

# Germline Screening of Cancer-Related Genes in Turkish Ovarian Cancer Patients

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## ABSTRACT

**Objective:** Ovarian cancer (OC) is one of the most fatal types of cancer and affects 1%-1.5% of women worldwide. The most common genes causing OC are the *BRCA1* and *BRCA2* genes. However, improvements in next-generation sequencing (NGS) technologies have allowed for screening of the various genes related to hereditary cancer syndromes. The aim of this study was to evaluate cancer-related gene variations among cases of ovarian cancer.

**Materials and Methods:** The study evaluated 63 cases that were referred to the Marmara University Pendik Training and Research Hospital Genetic Diseases Diagnostic Center between 2016-2021 with a diagnosis of OC for germline variations in 25 cancer-related genes using NGS. Large intragenic rearrangements of the *BRCA1* and *BRCA2* genes were screened using multiplex ligation-dependent probe amplification (MLPA).

**Results:** The study detected 12 distinct pathogenic variations in the *BRCA1*, *BRCA2*, *BRIP1*, and *RAD50* genes in 13 OC cases. Four of the 13 cases involved copy number variations that included at least one exon of the *BRCA1* gene.

**Conclusion:** This study detected pathogenic *BRCA1* variations to be the leading cause of hereditary OC. The study showed just screening for *BRCA1* to reveal the underlying hereditary defect in 76.9% of the cases, which seems higher compared to literature. More studies involving larger cohorts are necessary to figure out the exact frequency of *BRCA1* variations in Turkish OC cases.

**Keywords:** Ovarian cancer, hereditary cancer syndromes, germline variation

## INTRODUCTION

Ovarian cancer (OC) is one of the leading causes of cancer-related deaths worldwide among women. Every year, 240,000 women are diagnosed with OC, making it the seventh most common cancer globally. OC is frequently diagnosed in the later stages of the disease and is known as the most fatal gynecologic cancer with a five-year survival rate of less than 45% (1, 2).

Germline predisposition is one of the most significant risk factors for developing OC (3). A germline pathogenic

variation is detected in cancer-related genes in approximately 23% of OC cases (4). *BRCA1* and *BRCA2* are the most common genes associated with hereditary ovarian cancer (5), with the worldwide population of women having a 1.8% lifetime risk for ovarian cancer. However, this risk increases up to 15%-45% for germline *BRCA1* pathogenic variant carriers, and 10%-20% for *BRCA2* pathogenic variant carriers (6). Among all hereditary OC patients, 15%-35% of pathogenic variations may be present in other tumor suppressor genes or oncogenes including mismatch repair (MMR) genes, *TP53*, *ATM*, *CHEK2*, *PALB2*, *RAD50*, and *BRIP1* (5, 7). Identifying the underlying molecular defects in ovarian

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cancer is an important approach for the medical management of patients and guidance regarding treatment options, and this study aimed to reveal the relationship between genetic variations and clinical outcomes.

## MATERIALS AND METHODS

### Patients Data

The study involved 63 patients who were referred to the medical genetics department with a diagnosis of OC between 2016-2021 and has obtained approval from the institutional review board with the protocol number 09.2020.751. Informed consent was obtained from all patients during the face-to-face interviews. The patients were evaluated in terms of age of diagnosis, clinical outcomes, and family history. CA-125 levels were obtained from their patient follow-up documents at the time of diagnosis.

### Genetic Tests

DNA isolation from peripheral blood samples was performed using the QIAamp DNA Mini Kit (Qiagen, MD, USA). The *BRCA1* and *BRCA2* genes were amplified using the Multiplicom BRCA Master Dx (Agilent, CA, USA). Copy number variations (CNVs) in the *BRCA1* and *BRCA2* genes were screened using the SALSA multiplex ligation-dependent probe amplification (MLPA) Probemix P002 BRCA1 and P045 BRCA/CHEK2 kits (MRC Holland, Amsterdam, the Netherlands). The 25 genes associated with cancer predisposition (i.e., *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *FAM175A*, *MRE11A*, *NBN*, *PALB2*, *PIK3CA*, *RAD50*, *RAD51C*, *RAD51D*, *TP53*, *XRCC2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *MUTYH*, *APC*, *PTEN*, and *STK11*) were amplified using the Multiplicom BRCA Hereditary Cancer MASTR Plus kit (Agilent, CA, USA). Sequencing was performed on the Illumina NextSeq platform (Illumina Inc., San Diego, CA, USA). The obtained data have been analyzed in the analysis program Sophia DDM (Sophia Genetic Inc. Boston, MA 02116, USA). For the confirmation and segregation analyses of the detected variants, the target region was replicated with the designed primers and then sequenced with the ABI Prism 3500 Genetic Analyzer (Thermo Fisher Scientific, MA, USA) device using the Sanger sequencing method. Human reference genome Hg 19 was used for variant annotation and evaluated according to the American College of Medical Genetics and Genomics (ACMG) criteria (8).

### Statistical Analysis

Data were evaluated via Microsoft Excel for Mac (version 15.33) application. Mean ages and percentage values were obtained using this software.

## RESULTS

Between 2016-2021, 63 ovarian cancer cases were referred to the medical genetics department for genetic testing. These patients' ages ranged between 24-83, with the age at diagnosis ranging from 22-83 and a median age of diagnosis of 50 years. Two (3%) cases involved bilateral ovarian cancer, while three (4.7%) cases also had a history of breast cancer. Among the 63 cases, 48 (76%) reported at least one cancer case among family

members, with 31 being first-degree, 13 being second-degree, and four being third-degree relatives. At least one family member had also been diagnosed with ovarian cancer in 17 (26.9%) of the cases, while 13 (20%) cases also had at least one family member who suffered from breast cancer.

Other cancer types such as gastrointestinal tract, lung, and endometrium cancers were reported for family members in 18 (28%) of the cases; these cases also showed no family history of ovarian or breast cancer. In 15 (23.8%) cases, no family history was found for any kind of cancer.

Firstly, the *BRCA1/2* genes were evaluated for single nucleotide variations (SNVs) and CNVs, with a pathogenic variation related to hereditary breast/ovarian cancer being detected in 11 (17%) patients, 10 of the 11 variants were found in the *BRCA1* gene and one of the 11 variant was found in the *BRCA2* gene. In three cases, two missense mutations, one nonsense mutation, and two frameshift mutations in the *BRCA1* gene were detected. In four cases, the MLPA revealed three distinct intragenic deletions and one duplication. No variations were detected in the related exons or adjacent sequences within at least 20 base pairs in the introns. A frameshift *BRCA2* variation be detected in only one case.

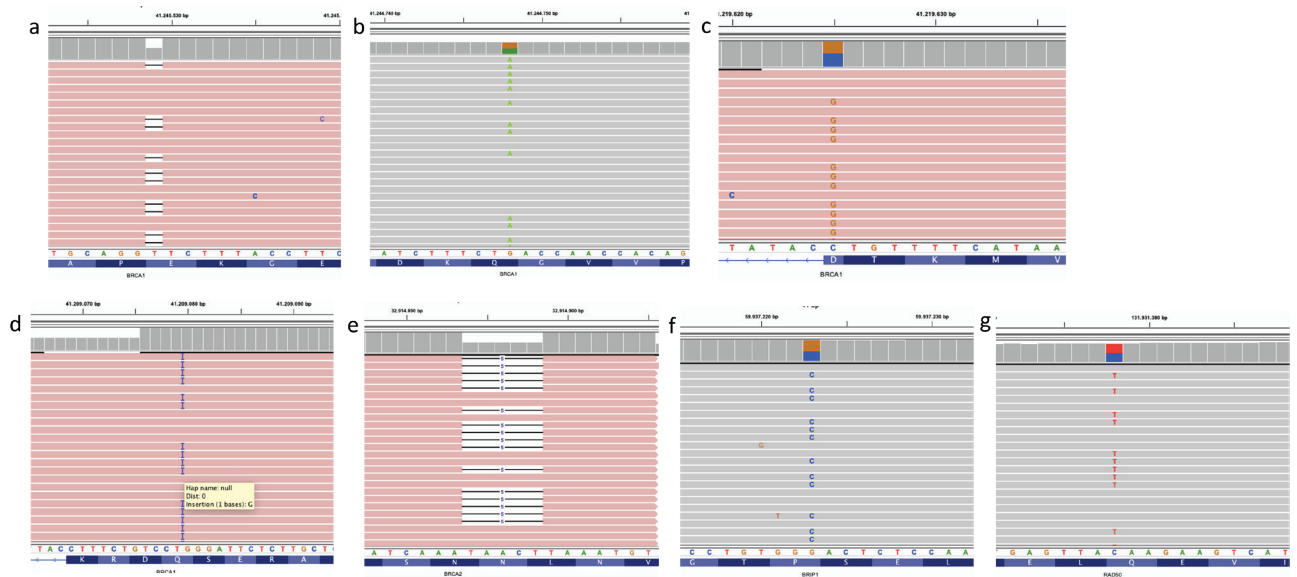
Non-BRCA cases were screened for 25 breast cancer-causing genes. Among 52 cases, only two (2.8%) cases, pathogenic variations were detected in the *BRIP1* and *RAD50* genes. The *BRIP1* c.139C>G (p.Pro47Ala) variation was detected in a 55 year-old OC patient who had multiple family members diagnosed with breast and/or ovarian cancer. The *RAD50* c.2083C>T (p.Gln695\*) variation causing a truncated protein was detected in a 28-year-old OC patient with no records in the ClinVar or Human Gene Mutation Database (HGMD). According to ACMG criteria, this variation is predicted to be deleterious. She had an aunt who died at the age of 60 from skin cancer, but no further data was available regarding her cancer histopathology or clinical outcome. The CNVs analyses of these 25 genes using the Sophia DDM CNV detection algorithm detected no copy number variations; however, the study was not able to screen CNVs using MLPA. This case was also reported in a previous study (9) evaluating hereditary cancer cases independent of cancer type. Table 1 specifies all pathogenic variations and characteristics of the patients carrying pathogenic variations, Figure 1 presents the visualizations from the Integrative Genomics Viewer (IGV), and Figure 2 shows the data from the MLPA.

A positive family history was present in 11 of 13 (84%) cases involving a pathogenic variation, with four reported ovarian cancer diagnoses in a first-degree relative, three reported breast cancer cases in first- and second-degree relatives, and three cases reporting other types of cancers including gastrointestinal, lung, and endometrial cancers in more than two relatives.

In six cases, the study detected six variations in the *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, and *CDH1* genes that were classified as "variant of uncertain significance" (VUS) according to the ACMG criteria (Table 2; Figure 3).

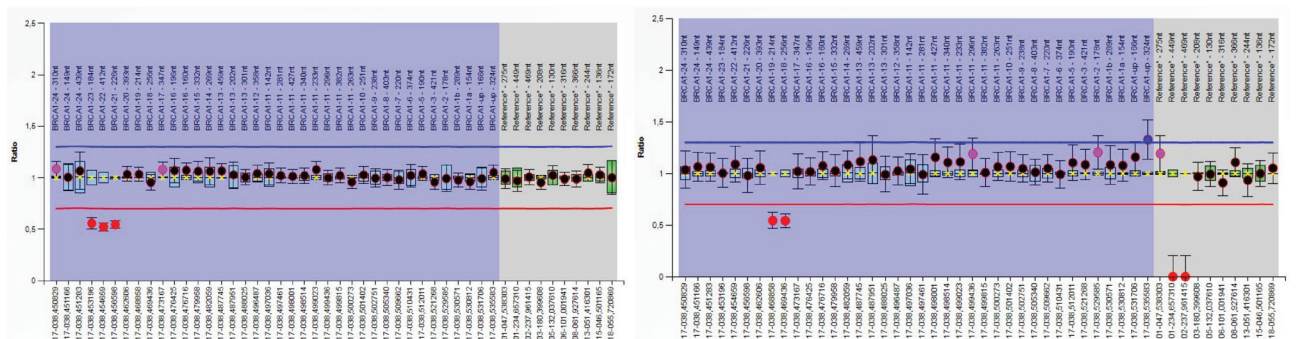
**Table 1.** Clinical features and molecular findings of ovarian cancer cases having pathogenic/likely pathogenic variants.

Age at Diagnosis	Clinical Presentation	Family History	Gene (Transcript)	Variation	Coding Consequence	HGMD
45	Unilateral Ovarian Ca	-	<i>BRCA1</i> (NM_007294)	c.181T>G (p.Cys61Gly)	Missense	CM940172-DM (Breast cancer)
34	Unilateral Ovarian Ca	+ Pancreas Ca (Second degree relative)	<i>BRCA1</i> (NM_007294)	c.2019delA (p.Glu673Aspfs*28)	Frameshift	CD021407-DM (Ovarian cancer)
57	Unilateral Ovarian Ca	-	<i>BRCA1</i> (NM_007294)	c.2800C>T (p.Gln934*)	Nonsense	CM004607-DM (Ovarian cancer)
50	Unilateral Ovarian Ca	+ Breast and Ovarian ca (First and second degree relative)	<i>BRCA1</i> (NM_007294)	c.5074G>C (p.Asp1692His)	Missense	CM129092-DM? (Breast cancer)
47	Bilateral Ovarian Ca+ Breast Ca	+ Breast and Ovarian ca (First degree relative)	<i>BRCA1</i> (NM_007294)	c.5266dupC (p.Gln1756Profs*74)	Frameshift	CI941841-DM (Breast cancer)
56	Unilateral Ovarian Ca	+ Ovarian Ca (First degree relative)	<i>BRCA1</i> (NM_007294)	c.5266dupC (p.Gln1756Profs*74)	Frameshift	CI941841 (Breast cancer)
54	Unilateral Ovarian Ca	+ Breast Ca (First degree relative) Thyroid ca (Second Degree Relative)	<i>BRCA1</i> (NM_007294)	Exon 3-8 dup	CNV	CN025048-DM (Breast and/or ovarian cancer)
42	Unilateral Ovarian Ca+ Breast Ca	+ Breast Ca (First degree relative)	<i>BRCA1</i> (NM_007294)	EX 18-19 DEL	CNV	CG146559-DM (Breast cancer)
45	Unilateral Ovarian Ca	+ Breast Ca (First degree relative)	<i>BRCA1</i> (NM_007294)	EX21-23 DEL	CNV	CG052603-DM (Breast and/or ovarian cancer)
40	Unilateral Ovarian Ca+ Breast Ca	+ Endometrium Ca (First degree relative)	<i>BRCA1</i> (NM_007294)	Exon 24 del	CNV	CG146555-DM (Ovarian cancer)
50	Unilateral Ovarian Ca+ Breast Ca	+ Endometrium Ca (second degree relative)	<i>BRCA2</i> (NM_000059)	c.6405_6409del (p. Asn2135Lysfs*3)	Frameshift	CD972084-DM (Breast cancer)
55	Unilateral Ovarian Ca	+ Breast and Ovarian Ca (First Degree relative) Pancreas Ca (Second Degree Relative)	<i>BRIP1</i> (NM_032043)	c.139C>G (p.Pro47Ala)	Missense	CM014756-DM (Breast cancer)
28	Unilateral Ovarian Ca	+ Malign Melanoma (second degree relative)	<i>RAD50</i> (NM_005732)	c.2083C>T (p.Gln695*)	Nonsense	Novel



**Figure 1.** Integrative genomics viewer (IGV) visualizations of detected pathogenic variants.

- a) BRCA1 heterozygous c.2019delA (p.Glu673Aspfs\*28),
- b) BRCA1 heterozygous c.2800C>T (p.Gln934\*),
- c) BRCA1 heterozygous c.5074G>C (p. Asp1692His),
- d) BRCA1 heterozygous c.5266dupC (p.Gln1756Profs\*74),
- e) BRCA2 heterozygous c.6405\_6409del (p. Asn2135Lysfs\*3),
- f) BRIP1 heterozygous c.139C>G (p.Pro47Ala),
- g) RAD50 heterozygous c.2083C>T (p.Gln695\*)



**Figure 2.** Multiplex Ligation-Dependent Probe Amplification (MLPA) data of copy number variants.

- a) BRCA1 heterozygous exon 21-23 deletion,
- b) BRCA1 heterozygous exon 18-19 deletion.

## DISCUSSION

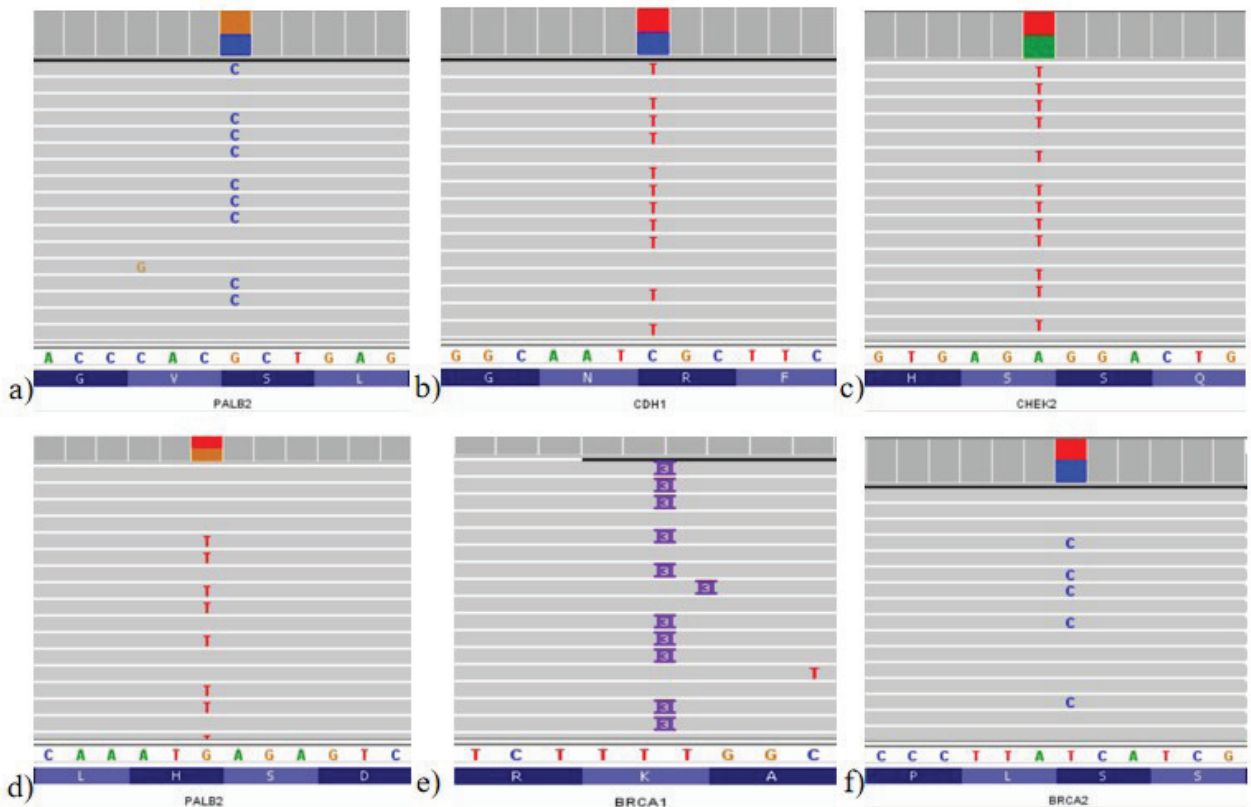
This study has investigated 63 ovarian cancer patients for germline variations among 25 cancer-related genes. A family history of ovarian cancer and certain other neoplasms including breast, colorectal, and endometrium cancers are also well-known risk factors for OC (10). The current study reported 49% of cases ( $n = 31$ ) to have at least one first-degree relative with

a history of cancer. This finding is consistent with a previous study which had reported as 40% in a large cohort (11). The current study also evaluated family history up to third-degree relations, which observed this ratio increase up to 76% ( $n = 48$ ). Although family history was not an inclusion criterion for this study, this high rate is thought to be due to the tendency of clinicians to refer patients to genetics department when a family history of cancer is already present.

**Table 2.** The VUSs detected in the study.

Age at diagnosis	Gene/ Transcript	Variation	Frequency in our Inhouse database	MAF (GnomAD)	Mutation Taster	DANN	GERP	ClinVar/ HGMD	dbSNP
36	<i>PALB2</i> NM_024675	c.3306C>G (p.Ser1102Arg)	0.00005	0.000007953	Polymorphism	0.7592	6.1399	VUS/DM? (Breast cancer)	rs515726112
55	<i>PALB2</i> NM_024675	c.3508C>A p.His1170Asn	0,00005	-	Polymorphism	0.9857	5.9	VUS/-	rs200283306
60	<i>CDH1</i> NM_004360	c.2602C>T p.(Arg868Cys)	0.00006	-	Disease Causing	0.9984	6.17	VUS/-	rs864622630
50	<i>CHEK2</i> NM_001005735	c.157T>A (p.Ser53Thr)	0.00005	0.00004773	Disease Causing	0.9981	5.42	VUS/-	rs371657037
53	<i>BRCA1</i> NM_007294	c.401_403dupCCA (p.Ala134_ Lys135insThr)	0.00003	-	Polymorphism	-	5.32	VUS/-	rs1555596338
30	<i>BRCA2</i> NM_000059	c.8416T>C (p.Ser2806Pro)	0.00003	-	Disease Causing	0.9989	5.19	VUS/DM (Prostate cancer)	rs1280487930

VUS: Variant of uncertain significance, MAF: Minor allele frequency, DANN: Deep neural network variant predictor, GERP: Genomic evolutionary rate profiling, DM: Disease mutation.



**Figure 3.** Integrative genomics viewer (IGV) visualizations of detected VUS.

- a) PALB2 heterozygous c.3306C>G (p.Ser1102Arg),
- b) CDH1 heterozygous c.2602C>T (p.Arg868Cys),
- c) CHEK2 heterozygous c.157T>A (p.Ser53Thr),
- d) PALB2 heterozygous c.3508C>A (p.His1170Asn),
- e) BRCA1 heterozygous c.401\_403dupCCA (p.Ala134\_Lys135insThr),
- f) BRCA2 heterozygous c.8416T>C (p.Ser2806Pro).

Among the 48 family-history positive patients, 30 (62.5%) reported breast and/or ovarian cancer in other family members, which suggests that hereditary breast and ovarian cancer syndrome (HBOCS) is related to the *BRCA1* and *BRCA2* genes. Germline pathogenic variations in *BRCA1* and *BRCA2* have also been detected in about 65%-85% of hereditary OC as its most common cause (5). Based on these data, the study screened the *BRCA1* and *BRCA2* genes for pathogenic variations as a first step. Pathogenic *BRCA1* and *BRCA2* variations are known to be related with HBOCS and were detected in a total of 11 cases, with pathogenic *BRCA1* variations being detected in 10 (90.9%) cases diagnosed as HBOCS. Only one case saw a pathogenic *BRCA2* variation (c.6405\_6409del; p. Asn2135Lysfs\*3) was detected in only one case. The 1:10 ratio for *BRCA2:BRCA1* variations is an unexpected result, as variations have been reported as being one and a half to two times higher in *BRCA1* than in *BRCA2* with regard to ovarian cancer (5). The ratio in this study could not be explained through the ancestry of the population as a previous study (12) of 102 Turkish ovarian cancer patients contrarily detected this ratio to be 7:10. Although their study group had a predominance of non-familial cases, which is slightly different from the current study and its predominance of familial cases, the current study's data are not supportive enough to compare the penetrance of *BRCA* genes for ovarian cancer, as performing a segregation analysis was not possible here. However, another study (13) from Turkey involved 44 ovarian cancer patients, similar to the current study, and detected pathogenic *BRCA1* variations in 18 of the cases, while detecting only one patient with a *BRCA2* variation. The pathogenic variation detection rate of sequencing of whole exons and the deletion duplication analysis for *BRCA1* and *BRCA2* genes are known to respectively be around 90% and 10% in *BRCA*-related HBOCS. Maistro et al. (14) reported *BRCA1* rearrangements in two out of 100 OC cases, while Zhang et al.'s study (15) on 1,342 OC patients reported a gross deletion rate of 3.9% for all detected pathogenic variations in 0.5% of the cohort. This study detected CNVs in four out of 11 (36%) cases, all of which affected at least one exon of the *BRCA1* gene and corresponding to 6.3% of all the OC cases. This study speculates that the approximately 10x higher rate of gross deletion duplications may be due to the small number of patients included in the study. However, the largest cohort study screening large *BRCA1* rearrangements among a Turkish population including 667 OC patients detected 27 large genomic rearrangements, which corresponded to 4% of the cohort and 78% of the *BRCA1* pathogenic variation carriers (16). Because of the insufficient information regarding a methodology for SNV screening, the SNV detection rates from these two studies cannot be compared. However, these two studies do indicate a higher CNV detection rate in Turkish OC patients. Yazıcı et al.'s study (17) also reported a *BRCA1* rearrangement rate of 4% in ovarian cancer cases, which supports the previous statement.

Among the 52 non-*BRCA* cases, this study detected pathogenic variations in the *BRIP1* and *RAD50* genes of two cases. *BRIP1* encodes the *BRCA1*-associated C-terminal helicase 1 and

is one of the most commonly affected genes in non-*BRCA* OC patients, with approximately one-third of OC patients carrying a pathogenic variation in their *BRIP1* gene (18). The *BRIP1* c.139C>G (p.Pro47Ala) variation was reported previously and shown to result in complete loss of helicase activity (19). The case in the current study carrying the *BRIP1* c.139C>G (p.Pro47Ala) variant had been diagnosed at the age of 55 and had first- and second-degree relatives with breast and ovarian cancer. The study detected a novel variation in the *RAD50* gene (c.2083C>T; p.Gln695\*) in one case, and this is predicted as being a likely pathogenic variation related to the ACMG criteria. The patient in this case was one of the youngest in the study's cohort, with a diagnosis age of 28. Her aunt (father's sister) was the only other known cancer case in her family, with the aunt having been diagnosed with skin cancer and dying at the age of 60. The *RAD50* gene is a relatively rare one to be affected in OC patients, with Minion et al. reporting a 3% incidence rate of non-*BRCA* in OC cases (17). The *RAD50* gene encodes an essential protein that plays an important role in repairing DNA double-strand breaks, with biallelic variations being related to a Nijmegen breakage syndrome-like disorder (OMIM: #613078) that presents itself with dysmorphic features, growth retardation, and developmental delay (20).

*BRCA2* and *BRIP1* biallelic variations have been related to Fanconi anemia (21), with patients possessing monoallelic variations in the *BRCA2* and *BRIP1* genes having been evaluated with the related autosomal recessive disorders and no such history being reported in the families. However, segregation analysis and genetic counseling were planned for at risk family members.

## CONCLUSION

This study has evaluated 63 OC cases for underlying molecular deficiencies and detected the *BRCA1* gene as the most commonly affected gene in OC cases, with the *BRCA2*, *BRIP1*, and *RAD50* genes being the other ones in which germline cancer-related variations were detected. The high rate of CNVs in *BRCA1* indicates the sequencing of cancer predisposition genes to be insufficient for OC cases and the CNV analysis of genes (especially *BRCA1*) should be done as the second step in molecular analysis following the *BRCA1* sequencing. However, the widespread use of multigene panel tests and improvement of the CNV analysis algorithms in sequence analysis tools would help accelerate diagnostic processes. Additionally, countries with high consanguineous marriage rates such as Turkey will benefit by informing the families of patients to be aware that preconception and/or prenatal diagnostic opportunities through genetic counseling are very important with regard to these autosomal recessive conditions and that a family-oriented approach is a required.

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**Ethics Committee Approval:** This study was approved by the Clinical Research Ethics Committee of Marmara University Medical Faculty (24.07.2020-09.2020.751).

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Conception/Design of Study – E.A.A., C.A., B.B.G., A.İ.G., T.G.; Data Acquisition – E.A.A., C.A., B.B.G., A.İ.G., T.G.; Performing experiments – E.A.A., C.A., B.B.G., A.İ.G., T.G.; Data Analysis/ Interpretation – E.A.A., C.A., B.B.G., A.İ.G., T.G.; Statistical Analyses – E.A.A., C.A., B.B.G., A.İ.G., T.G.; Drafting Manuscript – E.A.A., C.A., B.B.G., A.İ.G., T.G.; Critical Revision of Manuscript – E.A.A., C.A., B.B.G., A.İ.G., T.G.; Final Approval and Accountability – E.A.A., C.A., B.B.G., A.İ.G., T.G.;

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