Osmangazi University Department of Medical Genetics between 2014 and 2024. The median age at diagnosis ranged from 2 to 51 years, with a mean of 25.2 years. A heterozygous pathogenic variant in the NF1 gene or a microdeletion involving the NF1 gene was identified in 37 patients. The most common clinical and molecular findings are summarized in Table 1. Among the identified variants, two (5%) were microdeletions, five (13%) were missense variants and 29 (78%) were nonsense variants. Three variants (11%) were novel, while 34 variants (89%) had been previously reported in the literature. Variants were classified according to ACMG criteria: 28 (75%) were pathogenic, seven (18%) were likely pathogenic, and two (5%) were variants of uncertain significance (VUS). Family members with similar clinical findings were identified in 16 patients. Sanger sequencing of known variants was recommended for family members and screening suggestions were provided in line with current clinical guidelines. Through this study, we aim to contribute to the literature by reporting novel NF1 variants and exploring genotype-phenotype correlations in our Turkish patient cohort.

Keywords: NF1 gene, neurofibromatosis, cancer predisposition, genotype-phenotype correlation

Table 1

Patient Number	> 6 Cafe A u Lait macules	Freckling	> 2 Neurofibroma or Plexiform Neurofibroma	Optic Pathway Glioma	> 2 or more Lisch nodule	Osseous lesions	Family History	Molecular Change
1	+	+	-	-	+	-	-	arr[GRCh37] 17q11.2 (29016360_30343146)x1
2	+	+	-	-	-	-	+	NF1(NM_001042492.3):c.3569G>A p.Gly1190Asp (heterozygous)
3	+	+	+	-	-	-	+	NF1(NM_000267.3):c.5990G>A p.Trp1997* (heterozygous)
4	+	-	-	-	-	-	-	NF1(NM_001042492.3):c.2704dup p.Met902Asnfs*4 (heterozygous)
5	-	-	+	-	-	-	-	NF1(NM_001042492.3):c.379G>T p.Gly127* (heterozygous)
6	+	+	-	-	-	-	+	NF1(NM_001042492.3):c.6246del p.Arg2083Alafs*4 (heterozygous)
7	+	-	-	-	+	-	-	NF1(NM_001042492.3):c.7549C>T p.Arg2517* (heterozygous)

8	+	+	-	-	-	-	+	NF1(NM_001042492.3):c.6855C>A p.Tyr2285* (heterozygous)
9	+	+	-	-	-	-	-	NF1(NM_001042492.3):c.7602dupT p.Lys2535* (heterozygous)
10	-	+	-	-	-	-	-	NF1(NM_001042492.3):c.4600C>T p.Arg1534* (heterozygous)
11	+	+	+	-	-	-	+	NF1(NM_000267.3):c.5902C>T p.Arg1968* (heterozygous)
12	-	-	+	-	-	-	-	NF1(NM_00104249.2):c.3656G>A p.Gly1219Glu (heterozygous)
13	+	+	+	-	-	-	+	NF1(NM_001042492.3):c.6246del p.Arg2083Alafs*4 (heterozygous)
14	+	-	+	-	-	-	-	NF1(NM_001042492.3):c.4520T>G (p.Leu1507*) (heterozygous)
15	+	+	-	-	-	-	-	arr[GRCh37] 17q11.2 (29375177_30350798)x1
16	+	+	+	-	+	-	-	NF1(NM_001042492.3):c.7348C>T p.Arg2450* (heterozygous)
17	+	-	-	-	+	-	-	NF1(NM_001042492.3):c.1756_1759del p.Thr586Valfs*18 (heterozygous)
18	+	+	-	+	-	-	+	NF1(NM_001042492.3):c.1658A>G p.His553Arg (heterozygous)
19	+	+	-	-	-	-	-	NF1(NM_001042492.3):c.5305C>T p.Arg1769* (heterozygous)

20	+	-	-	-	-	-	-	NF1(NM_001042492.3):c.6799del p.Ile2267* (heterozygous)
21	+	-	+	-	-	-	+	NF1(NM_001042492.3):c.5645del p.Cys1882Leufs*5 (heterozygous)
22	+	-	+	-	-	-	+	NF1(NM_000267.3):c.1756_1759delACTA p.Thr586Valfs*18
23	+	+	-	-	+	-	+	NF1(NM_001042492.3):c.574C>T p.Arg192* (heterozygous)
24	+	-	-	-	-	-	+	NF1(NM_000267.3):c.2252-2A>G p.Tyr2285* (heterozygous)
25	+	+	+	-	-	-	-	NF1(NM_001042492.3):c.6148del p.Val2050Leufs*8) (heterozygous)
26	+	+	-	-	-	-	+	NF1(NM_000267.3):c.4426_4429del (heterozygous)
27	+	+	+	-	-	-	-	NF1(NM_001042492.3):c.4600C>T p.Arg1534* (heterozygous)
28	+	-	+	-	-	-	-	NF1(NM_001042492.3):c.1392+1G>T (heterozygous)
29	+	-	-	-	-	-	+	NF1(NM_001042492.3):c.6238A>G p.(Ile2080Val) (heterozygous)
30	+	+	+	-	-	-	-	NF1(NM_001042492.3):c.1318C>T (p.Arg440Ter) (heterozygous)
31	+	+	+	-	-	-	-	NF1(NM_001042492.3):c.8327T>G (p.Leu277Arg) (heterozygous)
32	-	-	+	-	-	-	-	NF1(NM_001042492.3):c.7989dup p.Lys2664* (heterozygous)

33	-	-	-	-	-	-	+	NF1(NM_001042492.3):c.5036_5041de (p.Asn376Ser) (heterozygous)
34	+	-	-	-	-	-	+	NF1(NM_001042492.3): c.6855C>A (p.Tyr2285Ter) (heterozygous)
35	-	+	+	-	-	-	-	NF1(NM_001042492.3): c.2356C>T (p.Gln786Ter) (heterozygous)
36	+	+	-	-	+	-	-	NF1(NM_001042492.3): c.3496+5G>A (heterozygous)
37	-	-	+	-	-	-	+	NF1(NM_001042492.3): c.4084 C>T (p.Arg1362Ter) (heterozygous)
Percentage	81%	56%	56%	2%	16%	0%	43%	

[Abstract:0206]

Multilocus Inherited Neoplasia Allelic Syndrome: A Case Series and Report of Two Uncommon Combinations Involving *CHEK2/TP53* and *MUTYH/RAD51C* Genes

Emine İpek Ceylan[1], Dilek Özata Aksoy[1], Hande Nur Cesur Baltacı[1], Mutlu Doğan[2], Özge Özalp[1]

[1]Clinic of Medical Genetics, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye
[2]Clinic of Medical Oncology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye

Objective: Hereditary cancer syndromes, which account for approximately 5-10% of all cancer cases, constitute a group of disorders caused by germline pathogenic variants detected in an increasing number of genes. The identification of a pathogenic variant can have significant implications for treatment strategies, personalized preventive programs, family screening, and genetic counseling.
With the widespread adoption of next-generation sequencing technologies and the increasing use of comprehensive gene panels, the number of cases with pathogenic variants in two or more genes is also on the rise. Multilocus hereditary neoplasia allelic syndrome (MINAS) refers to the presence of germline pathogenic variants in multiple cancer susceptibility genes within a single patient. Although an increasing number of patients with MINAS have been reported, the phenotypic effects and clinical manifestations of combinations of these variants are highly heterogeneous. In this study, we present five cases of MINAS resulting from combinations of pathogenic variants in cancer susceptibility genes.
Case: All cases were female, and their ages at diagnosis ranged from 44 to 76 years. All patients were referred with a primary cancer diagnosis. One patient had ovarian cancer, one had breast cancer, and the remaining three cases had nasopharyngeal cancer, cervical cancer, and endometrial cancer, with breast cancer as a concomitant condition. As a result of genetic analysis, pathogenic variants were detected in the combinations of BRCA1/ATM, TP53/CHEK2, RAD51C/MUTYH, ATM/FANCA, and BRCA2/PALB2 in these patients. To the best of our knowledge, the combination of pathogenic variants in the TP53/CHEK2 and RAD51C/MUTYH genes has not been previously reported.
Conclusion: This study is significant for elucidating the clinical and genetic findings of MINAS, which was relatively recently described, and for contributing to the existing literature. Furthermore, it will aid in the long-term follow-up of patients, family screening, and ensuring that they receive appropriate genetic counseling.
Keywords: MINAS, Hereditary Cancer Syndromes, Next Generation Sequencing

[Abstract:0207]

The Place of Screening Performed in Primary Health Care Center in Diagnosis of Hereditary Cancer and Reccommendations for Follow-up of Other Family Members

Sena Akbaş

Department of Family Medicine, Eskisehir Osmangazi University, Eskişehir, Türkiye

Objective: Screening programs carried out in primary health care centers (PHCC) greatly contribute to ensuring individuals' access to healthy life programs and risk factors for chronic diseases, in Türkiye.
This paper discusses the place of current screenings performed in PHCC in the early diagnosis and treatment of hereditary cancers. Afterward, recommendations were made regarding developing strategies for genetic test reminders to necessary individuals through health record systems and the roles that family practitioners (FP) can undertake for ideal patient follow-up.
Materials-Methods: According to the screening guide in the current PHCC, breast, colon, and cervix cancer screenings are performed in Türkiye. Individuals are invited and the necessary information is provided every two years. While the target audience for breast cancer is women aged 40-69, for colon cancer is women and men aged 50-70. Those who accept are directed to centers that perform mammography and the fecal occult blood (FOBT) test taken is sent to the relevant center. FP processes the mammography and FOBT test results of individuals into their systems as breast/colon cancer screening and monitors their transmission to e-Nabız. Individuals should be directed to the relevant specialist if the sample result is positive/suspicious. In a study examining the effectiveness of breast cancer screenings (Eryılmaz, 2010), it was observed that 48 (57.8%) of 83 breast cancer patients who underwent surgery were diagnosed owing to family medicine screening programs. This shows how important the relevant screenings are
Conclusion: By integrating cancer pedigree information into e-Nabız, a warning note can be added to the system regarding family members at risk for patients with pathogenic variants. Like pregnancy follow-up, genetic test reminders can be carried out within family medicine. In addition, the periodic checks that individuals with pathogenic variants who have not yet developed cancer should have in the relevant departments can be followed up by their closest physicians, similar to chronic disease follow-up, by adding a section to e-Nabız. In this way, the rate of genetic tests and appropriate follow-ups, which are very important for early diagnosis and effective treatment, can be significantly increased.
Keywords: Primary health care, hereditary cancer syndromes, screening programs, breast cancer, colon cancer

[Abstract:0208]

Difficulties in Genetic Counseling for Moderate Penetrance Gene Variants Detected in Cases Evaluated for Hereditary Cancers

Dilek Özata Aksoy[1], Emine İpek Ceylan[1], Hande Nur Cesur Baltacı[1], Öztürk Ateş[2], Özge Özalp[1]

[1] Department of Medical Genetics, University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Medical Genetics, Ankara, Türkiye
[2] Department of Medical Oncology, University of Health Sciences, Dr.Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye

With the widespread use of next-generation sequencing (NGS) techniques, gene mutations showing moderate penetrance are being encountered more frequently in cancer genetics. The inclusion of moderate penetrance genes in multigenic panels presented challenges in providing genetic counseling for pathogenic/likely pathogenic variants detected in these genes. The risks associated with CHEK2, APC I1307K and monoallelic MUTYH variants frequently detected in these panels have not been clarified yet. In this respect, the APC I1307K variant has been evaluated in many studies. In this study, cases evaluated for hereditary cancers in our hospital's medical genetics outpatient clinic and in which the APC I1307K variant was detected are presented. Of the 5 cases in which the variant was detected; 1 was male with the diagnoses of colon cancer and prostate cancer and 4 were female with the diagnoses of breast cancer. None of the patients had a family history of colorectal cancer. In the hereditary cancer panel studied with targeted NGS using DNA obtained from peripheral blood samples of the cases, APC:c.3920T>A p.(Ile1307Lys) p.(I1307K) variant was detected as heterozygous. No other pathogenic/likely pathogenic variant was detected in other genes. The detected APC variant was not associated with familial adenomatous polyposis (FAP) syndrome. However, it is a variant showing moderate penetrance in terms of colorectal cancers and it is useful to benefit from the variant-specific management algorithms reported in current guidelines. The aim of our study is presenting cases with moderate penetrance APC:c.3920T>A p.(Ile1307Lys) variant, which has conflicting associations in studies and to contribute to the literature with the long-term follow-up of these cases. At the same time we highlight the importance of utilizing variant-specific guidelines for the clinical management and genetic counseling of patients and other unaffected family members.

Keywords: APC, hereditary cancer, moderate penetrance, NGS

[Abstract:0210]

Incomplete Penetrance and Expression Variabililty in SUFU Gene Pathogenic Variants: A Study of Two Families Across Three Generations

Ezgi Susam

Clinic of Medical Genetics Clinic, Sakarya Training and Research Hospital, Sakarya, Türkiye

Introduction: SUFU related basal cell nevus syndrome (BCNS), also known as Gorlin syndrom, is a familial tumor predispositon syndrome typically associated with medulloblastoma, meningioma and basal cell carcinoma (BCC) caused by monoallelic null variants. Recent studies highlight the role of SUFU gene monoallelic null variants also in a different spectrum of phenotypic outcomes, including neurodevelopmental delay(NDD), oculomotor apraxia and cranial anomalies.

Objectives: This study evaluates the phenotypic variability, incomplete penetrance and expression variabililty in two unrelated families across three generations with SUFU mutations. It was also discussed the implications for genetic counseling, particularly in tumor screening, surveillance, and assessing recurrence risk in subsequent generations.

Cases: Proband-A (Family-A): 6 year-old male was evaluated due to medullablastoma with notable family history of cancer and NGS panel revealed heterozygous SUFU(NM_016169.3);c.825G>A;p.Trp275Ter variant. Segregation analysis confirmed several members carried the same variant spanning three generations. Proband-B (Family-B): 3 year-old male presented with NDD accompanying saccadic eye movements was examined. He had autistic features including; stereotypes and self-mutilation. Planned NGS panel revealed de novo heterozygous SUFU(NM_016169.3);c.71dup;p.Ala25GlyfsTer23 variant.

Results: Family-A: Across 3 generations, 5 out of 10 variant carriers had been diagnosed with tumors: 2 medulloblastomas, 2 meningiomas, and 1 ovarian fibroma. No carriers presented with BCC or jaw cysts. Mild macrocephaly and prominent forehead were observed in all, while coarse facial features and prognatism were predominantly seen in adults. Milestones achivement and mental performance were assessed in all, no signs of NDD or cerebellar findings were observed. MRI findings were unremarkable. Tumor surveillance protocols formulated primarily based on BCNS literature.

Given the higher incidence of medulloblastoma and meningioma in SUFU-associated cases compared to PTCH1 gene-related BCNS, more frequent cranial MRI was recommended, particularly for pediatric patients. Family-B: Cranial MRI revealed benign hydrocephaly and mild vermis hypolasia. Since

SUFU-related NDD was recently defined in only 24 cases (children and adults) across nine families and no SUFU-associated tumors were reported in these cases, tumor surveillance were planned predominantly based on clinical findings rather than radiography.

Conclusion: SUFU gene null variants exhibit diverse clinical presentations, characterized by incomplete penetrance and variable expressivity, necessitating nuanced approaches in genetic counseling and tumor surveillance.

Keywords: familial tumor predispositon syndromes, Gorlin syndrome, SUFU related basal cell nevus syndrome, SUFU related neurodevelopmental delay syndrome, SUFU related oculomotor apraxia

[Abstract:0211]

SH2B3; A Case Report with a Germline Novel Biallelic Variant

Zeynep Esener[1], Ayşegül Ünüvar[2], Zeynep Karakaş[2]

[1] Department of Medical Genetics, Balikesir University Faculty of Medicine, Balıkesir, Türkiye
[2] Division of Pediatric Hematology and Oncology, Istanbul University Faculty of Medicine, İstanbul, Türkiye

Objective: The SH2B3 (Lnk) gene serves as a critical negative regulator, particularly in the JAK-STAT signaling pathway. Somatic variants in SH2B3 have been implicated in the pathogenesis of various myeloproliferative neoplasms. Germline polymorphisms and variants in the SH2B3 gene have been linked to hematological disorders/malignancies (including acute myeloid leukemia and myelodysplastic syndromes), coronary heart disease, hypertension, and autoimmune conditions. Despite reports of germline variants in different clinical contexts, the gene-phenotype correlation remains incompletely understood. Herein, we present a case with a biallelic germline variant in the SH2B3 gene, aiming to contribute to the current body of literature.

Case: A 16-year-11-month-old female case referred to the medical genetics clinic for evaluation of massive splenomegaly, thrombocytosis and suspected myeloproliferative disease. The patient's parents were first-degree cousins, and her younger brother passed away at five days old with suspected juvenile myelomonocytic leukemia. Splenomegaly was first identified during the neonatal period. Her weight was 62 kg (0.68 SD), height 151 cm (-1.99 SDS), and head circumference 55 cm
(-0.69 SDS). On physical examination, the spleen was palpable 8 cm below the costal margin. Peripheral blood smear analysis revealed hypersegmented neutrophils with increased cytoplasmic granulation; erythrocytes displaying spherocytes, occasional stomatocytes, and teardrop cells; and platelets with variable sizes. Whole-exome sequencing was performed on the patient. We detected a homozygous c.1093T>C variant in the SH2B3 (NM_005475.2) gene. Segregation analyses were performed with next-generation sequencing. Written informed consent was obtained from the parents prior to participation in the study.

Conclusion: Deletions or variants in the SH2B3 gene are hypothesized to result in excessive activation of the JAK-STAT signaling pathway, leading to abnormal cellular proliferation. Both somatic and germline variants of the SH2B3 gene have been associated with a diverse clinical spectrums. This case underscores a rare phenotype in the SH2B3 gene.

Comprehensive identification and characterization of SH2B3-associated phenotypes, along with their clinical implications, are essential for advancing therapeutic strategies and refining genetic counseling practices.

Keywords: SH2B3, JAK-STAT, hematological disorders, hematological malignancies

[Abstract:0212]

Low Penetrance TNFRSF13B Variant in a Patient Diagnosed With Diffuse Large B-Cell Lymphoma

Emine Karataş[1], Maide Korkmaz1, Veysel Gök[2], Ebru Yılmaz[2], Munis Dündar[1]

[1]Department of Medical Genetics, Faculty of Medicine, Erciyes University, Kayseri, Türkiye
[2]Division of Pediatric Hematology and Oncology, Department of Pediatrics, Faculty of Medicine, Erciyes University, Kayseri, Türkiye

Introduction: Developmental defects of myeloid or lymphoid cells and stem cells are among the molecular mechanisms underlying immunodeficiency, leukemia and lymphoma. In common variable immunodeficiency disorder (CVID), B cell number and function are reduced and T cell response is irregular. Chronic bacterial and viral infections, facilitate the development of lymphoproliferative diseases and lymphoma. The genetic etiology of approximately 25% of CVID has been elucidated, one of which is the TNFRSF13B gene.The TNFRSF13B gene encodes TACI, a trimeric transmembrane receptor involved in the counter-selection of early B cells.
Case: We present a case of DLBCL diagnosed with the TNFRSF13B C104R variant. The patient, a 9-year-old girl, applied with a complaint of swelling in her neck for 1 year and was diagnosed with DLBCL as a result of the pathology result in the biopsy. There was no recurrent bacterial or viral
infection in her history. In the family history, there was a relative diagnosed with lymphoma from the mother's side. EBV-IGG was positive in serological tests. IG subgroups were within the normal range. The bone marrow was normocellular. In the whole exome sequencing analysis performed for immune deficiency and germline predisposition, exon 3 c.310T>C p.Cys104Arg variant was detected in the TNFRSF13B gene. In the family segregation, the variant was also detected in the mother.
Discussion and Conclusion: Approximately 10% of CVID patients carry heterozygous mutations in the TNFRSF13B gene. One of the most common mutations is C104R. It is also seen in 1-2% of healthy populations. It is known that the monoallelic C104R variant increases the susceptibility to autoimmune diseases, affects the development of naive B cells, causes decreased TACI expression in memory B cells and as a result, impaired activation and antibody secretion. It has been shown that reduction of MYC and E2F target genes involved in the cell cycle contributes to the impaired proliferation of naive B cells. This variant has been reported in patients with lymphoma diagnosis before. Our case also supports the fact that it plays a role as a modifying factor rather than being the sole monogenic cause in the development of lymphoma.
Keywords: DLBCL, TNFRSF13B, C104R, Low Penetrance

[Abstract:0213]

Functional and Statistical Analysis of CDH1 Gene Variants in Different Stages of Breast Carcinoma (In Situ and Invasive)

Zeynal Sütkurt, Ali Torabi, Hüseyin Saylam, Özkan Bağcı, Süleyman Nergiz

Department of Medical Genetics, Selçuk University, Konya, Türkiye

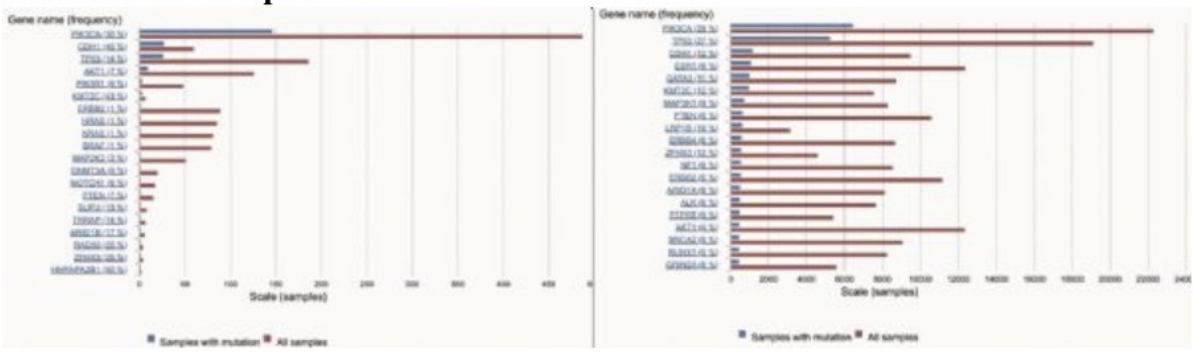
Objective: To investigate the distribution and functional impact of CDH1 gene variants in in situ (CIS) and invasive breast carcinoma stages. This study aims to: Investigate the notable decrease in CDH1 mutation frequency from CIS(45%) to invasive carcinoma (12%) and its implications for stage-specific tumor progression. Examine the prevalence of dominant negative and loss-of-function (LOF) mutations across cancer stages. Evaluate the biological implications of mutations in protein domains.
Materials-Methods: CDH1 gene mutation data were extracted from the COSMIC database for breast cancer cases, including: CIS cohort: 60 total samples, with 27 samples exhibiting CDH1 mutations.
Invasive Carcinoma cohort: 9484 total samples, with 1154 samples exhibiting CDH1 mutations.
Statistical Analysis: Chi-square test was employed to assess the differences in mutation types (missense, frameshift, nonsense) between stages. The impact of mutations on protein domains was analyzed to infer dominant negative or LOF effects, supplemented by literature review.
Results: CIS: Missense mutations were predominant (66.67%), indicating dominant negative effects. Frameshift and nonsense mutations were found at low frequencies. Invasive Carcinoma: LOF mutations (frameshift: 43.53%, nonsense: 23.51%) were more frequent. Missense mutations accounted for 11.36%, with a statistically significant difference between stages ($p < 0.05$). These mutations were concentrated in extracellular protein domains, suggesting a potential indirect LOF effect.
Conclusion: This study highlights the transition of CDH1 mutations from dominant negative effects in CIS to biallelic LOF mutations in invasive carcinoma, emphasizing their critical role in tumor progression. The observed decrease in CDH1 mutation frequency from 45% CIS to 12% in invasive carcinoma underscores a potential shift in the CDH1's functional role and contribution other genes (TP53, PIK3CA) across tumor stages. Additionally, the findings propose that the observed 11.36% missense mutations in invasive carcinoma may contribute through indirect LOF effects rather than dominant negative mechanisms. These insights support stage-specific functional roles of CDH1 mutations in breast cancer, providing evidence for distinct molecular mechanisms driving in situ and invasive stages. This is one of the first systematic analyses to statistically validate the functional differences in CDH1 variants across in situ and invasive carcinoma stages. The findings provide valuable insights into stage-specific biological roles of CDH1 mutations.
Keywords: CDH1, Breast Cancer, In Situ Carcinoma, Invasive Carcinoma, Statistical Analysis

CDH1 Mutation Comparison in Breast Cancer Stages

Mutation Type	CIS (n)	CIS (%)	Invasive (n)	Invasive (%)
Nonsense substitution	2	7.41	269	23.51
Missense substitution	18	66.67	130	11.36
Synonymous substitution	0	0.00	6	0.52
Inframe insertion	0	0.00	3	0.26
Frameshift insertion	0	0.00	230	20.10
Inframe deletion	1	3.70	17	1.49
Frameshift deletion	1	3.70	268	23.43
Complex mutation	5	18.52	14	1.22
Other	0	0.00	65	5.68
Total	**27**	**100**	**1144**	**100**

Data highlights the prevalence of missense mutations (dominant negative effects) in CIS compared to LOF mutations (frameshift, nonsense) in invasive carcinoma. Statistical analyses indicate a significant difference in mutation types between the stages ($p < 0.05$).

Common Gene Variants Distribution In Situ Carcinoma and Invasive Carcinoma in Breast Cancer Samples



The charts illustrate the most common gene variants in in situ carcinoma and invasive carcinoma of breast cancer. Notably, CDH1 mutations are more frequent in in situ carcinoma (45%) compared to invasive carcinoma (12%), highlighting a potential shift in its functional role from dominant negative effects in the early stage to loss-of-function mutations in the invasive phase.

[Abstract:0214]

A Case of Lynch Syndrome with Atypical Presentation

Sevinç Ballı[1], Yüksel Ürün[2]

[1]Department of Medical Oncology, Samsun Training and Research Hospital, Samsun, Türkiye
[2]Department of Medical Oncology, Ankara University Faculty of Medicine Hospital, Ankara, Türkiye

Objective: Lynch syndrome is among the most prevalent cancer predisposition syndromes. A constitutional detrimental mutation in a DNA mismatch repair gene accounts for almost 70% of instances of this condition. The oncogenetic consultation and identification of the genetic cause enable the establishment of particular monitoring and the provision of a pre-symptomatic test to all first-degree relatives of the index case.
Case: The patient, who had no complaints due to having two colon and one ovarian cancer in the family, underwent prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy surgery due to the presence of MSH-2 heterozygous mutation compatible with Lynch syndrome in the genetic analysis sent. Subsequently, at the age of 58, the patient, who presented a brain mass, underwent surgery. The patient's pathology was evaluated as a high-grade glial tumor and mutations were observed in the TP53 and MMR genes. It was evaluated to be associated with Lynch syndrome. The patient, who received adjuvant temozolomide after adjuvant radiotherapy, could not complete the adjuvant treatment due to toxic hepatitis. The patient who had an intracranial recurrence in the 4th month was given immunotherapy treatment due to MSI-H. The patient, who had a clinical and radiological response, later died due to infection and sepsis.
Conclusion: This case report highlights that patients with a familial history can show varied clinical presentations despite receiving genetic counseling and preventative interventions, necessitating may more rigorous and comprehensive follow-up for these individuals.
Keywords: Lynch syndrome, high-grade glial tumor, MSI-H cancers, prophylactic surgery, hereditary cancers

[Abstract:0215]

MUTYH Variants in the Çanakkale Population: Genotype-Phenotype Correlation of Monoallelic Variants in Cancer

Koray Tekin[1], Romyla Bourouba Bourouba[2], Mehmet Berkay Akcan[3], Fatma Sılan[1]

[1]Department of Medical Genetics, Faculty of Medicine, Çanakkale On sekiz Mart University, Çanakkale, Türkiye
[2]Department of Biology and Animal Physiology, Faculty of Nature and Life Sciences, Ferhat Abbas Sétif 1 University, Sétif, Algeria
[3]İzmir City Hospital, İzmir, Türkiye

Our aims to investigate the relation between the monoallelic MUTYH(MutY human homolog) gene variants and extracolonic malignancies such as breast, hepatocellular, gastric, and pancreatic cancers, which have not yet been clearly linked to the MUTYH gene. This study involved 1990 probands with diverse clinical symptoms, who underwent next-generation sequence analysis including clinical exome sequencing, whole-exome sequencing, and inherited cancer panel testing. A total of 1618 individuals older than 18 years were included, with 27 individuals carrying MUTYH pathogenic/likely pathogenic variants integrated into the current study. We identified 27 individuals with 10 different monoallelic pathogenic/likely pathogenic variants from 24 different families. 1 novel variant (c.1143_1144dupGG p.E382fs*43) was detected in a patient with cerebellopontin angle tumor. Different monoallelic variants were detected in 3 patients with breast cancer (c.849+3A>C; c.1353_1355delGGA,p.E452del; c.736C>T, p.R246W) with onsets at ages 63, 49, and 24 years, respectively. Additionally, two variants emerged as compound heterozygous (c.649C>T p.R217C; c.849+3A>C) in a male patient diagnosed with colorectal cancer (CRC) without polyposis at the age of 43 years old. We found a novel and interesting variant that could be related to breast and thyroid cancers; and potentially two founder mutations linked to a familial cancer history.

Keywords: Breast cancer, Heterozygotes, MUTYH, Monoallelic, Neoplasm

[Abstract:0216]

Insights from Germline Variant Analysis in a Turkish Cohort Diagnosed with Ovarian Cancer

Gülin Yılmaz[1], Metin Demir[2], Sinem Kocagil[1], Oğuz Çilingir[1]

[1]Department of Medical Genetics, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye
[2]Department of Internal Diseases, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Türkiye

Abstract

Ovarian cancer (OC) is the leading cause of death among gynecological malignancies, accounting for approximately 225,000 new cases (3.7% of all female cancers) and 140,000 deaths (4.2% of all cancer-related deaths in women) globally each year. Germline pathogenic variants in cancer-related genes are detected in approximately 23% of OC cases, with the majority occurring in BRCA1 and BRCA2, as well as other genes involved in homologous recombination or DNA mismatch repair pathways. Variability in germline testing rates across populations may stem from heterogeneous clinical practices. Guidelines from the European Society of Gynecological Oncology and the European Society of Medical Oncology recommend BRCA1/2 testing for all OC patients, except those with mucinous histology, while the American Society for Clinical Oncology advocates for germline multi-gene testing for all OC patients. This study evaluated the results of a Hereditary Cancer Panel and BRCA1/BRCA2/CHEK2 MLPA tests performed on peripheral blood samples from 80 OC patients referred to Eskişehir Osmangazi University Hospital Genetic Diagnosis Center in between January 2017 and August 2024. A total of 53 variants of uncertain significance (VUS), likely pathogenic (LP) or pathogenic (P) were identified in 45 patients Pathogenic/likely pathogenic variants were detected in %27,5 of the patients (22/80). Among the variant detected genes, BRCA1 (18/53, 34%) was the most common, followed by BRCA2 (5/53, %9,4), BRIP1, MSH2 and APC (each 3/53, 5,6%). In total, 53 variants were detected, with 34% classified as pathogenic, 9,4% as likely pathogenic, and 56,6% as VUS. Variant types included missense (62,2%), nonsense (24,5%), splice-site (5,6%), and deletions (7,5%). A gross exonic deletion in CHEK2 was detected in one patient using MLPA method. All patients received genetic counseling, and unique variant screening for family members was recommended. Screening programs were suggested to patients according to current guidelines. This study highlights the genetic heterogeneity of OC in a Turkish cohort, emphasizing the importance of identifying common germline mutations to guide personalized risk assessment and management.

Keywords: Germline, Ovarian cancer, Turkish cohort

[Abstract:0217]

Multigene NGS Panel Testing in Gastric and Colorectal Cancers: A Single-Center Experience

Mustafa Mert Aydın[1], Aslıhan Kiraz[1], Metin Özkan[2], Munis Dündar[1]

[1]Department of Medical Genetics, Erciyes University Medical Faculty Hospital, Kayseri, Türkiye
[2]Department of Medical Oncology, Erciyes University Medical Faculty Hospital, Kayseri, Türkiye

Objective: Hereditary gastric and colorectal cancers (CRC) contribute significantly to global cancer morbidity and mortality. While well-defined syndromes like familial adenomatous polyposis (FAP) and Lynch syndrome exist, many CRC patients harbor pathogenic variants outside these classifications.
This study analyzes next-generation sequencing (NGS) data from a single center to better understand hereditary cancer risk and the impact of genetic testing in clinical practice.
Materials-Methods: Between 2021 and today, 1430 patients underwent NGS-based hereditary predisposition gene panel testing in our department. This cohort included individuals with a family history of cancer, non-cancer probands, and other malignancies. A subset of 170 patients diagnosed with gastric or colorectal carcinoma was analyzed separately (Gastric cancers: 33, Polyposis cancers: 20, Nonpolyposis cancers: 117). Variants were classified per ACMG/AMP guidelines, and variants of uncertain significance (VUS) were systematically reanalyzed. The dataset remains subject to future updates.
Results: A notable proportion of patients carried germline alterations beyond Lynch and FAP criteria, reinforcing the need for broader genetic screening. The observed variant rate per patient was higher than expected, potentially highlighting new gene-disease associations or reflecting the selection criteria for genetic testing. Family history analysis further emphasized hereditary patterns in these cancers. The findings suggest that multigene panel testing can detect previously unrecognized risks, offering critical insights for clinical management and genetic counseling.
Conclusion: Expanding genetic testing beyond classical syndromic definitions is crucial. This study highlights the value of NGS-based multigene panels in detecting hereditary cancer risks that may otherwise go unnoticed. Continuous reassessment of variants of uncertain significance (VUS) and improvements in panel composition enhance risk evaluation and diagnostic precision. A structured genetic screening approach facilitates early intervention, improves surveillance, and helps mitigate the hereditary cancer burden.
Keywords: Cancer screening, colorectal cancer, gastric cancer, germline, next-generation sequencing

[Abstract:0218]

Evaluation of Genetic Variants in Patients with Ovarian, Pancreatic, and Prostate Cancer Using Multigene Hereditary Cancer Panel Analysis

Sema Nur Kır[1], Oktay Bozkurt[2], Yusuf Özkul[1], Munis Dündar[1]

[1]Department of Medical Genetics, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[2]Department of Medical Onkology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

Objective: Hereditary cancers constitute approximately 10-15% of all malignancies, with ovarian, pancreatic, and prostate cancers being of particular clinical significance. Genetic testing is essential for risk assessment and clinical management. While single-gene analyses were traditionally employed, the advent of Next-Generation Sequencing (NGS) technology has enabled the comprehensive assessment of multiple cancer susceptibility genes. This study aims to investigate the genetic profiles of patients diagnosed with ovarian, pancreatic, and prostate cancer referred to our clinic, focusing on the distribution and characteristics of detected variants.

Materials-Methods: Between 2021 and the present, 1,430 patients were referred to our clinic for genetic evaluation. Among them, 91 ovarian, 36 pancreatic, and 32 prostate cancer patients were selected for further analysis. The study examined demographic characteristics such as gender, age, and cancer classification, alongside the distribution of genetic variants to explore potential correlations. All patients underwent genetic testing using the NGS-based Multigene Hereditary Cancer Panel.

Results: Pathogenic variants were detected in nearly one-third of ovarian cancer patients, with BRCA1 being the most frequently mutated gene. A substantial proportion of these patients also carried variants of uncertain significance (VUS). Similarly, pancreatic cancer patients exhibited pathogenic variants in approximately one-fourth of cases, with over half harboring VUS. Prostate cancer patients showed a lower prevalence of pathogenic variants, while a notable proportion had VUS, highlighting the heterogeneous nature of genetic findings across cancer types.

Conclusion: This single-center study highlights the importance of multigene hereditary cancer panel testing in assessing hereditary cancer risk. Detecting both pathogenic and uncertain variants supports a better understanding of genetic susceptibility and helps guide personalized risk management and follow-up strategies. These findings emphasize the need to incorporate genetic testing into routine clinical practice to support early diagnosis and appropriate patient care.

Keywords: Ovarian cancer, pancreatic cancer, prostate cancer, multigene panel, NGS

[Abstract:0219]

Secondary ACMG and Non-ACMG Genetic Findings in Genes Related to Cancer Phenotypes in Whole Exome Sequencing Data From 229 Individuals

Kübra Özen, Deniz Torun, Yusuf Tunca

University of Health Sciences, Ankara Gülhane Training and Research Hospital, Ankara, Türkiye

Abstracts

Between 2018 and 2021, DNA isolated from the peripheral blood of 229 individuals who presented to Ankara Gülhane Training and Research Hospital with non-cancerous indications was sequenced using the xGen™ Exome Hyb Panel v1 on the NovaSeq6000 platform. Pathogenic and likely pathogenic variants in the ACMG SF v3.2 genes related to cancer phenotypes (APC, RET, BRCA1, BRCA2, PALB2, SDHD, SDHAF2, SDHC, SDHB, MAX, TMEM127, BMPR1A, SMAD4, TP53, MLH1, MSH2, MSH6, PMS2, MEN1, MUTYH, NF2, STK11, PTEN, RB1, TSC1, TSC2, VHL, WT1) and other cancer-related
genes (CHEK2, ATM, BRIP1, RAD51C, RAD51D, BARD1) were evaluated according to ACMG guidelines and Clingen SVI recommendations. Pathogenic and likely pathogenic variants were detected in six individuals in BRCA2, MEN1, MLH1, MSH2, and PMS2 genes. Four of these variants have been previously reported as pathogenic in ClinVar, while two variants in MEN1 and MLH1 genes were reported as VUS (variant of uncertion significance), suggesting the need for further evaluation of their pathogenicity. The prevalence of pathogenic variants was found to be 1.7%, and the prevalence of MUTYH carrier status in this study was 2.18%. In cancer-related genes with moderate penetrance, pathogenic and likely pathogenic variants were found in four individuals in CHEK2 gene, two individuals in ATM gene, and one individual in both BRIP1 and BARD1 genes. One variant in CHEK2 had previously been reported as VUS the prevalence of pathogenic and likely pathogenic variants in these moderate penetrance genes was evaluated at 3%. When considering variants recommended for reporting in the ACMG SF v3.2 list, as well as those not included in this list but recommended in the NCCN guidelines and previously reported as pathogenic in databases, the prevalence of
cancer-related variants was 4.7%. The identification of variants linked to actionable diseases crucial impact on enabling genetic counseling, appropriate follow-up, preventive treatments, and early surveillance for family members through segregation analysis. Additionally, determining carrier rates for recessive diseases in actionable conditions is particularly important in countries like ours, where consanguineous marriages are common.

Keywords: Exome sequencing, hereditary cancer, secondary findings

[Abstract:0223]

Diagnosis with FISH Technique in a Patient with Suspected Neurofibromatosis: A Case Report

Tuğba Deniz Kurnaz Demir, Sonay Talan, Huriye Sel Özdemir, Mahmut Selman Yıldırım

Department of Medical Genetics, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye

Objective: Neurofibromatosis type 1 (NF1) is a common genetic disorder caused by variants in the NF1 tumor suppressor gene, which predisposes individuals to both benign and malignant tumors. The global prevalence is approximately 1 in 3,000 individuals, with life expectancy reduced by 8 to 21 years, often due to early mortality from malignant tumors. Up to 50% of NF1 patients develop plexiform neurofibromas, and 8-13% have a lifetime risk of malignant peripheral nerve sheath tumors (MPNSTs), which can originate from these benign growths. Other associated features include brain tumors, spinal neurofibromas, cognitive impairments, and behavioral difficulties.
Case: A 9-year-old male admitted to the Medical Genetics Outpatient Clinic with a complaint of multiple Café-au-lait macules (CALMs) and widespread freckling, including in the axillary and inguinal regions. Physical examination revealed dysmorphic features such as relative macrotia with hypoplastic lobules, a flat occiput, a flat face, convex nasal ridge, pectus excavatum, and bilateral pes planus. The patient had a history of cryptorchidism, surgically corrected. He also exhibited neuromotor developmental delays, learning disabilities, and regression in both linguistic and motor skills. Genetic testing was initially performed using next-generation sequencing (NGS) of the NF1 gene, with no pathogenic or likely pathogenic variants detected. However, due to the strong clinical suspicion, further investigation using a 17pter probe (Cytocell, UK) revealed a deletion in one NF1 allele, reported as "ish del(17)(q11.2)(NF1-) [10], nuc ish(NF1x1) [100/100]". Confirmatory testing via multiplex ligation-dependent probe amplification (MLPA) of the NF1 and NF2 genes identified a deletion in the NF1 gene using MRC-Holland SALSA MLPA probes. Chromosomal microarray analysis was subsequently planned for further characterization. The diagnosis of NF1 was confirmed, and genetic counseling was provided to the patient and his family.
Conclusion: NF1 is caused by pathogenic variants in the NF1 gene, which encodes neurofibromin. In 5-11% of cases, a microdeletion at 17q11.2, known as NF1 microdeletion syndrome, is observed. This case underscores the genetic heterogeneity of NF1 and highlights the necessity for comprehensive genetic testing. Despite initial negative results, subsequent FISH and MLPA analyses identified the deletion, illustrating the importance of detailed genetic investigations in clinically suspected cases.
Keywords: FISH technique, neurofibromatosis, café-au-lait macules

[Abstract:0224]

Revealing and Classifying Mismatch Repair (MMR) Gene Variants in Patients Undergoing Hereditary Cancer Panel Testing (2021 to Present)

Rumeysa Rezzan Sayın[1], Metin Özkan[2], Yusuf Özkul[1], Munis Dündar[1]

[1]Department of Medical Genetics, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[2]Department of Medical Oncology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

Objective: This study investigated mismatch repair (MMR) gene variants (MLH1, MSH2, MSH6, PMS2) in patients who underwent hereditary cancer panel testing in our department from 2021 to the present. The primary goals were to determine how these variants are distributed, identify their types (e.g., missense, nonsense, frameshift), and classify them according to the American College of Medical Genetics and Genomics (ACMG) criteria. All patients had a personal and/or family history of cancer, indicating the need for genetic testing.
Materials-Methods: Multigene hereditary cancer panels were performed using Next-Generation Sequencing (NGS) to detect hereditary predispositions. Variants identified were classified as pathogenic, likely pathogenic, or variants of uncertain significance (VUS) based on ACMG guidelines; benign and likely benign variants were excluded from further evaluation. Analyses focused on variant type, as well as patient demographics (age and gender).
Results: A total of 1430 patients underwent hereditary cancer panel testing during the study period. Among these, 112 individuals were found to carry at least one variant in the MMR genes. These variants were characterized with respect to their types and ACMG classifications, and their distribution was examined based on demographic factors such as age and gender. The findings suggest patterns in MMR gene variant occurrence that may help clarify potential risk factors in specific subsets of patients.
Conclusion: Identifying and classifying MMR gene variants in this cohort underscores their potential clinical relevance in understanding hereditary cancer risk. Further investigation into the demographic and molecular patterns of MMR variants may refine our ability to assess genetic risk and provide more focused guidance to individuals with a personal or family history of cancer.
Keywords: Mismatch repair (MMR) genes, hereditary cancer panel testing, next-generation sequencing (NGS)

[Abstract:0228]

Impact of Germline HOXB13 Mutations on Hormone-Positive Breast Cancer

Diyar Sayıt[1], Elif Yılmaz Güleç[1], Filiz Özen[2]

[1] Department of Medical Genetics, İstanbul Medeniyet University Medical School, İstanbul, Türkiye
[2] Clinic of Medical Genetics, İstanbul Göztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Türkiye

Objective: The HOXB13 gene, a member of the Homeobox gene family, plays a crucial role in embryonic development and the regulation of adult tissues. The protein encoded by this gene acts as a transcriptional regulator, participating in essential biological processes such as cell cycle control, differentiation, and apoptosis. Somatic HOXB13 gene amplifications in breast cancer and germline mutations in prostate cancer are known to influence androgen receptor signaling pathways, significantly contributing to pathogenesis and oncogenesis. This study investigates the potential impact of germline variants on hormone-positive breast cancer. Previous studies have also established that germline BRCA1/2, CHEK2, and PALB2 gene variants are associated with hormone-positive cancers.

Materials-Methods: Sequencing was performed using the Illumina NextSeq 500 platform with the Mid Output v2 Kit and Hereditary Cancer Panel (Sophia) kit, including 60 genes. Bioinformatic analyses, including variant calling, were conducted using the Sophia-DDM-V4 software. Results from 3200 test panels were evaluated.

Results: HOXB13 germline mutations were observed at a notable frequency in patients (n=12). Ten of these patients had hormone-positive breast cancer, one was the unaffected daughter of a patient, and one had insulinoma. None of the patients had additional pathogenic variants.

Conclusion: The potential role of HOXB13 germline variants in hormone-positive breast cancer highlights the biological and clinical significance of this gene. A considerable proportion of these mutations were found in hormone-positive breast cancer cases, suggesting a critical involvement of HOXB13 in hormone signaling pathways. HOXB13 is essential for the development and differentiation of endodermal and ectodermal tissues. Additionally, its ability to regulate androgen receptor pathways underscores its role in the pathogenesis of hormone-sensitive tumors. These findings emphasize the need to investigate HOXB13 variants further, both prognostically and therapeutically. Further functional and protein studies focusing on the effects of HOXB13 in hormone-positive breast cancer are required. Large-scale prospective studies are necessary to determine the clinical relevance of these variants. In conclusion, HOXB13 germline variants seems to be associated with hormone-positive breast cancer. Continued research into the biological and clinical aspects of this gene is essential to improve our understanding and management of hormone-sensitive malignancies

Keywords: breast, cancer, hormon, HOXB13

[Abstract:0231]

Receptor Status and Demographic Features of Patients with Germline BRCA Variants: Single Center Study

Sezin Sungur, Deniz Torun, Oya Demirkaya, Ali Öztuna, Hatice Akar, Yusuf Tunca

Gülhane Training and Research Hospital Genetic Diseases Evaluation Center, Ankara, Türkiye

Objective: Pathogenic variants in the BRCA1 and BRCA2 genes are commonly associated with Hereditary Breast-Ovarian Cancers. They can also be linked to less frequently occurring cancers such as prostate cancer and pancreatic cancer. These variants can affect the age of cancer onset and the hormone receptor status of breast cancers.
Materials-Methods: In our study, we retrospectively evaluated 1,100 patients who were referred to Gülhane Training and Research Hospital Genetic Diseases Evaluation Center between 2018-2024 with hereditary cancer suspicion, and compared the hormon receptor status of germline BRCA1 and BRCA2 positive patients.
Results: Out of 1100 patients, 137 patients had BRCA1/2 variants of significance. 46 patients had BRCA1 variants, and 89 patients had BRCA2 variants. Our testing indications included breast cancer in 92, ovarian cancer in 24, significant family history in 14, prostate cancer in 4 and pancreas cancer in 3 patients. The variants detected in the BRCA1 gene are found in 50% of cases on exon 10, while 48% of the variants in the BRCA2 gene are found on exon 11. Out of 64 breast cancer patients with accessible hormone receptor status, 19 patients had BRCA1 and 45 had BRCA2 variants. In terms of hormone receptor profiles, 50% of the breast cancer patients with BRCA1 variants were
triple-negative, and this rate increased with age(p=.006). In contrast, the majority of patients with BRCA2 variants had estrogen and progesterone receptor positivity(p=.681). Patients with a variant in BRCA1 compared to those with a variant in BRCA2 have 7.2 (95%CI,p=.009), considering the increase along with age 8.8 times higher odds of triple negativity (95%CI,p=.005). ER positivity in BRCA1 patients decreased with age(p=.006) and no correlation was found between age and PR(p=.065).
Among BRCA2 patients, no correlation was found between age and receptor status (ER, p=.681; PR, p=.225).
Conclusion: In our study, in patients with a variant in the BRCA1 gene the triple-negative status changes with age, whereas in BRCA2 gene no significant difference was observed. However, different studies analyzing the effect of age on receptor status have reported varying results. Conducting larger-scale studies in the future is of great importance.
Keywords: BRCA1, BRCA2, Hereditary Breast-Ovarian Cancers, Receptor Status

[Abstract:0232]

From Squamous Cell Carcinoma to Fanconi Anemia: A Case Report of Late Diagnosis

Okan Kurtçu[1], İrem Hartuç Çevik[1], Beliz Bahar Karaoğlan[2], Hakan Akbulut[2], Sadiye Ekinci[1]

[1]Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Türkiye
[2]Department of Medical Oncology, Ankara University Faculty of Medicine, Ankara, Türkiye

Abstract

Fanconi anemia (FA) is a rare genetic disorder characterized by susceptibility to malignancies, various physical anomalies, and bone marrow failure, most commonly diagnosed during childhood. This syndrome typically presents with congenital anomalies, progressive bone marrow failure, and pancytopenia during childhood, while increasing the risk of leukemia and solid tumors-particularly in the head and neck, skin, and genitourinary system-in later years. Mutations in 23 genes associated with FA, most notably FANCA, result in impaired DNA damage repair and genomic instability. Here, we present a case of a 45-year-old patient who was followed with a diagnosis of squamous cell carcinoma (SCC) in the oral cavity and had a history of bicytopenia since childhood. The patient initially presented with a lesion on the base of the tongue. Subsequent investigations revealed SCC, and surgery was performed. However, post-operative radiotherapy could not be completed due to severe side effects. During follow-up, the patient was diagnosed with SCC of the lip and was referred to our department for further investigation of the underlying etiology. Physical examination revealed microcephaly, short stature, café-au-lait spots, and a hypoplastic left thumb. The family history indicated consanguinity between the parents and deceased sibling who had similar hematological findings and passed away at the age of 25. A preliminary diagnosis of FA was considered, and DEB (diepoxybutane) testing on the patient's peripheral blood revealed a chromosomal breakage rate of 155%. Subsequent next-generation sequencing (NGS) analysis of FA-associated genes identified a suspected homozygous deletion in exons 6-31 of the FANCA gene, which was confirmed by multiplex ligation-dependent probe amplification (MLPA). Based on these findings, a definitive diagnosis of FA was established, and analyses of family members are currently ongoing. Without proper diagnosis and follow-up, FA patients face risks of early mortality and morbidity. Even in patients who have received bone marrow transplantation, the risk of solid tumors persists throughout life. The increased susceptibility of FA patients to chemotherapy and radiotherapy toxicity complicates tumor management. Therefore, early detection and surgical removal of tumors, alongside preventative measures such as HPV vaccination starting in childhood, are critical for improving outcomes in these patients.

Keywords: Fanconi anemia, susceptibility to cancer, squamous cell carcinoma, radiotherapy toxicity, late diagnosis

[Abstract:0233]

Reevaluation of APC Variants: Single-Center Experience

Delil Serhat Yigit[1], Fatma Demir[1], Ahmet Cevdet Ceylan[2], Erdal Birol Bostancı[3], Gülay Güleç Ceylan[2]

[1]Clinic of Medical Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Clinic of Medical Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye; Department of Medical Genetics, Medical School, Ankara Yıldırım Beyazıt University, Ankara, Türkiye
[3] Clinic of Gastrointestinal Surgery, Ankara Bilkent City Hospital, Ankara, Türkiye; Department of General Surgery, Medical School, University of Health Sciences, Ankara, Türkiye

Introduction: APC is a tumor suppressor gene in which deleterious variants cause polyposis syndrome with a predisposition to different cancers. In the era of multigene panels for patients with a cancer history, the number of patients with Variants of Unknown Significance (VUSs) in APC gene has exponentially increased. This study aims to reevaluate detected variants of the APC gene in Ankara Bilkent City Hospital with the help of up-to-date gene-specific criteria provided by ClinGen.

Materials-Methods: This study retrospectively evaluated 155 APC single–gene sequence analyses and 619 Next-Genereation-Sequencing(NGS) multigene cancer panels performed at the Ankara Bilkent City Hospital between 2019 and 2024. 44 variants reported in the APC gene in 55 patients were reclassified according to current criteria. The frequency of new pathogenicity classes and the protein effects of variants were assessed.

Results: Out of 44 APC variants detected (previous classification included 24 pathogenic/likely pathogenic(P/LP) variants, 20 VUSs), the classification of 32 variants has not changed after reevaluation. These unchanged variants were classified as 23 P/LP variants, eight missense VUSs and one in-frame deletion VUS. 21 of the 23 P/LP variants in 32 patients were detected by APC single gene sequence analysis and two variants were detected by multigene panel. All P/LP variants were truncating variants (7-nonsense/14-frameshift/2-splice-site). 55% of VUSs(11/20) are reclassified as benign/likely-benign(B/LB). All of these variants were missense variants and they were detected by multigene panels. Only one nonsense pathogenic variant was reclassified as VUS.

Conclusion: As previously demonstrated by Yin et al.(2024), reclassification of more than 10000 APC variants results in a substantial decrease in missense VUSs. Compatible with the literature, our study also confirmed that VUSs in the APC gene should be considered cautiously. Patients with various cancer types were analyzed using different multigene panels. Most of the VUSs of APC gene detected in these patients were reevaluated as B/LB. Since these variants may lead to unnecessary screening tests and may affect patient psychological health status, It is crucial to use gene-specific criteria for precise and cost-effective patient management.

Keywords: APC, ClinGen, missense, reclassification, VUS

[Abstract:0234]

Results of Hereditary Cancer Multigene Panel Testing in Patients Referred for Germline Mutation Analysis Due to Loss of MMR Protein Expression: One Center Experience

İrem Oflaz[1], Aslı Ece Solmaz[1], Gürdeniz Serin[2], Başak Doğanavşargil Yakut[2], Haluk Akın[1]

[1] Department of Medical Genetics, Ege University Faculty of Medicine, İzmir, Türkiye
[2] Department of Pathology, Ege University Faculty of Medicine, İzmir, Türkiye

Objective: Immunohistochemical (IHC) analysis of mismatch repair (MMR) proteins in tumor tissues is widely used as an effective approach for screening Lynch syndrome (LS), offering relatively high sensitivity and specificity, quick and cost-effective results, clear interpretation, and being widely available. Numerous guidelines (e.g., NCCN) recommend tumor screening for MMR deficiency in all colorectal cancers (CRCs) and endometrial cancers (ECs), regardless of the age at diagnosis, along with the recommendation to consider various other LS-related tumors. Along with BRAF p.V600E (PV) testing and MLH1 promoter methylation testing in certain scenarios, abnormalities of MMR proteins in IHC commonly lead to referrals for germline genetic testing.
Materials-Methods: A retrospective evaluation was conducted on patients referred to the Department of Medical Genetics at Ege University due to abnormalities of MMR proteins in their tumor tissue detected by immunohistochemistry, who were included in the hereditary cancer multigene panel test over the past two years.
Results: Among the 27 patients referred with abnormal MMR expression, 6 (22.2%) had colon cancer, 18 (66.7%) had endometrial cancer, 2 (7.4%) had ovarian cancer, and 1 (3.7%) had gastric cancer. In terms of MMR protein loss, 18 (66.7%) patients had loss of MLH1 and PMS2, 3 (11.1%) had loss of PMS2, 1 (3.7%) had unspecified MMR protein loss, 3 (11.1%) had loss of MSH2 and MSH6 expression, 1 (3.7%) had loss of MLH1 and PMS2 with focal clonal loss of MSH6, and 1 (3.7%) had focal loss of MSH6 expression. Regarding the MGPT results (including P, LP, and VUS classified variants), 13 (48.1%) patients had normal results, 6 (22.2%) had genes reported other than the 4 MMR genes, and 8 (29.6%) had MMR genes reported, 6 (22.2%) of which were correlated with IHC findings, while the other 2 (7.4%) differed from the genes identified by IHC.
Conclusion: The results of this study emphasize the importance of IHC analysis for the detection of MMR protein loss, which serves as a critical screening tool for LS. Our findings also contribute to the growing body of evidence supporting the integration of multigene panels into the clinical management of hereditary cancer syndromes.
Keywords: Hereditary Cancer Syndromes, Lynch Syndrome, Mismatch repair protein, MMR

[Abstract:0235]

Reviewing the Occurence of Neoplasms in Neurofibromatosis Type 1 Patients

Kutalp Özekicioğlu[1], Mustafa Altan[1], Ahmet Cevdet Ceylan[2], Esra Kılıç[3], Büşranur Çavdarlı[2]

[1]Department of Medical Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Medical Genetics, Ankara Yıldırım Beyazıt University, Ankara, Türkiye; Department of Medical Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye
[3]Department of Pediatric Genetics, University of Health Sciences, Ankara, Türkiye; Department of Pediatric Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye

Objective: Neurofibromatosis type 1 (NF1) is a multisystem disorder inherited in an autosomal dominant manner, which mostly presents with cafe-au-lait macules, axillary/inguinal freckling and neurofibromas. Diagnosis of NF1 requires a thorough physical examination and often molecular testing of the NF1 gene. The average life expectancy of NF1 patients are approximately 8 years shorter than the average human and an important cause of mortality is malignancy. In this retrospective study we present patients with pathogenic NF1 variants who concurrently have a history of neoplasm. We aim to highlight the prevalency of neoplasms in NF1 patients.
Materials-Methods: Between 2019-2024, 717 patients who had suggestive neurofibromatosis findings have been tested via multigene panels for gDNA sequence analysis and multiplex-ligand-probe-amplification(MLPA) for gene-targeted deletion analysis. Variants that were found in the NF1 gene have been retrospectively analyzed and patients' clinical history and notes were reviewed for neoplasms.
Results: 213 patients were found to have disease causing variants, 206 were detected with sequencing via multigene panels and 7 were detected with gene-targeted deletion analysis. Disregarding neurofibromas, 38 patients with disease causing variants had a history of 26 benign and 21 malignant neoplasms (6 patients had more than one neoplasms). Benign neoplasms include 12 optic gliomas, 6 schwannomas, 3 hemangiomas, 2 pheochromocytomas and other neoplasms such as gastrointestinal stromal tumor, meningioma and parathyroid adenoma. Malignant neoplasms consisted of 6 diffuse low-grade gliomas, 4 diffuse midline gliomas, 4 malignant peripheral nerve sheath/mesenchymal tumors, 3 invasive breast carcinomas and other malignancies such as rectal adenocarcinoma, pancreatic neuroendocrine tumor, synovial sarcoma and juvenile myelomonocytic leukemia. The median age of diagnosis was 11 (1 month-67 years), median age of patients with neoplasms was 11.5 (6 months-67 years) and the median age of patients with malignant neoplasms was 22 (2-67 years).
Conclusion: NF1 is widely regarded as one of the most common tumor-predisposition syndromes. Most patients only receive a diagnosis after the incidence of malignancies due to phenotypic heterogeneity and age-dependent manifestations of NF1. Although this study constitutes of a relatively small group of patients we can observe malignancies presenting later in life showing consistency with the two-hit hypothesis.
Keywords: Hereditary Cancer, Neurofibromatosis, NF1, Tumor Predisposition Syndrome

[Abstract:0236]

The Importance of Varying Cancer Risk Among Different ERCC2 Variants

Nesligul Hasibe Gonen[1], İsa An[2]

[1]Department of Medical Genetics, Şanlıurfa Training and Research Hospital, Şanlıurfa, Türkiye
[2]Department of Dermatology, Şanlıurfa Training and Research Hospital, Şanlıurfa, Türkiye

Trichothiodystrophy-1 (TTD) (MIM 601675) is a rare disease characterized by ichthyosis, dry-brittle hair, motor retardation, intellectual disability and recurrent infections. It results from biallelic mutations in the ERCC2 (XPD), which encodes one of the helicase subunits of the transcription/repair factor TFIIH. In addition to being a highly conserved transcription factor, TFIIH also plays a critical role in Nucleotide Excision Repair (NER). Different biallelic mutations in ERCC2 lead to a wide spectrum of distinct phenotypes, such as Xeroderma Pigmentosum (XP)/Cockayne Syndrome (CS), XP, and Trichothiodystrophy (TTD), characterized by higher and lower cancer susceptibility, respectively. This study presents a family with a diagnosis of TTD confirmed by molecular genetic analysis. Our proband, born to consanguineous parents and followed up intrauterine growth retardation (IUGR), was delivered at term weighing 1450 grams. Postnatally, the affected individual presented with generalized ichthyosis. Developmental milestones were delayed, and he exhibited global developmental delay, requiring special education since age 5. Additionally, he had neutropenia, multiple hospitalizations due to recurrent infections. Family history revealed four siblings with similar findings. At 7 years and 1 month, physical examination revealed that height: 100.2 cm (SDS: -4.32), weight: 12.5 kg (SDS: -5.34), photosensitivity, dysmorphic facial features (triangular face, frontal bossing, pointed nose, sparse lateral eyebrows, protruding ears, pointed chin, dystrophic teeth), widespread ichthyosis, sparse-dry-brittle hair, palmoplantar keratosis and nail dystrophy. Similar findings were observed in his siblings. Based on clinical findings, consanguinity, and the presence of similar symptoms in siblings, the patient was followed up with diagnosis of TTD. ERCC2, the most common responsible for TTD, has been sequenced and identified a homozygous pathogenic variant, c.2164C>T (p.Arg722Trp), previously associated with TTD. Segregation analysis was performed with available family members. DNA repair defects are known to lead to cancer predisposition syndromes such as XP, CS, Bloom syndrome, and Werner syndrome. TTD, despite a defect in the NER, stands out due to its low cancer risk. Therefore, considering the pleiotropy of ERCC2, it should be kept in mind that precise diagnosis within these allelic disorders may vary depending on the different mutation, and accurate genetic counseling is crucial for patient surveillance and family planning.

Keywords: ERCC2, trichothiodystrophy, allelic disorders, cancer risk

[Abstract:0237]

Single-Center Analysis of TP53 Pathogenic Variants in Turkish Cancer Patients

Said Furkan Yıldırım[1], Ahmet Cevdet Ceylan[2], Emin Emre Kurt[2], Bülent Yalçın[3]

[1] Department of Medical Genetics, Ankara Bilkent City Hospital, Ankara, Türkiye
[2] Department of Medical Genetics, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Ankara, Türkiye; Ankara Bilkent City Hospital Department of Medical Genetics, Ankara, Türkiye
[3] Department of Medical Oncology, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Ankara, Türkiye; Ankara Bilkent City Hospital Department of Medical Oncology, Ankara, Türkiye

Objective: Transcription factor p53, the "guardian of the genome," responds to various cellular stresses to regulate target genes that induce cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Variants in TP53 are frequently implicated in cancer development, but the genotype-phenotype correlation has not been fully established yet. This study aims to retrospectively analyze TP53 gene variants identified in a patient cohort to investigate potential genotype and phenotype relationships.
Method: In this study, a retrospective review was carried out on genomic sequencing studies conducted on patients who presented to Ankara Bilkent City Hospital Medical Genetics Clinic with a history of malignancy between April 2019 and November 2024. Pathogenic/likely pathogenic variants were identified in 714 patients whose TP53 genes were sequenced in various panels. The clinical data of patients with variants were evaluated.
Results: Pathogenic/likely pathogenic variants were reported in 11 out of 714 patients (1.55%). It was observed that 7 of the variants were missense, 1 was frameshift and 2 were splice variants. It was observed that all exonic variants were located between exons 4-8, which is the DNA binding region where hot-spot regions are located. The only variant detected more than once was the c.375G>A (p.Thr125Thr) variant, which was located in the last nucleotide of exon 4 and affected splice despite being synonymous, and both patients presented with choroid plexus carcinoma. Curiously, as a quite rare event in TP53 gene, we observed this variant in a germline homozygous state with infant-onset malignancies in an infant from consanguineous marriage.
Conclusion: This study provides single center data on the prevalence and clinical effects of TP53 gene variants and their clinical significance. Further studies are needed to determine the variant spectrum in the Turkish population and to better establish genotype-phenotype correlation. These efforts are also crucial to improve preventive medicine practices and genetic counseling.
Keywords: TP53, Li-Fraumeni, homozygous

[Abstract:0238]

"High-Resolution Array CGH Confirmation of an Intragenic Deletion Variant in the FANCA Gene: A Case Report of a 6-Year-Old Female Patient with Suspected Fanconi Anemia"

Halil İbrahim Yılmaz, Mustafa Doğan, Alper Gezdirici, Tuba Nur Tahtakesen Güçer

University of Health Sciences, Başaksehir Çam and Sakura City Hospital, İstanbul, Türkiye

Objective: Fanconi Anemia is a genetically heterogeneous hematologic disorder with autosomal recessive, dominant and X-linked manner. Although the spectrum of disease is wide, most characteristic findings are physical abnormalities, thrombocytopenia/leukopenia in the first decade and increased risk for malignancies. Currently, more than 20 genes responsible for the pathogenesis have been identified and the main responsible gene is FANCA. Approximately 40% in FANCA variants are large intragenic deletions.
Methods: DEB, MMC-induced and control lymphocyte cultures were analyzed for chromosomal breakage analysis. Genomic DNA was isolated from a peripheral blood sample, and clinical exome sequencing was performed using the MGI DNBSEQ-G400 ‘’Twist CES Kit’’ system. CES-CNV revealed chr16:(89828101-89866301)X0, variant confirmed via high-resolution Array (GeneTitan).
Case: 6-year-old female patient is being followed up by hematology due to short stature and moderate thrombocytopenia. Her prenatal history was unremarkable, normal birth weight, cognitive functions are fine, there are no pathological findings both Cranial MRI and ECHO. Bone marrow biopsy showed hypocellular parenchyma according to age. Mitomycin C and DEB test from peripheral blood sample are compatible with Fanconi Anemia: scores were summed and classified based on IFAR. CES(Clinical Exome Sequencing) analysis was performed for detect the genetic etiology. NGS based CNV analysis result as a FANCA exon 9-29 homozygous deletion. We used high resolution array for verification; after genotype-phenotype corregulation patient has diagnosed with Fanconi Anemia.
Conclusion: Nowadays NGS based CNV analysis has importance for genotype-phenotype correlations, especially in diseases where copy number alterations lead to pathogenesis. Although it is not yet gold standard, the accuracy rate enhances with variabilities such as larger sample number and comparing unrelated patients with different phenotypes in the same run. The developments in Array CGH, it was seen that it could be an alternative to MLPA and Long Read PCR with the increase in resolution quantity. In the future, combined molecular methods, long read HiFi sequencing promises reliable and more accurate diagnosis in such patients.
Keywords: Key Worlds: Fanconi Anemia, FANCA, CNV, high-resolution Array CGH

[Abstract:0239]

Diverse Oncologic Presentations in CHEK2 Variant Carriers: A Multi-Cancer Case Series

Saliha Esra Olgun[1], Zeynep Münteha Başer[1], Şenol Demir1, Ceren Alavanda[3], Ayşenur Ersoy Karayumak[1] ,Onur Hanoğlu[1], Esra Arslan Ateş[2], Ahmet İlter Güney[3]

[1]Department of Medical Genetics, Marmara University Faculty of Medicine, İstanbul, Türkiye
[2]Department of Medical Genetics, İstanbul University-Cerrahpaşa Faculty of Medicine, Istanbul, Türkiye
[3]Department of Medical Genetics, Ministry of Health Van Training and Research Hospital, Van, Türkiye

Abstract

CHEK2 encodes a checkpoint kinase involved in DNA damage repair and tumor suppression. Pathogenic variants in CHEK2 are associated with an increased risk of several malignancies, particularly breast cancer, yet the full clinical spectrum and optimal management strategies remain under investigation. Here, we describe 37 patients harboring pathogenic or likely pathogenic CHEK2 variants, some also with co-occurring BRCA mutations, illustrating a diverse range of cancer phenotypes and disease courses, with clinical data collected and analyzed. After DNA isolation from the peripheric blood of the patients, SOPHIA Custom Solution CHCS_C_V2 next generation sequencing kit and NovaSeq® system were used for the detection of variations in all exons and exon-intron junctions of 50 genes including CHECK2. Sophia DDM was used for data analyse. Clinical data reveal that most patients presented with invasive breast cancer, including ductal and lobular subtypes, encompassing hormone receptor-positive, HER2-positive and triple-negative disease.

Several individuals required bilateral mastectomies, while others exhibited additional malignancies or high-grade premalignant lesions. Notably, one patient had both BRCA2 (c.3847_3848del, p.Val1283Lysfs*2) and CHEK2 (c.1556C>T, p.Thr519Met) variants with concurrent breast cancer and endometrial polyp. Other remarkable findings included a patient with prostate cancer and colon polyps (CHEK2 c.58C>T, p.Gln20*), another with medullary thyroid cancer and parathyroid adenoma (CHEK2 c.58C>T, p.Gln20*) and several with gastrointestinal polyps or over metastases, suggesting broader cancer predisposition. These cases underscore that CHEK2 variants can manifest in heterogeneous ways, affecting multiple organ systems and highlighting the importance of multidisciplinary surveillance. Given the variability of cancer phenotypes -even among carriers of the same variant- further research is needed to clarify genotype-phenotype correlations and to refine risk assessment models. Current debates include the extent of prophylactic surgery, optimal surveillance intervals and the potential utility of targeted therapies aimed at DNA repair pathways. Advancements in next generation sequencing panels and genetic counseling remain crucial for identifying and managing at-risk individuals. In conclusion, this series illustrates the complexity of CHEK2-related tumorigenesis and supports the ongoing expansion of genetic testing beyond BRCA genes to capture moderate-penetrance variants. Improved understanding of CHEK2-driven carcinogenesis will facilitate personalized preventive and therapeutic strategies, ultimately enhancing patient outcomes.

Keywords: CHEK2, NGS, Breast Cancer, Genotype-Phenotype Correlation

[Abstract:0240]

Double Heterozygous Variants in BRCA2 and ATM Genes: A Male Case

Süheyl Önal, İpek Şahin, Aydın Demiray, Kadri Karaer

Department of Medical Genetics, Pamukkale University Faculty of Medicine, Denizli, Türkiye

Introduction: Pathogenic variants (PVs) in the BRCA2 and ATM genes are associated with an increased risk of various cancers. Both genes are integral components of the homologous recombination repair pathway. However, the tumor development risk and phenotypic effects in individuals carrying simultaneous pathogenic variants in both genes remain largely unknown. Literature reports suggest that carriers of double heterozygous variants in these genes are predisposed to developing multiple malignancies and may receive cancer diagnoses at an earlier age. Nevertheless, more case reports are needed to fully understand the clinical implications of double heterozygosity in BRCA2 and ATM genes.

Case Presentation: An 80-year-old male patient, who does not smoke or consume alcohol, presented to our clinic with a history of multiple primary cancers. The family history revealed a suspected case of lung cancer in his father and a niece (the daughter of his brother) who passed away due to cancer. His cancer history began at the age of 76 with a diagnosis of left breast cancer with axillary metastasis, for which he underwent modified radical mastectomy. Subsequently, he was diagnosed with primary lung adenocarcinoma and underwent left upper lobectomy. Four years later, at the age of 80, he was diagnosed with primary prostate adenocarcinoma.mThe patient underwent next-generation sequencing (NGS) of a 60-gene hereditary cancer panel. This analysis revealed a heterozygous pathogenic frameshift variant in the BRCA2 gene (c.3189_3192del, p.Ser1064Leufs12) and a heterozygous pathogenic stop-gain variant in the ATM gene (c.6100C>T, p.Arg2034Ter). Both variants are reported in the literature as pathogenic. Genetic counseling was provided, and the patient's family was invited for genetic screening. The patient's 47-year-old son was tested, and the heterozygous BRCA2 variant (c.3189_3192del, p.Ser1064Leufs12) was identified.

Results: This study aims to present a rare case of a patient with simultaneous pathogenic variants in the BRCA2 and ATM genes and multiple cancer diagnoses, emphasizing the clinical significance of this genetic profile and the necessity of screening programs.

Keywords: BRCA2, ATM, double heterozygous, hereditary cancer, multiple primary cancers

[Abstract:0241]

FH Gene Mutations in Cancer Patients: Single Center Experience

Ayşenur Ersoy Karayumak[1], Zeynep Münteha Başer[1], Çekdar Kapazan[1], Esra Dirimtekin[1], Şenol Demir[2], Ceren Alavanda[2], Ayberk Türkyılmaz[3], Esra Arslan Ateş[4], Ahmet İlter Güney[1]

[1] Department of Medical Genetics, Marmara University Faculty of Medicine, İstanbul, Türkiye
[2] Clinic of Medical Genetics, University of Health Sciences, Van Training and Research Hospital, Van, Türkiye
[3] Department of Medical Genetics, Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye
[4] Department of Medical Genetics, Istanbul University-Cerrahpasa Faculty of Medicine, İstanbul, Türkiye

Introduction: Heterozygous mutations in the Fumarate Hydratase (FH) gene cause an autosomal dominant hereditary cancer predisposition syndrome, known as the Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC). This syndrome is characterized by uterine leiomyomata, leiomyosarcoma and fibroids, renal cell cancer and cutaneous piloleiomyomas. It has high phenotypic variability and harbours incomplete penetrance. In this study, we evaluated the clinical features and genetic mutations of patients who were identified with pathogenic or likely pathogenic heterozygous FH mutations after undergoing genetic testing at our center.

Materials-Methods: Patients who visited our clinic between September 2021 and January 2025 and underwent genetic testing via hereditary cancer next generation sequencing panel were included in the analysis. DNA isolation was performed using the ZeeSan Lab-Aid® 824s Blood DNA isolation kit. Variations in all exons and exon-intron junctions of the panel genes were identified using the SOPHIA Custom Solution CHCS_C_V2 next-generation sequencing kit and the NovaSeq® system. The data were analyzed with Sophia DDM and interpreted in light of relevant databases.

Results: A total of 17 patients were identified with variants in the FH gene. Among these, 8 variants were reported as variants of uncertain significance (VUS) according to ClinVar. The most frequently observed VUS was c.73G>A (p.Ala25Thr), rs999146815. 2 variants were classified as pathogenic or likely pathogenic in both ClinVar and ACMG criteria. 5 variants were classified as likely pathogenic or pathogenic according to ACMG criteria but were not reported in ClinVar. 2 variants were classified as likely pathogenic according to ACMG criteria but were reported as VUS in ClinVar. Patients were diagnosed with a wide range of cancer types, including malignant melanoma, breast cancer, renal cancer with lung metastases, and colon and cervical cancers.

Conclusion: Although FH gene variants are associated with HLRCC, the clinical presentations of affected patients show significant variability. Non-malignant manifestations of the syndrome may be overlooked in diagnosis. A detailed patient history and a comprehensive approach to cancer patients are critical for accurate diagnosis and effective preventive care, ultimately benefiting the patient.

Keywords: HLRCC, renal cell cancer, FH gene

[Abstract:0243]

Analysis of ATM Germline Pathogenic Variants: a Third Grade Center Cohort

Esra Hilal Ceylan, Esra Dirimtekin, Ayşenur Ersoy, Zeynep Münteha Başer, Pınar Ata

Department of Medical Genetics, Marmara University Faculty of Medicine, İstanbul, Türkiye

Introduction: The ATM gene encodes a serine protein kinase that plays a critical role in response to DNA damage. Biallelic forms have been associated with Ataxia-telangiectasia (#208900) and heterozygous forms with Breast Cancer Susceptibility (#114480) in the Omim database. There are publications in the literature reporting the association of ATM gene with other cancer types. This study examined individuals who underwent testing with a multi-gene hereditary cancer panel, from September 2021 to December 2024. Patients with pathogenic/likely pathogenic variants according to ACMG and ClinVar databases in ATM gene, were included in the study.
Method: After DNA isolation using ZeeSan Lab-Aid® 824s Blood DNA isolation kit, SOPHIA Custom Solution CHCS_C_V2 next generation sequencing kit and NovaSeq® system were used for the detection of variations in all exons and exon-intron junctions of 50 genes including ATM. Data were analysed with Sophia DDM and interpreted in the light of relevant databases.
Results: 6 of the 18 patients included in the study were male and twelve were female. The age at diagnosis was between 43-60 years. Ten of the patients had breast cancer, three had colon cancer, one had prostate cancer, two had pancreas cancer, one had stomach cancer and one had thyroid cancer.Truncating variants leading to premature protein termination were found in the majority of the cases.
Discussion: The association between pathogenic variants in the ATM gene and breast cancer has been demonstrated, but more data are needed to elucidate the relationship between the germline ATM gene mutations and other cancer types. This study aims to enrich the genotype-phenotype correlation with novel variants and to elucidate ATM-related cancer types.
Keywords: ATM, gene, cancer

[Abstract:0244]

Germline Homozygous RAG1 Missense Mutation Associated with Epstein-Barr Virus Negative Childhood Burkitt Lymphoma: A Case Report

Nurana Mammadova[1], Abdulbaki Yıldırım[1], Nuriye Gökce[1], Alper Özcan[2], Munis Dündar[1]

[1]Department of Medical Genetics, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[2] Department Pediatric Hematology-Oncology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

Abstract

RAG1 and RAG2 are crucial for V(D)J recombination, which generates antigen-specific B- and T-cell receptors. RAG1 regulates immune responses and cancer progression, with its high expression linked to aggressive tumors, poor prognosis, and treatment resistance. It is highly expressed in B-cell acute lymphoblastic leukemia (B-ALL) and chronic myelogenous leukemia (CML), contributing to disease progression. RAG1 expression is reduced in myelodysplastic syndromes (MDS), with rare mutations. This study explores the connection between homozygous RAG1 missense mutations and Epstein-Barr virus (EBV) negative childhood Burkitt lymphoma. DNA was isolated from peripheral blood samples using automated systems. Next Generation Sequencing (NGS) analyses were performed with the Twist Human Core Exome kit on the Genomize SEQ platform, using hg19 as the reference genome. Additionally, products obtained from PCR with primers specific to the second exon of the RAG1 gene were analyzed using an automated DNA sequencing method based on fluorescence technology.

Case: We present a 9-year-old male patient who underwent surgery due to ileocolic intussusception. The pathological examination results were consistent with Burkitt lymphoma. Additionally, the Epstein-Barr Virus (EBV) PCR test was negative. The patient did not exhibit significant dysmorphic features, and his developmental milestones were within the normal range for his age. There was no family history of consanguinity. Molecular analysis of the patient's blood and tissue samples, performed through whole exome sequencing, revealed a homozygous missense variant, c.460C>T p.(Leu154Phe), in the second exon of the RAG1 gene. The identified variant was considered novel.

Conclusion: Our study investigates the potential role of the RAG1 gene in childhood Burkitt lymphoma and demonstrates that RAG1 may play a crucial role in childhood cancers, particularly in EBV-negative Burkitt lymphoma. Furthermore, the novel variant we identified has contributed to the variant spectrum.

Keywords: Childhood Burkitt lymphoma, RAG1, NGS

[Abstract:0245]

Clinical and Genetic Characteristics of Hereditary Cancer Patients

Sahra Acır[1], Biray Ertürk[2], Esra Arslan Ateş[1]

[1] Department Medical Genetics, İstanbul University-Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye
[2] Clinic of Medical Genetics, Prof. Dr. Cemil Taşçıoğlu City Hospital, İstanbul, Türkiye

Objective: Hereditary cancer syndromes arise from inherited genetic mutations that elevate cancer susceptibility. This study aimed to characterize the genetic landscape of multi-gene hereditary cancer syndromes in patients, elucidating variant distribution and prevalence.
Materials-Methods: A cohort of 99 participants (91 women, 8 men; aged 26–78) underwent analysis using a multi-gene panel (HGS) encompassing 49 cancer-associated genes. Variants were classified following American College of Medical Genetics and Genomics (ACMG) criteria.
Results: The most common cancer types among participants were breast (63.3%) and ovarian cancer (15.15%), followed by colon (4,04%), prostate (4,04%), gastric (0,99%), endometrium (0,99%), pancreas (0,99%), rectum (0,99%) and combinations such as endometrial+breast (2,02%), endometrial+ovarian (0,99%), colon+breast (0,99%), thyroid+renal (0,99%), thyroid+breast (0,99%), colon+gastric (0,99%), and colon+gastric+ovarian (0,99%). Family history was reported in 56/99 patients, while 43 had none. In 35 patients, 39 variants were identified, including 19 pathogenic (P), 5 likely pathogenic (LP), and 15 variants of uncertain significance (VUS). Among breast cancer patients with identified variants, the most commonly affected genes were BRCA1 (21,73%, n=5/23), CHEK2 (13,04%, n=3/23), and BRCA2 (8.69%, n=2/23). In 6 ovarian cancer patients with identified variants, pathogenic variants were detected in BRCA1, BRCA2, NBN, ATM, and RAD51C, with a VUS was detected in TSC2. LP, P and VUS variants detected also in MUTYH, MLH1, RET, POLD1, PALB2, TSC2, ERCC4, MSH6, POLE, RAD51D, FH, VHL, BARD1, BLM, BMPR1A and GALNT12.mConclusion: This study identifies two novel variants, including a VUS in FH and an LP in ERCC4. Genes such as MSH6, POLE, POLD1, MUTYH, and BLM are low-risk in breast cancer, but their impact may become clearer if there's a family history of cancer. In contrast, higher-risk genes like BRCA1/2, ATM, CHEK2, and PALB2 can cause cancer on their own, even without a family history, making them important to monitor in all cases. Notably, ovarian cancers exhibited a higher prevalence of pathogenic variants compared to other cancers. Multigene panel testing plays a critical role in identifying hereditary cancers and genetic alterations within individuals, offering significant benefits for genetic counseling and familial health.
Keywords: Hereditary cancers, novel variants, multi-gene panel testing

[Abstract:0246]

"Unveiling Genetic Insights in Breast Cancer Patients: A Study Through Multigene Panel Testing"

Nuh Altunoğlu[1], Aslıhan Kiraz[1], Oktay Bozkurt[2], Munis Dündar[1]

[1] Clinic of Medical Genetics, Erciyes University Medical Faculty Hospital, Kayseri, Türkiye
[2] Clinic of Medical Oncology, Erciyes University Medical Faculty Hospital, Kayseri, Türkiye

Objective: Breast cancer is the most common malignancy among women and a leading cause of cancer-related mortality worldwide. Genetic predisposition plays a critical role in its pathogenesis, with mutations in high-penetrance genes such as BRCA1, BRCA2, CHEK2, and ATM significantly contributing to disease development. This study evaluates the genetic and pathological profile of breast cancer patients in our clinic over a four-year period, focusing on hereditary predisposition genes, hormone receptor status, and their association with clinical features.

Materials-Methods: Between 2021 and present, a total of 1430 cancer patients were evaluated in our clinic, of whom 598 were diagnosed with breast cancer (582 females, 16 males). Hereditary cancer panel testing was performed using next-generation sequencing (NGS) on 49 cancer-associated genes. Pathological evaluation included hormone receptor status (ER, PR, HER2) and histological subtypes.

Variants were classified according to ACMG guidelines as pathogenic, likely pathogenic, VUS, and benign/likely benign. Benign and likely benign variants were excluded. Hormone receptor positivity, genetic findings, and family history were analyzed for potential correlations

Results: Invasive ductal carcinoma accounted for over 60% of cases, while invasive lobular carcinoma was observed in approximately 3%. Hormone receptor analysis showed that around 40% of patients were ER-positive and PR-positive, with the majority being HER2-negative. Genetic testing revealed that nearly 60% of patients carried heterozygous variants, with a small fraction carrying homozygous changes. Pathogenic and likely pathogenic variants made up about 20% of identified mutations, and VUS constituted the largest proportion. BRCA1, BRCA2, and CHEK2 were the most frequently mutated genes, with missense, frameshift, and nonsense variants being predominant. Approximately 15% of patients had a first-degree relative with breast cancer.

Conclusion: This study highlights the genetic and pathological diversity of breast cancer patients. Comprehensive genetic testing, combined with hormone receptor evaluation, is essential for identifying high-risk individuals and tailoring personalized treatments. Further research is necessary to clarify the clinical relevance of VUS and rare mutations in hereditary breast cancer syndromes.

Keywords: breast cancer, genetic predisposition, hereditary cancer panel, BRCA

[Abstract:0250]

Germline Exonic Deletion and Duplication Variants in the BRCA1 and BRCA2 Genes: A Single-center Experience

İbrahim Kaplan, Özge Hacer Demirbilek

Adana City Hospital, Adana, Türkiye

Objective: Germline BRCA1 and BRCA2 pathogenic / likely-pathogenic variants cause to hereditary breast and ovarian cancer syndrome (HBOC). Besides breast and ovarian cancer, these genes are associated to cancer predisposition to pancreatic, prostate cancer and melanoma. Approximately 90% of BRCA1/2 gene variants are sequence variants could be detected by using sequencing techniques and the remaining 10% of variants are deletion-duplication variants. In clinical practice, after sequencing the BRCA1 and BRCA2 genes, Multiple-Ligation dependent Probe Amplification (MLPA) has been widely used for detecting the exonic deletion and duplication variants.

Case: In this study, we retrospectively evaluated the deletion / duplication variants in the BRCA1 and BRCA2 genes in patients who admitted to Adana City Hospital Medical Genetics Department for genetic counseling and genetic testing because of different cancer types and or family history of cancer. Three different deletion / duplication variants were found in patients' germline genetic material extracted from patients' peripheral blood. In case 1, 28-year- old female patient, referred because of invasive breast cancer and exon 8-13 duplication in BRCA1 gene was identified. In case 2, 46-year- old female consultant, who admitted to medical genetics department for demanding genetic counseling because of the family history of ovarian cancer and mother's (deceased because of ovarian cancer) BRCA2 gene exon 3-8 duplication variant. In case 3, 50-year-old female patient, who was diagnosed as breast cancer and tested for somatic testing before and found as exon 24 deletion in BRCA1 gene, admitted our clinic for genetic counseling and germline genetic testing.

Conclusion: Here we present, three different variants that identified in the BRCA1 and BRCA2 genes. From the medical genetics view, along with cancer patients' genetic counseling, the predictive test issue is also very important. The classification of rare variants identified in the high-risk cancer susceptibility genes BRCA1 and BRCA2 is essential for appropriate genetic counseling and planning the at-risk family members genetic tests. Even though, as a general rule, deletion and duplication variants are thought to be related to cancer predisposition; further researches are needed to explain the roles of these rare types of variants -especially for the duplication variants- in carcinogenesis.

Keywords: BRCA1, BRCA2, Cancer predisposition, Genetic counseling, MLPA

[Abstract:0251]

BRCA1 and BRCA2 Germline Sequence Analysis Data: A Single-Center Experience

Can Berk Leblebici, Nüket Yürür Kutlay, Hatice Ilgın Ruhi, Timur Tuncalı, Halil Gürhan Karabulut, Sadiye Ekinci, Şule Altıner, Ezgi Gökpınar İli

Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Türkiye

Objective: Germline heterozygous pathogenic/likely pathogenic variants in the BRCA1 and BRCA2 genes are most commonly responsible for hereditary breast-ovary-pancreas-prostate (HBOPP) cancer predisposition. This study presents the analysis of BRCA1 and BRCA2 variants in patients evaluated in our department.
Materials-Methods: Patients who underwent BRCA1 and BRCA2 sequence analysis using peripheral blood samples between 2022 and 2024 were included in the study. Hereditary cancer panel and "multiplex ligation-dependent probe amplification (MLPA)" analyses were excluded from the study.
Results: The study included a total of 399 individuals, consisting of 357 women and 42 men diagnosed with HBOPP and one case of rectal adenocarcinoma. The average age of the patients was 55. In BRCA1, 20 different pathogenic (P)/likely pathogenic (LP)/variants of uncertain significance (VUS) were detected in 27 cases. Of these, 22 individuals had a history of cancer, while segregation analysis was conducted for five cases who had no cancer but had a family history of a known variant. Two patients had a combination of breast-ovarian cancer. In BRCA2, 17 different P/LP/VUS variants were identified in 35 cases. Among them, 27 had various cancers, while eight individuals were referred to our department for segregation purposes. In a patient with rectal adenocarcinoma, the BRCA2: c.8524C>T(p.R2842C) variant was identified as heterozygous. Variants were most commonly found in exon 10 of BRCA1 and exon 11 of BRCA2. These variants were frame-shift types leading to loss of function in both genes. The clinical conditions observed in patients based on the variants detected in BRCA1 and BRCA2 are summarized in the table below.
Conclusion: BRCA1 and BRCA2 are two genes responsible for homologous recombination in DNA repair. Although there is no "hot-spot" mutation region in these genes, changes in exon 10 for BRCA1 and exon 11 for BRCA2 account for approximately half of the variants. Identifying at-risk individuals within families, offering prophylactic options, and identifying potential therapeutic targets make it essential to detect germline changes in these genes and provide genetic counseling.
Keywords: BRCA1, BRCA2, germline

Clinical conditions based on variants detected in BRCA1 and BRCA2

Clinical conditions	Breast cancer	Ovarian cancer	Two cancer	Pancreatic/Prostate/Rectal cancer	Segregation analysis
Gene					
BRCA1	11	8	2	1/0/0	5
BRCA2	20	5	0	0/1/1	8

[Abstract:0252]

Retrospective Analysis of Hereditary Cancer Panel Results in Ovarian Cancer Patients

Aydan Mengübaş Erbaş, Zehra Manav Yiğit

Department of Medical Genetics, Adnan Menderes University Faculty of Medicine Aydın, Türkiye

Abstarct

Ovarian cancer ranks as the seventh most common cancer in women worldwide, accounting for 4% of all female malignancies, according to 2022 WHO data. Hereditary factors are implicated in approximately 20–25% of cases, with most patients being diagnosed at advanced stages, leading to high mortality rates. These findings emphasize the importance of genetic testing in ovarian cancer, with many institutions recommending genetic analysis for all diagnosed individuals. This study retrospectively analyzes 48 ovarian cancer cases referred to our clinic between 2021 and 2024. Clinical and demographic data, including age at diagnosis, pathological diagnosis, family history, parity, and and results of a 60-gene hereditary cancer panel analyzed in our laboratory, are presented. The mean age at diagnosis was 50.4 years (range: 18–79). Among the patients, 26 (54.2%) had a first-degree relative with a cancer history, 3 (6.3%) had a second-degree relative with a cancer history, and 8 (16.7%) reported no familial history of cancer. Pathogenic or likely pathogenic variants were identified in 17 cases (35.4%) through hereditary cancer panel analysis. These included BRCA1 variants in 9 cases (18.8%), BRCA2 variants in 5 cases (10.4%), CHEK2 variant in 1 case (2%), TP53 variant in 1 case (2%), and XPC variant in 1 case (2%). Variants of uncertain clinical significance were observed in 10 cases (20.8%), while no clinically significant variants were detected in 20 cases (41.2%). The genetic etiology detection rate observed in our study differs from the rates reported in the literature. Possible explanations for this discrepancy include the relatively small sample size, differences in the gene composition of the panels utilized, and variability in patient selection criteria. Nevertheless, the detection of pathogenic or likely pathogenic variants in 35.4% of cases highlights the significance of genetic analyses in the diagnosis, management, and prevention of ovarian cancer. Our results also indicate that BRCA1 and BRCA2 variants are the most frequently detected pathogenic variants, which is in line with current literature. However, the detection of rare variants in other genes and variants of uncertain significance emphasizes the need for further large-scale studies to better understand the genomic landscape of ovarian cancer.

Keywords: BRCA1, BRCA2, Hereditary Cancer, Next-Generation Sequencing, Ovarian Cancer

[Abstract:0253]

Evaluation of Hereditary Cancer Panel and BRCA1 /BRCA2 Deletion/Duplication Analysis Results in Patients with Breast Cancer

Levent Şimşek[1], Behiye Tuğçe Yıldırım[1], Nurullah İlhan[2], Akif Doğan[2]

[1]Clinic of Medical Genetics, Sancaktepe Şehit Prof.Dr. İlhan Varank Training and Research Hospital, İstanbul, Türkiye
[2]Clinic of Medical Oncology, Sancaktepe Şehit Prof.Dr. İlhan Varank Training and Research Hospital, İstanbul, Türkiye

Objective: Germline genetic tests are critical in management of breast cancer. However, there is no clear consensus regarding the content and application algorithm of germline genetic tests in breast cancer. In multi-gene panels, in addition to genes with high penetrance that cause an increased risk of cancer, there may also be genes with lower penetrance and/or whose relationship with breast cancer has not been clearly demonstrated. For this reason, introducing data obtained from multi-gene panels to the literature is important. In this presentation, it is aimed to evaluate the germline variants detected in the hereditary cancer panel and BRCA1 / BRCA2 deletion/duplication analysis in patients diagnosed with breast cancer who applied to a single center.
Materials-Methods: Peripheral blood of 62 female patients with breast carcinoma was collected and DNA isolation was performed. Afterwards, all coding exons and exon-intron junctions of 60 different genes were sequenced using the next generation sequencing (NGS). In addition, BRCA1 and BRCA2 deletion/duplication analysis was performed on 60 of 62 patients using the multiplex
ligation-dependent probe amplification (MLPA) method.
Results: Heterozygous pathogenic variants were detected in 7 of 62 patients (BRCA1, BRCA2, BRIP1, CHEK2, FANCA, TSC2, XPA) in the hereditary cancer panel. In addition, a heterozygous exon 21 deletion in the BRCA1 gene was detected in one of the 60 patients who underwent BRCA1/BRCA2 deletion/duplication analysis.
Conclusion: Pathogenic variants in the BRCA1, BRCA2, BRIP1, CHEK2 and FANCA genes have been associated with breast cancer cases in the literature. Pathogenic variants in the TSC2 gene cause tuberous sclerosis and increase the risk of various malignancies. It has also been reported that heterozygous pathogenic variants in the XPA gene cause an increased risk of non-melanocytic skin cancer. However, no publication has been found in the literature linking germline variants in the TSC2 and XPA genes with breast cancer risk. Genetic tests involving multiple genes have the potential to provide useful knowledge regarding patients' cancer risk, but they also present difficulties in terms of patient management and genetic counseling due to genes for which there is insufficient data on the genotype-phenotype relationship for specific cancer types.
Keywords: Breast cancer, TSC2, XPA

[Abstract:0255]

Clinical and Molecular Characteristics of Six Cases with Germline TP53 Mutations

Zeynep Münteha Başer[1], Esra Arslan Ateş[2], Ceren Alavanda[3], Şenol Demir[3], Ahmet İlter Güney[4]

[1]Clinic of Medical Genetics, Marmara University Pendik Training and Research Hospital, İstanbul, Türkiye
[2]Department of Medical Genetics, Istanbul University-Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye
[3]Clinical of Medical Genetics, University of Health Sciences, Van Training and Research Hospital, Van, Türkiye
[4]Department of Medical Genetics, Marmara University Faculty of Medicine, İstanbul, Türkiye

Introduction: The TP53 gene is among the most extensively researched tumor suppressor genes in humans. Both somatic and germline TP53 mutations are involved in a wide range of cancer types. While somatic TP53 mutations are one of the most frequent alterations in cancer tissues, the rarer germline TP53 pathogenic variants are associated with Li Fraumeni Syndorme. (MIM: #151623)
Materials-Method: Genomic DNA was isolated from patients'peripheral blood. Exons and exon-intron junctions of 59 cancer-related genes, including TP53, were sequenced by NGS. Variants were evaluated based on ACMG criteria and online mutation databases.
Results: A male patient was diagnosed with ependymoma at the age of 17 and exhibited the p.Asp281Glu variant. Four female patients had breast cancer, with ages at diagnosis ranging from 40 to 58 years. The p.Gly245Ser, p.Arg175His, and p.Arg158His variants, previously associated with Li Fraumeni Syndrome, were detected in three of these patients. One patient was diagnosed with breast cancer at the age of 45 and had a prior diagnosis of CML at the age of 42. This patient exhibited the p.Arg337* variant in peripheral blood, with a VAF of 44%. This variant has not been reported in germline or somatic mutation databases previously, and confirmation from non-hematopoietic tissue was not performed. The last patient, diagnosed with endometrial carcinoma at the age of 69, was found to be a carrier of the p.Gly245Val variant.
Discussion: Detection of germline TP53 variants is important for the prevention and early diagnosis of cancer, not only in the proband but also his/her family. Assessing genetic variants of TP53 in genomic DNA from blood is challenging due to clonal hematopoiesis in hematologic malignancies. Though, p.Arg337* variant was detected in a patient with CML and was not confirmed from a second tissue, development of breast cancer at the age of 45 in the patient is suggestive of a germline variant. Two of the six patients had p.Gly245 alterations. The p.Arg158His variant has conflicting definitions in ClinVar database. More studies would illuminate the pathogenicity of this variant. Here, we report six patients with germline pathogenic/likely pathogenic TP53 variants.
Keywords: Cancer susceptibility, Li Fraumeni, TP53

[Abstract:0256]

A Candidate Gene in Hereditary Colon Cancer: HLTF (SMARCA3)

Aysel Ünal[1], Vahhaç Alp[2]

[1]Antalya Training and Research Hospital, Antalya, Türkiye
[2]Diyarbakır Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye

Objective: According to the 2022 Global Cancer Statistics from the International Agency for Research on Cancer, colorectal cancer ranks as the third most commonly diagnosed cancer worldwide and is the second leading cause of cancer-related deaths. Several genes have been linked to hereditary colorectal cancers, including high-penetrance genes like APC, MUTYH, and MLH1, as well as
lower-penetrance genes such as MSH2 and MSH6. However, the full range of genes that contribute to colorectal cancer risk is not yet fully understood, and research into potential candidate genes is ongoing. Cancer genome studies have identified a significant prevalence of mutations in genes involved in chromatin remodeling complexes. The HLTF protein, part of an ATP-dependent chromatin remodeling complex with helicase and E3 ubiquitin activity, has been minimally studied, but emerging reports suggest it may be associated with colorectal cancer. This study aimed to investigate the potential link between the HLTF gene and colorectal cancer, as well as contribute to the existing literature by reporting a variant in this candidate gene.
Materials-Methods: A family with three members diagnosed with signet-ring cell colon cancer was referred to our Medical Genetics outpatient clinic. Initially, a hereditary cancer panel covering 60 genes was analyzed using next-generation sequencing. When no disease-associated variants were identified, whole exome sequencing was subsequently performed. A heterozygous HLTF:c.485A>G (p.Asp162Gly) variant was identified in the family.
Conclusion: HLTF gene is thought to be associated with hereditary colorectal cancer and clinical and molecular findings are discussed.
Keywords: colorectal cancer, HLTF, signet-ring cell, SMARCA3, whole exome sequencing

[Abstract:0257]

Correlation Between MUTYH Pathogenic Variants and Breast Cancer Risk

Çekdar Kapazan[1], Ayşenur Ersoy Karayumak[1], Esra Dirimtekin[1], Zeynep Münteha Başer[1], Şenol Demir[4], Ceren Alavanda[4], Ayberk Türkyılmaz[3], Esra Arslan Ateş[2], Ahmet İlter Güney[1]

[1]Department of Medical Genetics, Marmara University Faculty of Medicine, İstanbul, Türkiye
[2]Department of Medical Genetics, İstanbul University-Cerrahpasa Faculty of Medicine, İstanbul, Türkiye
[3]Department of Medical Genetics, Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye
[4]Clinic of Medical Genetics, Van Research and Training Hospital, Van, Türkiye

Objective: MUTYH is a gene that encodes MUTYH glycosylase. MUTYH glycosylase is involved in oxidative DNA damage repair and base excision repair pathways. Biallelic pathogenic variants in MUTYH have been associated with Familial Adenomatous Polyposis 2 (FAP2; MIM#608456). However, recently published studies have shown that monoallelic pathogenic MUTYH variants may increase risk of breast, colorectal, gastric, ovarian and endometrial cancers. In this study, we aimed to show whether MUTYH pathogenic variant carriers have an increased risk of breast cancer (BC).

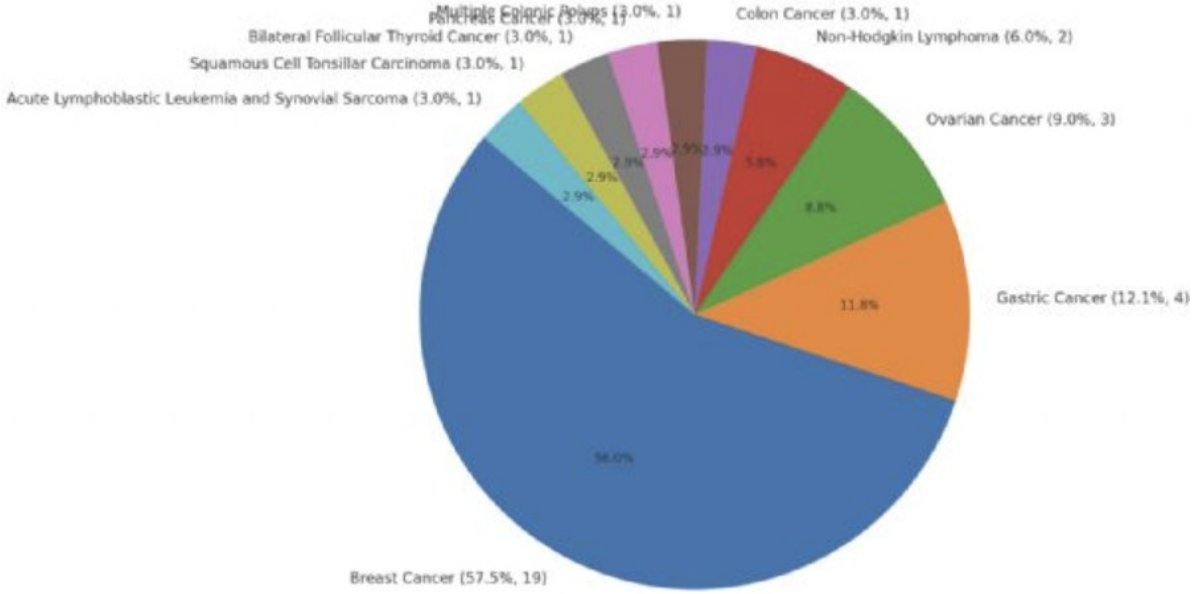
Materials-Methods: 694 patients included in the hereditary cancer panel were retrospectively screened. After DNA isolation using ZeeSan Lab-Aid® 824s Blood DNA isolation kit, SOPHIA Custom Solution CHCS_C_V2 next generation sequencing kit and NovaSeq® system were used to detect variations in all exons and exon-intron junctions of 60 genes including MUTYH. Data were analyzed with Sophia DDM and interpreted in the light of relevant databases.

Results: 277 of the patients (39.9%) had BC. 33 (0.04%) were found to be carriers of MUTYH pathogenic variants. 26 of 33 included patients were female, seven patients were male. Patients' ages ranged from 42 to 67 (median age: 54). 19 patients (57.5%) had BC and one of them was male, 4 patients (12.1%) had gastric cancer, 3 patients (9%) had ovarian cancer, 2 patients (6%) had
non-hodgkin lymphoma and one of them also had BC, 1 (3%) patient had colon cancer, 1 patient had multiple colonic polyps, 1 patient had pancreas cancer, 1 patient had bilateral follicular thyroid cancer, 1 patient had squamous cell tonsillar carcinoma and family history of gastric cancer, 1 patient had acute lymphoblastic leukemia and synovial sarcoma. We detected previously reported 3 missense variants (p.Gly368Asp, p.Pro267Leu, p.Arg154His), 2 truncated variants (p.Glu452*, p.tyr76*) and one in-frame duplication (p.Trp124_Met125insIleTrp) in MUTYH gene.

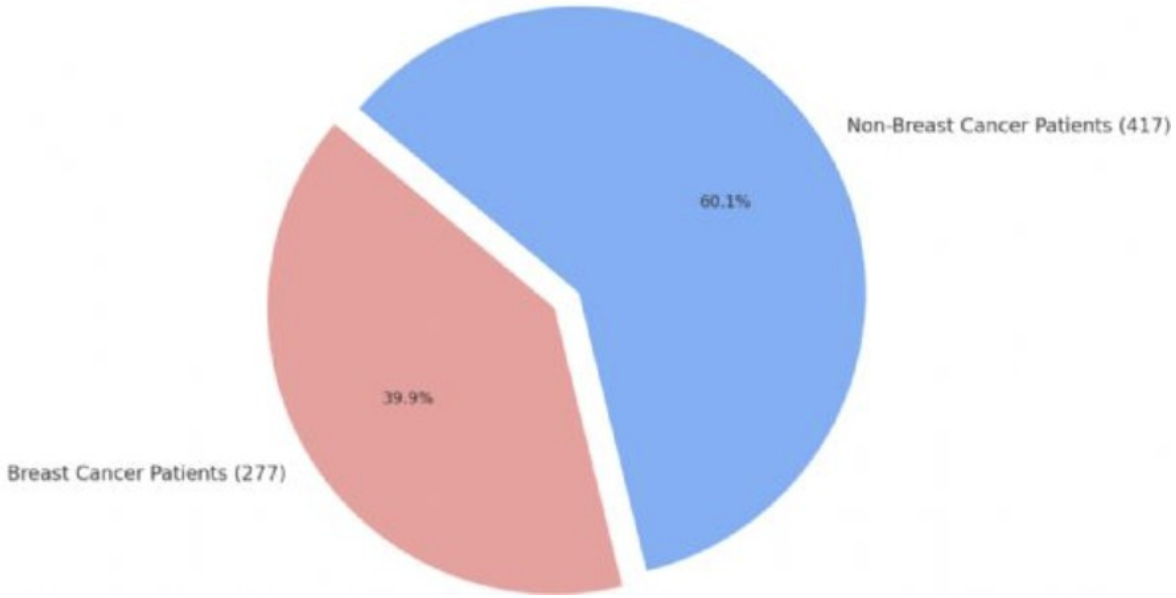
Conclusion: We have found that the risk of BC in MUTYH pathogenic variant carriers is relatively increased. Larger population studies are needed for the correlation between MUTYH pathogenic variants and BC risk.

Keywords: Breast cancer, Carrier, Hereditary cancer, MUTYH

Cancer Rates in MUTYH Pathogenic Variant Carriers



Proportion of Breast Cancer Patients



[Abstract:0258]

Lynch Syndrome-Associated Gene Variants: Findings From Ege University

Alper Baysal, Zeki Sakallı, Haluk Akın, Aslı Ece Solmaz

Department of Medical Genetics, Ege University Faculty of Medicine, İzmir, Türkiye

Objective: Lynch syndrome (LS), previously known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant genetic condition associated with a significantly increased risk of colorectal, endometrial, and various other cancers. The syndrome results from mutations in DNA mismatch repair (MMR) genes, most commonly MLH1, MSH2, MSH6, and PMS2, EPCAM. These mutations lead to microsatellite instability (MSI) and a cascade of genomic alterations that promote tumorigenesis. Lynch syndrome accounts for approximately 3-5% of colorectal cancers, making it one of the most common hereditary cancer syndromes. Clinical diagnosis is guided by family history criteria, such as the Amsterdam II and revised Bethesda guidelines, alongside molecular and genetic testing for MSI, MMR deficiency, or germline mutations.
Materials-Methods: Between 2018 and 2024, 131 patients who applied to the Medical Genetics Department of Ege University Hospital and were found to have variants in genes associated with Lynch syndrome on the cancer panel were analyzed.
Results: Variants in the MLH1 gene were identified in 49 patients, with colon cancer as the most frequent diagnosis (20 cases). Copy number variations (CNVs) were found in 7 patients (3 deletions, 4 duplications), with 6 pathogenic and 7 likely pathogenic variants. In MSH2, variants were detected in 25 patients, including 11 with colon cancer. CNVs were present in 3 patients (2 deletions, 1 duplication), with 3 pathogenic and 3 likely pathogenic variants. For MSH6, 34 patients were studied, and breast cancer was the most common finding (16 cases). CNVs (2 deletions, 2 duplications) were identified in 4 patients, with 4 pathogenic variants reported. Variants in PMS2 were found in 26 patients, with colon cancer in 7 cases. CNVs (3 deletions, 2 duplications) were identified in 5 patients, with 2 pathogenic variants.
Conclusion: These findings highlight the role of MLH1, MSH2, MSH6, and PMS2 variants in cancer predisposition, emphasizing the importance of genetic analysis in identifying at-risk individuals. This study also contributes to the literature by shedding light on variants in Lynch syndrome-related genes found in Türkiye.
Keywords: Lynch, Mismatch repair, cancer

[Abstract:0259]

Retrospective Analysis of Liquid Biopsy-Detected Mutations in Advanced Non-Small Cell Lung Cancer: A Single-Center Study

Ekin Cemre Bayram Tokaç, Alp Peker, Ayça Aykut, Asude Alpman Durmaz, Haluk Akın

Clinic of Medical Genetics, Ege University Hospital, İzmir, Türkiye

Objective: Lung cancer (LC) is one of the leading causes of cancer-related mortality worldwide. Approximately 80% of LC cases are classified as non-small cell lung cancer (NSCLC), with nearly two-thirds diagnosed at advanced stages. Identifying mutations driving LC is crucial for selecting
effective treatment strategies. Noninvasive methods are increasingly needed for real-time molecular monitoring. Liquid biopsy (LB) has emerged as a promising tool. more than 200 different actionable mutations. This study aimed to evaluate the clinical utility of next-generation sequencing (NGS) of plasma cell-free DNA (cfDNA) for molecular profiling of patients with NSCLC during disease progression.
Materials-Methods: Plasma cell-free DNA (cfDNA) examined through next-generation sequencing in 245 patients with stage IIIB and IV NSCLC, comprising 67% male and 33% female participants. The patient cohort included adenocarcinoma (51%), squamous cell carcinoma (13%), unclassified histological subtypes (35%), and other types (1%). Mutation analyses were conducted using the AVENIO Tumor Expanded Panel and Illumina NextSeq technology.
Results: Somatic alterations were detected in 48% of patients. EGFR variants were identified in 10%, with amplifications in 8%, and 2% exhibiting both. Uncommon variants in EGFR included p.L858R and p.L861Q. MET and ERBB2 amplifications were observed in 12%, indicating potential responsiveness to targeted therapies. TP53 mutations, associated with poor prognosis and resistance, were found in 26% of cases. Additional mutations included KRAS (12%), PIK3CA (7%), and BRAF (1%). Driver mutations were identified in 40% of cases, with 34% (83 patients) having ESCAT tier I and II druggable variants. Resistance-associated mutations, including TP53 and EGFR amplifications, were present in 29% (71 patients).
Conclusion: The liquid biopsy approach demonstrated remarkable utility in providing a non-invasive method for molecular profiling. By enabling real-time monitoring of tumor heterogeneity, this technique offers insights into potential treatment strategies. The detected mutations, particularly EGFR, ERBB2, KRAS and PIK3CA alterations, present opportunities for personalized therapeutic interventions. Tyrosine kinase inhibitors remain standard for EGFR-positive NSCLC, but the presence of amplifications necessitates alternative treatment considerations. The comprehensive molecular characterization underscores the importance of precision medicine in managing advanced lung cancer. This study highlights liquid biopsy's potential use for more targeted, individualized treatment approaches in NSCLC.
Keywords: Liquid biopsy (LB), Non-small cell lung cancer (NSCLC), Next-generation sequencing (NGS), EGFR mutations, Precision medicine

[Abstract:0261]

Evaluating the Age of Onset Criteria for Germline BRCA1/2 Testing in Breast Cancer: How Many Patients Are We Missing?

Oya Demirkaya, Deniz Torun, Sezin Sungur, Ali Öztuna, Hatice Akar, Yusuf Tunca

Clinic of Medical Genetics, Gülhane Training and Research Hospital, Ankara, Türkiye

Abstract: Identification of germline BRCA1/2(gBRCA1/2) mutations in patients diagnosed with breast cancer(BC) has impacts on therapeutic decisions and prognosis and offers the opportunity to prevent potential future cancers. It has been observed that breast cancer cases with gBRCA1/2 mutations have an earlier age of onset. Therefore, age of onset is one of the significant criteria for testing gBRCA1/2 mutations in BC. Currently, distinct guidelines recommend different ages for testing. Consequently, this study aimed to identify the most appropriate age for gBRCA1/2 testing in BC.

Materials-Methods: A total of 1,100 patients who applied to the Department of Medical Genetics at Gülhane Training and Research Hospital between 2018-2024 for gBRCA1/2 analysis were evaluated retrospectively based on their age of diagnosis.

Results: Out of the 1,100 patients who underwent BRCA1/2 sequencing analysis, 851 were diagnosed with BC. Among these patients, 92 (10.8%) had mutations in BRCA1/2. Testing only patients diagnosed at the age of 45 or below would have identified 59.8% of the mutation carriers. If the age limit for testing is increased to 50, 55, 60 and 65 years, 77.2%, 89.1%, 96.7% and 97.8% of mutation carriers can be identified, respectively. For each age of diagnosis threshold of 45, 50, 55, 60 and 65 years, the phi correlation coefficients were calculated as 0.755, 0.867, 0.938, 0.982, and 0.988 respectively. ($p<0.001$)

Discussion: If patients are tested according to the diagnostic age criterion of 50 years or below, as recommended by National Comprehensive Cancer Network(NCCN) guideline for detecting gBRCA1/2 mutations, 22.8% patients would be missed. As the age criterion for onset is expanded, the sensitivity of the test increases, with the highest sensitivity achieved when all patients below 65 years are tested. However, in this case, 10% of patients would undergo unnecessary genetic testing. Statistically, the diagnostic age criterion of 55 years or below is identified as providing a highly robust and reliable association(phi>0.90) while maintaining a sensitivity of >90%.

Conclusion: It was determined that the optimal balance of sensitivity, specificity, and reliable association was achieved with a testing age of onset of 55 years or below, although testing may still be suitable for older patients in certain situations.

Keywords: Age of onset, breast cancer, germline BRCA1/2

[Abstract:0262]

Two BRCA1 pathogenic variants in a family: implications for cancer risk and genetic counseling

Muhammed Faruk Ürkmez, Ezgi Gökpınar İli

Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Türkiye

Abstract

Objective: BRCA1-related hereditary breast and ovarian cancer syndrome is well-established. However, observing different BRCA1 pathogenic variants within a single family is rare and raises intriguing genetic and clinical implications.

Case Presentation: We present a unique case of a mother-daughter pair with hereditary cancer predisposition. The proband, a 40-year-old female with stage I typical medullary breast carcinoma, and her mother, a 60-year-old with serous papillary ovarian carcinoma were evaluated simultaneously due to their concurrent cancer diagnoses. The family history revealed additional cancer cases: the mother's paternal aunt and two paternal cousins had pancreatic cancer. The proband's father had a sister with breast cancer. The parents are second-degree cousins. The mother also reported two early pregnancy losses. A 36-gene hereditary cancer NGS panel revealed two different BRCA1 (NM_007294.4) variants: pathogenic c.1961delA (p.K654fs47) in the mother and likely pathogenic c.5027dupT (p.L1676fs3) in the daughter. To exclude technical errors or sample misidentification, the tests were repeated with fresh samples, confirming the initial findings. Subsequent testing of the father showed paternal transmission of the BRCA1:c.5027dupT variant in the daughter.

Discussion: Although hereditary breast and ovarian cancer associated with BRCA1 is well-known, two BRCA1 pathogenic variants in a single family are rare. Cases of biallelic BRCA1 pathogenic variants are rarely reported in patients with Fanconi aplastic anemia with a family history of cancer on both sides. Here, we present a multigenerational cancer family with two different BRCA1 pathogenic variants. Both variants are frameshift variants causing premature termination codons and possible nonsense-mediated decay. Complete loss of BRCA1 is widely considered embryonic lethal. Thus, there are no known FA patients in the family. Notably, the mother reported two early pregnancy losses, which may be attributed to homozygous BRCA1 variants. However, further analysis is required to substantiate this hypothesis.

Conclusions: This family with two pathogenic BRCA1 variants highlights possible allelic heterogeneity in cancer families with multiple affected members. This study emphasizes careful pre- and post-test genetic counseling, comprehensive genetic testing of family members, and exclusion of any possible laboratory errors. Additionally, the possible contribution of BRCA1 homozygosity to pregnancy losses represents an intriguing observation that warrants further investigation.

Keywords: BRCA1, Fanconi anemia, allelic heterogeneity

[Abstract:0263]

Genetic Heterogeneity in Patients with Lynch Syndrome: A Single Center Retrospective Cohort Study

Cemal Onur Onaran, Esra Dirimtekin, Saliha Esra Olgun, Samet Dilce, Ahmet İlter Güney

Department of Medical Genetics, Marmara University Faculty of Medicine, İstanbul, Türkiye

Abstract

Objective: Lynch syndrome (MIM#120435) also known as hereditary non-polyposis colorectal cancer (HNPCC), is one of the most common inherited cancer syndromes. It is caused by pathogenic variants in mismatch repair (MMR) genes, such as MLH1, MSH2, MSH6 and PMS2, or by alterations in the EPCAM gene, which lead to microsatellite instability (MSI) and an increased risk of various malignancies. The syndrome is most strongly associated with colorectal cancer and endometrial cancer, but it also predisposes individuals to other cancers, including ovarian, gastric, and urinary tract cancers.

Material-Methods: 54 cancer patients who had colorectal, endometrium, breast and stomach cancers included in the hereditary cancer panel were retrospectively screened. 15 of that patients had endometrium cancer, 34 patients had colorectal cancer, 2 of that patients had stomach cancer, 3 patients had breast cancer and 1 patient had ovary cancer. Notably, 1 patient had both endometrial and colon cancer. After DNA isolation using ZeeSan Lab-Aid® 824s Blood DNA isolation kit, SOPHIA Custom Solution CHCS_C_V2 next generation sequencing kit and NovaSeq® system were used to detect variations in all exons and exon-intron junctions of 60 genes including MLH1, MSH2, MSH6, PMS2 and EPCAM genes.

Results: Among the 54 patients diagnosed with Lynch syndrome, 38(%70) were female, while the remaining 16(%30) were male. Patients' median age was 52 and their ages ranged from 36 to 69. We found that heterozygous pathogenic variants were identified as follows: 10(%18.5) patients had in the MLH1, 23(%42.5) patients had in the MSH2, 13(%24) patients had in the MSH6, 7(%13) patients had in the PMS2 and 1(%3) in the EPCAM. In a patient with endometrial cancer, pathogenic variants have been detected in both the MSH2 and MSH6 genes.

Discussion: In this study, we aimed to identify the types of cancers present in patients diagnosed with Lynch syndrome and determine which variants were detected in the MLH1, MSH2, MSH6, PMS2, and EPCAM genes associated with these cancers. Larger studies are needed for the correlation between MLH1, MSH2, MSH6, PMS2 and EPCAM pathogenic variant carriage and risk of cancers such as; colorectal, endometrium, breast, ovary and stomach cancer.

Keywords: Lynch Syndrome, MLH1, MSH2, MSH6, PMS2

POSTER BİLDİRİLER

[Abstract:0086]

CDH1 Mutation and Gastric Signet Ring Cell Cancer Detected in a 16-Year-Old Patient Without a Family History: A Case Report

Delyadıl Karakaş, Zuhat Urakçı

Department of Oncology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye

Abstract

Objective: Hereditary diffuse gastric cancers are one of the genetically inherited cancer syndromes that include pathogenic or likely pathogenic mutations in various genes, including the CDH1 (Cadherin 1) gene. This gene plays a critical role in genetic diffuse gastric cancer and lobular breast cancer.

Pathogenic variants of this gene exhibit an autosomal dominant inheritance pattern, and diagnosis is usually made before the age of 20. Isolated diffuse gastric cancer may occur, or it may be seen in first- or second-degree relatives. Family history is not neccessary for diagnosis.

Case: A 16-year-old female patient presented to the emergency department in February 2024 with complaints of abdominal pain. Laboratory tests showed glucose: 430 mg/dL, creatinine: 1.3 mg/dL, positive urinary ketones, and venous blood gas pH: 7.0, leading to a diagnosis of diabetic ketoacidosis, and the patient was admitted for treatment. Due to persistent abdominal pain during follow-up, antibodies for Celiac disease, which can be associated with Type 1 DM, were tested. Because of Anti-tissue transglutaminase IgG antibodies were positive, endoscopy was performed. Endoscopic imaging revealed polypoid lesions throughout the stomach, and multiple biopsies were taken. Histological examination of the biopsies showed findings consistent with signet ring cell carcinoma (diffuse) of the stomach. Imaging studies performed for disease staging revealed localized disease, and the patient was referred for surgery. Postoperative pathological evaluation confirmed signet ring cell carcinoma. A germline next-generation DNA sequencing analysis was performed, revealing a heterozygous, autosomal dominant CDH1 gene mutation (c.187>T p(Arg63)). According to the patient's surgical pathology, the tumor was staged as T1aN0M0, classified as Stage I. Since there was no need for adjuvant therapy, the patient was placed under follow-up. Annual breast ultrasound screening was recommended for lobular breast cancer surveillance, and family screening was also advised.

Conclusion: Here, we present a case of a 16-year-old with no family history who was found to have a CDH1 mutation and diffuse carcinoma of the stomach. If positive, patients should also be evaluated and followed up for lobular breast carcinoma. The follow-up and treatment of such cases should be conducted by a multidisciplinary team, including molecular geneticists, medical oncologists, and surgical oncologists.

Keywords: CDH1, Diffuse gastric cancer, Family history, Lobular breast carcinoma

Author To Editor: Bildiriyi göndermekte ki amacım; aile öyküsü olmadan da hastalarda mutasyon bakmanın önemini göstermektektir. Bu sayede hastalarda önleyici onkolojik tarama ve taramalar yapılabilmektedir.

[Abstract:0099]

Multiple Primary Cancers with BRCA Mutation: Two Case Reports

Tolga Doğan

Clinic of Medical Oncology, Denizli State Hospital, Denizli, Türkiye

Abstract

Objective: Hereditary breast and ovarian mancer attributable to pathogenic variants in BRCA1/2 is characterized by an autosomal-dominant pattern of inheritance, markedly increased susceptibility to breast and ovarian cancer, with an especially early onset of breast cancer, and an increased incidence of tumors of other organs,such as the fallopian tubes, prostate, male breast, and pancreas. Multiple primary tumours are usually metachronous or synchronous, depending on the time of presentation between the two malignancy diagnoses. Although synchronous diseases often occur as a result of exposure to similar carcinogens, metachronous ones are more often related to the treatment of the primary tumour.

Case: A 64-year-old woman the biopsy taken from the omentum was found as ovarian serous carcinoma metastasis. She was given 6cycles of paclitaxel-carboplatin treatment with a diagnosis of stage 4 ovarian carcinoma. In the response evaluation of the patient,a complete response to liver metastasis was obtained on abdominal MRI.TAH+BSO was performed and pathological complete response was obtained.After 1 year of treatment-free follow-up, a 2.5x1.5 cm lesion was detected in the head of the pancreas in the control examination.The patient underwent whipple operation.Pathology was evaluated as pancreatic adenocarcinoma.After adjuvant treatment a 15 mm nodular lesion with pathological FDG uptake in the right breast.Breast tru-cut biopsy was evaluated as invasive ductal carcinoma. The patient underwent modified radical mastectomy.Adjuvant letrozole treatment was started. According to NGS results the patient carries the BRCA1 gene mutation.mCase 2:A 72-year-old patient was examined with cough and shortness of breath.Pet-CT revealed a
pleura-based 74*42*73 mm mass (SUVmax:11.51) in the lower lobe of the right lung and heterogeneous involvement in the prostate.Right lung lower lobectomy was performed. Pathology was evaluated as squamous cell carcinoma.He received 4cycles of carboplatin-paclitaxel treatment. TRIB pathology result was compatible with prostate adenocarcinoma with Gleason score 3+3=6.Androgen deprivation therapy was started. In the 10th month of follow-up,a 3 cm lesion compatible with metastasis in the pancreas. The patient underwent whipple operation. Pathology was evaluated as pancreatic adenocarcinoma (T2N0M0.)According to NGS results the patient carries the BRCA 1 gene mutation

Conclusion: Inherited mutations in BRCA1 and BRCA2 genes increase the risk of development of cancer in organs especially in breast and ovary. Prevention and screening in BRCA mutation carriers are of high importance

Keywords: BRCA carriers, multiple primary tumors, synchronous tumor

[Abstract:0100]

A Rare Case: Germline PRKN Mutant Primary Peritoneal High Grade Serous Carcinoma

Ahmet Unlu, Banu Ozturk

Clinic of Medical Oncology, Antalya Training and Research Hospital, Antalya, Türkiye

Objective: Primary peritoneal serous carcinoma (PPSC) is an extremely rare malignancy. It is an epithelial tumor arising from the peritoneum and is histopathologically similar to serous ovarian carcinoma. The prognosis is poor and the median survival time is 11-17 months. Because the frequency of BRCA mutations in peritoneal and ovarian cancer cases is similar, PPSC is thought to be part of the hereditary breast-ovarian cancer syndrome. Parkin (PRKN) gene mutations are not common. But many studies have demonstrated Parkin gene alterations in a wide variety of cancers. It is associated with poor survival in patients with advanced breast cancer. However, its clinical significance in primary peritoneal cancers is unknown. In this case report, it is aimed to contribute to the literature by presenting a case of primary peritoneal high grade serous carcinoma with germline parkin gene mutation, to better recognize this extremely rare clinical problem and to describe its clinical features.

Case: A 38-year-old pregnant woman had a cesarean section at 31 weeks of pregnancy due to respiratory problems. Peritonitis carcinomatosis was detected during surgery. Peritoneal biopsy sampling revealed a histopathological diagnosis of high-grade serous carcinoma. The patient was administered 3 cycles of carboplatin-paclitaxel protocol. Then, debulking surgery was performed and 8 cycles of carboplatin-paclitaxel were completed. A partial response was achieved. In the NGS analysis; BRCA 1/2 was wild type, PRKN gene was mutant. After 3 months of niraparib treatment, progression was detected and the patient was started on the cisplatin-gemcitabine-bevacizumab protocol. The patient, who was found to have a complete response on PET-CT taken 6 cycles later, was continued with maintenance bevacizumab. Liposomal doxorubicin was started in the patient whose disease progressed after 6 months of maintenance bevacizumab. The patient, who was given the second course of liposomal doxorubicin 2 weeks ago, continues to live with an overall survival of approximately 50 months.

Conclusion: The clinical significance of parkin gene mutation in primary peritoneal high-grade serous carcinoma, a very rare malignancy, is unknown. More data are needed to better define the clinical significance of PRKN gene mutation in these patients.

Keywords: Peritoneal cancer, PRKN gene mutation, serous carcinoma

[Abstract:0101]

A Rare Case of Genetic Skin Tumor: Brooke-Spiegler Syndrome

Gülhan Özçelik Köker, Mustafa Karaca, Sema Sezgin Göksu

Department Medical Oncology, Akdeniz University Faculty of Medicine, Antalya, Türkiye

Introduction: Brooke-Spiegler syndrome (BSS) is a rare autosomal dominant disorder associated with mutations in the CYLD gene. It is characterized by the development of cutaneous tumors, including basal cell carcinoma (BCC), cylindroma, and multiple trichoepitheliomas. The syndrome typically presents in childhood or early adulthood as slow-growing, painless skin lesions. If untreated, it can lead to significant tissue destruction in advanced stages. Herein, we report a rare case of BSS diagnosed at an advanced stage, notable for familial predisposition and extensive tissue involvement.

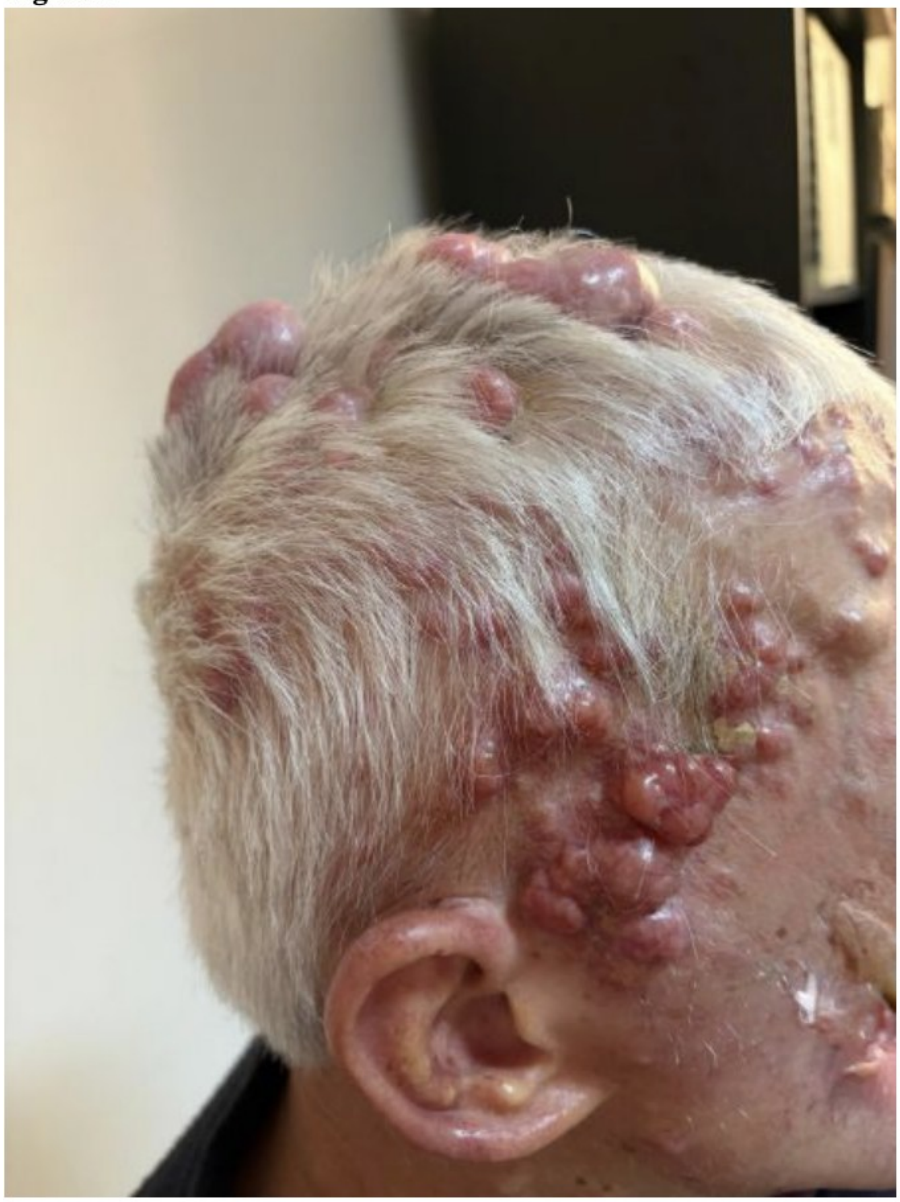
Case: A 56-year-old male presented to the dermatology clinic with a progressively enlarging lesion on the side of his nose over the past 10 years. His family history revealed similar scalp lesions in a cousin and an aunt. A biopsy of the nasal lesion confirmed the diagnoses of BCC and cylindroma. The patient was referred to our clinic with a diagnosis of Brooke-Spiegler syndrome and BCC. On physical examination, significant destruction of the right side of the face, including the mandible and maxilla, was observed, with exposed teeth in the affected area. Multiple nodular lesions were noted on the scalp and bilaterally on the face. Radiological evaluation revealed a thick-walled necrotic lesion measuring 14x15 mm in the left maxillary sinus, and a 3 mm nodule in the posterobasal segment of the right lower lung lobe on chest CT. The nodular scalp lesions were considered consistent with cylindroma. Skin biopsies confirmed BCC in the nasal region and cylindroma in the forehead, with histopathological findings indicating tumor persistence at the surgical margins. The patient was started on vismodegib, a targeted Hedgehog pathway inhibitor, at a daily dose of 150 mg. He was also referred to the medical genetics department for comprehensive analysis of CYLD gene mutations.

Conclusion: This case highlights the diagnostic challenges and treatment strategies for Brooke-Spiegler syndrome. A thorough family history is crucial for early diagnosis. In advanced cases, combining targeted therapies with surgical interventions can lead to successful outcomes.

Identification of CYLD gene mutations can guide genetic counseling and family screening. This report underscores the clinical features and management of a rare disease at an advanced stage.

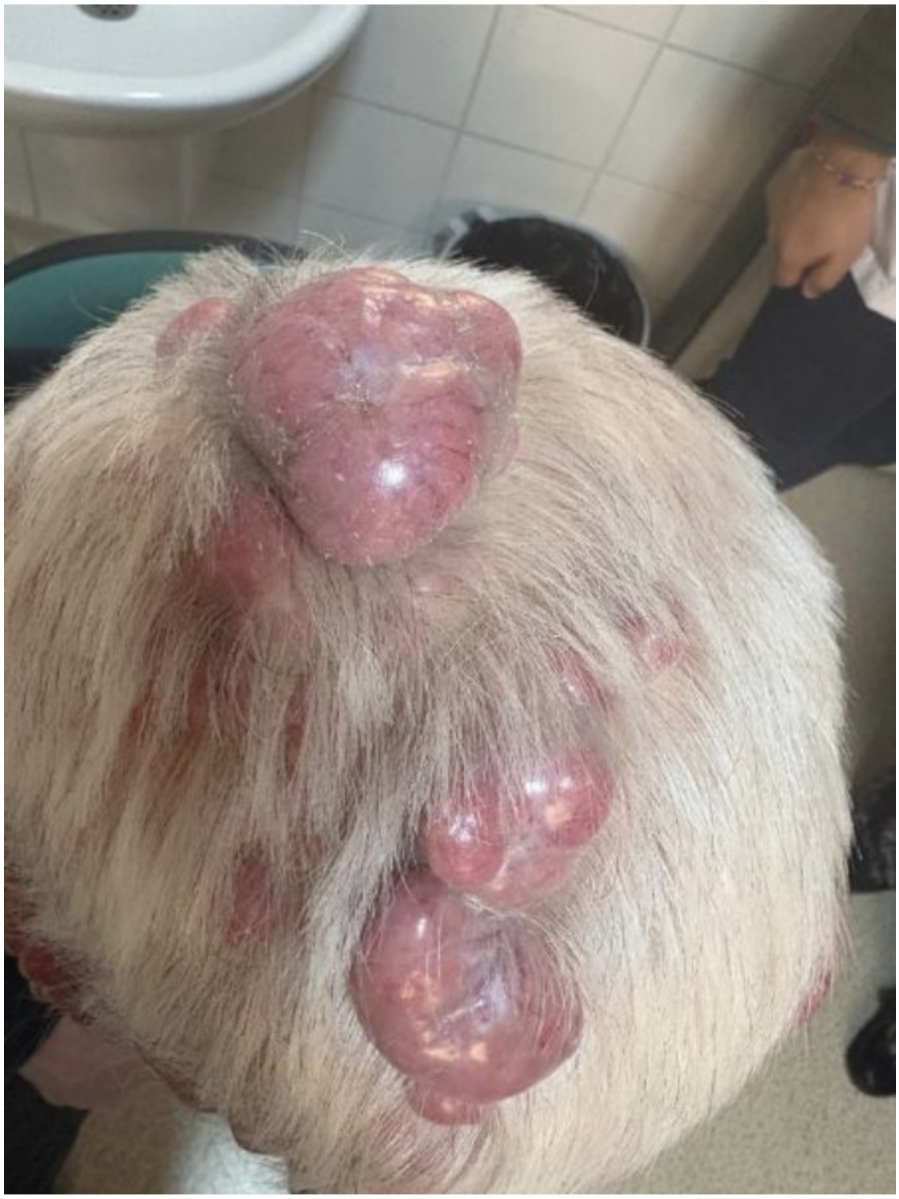
Keywords: Brooke-Spiegler syndrome, CYLD gene mutation, basal cell carcinoma, cylindroma, genetic skin tumors

Figure 1



Nodular Lesions Observed on the Scalp and Face Associated with Brooke-Spiegler Syndrome

Figure 2



Giant Nodular Lesions on the Scalp in Brooke-Spiegler Syndrome

Author To Editor: Sayın Bildiri Değerlendirme Kurulu Üyeleri, Sizlere nadir görülen genetik bir deri tümör sendromu olan Brooke-Spiegler sendromuna ait bir olguyu sunmaktan mutluluk duyuyoruz. Çalışmamızda, ileri evrede tanı almış ve belirgin klinik bulgularla karakterize bu olguyu literatüre katkı sağlayacak şekilde detaylı olarak ele aldık. Genetik, klinik ve radyolojik açıdan kapsamlı bir şekilde değerlendirilmiş olan bu hasta, Brooke-Spiegler sendromunun tanı ve tedavi süreçlerindeki zorluklara ışık tutmaktadır. Bu bildiriyi, ilgili alandaki farkındalığı artırmak ve bilimsel toplulukta tartışma yaratmak amacıyla dikkatinize sunuyoruz. Değerlendirme sürecinde göstereceğiniz kıymetli katkılarınız ve önerileriniz için şimdiden teşekkür ederiz. Ayrıca, bildirinin değerlendirilmesinde başarılı bulunması halinde verilecek olan kurs ödülüne büyük bir ilgi ve heyecan duyduğumu belirtmek isterim. Bu ödülün, bilimsel bilgi birikimimi geliştirme ve mesleki donanımımı artırma yönünde önemli bir fırsat sunacağına inanıyorum. Bu vesileyle, bildirime gösterdiğiniz değerli zaman ve ilginiz için tekrar teşekkür ederim.
Saygılarımla, Dr. Gülhan Özçelik Köker Akdeniz Üniversitesi Tıbbi Onkoloji Yandal Asistanı

Dear Members of the Scientific Committee, It is a great pleasure to present a case of Brooke-Spiegler syndrome, a rare genetic skin tumor syndrome, to your esteemed committee. In our study, we have detailed this case, which was diagnosed at an advanced stage and is characterized by prominent clinical findings, in a way that contributes to the literature. This patient has been comprehensively evaluated from genetic, clinical, and radiological perspectives, shedding light on the diagnostic and therapeutic challenges associated with Brooke-Spiegler syndrome. We submit this abstract to increase awareness in the field and to foster discussion within the scientific community. We are sincerely grateful for your valuable contributions and suggestions during the evaluation process. Furthermore, I would like to kindly express my great interest and excitement regarding the course award that will be given following the evaluation of the abstracts. I believe this award represents a unique opportunity to enhance my scientific knowledge and professional skills. Once again, I thank you for the time and attention you have devoted to reviewing my abstract.
Kind regards, Dr. Gülhan Özçelik Köker Medical Oncology Fellow, Akdeniz University

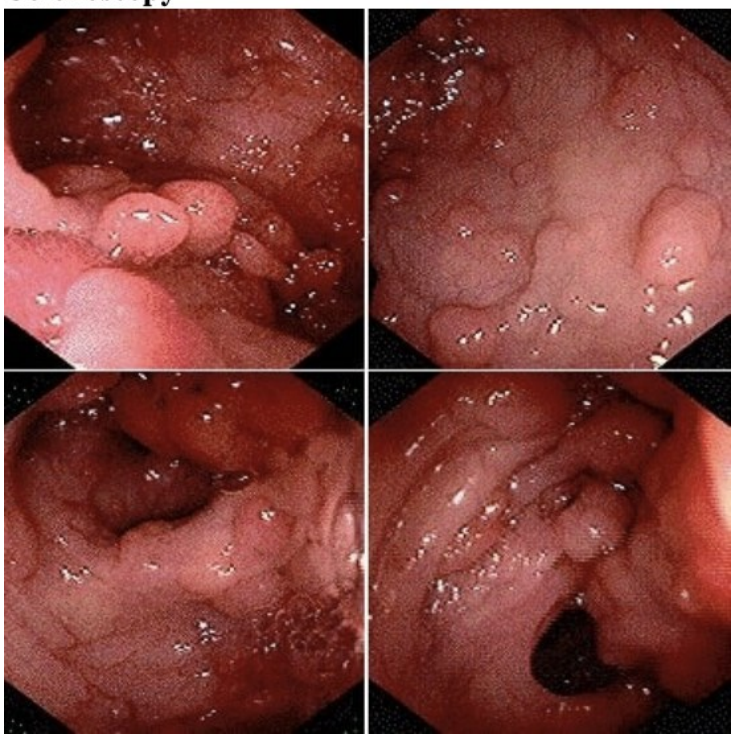
[Abstract:0106]
Familial Adenomatosis Polyposis Coli

Doğan Pakalın, Banu Öztürk

Clinic of Medical Oncology, Antalya Training and Research Hospital, Antalya, Türkiye

Objective: Familial adenomatous polyposis is a genetic disorder that predisposes you to develop precancerous colon polyps called adenomas. Colon polyps are abnormal growths in the lining of your colon or rectum. They aren't cancer, but certain types, like adenomas, can change into colorectal cancer. Without treatment, the risk of developing colorectal cancer with familial adenomatous polyposis is close to 100%. It also develops relatively earlier and faster with FAP than in those without. Children in families known to be affected by the syndrome begin yearly colonoscopy screenings at the age of 10.
Case: A 32-year-old male patient who applied due to diarrhea was examined because his father had a history of colon cancer. During the colonoscopy, multiple polyps were detected covering the entire colon, the largest measuring 3cm. An ulcerovegetating mass was observed covering 50% of the distal wall of the rectum. In the polyp biopsy taken, the polyps in the colon were detected as tubular adenoma. Rectum biopsy revealed adenocarcinoma. A mutation in the APC gene was detected in the somatic genetic test. Abdominal MRI performed for staging purposes revealed a T4aN2nM0 high + mid rectum tumor. No distant metastases other than the primary tumor were detected in the PET/CT scan. Total colectomy was planned after 12 courses of neoadjuvant FOLFIRINOX. Chemotherapy was started after the patient's blood test and echocardiography were found to be normal. His treatment is still ongoing.
Conclusion: Without timely treatment, the median life expectancy is 42 years. But with appropriate care, you can live a normal life. Once your colon has been removed, your biggest risk is from other gastrointestinal cancers or problematic desmoid tumors. These occur much less frequently than colorectal cancer.
Keywords: FAP, colorectal cancer, polyposis

Colonoscopy



[Abstract:0115]

Belzutifan Treatment in von Hippel-Lindau Disease: A Case Report

Engin Eren Kavak

Department of Medical Oncology, Etlik City Hospital, Ankara, Türkiye

Abstract

Objective: Von Hippel-Lindau (VHL) disease is a rare autosomal dominant genetic syndrome, characterized by germline pathogenic variants in the VHL gene. Its prevalence is estimated to be approximately 1-2/39,000 cases of. VHL disease is characterized by the presence of multiple benign and malignant tumors, including clear cell renal cell carcinomas (RCCs), central nervous A study published in 2021 investigated VHL-associated kidney cancer in an open-label clinical trial involving 61 patients diagnosed with VHL-associated kidney cancer based on a VHL germline alteration and with at least one measurable tumor in the kidney. The study reported an overall response rate of 49% in patients with VHL-associated renal cancer, 63% in 24 patients with measurable central nervous system haemangioblastomas, and 83% in 12 patients with measurable pancreatic neuroendocrine tumors. The objective of presenting this case is to raise awareness of this rare disease.

Case: A 28-year-old female patient was evaluated in March 2013 with complaints of hirsutism. Two masses compatible with malignancy were detected in the right kidney. Following the right partial nephrectomy on 07.03.2013, the pathology result was reported as renal cell carcinoma (RCC). The patient was subsequently observed without undergoing any further treatment. In 2020, a genetic examination revealed a positive Von Hippel-Lindau (VHL) mutation, identified following the detection of RCC in the patient's family, specifically her mother and sisterDuring the follow-up period at the Göztepe Prof. Dr. Süleyman Yalçın City Hospital, approximately 11 years later, on 24/02/2024, pancreatic cysts and Bosniak Type 3 cysts (with high malignant potential) in the kidney were detected on abdominal magnetic resonance imaging (MRI); 2 mm diameter lesions compatible with cerebellar hemangioblastoma were detected on brain MRI. Following the approval of overseas drug use, Belzutifan 120 mg was initiated in March 2024. Subsequent follow-ups revealed that the patient's masses remained stable and exhibited no active complaints, except for Grade 1 anemia.

Conclusion: Belzutifan is vital in treating Von Hippel-Lindau (VHL) disease and is an indispensable agent in the treatment protocol.To evaluate responses to treatment in this rare disease, multicentre clinical trials involving a large patient population are required.

Keywords: Von Hippel Lindau Disease, Renal Cell carcinoma, hemangioblastomas, Belzutifan, effectiveness

[Abstract:0117]

Clinicopathologic Features of Male Breast Cancer Patients: A Single Center Experience

Taliha Güçlü Kantar

Pamukkale University, Denizli, Türkiye

Objective: Breast cancer is rare in men, accounting for about 1% of all breast cancer patients and 0.2% of cancers in men.The risk of male breast cancer appears to be higher with inherited BRCA2 rather than BRCA1 mutations. We aimed to retrospectively evaluate the clinicopathologic features of our male breast cancer patients.
Materials-Methods: All breast cancer patients admitted to Pamukkale University Medical Oncology Clinic between September2005 and July2022 were screened and 21 male breast cancer patients were included. Age at diagnosis,family history,localization of the primary tumor, presenting symptom, stage, histological type,ER,PR,HER2,Ki67,BRCA mutation,
chemotherapy, surgery, progression-free and overall survival data were evaluated and the literature was reviewed.
Results: The median age of the patients was 59+11.7(40-82)years.Stage1 was 5(23.8%),Stage2 was 6(28.6%),Stage3 was 4(19%),and Stage4 was 6(28.6%).The presenting symptom was a palpable mass in the breast or axilla in 16(76.2%) patients. Primary tumor localization was right breast in 11(52.4%),nipple/central in 12(57.1%)and upper outer quadrant in 2patients(23.8%).4patients(19%)had multicentric tumors.The most common histologic type was invasive ductal carcinoma in 14 patients(66.7%). According to hormone profile,16(76.2%) patients were ERpositive,13(61.9%) patients were PRpositive,4(19%)patients were Her2positive and 14(66.7%)patients had Ki67 of 20% or higher.Accordingly, LuminalA was 4(19%),Luminal B/her2negative 10(47.6%),Luminal B/her2 positive 2(9.5%),Her2 positive/nonluminal 2(9.5%)and triple negative 3(14.3%). Grade3-4 according to tumor grade was detected in 11patients (52.4%).16(76.2%)patients underwent MRM or simple mastectomy.There were 4(19%) patients with BRCA1 mutation and 10 (47.6%)patients with BRCA2 mutation. Adjuvant chemotherapy 9(42.9%)and adjuvant radiotherapy 8(38.1%).All hormone receptor positive patients received Tamoxifen treatment. Triple negative patients received anthracycline-taxane based chemotherapy.There were 7 (33.3%)patients with a family history of cancer. Progression developed in 2 patients(9.5%) and 6 patients(28.6%)died.mPFS was 96.5+7.3(95%CI 82.2-110.9) months and mOS was 87.2+11.5(95%CI 64.6-109.8)months.
Conclusion: As with breast cancer in women, a family history of breast cancer in first-degree relatives is associated with an increased risk of breast cancer in men. The BRCA1 and BRCA2 gene leads to the majority of cases of known hereditary breast cancer in women. Genes other than BRCA may also play a role in predisposing men to breast cancer. PTEN mutation, PALB2, Cowden syndrome, Li-Fraumeni syndrome and Lynch syndrome have been associated with an increased risk of breast cancer in men. Diagnosis of male breast cancer at an early stage, hereditary gene analysis and appropriate treatment are very important for a good prognosis.
Keywords: Male breast cancer, clinicopathologic features, BRCA

[Abstract:0135]

Rare Genetic Insights: A Young Colorectal Cancer Patient with MUTYH Heterozygosity

Mehmet Mutlu Çatlı, Derya Kıvrak Salim

Clinic of Medical Oncology, University of Health Scienes, Antalya Training and Research Hospital, Antalya, Türkiye

Objective: To present a rare case of early-onset colorectal cancer in a young patient with heterozygous MUTYH mutation, highlighting the clinical challenges, genetic implications, and potential considerations for personalized management and family screening strategies.

Case: A 34-year-old male patient with a significant family history of colorectal cancer presented with rectal bleeding in 2017. His father, two paternal uncles, and a cousin had been previously diagnosed with colorectal cancer, suggesting a potential hereditary predisposition. The patient had no known comorbidities or history of regular medication use. Colonoscopy performed due to lower gastrointestinal bleeding revealed two polyps in the descending colon and an ulcerovegetative mass in the ascending colon, which was partially obstructing the lumen. Biopsy of the mass confirmed adenocarcinoma. Pathological staging revealed a T2N0, grade 2 lesion, consistent with stage 1 colon cancer. Immunohistochemical analysis showed the loss of MLH1 and PMS2 expression. Further molecular testing identified wild-type KRAS, NRAS, and BRAF. Due to a suspicion of hereditary colorectal cancer, a next-generation sequencing (NGS) solid tumor panel was performed, focusing on genetic mutations associated with colorectal cancer. The analysis detected a heterozygous c.36+11C>T p.(=) variant in the MUTYH gene, implicating a potential role of MUTYH-associated polyposis (MAP) in the carcinogenesis. The patient did not receive adjuvant chemotherapy or radiotherapy. Close clinical and radiological follow-ups were conducted as part of the management plan. At his most recent evaluation in January 2025, there was no evidence of recurrence or metastasis.

Conclusion: This case highlights the importance of thorough genetic evaluation in young-onset colorectal cancer patients with a significant family history. The identification of a heterozygous MUTYH mutation underscores the potential contribution of carrier status to early-onset colorectal cancer and emphasizes the necessity of genetic counseling and family screening in such scenarios. The absence of recurrence or metastasis in the patient reinforces the importance of individualized treatment and vigilant surveillance strategies in hereditary cancer syndromes.

Keywords: Hereditary cancer syndromes, young-onset colorectal cancer, heterozygous mutyh mutation

[Abstract:0141]

Spectrum of Germline Cancer Susceptibility Gene Mutations in Turkish Cancer Patients: A Single Center Study

Mustafa Ozdogan[1], Onder Kirca[1], Mahmut Cerkez Ergoren[2], Ilker Nihat Okten[3], Bulent Karabulut[4], Gurbuz Gorumlu[4], Osman Butun[4], Hasan Senol Coskun[5], Sercan Aksoy[6], Yesim Eralp[7], Kerim Kaban[8], Sualp Tansan[9], Nese Gulum[10], Angeliki Meintani[11], Dimitra Bouzarelou[11], Kevisa Potska[11], Anastasia Katseli[11], Christina Ntogka[11], Georgios Tsaousis[11], Irene Papadopoulou[11], George Nasioulas[11]

[1]Clinic of Medical Oncology, Memorial Antalya Hospital, Antalya, Türkiye
[2] Department of Medical Genetics Diagnosis Laboratory, Near East University, Near East University Hospital, Nicosia, North Cyprus
[3] Clinic of Medical Oncology, İstanbul Oncology Hospital, İstanbul, Türkiye
[4] Clinic of Medical Oncology, Acıbadem İzmir Kent Hospital, İzmir, Türkiye
[5] Clinic of Medical Oncology, Akdeniz Sağlık Vakfi Yaşam Hospital, Adana, Türkiye
[6] Clinic of Medical Oncology, Hacettepe University Hospital, Ankara, Türkiye
[7] Clinic of Medical Oncology, Acıbadem Maslak Hospital, İstanbul, Türkiye
[8] Clinic of Medical Oncology, American Hospital, İstanbul, Türkiye
[9]Private Tansan Polyclinic, İstanbul, Türkiye
[10]Genekor Biyoteknoloji, İstanbul, Türkiye
[11]Genekor Medical S.A. (Société Anonyme), Athens, Greece

Objective: The application of multigene panel testing in the genetic investigation of hereditary cancer in the years of personalized medicine is crucial for clinical surveillance, therapeutic approach, and risk-reducing management. The aim of the study was to reveal the genetic predisposition in a Turkish cohort of individuals referred for hereditary cancer.

Materials-Methods: A total of 1,105 individuals were referred for multigene genetic testing using NGS technology, during the period 2020-2024 in the laboratory. Among the examined individuals, 48.14% were diagnosed with breast cancer, 5.4% with ovarian cancer, 3.50% with colorectal cancer, 2.80% with prostate cancer and 4.60% with pancreatic cancer. 11.2% were healthy with a significant family history of cancer, while ~6.5% had a different type of cancer.

Results: 19.8% of the examined individuals carried a pathogenic variant. Specifically, 49.8% of the patients had a pathogenic variant in a clinically significant gene (BRCA1, BRCA2, BRIP1, PALB2, RAD51C, PMS2, CDKN2A, MLH1, MSH2, TP53, APC and RAD51D), of whom 16.9% were referred with no family history. When age cut-off is applied, 35.5% of individuals over 50 years old were harboring mutations in the aforementioned. Among the different types of pathogenic variants detected, a significant percentage (4.7%) represented copy number variation (CNV). Additionally, in 49.8% of the individuals tested, a variant of uncertain significance (VUS) was detected.

Conclusion: Comprehensive multigene genetic testing is necessary for appropriate clinical management of pathogenic variants' carriers, regardless age of diagnosis and family history of malignancies. Additionally, the information obtained is important for determining the risk of malignancy development in family members of the examined individuals.

Keywords: Germline cancer, multigene panel testing, Turkish cohort

Figure 1. Cancer type distribution in 1,105 individuals tested with hereditary cancer panel of 52 genes.

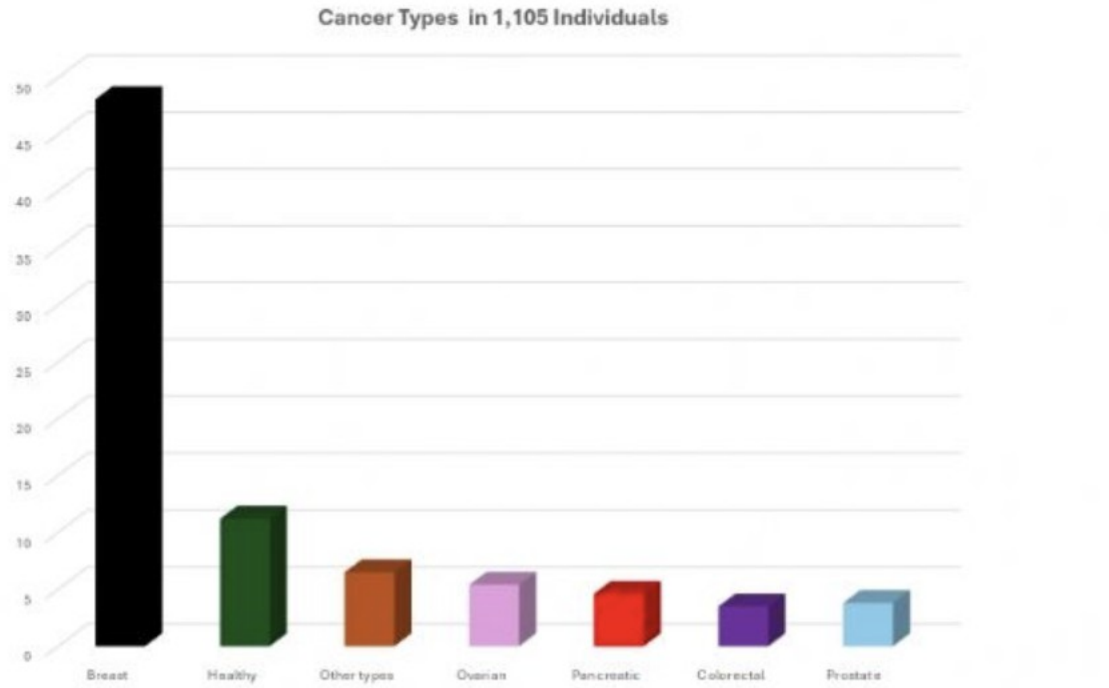
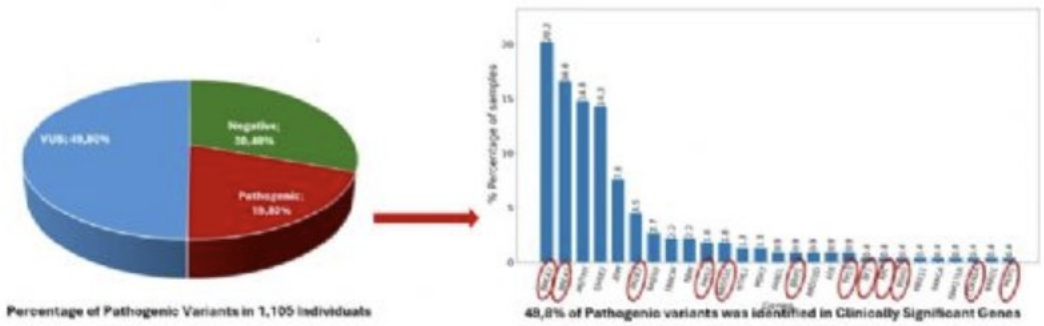


Figure 2. Mutational Distribution among positive (pathogenic) findings in 1,105 individuals



[Abstract:0170]

Transient Abnormal Myelopoiesis Associated with a Somatic Novel GATA1 Mutation in a Down Syndrome Case

Günay Garibova[1], Nurana Mammadova[1], Alper Özcan[2], Munis Dündar[1]

[1]Department of Medical Genetics, Erciyes University, Kayseri, Türkiye
[2]Department of Pediatric Hematology and Oncology, Faculty of Medicine, Erciyes University, Kayseri, Türkiye

Abstract

Down syndrome (trisomy 21) is a genetic disorder caused by the presence of all or a portion of a third chromosome 21. Patients typically present with short stature, characteristic facial features, protruding tongue, conductive hearing loss, congenital heart defects, duodenal stenosis/atresia, imperforate anus, Hirschsprung disease, joint laxity, short, broad hands, mild to moderate intellectual disability, Alzheimer disease, hypothyroidism, leukemia (both ALL and AML) and growth retardation. Here, we report a newborn with dysmorphic features, respiratory distress, congenital pneumonia, chorioretinal atrophy, hypothyroidism, pericardial effusion, a small atrial septal defect (ASD), jaundice, widespread erythema and skin rashes, hepatomegaly, bilateral hydrocele, micropenis, leukocytosis, thrombocytopenia, and a peripheral smear showing a predominance of blastic white cells, along with transient abnormal myelopoiesis and acute myeloid leukemia (AML). Dysmorphic facial features included upslanting palpebral fissures, epicanthal folds, small ears, a flat nasal bridge, and a broad nasal bridge. Whole exome sequencing detected a nonsense variant in exon 2 of the GATA1 gene (NM_002049: c.168_185dup). We classified the variant as likely pathogenic according to the ACMG criteria. This study contributes to the role of next-generation sequencing in the detection of somatic mutations. However, it should be noted that somatic variants may not be blood-derived, and therefore, it is recommended to study non-hematopoietic samples such as buccal mucosa. This mutation was not reported previously in the literature. The mutation has been identified as novel.

Keywords: AML M5, Down syndrome, GATA1, Transient abnormal myelopoiesis

[Abstract:0181]

A Case Report of Low-Grade Serous Ovarian Carcinoma with Somatic BRCA Mutations and Discordant Germline Testing

Ender Kalacı

Bitlis Tatvan State Hospital, Bitlis, Türkiye

Objective: Low-grade serous ovarian carcinoma (LGSOC) is an uncommon subtype of epithelial ovarian cancer characterized by indolent behavior and resistance to conventional chemotherapy. BRCA mutations are rarely associated with LGSOC (1). This report aims to present a unique case of LGSOC with somatic BRCA1 and BRCA2 mutations, contrasting with the negative germline BRCA findings and highlighting its clinical and therapeutic implications.

Case: A 53-year-old woman presented with abdominal pain. She had no known family history of ovarian or breast cancer. Initial imaging in 2020 revealed a 92x93 mm solid pelvic mass, but the patient did not seek further medical attention. A pelvic MRI in February 2024 identified a 14x10.5 cm lobulated, heterogeneously enhancing mass. Total abdominal hysterectomy and bilateral salpingo-oophorectomy revealed bilateral low-grade serous carcinoma of the ovaries. Staging with FDG-PET in March 2024 revealed no evidence of distant metastasis. Adjuvant chemotherapy with six cycles of carboplatin and paclitaxel was initiated. Next-generation sequencing in the tumor tissue revealed three pathogenic frameshift mutations: BRCA1 c.1961delA (p.K654fs47, allelic fraction 4.4%), BRCA2 c.1813delA (p.I605fs9, allelic fraction 2.56%), and BRCA2 c.9097delA (p.T3033fs*29, allelic fraction 2.73%). Variant interpretation followed ACMG/AMP guidelines, with all mutations classified as Tier IA. Germline BRCA1/2 testing via liquid biopsy and MLPA analysis using the SALSA MLPA Probemix P002-D1 BRCA1 kit confirmed the absence of deletions, duplications, or pathogenic variants, supporting the somatic nature of the mutations. Immunohistochemistry demonstrated estrogen receptor positivity, leading to the initiation of letrozole therapy.

Conclusion: This case highlights the discordance between somatic and germline BRCA findings in LGSOC. Somatic BRCA mutations may expand therapeutic options, but data on the efficacy of PARP inhibitors in LGSOC remain limited and investigational (2). Further studies are required to evaluate the therapeutic potential of PARP inhibitors and other targeted therapies in LGSOC with somatic BRCA alterations.

Keywords: Low-grade serous ovarian carcinoma, Somatic BRCA mutations, BRCA testing discordance

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[Abstract:0187]

Identification of Pathogenic and Novel Variants in BRCA1 and BRCA2 Genes Using Next-Generation Sequencing in Hereditary Cancer Patients

Freshta Jurat, Muhammet Güllük, Sahra Acır, Seda Salman Yılmaz, Sinem Fırtına, Esra Arslan Ateş, Mustafa Özen

Department of Medical Genetics, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye

Objective: BRCA1 and BRCA2 mutations are significant contributors to the risk of various cancers, particularly breast and ovarian cancers. Accurate identification of these mutations is essential for risk assessment, management, and treatment strategies. This study investigates BRCA1 and BRCA2 mutations in a cohort of 30 cancer patients using next-generation sequencing (NGS) to identify pathogenic variants and their association with different cancer types.
Materials-Methods: Genomic DNA from peripheral blood samples of 30 hereditary cancer patients was analyzed for BRCA1 and BRCA2 mutations via next-generation sequencing. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines.
Results: The study cohort included 22 breast cancer, 5 ovarian cancer, 2 endometrial cancer, and 1 prostate cancer case. A pathogenic variant in either BRCA1 or BRCA2 was detected in 5 individuals, one of which was novel. Additionally, two distinct variants of uncertain significance (VUS) were identified in two cases. Three frameshift variants in BRCA2 (c.1773_1776del, c.3545_3546del, c.4772_4773del) were detected in two ovarian and one breast cancer case. Two distinct truncating variants were detected in the BRCA1 gene (c.2395A>T and c.844_850dup) in a breast cancer and an ovarian cancer patient, respectively.
Conclusion: This study highlights the role of BRCA1 and BRCA2 mutations in hereditary cancer syndromes, particularly in breast and ovarian cancers. Among the cohort of 30 patients, 5 individuals harbored pathogenic variants, including a novel mutation, demonstrating the utility of next-generation sequencing in identifying rare and potentially clinically relevant genetic variations. The detection of three frameshift variants in BRCA2 and two distinct truncating variants in BRCA1 further underscores the genetic heterogeneity of these mutations and their implications for different cancer types. The identification of two VUSs emphasizes the need for continued research and functional studies to determine their clinical relevance. These findings reinforce the importance of comprehensive genetic testing and interpretation to guide personalized cancer risk management and treatment strategies.
Keywords: BRCA1, BRCA2, genetic testing, hereditary cancer, next-generation sequencing

[Abstract:0221]

Development of a targeted mass spectrometry-based workflow for endometrial cancer biomarker verification

Öykü Su Yıldırım[1], Berat Doğan[2], Esin Şahin[1], Senem Arda Düz[3], Yıldırım Karslıoğlu[4], Murat Öz[5], Abdullah Karaer[3], Süreyya Özcan Kabasakal[1]

[1]Department of Chemistry, Middle East Technical University (METU), Ankara, Türkiye
[2]Department of Biomedical Engineering, Inonu University, Malatya, Türkiye
[3]Department of Obstetrics and Gynecology, Faculty of Medicine, İnonu University, Malatya, Türkiye
[4] Clinic Pathology, Memorial Ankara Hospital, Ankara, Türkiye
[5] Clinic of Obstetrics and Gynecology Gynecologic Oncology Surgery, Memorial Ankara Hospital, Ankara, Türkiye

Abstract

Endometrial cancer (EC) is the most common gynecologic disease in developed countries, with increasing incidence and mortality among women. Proteomics offers a promising approach for the discovery of novel biomarkers that can aid in early detection of disease. Mass spectrometry (MS)-based proteomics provides robust analytical capabilities and in-depth understanding of protein changes. Among MS techniques, multiple reaction monitoring mass spectrometry (MRM-MS) has emerged as a powerful tool for biomarker verification. It effectively meets the need for a high-throughput, selective and reliable method to verify candidate biomarkers identified in discovery studies. The aim of this study was to develop MRM-MS method to validate nine candidate protein biomarkers (Q01995, P14618, P40121, P09211, P28838, Q00688, P62937, P04179) that were previously identified as candidate biomarkers for EC. Nine unique peptides (LVNSLYPDGSKPVK, IYVDDGLISLQVK, QAALQVAEGFISR, MLLADQGQSWK, AAGIDEQENWHEGK, LEIEPEWAYGK, FEDENFILK, DSSTWLTAFVLK, and HHAAYVNNLNVTEEK) were determined to represent the nine candidate proteins. The development of an MRM method includes selecting transitions, optimizing instrument and chromatographic conditions. Isotope-labeled standard peptides ([13C6,15N2]-lysine or arginine) were used to develop the MRM-MS method for quantifying nine biomarkers in the representative tissue samples. Representative tissue samples were collected in Memorial Hospital (Ankara, Türkiye). Representative samples were subjected to protein extraction in Tris-HCl buffer (pH 7.6) using a homogenizer and protein digestion steps: denaturation in sodium deoxycholate, alkylation with dithiothreitol, reduction with iodoacetamide, and enzymatic digestion using Trypsin/Lys-C. The MRM-MS method has been successfully developed to ensure reliable results. The methods effectively monitor nine target proteins. The analytical merits including linearity, limit of detection, and matrix effect in tissue samples were extensively studied. The method performance was also tested using Quality control (QC) samples to assess variations arising from sample processing and instrumental analysis. The results demonstrated consistent performance with low variability and high reproducibility. Discovering and verifying biomarkers is essential for enhancing cancer diagnosis and prognosis. This is particularly important for hereditary cancers, as early detection can significantly improve disease outcomes. Our findings show the potential of MRM-MS to validate diagnostic biomarkers for EC. The method has been applied to a clinical cohort and data analysis is in progress.

Keywords: Biomarker, endometrial cancer, mass spectrometry, proteomics

[Abstract:0222]

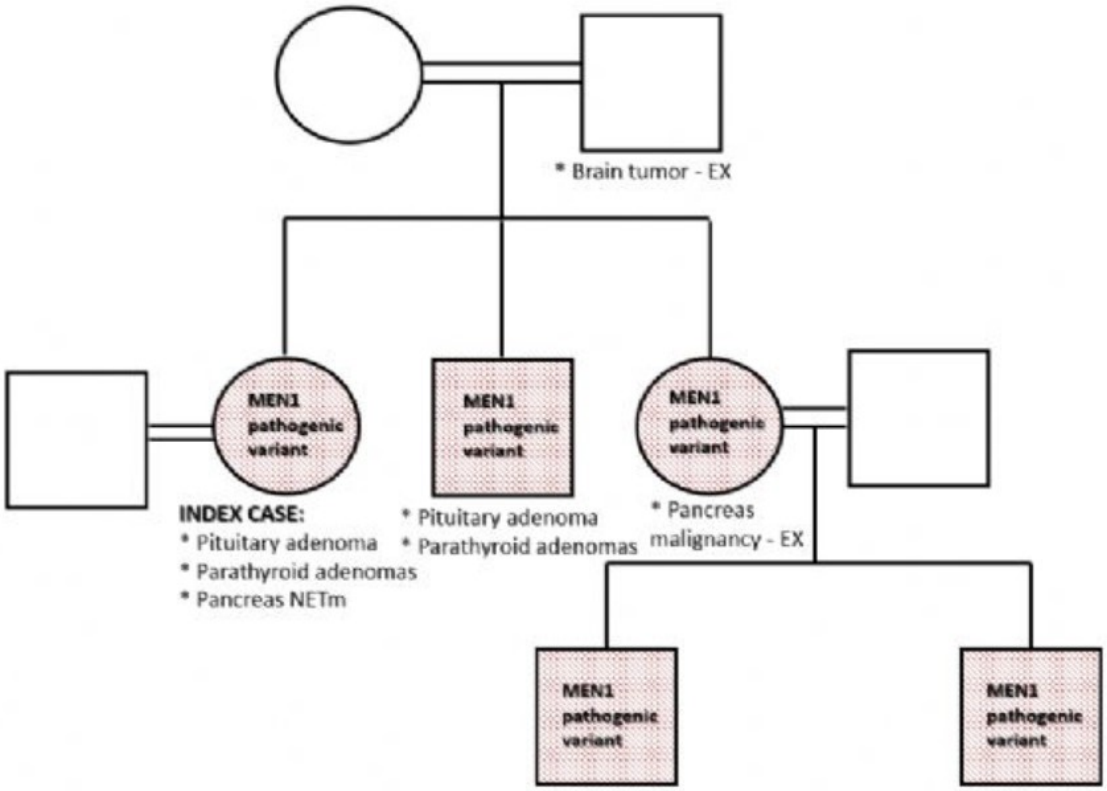
A Case Report of MEN 1 Syndrome with Confirmed Mutation and Complete Clinical Features in Multiple Affected Family Members

Eda Eylemer Mocan, Nadire Küçüköztaş

İzzet Baysal Training and Resource Hospital, Bolu, Türkiye

Objective: Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant inherited disorder, typically presenting with parathyroid, pituitary, and gastro-pancreatic neuroendocrine tumors (NETs), caused by germline heterozygous mutations in the MEN1 gene on chromosome 11q13.
Case: A 40-year-old female patient underwent surgery for prolactinoma in 2006. During routine follow-up, hypercalcemia and hyperparathyroidism were detected, and further investigations revealed a parathyroid adenoma. As a result, a right inferior parathyroidectomy was performed in 2007. While under observation without treatment for 13 years, the patient was referred to a tertiary care hospital in 2020 after the detection of hypercalcemia and hyperparathyroidism. Investigations revealed four parathyroid adenomas, which were subsequently excised. Upon suspected MEN 1, the patient underwent MR imaging of the pancreas. A mass lesion measuring 23x19 mm was identified in the body-tail region of the pancreas. Following this, a Ga-68 peptide (DOTA-TATE) PET scan was performed, which revealed a hypodense lesion with approximately 2 cm in diameter and a SUV max of 24.74, showing intense uptake of increased activity in the body-tail junction of the pancreas. The chromogranin level was found to be 65.5 ng/ml. The patient underwent distal pancreatectomy. The pathology report confirmed a grade 2, well-differentiated neuroendocrine tumor. The tumor was positive for chromogranin and synaptophysin, and the Ki-67 proliferation index was 5%. During the evaluation of the pancreas, genetic testing for MEN 1 was conducted, revealing a heterozygous c.1594C>T (p.Arg532*) nonsense mutation in exon 10 of the MEN1 gene. This was considered a pathogenic variant, leading to a diagnosis of MEN 1 syndrome. Family members who received genetic counseling also carry the same pathogenic variant.mAfter the pancreatic neuroendocrine tumor surgery, the patient received somatostatin therapy for one year based on a multidisciplinary decision involving medical oncology and endocrinology specialists. The patient's family history is detailed in the pedigree (Figure 1).
Conclusion: MEN 1 is a very rare disease. The diagnosis in our patient was made 13 years after the identification of a pituitary adenoma and parathyroid adenoma. Early diagnosis allows for the prediction and early intervention of the developing neoplasms.
Keywords: Neoplasia, neuroendocrine, parathyroid, pancreatic, pituitary

Pedigree chart illustrating the inheritance pattern of MEN1 and the clinical profiles of affected family members.



[Abstract:0226]

Case Presentation: A Case of Pancreatic Gastrointestinal Stromal Tumor Associated with Medullary and Papillary Thyroid Carcinoma

Mehmet Acun, Arif Hakan Önder

Clinic of Medical Oncology, Antalya Education and Resource Hospital, Antalya, Türkiye

Introduction: Gastrointestinal stromal tumors (GISTs), the most common mesenchymal tumors of the gastrointestinal tract, are characterized by a 5% hereditary etiology. Known hereditary GIST syndromes are caused by germline mutations in the c-KIT, PDGFR-alpha, neurofibromin 1, and succinate dehydrogenase subunits. Results from several single-center case series have shown that approximately 1 in 9 patients with sporadic GISTs develop synchronous and metachronous secondary malignancies. We present a case of a patient who, approximately two years after being diagnosed with a pancreatic GIST, developed concurrent medullary and papillary thyroid carcinoma.
Case: A 70-year-old female patient presented with abdominal pain in 2022, which prompted further investigation. Imaging revealed a 46x39 mm cystic mass in the head of the pancreas. The patient underwent a Whipple procedure, during which a 6 cm tumor was identified. The mitotic index was high, with 10 mitoses per 5 mm^2. Given these high-risk features, c-kit mutation analysis was performed, which confirmed a positive result. As a result, adjuvant imatinib therapy was initiated. Two years after the start of imatinib therapy, the patient developed a multinodular goiter, which led to the decision for total thyroidectomy. During surgery, multifocal papillary thyroid carcinoma and unifocal medullary microcarcinoma were identified. Post-thyroidectomy, the patient received radioactive iodine therapy and has since been followed up in remission.
Conclusion: This case presents a rare coexistence of pancreatic GIST with papillary and medullary thyroid cancers. GISTs are primarily associated with c-kit and PDGFRA mutations, while BRAF and RET mutations dominate in thyroid cancers. The genetic profiles of GISTs typically differ from those of papillary and medullary thyroid cancers. However, some studies have reported the presence of RET mutations in both cancer types, although this association is rare. The BRAFmutation is commonly found in papillary thyroid cancer and rarely in GISTs. Treatment approaches targeting genetic alterations, such as imatinib for GISTs and BRAF inhibitors for papillary thyroid cancer, share certain similarities In conclusion, while the genetic relationship between GISTs and thyroid cancers remains unclear, it is emphasized that such rare cases should be managed with a multidisciplinary approach.
Keywords: Gastrointestinal stromal tumor, hereditary syndromes, tyroid carcinoma

[Abstract:0227]

Atypical Clinical Course in Nijmegen Breakage Syndrome: A Case Presented with Cancer

Abdullah İsa Bulat, Hülya Tarım, Mahmut Selman Yıldırım

Department Of Medical Genetics, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye

Introduction: Nijmegen Breakage Syndrome (NBS) is a chromosomal instability disorder inherited in an autosomal recessive manner, characterized by microcephaly, immunodeficiency, intellectual disability, dysmorphic facial features, and a predisposition to various cancers. The gene responsible for NBS, NBN (NBS1), is located on chromosome 8q21, and its product, the Nibrin protein, is thought to play a critical role in the repair of DNA double-strand breaks and the activation of DNA damage response checkpoints. Here, we present a case of NBS diagnosed in a patient with isolated ovarian cancer without the typical findings associated with the syndrome.

Case: A 45-year-old female patient with serous ovarian cancer was referred to us for hereditary cancer evaluation. Physical examination revealed a prominent nose and a high-arched palate. Her family history showed that her sister had undergone a hysterectomy at the age of 38 due to uterine myoma, and her parents were not consanguineous. Pathogenic variants were not detected in BRCA1 and BRCA2 genes by MLPA and sequencing analysis. However, sequencing analysis of a hereditary cancer panel encompassing 226 genes identified a homozygous ENST00000265433.3:c.163_171+3del variant in the NBN gene. This variant was classified as "Pathogenic" according to the American College of Medical Genetics (ACMG) criteria (PVS1, PM2, PM3, PP5). Karyotype analysis was reported as 46,XX. The patient was referred to relevant specialties to evaluate additional findings related to NBS. Advanced investigations and consultations revealed no additional findings associated with NBS. Segregation analysis was planned for the family.

Conclusion: NBS is a cancer predisposition syndrome in which both lymphoid and solid malignancies can be observed. The alternative splicing mechanism in NBN transcription may contribute to a milder phenotype. This case highlights the atypical presentation of NBS and emphasizes that it can manifest in isolation with cancer. These findings shed light on the genetic and clinical diversity of NBS. Moreover, while the NBN gene is responsible for NBS, it can also predispose individuals to cancer.

Therefore, it is crucial to consider this gene in hereditary cancer evaluations and include it in hereditary cancer panels.

Keywords: Hereditary cancer, Nijmegen breakage syndrome, NBN gene

[Abstract:0230]

Case Report of DICER1-Associated Bilateral Cystic Nephroma

Hilal Gölcür, Elif Saraç, Sinem Kocagil

Department of Medical Genetics, Eskisehir Osmangazi University, Eskişehir,Türkiye

Objective: This study presents a 4-year-old male patient diagnosed with bilateral cystic nephroma, in whom a pathogenic germline DICER1 variant was identified.

Case: The patient was referred to our clinic after the parents noticed an abdominal mass when the child was 1 year old. An abdominal ultrasound revealed a multilocular cystic structure in the left kidney, prompting further evaluation with a differential diagnosis of nephroblastoma and nephroma. After performing a left radical nephrectomy, the pathology result confirmed cystic nephroma. Clinical exome sequencing (CES) analysis revealed the DICER1 (NM_030621.4): c.1525C>T (p.Arg509Ter) (heterozygous) variant. The variant was classified as pathogenic according to ACMG criteria. Pedigree analysis revealed a history of nephrolithiasis in the mother and maternal grandmother, as well as a family history of kidney tumors in the maternal grandmother's brother's son. Parent segregation analysis showed that the variant was inherited from the healthy father.

Conclusion: DICER1 syndrome is a pleiotropic tumor predisposition disorder caused by pathogenic germline variants in the DICER1 gene, which encodes an endoribonuclease crucial for the processing of microRNAs. DICER1 tumor predisposition is characterized by an increased risk of pleuropulmonary blastoma (PPB), pulmonary cysts, thyroid neoplasms, ovarian tumors, and cystic nephroma. Less common tumors associated with this syndrome include ciliary body medulloepithelioma, nasal chondromesenchymal hamartoma, embryonal rhabdomyosarcoma, pituitary blastoma, pineoblastoma, central nervous system sarcoma, other central nervous system tumors, and presacral malignant teratoid tumors. Most tumors are observed in individuals under the age of 40. DICER1 syndrome is inherited in an autosomal dominant manner with low penetrance. In individuals with DICER1 syndrome who carry pathogenic variants in the germline DICER1 gene, approximately 80% of variants are inherited from one parent, while about 20% are de novo. Cystic nephroma (CN) is a rare benign kidney tumor characterized by cysts of various sizes within the kidney, accounting for less than 1% of all kidney tumors. It usually presents with an asymptomatic, enlarging abdominal or flank mass. This study highlights the importance of low penetrance DICER1 gene analysis in patients diagnosed with bilateral cystic nephroma and contributes a new patient to the literature.

Keywords: Bilateral cystic nephroma, DICER1 syndrome, Hereditary cancer syndrome