Spectrum and Prevalence of *BRCA1/BRCA2* Variants in Aegean Region Hereditary Breast and Ovarian Cancer Cases

Ege Bölgesi'nde Kalıtsal Meme ve Yumurtalık Kanseri Olgularında *BRCA1/BRCA2* Varyantlarının Spektrumu ve Yaygınlığı

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Öz

Batı toplumlarında meme kanseri vakalarının %5-10'u kalıtsaldır ve başlıca *BRCA1* ve *BRCA2* genlerindeki patojenik germ hattı varyantlarından kaynaklanır. Bu varyantları taşıyan kadınların meme kanseri için yaşam boyu riski %40-57 ve over kanseri için %18-40'tır. Bu çalışma, Türkiye'nin Ege Bölgesi'ndeki kalıtsal meme ve over kanseri vakaları arasında *BRCA1* ve *BRCA2* varyantlarının sıklığını ve dağılımını araştırmayı amaçlamaktadır. Bu retrospektif çalışmada, Aydın Adnan Menderes Üniversitesi'nde 2013-2019 yılları arasında Tıbbi Genetik Polikliniği'ne başvuran ve Sanger dizilemesi ile *BRCA1*/2 genleri analiz edilen 157 kalıtsal meme ve over kanseri olgusunun dosyaları taranmıştır. Sonuçlar tümör özellikleri ve aile öyküsü de dahil olmak üzere demografik ve klinik veriler toplanarak analiz edilmiştir. *BRCA1* için 17 vakada (%11) ve *BRCA2* için 6 vakada (%4) patojenik veya muhtemel patojenik varyant saptanmıştır. En yaygın *BRCA1* varyantları c.66dupA ve c.5266dupC iken, *BRCA2* varyantları kümeleşme yapmadan daha fazla heterojenlik göstermiştir. Meme kanseri (%72,6) en sık tanı olarak belirlenmiş ve baskın histolojik alt tip olarak invaziv duktal karsinom görülmüştür. Çalışma, *BRCA1*/2 varyantlarını belirlemek için popülasyona özgü genetik test stratejilerinin önemini vurgulamaktadır. Bulgular, Ege Bölgesi popülasyonunda benzersiz bir varyant spektrumunu ortaya koyarak, küresel olarak yaygın varyantların çalışma ile uyumlu olmadığını göstermektedir. Ayrıca kalıtsal meme ve yumurtalık kanseri hastalarında risk değerlendirmesini ve hasta yönetimini iyileştirmek için kapsamlı genetik danışmanlığa olan ihtiyacı vurgulamaktadır.

Anahtar Kelimeler: *BRCA1*, *BRCA2*, Ailesel Meme ve Yumurtalık Kanseri, Sanger Sekanslama

Abstract

In Western populations, 5–10% of breast cancer cases are hereditary, primarily due to pathogenic germline variants in *BRCA1* and *BRCA2* genes. Women carrying these variants have a lifetime risk of 40–57% for BC and 18–40% for ovarian cancer. This study aims to investigate the prevalence and distribution of *BRCA1* and *BRCA2* variants among hereditary breast and ovarian cancer cases in the Aegean region of Turkey. In this retrospective study, the medical records of 157 hereditary breast and ovarian cancer cases who presented to the Medical Genetics Clinic at Aydın Adnan Menderes University between 2013 and 2019 were reviewed. *BRCA1* and *BRCA2* gene analyses for these cases were performed using Sanger sequencing. The results were analyzed by collecting demographic and clinical data, including tumor characteristics and family history. Pathogenic or likely pathogenic variants were identified in 17 cases (11%) for *BRCA1* and 6 cases (4%) for *BRCA2*. The most common *BRCA1* variants were c.66dupA and c.5266dupC, while *BRCA2* variants exhibited greater heterogeneity, with no recurrent variants. Breast cancer (72.6%) was the most frequent diagnoses, with invasive ductal carcinoma as the predominant histological subtype. The study underscores the importance of population-specific genetic testing strategies to identify *BRCA1/2* variants. The findings reveal a unique variant spectrum in the Aegean Region population, highlighting the absence of globally common variants and the need for comprehensive genetic counseling to improve risk assessment and management for hereditary breast and ovarian cancer patients.

Keywords: *BRCA1*, *BRCA2*, Hereditary Breast and Ovarian Cancer, HBOC, Sanger Sequencing

Introduction

Cancer remains one of the most significant global health challenges, with an estimated 20 million new cases and 9.74 million cancer-related deaths reported worldwide in 2022, according to GLOBOCAN statistics. It is projected that one in five individuals will face a cancer diagnosis by the age of 75, with approximately 10% of these cases resulting in mortality. Among women, breast cancer (BC) is the most frequently diagnosed malignancy, accounting for 24.2% of all cancer cases and 15% of cancer-related deaths globally (1).

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In Turkey, GLOBOCAN 2022 data highlights 240,013 newly diagnosed cancer cases, with 129,672 deaths attributed to cancer. In men, lung cancer remains the most common (24.9%), followed by prostate (13%) and colorectal cancers (8.8%). Among women, BC leads with a 23.5% incidence rate, followed by thyroid (11.6%) and colorectal cancers (9.3%) (1).

Hereditary breast and ovarian cancer (HBOC) syndrome is a hereditary condition linked to a heightened risk of developing malignancies, such as breast, ovarian, fallopian tube, and peritoneal cancers, affecting individuals of all genders. This syndrome predominantly results from germline pathogenic variants in *BRCA1* and *BRCA2*, which are crucial for repairing double-stranded DNA damage. variants in these genes are also linked to an elevated risk of prostate and pancreatic cancers. The prevalence of HBOC is approximately 1 in 400 individuals (2).

In Western countries, 5–10% of BC cases are hereditary and are strongly linked to *BRCA1*/2

variants. Women with *BRCA1*/2 variants face a 40–57% lifetime risk for BC and an 18–40% risk for ovarian cancer (OC) (3). Additionally, individuals with these variants show higher rates of contralateral BC compared to non-carriers, with risks reaching up to 44.1% within 25 years of the initial diagnosis (4).

Variants in *BRCA1*/2 genes frequently result in truncated, non-functional proteins, leading to increased cancer aggressiveness. These variants are primarily small deletions, small insertions, nonsense variants, and splice-site alterations. Loss of heterozygosity (LOH) is also highly prevalent in *BRCA*-associated cancers, further contributing to tumorigenesis (5,6).

Given Anatolia's historical role as a crossroads for civilizations and the prevalence of consanguineous marriages in the region, unique *BRCA1*/2 variants specific to the Turkish population are hypothesized. This study aims to determine the prevalence and distribution of *BRCA1*/*BRCA2* variants among Aegean Region HBOC cases, emphasizing population-specific variations and potential founder variants.

Material and Method

Study Population and Inclusion Criteria

This study retrospectively analysed cases diagnosed with HBOC at the Medical Genetics Polyclinic, Aydın Adnan Menderes University Faculty of Medicine Hospital, between January 1, 2013, and June 30, 2019. Patients were selected based on *BRCA1*/*BRCA2* genetic testing criteria outlined in the National Comprehensive Cancer Network (NCCN) guidelines, version 3.2019. The inclusion criteria are summarized in Table 1.

Table 1. Study inclusion criteria

Being diagnosed with BC + having at least one of the following criteria	**Diagnosed with BC at age ≤ 45**
	In a case diagnosed with BC at the age of 46-50:
	Having more than one primary BC
	Having at least one relative diagnosed with BC at any age
	Having at least one relative diagnosed with pancreatic cancer at any age
	Having at least one relative diagnosed with prostate cancer at any age (Gleason≥7)
	Unknown or limited family history
	For those diagnosed at age ≤60:
	Having triple negative BC
	In those diagnosed at any age:
	Having one or more relatives diagnosed with BC at age ≤50
	Having one or more relatives with OC
	Having one or more male relatives diagnosed with BC
	Having metastatic prostate cancer in one or more relatives
	Having one or more relatives with pancreatic cancer
	Diagnosis of BC at any age in the patient and/or two or more relatives
Being diagnosed with OC	
Being male and diagnosed with BC	
A case that does not meet the above criteria has ≥1 first or second degree relative who meets one of the criteria (Family history)	

BC: Breast Cancer, OC: Ovarian Cancer

For cases with familial connections, only the proband's genetic analysis was included to ensure accuracy in statistical evaluation. Cases involving non-germline variant testing or tissue-only variant analysis were excluded. Additionally, individuals of foreign nationality or those who acquired Turkish citizenship were not included, as the study aimed to focus on population-specific genetic data.

Genetic Testing and Data Collection

Genetic testing was performed on 157 patients who met the inclusion criteria. DNA was extracted from peripheral blood, and Sanger sequencing was conducted using the *BRCA1*/*BRCA2* gene analysis kit on the Applied Biosystems 3500 platform. The SeqScape software was employed to analyse 23 exons and exon-intron junctions of the *BRCA1* gene and 27 exons and exon-intron junctions of the *BRCA2* gene.

Patient data were retrospectively collected and included demographic details, age at diagnosis, cancer type, tumor hormone receptor characteristics [oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)], pedigree information, and genetic test results. Statistical analyses were performed using SPSS version 18, with descriptive statistics presented as frequencies and percentages.

Study Design

This study employed a descriptive retrospective design, focusing on the variant spectrum and frequency of *BRCA1*/*BRCA2* genes among HBOC cases in the Aegean Region population. By examining the specific variants and their distribution, the study aimed to identify potential founder variants and assess the genetic variability unique to this cohort.

Table 2. Tumor histopathology results

		Frequency	Percentage
ER	Positive	64	50%
	Negative	22	17.2%
	NA	42	32.8%
	Total	128	100%
PR	Positive	62	48.4%
	Negative	24	18.8%
	NA	42	32.8%
	Total	128	100%
HER2	Positive	52	40.6%
	Negative	24	18.8%
	NA	52	40.6%
	Total	128	100%

(NA: Not Available, ER: Estrogen Receptor, PR: Progesterone Receptor, HER2: Human Epidermal Growth Factor Receptor 2)

Results

Patient Demographics

The study included 157 cases, comprising 154 females (98.1%) and 3 males (1.9%). Of these, 114 cases (72.6%) were diagnosed with BC, 10 cases (6.4%) with OC, 4 cases (2.5%) with both breast and OC, and 29 cases (18.5%) were included based on familial history. The mean age at diagnosis for female BC cases was 40.36 years, while the mean age for male BC cases was 47.66 years. For OC cases, the mean age at diagnosis was 45.2 years.

When the mean age at diagnosis was compared between *BRCA1/2* variant-positive and *BRCA*-negative patients, the mean age at diagnosis was 41.5 years in *BRCA*-positive patients and 41 years in *BRCA*-negative patients.

When the distribution of cancer types was analysed, no ovarian cancer was found in *BRCA2*-positive patients, whereas ovarian cancer was found in 6.6% of *BRCA*-negative patients. However, this difference did not reach statistical significance ($p>0.05$, chi-squared test).

Tumor Histopathology

Among the 114 BC cases, invasive ductal carcinoma (IDC) was the most common histological subtype, identified in 74 cases (64.9%). Other subtypes included phyllodes tumor (0.9%), invasive lobular carcinoma (0.9%), and ductal carcinoma in situ (2.6%). In 35 cases (30.7%), the tumor histology was not specified. Of the 10 OC cases with available histology data, 90% (9 cases) were serous carcinoma, while the tumor histology was unspecified in one case.

Hormone receptor statuses for ER, PR, and HER2 were identified for cases with available data (Table 2). Among the 128 tumors analyzed, 50% were ER-positive, 48.4% were PR-positive, and 40.6% were HER2-positive.

Variant Analysis

Pathogenic and likely pathogenic variations were identified in 17 cases (11%) for *BRCA1* and in 6 cases (4%) for *BRCA2*, following classification criteria from the American College of Medical Genetics and Genomics (ACMG). Among the detected variants, small duplications (35%) and splice-site variants (31%) were the most common types, followed by small deletions (17%), nonsense variants (9%), missense variants (4%), and small insertions (4%). Pathogenic/possible pathogenic variants in *BRCA1*/2 genes are shown in Table 3.

Table 3. Heterozygous pathogenic variants detected in *BRCA1* and *BRCA2*

		Frequency	Percentage
BRCA 1	c.66dupA (p.Glu23Argfs*18)	4	17.39%
	c.135-2 A>G	3	13.04%
	c.5266dupC (p.Gln1756Profs*74)	3	13.04%
	c.4358-3 A>G	2	8.69%
	c.181 T>G (p.Cys61Gly)	1	4.35%
	c.302-3 C>G	1	4.35%
	c.2611_2612delCC (p.Pro871Valfs*31)	1	4.35%
	c.2963 C>A (p.Ser988Ter)	1	4.35%
	c.4986+5 G>A	1	4.35%
BRCA 2	c.658_659delGT (p.Val220Ilefs*4)	1	4.35%
	c.3751dupA (p.Thr1251Asnfs*14)	1	4.35%
	c.6246delA (Glu2082Aspfs*4)	1	4.35%
	c.6468_6469delTC (p.Gln2157Ilefs*18)	1	4.35%
	c.8414_8415insT (p.Leu2805Phefs*7)	1	4.35%
	c.9318 G>A (p.Trp3106Ter)	1	4.35%
Total		23	100%

The most frequent variants in *BRCA1* were c.66dupA (17.39%), c.135-2A>G (13.04%), and c.5266dupC (13.04%). Notably, globally common variants such as *BRCA1* 5382insC and 185delAG were not identified in this cohort. In *BRCA2*, rare variants previously reported in the literature were identified, with all *BRCA2*-positive patients carrying distinct variants. No clustering of a specific variant was observed among *BRCA2* cases, highlighting the genetic heterogeneity of *BRCA2* variants in this population. All identified variants were classified as pathogenic or likely pathogenic based on ACMG guidelines, with in-silico analyses supporting their deleterious nature. Clinical and pathological features of cases with *BRCA* variants are given in Table 4.

Table 4. Clinical and pathological features of cases with *BRCA* variants

Patient	Age of diagnosis	Diagnosis	Tumor Type	*BRCA1* variant	*BRCA2* variant
P1	18	Breast Ca	NA	c.181 T>G (p.Cys61Gly)	ND
P2	29	Breast Ca	NA	ND	c.9318G>A (p.Trp3106Ter)
P3	44	Breast Ca	NA	ND	c.6246delA (p.Glu2082DAsps*4)
P4	46	Ovarian Ca	Serous carcinoma	c.66dupA (p.Glu23Argfs*18)	ND
P5	-	Family History	NA	c.135-2 A>G	ND
P6	42	Breast Ca	IDK	c.2963C>A (p.Ser988Ter)	ND
P7	48	Breast Ca	IDK	c.4986+5 G>A	ND
P8	39	Breast Ca	Medullary carcinoma	c.5266dupC (p.Gln1756Profs*74)	ND
P9	52	Ovarian + Breast Ca	NA	c.135-2 A>G	ND
P10	43	Ovarian Ca	Serous carcinoma	c.4358-3 A>G	ND
P11	55	Breast Ca	NA	c.2611_2612delCC (p.Pro871Valfs*31)	ND
P12	34	Breast Ca	IDK	c.302-3 C>G	ND
P13	39	Breast Ca	IDK	ND	c.8414_8415insT (p.Leu2805Phefs*7)
P14	41	Ovarian + Breast Ca	IDK	c.66dupA (p.Glu23Argfs*18)	ND
P15	48	Breast Ca	IDK	c.66dupA (p.Glu23Argfs*18)	ND
P16	36	Breast Ca	NA	c.5266dupC (p.Gln1756Profs*74)	ND
P17	27	Breast Ca	IDK	c.5266dupC (p.Gln1756Profs*74)	ND
P18	46	Breast Ca	NA	c.135-2 A>G	ND
P19	49	Ovarian Ca	Serous carcinoma	c.66dupA (p.Glu23Argfs*18)	ND
P20	38	Ovarian + Breast Ca	NA	ND	c.658_659delGT (p.Val220Ilefs*4)
P21	50	Breast Ca	IDK	c.4358-3 A>G	ND
P22	44	Breast Ca	NA	ND	c.6468_6469delTC (p.Gln2157İlefs*18)
P23	45	Breast Ca	NA	ND	c.3751dupA (p.Thr1251Asnfs*14)

(P: Patient, NA: Not Available, IDK: Intraductal Carcinoma, Ca: Cancer, ND: Not Detected, *BRCA1*: Breast Cancer 1 Gene, *BRCA2*: Breast Cancer 2 Gene)

A considerable portion of the cases with *BRCA1*/*BRCA2* variants in this study had unknown tumor type and histopathology results, including ER, PR, and HER2 status. While these missing data did not impact the primary objective of the study—investigating the gene variants and their population-specific frequencies—the incomplete information highlighted areas for self-reflection regarding the organization and completeness of the data collected.

Discussion

This study aimed to evaluate the frequency and distribution of *BRCA1* and *BRCA2* gene variants in individuals diagnosed with HBOC in Turkey, using Sanger sequencing. Our findings contribute to the growing body of knowledge about genetic variants in the Aegean Region population and offer insights into the specific mutational landscape in a region with unique historical and ethnic characteristics.

In our study, pathogenic *BRCA1* variants were identified in 11% of HBOC cases and pathogenic *BRCA2* variants were identified in 4% of HBOC cases. In *BRCA1*, c.66dupA, c.135-2A>G, and c.5266dupC were the most frequent variants, aligning with previous studies in similar populations (7,8). Globally common variants, such as *BRCA1* 5382insC and 185delAG, were notably absent in this cohort, suggesting population-specific differences in the *BRCA1* variant spectrum (9,10).

In *BRCA2*, rare variants previously reported in the literature were identified, with each *BRCA2*-positive patient carrying a distinct variant. Unlike *BRCA1*, where certain variants were recurrent, no clustering of a specific variant was observed among *BRCA2* cases. This finding underscores the genetic heterogeneity of *BRCA2* variants in the Aegean Region population. All identified *BRCA2* variants were classified as pathogenic or likely pathogenic based on ACMG guidelines, with in-silico analyses supporting their deleterious effects (11).

Although the mean age at diagnosis was not significantly different between *BRCA1/2* variant-positive and *BRCA*-negative patients in our cohort (41.5 vs. 41 years, respectively), this finding contrasts with the majority of the literature, where *BRCA1/2* variant carriers are typically diagnosed with breast cancer at a younger age than non-carriers.(12,13) Several factors may explain this discrepancy. First, the relatively small number of *BRCA*-positive cases (n=23) in our study may have limited the power to detect a statistically significant age difference. Second, the retrospective design and inclusion of patients based on specific genetic testing criteria may have introduced a selection bias, potentially skewing the age distribution. Finally, population-specific genetic and environmental factors unique to the Aegean region may influence

the age of onset differently than in other populations studied. Further large-scale, multicentre studies are needed to clarify these findings and to better characterise the age-related penetrance of *BRCA* variants in this population.

Frequency of BRCA Variants in the Turkish Population

The aim of this study was to determine the frequency and distribution of *BRCA1* and *BRCA2* gene variants in HBOC cases in the Aegean region of Turkey. When compared with similar studies conducted in other regions of the country, our results highlight both similarities and differences that provide valuable insights into the regional mutational landscape.

In the Trakya region study by Demir et al. (2020), *BRCA1/BRCA2* genes were analysed in 493 high-risk individuals using both next-generation sequencing (NGS) and multiplex ligation-dependent probe amplification (MLPA).(14) The overall frequency of pathogenic/likely pathogenic variants was reported to be 17.8%, with the *BRCA1* 5266dupC variant being the most common (5.47%). While this variant is recognised as a founder variant in the Ashkenazi Jewish population, its high frequency in the Trakya region suggests that it may also be relatively common in the Turkish population. Although the same variant was identified in our cohort, it was observed at a lower frequency. This discrepancy could be due to regional genetic variation, ethnic diversity or historical population migration patterns.

In the large nationwide ovarian cancer study by Tuncer et al. (2024), 630 Turkish ovarian cancer patients underwent *BRCA1/BRCA2* and multigene panel testing using NGS and MLPA. A pathogenic/likely pathogenic variant frequency of 20.63% was observed, with recurrent *BRCA1* variants including 5266dupC, Cys61Gly and Trp1815*.(15) Some of these variants were also detected in our study. However, consistent with our findings, the *BRCA2* variant spectrum was remarkably heterogeneous, with no recurrent variants observed. This supports the idea that *BRCA2* variants may follow a more dispersed pattern and highlights the need for broader panel testing in genetic counselling protocols.

An important methodological difference between our study and these two others is the extent of genetic testing. While we used Sanger sequencing, both Demir et al. and Tuncer et al. used NGS in combination with MLPA, allowing them to detect large genomic rearrangements such as exon-level deletions and duplications. The inclusion of MLPA allowed the identification of structural variants that are not detectable by sequencing alone. The inclusion of MLPA or comprehensive NGS approaches in future regional studies would provide a more complete picture of the *BRCA* variant spectrum.

In addition, our results show both similarities and differences when compared with other Turkish studies focusing on *BRCA* variants. Tacar et al studied 287 breast cancer patients and identified pathogenic or likely pathogenic *BRCA1/BRCA2* variants in 17.4% of cases, which is comparable to our variant frequency of 15%.(16) In Tacar's study, co-occurrence of *BRCA1* and *BRCA2* variants in the same patient was observed, whereas in our study, each variant-positive patient carried a pathogenic variant in only one gene. Similar to our findings, c.5266dupC was one of the most frequently observed variants, whereas *BRCA2* variants showed a greater heterogeneity with no recurrent variant.

Furthermore, Işıklı et al. reported a *BRCA1/2* pathogenic variant frequency of 16% in breast cancer patients aged ≤40 years.(17) In their study, *BRCA1* variants were mostly associated with triple-negative breast cancer, whereas our cohort did not show a clear predominance of the triple-negative phenotype among *BRCA1* variant carriers. This discrepancy may be due to sample size limitations and lack of pathological data in our study.

Overall, these comparative analyses suggest that the *BRCA1/2* variant landscape in Turkey is highly heterogeneous, with certain recurrent variants - such as c.66dupA, c.5266dupC and c.135-2A>G - emerging as potentially significant at the national level. Determining whether these variants represent founder variants will require multicentre, large-scale studies and the establishment of national variant databases. Our study contributes important region-specific data from the Aegean population and highlights the need for tailored genetic testing strategies and counselling protocols that take into account local variant profiles.

Comparative Analysis with Other Populations

The variant profiles in our study contrast with those of other populations, such as the French Canadian and Belgian populations, where specific variants like *BRCA1* C4446T and *BRCA2* 8765delAG are more frequent (7,8). Similarly, in populations like the Finnish and Polish, variants such as *BRCA2* T8555G and 999del5, and *BRCA1* 5382insC and 4153delA, respectively, are more common (18,19). These regional differences highlight the influence of ethnicity and founder effects on the variant spectrum (20,21).

Interestingly, studies in Turkey, including those by Manguoglu et al. (2003) and Yazıcı et al. (2000), have previously reported a lower prevalence of *BRCA* variants compared to Western countries. This aligns with our findings, where *BRCA1* 5382insC and *BRCA2* 6174delT variants were absent, and other variants like c.66dupA and c.5266dupC were more prevalent. These differences could be due to

various factors, including genetic diversity, consanguinity, and geographical factors (20,21).

Variant Types and Associated Cancer Risks

The variant types identified in our study, such as small deletions, duplications, and splice-site variants, are consistent with the types of variants commonly observed in *BRCA1* and *BRCA2* genes, which result in truncated proteins and loss of DNA repair function (5,22). These variants are thought to contribute to the increased aggressiveness of breast and OCs in variant carriers, as seen in studies reporting higher rates of triple-negative BC in *BRCA1* carriers (22). Our study did not observe the expected higher frequency of triple-negative BC in *BRCA1* variant carriers, which could be due to the limited sample size or incomplete histopathological data in some cases.

Genetic Counseling in the Context of BRCA1/2 Testing

Integrating genetic counselling into the management of HBOC cases is essential to optimise patient outcomes. As recent studies have shown, early *BRCA1/2* testing can guide treatment decisions, influence surgical planning and enable risk-reduction strategies.(23) However, the success of genetic testing initiatives depends heavily on comprehensive pre- and post-test genetic counselling.

Pre-test counselling should inform patients about the potential medical, psychological and familial implications of testing. It is essential to discuss the likelihood of identifying pathogenic variants, variants of uncertain significance, or negative results, and the consequences of each. It is important that counselling sessions address the emotional impact of learning about one's genetic risk and its impact on family members.(24)

Post-test counselling plays a key role in interpreting the results in a clinically meaningful way and ensuring that patients understand their options for surveillance, prophylactic surgery, and systemic therapy. Particularly for *BRCA1/2* variant carriers, recommendations for increased surveillance, prophylactic surgery such as bilateral mastectomy or salpingo-oophorectomy, and consideration of targeted therapies such as PARP inhibitors need to be tailored based on patient-specific factors.(23,24)

Despite its recognised value, barriers to genetic counselling remain significant, particularly in developing countries. In Turkey, challenges such as limited awareness, fear of stigma, logistical constraints and financial barriers hinder widespread access to genetic counselling services.(24) Expanding access through the integration of mainstream genetic counselling models, clinician education and cost-effective testing strategies is critical to ensure equitable care.

Given the spectrum of *BRCA1/2* variants observed in different populations, including our Aegean study population, the role of personalised genetic counselling becomes even more important. Population-specific knowledge needs to be incorporated into risk assessment and management plans, highlighting the need for culturally sensitive and regionally adapted counselling services.

Limitations and Future Directions

One limitation of our study is the lack of large genomic rearrangement (LGR) analysis, which has been shown to account for a significant portion of *BRCA* variants in some populations (25). The absence of this analysis means that some variants may have been overlooked, particularly those involving larger deletions or duplications. The future incorporation of techniques like MLPA or NGS would allow for a more comprehensive understanding of the *BRCA* variant spectrum in this population (26).

Moreover, while our study focused on *BRCA1* and *BRCA2* variants, other genes associated with HBOC such as *ATM*, *PALB2*, and *TP53*, are also important for genetic counseling and management. Expanding the genetic panel to include these genes in future studies would provide a more complete picture of the genetic factors contributing to HBOC in Turkey (27).

Conclusion

The genetic heterogeneity in *BRCA2* was notable, with no clustering of specific variants among *BRCA2*-positive cases. These findings contribute to a better understanding of HBOC in this population and underscore the need for comprehensive genetic analysis in clinical practice.

One limitation of this study was the inability to perform multiplex ligation-dependent probe amplification (MLPA) to detect large deletions and duplications in *BRCA1* and *BRCA2* genes. Incorporating MLPA into future studies would provide a more complete picture of the variant spectrum, allowing for the identification of structural variants that may play a significant role in hereditary cancer predisposition. This addition would also help determine the prevalence of large genomic rearrangements specific to the Aegean Region population, addressing an important gap in this research.

Overall, our findings emphasize the importance of utilizing population-specific genetic testing strategies and comprehensive analysis methods to improve genetic counseling, risk assessment, and management for individuals with HBOC.

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Conflict of interest statement

The authors declare no conflicting interest in this study.

Ethics Committee Approval: This study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent for the use of genetic information for research purposes was obtained from patients who underwent genetic testing at Aydın Adnan Menderes University. Since this is a retrospective study ethical approval was obtained from the Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Evaluation Committee (Protocol No: 2019/136; Date: 21.11.2019).

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