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Original Article

Clinicopathological Characterization of Double Heterozygosity for *BRCA1* and *BRCA2* Variants in Korean Breast Cancer Patients

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Purpose Double heterozygosity (DH) for *BRCA1* and *BRCA2* variant is very rare with only a few cases reported, and most those in Caucasians. In this article, we present seven unrelated cases of DH for *BRCA1/2* identified from a single institution in Korea, and describe the characteristics and phenotype of DH individuals compared to those with a single *BRCA* variant.

Materials and Methods This study included 27,678 patients diagnosed with breast cancer and surgically treated at Samsung Medical Center (SMC) between January 2008 and June 2020. In total, 4,215 high-risk breast cancer patients were tested for the *BRCA1/2* genes, and electronic medical records from 456 cases with pathogenic/likely pathogenic variants were reviewed.

Results A younger mean age at diagnosis was associated with DH than a single variant of *BRCA1/2*. More triple-negative breast cancer and higher nuclear and histologic grade cancer occurred with DH than *BRCA2* variant. All seven cases of DH were unrelated, and their mutation combinations were different. There were no Ashkenazi founder variants detected.

Conclusion We suggest that patients with DH for *BRCA1/2* variants develop breast cancer at a younger age, but the histopathologic features are similar to those of *BRCA1*.

Key words *BRCA1*, *BRCA2*, Double heterozygosity, Hereditary breast cancer

Introduction

Breast cancer is the most common cancer and one of the leading causes of cancer death in women [1]. Family history is a well-established risk factor for breast cancer. In an effort to identify the causative genes, *BRCA1* was first isolated from chromosome 17 in 1994 [2] and *BRCA2* was isolated from chromosome 13 in 1995 [3]. Since then, various causative genes have been identified, but *BRCA1* and *BRCA2* are still considered the most common cause of hereditary breast cancer. Germline variants of *BRCA1/2* genes, identified with a frequency of less than 0.1% in the general population, have a frequency of 2%-3% of all breast cancer cases and 19.4%-22.1% of breast cancer cases with a family history [4-6]. *BRCA1*-related breast cancers are clinically and pathologically different from *BRCA2*-related breast cancers. More patients with a *BRCA1* variant have triple-negative breast cancer (TNBC) and poorly differentiated cancer with a high histologic grade and nuclear grade than patients who are *BRCA*-negative or those who have a *BRCA2* variant [7-11].

However, the co-existence of variants in *BRCA1* and *BRCA2* genes is very rare, with only a few cases reported to date; the clinical implications of double heterozygosity (DH) have not been established [12-14]. Some studies have found that DH for *BRCA1/2* leads to a higher probability of breast cancer at an earlier age [15,16] and a poorer prognosis than a single *BRCA* variant [16], but several other studies have shown no difference from patients with only a *BRCA1* variant [12,17,18]. This controversy is partially due to relatively small sample sizes because DH for *BRCA1/2* is rare in the breast cancer population. In addition, the prevalence of certain gene mutation can vary among ethnicities. Most reports on DH for *BRCA1/2* were from Caucasians patients, so study on Asians may yield different results [19,20].

In this article, we present seven unrelated cases of DH for *BRCA1/2* identified at a single institution in Korea, and describe patient clinical characteristics and phenotype compared to patients with a single *BRCA1* or *BRCA2* variant.

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Materials and Methods

1. Patient population

This study included patients diagnosed with breast cancer and surgically treated at Samsung Medical Center (SMC) between January 2008 and June 2020. Among 27,678 patients, 4,215 high-risk breast cancer patients were tested for *BRCA1/2* genes, and electronic medical records from 456 cases with pathogenic/likely pathogenic variants (PVs/LPVs) were reviewed.

2. Genetic tests

All breast cancer patients were asked about family history at the first visit and genetic counseling was provided to patients in known high-risk groups for breast cancer caused by *BRCA1/2* gene variants. *BRCA1/2* testing was performed and pedigree was obtained if the patient consented. The five categories of the high-risk groups were as follows: (1) patients with a family history of breast or ovarian cancer; (2) patients with both breast and ovarian cancer; (3) patients diagnosed with breast cancer at a young age (< 40); (4) patients diagnosed with bilateral breast cancer; and (5) male patients [19].

Before September 2016, we performed Sanger sequencing for all samples. Genomic DNA was extracted and purified from peripheral blood leukocytes using the Wizard Genomic DNA Purification kit according to the manufacturer's instructions (Promega, Madison, WI). The all coding exons and their flanking intrinsic sequences of the *BRCA1/2* genes were amplified by polymerase chain reaction (PCR). The amplified products were directly sequenced and the sequences were compared with reference sequences using Sequencher software (Gene Codes Co., Ann Arbor, MI).

From September 2016, we performed all coding exon sequencing using the Ion Torrent S5 XL sequencer and Oncomine. Library preparation was carried out using the Ion Chef System (Thermo Fisher Scientific, Waltham, MA) according to the manufacturer's instructions. Barcoded libraries were generated from 10 ng of DNA per sample using the Ion AmpliSeq Chef Solutions DL8 Kit (Thermo Fisher Scientific) and the Oncomine BRCA Research Assay (Thermo Fisher Scientific). Two premixed pools of 265 primer

Table 1. Clinicopathological characteristics of breast cancer patients according to *BRCA* mutation status

Variable	*BRCA1/2*+ (n=7) (%)	*BRCA1*+ (n=230) (%)	*BRCA2*+ (n=229) (%)	p-value
Age (yr)	33.7±4.8	41.1±9.2	43.5±9.8	0.001
Sex				
Female	7 (100)	229 (99.6)	227 (99.1)	0.64
Male	0	1 (0.4)	2 (0.9)	
Nuclear grade				
I	0	6 (2.6)	12 (5.2)	< 0.001
II	3 (42.9)	58 (25.2)	130 (56.8)	
III	4 (57.1)	166 (72.2)	87 (38.0)	
Histologic grade				
I	0	13 (5.7)	21 (9.2)	< 0.001
II	4 (57.1)	60 (26.1)	130 (56.8)	
III	3 (42.9)	157 (68.3)	78 (34.1)	
ER				
Positive	2 (28.6)	63 (27.4)	184 (80.3)	< 0.001
Negative	5 (71.4)	167 (72.6)	45 (19.7)	
PR				
Positive	2 (28.6)	46 (20.0)	172 (75.1)	< 0.001
Negative	5 (71.4)	184 (80.0)	57 (24.9)	
HER2				
Positive	0	14 (6.1)	14 (6.1)	0.795
Negative	7 (100)	216 (93.9)	215 (93.9)	
Subtype				
TNBC	5 (71.4)	153 (66.5)	40 (17.5)	< 0.001
Non-TNBC	2 (28.6)	77 (33.5)	159 (82.5)	

Values are presented as mean±SD or number (%). ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; PR, progesterone receptor; TNBC, triple-negative breast cancer.

Table 2. Clinicopathological characteristics of breast cancer patients with double heterozygotes for *BRCA1/2* genes

Variable	Patient No.						
	1	2	3	4	5	6	7
Age at initial diagnosis (yr)	35	31	35	42	35	26	34
Laterality	Unilateral	Bilateral	Unilateral	Unilateral	Unilateral	Unilateral	Unilateral
Histology	IDC	IDC	IDC	IDC	IDC	IDC	IDC
NAC	No	No	No	Yes	No	Yes	Yes
TNM stage	pT1N0	pT2N0 (R) pTisN0 (L)	pT2N0	cT2N0 ypT1N0	pT1N0	cT2N0 ypT0N0	cT2N0 ypT1N0
No. of involved LNs	0/2	0/6 (R) 0/2 (L)	0/4	0/6	0/5	0/2	0/3
Nuclear grade	II/III	II/III	III/III	III/III	II/III	III/III	III/III
Histologic grade	III/III	II/III	III/III	II/III	II/III	III/III	III/III
ER	Negative	Positive	Negative	Negative	Positive	Negative	Negative
PR	Negative	Positive	Negative	Negative	Positive	Negative	Negative
HER-2/neu	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Ki-67 (%)	82.1	25.6	90.0	1.4	20.6	89.7	10.9
CRRM	No		No	Yes	Yes	Yes	No
RRSO	Yes	Yes	No	Yes	No	No	No
Regional recurrence	Yes	No	No	No	No	No	No
Distant metastasis	No	No	No	Yes	No	No	No
Family history							
Breast cancer	No	Yes[b]	Yes[a]	Yes[a]	Yes[a]	No	Yes[b]
Ovarian cancer	Yes[a]	No	No	No	No	No	No
Other cancers	Esopagus[a] Prostate[b]			Colon[b]	Lung[a] Pancreas[b] Stomach[a]	Stomach[b] Thyroid[a] Pancreas[a]	
Follow-up	17 yr 7 mo	9 yr 5 mo	5 yr 2 mo	3 yr 6 mo	1 yr 9 mo	1 yr 5 mo	1 yr 5 mo

BC, breast cancer; CRRM, contralateral risk-reducing mastectomy; ER, estrogen receptor; HER-2/neu, human epidermal growth factor receptor; IDC, invasive ductal carcinoma; L, left; LN, lymph node; NAC, neoadjuvant chemotherapy; PR, progesterone receptor; R, right; RRSO, risk-reducing salphingo-oophorectomy. [a]Maternal history, [b]Paternal history.

pairs were used to generate the sequencing libraries. Clonal amplification of the libraries was carried out by emulsion PCR using the Ion AmpliSeq IC 200 Kit (Thermo Fisher Scientific). The prepared libraries were then sequenced on the Ion S5 XL Sequencer using the Ion 520 Chip and an Ion 520 kit–Chef Kit (Thermo Fisher Scientific). When PVs and LPVs were identified by next generation sequencing, we confirmed the results via the Sanger sequencing.

Sequences were compared with the *BRCA1* (NM_007294.3) and *BRCA2* (NM_000059.3) reference sequences for variant detection. Results were interpreted and reported following the American College of Medical Genetics and Genomics–Association for Molecular Pathology guidelines 2015 (ACMG-AMP 2015) [21].

3. Statistical analysis

All statistical analyses were performed using SPSS ver. 27.0 software (IBM Corp., Armonk, NY). Continuous variables are presented as mean±standard deviation, and categorical variables are presented as number and percentage of cases. The Kruskal-Wallis exact test was used to compare the continuous variables. Fisher's exact test was used to compare categorical variables. $p < 0.05$ represented statistical significance.

Results

1. Clinicopathological characteristics of PVs/LPVs

From January 2008 to June 2020, 27,678 patients were diagnosed with breast cancer and 4,215 high-risk patients were tested for the *BRCA1/2* gene at SMC. PVs/LPVs were detected in 456 cases. Of the 456 patients included in this study, 230 patients (50.4%) had a *BRCA1* variant, 220 patients (50.2%) had a *BRCA2* variant, and seven patients (1.5%) had both *BRCA1* and *BRCA2* variants. The clinicopathological

Table 3. Detected variants in double heterozygosity of *BRCA1/2* patients found in Korea

Patient No.	*BRCA1* gene		*BRCA2* gene		Remark
	Nucleotide change	Amino acid change	Nucleotide change	Amino acid change	
1	c.5030_5033del	p.(Thr1677Ilefs*2)	c.1399A>T	p.(Lys467*)	3
2	c.5496_5506delinsA	p.(Val1833Serfs*7)	c.7480C>T	p.(Arg2494*)	1
3	c.922_924delinsT	p.(Ser308*)	c.3599_3600del	p.(Cys1200*)	1
4	c.390C>A	p.(Tyr130*)	c.5576_5579del	p.(Ile1859Lysfs*3)	1
5	c.3627dup	p.(Glu1210Argfs*9)	c.1399A>T	p.(Lys467*)	1
6	c.38_39delinsGGG	p.(Asn13Argfs*4)	c.1399A>T	p.(Lys467*)	1
7	c.922_924delinsT	p.(Ser308*)	c.6437_6440del	p.(Asn2146Thrfs*21)	1
8	c.1504_1508del	p.(Leu502Alafs*2)	c.2798_2799del	p.(Thr933Argfs*2)	2
9	c.4981G>T	p.(Glu1661*)	c.6486_6489del	p.(Lys2162Asnfs*5)	2
10	c.3627dup	p.(Glu1210Argfs*9)	c.6724_6725del	p.(Asp2242Phefs*2)	2
11	c.390C>A	p.(Tyr130*)	c.3018del	p.(Gly1007Valfs*36)	2

All variants are marked according to the Human Genome Variation Society recommendations. 1, found in this study; 2, found in before Noh et al. [17]; 3, overlapped in both.

characteristics of each carrier are described in Table 1 according to *BRCA* variant. Mean age at diagnosis was youngest in cases of *BRCA1/2* DH among the three groups (p=0.001). *BRCA1/2* DH was associated with higher nuclear and histologic grade cancer than the *BRCA2* variant ($p < 0.001$). Also, *BRCA1* variants and *BRCA1/2* DH led to more frequent estrogen receptor– and progesterone receptor–negative cancer than *BRCA2* variant carriers ($p < 0.001$). Human epidermal growth factor-2 expression did not differ significantly between each groups (p=0.795). TNBC was more common in those with *BRCA1* variants and *BRCA1/2* DH than *BRCA2* variants ($p < 0.001$).

2. Clinicopathological characteristics of DH

The clinicopathological characteristics of patients with DH are summarized in Table 2. The mean age at diagnosis was 33.7±4.8 years and six (85.7%) were under 40 years. All patients were diagnosed with invasive ductal carcinoma with no metastasis to axillary lymph nodes. For three patients who received neoadjuvant chemotherapy, both the clinical stage and pathological stage were described. All seven patients had breast cancer with grade II or higher nuclear and histologic staging.

Five patients (71.4%) had TNBC. Five patients (71.4%) had a family history of breast cancer, one patient (14.3%) had a family history of ovarian cancer, and only one patient had no family history of breast cancer or ovarian cancer. However, this patient had a family history of gastric cancer, thyroid cancer, and pancreatic cancer. Of the six patients with a family history of ovarian or breast cancer, four patients (66.7%) had a maternal family history and two (33.3%) had a paternal family history. The pedigree of six patients who agreed to provide information is shown in S1 Fig. After post-test counseling, only two family members had family genetic testing. In the case or patient No. 4, one of her sisters was an unaffected carrier of DH and in the case of patient No. 6, her mother was identified carrying single heterozygosity for *BRCA2* PVs/LPVs.

There was only one patient with bilateral breast cancer at diagnosis; however, during follow-up, contralateral breast cancer occurred 6 years after the first breast cancer in another patient. During follow-up, one patient developed distant metastasis 3 years and 6 months after initial diagnosis.

3. Genetic tests

The detected variants of DH in Korea are listed in Table 3. All variants are marked according to the Human Genome Variation Society recommendations. Among the seven DH cases in this study, one case was already enrolled in a previous study by Noh et al. [17] that reported five DH cases. All seven cases of DH were unrelated, and their mutation combinations were different. There were no Ashkenazi founder variants detected (c.68_69del and c.5266dup in *BRCA1* gene and c.5946del in *BRCA2* gene) [22]. All variants detected, including those related to ovarian, fallopian, and peritoneal cancers in SMC are listed in S2 Table and S3 Table.

Discussion

Here we described seven cases that were DH for two high-penetrance breast cancer susceptibility genes, *BRCA1* and *BRCA2*, who were identified at a single center in South Korea. DH was associated with significantly younger diagnosis of breast cancer than a single *BRCA1* or *BRCA2* variants (p=0.001) (Table 1). The pathological features of cases with

Table 4. List of common (7 variants) PV/LPVs of *BRCA1* and *BRCA2* genes in this study and KOHBRA study

BRCA1				*BRCA2*			
This study	No.	KOHBRA	No.	This study	No.	KOHBRA	No.
c.390C>A	26	c.390C>A	21	c.7480C>T	40	c.7480C>T	38
c.5496_5506delinsA	23	c.5496_5506delinsA	15	c.1399A>T	23	c.3744_3747del	20
c.3627dup	19	c.922_923del	11	c.3744_3747del	14	c.1399A>T	18
c.5339T>C[a)]	16	c.5030_5033del	10	c.5576_5579del	10	c.5576_75579del	14
c.922_924delinsT	15	c.3627dup	9	c.6724_6725del	6	c.9076C>T	7
c.5445G>A	14	c.5445G>A	7	c.8991T>G	6	c.6724_6725del	6
c.5080G>T	7	c.5080G>T	5	c.6724_6725del	6	c.8991T>G	5

All variants are marked according to the Human Genome Variation Society recommendations. KOHBRA, Korean Hereditary Breast Cancer; PV/LPV, pathogenic/likely pathogenic variant. [a)]This variant was classified as variant of uncertain significance (VUS) before Ryu et al. [24].

DH were similar to those of *BRCA1* variant carriers. Breast cancer was diagnosed at grade II or higher nuclear and histologic grade staging in DH. Five patients (71.4%) had TNBC (Table 2).

Identifying any differences in the phenotype of breast cancer with DH versus single *BRCA* variants is important for any necessary change to treatment strategy and follow-up care. According to a study by Lavie et al. [12] on DH in Jewish patients, cancer occurred at an earlier age than in single mutation carriers. In a review of non-Ashkenazi Caucasian women with *BRCA1/2* DH by Heidemann et al. [16], German women with DH were not associated with a significantly younger at diagnosis of breast cancer than carriers of a single heterozygous *BRCA* mutation. However, Caucasian women with DH seem to develop breast cancer at a younger age than their relatives with a single *BRCA* mutation. In contrast to the previous study by Lavie et al. [12], Heidemann et al. [16] suggested that DH in Caucasian women leads to more severe disease than single heterozygous *BRCA* mutation, warranting changes to the counseling process and treatment strategy. In this study, the mean age at diagnosis of breast cancer was 33.7 years in DH, younger than those with a single *BRCA* mutation carriers, similar to the results of previous studies except for the German DH group. However, the histopathologic features were similar to those of *BRCA1* variant carriers. A recently published study by Rebbeck et al. [15] analyzed 332,295 *BRCA* mutation carriers in the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) dataset and detected 93 individuals with DH, of which 64 were breast cancer patients. Their study, which included most cases of DH reported worldwide, suggested that DH for *BRCA1/2* variants leads to an intermediate phenotype between *BRCA1* and *BRCA2* variant carriers [15]. These results may have differed from our findings due to the small number of DH cases and differences in ethnicity compared to our study population.

Combined with a previous study by Noh et al. [17], 11 cases of DH were found in Korea. All 11 cases of DH were unrelated, and their mutation combinations were different. There were no Ashkenazi founder variants detected (Table 3). To compare the DH variants identified with those of the entire Korean population, the variants with high frequency among those identified in this study and the Korean Hereditary Breast Cancer (KOHBRA) study [23] are summarized in Table 4. Most recurrent variants in this study were common in the KOHBRA study, too. The variant c.922_924delinsT of *BRCA1* was found in 15 cases in this study, but not in KOHBRA. On the other hand, the c.922_923del of *BRCA1* was commonly detected in KOHBRA, but was not found in this study. We suspect that these two variants were identical but we could not prove this suspicion. In the *BRCA2* gene, the c.9076C>T variant was commonly detected in KOHBRA but detected in only two cases in this study. Especially, the variant c.5339T>C in *BRCA1* gene was classified as variant of uncertain significance (VUS) in KOHBRA but was reassessed as LPV [24].

BRCA1 and *BRCA2* are the causative genes for hereditary breast and ovarian cancers by a heterozygous pathogenic variant. However, the biallelic pathogenic variants in these two genes with other genes such as FANCA gene are known as the genetic background of Fanconi anemia (FA) and these two genes attributed to FA by < 1% (FA_S) and 2% (FA_D1), respectively [25]. We reviewed all patients whether there were compound heterozygosity or not. There were only three cases who had PVs/LPVs and VUS, and the VUSs had no evidences to be thought as PVs/LPVs. Although, the causative genes are the same, it is not difficult to distinguish the two diseases because the clinical features and onset ages at diagnosis are totally different. With these aspects, we could exclude the possibility of FA.

Since DH for *BRCA1* and *BRCA2* was first reported in 1997 [26], few cases have been reported, most among Ashkenazi Jewish and individuals with Ashkenazi founder mutations [15]. Outside of Ashkenazi Jewish population, approximately 40 cases of DH have been reported worldwide, but most cases were in non-Jewish Caucasians [16,20]. *BRCA1/2* DH is even rarer in Asians, with only five cases of DH previously reported in Korea and two in Japan [17,20]. This could be because the prevalence of *BRCA* variants varies by race, or may be because few studies on *BRCA* genes have been conducted among Asian populations. This study is the largest report on *BRCA1/2* DH not only from a single institution in Korea, but also from anywhere in Asia. It also represents one of the largest reports of non-Ashkenazi DH worldwide.

There are more than 30 guidelines on *BRCA* testing worldwide, but almost guidelines do not represent exact recommendations for DH for *BRCA1/2*. Because DH for *BRCA1/2* is very rare, it was not established the difference between single heterozygosity and DH and it is difficult to make recommendations for them. Bases on this study, we suggest that patients with DH for *BRCA1/2* develop breast cancer at a younger age, but with histopathologic features similar to those of *BRCA1*. Therefore, in the case of DH, we suggest starting clinical breast examination after age 20, earlier than the general guideline. Additional, in the case of a family history of breast cancer diagnosed before age 30, annual breast magnetic resonance imaging screening should be considered before age 25. In addition, it is important to provide specific information about chance of *BRCA* variants in post-test counseling for individuals carrying DH for *BRCA1/2* and their family. Because both *BRCA1* and *BRCA2* are inherited in an autosomal dominant fashion, the sibling of DH has only a 25% chance of having no variant, a 50% chance of having single heterozygosity, and a 25% chance of having DH. The chance of inheriting the DH is same for the offspring between the DH and non-carrier.

However, this study has the following limitations. As this is a retrospective study, additional genetic tests on family members could not be performed and recent changes in the pedigree were not updated. Therefore, it remains unclear whether these variants were both inherited from a single parent or one from each parent. If additional genetic tests on family members are performed, it is expected that more unaffected DH carriers will be found. In addition, information on the long-term prognosis of breast cancer could not be obtained. In future studies, long-term follow-up of the *BRCA1/2* DH is needed to determine survival rates compared to single variant carriers or as well as the incidence of other cancers.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The Institutional Review Board of Samsung Medical Center (SMC) approved this study (IRB file No. 2021-06-009). Since this study was retrospective in nature, patient consent was not required.

Author Contributions

Conceived and designed the analysis: Bang YJ, Kwon WK, Ryu JM, Kim JW, Yu J, Lee JE.
Collected the data: Bang YJ, Kwon WK, Nam SJ, Kim SW, Chae BJ, Lee SK, Ryu JM, Kim JW, Yu J, Lee JE.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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