THE ATLANTIC Journal of Medical Science and Research

Atlantic J Med Sci Res 2026;6(1):93-9
DOI: 10.5455/atjmed.2025.11.036

Original Article

Analysis of the results of the *BRCA1* and *BRCA2* genes in early-onset breast cancer patients from the Ordu province

Cagri Dogan[1], Cengiz Akosman[2], Muge Sonmez[3]

[1]Ordu University, Faculty of Medicine, Department of Medical Genetic, Ordu, Türkiye
[2]İstinye University, Ordu Medical Park Hospital, Department of Medical Oncology, Ordu, Türkiye
[3]Ordu University, Faculty of Medicine, Department of Medical Oncology, Ordu, Türkiye

Received: 21 November, 2025
Accepted: 03 February, 2026
Published: 11 March, 2026

Corresponding Author: Cagri Dogan, Ordu University, Faculty of Medicine, Department of Medical Genetic, Ordu, Türkiye
Email: mdgencagri@gmail.com

CITATION
Dogan C, Akosman C, Sonmez M. Analysis of the results of the *BRCA1* and *BRCA2* genes in early-onset breast cancer patients from the ordu province. Atlantic J Med Sci Res. 2026;6(1):93-9. DOI: 10.5455/atjmed.2025.11.036

Abstract

Aim: This study aimed to determine the spectrum *BRCA1/2* variants in patients with suspected hereditary breast cancer from Ordu Province.
Materials and Methods: The medical records of patients evaluated at Ordu University between January 1, 2023, and September 1, 2025, were retrospectively reviewed. A total of 357 patients who underwent *BRCA1/2* gene sequencing and MLPA analyses were included. All variants were classified according to ACMG guidelines. Findings were summarized descriptively.
Results: Of the 357 individuals, 41 patients (11.5%) carried at least one *BRCA1/2* variant classified as pathogenic (P), likely pathogenic (LP), or variant of uncertain significance (VUS). A total of 28 *BRCA1* and 15 *BRCA2* variants were identified. In *BRCA1*, pathogenic variants predominated (n=19), whereas *BRCA2* showed a higher proportion of VUS (n=11). The most frequent alteration was the *BRCA1* exon 18–19 deletion, detected in eight patients. Recurrent sequence-level variants included *BRCA1*:c.788dup (n=4), *BRCA2*:c.5975C>T (n=3), *BRCA1*:c.1504_1508del (n=2), *BRCA1*:c.135-8A>G (n=2), *BRCA2*:c.5120del (n=2), and *BRCA2*:c.7481G>A (n=2). Variation-type analysis revealed that missense variants (n=18) were the most common, followed by frameshift variants (n=10) and large genomic deletions (n=9). Five patients (1.4%) harbored more than one variant simultaneously.
Conclusion: This study represents the first comprehensive analysis of *BRCA1/2* variant distribution in the Central Black Sea region of Türkiye and highlights a distinct mutational spectrum compared with previously published national data. The high frequency of the *BRCA1* exon 18–19 deletion and the detection of region-specific recurrent variants emphasize the importance of incorporating MLPA and broad NGS panels into routine genetic evaluation. Given the dominance of VUS findings in *BRCA2* and the presence of multiple variants in individual patients, regular reclassification and family-based cascade screening are essential. These results underscore the need for region-specific genomic databases to improve risk assessment, early diagnosis, and precision-guided management in hereditary breast cancer.

Keywords: *BRCA1*, *BRCA2*, breast cancer

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy worldwide, with an estimated 2.3 million new cases in 2020 (1). Despite advances in screening and treatment, the global burden of the disease continues to rise, particularly in younger women who often present with more aggressive subtypes. Approximately 5–10% of breast cancers are considered hereditary, with a significant proportion of these cases attributable to pathogenic variants in the *BRCA1* and *BRCA2* genes (2,3).

The *BRCA1* gene is located on chromosome 17 at the 17q31.31 region of the genome, and spans approximately 110 kb. It contains a total of 22 exons, of which exon 11 is the largest, encoding about 60% of the 1863-amino-acid protein produced by the gene. The *BRCA1* gene interacts with more than 50 other genes and plays key roles in tumor suppression, double-strand DNA break repair, maintenance of genomic stability, cell-cycle

checkpoint control, and apoptosis.

The *BRCA2* gene is located on chromosome 13 at the 13q13.1 region, contains 27 exons, and encodes a protein composed of 3.418 amino acids. The *BRCA2* gene interacts with a broad network of proteins including *PALB2, RAD51, FANCD2* and p53, and plays essential roles in tumor suppression, homologous recombination-mediated double-strand DNA break repair, maintenance of genome stability, cell-cycle checkpoint control and apoptosis (4,5).

The function of the *BRCA1* and *BRCA2* genes is to repair DNA double-strand breaks (DSBs) through a complex and tightly regulated mechanism known as homologous recombination (HR). Through the hierarchical cooperation of multiple genes (including, but not limited to, *BRCA1, BRCA2, PALB2, ATM, and RAD51*), DSB mutations that pose critical risks to the genome are corrected with high fidelity, thereby maintaining genomic stability (6-8).

Mutations in the *BRCA1* and *BRCA2* genes are transmitted to the next generation with approximately a 50% probability, akin to autosomal dominant disorders. In addition to the existing mutation in these genes, the development of subsequent pathogenic or likely pathogenic mutations leads to genome instability and drives the development of cancer (9).

Individuals who carry pathogenic or likely pathogenic (LP) variants in the *BRCA1* or *BRCA2* genes exhibit a markedly increased lifetime risk of developing breast, ovarian, prostate, and pancreatic cancers in comparison with the general population. Among women harbouring a mutation in the *BRCA1/2* gene, the lifetime risk of developing breast cancer is approximately 60%, whereas in the general population, this risk is approximately 13% (10). Similarly, by the age of 70, the risk of male breast cancer is estimated at 0.2–1.2% in *BRCA1* mutation carriers and 1.8–7.1% in *BRCA2*:carriers, compared with 0.1% among men in the general population . The lifetime risk of pancreatic cancer is also elevated, ranging from 2–5% in *BRCA1*:carriers and 5–10% in *BRCA2*:carriers, whereas the general population risk is approximately 1.7%10. Furthermore, by the age of 80, the risk of prostate cancer is estimated to be 7–26% in *BRCA1*:carriers and 19–60% in *BRCA2* mutation carriers, compared with 10.6% in the general population. For women carrying harmful *BRCA1/2* variants, the lifetime risk of ovarian cancer is estimated at 39–58% and 13–29%, respectively, while the corresponding risk in the general population is only 1.1% . These findings emphasise the significant impact of *BRCA1/2* mutations on cancer susceptibility and underscore the necessity for personalised risk assessment and targeted surveillance strategies (10).

In addition, pathogenic mutations in the *BRCA1* and *BRCA2* genes have also been associated with an increased risk of developing melanoma (both cutaneous and ocular types), as well as gastric and endometrial cancers (11-14). Moreover, individuals carrying germline mutations in both alleles of the *BRCA1* or *BRCA2* genes may develop Fanconi anemia, as well as rare solid tumors and acute myeloid leukemia (AML) during childhood (15-17).

The function of the *BRCA1* and *BRCA2* genes, in conjunction with the PARP family of genes, is to facilitate genomic stability through the orchestration of DNA-repair mechanisms. This molecular rationale has served as the foundation for the development and expanding clinical utilisation of the PARP inhibitor Olaparib. In tumours associated with *BRCA1/2* deficiency, the inhibition of PARP enzymes artificially compromises genomic stability and leads to tumour-cell death. Clinical studies have demonstrated that Olaparib is effective in treating patients with HER2-negative, *BRCA1/2* mutation–positive breast cancer (18,19).

In consideration of these findings, genetic testing has been demonstrated to have considerable value in three principal areas: firstly, in the diagnostic process, secondly, in the planning of treatment, and thirdly, in the evaluation of prognosis. As is well established, individuals carrying P/LP variants in the *BRCA1/2* genes have a 50% probability of transmitting these mutations to the next generation . Therefore, the early genetic screening of relatives of individuals carrying *BRCA1/2* mutations, followed by risk-reducing interventions, can help prevent cancer development. Furthermore, in patients with germline or somatic *BRCA1/2*-positive tumors, such testing facilitates the use of targeted therapies such as Olaparib, which contribute to improved treatment outcomes.

The aim of this study is to determine the mutation detection rate in the *BRCA1/2* genes among breast cancer patients diagnosed in Ordu province and its surrounding region. The study will also analyse the demographic characteristics of the patients and report the identified variants to the scientific literature.

MATERIALS AND METHODS

In our study, the medical records of patients who presented to the outpatient clinic of Ordu University between January 1, 2023, and September 1, 2025, with a preliminary diagnosis of Hereditary Breast Cancer were reviewed retrospectively. All patients for whom *BRCA 1-2* gene sequencing was requested were included in the study. Our study was designed to describe patient data, and the findings are presented as percentage distributions. The clinical findings and mutations identified in the patients were explained descriptively. A total of 357 patients referred to the Department of Medical Genetics at Ordu University Hospital, with a preliminary diagnosis of hereditary breast cancer, were evaluated. Peripheral blood samples were collected in Cell Blood Count (CBC) tubes for DNA extraction.

The genomic DNA was isolated using the DiaRex® Whole Blood Genomic DNA Extraction Kit (Cat. No. BLD-5295, Diagen, Ankara). This process involved lysis, proteinase K digestion, ethanol precipitation, and column-based purification to obtain high-quality DNA. Nucleic acid concentrations were measured using a Colibri Microvolume Spectrometer (Titertek-Berthold, Germany). All exons of the *BRCA1/2* genes were amplified via PCR and sequenced on the Illumina

MiSeq platform using the Nextera XT DNA Library Prep Kit (Illumina, San Diego, CA). The variants were visualised using the Integrative Genomics Viewer (IGV) and classified according to the Franklin, VarSome, HGMD Public®, ClinVar, gnomAD, ExAC, KGP, and dbSNP databases. The MLPA analysis was utilised to detect large genomic deletions in the *BRCA1*-2 genes. For the present study, SALSA® MLPA® Probemix P002-D1/Probemix P045 (MRC-Holland) kits were utilised, and the Coffalyser® analysis programme was used for the analysis. Each detected variant was categorised according to the framework stipulated by the American College of Medical Genetics and Genomics (ACMG).

Our study was conducted with the approval of the Non-Interventional Clinical Research Ethics Committee of Ordu University (Decision No: 2025/267 - 09/07/2025).

RESULTS

In the present study, which involved the evaluation of 357 individuals, 41 patients (12%) were found to carry at least one reportable variant in either *BRCA1* or *BRCA2* (Table 1). These variants were classified as P/LP, or of uncertain significance (VUS). A subset of these patients demonstrated multilocus or multi-hit variation: Of the 41 variant-positive individuals, five (12%) exhibited more than one mutation. Within this group, two patients carried variants affecting both *BRCA1* and *BRCA2* simultaneously, while the remaining three patients exhibited multiple alterations restricted to a single gene (two within *BRCA2* and one within *BRCA1*).

Genes with Detected Mutations

Across the cohort, a total of 28 variants were identified in the *BRCA1* gene, compared with 15 variants in the *BRCA2* gene. The classification of *BRCA1* variants revealed a predominance of pathogenic alterations (19 variants), followed by four likely pathogenic variants and five variants of uncertain significance. Conversely, the variant spectrum of the *BRCA2* gene exhibited a predominance of variants classified as VUS with a total of 11 identified variants. However, only four of these were determined to be pathogenic, while none were classified as likely pathogenic.

Frequently Observed Variants

The most recurrent alteration in the study population was the large genomic rearrangement (LGR) involving the deletion of *BRCA1* exons 18–19, representing the leading variant detected. Following this prominent LGR event, several recurrent sequence-level variants were observed with lower but notable frequencies: *BRCA1*:c.788dup (n=4), *BRCA2*:c.5975C>T (n=3), *BRCA1*:c.135-8A>G (n=2), *BRCA1*:c.1504_1508del (n=2), *BRCA2*:c.5120del (n=2), and *BRCA2*:c.7481G>A (n=2).

Types of Mutations

A more detailed classification of the detected variants showed that missense mutations were the most common alteration (n=18). These were followed by frameshift mutations (n=10) and large genomic deletions involving multi-exon loss events (n=9). Nonsense mutations (n=6) constituted a smaller but clinically significant subset, while variants located in non-coding regions (n=3) were the least frequent category observed in the cohort studied (Figure 1).

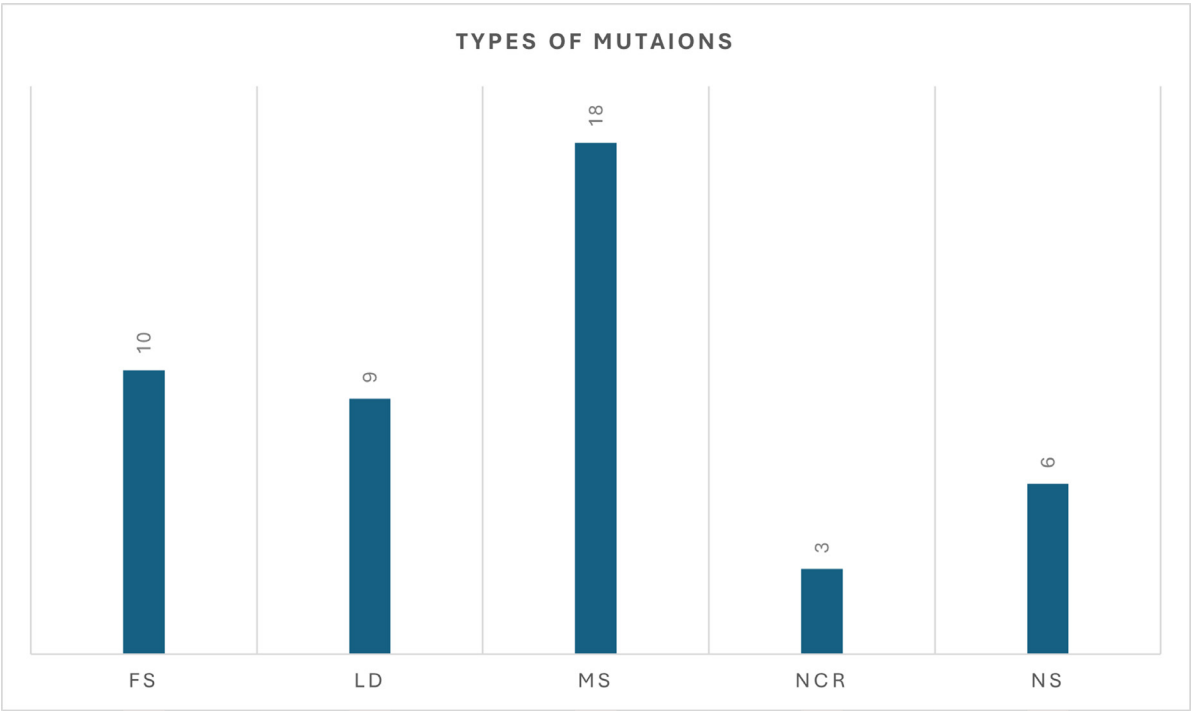

Figure 1. Types of Mutations. FS: Frameshift, MS: Missense Mutation, NS: Nonsense Mutation, LD: Large Deletion, NCR: Non-Coding Region

Table 1. *BRCA1 and BRCA2* positive patient and mutations

ID	Sex	Gene	Mutation	dbSNP	Mut. Type	Variant Type
P1	F	*BRCA1*	Exon 18-19 deletion	-	LGD	P
P2	F	*BRCA2*(NM_000059.4)	c.8881 G>A	rs878853614	M	VUS
P2	F	*BRCA1*(NM_007294.4)	c.788_789insC	-	NS	LP
P3	F	*BRCA2*(NM_001432077.1)	c.4403 C>G	rs1555283769	M	VUS
P4	F	*BRCA1*(NM_007294.4)	c.1504_1508del	rs80357888	FS	P
P5	M	*BRCA1*(NM_007294.4)	c.5096G>A	rs41293459	M	P
P6	F	*BRCA1*	Exon 18-19 deletion	-	LGD	P
P7	F	*BRCA1*(NM_007294.4)	c.135-8 A>G	rs2054798254	NCR	VUS
P8	F	*BRCA1*(NM_007294.4)	c.1504_1508del	rs80357888	FS	P
P9	F	*BRCA1*	Exon 18-19 deletion	-	LGD	P
P10	M	*BRCA2*(NM_001432077.1)	c.3599_3600del	rs80359391	NS	P
P11	F	*BRCA2*(NM_001432077.1)	c.1834 G>A	rs1135401938	M	VUS
P12	F	*BRCA1*	Exon 24 DEL	-	LGD	P
P13	F	*BRCA2*(NM_001432077.1)	c.5975 C>T	rs80358830	M	VUS
P14	F	*BRCA2*(NM_001432077.1)	c.7481 G>A	rs80358973	M	VUS
P15	F	*BRCA1*(NM_007294.4)	c.230 C>T	rs80357209	M	VUS
P16	M	*BRCA1*(NM_007294.4)	c.1504_1508del	rs80357888	FS	P
P17	F	*BRCA1*	Exon 18-19 deletion	-	LGD	P
P18	F	*BRCA1*(NM_007294.4)	c.788dup	rs886040319	NS	P
P19	M	*BRCA1*(NM_007294.4)	c.788dup	rs886040319	NS	P
P20	F	*BRCA1*(NM_007294.4)	c.1987_1988del	-	FS	LP
P21	F	*BRCA1*(NM_007294.4)	c.*186 G>A	rs748299111	NCR	VUS
P22	F	*BRCA1*(NM_007294.4)	c.2706 A>C	rs398122665	M	VUS
P23	F	*BRCA2*(NM_001432077.1)	c.7481 G>A	rs80358973	M	VUS
P24	F	*BRCA2*(NM_001432077.1)	c.5975 C>T	rs80358830	M	VUS
P24	F	*BRCA2*(NM_001432077.1)	c.5120del	rs886039318	FS	P
P25	F	*BRCA2*(NM_001432077.1)	c.7985 C>T	rs431825362	M	VUS
P26	F	*BRCA2*(NM_001432077.1)	c.5975 C>T	rs80358830	M	VUS
P26	F	*BRCA2*(NM_001432077.1)	c.5120del	rs886039318	FS	P
P27	M	*BRCA1*(NM_007294.4)	c.5241del	rs80357791	FS	P
P28	M	*BRCA2*(NM_001432077.1)	c.8881G>A	rs878853614	M	VUS
P29	F	*BRCA1*(NM_007294.4)	c.788dup	rs886040319	NS	P
P30	M	*BRCA2*(NM_001432077.1)	c.6755 C>T	rs876658504	M	VUS
P30	M	*BRCA1*(NM_007294.4)	c.5241del	rs80357791	FS	P
P31	F	*BRCA2*(NM_001432077.1)	c.4593dup	rs397507731	FS	P
P32	F	*BRCA1*	Exon 18-19 deletion	-	LGD	P
P33	F	*BRCA1*	Exon 18-19 deletion	-	LGD	P
P34	F	*BRCA1*	Exon 18-19 deletion	-	LGD	P
P35	F	*BRCA2*(NM_001432077.1)	c.2779 A>G	rs786201837	M	VUS
P36	M	*BRCA1*(NM_007294.4)	c.788dup	rs886040319	NS	P
P37	M	*BRCA2*(NM_001432077.1)	c.4081 C>G	rs587780652	M	VUS
P37	M	*BRCA2*(NM_001432077.1)	c.1235 C>G	rs876659628		
P38	F	*BRCA1*	Exon 18-19 deletion	-	LGD	P
P39	F	*BRCA1*(NM_007294.4)	c.789_790insG	-	FS	LP
P40	F	*BRCA1*(NM_007294.4)	c.135-8 A>G	rs2054798254	NCR	LP
P41	F	*BRCA1*(NM_007294.4)	c.3877 G>C	rs397507223	M	VUS

DISCUSSION

Globally, approximately 2.3 million individuals are diagnosed with breast cancer each year, making it the most common malignancy among women; moreover, an estimated 5–10% of breast cancer cases arise from hereditary causes (1).

While subject to geographic heterogeneity, the reported detection rate of P/LP variants in the context of the *BRCA1/2* gene ranges from 5% to 20%, in line with global estimates (19-22). A range of studies conducted in diverse regions of Türkiye have indicated the presence of inter-regional variability in the prevalence of breast cancer susceptibility genes (*BRCA1/2*), emphasising the necessity for region-specific, locally conducted investigations. In the present cohort, in accordance with global and Turkish data, 11.5% of patients exhibited P/LP/VUS findings in *BRCA1/2*. Although the Ordu region—where this study was conducted—is geographically relatively isolated, characterized by a high rate of consanguineous marriage, elevated cancer burden, and historical exposure to the Chernobyl disaster, the similarity of our results to reports from other parts of Türkiye suggests that *BRCA1/2* variant detection rates may not be strongly shaped by geographic isolation. Nevertheless, replication with larger sample sizes in the coming years will be necessary to substantiate these observations.

All detected variants in this study were interpreted according to the ACMG/AMP 2015 guidelines and cross-referenced with multiple international databases, including ClinVar, VarSome, HGMD Public®, and population frequency resources such as gnomAD. This multi-database approach enhances interpretative robustness and reduces misclassification risk, particularly for rare or population-specific variants. Nevertheless, discrepancies between databases remain possible, reinforcing the importance of periodic reassessment as classification frameworks and reference datasets continue to evolve.

In previous cohorts conducted in our country, the most frequently detected mutations in the *BRCA1* gene were c.5266dupC (22,23), and c.1444_1447delATTA (24). It is noteworthy that none of these recurrent mutations were identified in any patient included in our cohort. Instead, the variants that predominated in the *BRCA1* dataset under consideration were c.788dup (n=4) and c.1504_1508del (n=3). It is hypothesised that this deviation from earlier national findings may be explained by regional genetic structure, particularly the relatively isolated population characteristics of Ordu province. These observations underscore how local genetic landscapes can differ meaningfully and highlight the value of region-specific studies.

In accordance with the findings of previously published Turkish cohorts, the most prevalent variants of the *BRCA2* gene reported included c.1773_1776delTTAT, c.5969delA, c.2765dupT, and c.9097dupA (22,24). None of these variants were encountered in our study. Instead, the variants we observed most frequently were c.5975C>T (n=3), c.8881G>A (n=2), c.7481G>A (n=2), and c.5120del (n=2). As with *BRCA1*, the distinct variant spectrum in our cohort likely reflects the geographically isolated nature of the population we examined. In geographically semi-isolated populations, reduced gene flow and increased endogamy can lead to the enrichment of locally recurrent variants. Considering the demographic characteristics of Ordu province, these factors may have contributed to the distinct *BRCA1/2* variant spectrum observed in our cohort compared with national data. The absence of commonly reported founder mutations and the presence of region-specific recurrent variants support this interpretation.

In the present study, 5 of 357 individuals (1.4%) carried more than one *BRCA1/2* variant simultaneously.Earlier studies from Türkiye have reported a comparable but slightly lower rate of approximately 1% (21,25). The somewhat higher rate recorded in our cohort may be attributed to two factors: the inclusion of VUS variants in our analysis and the relatively high prevalence of consanguineous marriages in the Ordu region. Notably, studies in populations with higher levels of endogamy – such as Ashkenazi Jews – have reported a similar frequency of multiple *BRCA1/2* variants, ranging from 1.4% to 1.8% (26,27). Although such "multi-hit" cases remain uncommon, they illustrate the potential for considerable genetic complexity even within a geographically restricted population.

The high proportion of VUS, particularly within the *BRCA2* gene, represents a well-recognized challenge in hereditary cancer genetics. Although VUS findings are not directly actionable in clinical practice, their interpretation may evolve over time as additional population data, functional studies, and segregation analyses become available. In our cohort, several *BRCA2* VUS were recurrent and detected in unrelated individuals, suggesting that these variants may warrant closer follow-up. Periodic re-evaluation of VUS classifications using updated ACMG criteria, expanding population databases, and family-based segregation analyses may facilitate future reclassification toward either benign or pathogenic categories. Therefore, systematic longitudinal reassessment is essential, especially in regions with distinct genetic backgrounds.

LGRs, including extensive deletions and duplications within the *BRCA1* and *BRCA2* genes, are well-recognised causes of loss-of-function and contribute significantly to hereditary breast–ovarian cancer syndromes. Turkish cohort studies have reported that approximately 3.5% of *BRCA1/2* mutations consist of such large rearrangements (28). In the present cohort, an exon 18–19 deletion of the *BRCA1* was identified in eight of 357 individuals (2.2%). This deletion is considered to be a recurrent LGR. The repeated identification of this deletion provides substantial support for the routine incorporation of LGR analyses into standard genetic testing workflows.

This study has several limitations. First, its retrospective and single-centre design may limit the generalisability of the findings. Second, detailed demographic stratification could not be fully performed due to incomplete retrospective clinical records. In addition, long-term clinical follow-up and

segregation analyses were not available. Therefore, larger multi-centre prospective studies are required to validate and expand upon these findings.

CONCLUSION

This study constitutes the first comprehensive effort to delineate the mutational landscape of the *BRCA1* and *BRCA2* genes within the Central Black Sea region, offering a region-specific genomic perspective that has previously been absent from the national literature. By characterising the distribution, recurrence patterns, and clinical significance of detected variants, our work provides an essential reference framework for understanding hereditary breast cancer susceptibility in a population with unique demographic and genetic features. These findings not only enrich the regional database but also carry substantial relevance for forthcoming large-scale national cohort studies and meta-analyses aimed at forming an integrated variant spectrum for Türkiye.

It is important to note that the present analysis encompassed not only pathogenic and likely pathogenic alterations but also detailed reporting of VUS findings. Given the dynamic nature of variant interpretation, the necessity of systematic annual re-evaluation, in alignment with updated ACMG criteria, evolving clinical correlations, and expanding population databases, is underscored for the refinement of the diagnostic classification of these variants. The presence of multiple carcinogenic variants within the same individual further emphasises a critical public health concern: in communities with high rates of consanguinity, autosomal dominant hereditary cancer syndromes may manifest with an increased mutational burden or more complex genotypic combinations, potentially intensifying disease penetrance and modifying clinical expressivity.

The results of this study demonstrate the importance of incorporating regional genomic data into national hereditary cancer screening strategies. This incorporation should ensure that genetic counselling, cascade testing of first-degree relatives, and vigilant variant reclassification processes are systematically implemented. Strengthening these components will be essential for advancing early detection, risk assessment, and precision-guided management in hereditary breast cancer across Türkiye.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that there is no financial support.

Ethical Approval
The study protocol received approval from the Non-Interventional Clinical Research Ethics Committee of Ordu University (Decision No: 2025/267 - 09/07/2025).

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.
2. Harbeck N, Gnant M. Breast cancer. Lancet. 2017;389:1134-50.
3. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. JAMA. 2017;317:2402-16.
4. Andreassen PR, Seo J, Wiek C, Hanenberg H. Understanding *BRCA2* function as a tumor suppressor based on domain-specific activities in DNA damage responses. Genes (Basel). 2021;12:1034.
5. Warren M, Smith A, Partridge N, Masabanda J, Griffin D, Ashworth A. Structural analysis of the chicken *BRCA2* gene facilitates identification of functional domains and disease causing mutations. Hum Mol Genet. 2002;11:841-51.
6. Gorodetska I, Kozeretska I, Dubrovska A. BRCA genes: the role in genome stability, cancer stemness and therapy resistance. J Cancer. 2019;10:2109-27.
7. Le HP, Heyer WD, Liu J. Guardians of the genome: *BRCA2* and its partners. Genes (Basel). 2021;12:1229.
8. Prakash R, Zhang Y, Feng W, Jasin M. Homologous recombination and human health: the roles of *BRCA1*, *BRCA2*, and associated proteins. Cold Spring Harb Perspect Biol. 2015;7:a016600.
9. Ferreyra Y, Rosas G, Cock-Rada AM, et al. Landscape of germline *BRCA1*/*BRCA2* variants in breast and ovarian cancer in Peru. Front Oncol. 2023;13:1227864.
10. Daly MB, Pal T, Maxwell KN, et al. NCCN guidelines insights: genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2024. J Natl Compr Canc Netw. 2023;21:1000-10.
11. Li S, Silvestri V, Leslie G, et al. Cancer risks associated with *BRCA1* and *BRCA2* pathogenic variants. J Clin Oncol. 2022;40:1529-41.
12. Gumaste PV, Penn LA, Cymerman RM, Kirchhoff T, Polsky D, McLellan B. Skin cancer risk in *BRCA1/2* mutation carriers. Br J Dermatol. 2015;172:1498-506.
13. de Jonge MM, de Kroon CD, Jenner DJ, et al. Endometrial cancer risk in women with germline *BRCA1* or *BRCA2* mutations: multicenter cohort study. J Natl Cancer Inst. 2021;113:1203-11.
14. Sherman ME, Foulkes WD. *BRCA1/2* and endometrial cancer risk: implications for management. J Natl Cancer Inst. 2021;113:1127-28.
15. Howlett NG, Taniguchi T, Olson S, et al. Biallelic inactivation of *BRCA2* in Fanconi anemia. Science. 2002;297:606-09.
16. Alter BP. Fanconi anemia and the development of leukemia. Best Pract Res Clin Haematol. 2014;27:214-21.
17. Sawyer SL, Tian L, Kahkonen M, et al. Biallelic mutations in *BRCA1*:cause a new Fanconi anemia subtype. Cancer Discov. 2015;5:135-42.
18. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with *BRCA1*- or *BRCA2*-mutated breast cancer. N Engl J Med. 2021;384:2394-405.

19. Morganti S, Bychkovsky BL, Poorvu PD, et al. Adjuvant olaparib for germline BRCA carriers with HER2-negative early breast cancer: evidence and controversies. Oncologist. 2023;28:565-74.

20. Cecener G, Sabour Takanlou L, Sabour Takanlou M, et al. Clinicopathologic features and genetic characteristics of the *BRCA1/2* mutation in Turkish breast cancer patients. Cancer Genet. 2020;240:23-32.

21. Boga I, Ozemri Sag S, Duman N, et al. A multicenter study of genotype variation/demographic patterns in 2475 individuals including 1444 cases with breast cancer in Turkey. Eur J Breast Health. 2023;19:235-52.

22. Bahsi T, Erdem HB. Spectrum of *BRCA1*/*BRCA2* variants in 1419 Turkish breast and ovarian cancer patients: a single center study. Turk J Biochem. 2020;45:83-90.

23. Tuncer SB, Celik B, Erciyas SK, et al. Germline mutational variants of Turkish ovarian cancer patients suspected of hereditary breast and ovarian cancer by next-generation sequencing. Pathol Res Pract. 2024;254:155075.

24. Bisgin A, Sag SO, Dogan ME, et al. Germline landscape of BRCAs by 7-site collaborations as a BRCA consortium in Turkey. Breast. 2022;65:15-22.

25. Agaoglu NB, Doganay L. Concurrent pathogenic variations in patients with hereditary cancer syndromes. Eur J Med Genet. 2021;64:104366.

26. Mampel A, Sottile ML, Denita-Juarez SP, Vargas AL, Vargas-Roig LM. Double heterozygous pathogenic variants in the *BRCA1* and *BRCA2* genes in a patient with bilateral metachronous breast cancer. Cancer Genet. 2022;260-261:14-17.

27. Heidemann S, Fischer C, Engel C, et al. Double heterozygosity for mutations in *BRCA1* and *BRCA2* in German breast cancer patients: implications on test strategies and clinical management. Breast Cancer Res Treat. 2012;134:1229-39.

28. Akin Duman T, Ozturk FN. Frequency and distribution of *BRCA1*/*BRCA2* large genomic rearrangements in Turkish population with breast cancer. J Hum Genet. 2023;68:485-90.