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Determination of BRCA1 and BRCA2 Gene Mutations in Patients at Risk of Breast and/or Ovarian Cancer by Next Generation Sequencing in the Isparta Region

Isparta Bölgesinde Meme ve/veya Over Kanseri Riski Taşıyan Hastalarda BRCA1 ve BRCA2 Gen Mutasyonlarının Yeni Nesil Dizileme Yöntemi ile Belirlenmesi

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ABSTRACT

Aim: The tumor suppressor genes BRCA1 and BRCA2 are used for screening and diagnosis of breast and/or ovarian cancers. BRCA1 / BRCA2 genes are associated with 20-25% of these diseases. The spectrum and prevalence of BRCA1 and BRCA2 gene mutations are different in each population. Determining the prevalence of pathogenic mutations in susceptibility genes and identifying new mutations are important for developing national health policies. In this retrospective study, mutations in the BRCA1 / 2 genes of patients who applied to Süleyman Demirel University Faculty of Medicine Medical Genetics Clinic between 2018-2020 with the suspicion of breast / or ovarian cancer in the Isparta region were investigated.

Material and Methods: In our study, BRCA1 and BRCA2 gene mutation analyzes were performed by Next Generation Sequencing (NGS) method in 76 patients who applied to the Medical Genetics Clinic with the indication of breast cancer, breast mass, family history, and ovarian cancer.

Results: As a result of our data analysis, 4 pathogenic, 1 likely pathogenic, 5 variants of unknown significance (VUS), and 11 benign variants were detected in the BRCA1 gene. Also, 3 pathogenic, 3 VUS, 11 benign, and 1 new variant were detected in the BRCA2 gene.

Conclusion: We believe that the results of our study will contribute to the determination of the prevalence of BRCA1 and BRCA2 gene mutations and the detection of breast and/or ovarian cancer.

Keywords: BRCA1 and BRCA2 gene, Breast and/or ovarian cancer, Next Generation Sequencing

ÖZ

Amaç: Tümör baskılayıcı genler BRCA1 ve BRCA2, meme ve / veya over kanserlerinde tarama ve teşhis için kullanılmaktadır. BRCA1 / BRCA2 genleri bu hastalıkların % 20-25'i ile ilişkilidir. BRCA1 ve BRCA2 gen mutasyonlarının spektrumu ve prevalansı her popülasyonda farklıdır. Duyarlılık genlerindeki patojenik mutasyonların prevalansını belirlemek ve yeni mutasyonları tanımlamak ulusal sağlık politikaları geliştirmek için önemlidir. Bu retrospektif çalışmada, Isparta bölgesinde meme / veya over kanser şüphesi ile 2018-2020 yılları arasında Süleyman Demirel Üniversitesi Tıp Fakültesi Tıbbi Genetik Kliniği'ne başvuran hastaların BRCA1/2 genlerindeki mutasyonlar araştırılmıştır.

Gereç ve Yöntemler: Çalışmamızda meme kanseri, memede kitle, aile öyküsü ve over kanseri endikasyonu ile Tıbbi Genetik Kliniğine başvuran 76 hastanın Yeni Nesil Dizileme (NGS) yöntemi ile BRCA1 ve BRCA2 gen mutasyon analizleri yapılmıştır.

Bulgular: Verileri değerlendirmelerimiz sonucunda, BRCA1 geninde 4 patojenik, 1 muhtemel patojenik, 5 önemi bilinmeyen varyant (VUS) ve 11 benign varyant tespit edildi. Ayrıca BRCA2 geninde 3 patojenik, 3 VUS, 11 benign ve 1 yeni varyant tespit edildi.

Sonuç: Çalışmamızın sonucunda elde ettiğimiz verilerin BRCA1 ve BRCA2 gen mutasyonlarının prevalansının belirlenmesine ve meme ve / veya over kanserinin saptanmasına katkıda bulunacağına inanıyoruz.

Anahtar Sözcükler: BRCA1 ve BRCA2 gen, Meme ve/veya over kanseri, Yeni nesil dizileme

INTRODUCTION

Breast cancer is the most common cancer type seen in women all over the world and in our country (1). The prevalence of breast cancer in women in the world is 43.1 / 100,000 and it is 7.32 / 100,000 in Turkish women (2, 3). Ovarian cancer is the second most common gynecological cancer and is known as the deadliest gynecological cancer (4). According to the Turkey Statistical Institute data from 2009, the incidence of ovarian cancer in women in Turkey was reported to be 3.9% (5). The number of people who get both types of cancer and die is increasing every year.

Some factors such as age, gender, diet, reproductive history, hormone use, exposure to radiation, obesity, lack of breastfeeding, family history of breast cancer, and genetic predisposition have been found to increase the risk of breast cancer (6, 7). It has been demonstrated that the rate of genetic predisposition in breast and ovarian cancers is seen in a few generations in 15-20% of all cases (5). BRCA1 gene 17q12-21 and BRCA2 gene are located on chromosome regions 13q12-13, and germline mutations in these genes increase susceptibility to breast and/or ovarian cancer (8, 9). The germline mutations that occur in BRCA1 and BRCA2 tumor suppressor genes are inherited autosomal dominantly and are linked to hereditary breast and ovarian cancer (HBOC) (10). Detecting mutations in BRCA1 and BRCA2 tumor suppressor genes has become faster and easier thanks to the new generation sequencing technology. As a result of the studies conducted to date, 2987 germline pathogenic or possible pathogenic variants in the BRCA1 gene and 3407 pathogenic or possible pathogenic variants in the BRCA2 gene were specified in the Clinvar database. In addition to the recognized pathogenic or likely pathogenic variants, a large number of variants are classified as unknown significance (VUS). The rate of VUS variants is influenced by regional differences and the knowledge of common polymorphisms in a national population database. In addition, since the genome database of the Turkish population has not been completed yet, it could not be used in our study. The presence of inherited BRCA1 and BRCA2 gene mutations varies widely between populations. Investigations have shown that such dominant mutations in these genes are the 5382insC and the 185delAG in BRCA1 and the 6174delT in BRCA2 whereas the 5382insC in exon 20 of BRCA1 is one of the most common mutations in Central and Eastern Europeans (2, 11, 12). This exon also contains the 5331G>A BRCA1 mutation recently shown to be a founder mutation in Greek Europeans (13). The 185delAG was also observed in non-Ashkenazi Jews and non-Jewish individuals from several ethnic backgrounds (14-17).

As a result of the studies you have done above, it has been determined that BRCA gene mutations show ethnic and regional differences. Therefore, studies are needed to better understand the mutations that occur in BRCA1 and BRCA2 genes and to predict cancer risk in Turkish population.

MATERIAL and METHODS

Sample Collection

5 ml peripheral blood EDTA tubes were included in the study to detect BRCA1 and BRCA2 whole gene mutations from individuals who were diagnosed with breast and/or ovarian cancer, had a breast mass or family history, and were referred to the Medical Genetics outpatient clinic. DNA isolation was performed without waiting for the samples.

DNA Isolation

DNA isolation was done from patients' peripheral blood samples. Spin column-based extraction was performed on a MagPurix apparatus containing the MagPurix® Blood DNA Extraction Kit 200 (Zinexts Life Science Corp., Taiwan) following the manufacturer's instructions. After DNA extraction in all samples was stored at -20 ° C. Before the analysis, the DNA concentration was determined by Qubit fluorometer.

Next-Generation Sequencing (NGS)

Targeted (target regions in BRCA1 and BRCA2 genes) Oncomine BRCA1 and BRCA2 panels containing 167 base pairs (bp) were used in 3 primer pools for NGS analysis (Life Technologies, USA).

Multiplex PCR was performed using 50-100 ng genomic DNA with a premixed primer pool and Oncomine HiFi Master mix. PCR conditions, according to the manufacturer's protocol; 2 minutes. 99 ° C, 15 sec 99 ° C, 4 min 60 ° C (19 cycles) and a maximum of 16 hours at 10 ° C in the final. The PCR amplicons were treated with 2 IL FuPa reagent for 10 minutes, then treated with 60 ° C for 10 minutes at

50 ° C, 55 ° C for 10 minutes, and then for 20 minutes. The amplicons were designed for 30 minutes at 22 minutes and then at 72 ° C for 20 minutes.

The primary sequences were then partially cleaved, adapters, and barcodes were ligated as described in the Amplicon Lara Ion AmpliSeq library preparation protocol. Each library is marked with a unique adapter provided in Ion Xpress Barcode Adapters 1 to 16 Kit (Life Technologies). Purified libraries were measured using the AMPure ™ XP Reagent kit, diluted to approximately 100 pmol / L, and combined in an equimolar ratio. The enriched preparations used freshly prepared library stock dilutions on the same day for the preparation of template-positive ion sphere particles. The automated protocols were performed according to the version of the manual and using the 200-bp chemical kits for the Ion OneTouch 2 System and the Ion OneTouch ES Instrument (Carlsbad/USA).

Data Analysis

The sequence data were evaluated using the standard Ion Torrent SuiteTM Software running on the Torrent Server. The raw signal data were analyzed using Torrent SuiteTM version 5.10. The analysis included a reference to the human genome 19 (h19), removal of PCR duplications, control of mapping quality, adapter trimming, evaluation of quality score, coverage analysis, and variant nomenclature. Coverage analysis and variant nomenclature were evaluated using Torrent Variant Caller plugin software on Torrent Server. Following data analysis, annotation of single nucleotide variants, insertion, deletion, and junction changes was performed by the Ion ReporterTM Server System, which identifies unnamed mutations. The sequence data were visually confirmed with the Integrative Genomics Viewer (IGV) and any sequence alignment or variant naming error artifact was discarded. Non-anonymous mutations were disclosed using ClinVar and VarSome (18).

RESULTS

Between 2018-2020, the data of individuals who were diagnosed with breast and/or ovarian cancer, breast mass, or family history, who applied to the Medical Genetics Clinic of Süleyman Demirel University Faculty of Medicine, were evaluated. The results of 76 patients with mutations in the BRCA1 and BRCA 2 genes were included in the study and were evaluated.

The clinical and demographic characteristics of 76 patients screened for BRCA1 and BRCA2 gene mutations are shown in table 1. According to the clinical characteristics of the patients, breast cancer, breast mass, family history of cancer, and ovarian cancer were determined (Table 1).

As a result of our assessment, BRCA1 gene mutation data analysis revealed 4 pathogenic, 1 likely pathogenic, 5 uncertain variant (VUS), and 11 benign variants (Table 2). Besides, as a result of BRCA2 gene mutation data analysis, 3 pathogenic, 3 uncertain variants (VUS), 11 benign variants, and 1 Novel variant (Table 3).

We evaluated BRCA1 and BRCA2 mutation analysis results in terms of breast cancer, breast mass, family history, and ovarian cancer. According to the results obtained in the BRCA1 gene; breast cancer patients; 2 likely pathogenic and 1 VUS, 2 pathogenic, breast mass; 1 VUS, family history; 2 likely pathogenic, 4 VUS 1 pathogenic, ovarian cancer; 1 VUS. Also, according to the results obtained in the BRCA2 gene; breast cancer patients; 2 likely pathogenic, 1 VUS and 3 pathogenic and 1 Novel variant, breast mass; 1 VUS, ovarian cancer; 1 VUS (Table 4).

DISCUSSION

Our aim in this study was to determine the distribution of mutations in BRCA1 and BRCA2 genes and contribute to the prediction of cancer in the Turkish population. Also, the patients were grouped according to breast mass, family history, and ovarian cancer indications, and the distribution of BRCA1 and BRCA2 gene mutations were determined.

A wide range of variation has been reported for BRCA1 and BRCA2 gene mutations in different populations. As a result of the studies, it was determined that the most common BRCA1 gene mutation in all societies was 5382insC (c.5266dupC) (19). It has been determined that this mutation is seen especially in Ashkenazi Jewish and Russian populations (20). It is also common in European countries, but it has been reported that it is rare in Asia and America (21). Also, c.185delAG in the BRCA1 gene is common in the Ashkenazi Jewish, Asia, American, Africa, and European populations. c.6174delT in the BRCA2 gene is common in the Ashkenazi Jewish. BRCA1:c.5266dupC has also been found to be one of the most common mutations in many countries (2). BRCA1: c.2800C>T and BRCA2: c.5969delA are the second most common mutations. We could not detect any of these mutations in our study. In Spain, the c.5123C> A mutation in the BRCA1 gene is reported as a common mutation (22). In our study, we detected this mutation in a Turkish population (Table 2).

Table 1: Demographic characteristics of patients with mutations detected according to their indications

Indication	Patient Number (%)	Age (Mean±SD)
Breast cancer	42 (55.3)	47.2±12.6
Mass in the breast	14 (18.4)	39.9±15.2
Family history	14 (18.4)	44.6±14.9
Over cancer	6 (7.9)	46.6±15.6
Total	76 (100)	45.4±13.8

Table 2: Mutations in the BRCA1 gene in patients

	Gene	Coding	Predicted effect	RS number	Type	ClinVar
1	BRCA1	c.3113A>G	p.Glu1038Gly	rs16941	SNV	Benign
2	BRCA1	c.3548A>G	p.Lys1183Arg	rs16942	SNV	Benign
3	BRCA1	c.2612C>T	p.Pro871Leu	rs799917	SNV	Benign
4	BRCA1	c.4900A>G	p.Ser1634Gly	rs1799966	SNV	Benign
5	BRCA1	c.2077G>A	p.Asp693Asn	rs4986850	SNV	Benign
6	BRCA1	c.1067A>G	p.Gln356Arg	rs1799950	SNV	Benign
7	BRCA1	c.4837A>G	p.Ser1613Gly	rs1799966	SNV	Benign
8	BRCA1	c.4946T>C	p.Met1649Thr	rs4986854	SNV	Benign
9	BRCA1	c.3119G>A	p.Ser1040Asn	rs4986852	SNV	Benign
10	BRCA1	c.1865C>T	p.Ala622Val	rs56039126	SNV	Benign
11	BRCA1	c.4883T>C	p.Met1628Thr	rs4986854	SNV	Benign
12	BRCA1	c.4417T>C	p.Ser1473Pro	rs398122686	SNV	VUS
13	BRCA1	c.4039A>G	p.Arg1347Gly	rs28897689	SNV	Likely pathogenic
14	BRCA1	c.2959A>T	p.Lys987Ter	rs878854941	SNV	Pathogenic
15	BRCA1	c.2685_2686delAA	p.Pro897fs	rs80357636	FS	Pathogenic
16	BRCA1	c.391A>T	p.Arg131Ter	rs80357207	SNV	Pathogenic
17	BRCA1	c.3955G>A	p.Gly1319Ser	rs431825403	SNV	VUS
18	BRCA1	c.4366A>G	p.T1456A	rs786201835	SNV	VUS
19	BRCA1	c.3784T>C	p.S1262P	rs1011096937	SNV	VUS
20	BRCA1	c.1747A>G	p.K583E	rs80356928	SNV	VUS
21	BRCA1	c.5123C>A	p.A1708E	rs28897696	SNV	Pathogenic

fs: Frameshift, **SNV:** Single-nucleotide variant, **DEL:** Deletion, **RS Number:** Mutation type according to the Human Genome Variant Society (HGVS) nomenclature, **VUS:** Uncertain variant

Table 3: Mutations in the BRCA2 gene in patients

	Gene	Coding	Predicted effect	RS number	Type	ClinVar
1	BRCA2	c.1114A>C	p.Asn372His	rs144848	SNV	Benign
2	BRCA2	c.2971A>G	p.Asn991Asp	rs1799944	SNV	Benign
3	BRCA2	c.5744C>T	p.Thr1915Met	rs4987117	SNV	Benign
4	BRCA2	c.125A>G	p.Tyr42Cys	rs4987046	SNV	Benign
5	BRCA2	c.9976A>T	p.Lys3326Te	rs11571833	SNV	Benign
6	BRCA2	c.5312G>A	p.Gly1771Asp	rs80358755	SNV	Benign
7	BRCA2	c.5590G>A	p.Asp1864Asn	rs587781536	SNV	VUS
8	BRCA2	c.2951A>G	p.Glu984Gly	rs767964776	SNV	VUS
9	BRCA2	c.6172T>A	p.Phe2058Ile	rs80358857	SNV	VUS
10	BRCA2	c.10234A>G	p.Ile3412Val	rs1801426	SNV	Benign
11	BRCA2	c.865A>C	p.Asn289His	rs766173	SNV	Benign
12	BRCA2	c.1054T>C	p.Tyr352His	rs542343726	SNV	Benign
13	BRCA2	c.7544C>T	p.Thr2515Ile	rs28897744	SNV	Benign
14	BRCA2	c.9018C>G	p.Tyr3006Ter	rs80359154	SNV	Pathogenic
15	BRCA2	c.8395delA	p.Arg2799fs	rs80359709	fs	Pathogenic
16	BRCA2	c.4258G>T	p.Asp1420Tyr	rs28897727	SNV	Benign
17	BRCA2	c.3751_3752dupA	p.Thr1251fs	rs397507683	fs	Pathogenic
18	BRCA2	c.3719_3720delTG	p.L1240X	-	DEL	Novel varyant

fs: Frameshift, **SNV:** Single-nucleotide variant, **DEL:** Deletion, **RS Number:** Mutation type according to the Human Genome Variant Society (HGVS) nomenclature, **VUS:** Uncertain variant

Table 4: Likely pathogenic, VUS (Variant of uncertain significance) and pathogenic variants in BRCA1 and BRCA2 genes in patients with breast cancer, mass in the breast, family history, and over cancer

Clinical Characteristic	Gene	Likely pathogenic	VUS	Pathogenic	Novel Varyant
Breast cancer	BRCA1	c.4039A>G p.Arg1347Gly (rs28897689) c.3955G>A p.Gly1319Ser (rs431825403)	c.4417T>C p.Ser1473Pro (rs398122686)	c.2959A>T p.Lys987Ter (rs878854941) c.391A>T p.Arg131Ter (rs80357207)	-
	BRCA2	c.865A>C p.Asn289His (rs766173) c.2951A>G p.Glu984Gly (rs767964776	c.5590G>A p.Asp1864Asn (rs587781536)	c.8395delA p.Arg2799fs (rs80359709) c.9018C>G p.Tyr3006Ter (rs80359154) c.3751_3752dupA p.Thr1251fs (rs397507683)	c.3719_3720delTG p.L1240X
Mass in breast	BRCA1	-	c.4417T>C p.Ser1473Pro (rs398122686)	-	
	BRCA2	-	c.6172T>A p.Phe2058Ile (rs80358857)	-	
Family history	BRCA1	c.3955G>A p.G1319S (rs431825403) c.3784T>C p.S1262P (rs1011096937)	c.4417T>C p.Ser1473Pro (rs398122686) c.4366A>G p.T1456A (rs786201835) c.1747A>G p.K583E (rs80356928) c.3784T>C p.S1262P (rs1011096937)	c.5123C>A p.A1708E (rs28897696)	
	BRCA2	-	-	-	
Over cancer	BRCA1	-	c.4417T>C p.Ser1473Pro (rs398122686)	-	
	BRCA2	-	c.6172T>A p.Phe2058Ile (rs80358857)	-	

fs: Frameshift, **SNV:** Single-nucleotide variant, **DEL:** Deletion, **RS Number:** Mutation type according to the Human Genome Variant Society (HGVS) nomenclature, **VUS:** Uncertain variant

Common mutations in BRCA1 and BRCA2 genes in our study are shown in tables 2 and 3. From the data obtained as a result of the screening of the BRCA1 and BRCA2 genes in 1419 Turkish breast and ovarian cancer patients in 2019, we found that only the c.8395delA and c.3751_3752dupA pathological mutations in the BRCA2 gene were the same (23). Also, as a result of our analysis, we detected a c.3719_3720delTG Novel variant in the BRCA2 gene.

In conclusion, we think that by analyzing BRCA1 and BRCA2 gene mutations in our study, we will contribute to the determination of the prevalence of these mutations in the Turkish population.

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Author Contrubitons

All of the authors contributed to the design of the study, the collection of samples, the analysis, and the interpretation of data.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Ethical Approval

This study was approved by the Süleyman Demirel University Faculty of Medicine ethics committee with the date of 10.08.2020 and number 220.

Peer Review Process

Extremely peer-reviewed

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