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BRIP1 variations analysis reveals their relative importance as genetic susceptibility factor for cervical cancer

X.D. Ma, G.Q. Cai, W. Zou, Y.H. Huang, J.R. Zhang, D.T. Wang, B.L. Chen *

Department of Obstetrics and Gynecology, Xijing Hospital, Fourth Military Medical University, 17 Changle West Road, Xi'an 710032, PR China

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ABSTRACT

To evaluate the association between gene variations in BRIP1 (BRCA1-interacting protein 1) and the risk of cervical cancer, we examined eight single nucleotide polymorphisms (SNPs: rs2048718, rs12937080, rs4988344, rs6504074, rs4988345, rs4986764, rs4986763, and rs11079454) in the BRIP1 gene in cervical tissue from a Chinese population using the MassARRAY system. The participants enrolled included 454 cervical cancer patients and 562 healthy controls. Quantitative real-time reverse transcription PCR (qRT-PCR) was performed to examine the potential correlation between functional BRIP1 SNP genotypes and mRNA levels in cervical cancer tissues. Our results first showed that rs4986764, located in exon 18 in the BRIP1 gene, was significantly associated with cervical cancer ($\chi^2 = 11.191$, $P = 0.001$, odds ratio (OR) = 1.384, 95% confidence interval (CI) = 1.144–1.675). Another significant association was observed for rs4986763 located in exon 20 in BRIP1 ($\chi^2 = 4.988$, $P = 0.026$, OR = 1.241, 95% CI = 1.027–1.500). Strong linkage disequilibrium was observed in the rs11079454–rs4986763–rs4986764 SNP block ($D' > 0.9$). The frequencies of haplotype T–T–T are higher in controls than in these patients ($P = 2.01E{-}5$). Moreover, cervical cancer tissues with a homozygous C/C genotype for rs4986764 had the lowest level of BRIP1, which was 2.8 and 2.9-fold lower than the C/T heterozygote and the T/T homozygote, respectively. These findings indicate a role for BRIP1 gene variations in cervical cancer and may be informative for future genetic or biological studies on cervical cancer.

1. Introduction

Cervical cancer is the second most common cancer in women worldwide [1,2]. Human papillomavirus (HPV) infection is the etiological factor associated with cervical cancer [3,4]. Intense investigation on cervical cancer in recent decades has led to an increased understanding of the molecular biology of cervical cancer development and progression. However, the genetic etiology of cervical cancer is still lacking. Several genes, such as BRCA1 (breast cancer 1) and BRCA2 (breast cancer 2), have been suggested as potential candidates for cervical cancer progression [5,6].

Invasion and metastasis are major factors that significantly affect the mortality and prognosis of cervical cancer. Genes involved in invasion and metastasis and which control cell division and the maintenance of genome integrity (e.g. DNA repair) represent good candidates for genetic susceptibility. BRIP1 (BRCA1-interacting protein 1), a member of the DEAH helicase family, is a Fanconi anemia complementation group J (FANCJ) gene that directly interacts with the BRCT domain of BRCA1 and has a role in DNA damage repair [7,8]. The specific interaction between BRCA1 and phosphorylated BRIP1 is regulated by the cell cycle and is essential for DNA double-strand break repair and tumor suppressor function [9,10]. BRIP1 is required for homologous recombination-mediated double-strand break repair, for the execution of the G2/M cell cycle checkpoint and for normal progression through S phase by assisting in the resolution of stalled replication forks [11].

The BRIP1 gene, which is located on chromosome 17q22, encodes a 1249 amino acid helicase [12]. The C-terminal domain of the BRIP1 protein interacts with BRCA1. Accumulating evidence suggests that BRIP1 plays an anti-oncogenic role, and downregulation of BRIP1 has been reported in multiple cancers [7,13,14]. Specifically, common single nucleotide polymorphisms (SNPs) in the BRIP1 gene are associated with susceptibility to prostate, breast and ovarian cancers [14–16]. However, the genetic susceptibility of the BRIP1 gene to cervical cancer has not yet been investigated.

Due to the growing relevance of BRIP1 in tumorigenesis (including cancers of cervical origin), we hypothesized that common variants in the BRIP1 gene might contribute significantly to the predisposition to develop cervical cancer. In the present study, we investigated the association between eight single nucleotide polymorphisms (SNPs: rs2048718, rs12937080, rs4988344, rs6504074, rs4988345, rs4986764, rs4986763, and rs11079454) in the BRIP1 gene and the risk of cervical cancer in a Chinese population. Additionally, *in vivo* experiments showed that lower

* Corresponding author. Fax: +86 029 84775391.
E-mail address: maxiangdongfck@163.com (B.L. Chen).

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mRNA levels of BRIP1 from cervical cancer tissues associated with rs4986764 C/C homozygosity.

2. Subjects and methods

2.1. Subjects

This case-control study enrolled 454 unrelated female subjects with cervical squamous cell carcinoma (mean ± SD, 43.56 ± 4.66). The patients were hospitalized in the Department of Obstetrics and Gynecology, Xijing Hospital, Fourth Military Medical University, between May 2007 and July 2012. The clinical diagnosis was confirmed by histological examination of biopsies or resected tissues. Patients with cervical adenocarcinoma were excluded. The control group consisted of 562 healthy women (mean ± SD, 44.23 ± 5.24) selected from a regular gynecological examination. All subjects were from the Chinese Han population living in the Shaanxi province in China. All subjects gave written consent, and the study was approved by the Ethics Committee of the Fourth Military Medical University.

2.2. Selection of the polymorphisms

Functional SNPs in the promoter region, 5′- and 3′-UTRs, and exons of the BRIP1 gene were systematically screened. Marker selection was based on the following criteria. First, we examined tagSNPs in Haploview (v4.2), using the Han Chinese in Beijing (CHB) population and a minor allele frequency (MAF) cut-off ⩾5% (HapMap Data Release 27). Second, previous studies have shown significant associations between cancer and SNPs in promoter regions, 5′ and 3′-UTRs and introns. Eight SNPs in the BRIP1 gene were selected.

2.3. Genotyping

Three to five milliliters of peripheral blood were collected in tubes coated with ethylene diamine tetraacetic acid (EDTA). Genomic DNA was extracted from blood leukocytes using the EZNATM Blood DNA Midi Kit (Omega Bio-Tek, Norcross, GA, USA), according to the manufacturer's protocol. Genotyping of the BRIP1 polymorphisms was performed using the MassARRAY system (Sequenom Inc., San Diego, CA, USA) [17,18]. Primers and probes are listed in Table 1.

2.4. Quantitative RT-PCR analysis

Quantitative real-time reverse transcription PCR (qRT-PCR) was performed to determine BRIP1 mRNA levels in cervical cancer tissues. Total RNA was extracted from tumor tissue specimens with different genotypes using the RNAiso Plus kit (Takara, Shiga, Japan). cDNA was synthesized using an oligo (dT) 15 primer and Superscript II (Invitrogen, Carlsbad, CA). The 25 μL final reaction mixture consisted of 2 μL of cDNA, 12.5 μL of SYBR Green (Applied Biosystems, Foster City, CA), and 1 μM of appropriate primers. Product accumulation was monitored by SYBR Green fluorescence with ABI Prism 7000 Sequence Detection Systems. Relative expression levels were determined using a standard curve derived from serial dilutions of cDNA samples. Forward and reverse primers for BRIP1 and β-actin were used as described previously [19]. Data were normalized to β-actin levels, which served as an internal control.

2.5. Statistical analysis

All statistical analyses were carried out using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). Hardy–Weinberg equilibrium and associations between the case–control status and each polymorphism were assessed by the Pearson Chi-square test. Pair-wise linkage disequilibrium statistics (D' and r^2) and haplotype frequencies were computed using Haploview 4.0 to construct haplotype blocks. Bonferroni correction was used in multiple tests. The significance level (0.05) was divided by the total number of loci or haplotypes. For real-time RT-PCR, the normalized expression values of BRIP1 were analyzed using one-way ANOVA, followed by a Bonferroni t-test.

3. Results

The distribution frequencies of eight genotyped SNPs were in agreement with Hardy–Weinberg equilibrium. LD analyses of cervical cancer patients and healthy controls revealed that the SNPs rs11079454, rs4986763 and rs4986764 were located in haplotype blocks 1 (D' > 0.9, Fig. 1). The distribution of genotypes and allele frequencies and statistical analysis of the eight SNPs are listed in Table 2. The distribution of haplotype frequencies, together with the results of statistical analysis, are listed in Table 3.

The results revealed a significant association between the rs4986764 genotype distribution and cervical cancer patients (P = 0.002). Cervical cancer patients had a significantly higher frequency of the C allele (χ^2 = 11.191, P = 0.001, OR = 1.384, 95% CI = 1.144–1.675). There was a significant between-group difference in the genotype distribution of rs4986763 (P = 0.015). Cervical cancer patients had a higher frequency of the C allele (χ^2 = 4.988, P = 0.026, OR = 1.241, 95% CI = 1.027–1.500). However, the minor alleles for rs4988345 and rs12937080 are very rare (one C/C genotype for rs4988345 and one A/A genotype for rs12937080 were observed in the control group). These two SNPs have been excluded from the further statistical analysis because of its extreme rarity (Table 2).

Furthermore, strong linkage disequilibrium was observed in rs11079454–rs4986763–rs4986764 (D' > 0.9). The frequency of the T–T–T haplotype in block 1 (rs11079454–rs4986763–rs4986764) was higher in controls than in the patients (P = 2.01E−5).

To test whether the transcription of BRIP1 is regulated by rs4986764 and rs4986763, we measured the levels of BRIP1 mRNA in tumor tissues with different genotypes using qRT-PCR.

Table 1
Primer sequences used for genotyping of BRIP1 gene SNPs with the MALDI-TOF sequenom platform.

SNPS	Forward primers	Reverse primers	Extension primers
rs2048718	ACGTTGGATGAAGAGAAGAAAGGGCACGAG	ACGTTGGATGTGGGTCGAGGAAAGGTAACG	GGGTGCCTTGTGTGCAGGAC
rs4988344	ACGTTGGATGGCCTTTGAGAACAACTAGCC	ACGTTGGATGTCTGTTCCAAAGCAATGACG	ATCCAGTTAAACTTCTAGTTCACC
rs6504074	ACGTTGGATGTTTTCAGGGCTTGCAGAATC	ACGTTGGATGTTTCCCAGAGGGCACATAAC	GACTCAATTTGATAAGATTTTTGTCG
rs4986764	ACGTTGGATGACAGGACAATGAGTCTACAC	ACGTTGGATGAGATGACTTGCTGCTTCCAG	GACCTCTTTAAAGTACAGTACCC
rs4986763	ACGTTGGATGACAGAAGCAGAAGATGAATC	ACGTTGGATGCTATCAGTTTCAGCTAGGTC	CTCTCTATTTTACACCTGAACTTTAC
rs11079454	ACGTTGGATGGTAGGATGTAGGCCATTTTC	ACGTTGGATGAACTTGCAATGTGCCAGGTG	TATGCCATTTTCATTACTGATAACA
rs12937080	ACGTTGGATGATTACAAGTGTGAGCCACCG	ACGTTGGATGGAAGATATCTCCCGATTATG	TCCCAGCCTCCATTTTTCC
rs4988345	ACGTTGGATGGCCTTTGAGAACAACTAGCC	ACGTTGGATGGTGTACTTCTGTTCCAAAGC	CTGGTCTGTGTTTACAGATTAGAAAA

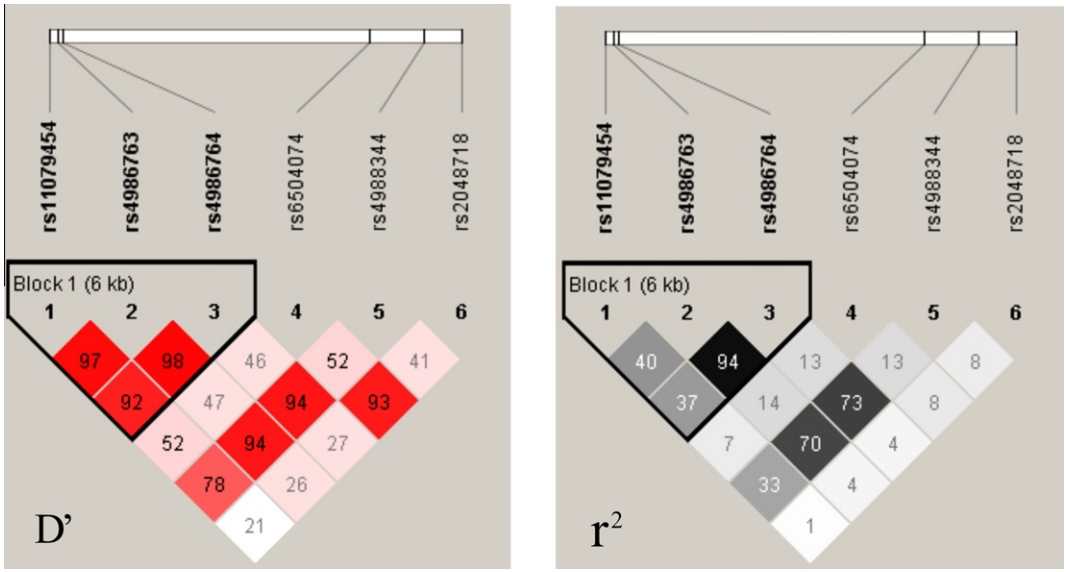

Fig. 1. LD plot of the 6 SNPs in the BRIP1 gene. Values in squares are the pair-wise calculation of D' (left) or r^2 (right).

Table 2
Genotype and allele frequencies of the BRIP1 gene polymorphisms in cases (n = 454) and controls (n = 562) and the results of their associations with risk of cervix cancer.

Variable	Location	Group	N	Genotype (n, %)			Allele (n, %)		P^a	P^b	P^c	OR, 95%CI[d]
				TT	TC	CC	T	C				1.091,
rs2048718	5′UTR	Control	560	326(58.2)	208(37.1)	26(4.6)	860(76.8)	260(23.2)	0.322	0.097	0.416	0.884–1.346
		Case	454	285(62.8)	141(31.1)	28(6.2)	711(78.3)	197(21.7)				
				CC	CG	GG	C	G				1.185,
rs4988344	Intron 5	Control	562	84(14.9)	270(48.0)	208(37.0)	438(39.0)	686(61.0)	0.812	0.082	0.062	0.992–1.415
		Case	454	92(20.3)	207(45.6)	155(34.1)	391(43.1)	517(56.9)				
				GG	GT	TT	G	T				1.207,
rs6504074	Intron 6	Control	558	317(56.8)	205(36.7)	36(6.5)	839(75.2)	277(24.8)	0.713	0.081	0.077	0.980–1.487
		Case	454	288(63.4)	137(30.2)	29(6.4)	713(78.5)	195(21.5)				
				CC	CT	TT	C	T				1.384,
rs4986764	Exon 18	Control	562	240(42.7)	258(45.9)	64(11.4)	738(65.7)	386(34.3)	0.670	0.002*	0.001*	1.144–1.675
		Case	454	247(54.4)	165(36.3)	42(9.3)	659(72.6)	249(27.4)				
				CC	CT	TT	C	T				1.241,
rs4986763	Exon 20	Control	558	247(44.3)	247(44.3)	64(11.5)	741(66.4)	375(33.6)	0.850	0.015	0.026	1.027–1.500
		Case	454	241(53.1)	163(35.9)	50(11.0)	645(71.0)	263(29.0)				
				TT	TA	AA	T	A				1.057,
rs11079454#	3′UTR	Control	562	172(30.6)	262(46.6)	128(22.8)	606(53.9)	518(46.1)	0.142	0.566	0.537	0.887–1.260
		Case	454	134(29.5)	234(51.5)	86(18.9)	502(55.3)	406(44.7)				
				AA	AG	GG	A	G				
rs12937080#	Intron 4	Control	562	562(100.0)	0(0.00)	0(0.00)	1124(100.0)	0(0.00)	–	–	–	–
		Case	454	452(99.6)	2(0.4)	0(0.0)	906(99.8)	2(0.2)				
				CC	CT	TT	C	T				
rs4988345	Exon 16	Control	562	562(100.0)	0(0.00)	0(0.00)	1124(100.0)	0(0.00)	–	–	–	–
		Case	454	452(99.6)	0(0.00)	2(0.4)	904(99.6)	2(0.4)				

[a] P values for Hardy–Weinberg equilibrium in controls.
[b] P values for genotype frequency distribution.
[c] P values for allele frequency distribution.
[d] OR and 95%CI values for allele.
* Statistically significant (P < 0.0083 = 0.05/6).
# These two SNPs have been excluded from the further statistical analysis because of its extreme rarity.

Table 3
BRIP1 haplotype in block 1 frequencies and the results of their associations with risk of cervix cancer.

Haplotype#	Cases (n, %)	Controls (n, %)	Statistics			
			χ^2	P	OR	95%CI
A-C-C	188(41.4)	251(44.7)	1.082	0.298	0.876	0.682–1.125
T-T-T	97(21.4)	188(33.5)	18.177	2.013E-5*	0.541	0.407–0.719
T-C-C	108(23.8)	116(20.6)	1.448	0.229	1.200	0.891–1.616

Haplotypes with frequency <0.05 were excluded.
* Statistically significant (P < 0.0167 = 0.05/3).

Statistical analysis revealed that the genotype of rs4986764 significantly affects the levels of BRIP1 mRNA [$F_{(2,59)} = 16.53$, $P < 0.001$], but BRIP1 mRNA levels are not affected by the rs4986763 genotype [$F_{(2,59)} = 2.478$, $P > 0.05$] (Fig. 2). A post hoc Bonferroni *t*-test revealed that BRIP1 mRNA levels in tissue from patients that were homozygous for C/C were significantly lower than those from patients homozygous for T/T and heterozygous for C/T ($P < 0.05$). No significant difference in the levels of BRIP1 mRNA was observed between tissue heterozygous for C/T and homozygous for T/T.

4. Discussion

DNA damage repair and genomic stability are complex and coordinated processes that are highly involved in human cancer development. As a DNA-dependent ATPase and a DNA helicase, BRIP1 forms a complex with the BRCT domain of BRCA1, whose main function is to mediate DNA double-strand break repair [7]. Considering the important role of BRIP1 in DNA damage-induced checkpoint control during the G2 to M phase transition, mutations and polymorphisms in the BRIP1 gene may partially account for a proportion of cervical cancer susceptibility [20]. Results from this study indicated a strong occurrence of C allele frequencies in rs4986764 (exon 18) and a weak occurrence of C allele frequencies in rs4986763 (exon 20) in cervical cancer. The rs4986764 SNP in the BRIP1 gene may play a potential role in the carcinogenesis and development of cervical cancer.

In our study, the frequency of the C allele in rs4986764 was significantly higher in patients than in healthy controls, and decreased BRIP1 expression was also found in patients carrying the CC genotype. To our knowledge, this report is the first to evaluate and elucidate the association between genetic variants in BRIP1 and cervical cancer. A recent study showed significant differences in genotypes and allele distributions for SNP rs12937080 (intron 4) between patients with ovarian cancer and control subjects [21]. Earlier studies revealed that rs4988345 (exon 16) impairs protein translocation to the nucleus and might modify breast cancer susceptibility [22,23]. In this study, we found no association between these two SNPs and cervical cancer because the minor alleles for rs4988345 and rs12937080 are very rare in the Chinese Han population. Due to the higher frequencies in controls, a protective effect may be implicated with the T–T–T haplotype (rs11079454–rs4986763–rs4986764). Also, the point-wise associations of these variants with cervical cancer were significant. These results indicated that subjects with the T–T–T haplotype are less prone to cervical cancer. To some extent, our study supports recent work showing the association of BRIP1 polymorphisms with ovarian cancer and breast cancer [21–23].

The BRIP1 gene is essential for DNA repair pathways in normal cellular responses to cisplatin and other DNA cross-linking agents. Germline mutations in the BRCA1 and BRCA2 genes confer high risks of breast and ovarian cancers [24,25]. BRIP1 also plays a critical role in the development and progression of cervical cancer by interacting with the BRCA genes. Indeed, germline mutations in BRIP1 are associated with Fanconi anemia (FA), which is an inherited disorder associated with progressive aplastic anemia, multiple congenital abnormalities and a predisposition to malignancies including leukemia and solid tumors [8]. The lifetime risk for developing cervical cancer in FA patients is also significantly higher than that in control subjects [26,27]. The BRCA–FA pathway is highly involved in tumor cell survival and tumorigenesis and offers potential therapeutic targets in cancer therapy [28]. Moreover, promoter hypermethylation of the FANCF gene disrupts the BRCA–FA pathway and induces cisplatin resistance [29]. FANCF promoter hypermethylation also occurs in squamous cell carcinomas of the lung and oral cavity [30].

The exact mechanism underlying BRIP1-related tumor susceptibility remains unknown. Variations in the DNA sequence have been shown to contribute to individual differences in disease susceptibility. Previous studies suggested that the rare variant Arg173Cys (tSNP rs4988345 in exon 16) played an important role in impedance of protein translocation to the nucleus. This evidence strengthened the hypothesis that the risk allele of BRIP1 may cause aberrant expression of genes and result in the transactivation of anti-apoptosis genes, which are important for DNA repair. Luo et al. suggested that this functional tSNP might affect breast cancer susceptibility in a Swedish population [23]. However, Song et al. could not confirm or refute this association using the case-control population in their study because the minor allele for rs4988345 is very rare [16]. We confirmed the rare allele for rs4988345 in a Chinese Han population. Moreover, the results from qRT-PCR indicated that BRIP1 mRNA levels from cervical cancer tissue correlated with different genotypes in exon 18 in the BRIP1 gene. Although no correlation between different genotypes of rs4986763 in exon 20 and BRIP1 mRNA expression was detected, the tumor tissue that was homozygous for C/C in SNP rs4986764 showed the lowest level of BRIP1, which was 2.8 and 2.9-fold lower than heterozygous C/T and homozygous T/T, respectively. Based on the critical role of the BRCA–FA pathway in tumor development and progression, the risk allele in rs4986764 in BRIP1 exon 18 may cause low-level activation of BRIP1, resulting in increased susceptibility to cervical cancer through an impaired DNA repair process. We are currently examining the possible association between this SNP and BRIP1 expression *in vitro*. However, the *in vivo* situation, where BRIP1 might be regulated by multiple mechanisms, is much more complex than the *in vitro* situation. The precise

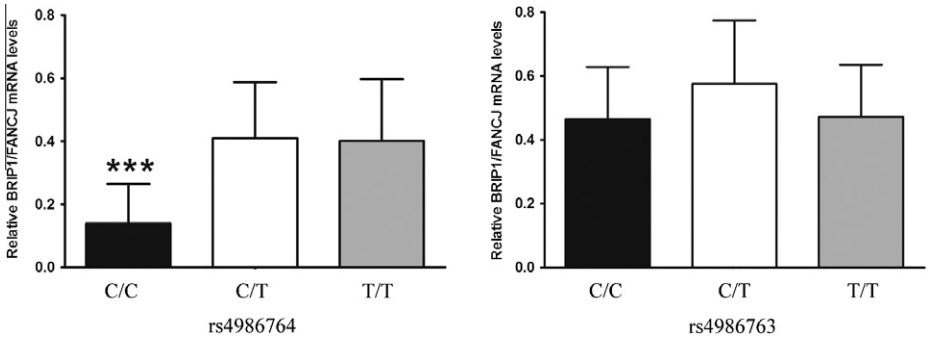

Fig. 2. mRNA levels of the BRIP1 gene from cervical cancer tissues with different genotypes. For rs4986764, a significant decrease in BRIP1 mRNA level was observed in a C/C homozygote compared with a C/T heterozygote and a T/T homozygote. No significant genotypic effect on BRIP1 mRNA levels among groups was observed for rs4986763. Results are expressed as the ratio of the concentration of the BRIP1 gene transcript to that of β-actin. The mean ± SD. ($n = 20$ for each genotype from 20 different individuals) is shown. ***$P < 0.001$, C/C vs. C/T or T/T (one-way ANOVA, followed by a Bonferroni *t*-test).

mechanisms by which functional SNPs in the BRIP1 gene affect BRIP1 levels *in vivo* requires further investigation.

It is should be noted that reports concerning the association of the BRIP1 gene with cancer in the literature are controversial. For instance, previous studies demonstrated an association of BRIP1 gene polymorphisms with breast cancer [15,23,31], while other studies did not confirm the significant contribution of common variants in BRIP1 to breast cancer susceptibility [16]. The discrepancy between these studies might be attributed to differences in regions, ethnic groups and sample sizes in these studies. Although our study demonstrated that BRIP1 gene polymorphisms were associated with a predisposition to cervical cancer in a Chinese population, further research is needed to confirm these findings in a different ethnic group and larger population. These studies would help to reveal the mechanisms by which BRIP1 gene polymorphisms affect cervical cancer phenotypes.

In summary, our study demonstrated that SNPs in the BRIP1 gene may influence cervical cancer susceptibility in a Chinese Han population. These SNPs may alter BRIP1 gene expression, which is possibly involved in the development and progression of cervical cancer.

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