Original paper

Clinicopathological characteristics and *BRCA1/BRCA2* pathogenic variants of patients with breast cancer

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Although *BRCA* genes are well-known breast cancer genes, the clinicopathological features of breast cancer patients carrying *BRCA1/2* pathogenic variants have not been adequately defined. The goals of this study were to determine the distribution of *BRCA1/2* variants in the Turkish population and its correlation with clinicopathological features.

Clinical data of 151 women who underwent *BRCA1/2* gene testing at Mersin University Medical Faculty Hospital between 2016 and 2019 were retrospectively analyzed. *BRCA1/2* variants were detected as pathogenic ($n = 11$), variants of uncertain significance ($n = 5$), likely benign ($n = 3$), and benign ($n = 81$) in breast cancer cases.

The *BRCA1/2* pathogenic variant carriers had a higher histological grade, rate of triple-negative type, Ki-67 proliferation index, and rate of no special type carcinoma than the group without mutation ($p = 0.03$, 0.01, 0.04, and 0.02 respectively).

We analyzed the distribution of variants we detected in women living in our region and found that pathogenic variants in patients with breast cancer were associated with high histological grade, triple-negative type, high Ki-67 proliferation index, and histological type. Studies in diverse populations are needed to establish a clinicopathological relationship with variants more easily.

Key words: *BRCA*, breast cancer, histological grade, Ki-67 proliferation index, triple-negative status, variant.

Introduction

Breast cancer constitutes an important public health problem with an estimated 1.7 million new cases worldwide each year [1]. Although the mortality rate has decreased with the improvements in screening, early diagnosis, and treatment in recent years, it still continues to be an important cause of death [2, 3].

It is thought that 20–30% of breast cancer occurs due to modifiable risk factors and 5–10% of it occurs due to genetic mutations and family history [4]. Chronic alcohol consumption, smoking, parity, not breastfeeding, exposure to estrogens and androgens, low physical activity, high-fat diet, and obesity are modifiable risk factors for breast cancer [1, 5, 6]. Gender, age, race, family history, genetic characteristics, immunological biomarkers, and reproductive factors (early menarche and late menopause) are non-modifiable predisposing risk factors that contribute to the development of breast cancer [6]. Ninety percent of breast cancers occur sporadically with a mutation developing within tissue cells, and these somatic mutations are not transmitted from generation to generation. The remaining 10% of breast cancers are hereditary and can be passed on to the next generations [2]. BReast CAncer 1/2 (*BRCA1/2*) mutation carriers account for 22–30% of hereditary breast can-

cer cases [7]. Although the best-known genes that increase susceptibility to breast cancer are *BRCA1* and *BRCA2*, as the genome is further analyzed, associations between other genes and clinicopathological features of breast cancer are revealed. For instance, the relationship between STARD3 protein expression and clinicopathological features of breast cancer patients was investigated and it was suggested that STARD3 levels may serve as a marker in breast cancer [8].

The *BRCA1* gene is localized on chromosome 17 and has 22 coding exons [9]. The *BRCA2* gene is located on chromosome 13q12-q13 and contains 27 exons [10, 11]. *BRCA1* and *BRCA2* genes are tumor-suppressive genes, and mutations in these genes cause the formation of damaged or dysfunctional proteins [12]. To date, approximately 1,600 mutations in *BRCA1* and more than 1,800 in *BRCA2* have been identified, and most of them are frameshift mutations [13].

The occurrence of familial breast cancer has been associated with pathogenic variants of the *BRCA1/2* genes. The lifetime risk of developing breast cancer in women with the *BRCA1* pathogenic variant is approximately 65%, while this rate is 45% or lower in women with the *BRCA2* variant. Clinicopathological features of the *BRCA* pathogenic variant and sporadic breast cancers differ from each other, and clinicopathological features of the *BRCA1* pathogenic variant breast cancer and *BRCA2* pathogenic variant breast cancer also differ [13].

The distribution of *BRCA 1/2* variants differs between populations. This complicates the interpretation between variants and clinicopathological conditions of patients receiving genetic counseling. Therefore, in our study, we aimed to determine the incidence and distribution of BRCA1/2 variants in Turkish women and to investigate the clinicopathological features of breast cancer patients carrying BRCA1/2 pathogenic variants.

Material and methods

In our study, the files of individuals who applied to Mersin University Faculty of Medicine, Department of Medical Genetics in the period 2016–2019 and were requested to have *BRCA1* and *BRCA2* mutation tests were reviewed retrospectively. Ethics committee approval for the study was obtained from Mersin University Ethics Committee with the decision dated 2019 and numbered 367.

Women who were 18 years of age or greater, had genetic testing for the *BRCA* mutation, and were diagnosed with breast cancer, and healthy women with a first-degree relative diagnosed with breast cancer before the age of 50 were included in the study. Breast cancer patients who refused the *BRCA* mutation test and were diagnosed with another cancer before breast cancer and individuals less than 18 years of age were excluded from the study. Current classifications of detected copy number variations (CNVs) were checked using the databases Franklin by Genoox (https://franklin.genoox.com/clinical-db/home), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), and Decipher (http://decipher.sanger.ac.uk/). Age, gender, histological grade, histological types, immunohistochemical prognostic markers, molecular subtypes of tumors and Ki-67 proliferation index values of breast cancer patients were obtained from the electronic medical records. The histological tumor grade was evaluated according to tubule structure, number of mitosis and nuclear features and was scored between 1 and 3. The tumors are classified as grade 1 (well differentiated), score 3, 4, or 5; grade 2 (moderately differentiated), score 6 or 7; grade 3 (poorly differentiated), score 8 or 9. Estrogen receptor (ER) and progesterone receptor (PR) staining was performed using an internal positive control; those with a nuclear staining percentage ≥ 1% without background staining were considered positive, and those with a nuclear staining percentage < 1% were considered negative. Cases were classified according to their molecular features as Luminal A (ER-positive and/or PR-positive, human epidermal growth factor receptor 2 (HER2)-negative), Luminal B (ER-positive and/or PR-positive and HER2-positive), HER2-enriched (ER-negative, PR-negative, and HER2 amplified) and triple-negative breast cancer (TNBC; ER-negative, PR-negative, and HER2-negative) [14]. Patients were grouped as those with a threshold value of less than and over 20% for Ki-67 immunohistochemical staining.

Statistical analysis

In statistical evaluations, the multinomial logistic regression analysis test was used to compare prognostic and predictive factors, the χ^2 test was used to compare categorical variables, and $p < 0.05$ was considered significant.

Results

Demographics and clinico-pathological features of breast cancer patients are shown in Table I. Between 2016 and 2019, 151 individuals who applied to our genetics outpatient clinic were investigated in terms of *BRCA* gene variants. Healthy individuals (59 females, 1 male) for whom *BRCA* testing was requested had a history of breast cancer in first-degree relatives, especially before age 50. The mean age of healthy individuals was 48.5 ±6.81. The mean age at diagnosis of patients with breast cancer was 42.8 ±9.11, and the ages of these women were in the range 33–82 years.

The variant distributions of 151 cases included in our study are shown in Table II. Pathogenic variants were detected in 11 cases, variants of uncertain significance (VUS) in 5 cases, likely benign in 3 cases, and benign variant in 81 cases. No likely pathogenic variant was found. The percentage of *BRCA* pathogenic variants was 63.6% (11 of 7) in the *BRCA1* gene and 36.4% (11 of 4) in the *BRCA2* gene. The *BRCA1* pathogenic variant was found in 5 patients with breast cancer and 2 healthy individuals with an increased risk for breast cancer. Three breast cancer patients and 1 healthy individual with a familial history of breast cancer had the pathogenic variant in the *BRCA2* gene. The rate of VUS variants was 20% (5 of 1) in the *BRCA1* gene and 80% (5 of 4) in the *BRCA2* gene. The spectrum of pathogenic, VUS and likely benign variants comprised 8 frame-shift variants, 6 missense variants, 2 nonsense variants, 1 in-frame deletion and 1 intronic sequencing variant.

In Table III, the demographic and clinicopathological features of the patients are evaluated according to whether they had the *BRCA* pathogenic variant or not. Thirty-seven and a half percent of patients with breast cancer carrying the *BRCA* pathogenic variant were < 40 years of age or younger, 62.5% had a family history of breast cancer, and 50% had ER- and PR- status and invasive ductal carcinoma no special type (NST). There was no statistically significant relationship between groups with and without the *BRCA1/2* pathogenic variant in terms of age at diagnosis, HER receptor positivity, and family history ($p > 0.05$). The *BRCA1/2* carrier group had a higher histological grade, rate of triple-negative type, and Ki-67 proliferation index ($p = 0.03$, 0.01, and 0.04, respectively).

Discussion

Lifestyle changes are insufficient to reduce the risk of development of breast cancer in individuals with unchangeable risk factors. Bilateral risk-reducing mastectomy (BRRM) and salpingo-oophorectomy (BRRSO) surgical interventions are recommended prophylactically [2, 15, 16]. It has been shown that the risk of developing breast cancer in women carrying the *BRCA* mutation is reduced by 90% with prophylactic BRRM. It was found that the risk of ER-positive breast cancer decreased after BRRSO surgery [2]. In a study by Kauff *et al.* [17], it was suggested that risk-reducing salpingo-oophorectomy may protect against breast and gynecological cancers at different rates, even in those with *BRCA1* and *BRCA2* gene mutations, and that the cases should be evaluated by classifying them according to the specific gene mutation. Demand for BRCA1 and BRCA2 genetic testing has increased since the discovery that *BRCA1* and *BRCA2* genes are important in the clinical man-

Table I. Demographic and clinicopathologic features of patients

Groups	Patients, *n* (%)
Age	
≤ 40	36 (39.5)
41–50	40 (44)
≥ 51	15 (16.5)
Family history	
Yes	57 (62.6)
No	34 (37.4)
Tumor localization	
Left	37 (40.7)
Right	51 (56)
Bilateral	3 (3.3)
Histologic grade	
Grade 1	10 (11)
Grade 2	30 (33)
Grade 3	22 (24.2)
Unknown	29 (31.8)
Molecular phenotype	
Luminal A	26 (28.6)
Luminal B	20 (22)
Her2 +	8 (8.8)
Triple negative	8 (8.8)
Unknown	29 (31.8)
Histological subtype	
Invasive ductal carcinoma/NST	55 (60.4)
Invasive lobular carcinoma	5 (5.5)
Medullary carcinoma	4 (4.4)
Others	17 (18.7)
Unknown	10 (11)
ER +/–	
ER+	52 (57.1)
ER–	15 (16.5)
Unknown	24 (26.4)
PR +/–	
PR+	51 (56)
PR–	16 (17.6)
Unknown	24(26.4)
HER2 +/–	
HER2+	16 (17.6)
HER2–	49 (53.8)
Unknown	26 (28.6)
Ki-67	
< 20	25 (27.5)
≥ 20	42 (46.1)
Unknown	24 (26.4)

ER – estrogen receptor, HER2 – human epidermal growth factor receptor-2, NTS – invasive carcinoma with no special type, PR – progesterone receptor

Table II. Characteristics of *BRCA1* and *BRCA2* variants

Gene	Transcript ID	dbSNP ID	cDNA change/amino acid change	Consequence	Variant type	*N*
BRCA1	NM_007294.3	rs80357783	c.66dupA/ p.Glu23fs	Frameshift	Pathogenic	1
BRCA1	NM_007294.4	rs80357906	c.5266dup/ p.Gln1756fs	Frameshift	Pathogenic	1
BRCA1	NM_007294.4	rs80357801	c.1444_1447delATTA/ p.Leu481_Ile482insTER	Frameshift	Pathogenic	2
BRCA1	NM_007294.4	rs80357788	c.4163dupA/ p.Ser1389fs	Frameshift	Pathogenic	1
BRCA1	NM_007294.4	rs28897696	c.5123C>A/ p.Ala1708Glu	Missense	Pathogenic	1
BRCA1	NM_007294.4	rs80357223	c.2800C>T/ p.Gln934Ter	Nonsense	Pathogenic	1
BRCA2	NM_000059.3	rs80359374	c.3189_3192delGTCA/ p.Ser1064fs	Frameshift	Pathogenic	1
BRCA2	NM_000059.3	rs397507419	c.9097dupA/ p.Thr3033fs	Frameshift	Pathogenic	1
BRCA2	NM_000059.3	rs80359636	c.7069_7070delCT/ p.Leu2357fs	Frameshift	Pathogenic	1
BRCA2	NM_000059.4	rs80359102	c.8504C>G/ p.Ser2835Ter	Nonsense	Pathogenic	1
BRCA2	NM_000059.4	rs80358866	c.6290C>T/ p.Thr2097Met	Missense	Likely Benign	1
BRCA1	NM_007294.3	rs80358341	c.4063_4065delAAT/ p.Asn1355del	In-frame deletion	VUS	1
BRCA2	NM_000059.4	rs80359228	c.9586A>G/ p.Lys3196Glu	Missense	VUS	1
BRCA2	NM_000059.4	rs80358982	c.7559G>T/ p.Arg2520Leu	Missense	VUS	1
BRCA2	NM_000059.4	rs80358939	c.7088A>G/ p.Tyr2363Cys	Missense	VUS	1
BRCA2	NM_000059.4	rs28897708	c.1514T>C/ p.Ile505Thr	Missense	Likely benign	1
BRCA2	NM_000059.4	rs81002803	c.9502-12T>G/-	Intronic sequencing variant	Likely Benign	1
BRCA2	NM_000059.3	rs1555288478	c.9065_9073delGAGCTAACA/ p.Arg3022_Asn3024del	Frameshift	VUS	1

agement of women with breast or ovarian cancer and their family members [18]. Reporting of de novo variants in literature contributes to BRCA databases. Currently, nearly 9,000 pathogenic and possibly pathogenic variants and more than 10,000 VUS are known in the ClinVar database for the *BRCA1* and *BRCA2* genes, and this number is increasing every year (https://www.ncbi.nlm.nih.gov/clinvar/). It has been found that pathogenic and likely pathogenic variants increase the risk of developing breast cancer and ovarian cancer, even pancreatic carcinoma, prostate cancer, and melanoma [19–21]. Variants of uncertain significance, on the other hand, are a variant group that has a probability of being reclassified as pathogenic between 5% and 94.9% [18]. Accurate classification of genetic variants is required in order for the obtained genetic information to be usefully used and associated with the clinic [22]. New studies are needed to reclassify variants of unknown clinical significance in the future, to include novel variants in the literature, and to comprehensively evaluate the relationship between these variants and clinicopathology. Therefore, in our study, we investigated the distribution of *BRCA1/2* variants and the relationship between pathogenic variants and clinicopathology of patients with breast cancer living in Mersin Province in the Mediterranean region of Turkey.

Approximately 3% of breast cancers are caused by mutations in the *BRCA1/2* genes [12]. However, this rate rises to 21–30% in Jewish women diagnosed with breast cancer at the age of 40 [23]. In studies conducted in the cities of Istanbul and Bursa in Turkey, the frequency of *BRCA1/2* mutations in women with breast cancer was 19% and 4.98%, respectively [24, 25]. In the study conducted by Bisgin *et al*. [26] across Turkey, the frequency of cancer patients with *BRCA1/2* variants was the highest in the Central Anatolian region (62.28%), the lowest in the Eastern Anatolian region (12.9%), and the Mediterranean region had the frequency of 13.03%. The frequency of *BRCA* pathogenic variants of breast cancer patients in our study was 8.79%. Bisgin *et al*. [26] also studied the distribution of pathogenic and likely pathogenic variants in the *BRCA1/2* genes of clinically unaffected individuals and patients with breast cancer. They found that c.1444_1447delATTA, c.5266dupC, c.2800C > T, c.4327C > T and c.5123C > A pathogenic variants were common in the *BRCA1* gene and c.2765dupT, c.9097dupA, c.7689delC, c.3751dupA and c.4169delT pathogenic variants were common

Table III. Characteristics of patients with breast cancer carrying the *BRCA1/2* pathogenic variant

Parameters	*BRCA* non-carriers, *n* (%)	*BRCA1/2* carriers, *n* (%)	*p*-value
Age at diagnosis, years			
> 50	14 (16.9)	1 (12.5)	0.92
41–50	36 (43.4)	4 (50)	
≤ 40	33 (39.7)	3 (37.5)	
Family history			
No	31 (37.3)	3 (37.5)	0.63
Yes	52 (62.7)	5 (62.5)	
Histologic grade			
Grade1	10 (12)	0 (0)	0.03
Grade 2	29 (34.9)	1 (12.5)	
Grade 3	17 (20.5)	5 (62.5)	
Unknown	27 (32.6)	2 (25)	
Subtypes			
Luminal A	26 (31.3)	0 (0)	0.01
Luminal B	18 (21.7)	2 (25)	
HER2	8 (9.7)	0 (0)	
Triple negative	4 (4.8)	4 (50)	
Unknown	27 (32.5)	2 (25)	
Ki-67 status			
< 20	25 (30.1)	0 (0)	0.04
≥ 20	35 (42.2)	7 (87.5)	
Unknown	23 (27.7)	1 (12.5)	
HER2 +/–			
HER2–	43 (51.8)	6 (75)	0.67
HER2+	15 (18.1)	1 (12.5)	
Unknown	25 (30.1)	1 (12.5)	
PR +/–			
PR–	12 (14.5)	4 (50)	0.04
PR+	48 (57.8)	3 (37.5)	
Unknown	23 (27.7)	1 (12.5)	
ER +/–			
ER–	11 (13.3)	4 (50)	0.04
ER+	49 (59)	3 (37.5)	
Unknown	23 (27.7)	1 (12.5)	
Tumor histology			
NST	51 (61.5)	4 (50)	0.02
Medullar	2 (2.4)	2 (25)	
Lobular	5 (6)	0 (0)	
Others	16 (19.3)	1 (12.5)	
Unknown	9 (10.8)	1 (12.5)	

ER – estrogen receptor, HER2 – human epidermal growth factor receptor-2, NTS –invasive carcinoma with no special type, PR – progesterone receptor

in the *BRCA2* gene [26]. Similarly, we found pathogenic variants of c.5266dupC, c.1444_1447delATTA, c.5123C > A and c.2800C > T in our study. In addition, we detected the pathogenic variants of c.9097dupA, c.4163dupA and 5266dupC, which were detected in 2 other studies conducted in our population [25, 27]. The c.4063_4065delAAT, c.7088A > G, and c.9065_9073delGAGCTAACA VUS variants were observed in patients with breast cancer. By adding de novo variants to the data to be found in future studies, the distribution of variants in *BRCA* susceptibility genes will be determined and cancer risk estimation in the population will be performed.

Breast cancer in women with *BRCA1/2* mutations develops at an earlier age compared to sporadic cases [27]. In a study, the mean age at diagnosis of breast cancer was found to be 40 and 42.6 ($p = 0.02$) in *BRCA1* and *BRCA2* variants, respectively [28]. In another study, it was determined that most (75.6%) of the *BRCA1* mutation carriers were > 40 years old ($p = 0.021$) [29]. In other studies, no relationship was found between *BRCA1/2* status and age in breast cancer patients [24, 27, 30–32]. Similarly, we did not find a relationship between *BRCA1/2* status and age in our study.

Most women with breast cancer have no family history of the disease [33]. However, having one first-degree relative with breast cancer doubles the risk in women, and having two first-degree relatives can triple the risk [5]. Similarly to other studies [27, 31], no relationship was found between family history and having a *BRCA1/2* variant.

BRCA1 carriers are more likely to have a higher histological grade than *BRCA2* carriers [13]. The frequency of *BRCA1* carriers with histological grade 3 was found to be 84.1% by Fountzilas *et al.* [28], 65.9% by Atci *et al*. [29] and 77.8% by Rijnsburger *et al.* [34]. In our study, 60% of patients with the *BRCA1* pathogenic variant had grade 3, but because the sample size was small, the relationship between variant and high grade could not reach a statistically significant level (data not shown).

Triple-negative breast cancer, which does not show expression of ER, PR, and HER2, is the most aggressive of all breast cancer subtypes due to its high early recurrence rate and poor prognosis of distant metastases [31]. Previous studies have shown that *BRCA1* is associated with TNBC [30, 32]. In our study, 50% of *BRCA1/2* carriers had TNBC.

The Ki-67 index is considered a reliable indicator of the proliferative activity of breast cancer and a prognostic biomarker [35]. You *et al*. [32] found a correlation between Ki-67 proliferation index and *BRCA* mutations, as in our study.

BRCA1 can inhibit the transcriptional activity of PR isoforms and induce epigenetic silencing of target promoters and degradation of PR protein. *BRCA1* germline mutation carrier status is generally associated with ER negativity as well as the PR receptor in the literature [36]. In a previous study, similarly to ours, PR- and ER-negative status was observed more frequently in *BRCA1/2* carriers [24], and in another study, the frequency of ER-positive status was higher in *BRCA1/2* carriers compared to ER status [27]. In two studies, HER2 negative status was also high in *BRCA1/2* variant carriers [27, 31]. Similarly, the frequency of HER2 negative status was higher in both *BRCA1/2* variants in our study, but it did not reach a statistically significant level due to the small sample size.

The relationships between *BRCA* mutations and histological types have been evaluated in studies, and the most common type of invasive ductal carcinoma was found in breast cancer patients with the *BRCA* pathogenic variant. The incidence of invasive ductal carcinoma is 84% in *BRCA1/2* pathogenic variants [27, 31]. Similarly, in our study, the most common histological type was NST, and 50% of patients with the *BRCA1/2* pathogenic variant had NST carcinoma.

Conclusions

Demonstrating the distribution of variants in the population and adding conflict variants to the literature may enable clinicians to establish the clinicopathological relationship with variants more easily. Therefore, in our study, we analyzed the distribution of variants we detected in women living in our region and found that pathogenic variants in patients with breast cancer were associated with high histological grade, triple-negative type, high Ki-67 proliferation index, and histological type.

The authors declare no conflict of interest.

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