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Spectrum of *BRCA1* and *BRCA2* Variants in Breast Cancer Cases: A Single-Center Experience

Zeynep ESENER [1], Seray SARAY [2], Yakup IRIAGAC [2], Dilan GENC AKDAG [1], Hilmi BOLAT [1]

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

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ABSTRACT

Objective: Hereditary breast cancers comprise approximately 5–10% of all breast cancer cases, with a significant portion linked to pathogenic alterations in the BRCA1 and BRCA2 genes. Detecting these variants is critical for risk assessment and clinical decision-making. The aim of this study is to contribute to the literature by examining the clinical spectrum and regional variant profile of *BRCA1* and *BRCA2*-related hereditary breast cancer in patients diagnosed with breast cancer. **Materials and Methods:** A total of 128 breast cancer patients evaluated at Balıkesir University between December 2023 and February 2025 were analyzed for *BRCA1* and *BRCA2* variants using next-generation sequencing retrospectively. Multiplex ligation-dependent probe amplification (MLPA) testing results were evaluated for cases without pathogenic variants. **Results:** Pathogenic/likely pathogenic variants in *BRCA1* and *BRCA2* were found in 18 patients (14.06%). Pathogenic/likely pathogenic variants were detected in 12 patients (9.3%) with equal distribution between the two genes. Variants of uncertain significance were identified in 6 patients (4.7%). One patient had a deletion in exon 8 of *BRCA1*. **Conclusion:** Our study reveals the distribution of BRCA variants consistent with national and international data. Providing genetic counseling, screening first-degree relatives, and regular re-evaluation of variants are essential for early diagnosis and effective management of hereditary breast cancer.
Keywords: Breast Cancer, *BRCA1* Gene, *BRCA2* Gene.

Meme Kanseri Vakalarında *BRCA1* ve *BRCA2* Varyantlarının Spektrumu: Tek Merkez Deneyimi

ÖZ

Amaç: Kalıtsal meme kanserleri, tüm meme kanserlerinin yaklaşık %5 ila %10'unu oluşturur ve bu vakaların önemli bir kısmı *BRCA1* ve BRCA2 genlerindeki patojenik değişimlerle ilişkilidir. Bu genlerdeki varyantların tespiti, risk değerlendirmesi ve klinik kararlar için kritiktir. Bu çalışmanın amacı meme kanseri tanısı almış hastalarda *BRCA1* ve *BRCA2* ilişkili kalıtsal meme kanserinin klinik spektrumu ve bölgesel varyant profili incelenerek literatüre katkı sağlamaktır. **Gereç ve Yöntem:** Aralık 2023 – Şubat 2025 tarihleri arasında Balıkesir Üniversitesi'nde değerlendirilen 128 meme kanseri olgusuna yeni nesil sekanslama yöntemi kullanılarak analiz edilen *BRCA1* ve *BRCA2* varyantları retrospektif olarak incelendi. Patojenik varyant saptanmayanlarda çoklu ligasyon bağımlı prob amplifikasyonu (MLPA) testi sonuçları değerlendirildi. **Bulgular:** 128 hastanın 18'inde (%14.06) *BRCA1* ve *BRCA2* de patojenik/olası patojenik varyantlar bulundu. 12 hastada (%9.3) patojenik/olası patojenik varyantlar eşit dağılım gösterdi. 6 hastada (%4.7) belirsiz klinik öneme sahip varyantlar saptandı. Bir hastada (0.78%) *BRCA1* ekzon 8 delesyonu tespit edildi. **Sonuç:** Çalışmamız, BRCA varyantlarının dağılımını ulusal ve uluslararası verilerle uyumlu olarak ortaya koymaktadır. Kalıtsal meme kanseri hastalarına genetik danışmanlık verilmesi, yakın akrabaların taranması ve varyantların düzenli değerlendirilmesi erken tanı ve etkili yönetim için önemlidir.
Anahtar Kelimeler: Meme Kanseri, *BRCA1* Geni, *BRCA2* Geni.

Sorumlu Yazar / Corresponding Author: Zeynep ESENER, Balıkesir University, Faculty of Medicine, Department of Medical Genetics, Balıkesir, Türkiye
E-mail: zeynepesenermd@gmail.com

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INTRODUCTION

Breast cancer ranks as the most commonly diagnosed malignancy in women globally (Sung et al., 2021) It is also the fifth most frequent cause of death from cancer across both genders. (Sung et al., 2021). In 2020, the World Health Organization (WHO) reported that breast cancer was diagnosed in over 2.25 million women worldwide. (Ferlay et al., 2020). While most cases arise sporadically, 5–10% of breast cancers have hereditary origins, with approximately one-quarter of these linked to pathogenic (P) or likely pathogenic (LP) germline variant in the *BRCA1* and *BRCA2* genes (Düzkale et al., 2024).

The *BRCA1* and *BRCA2* genes play essential roles in DNA repair, regulation of the cell cycle, and preservation of genomic stability. They also ensure that damaged cells are eliminated via apoptosis or necrosis if repair fails (Baykara, 2016). *BRCA1* is located on chromosome 17q21, comprises 24 exons, and encodes a protein of 1,863 amino acids. As a multifunctional protein, *BRCA1* interacts with 52 different proteins as documented in the STRING database by EXPASY, collaborating in preserving genomic integrity. *BRCA2*, located on chromosome 13q12-13, contains 27 exons and encodes a 3,418-developing pancreatic cancer in the general population is approximately 0.5%, which rises to 1–3% in *BRCA1* variant carriers and 2–7% in *BRCA2* variant carriers. Similarly, the risk of developing prostate cancer by age 69 is 6% in the general population, increasing to 8.6% in *BRCA1* carriers and up to 20% in *BRCA2* carriers (Bahsi & Erdem, 2020). *BRCA1* and *BRCA2* genes, in conjunction with PARP enzymes, are fundamentally involved in the process of repairing DNA damage. Concurrent disruptions in these genes can induce tumor cell death via synthetic lethality. PARP inhibitors, by targeting DNA repair pathways, provide an effective treatment option for *BRCA*-associated breast cancers. Findings from a recent double-blind, randomized Phase III trial indicated that olaparib significantly increased progression-free survival in early, high-risk, HER2-negative breast cancer cases associated with *BRCA1* and *BRCA2* variants (Petrucelli et al., 2025).

In light of these findings, genetic testing currently plays a crucial role in cancer diagnosis, treatment, and risk management. Early identification of P/LP variant carriers and high-risk individuals offers an effective strategy to reduce cancer morbidity and mortality. Given the autosomal dominant inheritance pattern of germline pathogenic *BRCA1* and *BRCA2* variants, offspring of carriers have a 50% chance of inheriting these genetic alterations. Moreover, the detection of variants in one family member indicates a high likelihood of similar risk among first-degree relatives. Identification of pathogenic variants in these individuals allows for the implementation of risk-reducing strategies such as enhanced screening protocols, variant-specific targeted therapies, and amino acid protein; with its tumor suppressor function, it contributes to transcriptional co-regulation and, by interacting with the RAD51 protein, regulates the homologous recombination repair (HRR) process (Alday-Montañez et al., 2025). Dysfunction in these genes results in DNA damage accumulation, a key driver of carcinogenesis (Baykara, 2016).

Individuals harboring P/LP variants in *BRCA1* and *BRCA2* genes generally inherit a single defective (heterozygous) allele; however, loss or mutation of the second allele significantly increases malignancy risk due to the loss of tumor suppressor function. Homozygous *BRCA2* P/LP variants can lead to rare syndromes such as Fanconi Anemia (Thorat & Balasubramanian, 2019).

Classified as high-penetrance genes, *BRCA1* and *BRCA2* P/LP variants confer a lifetime breast cancer risk of up to 69–72% (Thorat & Balasubramanian, 2019). *BRCA1*-associated tumors often exhibit triple-negative features, while *BRCA2*-related tumors tend to show higher histologic grades (Baretta et al., 2016).

Furthermore, P/LP variants in *BRCA* genes have been shown to significantly increase the risk of certain cancers other than breast cancer. The risk of prophylactic surgical interventions, thereby significantly altering disease course (Petrucelli et al., 2025; Gezdirici et al., 2024).

The objective of this study is to define the clinical and genetic features of hereditary breast cancer linked to *BRCA1* and *BRCA2* variants within a regional cohort.

MATERIALS AND METHODS

Selection of cases

A total of 128 patients were included in the study based on the following criteria:

- Presentation to the Balıkesir University Genetic Diseases Evaluation Center between December 2023 and February 2025
- Meeting the molecular genetic testing criteria for breast cancer as defined by the current National Comprehensive Cancer Network (NCCN) guidelines, including but not limited to:
  -Diagnosis of breast cancer at or before the age of 50
  -Triple-negative tumor characteristics (regardless of age)
  -Bilateral breast cancer or multiple primary breast cancers
  -A family history of breast, ovarian, pancreatic, or prostate cancer in a first- or second-degree relative
- Provision of written informed consent to participate in the study.

Molecular analysis

All participants initially underwent sequencing of the *BRCA1* and *BRCA2* genes. For those in whom sequencing did not reveal any pathogenic or likely

pathogenic variants, subsequent analyses were conducted to detect potential deletions or duplications in these genes.

Peripheral blood samples were collected from the patients, and leukocytes were isolated for genomic DNA extraction. DNA was isolated using the HiPurA® pre-filled clinical multi-purpose nucleic acid purification kit and the HIMEDIA InstaN Mag-96 automation system. DNA concentration measurements were performed using the Qubit® fluorometer (Thermo Fisher Scientific, USA).

Next-generation sequencing (NGS) was utilized to analyze the *BRCA1* and *BRCA2* genes. Library preparation was carried out using the Roche® KAPA HyperExome 96-reaction kit, and sequencing was performed on the MGI DNBSEQ-G400 platform. The raw data obtained in FastQ format were analyzed using the Genomize SEQ platform (version 8.7.0, https://seq.genomize.com). Variant visualization was performed using the Integrative Genome Viewer (IGV) software. Identified variants were classified in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al., 2015).

For patients in whom no variants were detected via NGS, deletion and duplication screening was conducted. For the *BRCA1* gene, the SALSA® MLPA® Probemix P002-D1 (MRC-Holland) kit was used; for the *BRCA2* gene, the SALSA® MLPA® Probemix P045 (MRC-Holland) kit was employed. MLPA results were analyzed using the Coffalyser® software

Ethical approval

Provided informed consent to participate in the study written informed consent was obtained from all participants before inclusion in the study, which was approved by the Ethics Committee of Balıkesir University. The research was conducted at Balıkesir University Training and Research Hospital, with ethical approval granted on 11/03/2025 (Approval No: 2025/124). After comprehensive evaluation, the committee confirmed that the study fulfilled all scientific and ethical standards.

RESULTS

A total of 128 breast cancer patients fulfilling the NCCN molecular genetic testing criteria were enrolled in the study, retrospectively. The patients' ages at the time of diagnosis ranged from 30 to 80 years, with a mean age of 53.25 years. Among all cases, BRCA gene-related variants were identified in 18 patients (14.06%), while no variants were detected in the remaining 110 patients (85.94%). A closer analysis of the detected variants showed that pathogenic or likely pathogenic (P-LP) variants in the BRCA1 gene were present in 6 patients (4.69%), and the same number of P-LP variants were found in the BRCA2 gene. Additionally, variants of uncertain clinical significance (VUS) were observed in 2 patients (1.56%) for BRCA1 and in 4 patients (3.13%) for BRCA2. All identified variants had been previously reported in the literature (Table 1). The average age at diagnosis for patients carrying P/LP variants in *BRCA* genes was determined to be 53.5 years. Furthermore, a deletion in the *BRCA1* gene was identified in one patient through multiplex ligation-dependent probe amplification (MLPA) analysis.

Among the P/LP variants, frameshift variants were the most frequently observed (66.6%), followed by nonsense mutation variants (16.66%), missense mutation variants (8.33%), and non-coding region variants (8.33%). The frequencies of missense and non-coding variants were equal. (Figure 1)

Among patients carrying P/LP variants, 75% had a family history of breast and/or ovarian cancer in at least one first- or second-degree relative, compared to 16.67% of those with VUS variants.

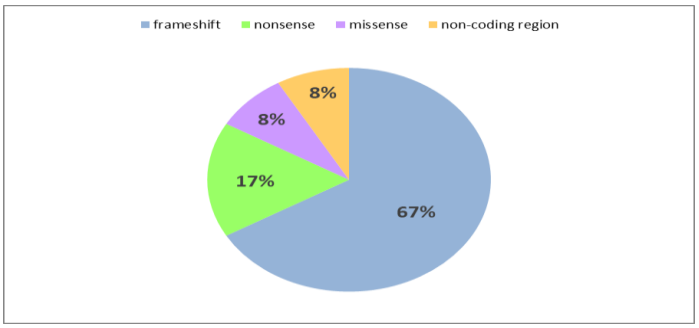

Figure 1. Distribution of P/LP variants by type

Table 1. *BRCA1* and *BRCA2* genes variants and their classification according to ACMG criteria.

Case	Gene	Exon	Variant type	Nucleotide change	Amino-acid change	Zygosity	gnomAD v4.1.0 Allele frequency	Clinvar	Acmg classification	Gender	dbSNP ID	Age at diagnosis	Family history
1	*BRCA1* (NM_007300.4)	Exon 20	Frameshift	c.5329dup	p.Gln1777ProfsTer74	Heterozygous	0.00004346	Pathogenic	Pathogenic (PVS1, PP5, PM2)	F	rs80357906	67	-
2	*BRCA1* (NM_007300.4)	Exon 20	Frameshift	c.5329dup	p.Gln1777rofsTer74	Heterozygous	0.00006754	Pathogenic	Pathogenic (PS4, PS3, PVS1, PM2)	F	rs80357906	55	+
3	*BRCA1* (NM_007300.4)	Exon 20	Frameshift	c.5329dup	p.Gln1777ProfsTer74	Heterozygous	0.00006754	Pathogenic	Pathogenic (PS4, PS3, PVS1, PM2)	F	rs80357906	70	+
4	*BRCA1* (NM_007300.4)	Exon 12	Nonsense	c.4327C>T	p.Arg1443Ter	Heterozygous	0.00001239	Pathogenic	Pathogenic (PS4, PS3, PVS1, PM2)	F	rs41293455	30	-
5	*BRCA1* (NM_007300.4)	Exon 18	Missense	c.5159G>A	p.Arg1720Gln	Heterozygous	0.00001859	Pathogenic	Pathogenic (PS3, PM1, PM5, PM2, PP3, PP5)	F	rs41293459	72	+
6	*BRCA1* (NM_007300.4)	Exon 22	Frameshift	c.5398del	p.Gln1800AsnfsTer14	Heterozygous	not found	Pathogenic	Pathogenic (PVS1, PP5, PM2)	F	rs80357590	41	+
7	*BRCA2* (NM_000059.3)	Intron 2	Non-Coding	c.67+1G>A	-	Heterozygous	not found	Pathogenic	Pathogenic (PVS1, PP5, PM2)	F	rs81002796	38	+
8	*BRCA2* (NM_000059.3)	Exon 10	Nonsense	c.1189C>T	p.Gln397Ter	Heterozygous	not found	Pathogenic	Pathogenic (PVS1, PP5, PM2)	F	rs760815829	45	+
9	*BRCA2* (NM_000059.3)	Exon 11	Frameshift	c.2588dup	p.Asn863LysfsTer18	Heterozygous	0.000005029	Pathogenic	Pathogenic (PVS1, PP5, PM2)	F	rs80359335	45	+
10	*BRCA2* (NM_000059.3)	Exon 11	Frameshift	c.4631dup	p.Asn1544LysfsTer4	Heterozygous	0.000005578	Pathogenic	Pathogenic (PVS1, PP5, PM2)	F	rs80359460	47	+
11	*BRCA2* (NM_000059.3)	Exon 23	Frameshift	c.9097dup	p.Thr3033AsnfsTer11	Heterozygous	0.000006200	Pathogenic	Pathogenic (PVS1, PP5, PM2)	F	rs397507419	65	-
12	*BRCA2* (NM_000059.3)	Exon 11	Frameshift	c.2765dup	p.Lys923GlnfsTer13	Heterozygous	not found	Pathogenic	Pathogenic (PVS1, PP5, PM2)	F	rs397507639	67	+
13	*BRCA1* (NM_007300.4)	Exon 10	Missense	c.1201G>A	p.Gly401Arg	Heterozygous	0.000001239	Conflicting	VUS (PM2)	F	rs1555592242	50	-
14	*BRCA1* (NM_007300.4)	Exon 8	Missense	c.556T>G	p.Ser186Ala	Heterozygous	0.000006198	VUS	VUS	F	rs397509298	31	-
15	*BRCA2* (NM_000059.3)	Exon 11	Missense	c.2386G>C	p.Asp796His	Heterozygous	Not found	VUS	VUS (PM2)	F	rs1555282650	58	+
16	*BRCA2* (NM_000059.3)	Exon 27	Frameshift	c.10095delinsGAATTATATCT	p.Ser3366AsnfsTer4	Heterozygous	Not found	Conflicting	VUS (PVS1, PM2, BP6)	F	rs276174803	43	-
17	*BRCA2* (NM_000059.3)	Exon 18	Missense	c.8117A>G	p.Asn2706Ser	Heterozygous	0.00003097	Conflicting	VUS (BP6)	F	rs80359055	65	-
18	*BRCA2* (NM_000059.3)	Exon 11	Missense	c.4237A>G	p.Lys1413Glu	Heterozygous	0.000001252	VUS	VUS (PM2, BP4)	F	rs876661198	47	-

DISCUSSION

Each year, an estimated 1.6 million new breast cancer cases are diagnosed globally, making it the most frequent cancer among women. (Thorat & Balasubramanian, 2019). It is estimated that approximately 1 in every 400–500 individuals in the general population carries a hereditary P/LP variant in the *BRCA1* or *BRCA2* gene (Olivia et al., 2024).

Multicenter studies conducted across various geographical regions of Türkiye have reported the frequency of P/LP variants in the *BRCA1* and *BRCA2* genes to range between 8% and 21% (Işıklar et al., 2023) (Table 2). Similarly, another study conducted in the Balıkesir region reported a frequency of P/LP variants of 12.49% in the *BRCA1* and *BRCA2* genes (Çelebi & Bolat, 2022) (Table 2). In our study, this frequency was found to be 9.3% (12/128) among patients who met the NCCN criteria for hereditary breast cancer, which is consistent with the existing literature. Notably, 25% (3/12) of the detected P/LP variants in the *BRCA1* and *BRCA2* genes were located in exon 11. This finding may be associated with the Ovarian Cancer Cluster Region (OCCR), which has been described in or near exon 11 of both genes (Petrucelli et al., 2025).

Table 2. BRCA1/2 Studies originating from Türkiye.

P/LP VARİANTS	Variant Frequency	References
BRCA1/2	%10.4 (11/105)	Yazıcı et al.,2000
	%9.7 (139/1419)	Bahsi & Erdem, 2020
	%16.6 (20/120)	Gerik-Çelebi & Bolat, 2022
	%20.6 (342/1655)	Bisgin et al., 2022
	%11.1 (34/308)	Işıklar et al., 2023
	%16.6 (239/1444)	Boğa et al., 2023
	%9.4 (16/170)	Düzkale et al., 2024
	%13.2 (420/3184)	Çelik-Demirbaş et al., 2025

In the literature, the most commonly reported *BRCA1* variants in the Turkish population are I482* (approximately c.1444_1447delATTA), Q1756fs74 (approximately c.5266dupC), and Q934 (approximately c.2800C>T) (Bisgin et al., 2022). However, these variants were not observed in our cohort. Instead, the c.5329dup variant was identified in 37.5% (3/8) of the cases with variants detected in the *BRCA1* gene. This relatively high frequency may be attributed to the geographic concentration of patients referred from the Balikesir province and surrounding regions. Regarding the *BRCA2* gene, the most frequently reported variants in previous studies are K923Qfs13 (approximately c.2765dupT) and T3033Nfs11 (approximately c.9097dupA) (Bisgin et al., 2022). In our dataset, one patient (9.09%, 1/11) was found to carry each of these two variants.

Large genomic rearrangements (LGRs) in the *BRCA1* and *BRCA2* genes detected via MLPA analysis have been reported in the literature at a frequency of approximately 3.4% (Akin Duman & Ozturk, 2023). In our study, this rate was observed to be 0.78% (1/128). This discrepancy may be due to the limited sample size of our cohort. Additionally, the literature reports that gene-targeted deletion/duplication analyses detect pathogenic variants in *BRCA1* at a frequency of 11–13% and in *BRCA2* at 2–3% (Petrucelli et al., 2025).In our study, the corresponding rates were found to be 16.67% (1/6) for *BRCA1* and 0% (0/6) for *BRCA2*.This study provides a meaningful contribution to the regional literature by evaluating the variant distribution and clinical characteristics of hereditary breast cancer cases associated with *BRCA1*/*BRCA2*. The data obtained demonstrate that the frequency of identified P/LP variants is consistent with findings reported at both national and international levels.Genetic testing should not be limited to the diagnostic process alone; it should also be actively utilized to guide risk-based screening strategies and treatment planning for both the individual and their family members. In our study, of the two cases with pathogenic variants identified in the *BRCA1* and *BRCA2* genes, one received a genetic diagnosis 20 years and the other 15 years after their initial cancer diagnosis, during family screening. In contrast, all other cases were referred for genetic evaluation following their pathological diagnosis. This may be attributed to the strengthening collaboration between oncology and genetics departments, in parallel with advances in targeted cancer therapies. In patients carrying pathogenic variants in *BRCA1* and *BRCA2*, targeted treatments such as PARP inhibitors have been shown to significantly improve disease prognosis. A multidisciplinary approach that includes genetic counseling and incorporates personalized follow-up and treatment planning offers a comprehensive roadmap for the effective management of hereditary breast cancer. Therefore, the clinical significance of *BRCA1* and *BRCA2* variants lies not only in cancer risk prediction but also in their critical role in early diagnosis, personalized therapy, and the implementation of preventive strategies. Screening individuals diagnosed with breast cancer for *BRCA1* and *BRCA2* gene variants contributes significantly to both clinical follow-up and treatment planning. In this context, we emphasize the importance of screening first-degree relatives of individuals with hereditary breast and ovarian cancer, as close clinical monitoring of those carrying pathogenic or likely pathogenic variants may enhance the chances of early diagnosis.

Furthermore, in cases where VUS are identified, regular re-evaluation in light of evolving literature and increasing data accumulation is becoming increasingly important for accurate clinical decision-making. We underscore the necessity of conducting detailed investigations, reporting, and identification of population-specific BRCA gene variants to expand therapeutic options and inform the development of national screening programs.

CONCLUSION

The study enhances regional literature through assessment of *BRCA1* and *BRCA2* variant distribution in hereditary breast cancer cases. Our study, which aims to reveal the regional variant profile, highlights the need for larger cohort studies to establish a comprehensive regional variant profile. Additionally, we emphasize the importance of evaluating cases with VUS not only in BRCA genes but also in non-BRCA genes in detail. We underline that providing genetic counseling to individuals with hereditary breast cancer, screening their first-degree relatives, and regularly re-evaluating VUS variants are critical for early diagnosis and effective management.

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Conflict of Interest

The authors declare no conflict of interest

Author Contributions

Plan, design: ZE; **Material, methods and data collection:** ZE, SS, Yİ, DGA, HB; **Data analysis and comments:** ZE, DGA, HB; **Writing and corrections:** ZE, DGA.

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Ethical Approval

Institution: Balikesir University Ethics Committee
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