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Analysis of *BRIP1* Variants among Korean Patients with *BRCA1/2* Mutation-Negative High-Risk Breast Cancer

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Purpose
The aim of the current study is to assess the spectrum of genetic variation in the *BRIP1* gene among Korean high-risk breast cancer patients who tested negative for the *BRCA1/2* mutation.

Materials and Methods
Overall, 235 Korean patients with *BRCA1/2* mutation–negative high-risk breast cancer were screened for *BRIP1* mutations. The entire *BRIP1* gene was analyzed using fluorescent-conformation sensitive gel electrophoresis. *In silico* analysis of *BRIP1* variants was performed using PolyPhen-2 and SIFT.

Results
A total of 20 sequence alterations including 12 exonic and eight intronic variants were found. Among the 12 exonic variants, 10 were missense and two were silent mutations. No protein-truncating mutation was found among the tested patients. Among the 10 missense variants, four (p.L263F, p.L340F, p.L474P, and p.R848H) were predicted to be pathogenic by both PolyPhen-2 and SIFT, and these variants were found in five patients. Of the four missense variants, p.L263F, p.L474P, and p.R848H localize to regions between the helicase motifs, while p.L340F resides in an iron-sulfur domain of *BRIP1*.

Conclusion
No protein-truncating mutation in *BRIP1* was found among the tested patients. The contribution of *BRIP1* variants is thought to be minor in Korean non-*BRCA1/2* high-risk breast cancer.

Key words
BRIP1, *BRCA1*, *BRCA2*,
Hereditary breast and ovarian cancer syndrome, Korea

Introduction

Inherited mutations of certain genes contribute to the risk of breast cancer in approximately 15% of breast cancer patients [1]. Among the susceptible genes for breast cancer, *BRCA1* and *BRCA2* (*BRCA1/2*) are considered most important as their mutations are associated with a high risk of breast cancer. Patients carrying deleterious mutations in one of the genes have a 40%-80% lifetime risk of breast cancer [2].

However, only about 20% of hereditary breast cancer is caused by the *BRCA1/2* mutations, suggesting that other genes account for the remaining non-*BRCA1/2*–mutated hereditary breast cancer [2].

Korean patients with breast cancer are characteristically younger than their Caucasian counterparts. As of 2011, the median age of Korean breast cancer patients is 50 years. This is more than 10 years younger than that of patients in the United States [3]. Given a strong correlation between early occurrence of cancer and cancer susceptibility of patients, specific genetic alterations are believed to be linked to the development of breast cancer among Korean patients. Previous studies on Korean patients found that 8.6%-21.7% of patients with high-risk breast cancer have *BRCA1/2* mutations [4]. In addition to *BRCA1/2*, other genes including *CHEK2* and *PALB2* were tested for significance in predisposition to Korean breast cancer. No mutation was found in these genes among the tested patients [5,6]. Thus, a significant proportion of genetic causes of Korean high-risk breast cancer remain unknown.

BRCA1-interacting protein C-terminal helicase 1 (*BRIP1*) encodes a protein binding partner of *BRCA1* and functions in the process of DNA repair [7]. Sequence variants in *BRIP1* are reported to be associated with development of breast cancer in Caucasian patients [2]. However, there is a paucity of data regarding the role of *BRIP1* variants in Korean high-risk breast cancer. In the current study, we analyzed the *BRIP1* gene in high-risk Korean breast cancer patients without the *BRCA1/2* mutation in order to assess the frequency of *BRIP1* mutation among the patients.

Materials and Methods

1. Patients and controls

High-risk breast cancer patients without the *BRCA1/2* mutation were enrolled in the current study. All participants were clinically screened for *BRCA1/2* mutations using fluorescent-conformation sensitive capillary electrophoresis (F-CSCE) and traditional sequencing. Detailed methods were previously described [8]. Because two previous studies reported that the large genomic rearrangements of *BRCA1/2* are rare in the Korean population [9], multiplex ligation-dependent probe amplification analysis for large genomic rearrangement was not performed in the current study.

All patients were participants in the Korean Hereditary Breast Cancer (KOHBRA) study, conducted from 2008 to 2013 to evaluate the distribution of the *BRCA1/2* mutation in Korean high-risk breast cancer patients [8]. Among the high-risk patients who did not have the *BRCA1/2* mutation, individuals who gave consent for analysis of the *BRIP1* gene were included in the current research. The criteria for high-risk breast cancer patients were as follows: patients with a family history of breast or ovarian cancer in any relative; patients with breast cancer diagnosed at age 40 years or younger; patients with bilateral breast cancer; and male patients with breast cancer. In addition, 50 healthy females aged 28-36 years were selected as a control group for analysis of *BRIP1* missense variants. The women in the control group underwent genetic testing during the prenatal screening program at the LabGenomics Clinical Research Institute and had no personal or familial history of breast or ovarian cancer. The current study was approved by the Institutional Review Board of the Ethics Committee of Samsung Medical Center.

2. Mutation detection

Genomic DNA was extracted from peripheral blood using a G-DEX IIb DNA Extraction Kit (Intron, Seongnam, Korea), following the protocol of the manufacturer. Sequence variations in the *BRIP1* gene were analyzed using the combination methods of F-CSCE and direct sequencing, based on the institute's own protocols, as described previously [4,10]. In short, fluorescent polymerase chain reaction (PCR) products were synthesized by amplifying 21 DNA fragments that overlapped the 19 coding exons and exon/intron boundaries of *BRIP1*. Primer sequences are available on request. Heteroduplexes were generated by denaturation and annealing of the PCR products, followed by separation on an AB 3130XL sequencer (Life Technology, Carlsbad, CA). F-CSCE peak pattern analysis was performed using GeneScane and Genotypere software (Life Technology). Following identification of a subset of PCR products with aberrant F-CSCE patterns, the PCR products were amplified using the same primers used for F-CSCE. These DNA fragments were sequenced in both directions on an AB 3730XL (Life Technology), in accordance with the manufacturer's instructions. All variants were confirmed by repeating both the PCR and sequencing analyses. All sequence variants are described according to the Human Genome Variation Society (HGVS) mutation nomenclature [11]. In the current study, variations are categorized as novel sequence variations when they cannot be found in publically available sequence variation databases including dbSNP (http://www.ncbi.nlm.nih.gov/snp/), Exome Aggregation Consortium (EXAC; http://exac.broadinstitute.org/), Leiden Open Variation Database (LOVD; http://www.lovd.nl/3.0/), Human Genome Mutation Database (HGMD; http://www.hgmd.cf.ac.uk/ac/), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), 1000 Genomes (http://www.1000genomes.org/), and Exome Variant Server (http://evs.gs.washington.edu/EVS/).

The *in silico* analyses of the *BRIP1* variants were performed using Polymorphism Phenotyping ver. 2 (PolyPhen-2; http://genetics.bwh.harvard.edu/pph2) and Sorting Intolerant From Tolerant (SIFT; http://sift.jcvi.org/index.html) to predict the impact on the function of a protein. In the PolyPhen-2 program, the investigated mutation is categorized as probably damaging (probability score greater than 0.85), possibly damaging (probability score between 0.16 and 0.85), or benign (probability score less than or equal to 0.15). SIFT is a tool for sorting intolerant from tolerant amino acids in the base of a sequence homology. The evaluated amino acid substitution is predicted as deleterious if the score is less than 0.05 and is predicted to be tolerated if the score is greater than or equal to 0.05. The missense variants predicted to be deleterious by *in silico* analyses were genotyped among females in the control group to compare frequencies of occurrence of the variants between the patients and the control groups.

Results

1. Patient characteristics

A total of 235 patients with breast cancer underwent genetic testing for *BRIP1* mutations. Of the participants, 89 had familial breast cancer, 76 had early-onset breast cancer, 43 had early-onset breast cancer along with a family history of breast or ovarian cancer, six had bilateral breast cancers, eight had bilateral breast cancer along with a family history of breast or ovarian cancer, four had bilateral breast cancer and were diagnosed at age 40 years or younger, two had early-onset bilateral breast cancer along with a family history of breast or ovarian cancer, and seven were male patients with breast cancer. The median age at diagnosis was 46 years (range, 21 to 68 years).

2. Genetic analysis of *BRIP1*

Detailed data of *BRIP1* sequence analysis are shown in Table 1. Overall, 20 *BRIP1* sequence variants were found. Of the variants, 12 were located in protein-coding regions, and eight were in introns. Among the 12 exonic variants, there were 10 missense and two silent mutations. Notably, no protein truncating mutation was found among the tested patients. Among the 10 missense variants, two (c.787C>T, and c.1421T>C) were novel and eight (c.430G>A, c.587A>G, c.1018C>T, c.1442G>A, c.2543G>A, c.2755T>C, 2830C>G, and c.2854A>G) were previously described.

The effects of the 10 coding missense variants were analyzed by PolyPhen-2 and SIFT. The c.787C>T (p.L263F), c.1018C>T (p.L340F), c.1421T>C (p.L474P), and c.2543G>A (p.R848H) variants were predicted to be pathogenic by both programs. These four missense mutations were found in five patients. Clinical information on the five patients is shown in Table 2. The four missense mutations were not detected among the females in the control group.

Discussion

In the current study, *BRIP1* sequence variations including three novel variants were identified in Korean patients with non-*BRCA1/2* high-risk breast cancer. Among the variants, four missense variants were predicted to be deleterious by *in silico* analyses and were found to be rare, with a frequency of 1.27% in the study population. In addition, no protein-truncating *BRIP1* mutation was identified among the tested patients. Therefore, it is less likely that variations in *BRIP1* account for a significant proportion of non-*BRCA1/2* high-risk breast cancer among Koreans.

BRIP1, also known as the *BRCA1*-associated C-terminal DNA helicase 1 (BACH1) or Fanconi anemia complementation group J (FANCJ), is a DNA helicase that directly interacts with the BRCT domain of *BRCA1* and participates in DNA repair and checkpoint control [7]. Homozygous mutations in *BRIP1* result in Fanconi anemia, which shows congenital anomalies, bone marrow failure, and increased prevalence of cancers [12]. In addition, inactivation of *BRIP1* alters certain functions of *BRCA1*, suggesting that *BRIP1* is a candidate breast cancer-associated gene [13]. Heterozygous germline mutations in *BRIP1* are reported to increase the risk of breast cancer. A case-control study found that carriers of truncating mutations in *BRIP1* showed a 2-fold increase in breast cancer risk compared to healthy individuals [12]. The study, which included 1,212 UK patients with non-*BRCA1/2* high-risk breast cancer, found five distinctive truncating mutations among nine patients. In addition, three different truncating mutations have been identified in other studies; however, the frequencies of the protein-truncating variants was low at 0.7%-2.0% in the patients with non-*BRCA1/2* high-risk breast cancer [14-16]. In addition, several studies conducted on patients with various ethnicities failed to identify *BRIP1* protein-truncating variants in their study cohorts [17-19]. Consistent with these studies, we found no *BRIP1* protein-truncating variants in our study population, suggesting that the *BRIP1* protein-truncating variant is less likely to contribute to the risk of breast cancer among Korean patients with non-*BRCA1/2* high-risk breast cancer. Nonetheless, there is a possibility of missing *BRIP1* truncating variants

Table 1. Sequence variants in the *BRIP1* gene among 235 Korean patients with high-risk breast cancer and 50 control subjects

Location	Nucleotide change	Effect on protein	Allele frequency		SIFT result	SIFT score	PolyPhen-2 result	PolyPhen-2 score	dbSNP	Reference database
			Patient	Control						
Coding region										
Exon 5	c.430G>A	p.A144T	3/470	-	Tolerated	0.55	Probably damaging	0.999	rs116952709	L, C, T, V, E
Exon 6	c.587A>G	p.N196S	2/470	-	Tolerated	0.74	Benign	0.030	-	L, C, E
Exon 7	c.787C>T	p.L263F	2/470	0/100	Damaging	0.01	Probably damaging	1.000	-	-
Exon 8	c.1018C>T	p.L340F	1/470	0/100	Damaging	0.04	Probably damaging	0.981	-	E
Exon 10	c.1421T>C	p.L474P	1/470	0/100	Damaging	0.02	Probably damaging	0.996	-	-
Exon 10	c.1442G>A	p.G481D	2/470	-	Tolerated	0.12	Probably damaging	1.000	-	C, E
Exon 18	c.2543G>A	p.R848H	1/470	-	Damaging	0.00	Probably damaging	1.000	rs374334794	C, T, V
Exon 19	c.2637A>G	-	118/470	-	-	-	-	-	rs4986765	L, D, T, V, E
Exon 19	c.2755T>C	p.S919P	119/470	-	Tolerated	0.28	Benign	0.001	rs4986764	L, C, D, T, V, E
Exon 19	c.2830C>G	p.Q944E	2/470	-	Tolerated	1.00	Possibly damaging	0.634	rs140233356	L, H, C, D, T, E
Exon 19	c.2854A>G	p.I952V	2/470	-	Tolerated	0.68	Benign	0.001	rs200239986	D, T, E
Exon 20	c.3411T>C	-	134/470	-	-	-	-	-	rs4986763	L, D, T, V, E
Non-coding region										
Intron 5	c.380-17T>A	-	1/470	-	-	-	-	-	-	E
Intron 6	c.508-31C>G	-	131/470	-	-	-	-	-	rs4988344	L, D, V, E
Intron 7	c.918+15T>A	-	11/470	-	-	-	-	-	rs117820198	L, C, D, E
Intron 8	c.1140+91dupT	-	133/470	-	-	-	-	-	rs11390869	-
Intron 12	c.1629-48T>C	-	1/470	-	-	-	-	-	-	-
Intron 13	c.1795-47G>C	-	114/470	-	-	-	-	-	rs4988351	L, D, V, E
Intron 14	c.1936-70C>A	-	1/470	-	-	-	-	-	-	C
Intron 15	c.2257+19A>C	-	13/470	-	-	-	-	-	rs77851913	L, D, V, E

SIFT, Sorting Intolerant From Tolerant; PolyPhen-2, Polymorphism Phenotyping ver. 2; L, Leiden Open Variation Database (LOVD; http://www.lovd.nl/3.0/); C, ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/); T, 1000Genome (http://www.1000genomes.org/); V, Exome Variant Server (http://evs.gs.washington.edu/EVS/); E, Exome Aggregation Consortium (EXAC; http://exac.broadinstitute.org/); D, dbSNP (http://www.ncbi.nlm.nih.gov/SNP/); H, Human Genome Mutation Database (HGMD; http://www.hgmd.cf.ac.uk/ac/).

Table 2. Clinical information on the five patients with missense variants predicted to be deleterious by *in silico* analyses

Patient No.	Variant	Age at diagnosis	Type of cancer	Family history of cancer
1	c.787C > T	25	Bilateral breast cancer	Hepatic cancer (grandfather), lung cancer (maternal grandfather)
2	c.787C > T	42	Breast cancer	Lung cancer (maternal uncle)
3	c.1018C > T	46	Breast cancer	Breast cancer (maternal cousin, diagnosed in her 50s), pancreas cancer (mother), stomach cancer (father)
4	c.1421T > C	33	Breast cancer	-
5	c.2543G > A	54	Bilateral breast cancer and ovarian cancer	Breast cancer (aunt, diagnosed in her 60s), leukemia (maternal aunt)

among Korean patients because we analyzed the *BRIP1* sequence in only 235 patients with high-risk breast cancer. Further research including a larger number of patients is warranted to accurately estimate the frequency of *BRIP1* truncating variants in Korean patients with breast cancer.

In addition to the protein-truncating *BRIP1* mutations, missense variants in *BRIP1* have been suggested to be related to breast cancer predisposition. Cantor and Andreassen [13] first described missense variants in *BRIP1*, p.P47A and p.M299I, among patients with early-onset breast cancer. Each variant was identified in one of the 86 patients with breast cancer, while the variants were not detected in healthy control subjects. In addition, the stability of *BRIP1* containing the p.P47A mutant was markedly reduced in cultured cells [12]. However, p.P47A was confirmed to be unrelated to breast cancer predisposition in a case-control study including a large number of patients and controls [14]. Since these studies, several *BRIP1* missense variants including p.R173C, p.V193I, p.Q944E, and p.P1034L have been identified and evaluated in terms of their roles in breast cancer susceptibility. Nonetheless, the contribution of *BRIP1* missense variants to breast cancer predisposition remains controversial [20]. In the current study, we found 10 missense variants in the coding region of *BRIP1*, four of which were predicted to alter *BRIP1* function by *in silico* analyses. Among the four missense variants, p.L263F, p.L474P, and p.R848H localize to regions between the helicase motifs of *BRIP1*. These variants are thought to be deleterious and are found among patients with high-risk breast cancer. However, functional evaluations of the variants and further case-control studies are needed to confirm their roles in breast cancer predisposition in Koreans.

Of note, we found a missense variant p.L340F, which resides in an iron-sulfur (Fe-S) domain of *BRIP1* in one of the 235 patients in the current analysis. The patient had a family history of cancer on the maternal side, pancreas cancer in the mother, and breast cancer in a maternal cousin. The Fe-S domain of *BRIP1* is proposed to play a fundamental role in DNA strand displacement, which is essential for helicase activity [21]. As a superfamily 2 helicase, *BRIP1* contains seven conserved helicase motifs in residues 1-888, along with the Fe-S domain (residues 276-362) [7,21]. Previously, a missense mutation, p.A349P, which resides in the Fe-S domain of *BRIP1*, was found in a stillborn fetus who presented with a severe phenotypic abnormality and intrauterine growth failure [22]. A subsequent functional analysis of a recombinant *BRIP1*-A349P protein showed that the A349P mutant protein was unable to couple ATP hydrolysis and translocase activity, which is necessary for DNA unwinding [23]. Another missense variant, p.M299I, which localizes to the Fe-S domain, was identified in a case of early-onset breast cancer [7]. Unlike the A349 mutant, the recombinant *BRIP1*-

M299I protein showed increased helicase activity compared to a wild-type recombinant *BRIP1*, along with proficient unwinding DNA substrates [24]. It is suggested that increased enzyme activity by p.M299I, which is caused by perturbation of the Fe-S cluster or structural effects, may contribute to cancer progression [25]. Based on the important functions of the Fe-S domain of *BRIP1*, the p.L340F variant found in the current study may have significant roles in breast cancer predisposition. The current study is the first to report a variant located in the Fe-S domain of *BRIP1* since finding the p.M299I variant in patients with early-onset breast cancer. Functional effects of the sequence alteration should be evaluated in future studies.

Because protein-truncating mutation in *BRIP1* was not identified in the current study, it is unlikely that alterations in *BRIP1* significantly contribute to the susceptibility of breast cancer in Korean patients. Furthermore, even though *BRIP1* missense variants were found, the role of the variants in the development of breast cancer among Korean patients with high-risk breast cancer is still inconclusive. Given the small sample size of the current study, there is a limitation in determining the precise function of *BRIP1* mutation for breast cancer occurrence in Koreans. Further research including a large number of patients and control subjects is necessary.

Conclusion

Several sequence alterations in *BRIP1* were found among the tested patients, suggesting that *BRIP1* sequence alterations have effects on breast predisposition among Korean breast cancer patients. However, given that no protein-truncating mutation was found and that the frequency of the sequence variations was low, the contribution of *BRIP1* variants is thought to be minor in Korean non-*BRCA1/2* high-risk breast cancer.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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