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Investigation of BRCA1-BRCA2 Gene Variations in Breast Cancer Patients in the Eastern Anatolian Region of Turkey: A Study of Genetic Predisposition and Clinical Outcomes

Türkiye'nin Doğu Anadolu Bölgesindeki Meme Kanseri Hastalarında BRCA1-BRCA2 Gen Varyasyonlarının Araştırılması: Genetik Yatkınlık ve Klinik Sonuçlar Üzerine Bir Çalışma

ABSTRACT

Objective

This study aims to investigate BRCA1 and BRCA2 gene variations in breast cancer patients in Eastern Anatolia Region and to evaluate the effects of these variations on patients' genetic predisposition and clinical outcomes.

Materials and Methods

The study was conducted on 146 women diagnosed with breast cancer or with a family history of multiple breast cancer cases between 2020 and 2023. Genomic DNA was isolated from the participants and the entire BRCA1/2 genes were sequenced. The data were statistically analysed.

Results

The study identified 17 different genetic variations in the BRCA genes. Four of these variations were classified as pathogenic, potentially causing significant changes in protein structure and increasing the risk of cancer. In addition, some variations were classified as Variants of Uncertain Significance (VUS), whose health effects remain unclear.

Conclusion

This study elucidates the relationship between genetic predisposition and cancer development by investigating BRCA1 and BRCA2 gene variations in breast cancer patients in the Eastern Anatolian region. Four pathogenic variations in the BRCA genes were identified that have the potential to increase cancer risk. In addition, 12 variations were classified as VUS and their health effects have yet to be determined. Our findings provide important information for genetic counselling and disease management, enabling the development of personalised treatment approaches for patients.

Key Words

BRCA1, BRCA2, Breast Cancer, Genetic Variation, Eastern Anatolia Region

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ÖZ

Amaç

Bu çalışmanın amacı Doğu Anadolu Bölgesi'ndeki meme kanserli hastalarda BRCA1 ve BRCA2 gen varyasyonlarını araştırmak ve bu varyasyonların hastaların genetik yatkınlığı ve klinik sonuçları üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntemler

Çalışma, 2020-2023 yılları arasında meme kanseri tanısı almış veya ailesinde birden fazla meme kanseri vakası öyküsü olan 146 kadın üzerinde yürütülmüştür. Katılımcılardan genomik DNA izole edilmiş ve BRCA1/2 genlerinin tamamı dizilenmiştir. Veriler istatistiksel olarak analiz edilmiştir.

Bulgular

Çalışmada BRCA genlerinde 17 farklı genetik varyasyon tespit edilmiştir. Bu varyasyonlardan dördü patojenik olarak sınıflandırılmış, potansiyel olarak protein yapısında önemli değişikliklere neden olmuş ve kanser riskini artırmıştır. Buna ek olarak, bazı varyasyonlar, sağlık üzerindeki etkileri belirsizliğini koruyan Belirsiz Öneme Sahip Varyantlar (VUS) olarak sınıflandırılmıştır.

Sonuç

Bu çalışma, Doğu Anadolu bölgesindeki meme kanseri hastalarında BRCA1 ve BRCA2 gen varyasyonlarını araştırarak genetik yatkınlık ve kanser gelişimi arasındaki ilişkiyi aydınlatmaktadır. BRCA genlerinde kanser riskini artırma potansiyeline sahip dört patojenik varyasyon tanımlanmıştır. Buna ek olarak, 12 varyasyon VUS olarak sınıflandırılmıştır ve bunların sağlık üzerindeki etkileri henüz belirlenmemiştir. Bulgularımız genetik danışmanlık ve hastalık yönetimi için önemli bilgiler sunmakta ve hastalar için kişiselleştirilmiş tedavi yaklaşımlarının geliştirilmesine olanak sağlamaktadır.

Anahtar Kelimeler

BRCA1, BRCA2, Meme Kanseri, Genetik Varyasyon, Doğu Anadolu Bölgesi

INTRODUCTION

Irrespective of ethnicity, breast cancer represents the most frequently diagnosed cancer and the most prevalent malignant disease among women on a global scale (1, 2). Approximately 25% of all cancers diagnosed in women in Turkey are breast cancers. This represents a significant public health concern, with thousands of new cases being identified annually (3). It is estimated that millions of women worldwide are affected by breast cancer, which is also responsible for a considerable number of cancer-related deaths (4). In order to achieve optimal outcomes in the treatment of breast cancer, it is imperative that the disease be identified at an early stage, thereby reducing mortality and morbidity rates (5). One factor that contributes to the early diagnosis of breast cancer is the fear of developing the disease (6). It has also been observed that prognostic variables for patients with breast cancer who receive their diagnosis at an early age vary. In comparison to other forms of cancer, research findings suggest that the annual incidence rate of breast cancer in women aged between 15 and 49 is 39.1% (7).

Genetic factors have a high correlation with breast cancer, and the risk of familial breast and ovarian cancer is significantly elevated by pathogenic germline mutations in tumour suppressor genes, such as BRCA1 and BRCA2 (8). In addition, mutations in other genes, such as TP53, ATM, and CHEK2, have been linked to an increased risk of developing breast cancer (9). To illustrate, the CHEK2 gene's c.1100delC mutation has been demonstrated to increase the risk of breast cancer by a factor of two (10). Furthermore, these genetic variants may influence a patient's survival and response to treatment (11).

In comparison to the general population, women who have mutations in either the BRCA1 or BRCA2 gene are significantly more prone to developing breast cancer. It is estimated that up to 87% of women who have mutations in these genes will eventually develop breast cancer (12, 13). It is established that early-stage breast cancer is significantly influenced by mutations in the BRCA1 and BRCA2 genes (14). Individuals with BRCA1 and BRCA2 mutations exhibit a consistently elevated risk of developing cancer as they age. Furthermore, individuals with these mutations are at an elevated risk of developing other cancers due to the presence of diverse genetic patterns associated with them (15).

A review of the literature reveals that mutations in the BRCA1 and BRCA2 genes are associated with an increased risk of developing cancers other than breast and ovarian cancer (16). Homologous recombination represents a vital mechanism for the repair of damaged DNA. The BRCA1 and BRCA2 genes have been linked to the development of flaws in the DNA repair pathways (17).
A significant number of deleterious mutations in the BRCA1 and BRCA2 genes have been identified through genetic studies conducted in Asian countries. A study con-

ducted in Malaysia investigated the utility of haplotypes in the BRCA1 and BRCA2 genes for disease prediction and the prevalence of variants in these genes in patients with early-stage breast cancer (18). Moreover, research has been conducted on the spectrum and frequency of BRCA1 and BRCA2 mutations in Hakka patients in China, as well as on the characterisation of these variants in individuals at risk of developing breast and ovarian cancer (18, 19). In order to ascertain an individual's risk and to gain insight into the genetic basis of the disease, such genomic investigations are of paramount importance. Further investigation into the mutation spectrum of these genes is required, particularly in underdeveloped countries where genomic data sets for clinically significant genes such as BRCA1 and BRCA2 are scarce (20).

MATERIALS and METHODS

The present study is a retrospective cohort study conducted between 2020 and 2023. The study included 146 women diagnosed with breast cancer or with a family history of multiple breast malignancies. The objective of the study was to examine the impact of BRCA1 and BRCA2 gene mutations on early-onset breast cancer. The study was approved by the Erzurum Medical Faculty of Health Sciences University Ethics Committee (decision number BAEK 2024/05-102). All participants provided written informed consent following a comprehensive explanation of the study protocols.

Selection of participants

The study population comprised women aged 18–50 years who had a diagnosis of breast cancer, were in good general health, and had no active infections.

The participants were asked to provide information regarding their family history. Individuals with a first- or second-degree family history of breast or ovarian cancer were given priority.

A history of genetic testing was also recorded. The participants were individuals who had not been identified as carrying a mutation or who had not undergone BRCA1 or BRCA2 testing previously.

Genetic testing

Genomic DNA was extracted from 200 µL of peripheral blood samples using the QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany), following the manufacturer's instructions. The BRCA1 and BRCA2 genes were amplified using the Agilent BRCA1/2 Master Dx Kit (Agilent, Santa Clara, CA, USA), which encompasses the entire exon sequence, exon-intron boundaries, selected deep intronic sections, and a portion of the promoter region. Sequencing of the amplified PCR products was conducted using the Illumina MiSeq platform (Illumina, Inc., San Diego, CA, USA). If no pathogenic variant was identified, or only a single variant was found, additional testing was performed. Deletion/duplication analysis for the BRCA1 and BRCA2 genes was conducted using the multiple ligation-dependent probe amplification (MLPA) approach (MRC Holland, Amsterdam, The Netherlands). The pathogenicity of the variants was evaluated using relevant databases, namely ClinVar and HGMD Professional. The pathogenicity of novel variants was evaluated using Varsome, the American College of Medical Genetics and Genomics (ACMG) criteria, and in silico analysis programs (Mutation Taster, SIFT, and PolyPhen2) (21, 22).

All variants were confirmed by Sanger sequencing.

Statistical Analysis Data were analyzed using statistical software. Categorical data were analyzed by Chi-square test or Fisher's exact test. Continuous data were analyzed by independent sample t-test or Mann-Whitney U test, as appropriate. $p < 0.05$ was considered statistically significant.

RESULTS

The mean age of the patient cohort, comprising women who attended the medical genetics outpatient clinic with a diagnosis of breast cancer or who were in good general health and did not have any active infectious disorders, was 33 years. Of the aforementioned individuals, 48 did not have a family history of breast or ovarian cancer, while 98 did. It was established that neither BRCA1 nor BRCA2 mutations had been previously identified in any of the individuals. Of the aforementioned individuals, 63 visited our outpatient clinic due to a family history, and 83 were diagnosed with breast cancer (Figure 1).

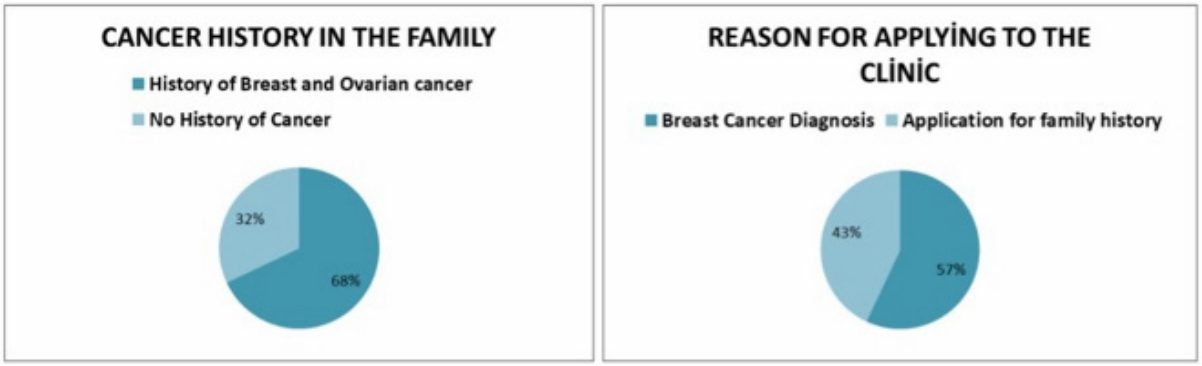

Figure 1. Demographic Analysis of Patients Visiting the Outpatient Clinic

A comprehensive analysis of the genetic test results revealed the presence of 17 distinct genetic variants in the heterozygous status of the BRCA1 and BRCA2 genes. Four of the variants, including BRCA1:c.4165_4166del and BRCA2:c.5073dup, were considered deleterious due to the potential for significant alterations in protein structure and an elevated risk of cancer. In particular, the BRCA2:c.5073dup variant is identified as a frameshift mutation that significantly impairs the protein's function. Nevertheless, variants such as BRCA2:c.8976A>T and BRCA2:c.8417C>T have been identified as likely benign and are not thought to have a significant impact on health. Twelve variations, including BRCA2:c.9254C>A and BRCA1:c.4180A>G, were also identified as variants of uncertain significance (VUS) in our study. It is not possible to make a definitive clinical interpretation of these variations based on the available information. BRCA2:c.9254C>A is a missense mutation among the VUS variants, resulting in a single amino acid alteration in the protein.

It was determined that each variant exhibited a frequency count of one, indicating that the variations are relatively uncommon. It is important to note that the limited sample size may have contributed to the observed results. In conclusion, pathogenic variants are clearly defined, providing valuable insights for genetic counselling and risk-reduction strategies. Further comprehensive genetic investigation and larger patient cohorts are necessary to corroborate the VUS findings (Table I).

The investigation yielded evidence of twenty benign variants in the BRCA1 and BRCA2 genes. The c.4837 A>G and c.3548 A>G mutations were identified among the benign variations in the BRCA1 gene, both in heterozygous and homozygous states, with a higher prevalence observed in the heterozygous state. For example, the BRCA1 c.4837 A>G mutation was identified in 26 instances in the heterozygous state and in 8 instances in the homozygous state. The same circumstances were observed with the c.3113 A>G mutation. These findings suggest that benign variants do not result in any health issues and are present in the genetic structure as dominant alleles (Table II).

Table I. Pathogenic, Likely Benign, and VUS Mutations Detected in BRCA1 and BRCA2 Genes

Variation Name	Zygosity	Clinical Significance (ACMG Criteria)	Frequency Count
BRCA1:c.4165_4166del p.Ser1389 NM_007294.4*	Heterozygous	Pathogenic	1
*BRCA2:c.5073dup p.Trp1692Metfs*3 NM_000059.4*	Heterozygous	Pathogenic	1
*BRCA2:c.8995_8996del p.Leu2999Valfs*18 NM_000059.4*	Heterozygous	Pathogenic	1
*BRCA2:c.994del p.Ile332Phefs*17 NM_000059.4*	Heterozygous	Pathogenic	1
BRCA2:c.9254C>A p.Thr3085Lys NM_000059.4	Heterozygous	VUS	1
BRCA1:c.4180A>G p.Thr1394Ala NM_007294.4	Heterozygous	VUS	1
BRCA2:c.7073C>G p.Ser2358Cys NM_000059.4	Heterozygous	VUS	1
BRCA2:c.8452G>A p.Val2818Ile NM_000059.4	Heterozygous	VUS	1
BRCA2:c.7073C>G p.Ser2358Cys NM_000059.4	Heterozygous	VUS	1
BRCA2:c.1514T>C p.Ile505Thr NM_000059.4	Heterozygous	VUS	1
BRCA2:c.1814T>C p.Ile605Thr NM_000059.4	Heterozygous	VUS	1
BRCA1:c.2215A>G p.Lys739Glu	Heterozygous	VUS	1
BRCA1:c.3752G>A p.Cys1251Tyr NM_007294.4	Heterozygous	VUS	1
BRCA1:c.397C>T p.Arg133Cys NM_007294.4	Heterozygous	VUS	1
BRCA2:c.8976A>T p.Pro2992= NM_000059.4	Heterozygous	Likely Benign	1
BRCA2:c.8417C>T p.Ser2806Leu NM_000059.4	Heterozygous	Likely Benign	1
BRCA1:c.5153-26A>G NM_007294.4	Heterozygous	Likely Benign	1

Table II. Benign Variations Detected in the BRCA1 Gene Among Study Participants

Variation Name	Zygosity	Clinical Significance (ACMG Criteria)	Frequency Count
BRCA1 c.4837 A>G p.S1613G NM_007294.4	Heterozygous	Benign	26
BRCA1 c.3548 A>G p.K1183R NM_007294.4	Heterozygous	Benign	26
BRCA1 c.3113 A>G p.E1038G NM_007294.4	Heterozygous	Benign	26
BRCA1 c.2612 C>T p.P871L NM_007294.4	Heterozygous	Benign	13
BRCA1 c.3548 A>G p.K1183R	Homozygous	Benign	8
BRCA1 c.3113 A>G p.E1038G NM_007294.4	Homozygous	Benign	8
BRCA1 c.2612 C>T p.P871L NM_007294.4	Homozygous	Benign	8
BRCA1 c.4837 A>G p.S1613G NM_007294.4	Homozygous	Benign	8
BRCA1 c.1067 A>G p.Q356R NM_007294.4	Heterozygous	Benign	8
BRCA1 c.4956 G>A p.M1652I NM_007294.4	Heterozygous	Benign	7
BRCA1 c.2077 G>A p.D693N	Heterozygous	Benign	7
NM_007294.4			
BRCA1 c.1703 C>T p.P568L NM_007294.4	Heterozygous	Benign	2
BRCA1 c.4132 G>A p.V1378I NM_007294.4	Heterozygous	Benign	1

The most prevalent variant observed in the BRCA2 gene population is the c.7397 T>C mutation, which was identified 47 times when the gene was in a homozygous state. However, in the heterozygous state, alterations such as c.1114 A>C and c.865 A>C were identified, and these variants were similarly determined to be non-pathogenic (Table III).

In this investigation, 26 patients exhibited the frequent BRCA1 gene variants c.4837 A>G p.S1613G, c.3548 A>G p.K1183R, and c.3113 A>G p.E1038G. Additionally, 27 patients exhibited the prevalent detection of the BRCA2 gene variants c.7397 T>C p.V2466A and c.1114 A>C p.N372H.

Following the completion of the MLPA gene analysis for the BRCA1 and BRCA2 genes, it was determined that all patients exhibited normal results.

Table III. Benign Variations Detected in the BRCA2 Gene Among Study Participants

Variation Name	Zygosity	Clinical Significance (ACMG Criteria)	Frequency Count
BRCA2 c.7397 T>C p.V2466A NM_000059.4	Homozygous	Benign	47
BRCA2 c.1114 A>C p.N372H NM_000059.4	Heterozygous	Benign	27
BRCA2 c.865 A>C p.N289H NM_000059.4	Heterozygous	Benign	6
BRCA2 c.2971 A>G p.N991D NM_000059.4	Heterozygous	Benign	5
BRCA2 c.5744 C>T p.T1915M NM_000059.4	Heterozygous	Benign	3
BRCA2 c.4258 G>T p.D1420Y NM_000059.4	Heterozygous	Benign	3

DISCUSSION

The present study examined the BRCA1 and BRCA2 genes in patients who were at risk of developing breast cancer in a retrospective manner. The study was conducted at Erzurum City Hospital between 2020 and 2023. The results emphasise the crucial role that genetic testing plays in the early diagnosis and treatment of disease, and provide valuable insights for genetic counselling and risk management.

This study illustrates the impact of BRCA gene mutations on the risk of ovarian and breast cancer, with the identification of four pathogenic variants. In particular, frameshift mutations such as BRCA2:c.5073dup can result in significant alterations to the protein structure, thereby increasing the probability of developing cancer. The findings can be integrated into the framework of genetic counselling and risk assessment. Moreover, despite their presence in the genetic structure, variants deemed likely benign (e.g., BRCA2:c.8976A>T and BRCA2:c.8417C>T) have not been demonstrated to significantly impact health outcomes. This demonstrates the capacity of genetic testing to identify benign mutations in addition to those that increase risk.

It is of the utmost importance to consider the specific variants that have been identified when assessing the impact of pathogenic variants in the BRCA genes on the risk of developing breast and ovarian cancer. Frameshift mutations, such as that observed in the BRCA2 gene (c.5073dup), can result in significant alterations to the protein structure, thereby increasing the likelihood of cancer development (23). These results are critical to risk assessment in patient genetic counseling.

Moreover, despite their presence in the genetic makeup, several mutations that are believed to be benign, such as

BRCA2:c.8976A>T and BRCA2:c.8417C>T, have been found to have no discernible impact on health (23). This underscores the vital necessity for genetic tests to be capable of differentiating between alterations associated with an elevated risk and those that are benign.

A comparison of BRCA-mutated and spontaneous breast tumours reveals variations in mutation signatures, copy number profiles, gene expression signatures and patterns of structural variation. These findings indicate that distinct tumour growth pathways are involved in the development of these malignancies (24). It is crucial to comprehend these distinctions in order to develop bespoke therapeutic strategies and to conduct accurate prognosis evaluations.
The 12 variations identified in the study, classified as VUSs, highlight the limitations and challenges associated with genetic testing. Additionally, the distribution of BRCA1 and BRCA2 gene mutations in the Turkish population has been examined with the aim of determining the prevalence and spectrum of these mutations. For instance, a study conducted in Ankara analysed pathogenic mutations in BRCA1 and BRCA2 genes and VUSs, confirming that mutations varied in the Turkish population (25). Given the current state of knowledge, it is challenging to provide a definitive clinical interpretation of these differences, as the impact on health remains unclear. This illustrates the inherent difficulties associated with the analysis of genetic data and the provision of genetic counselling. The VUS results underscore the necessity for further genetic investigation and a prudent interpretation of genetic test results to gain a comprehensive understanding of the relevance of these differences.

Given the lack of knowledge regarding the impact of these variations on health outcomes, genetic testing for BRCA gene variants presents a challenge in terms of clinical interpretation and therapeutic guidance (26). The absence of widely accepted guidelines for the management of BRCA VUS highlights the difficulty of making informed clinical decisions in the context of these findings (27). It is recommended that individuals with a BRCA VUS be treated in a manner similar to those with benign variations, as the majority of VUS do not significantly elevate the risk of cancer (28).

In order to gain a full understanding of the significance of these variations, it is essential to undertake a detailed analysis of the genetic test results and to conduct further genetic research. The existence of variants of uncertain clinical significance (VUS) in BRCA genes introduces complexity to the process of genetic counselling and testing (29). The findings of recent research indicate that BRCA VUS may give rise to a number of issues for both patients and healthcare professionals, particularly in relation to cancer-related anxiety, risk perception and the process of making surgical decisions (30). Moreover, the presence of VUS may influence the assessment of cancer risk management strategies, underscoring the importance of effective communication and a comprehensive understanding of these findings in clinical practice (31).

The complexity of BRCA VUS necessitates further investigation to enhance the precision of clinical decisions based on genetic test results and to develop more accurate guidelines for the management of these variants (27). The assessment of discrepancies in surgical decision-making and cancer anxiety between patients with BRCA negative results and those with VUS provides insight into the importance of clarifying these uncertainties in clinical practice, as well as the impact of VUS on patient management. The observation illustrates the genetic diversity and extensive distribution of variants within the population, indicating that certain benign variations are frequently present in both heterozygous and homozygous states. This suggests that these mutations are relatively common within the genetic population. These findings elucidate the manner in which genetic variants and architectural characteristics diverge among different populations.

CONCLUSION

The findings of this study reinforce the importance of BRCA gene mutation analysis and genetic testing in the management of inherited conditions such as breast cancer. Furthermore, the data provided offers useful insights for genetic counselling, while also emphasising the intricate and dynamic nature of genetic science.

Ethics Committee Approval

This research adheres to all relevant national regulations and institutional policies and aligns with the principles of the Helsinki Declaration. Ethical approval was granted by The Erzurum Medical Faculty of Health Sciences University's Ethics Committee, under approval number BAEK 2024/05-102.

Informed Consent

All participants' rights were protected, and written informed consent was obtained from each participant prior to the procedures, in accordance with the Helsinki Declaration.

Author Contributions

Concept - O.Y., İ.B.; Design - O.Y., O.B.G.O.; Supervision - İ.B., M.C.G.; Resources - M.B., A.K.S.; Materials - O.B.G.O, M.B.; Data Collection and/or Processing - M.C.G., A.K.S.; Analysis and/or Interpretation - İ.B., O.B.G.O.; Literature Search - O.Y., M.B.; Writing Manuscript - O.B.G.O., A.K.S.; Critical Review - O.Y., M.C.G.

Conflict of Interest

There are no disclosed conflicts of interest for the writers.

Financial Disclosure

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