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Further evidence for the contribution of the BRCA1-interacting protein-terminal helicase 1 (BRIP1) gene in breast cancer susceptibility

L.P. Ren, Y.S. Xian, D.M. Diao, Y. Chen, Q. Guo and C.X. Dang

Department of Oncological Surgery,
First Hospital Affiliated to the Medical College of Xi'an Jiaotong University,
Xi'an, Shanxi, China

Corresponding author: C.X. Dang
E-mail: renleipengxs@126.com

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ABSTRACT. BRCA1-interacting protein C-terminal helicase 1 (BRIP1) is a DNA helicase that influences the DNA repair ability and tumor suppressor function of BRCA1. Truncating *BRIP1* mutations have been described as cancer susceptibility alleles. To evaluate *BRIP1* polymorphisms as risk factors for breast cancer, we performed a detailed analysis of possible single nucleotide polymorphisms (rs2048718, rs4988344, rs8077088, rs6504074, rs4986764, rs4986763, rs11079454, rs7213430, rs34289250, rs4988345, and rs12937080) using the MassARRAY system. A total of 319 patients with breast cancer and 306 healthy control females from the Chinese Han population enrolled in the study. A weak association was found between the rs4986764 allele (exon 18) and breast cancer. The frequency of the rs4986764 C allele was significantly higher in breast cancer patients than in healthy controls [$\chi^2 = 4.089$, P = 0.043, odds ratio (OR) = 0.781, 95% confidence interval (CI) = 0.614-0.992]. Additionally, our study is the first to identify a significant association between rs7213430 and breast cancer. Compared to healthy controls, patients with breast cancer had a

higher frequency of the rs7213430 A allele (χ^2 = 8.865, P = 0.003, OR = 0.700, 95%CI = 0.553-0.886). Furthermore, linkage disequilibrium was observed in two blocks (D' > 0.9). While significantly more T-A-C haplotypes (P = 0.001, block 1) were found in breast cancer patients, the frequency of T-T haplotypes (P = 0.008, block 2) was significantly higher in healthy controls. The possible association among rs4986764, rs7213430, and breast cancer risk merits further validation in an independent case-control study.

Key words: BRCA1-interacting protein-terminal helicase 1; Breast cancer; Single nucleotide polymorphisms

INTRODUCTION

In the Chinese population, breast cancer has an incidence of 16.39 per 100,000 women and negatively affects the lives and health of those afflicted. It is estimated that monogenic traits account for approximately 5% of all breast cancer cases (Bradbury and Olopade, 2007). Germline breast cancer 1 (*BRCA1*) or *BRCA2* mutations account for 20-40% of familial breast cancer cases, but for less than 5% of breast cancer cases overall (Wooster and Weber, 2003). Despite this, more than 50% of genetic predisposition to breast cancer remains unexplained (Nathanson et al., 2001; Meindl, 2002; Turnbull and Rahman, 2008). Interestingly, recent studies have suggested that polymorphisms in BRCA1-interacting protein C-terminal helicase 1 (BRIP1) may be associated with breast cancer incidence (Barroso et al., 2009).

BRIP1 is a DNA-dependent ATPase and DNA helicase that influences BRCA-mediated DNA damage repair, and helps to maintain genomic stability (Cantor et al., 2001; Peng et al., 2006). BRIP1 is required for homologous recombination-mediated double-strand break repair (Litman et al., 2005), the execution of the G2/M cell-cycle checkpoint (Yu et al., 2003), and for normal progression through the S phase by assisting in the resolution of stalled replication forks (Kumaraswamy and Shiekhattar, 2007). *BRIP1* is located approximately 20 Mb telomeric to *BRCA1* in a region that is frequently lost in ovarian tumors; additionally, previous studies have suggested that BRIP1 may function as a tumor suppressor (Godwin et al., 1994). *BRIP1* mutation saffecting domain activity or messenger RNA (mRNA) expression have been identified in early onset breast cancer patients, suggesting that BRIP1 plays a role in breast cancer susceptibility (Cantor et al., 2001, 2004).

The human BRIP1 gene is located on chromosome 17q21. It is comprised of 19 introns and 20 exons and encodes a protein of 1249 amino acids. Germline mutations in *BRIP1* are associated with Fanconi anemia, a chromosome instability disorder characterized by developmental abnormalities, bone marrow failure, and predisposition to cancer (Levitus et al., 2005). Truncated variants of *BRIP1* have been identified as low-penetrance breast cancer susceptibility alleles (Seal et al., 2006). Two *BRIP1* missense mutations (P47A and M299I) were originally described in early onset familial breast cancer cases (Cantor et al., 2001), and the P47A mutation was later shown to disrupt the ATPase and helicase activities of the protein (Cantor et al., 2004). The C47G polymorphism (rs4988351) was associated with an increased risk effect in breast cancer patients (Garcia-Closas et al., 2006). These data suggest that *BRIP1* is a good candidate for moderate/low penetrance genetic susceptibility to breast

cancer. Previous studies have analyzed potential associations between *BRIP1* variants and breast cancer risk, either by mutation analysis or by genotyping, to select single nucleotide polymorphisms (SNPs) within the gene (Lei and Vorechovsky, 2003; Rutter et al., 2003; Sigurdson et al., 2004; Lewis et al., 2005; Garcia-Closas et al., 2006; Vahteristo et al., 2006). Although the rs2048718 (5'-untranslated region, UTR), rs4988345 (exon 15), and rs4986764 (exon 18) polymorphisms have been previously examined in the context of breast cancer, these genetic association studies have failed to produce consistent results (Luo et al., 2002; Lei and Vorechovsky, 2003; Song et al., 2007; Pabalan et al., 2013). Furthermore, several important SNPs, such as rs2048718, rs4986764, rs4986763, rs11079454, and rs7213430, have not been included in previous studies. Thus, additional study needs to be performed to determine whether these SNPs modulate the risk of disease on their own, or if they correlate with other causative SNPs, and if they are present in other populations.

The aim of this study was to evaluate whether common variants (rs2048718, rs4988344, rs8077088, rs6504074, rs4986764, rs4986763, rs11079454, rs7213430, rs34289250, rs4988345, and rs12937080) in *BRIP1* are associated with breast cancer risk using an SNP tagging approach within an association study design.

MATERIAL AND METHODS

Subjects

A total of 319 cases of breast adenocarcinoma were included in the study. All cases were confirmed to be invasive breast cancer by histopathology. The mean age of patients was 50.5 ± 6.6 years. All patients received surgical treatment between February 2006 and June 2012 in the Department of Oncological Surgery of the First Hospital Affiliated to the Medical College of Xi'an Jiaotong University. Patients diagnosed with cervical or ovarian cancers were excluded. In total, 306 healthy blood donors (mean age of 52.1 ± 7.8 years) were recruited at the Medical Examination Center of the First Hospital Affiliated to the Medical College of Xi'an Jiaotong University. Participants were excluded if they participated in other studies or had a history of seizures, hematological diseases, or severe liver or kidney impairment. All participants were Han Chinese from the Shanxi Province, but were not genetically related. Written informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee of the Medical College of Xi'an Jiaotong University.

Selection of polymorphisms and genotyping

To select potentially functional SNPs, we focused our attention on SNPs occurring within the promoter region, UTRs, and exons of *BRIP1*. Previous studies have shown significant associations between SNPs of *BRIP1* and cancer diseases. A total of 11 SNPs located within *BRIP1* were selected for genotyping. We used the Han Chinese population in Beijing and a minor allele frequency cut-off (MAF) ≥5% (HapMap Data Release 27). SNPs analyzed included rs2048718, located in the 5'-UTR, rs12937080, located in intron 4, rs4988344, located in intron 5, rs8077088 and rs6504074, located in intron 6, rs34289250, located in intron 7, rs4988345, located in exon 15, rs4986764, located in exon 18, rs4986763, located in exon 20, and rs11079454 and rs7213430, which are both locatedin the 3'-UTR.

Three to five milliliters peripheral blood was collected from each participant and placed in EDTA-containing specimen tubes. Genomic DNA was extracted using the EZNATM Blood DNA Midi Kit (Omega Bio-Tek, Norcross, GA, USA) according to manufacturer instructions; samples were then stored at -20°C until use. Sequences for primers and probes, along with specific assay conditions used for each polymorphism, are detailed in **Table S1**. SNP genotyping was performed using the Mass ARRAY system (Sequenom, San Diego, CA, USA) and matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry. Resulting spectra were processed with the Typer Analyzer software (Sequenom), and genotype data were generated for all samples. The final genotype call rate of each SNP was greater than 90%, and the total genotyping rate was 99.7%, thus ensuring the liability of further statistical analysis.

Statistical analysis

Genotype frequency and Hardy-Weinberg equilibrium were evaluated with the chi square test for each individual polymorphism. Potential associations between breast cancer and each polymorphism were analyzed using the Fisher exact test or the Pearson chi square test. All statistical analyses were carried out using SPSS16.0. The odds ratios (ORs) and the 95% confidence intervals (CIs) were calculated to estimate the strength of association by unconditional logistic regression analysis. The D' values for each pair of markers were calculated and visualized through the program Haploview v4.2 (Zaykin et al., 2002). Haplotype blocks were defined according to the criteria of Zhao (2004). These criteria were implemented in Haploview in order to examine if the SNPs identified as significant in the single-marker association analysis also existed in the haplotype blocks. Bonferroni's corrections were used in multiple tests, and the P value was divided by the total number of loci or haplotypes.

RESULTS

We genotyped 11 SNPs present within *BRIP1* in 319 breast cancer cases and 306 controls. The genotype distribution of the three polymorphisms was consistent with Hardy-Weinberg equilibrium and is shown in Table 1. Analysis of strong linkage disequilibrium in patients with breast cancer relative to healthy controls revealed that three SNPs (rs11079454, rs7213430, and rs4986763) were located in haplotype block 1, and two SNPs (rs4986764 and rs8077088) were located in haplotype block 2 (D' > 0.9, Figure 1). The distribution of genotype, allele, and haplotype frequencies, along with all statistical analyses, in patients with breast cancer compared to healthy controls are listed in Tables 1 to 3.

Compared to healthy controls, patients with breast cancer carried a higher frequency of the rs4986764 C allele ($\chi^2 = 4.089$, P = 0.043, OR = 0.781, 95%CI = 0.614-0.992); however, it did not pass the threshold value cut-off (P = 0.00625). We did find a significant association of the rs7213430 allele with breast cancer. The frequency of the A allele was significantly higher in breast cancer patients than in healthy controls ($\chi^2 = 8.865$, P = 0.003, OR = 0.700, 95%CI = 0.553-0.886). All differences remained statistically significant even after Bonferroni's corrections.

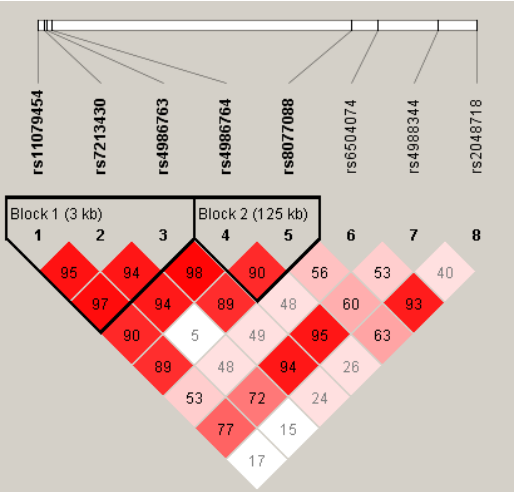

Figure 1. Linkage disequilibrium plot of the 11 SNPs in the *BRIP1* gene. Values in squares are the pairwise calculation of D'.

Table 1. Genotype and allele frequencies of the *BRIP1* gene polymorphisms in cases and controls and the results of their associations with risk of breast cancer.

Variable	Location	MAF	Genotype (N, %)			P[a]	χ^2, P[b]	Allele (N, %)		χ^2, P[c]	OR (95%CI[d])
rs2048718	5'-UTR	0.231	TT	TC	CC	0.288	4.053, 0.132	T	C	0.396, 0.529	0.918
Control (N = 305)			177 (58.0)	115 (37.7)	13 (4.3)			469 (76.9)	141 (23.1)		(0.703-1.198)
Case (N = 319)			201 (63.0)	98 (30.7)	20 (6.3)			500 (78.4)	138 (21.6)		
rs4988344	Intron 5	0.382	CC	CG	GG	0.674	4.404, 0.111	C	G	3.067, 0.080	0.817
Control (N = 306)			43 (14.1)	148 (48.4)	115 (37.6)			234 (38.2)	378 (61.8)		(0.652-1.024)
Case (N = 319)			65 (20.4)	145 (45.5)	109 (34.2)			275 (43.1)	363 (56.9)		
rs8077088	Intron 6	0.201	GG	GT	TT	0.553	3.832, 0.147	G	T	1.149, 0.284	0.862
Control (N = 306)			15 (4.9)	92 (30.1)	199 (65.0)			122 (19.9)	490 (80.1)		(0.657-1.131)
Case (N = 319)			12 (3.8)	119 (37.3)	188 (58.9)			143 (22.4)	495 (77.6)		
rs6504074	Intron 6	0.240	GG	GT	TT	0.882	2.892, 0.235	G	T	1.144, 0.285	0.865
Control (N = 304)			176 (57.9)	110 (36.2)	18 (5.9)			462 (76.0)	146 (24.0)		(0.664-1.128)
Case (N = 319)			203 (63.6)	95 (29.8)	21 (6.6)			501 (78.5)	137 (21.5)		
rs4986764	Exon 18	0.338	CC	CT	TT	0.608	5.804, 0.055	C	T	4.089, 0.043	0.781
Control (N = 306)			132 (43.1)	141 (46.1)	33 (10.8)			405 (66.2)	207 (33.8)		(0.614-0.992)
Case (N = 319)			168 (52.7)	120 (37.6)	31 (9.7)			456 (71.5)	182 (28.5)		
rs4986763	Exon 20	0329	CC	CT	TT	0.978	4.372, 0.112	C	T	1.868, 0.172	0.846
Control (N = 304)			137 (45.1)	134 (44.1)	33 (10.9)			408 (67.1)	200 (32.9)		(0.665-1.075)
Case (N = 319)			168 (52.7)	115 (36.1)	36 (11.3)			451 (70.7)	187 (29.3)		
rs11079454	3'UTR	0.472	TT	TA	AA	0.275	2.329, 0.312	T	A	0.721, 0.396	0.908
Control (N = 306)			90 (29.4)	143 (46.7)	73 (23,9)			323 (52.8)	289 (47,2)		(0.727-1.134)
Case (N = 319)			94 (29.5)	164 (51.4)	61 (19.1)			352 (55.2)	286 (44.8)		
rs7213430	3'UTR	0.379	AA	AG	GG	0.143	8.396, 0.015	A	G	8.865, 0.003	0.700
Control (N = 306)			124 (38.9)	132 (43.1)	50 (16.3)			380 (62.1)	232 (37.9)		(0.553-0.886)
Case (N = 319)			165 (51.7)	117 (36.7)	37 (11.6)			447 (70.1)	191 (29.9)		

[a]P values for Hardy-Weinberg equilibrium in controls. [b]P values for genotype frequency dirrerence. [c]P values for allele frequency dirrerence. [d]P values for allele frequency dirrerence. MAF = minor allele frequency. Alpha value is adjusted by Bonferroni's correction and statistically significant results (P < 0.00625).

Table 2. BRIP1 haplotype in block 1 frequencies and the results of their associations with risk of breast cancer.

Haplotype[a]	Cases (N, %)	Controls (N, %)	Statistics		
			χ^2	P[b]	OR (95%CI)
A - A - C	143 (44.8)	141 (46.1)	0.099	0.754	0.951 (0.694-1.303)
T - G - T	94 (29.5)	98 (32.0)	0.481	0.488	0.887 (0.631-1.246)
T - A - C	81 (25.4)	46 (15.0)	10.352	0.001	1.924 (1.286-2.876)

[a]Haplotypes with frequency <0.05 were excluded. [b]Alpha value is adjusted by Bonferroni's correction and statistically significant results (P < 0.0167).

Table 3. BRIP1 haplotype in block 2 frequencies and the results of their associations with risk of breast cancer.

Haplotype[a]	Cases (N, %)	Controls (N, %)	Statistics		
			χ^2	P[b]	OR (95%CI)
C - T	171 (53.6)	143 (46.7)	2.951	0.086	1.317 (0.962-1.804)
T - T	76 (23.8)	102 (33.3)	6.933	0.008	0.626 (0.441-0.888)

[a]Haplotypes with frequency <0.05 were excluded. [b]Alpha value is adjusted by Bonferroni's correction and statistically significant results (P < 0.025).

Additionally, we performed association analysis to determine if haplotype (blocks 1 and 2) was associated with increased risk of developing breast cancer. Interestingly, a significantly higher number of T-A-C haplotypes (block 1: $\chi^2 = 10.352$, P = 0.001, OR = 1.924, 95%CI = 1.286-2.876) were found in breast cancer patients compared to healthy individuals. In contrast, the frequency of T-T haplotypes (block 2: $\chi^2 = 6.933$, P = 0.008, OR = 0.626, 95%CI = 0.441-0.888) was significantly higher in the healthy controls. These differences remained statistically significant after Bonferroni's corrections.

DISCUSSION

Aberrant DNA helicase activity negatively affects DNA repair and genomic stability, thus increasing the likelihood of cancer development. Germline *BRIP1* mutations are associated with breast cancer and Fanconi anemia (Cantor et al., 2001; Litman et al., 2005). Thus, common variants in the BRIP1 gene are candidates for breast cancer susceptibility. We used an SNP tagging approach to evaluate the association between common variants in *BRIP1* and the risk of developing breast cancer. Here, we provide additional evidence for the contribution of *BRIP1* polymorphisms to breast cancer susceptibility.

BRIP1 rs4986764 is a missense mutation (T → C; Ser → Pro) in exon 18, and has been frequently reported (Pabalan et al., 2013). The C (Ser) allele variant in Pro919Ser has been associated with an increased risk of breast cancer in a kin-cohort study (Sigurdson et al., 2004). While some evidence suggests that there is an association between the *BRIP1* rs4986764 polymorphism and breast cancer (Seal et al., 2006), other studies have failed to reach the same conclusion (Vahteristo et al., 2006; Huo et al., 2009). Results from the present study support only a weak association between rs4986764 and breast cancer. The frequency of the rs4986764 C allele was significantly higher in breast cancer patients than in healthy control individuals. However, it did not pass the threshold value (P = 0.00625). Results using both an SNP tagging approach and a case-control study (Vahteristo et al., 2006)

found no association between this polymorphism and breast cancer (Song et al., 2007). While recent meta-analysis data suggest that the rs4986764 polymorphism is not a breast cancer predisposition allele, any association with low risk disease cannot be discounted (Pabalan et al., 2013). Based on these observations, our data indicate that the difference in rs4986764 C allele frequencies is nothighly significant. On its own, *BRIP1* likely only has a modest influence on breast cancer risk.

SNPs present within the 3'-UTR of genes can modify miRNA binding sites resulting in altered mRNA expression (Nana-Sinkam and Croce, 2011). Such a scenario has been described for *BRIP1*. SNPs in the 3'-UTR of *BRIP1* have been shown to influence mRNA stability and regulate gene expression (Jiang et al., 2013). As a result, these SNPs may affect genetic susceptibility to breast cancer. To the best of our knowledge, our study is the first to describe a significant association between the rs7213430 allele and breast cancer. The frequency of the A allele was significantly higher in breast cancer patients than in healthy controls. Our study design enabled 97% power to detect an allele with this frequency with a type I error rate of 0.0001, even if the true relative risk was 1.3. Despite this strong result, the association between the *BRIP1* rs7213430 allele and genetic susceptibility to breast cancer needs further investigation.

Previous studies have indicated that the rare *BRIP1* variant rs4988345 (Arg173Cys) impairs protein translocation to the nucleus and may also modify breast cancer susceptibility (Lei and Vorechovsky, 2003; Song et al., 2007). Since the MAF for this variant is very low (0.0065) in the Chinese Han population, we had limited power to confirm or refute this association using the case-control population of the current study. Song et al. (2007) reported that the MAF of rs4988344 was associated with increased risk of ovarian cancer, but not breast cancer. These associations were only borderline significant, and should be interpreted with caution. We did not find any association between this allele and genetic susceptibility to breast cancer in our study.

We performed additional analyses examining the interaction among polymorphisms and the observed strong linkage disequilibrium. Haplotype analysis revealed that significantly more T-A-C haplotypes (block 1) were found in patients with breast cancer. These results indicate that individuals with this haplotype of the BRIP1 gene are more susceptible to developing breast cancer. In contrast, significantly higher frequencies of T-T haplotypes were detected in healthy controls compared to breast cancer patients, suggesting that this haplotype may have a protective effect against breast cancer. This finding further supports a role of *BRIP1* polymorphisms in breast cancer.

In conclusion, these findings warrant additional efforts aimed at identifying functional polymorphisms within, and close to, the BRIP1 gene. Such analyses should use a systemic approach and a larger sample set. The results of our study, in conjunction with future research, may help elucidate the biological mechanisms governing breast cancer, which may allow us to devise better treatment strategies.

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Supplementary material

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