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Association of Single-Nucleotide Polymorphisms in Monoubiquitinated FANCD2-DNA Damage Repair Pathway Genes With Breast Cancer in the Chinese Population

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Abstract

Objective: The aim of the study was to estimate breast cancer risk conferred by individual single-nucleotide polymorphisms of breast cancer susceptibility genes. **Methods:** We analyzed the 48 tagging single-nucleotide polymorphisms of 8 breast cancer susceptibility genes involved in the monoubiquitinated FANCD2–DNA damage repair pathway in 734 Chinese women with breast cancer and 672 age-matched healthy controls. **Results:** Forty-five tagging single-nucleotide polymorphisms were successfully genotyped by SNPscan, and the call rates for each tagging single-nucleotide polymorphisms were above 98.9%. We found that 13 tagging single-nucleotide polymorphisms of 5 genes (*Parter and localizer of Breast cancer gene2* (*PALB2*), *Tumour protein 53* (*TP53*), *Nijmegen breakage syndrome 1*, *Phosphatase and tensin homolog deleted from chromosome 10* (*PTEN*), and *Breast cancer gene 1* (*BRCA1-interacting protein 1*)) were significantly associated with breast cancer risk. A total of 5 tagging single-nucleotide polymorphisms (rs2299941 of *PTEN*, rs2735385, rs6999227, rs1805812, and rs1061302 of *Nijmegen breakage syndrome 1*) were tightly associated with breast cancer risk in sporadic cases, and 5 other tagging single-nucleotide polymorphisms (rs1042522 of *TP53*, rs2735343 of *PTEN*, rs7220719, rs16945628, and rs11871753 of *BRCA1-interacting protein 1*) were tightly associated with breast cancer risk in familial and early-onset cases. **Conclusions:** Some of the tagging single-nucleotide polymorphisms of 5 genes (*PALB2*, *TP53*, *Nijmegen breakage syndrome 1*, *PTEN*, and *BRCA1-interacting protein 1*) involved in the monoubiquitinated FANCD2–DNA damage repair pathway were significantly associated with breast cancer risk.

Keywords

breast cancer, SNP, monoubiquitinated FANCD2–DNA damage repair pathway genes

Abbreviations

BRIP1, *BRCA1*-interacting protein 1; CI, confidence interval; DSB, double-strand break; HWE, Hardy-Weinberg equilibrium; MRN, MRE11/*RAD50*/NBS1; NBS, Nijmegen breakage syndrome; OR, odds ratio; PCR, polymerase chain reaction; SNP, single-nucleotide polymorphism; tSNP, tagging single-nucleotide polymorphism

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Introduction

It is estimated that 5% to 10% of breast cancer is caused by significant hereditary predisposition.[1] The major genes involved in familial breast cancer susceptibility are *Breast cancer gene 1 (BRCA1)* and *BRCA2*,[2,3] the mutations of which account for less than 5% of all patients with breast cancer and

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less than 25% of those with familial cancers.[4] Thus, it is likely that other breast cancer susceptibility genes exist. High-penetrance susceptibility genes like *TP53*, *Nijmegen breakage syndrome 1* (*NBS1*), and *PTEN*, which are rare cancer-predisposing syndromes, have been found to be associated with an increased breast cancer risk.[5-7] Another 5 genes—*ATM*, *BRCA1-interacting protein 1* (*BRIP1*), *CHEK2*, *PALB2*, and *RAD50*—with moderate-penetrance breast cancer susceptibility have odds ratios (ORs) for heterozygosity between 2.0 and 4.3.[8-12] Interestingly, the abovementioned 10 genes are directly or indirectly involved in the monoubiquitinated FANCD2–DNA damage repair pathway.[13] A complex of 8 Fanconi proteins (A, B, C, E, F, G, L, and M) activates FANCD2 through monoubiquitination, which enables FANCD2 to translocate to damage-induced nuclear foci that contain *BRCA1*, *BRCA2*, and RAD51. DNA damage activates *ATM* and *CHEK2* and then activates *BRCA1* through phosphorylation.[13] *PTEN* binds to the RAD51 promoter and regulates its transcription.[14] *PALB2*, a nuclear partner of *BRCA2*, which is also known as FANCN, is required for the intranuclear localization and stability of *BRCA2* to execute its functions in error-free DNA double-strand break (DSB) repair by homologous recombination and checkpoint control in intra–S phase DNA damage processes.[15]

BRCA1-interacting protein 1 (*BRIP1*), which is also known as Fanconi anemia complementation group J (FANCJ), is involved in certain DNA damage repair functions of *BRCA1*, interacting directly with the *BRCA1* C-terminal (BRCT) repeats.[16,17] The highly conserved MRE11/*RAD50*/NBS1 (MRN) complex participates in the initial processing of DSBs. Because of its nuclease activity and DNA-binding ability, its presence in the MeR11 protein is partly dependent on the interaction of MRE11 with *RAD50*, which provides the energy source for the MRN complex.[18,19] *Nijmegen breakage syndrome 1* recruits activated *ATM* to DNA damage sites and then promotes its phosphorylation and the triggering of DNA damage response steps.[20]

Single-nucleotide polymorphisms (SNPs) have been historically classified as a commonly occurring (>1%) genetic variation in the general population, whereas the rare variants with obvious functional consequences on the protein have been classified as mutations. To estimate breast cancer risk conferred by individual SNPs, we have analyzed the 48 tagging SNPs (tSNPs) of 8 breast cancer susceptibility genes involved in the monoubiquitinated FANCD2–DNA damage repair pathway which includes all the tSNPs of the 4 genes (*PALB2*, *PTEN*, *TP53*, and *RAD50*) and some of the tSNPs of the other 4 genes (*BRIP1*, *NBN*, *CHEK2*, and *ATM*), in Chinese women with sporadic or familial and early-onset breast cancer.

Materials and Methods

Patients

In this study, 734 patients with pathologically confirmed breast cancer were recruited unselectedly from the Department of Breast Surgery of Central South University's Xiangya Hospital, Changsha, between January 2007 and October 2011, and the Department of Breast Surgery of the Second People's Hospital of Sichuan Province, Chengdu, People's Republic of China, between November 2010 and May 2011. The patients with breast cancer were divided into 2 groups: the sporadic group and the familial and early-onset group, as described in our previous study.[21] All the participants have provided signed informed consent prior to blood extraction, and the ethics committees of Xiangya Hospital of Central South University and Second People's Hospital of Sichuan Province have approved this study.

Selection of tSNPs

Based on the HapMap CHB database (HapMap data, Rel 24/phaseII Nov08, on NCBI B36 assembly, dbSNP b126; population: Han Chinese in Beijing, People's Republic of China), finally a total of 48 SNPs were selected as tSNPs, including all the tSNPs of *PALB2*, *PTEN*, *TP53*, and *RAD50* and some of the tSNPs of *BRIP1*, *NBN*, *CHEK2*, and *ATM* as described in our previous study.[21]

Genotyping Methods

DNA was extracted from 5 mL of peripheral blood using standard procedures (the phenol–chloroform method). The SNP genotyping work was performed using a custom-by-design 2 × 48-Plex SNPscan Kit (Cat#: G0104; Genesky Biotechnologies Inc, Shanghai, People's Republic of China). This kit was developed according to an SNP genotyping technology patented by Genesky Biotechnologies Inc, which was based on double ligation and multiplex fluorescence polymerase chain reaction.

As described in our previous study,[21] finally, 45 tSNPs were successfully genotyped. Six cases and 1 control were excluded from further analyses due to failed genotyping. Thus, the final analysis included 728 cases and 671 controls.

Statistical Methods

The χ^2 test with 1 degree of freedom (*df*) was used to assess the Hardy-Weinberg equilibrium (HWE) in the case and control samples. Unconditional logistic regression was used to compare the genotype frequencies of each tSNP between cases and controls. The common homozygote was used to as the reference to calculate the genotype-specific OR and its 95% confidence intervals (CI) under the codominant, dominant, and recessive model. Statistical analysis was carried out using SPSS v. 17.0.

Results

Table 1 and Supplementary Table 1 present the genotype distributions and allele frequencies for 45 tSNPs of 8 genes in the unselected breast cancer group and control group. The genotype distributions of controls at each locus were consistent with HWE.

Table 1. Summary Data for Correlations of Some tSNPs Under the Codominant Model in Unselected Cases.

			Case	Control			
Gene	SNP	Genotype	n	n	OR[a] (95% CI)	*P* Value[b]	Call Rate
TP53	rs1042522	CC	205	227	1	.074	99.43%
		CG	386	327	1.31 (1.03-1.66)		
		GG	136	117	1.29 (0.94-1.76)		
		MAF[c]	0.45	0.42			
		HWE *P*[d]	0.061	1			
	rs12951053	AA	308	331	1	.024	99.29%
		CA	346	273	1.36 (1.09-1.70)		
		CC	71	67	1.14 (0.79-1.65)		
		MAF[c]	0.34	0.30			
		HWE *P*[d]	0.068	0.36			
NBS1	rs1061302	TT	246	190	1	.063	99.08%
		CT	351	349	0.78 (0.61-0.99)		
		CC	125	132	0.73 (0.54-1.00)		
		MAF[c]	0.42	0.46			
		HWE *P*[d]	1	0.24			
	rs1805812	TT	552	470	1	.037	99.43%
		CT	157	184	0.73 (0.57-0.93)		
		CC	19	16	1.01 (0.51-1.99)		
		MAF[c]	0.13	0.16			
		HWE *P*[d]	0.076	0.78			
	rs2735385	CC	290	210	1	.002	99.43%
		CA	343	345	0.72 (0.57-0.91)		
		AA	94	116	0.59 (0.42-0.81)		
		MAF[c]	0.37	0.43			
		HWE *P*[d]	0.69	0.24			
	rs6999227	GG	276	200	1	.003	99.36%
		CG	345	344	0.73 (0.57-0.92)		
		CC	106	126	0.61 (0.44-0.84)		
		MAF[c]	0.38	0.44			
		HWE *P*[d]	0.94	0.35			
PTEN	rs2299941	AA	349	268	1	.003	99.00%
		GA	314	314	0.77 (0.61-0.96)		
		GG	62	85	0.56 (0.39-0.81)		
		MAF[c]	0.3	0.36			
		HWE *P*[d]	0.54	0.68			
PALB2	rs513313	TT	489	434	1	.072	99.36%
		CT	217	203	0.95 (0.75-1.20)		
		CC	20	34	0.52 (0.30-0.92)		
		MAF[c]	0.18	0.2			
		HWE *P*[d]	0.61	0.12			
BRIP1	rs16945628	CC	322	271	1	.037	99.15%
		CT	290	313	0.78 (0.62-0.98)		
		TT	112	86	1.10 (0.79-1.52)		
		MAF[c]	0.35	0.36			
		HWE *P*[d]	0.00086	0.8			
	rs7220719	GG	479	429	1	.031	99.36%
		GA	202	217	0.83 (0.66-1.05)		
		AA	45	25	1.61 (0.97-2.67)		
		MAF[c]	0.20	0.20			
		HWE *P*[d]	0.00048	0.81			

Abbreviations: CI, confidence interval; HWE, Hardy-Weinberg equilibrium; NBS, Nijmegen breakage syndrome; OR, odds ratio; SNP, single-nucleotide polymorphisms; tSNPs, tagging single-nucleotide polymorphisms.

[a]Compared with common homozygote by logistic regression analysis.

[b]Genotype frequency *P*-value.

[c]MAF=minor allele frequency.

[d]HWE= Hardy-Weinberg equilibrium, *P*-value from chi square test with one degree of freedom.

Table 2. Risk Estimates Calculated Using the Dominant and Recessive Inheritance Models of Some tSNPs in Unselected Cases.[a]

		Dominant[b]		Recessive[c]	
Gene	SNP	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
TP53	rs1042522	1.30 (1.04-1.63)	.023	1.09 (0.83-1.43)	.54
	rs12951053	1.32 (1.07-1.63)	.01	0.98 (0.69-1.39)	.9
	rs8064946	1.24 (1.01-1.53)	.044	1.03 (0.72-1.49)	.87
NBS1	rs1061302	0.76 (0.61-0.96)	.02	0.85 (0.65-1.12)	.26
	rs1805812	0.75 (0.59-0.95)	.017	1.10 (0.56-2.15)	.79
	rs2735385	0.69 (0.55-0.86)	.001	0.71 (0.53-0.95)	.023
	rs6999227	0.70 (0.56-0.87)	.001	0.74 (0.56-0.98)	.034
PTEN	rs2299941	0.72 (0.59-0.90)	.003	0.64 (0.45-0.90)	.011
	rs2735343	1.13 (1.00-1.82)	.32	1.31 (1.02-1.68)	.032
PALB2	rs513313	0.89 (0.71-1.11)	.29	0.53 (0.30-0.93)	.025
BRIP1	rs11871753	0.94 (0.75-1.19)	.63	1.75 (1.00-3.04)	.044
	rs7220719	0.91 (0.73-1.14)	.42	1.71 (1.04-2.82)	.033
	rs16945628	0.85 (0.69-1.05)	.13	1.24 (0.92-1.68)	.16

Abbreviations: CI, confidence interval; NBS, Nijmegen breakage syndrome; OR, odds ratio; SNP, single-nucleotide polymorphisms; tSNPs, tagging single-nucleotide polymorphisms.
[a]A/A as common homozygote.
[b]Dominant model: B/B + A/B versus A/A.
[c]Recessive model: B/B versus A/B + A/A.

TP53

The tSNP rs12951053 was associated with an increased risk of breast cancer (OR = 1.36, 95% CI: 1.09-1.70 for the C/A genotype and OR = 1.14, 95% CI: 0.79-1.65 for the C/C genotype) compared to the common homozygote A/A ($P = .024$) in unselected cases under the codominant model (Table 1). It was also significant under the dominant model (OR = 1.32, 95% CI: 1.07-1.65 for C/A and C/C genotype to A/A genotype, $P = .01$; Table 2). However, when we divided the cases into the sporadic group and familial and early-onset group, we did not find significant correlation under the codominant model ($P = .073$ and $P = .079$, respectively), although they also showed increased risks of breast cancer (Table 3). In addition, under the dominant model, both groups showed increased risks of breast cancer for the C/A and C/C genotype to common homozygote A/A (OR = 1.29, 95% CI: 1.02-1.62, $P = .031$ in the sporadic group and OR = 1.41, 95% CI: 1.02-1.94, $P = .036$ in the familial and early-onset group; Tables 4 and 5). We did not find any significant associations under the recessive model in the unselected group or the other 3 groups (Tables 2, 4, and 5).

The tSNP rs1042522 was also associated with an increased risk of breast cancer in unselected cases under the codominant model (OR = 1.31, 95% CI: 1.03-1.66 for the C/G genotype; and OR = 1.29, 95% CI: 0.94-1.76 for the G/G genotype compared to the C/C genotype), but this was not significant ($P = .074$; Table 1). The statuses of the sporadic group and the familial and early-onset group were the same (Table 3). However, under dominant model, there were significant associations for the G/C and G/G genotype to the common homozygote C/C in the unselected group (OR = 1.30, 95% CI: 1.04-1.63, $P = .023$; Table 2) and the familial and early-onset group (OR = 1.48, 95% CI: 1.04-2.12, $P = .027$; Table 5). There were no significant associations under the recessive model in the unselected group or the other 2 groups (Tables 2, 4, and 5).

We have not found any significant associations in the other 2 tSNPs, rs2287497 and rs8064946, under the codominant or recessive model (Supplementary Tables S1-S5). We have only found that tSNP rs8064946 was associated with an increased risk of breast cancer in unselected cases under the dominant model (OR = 1.24, 95% CI: 1.01-1.53, $P = .044$ for the G/C and C/C genotype to common homozygote G/G; Table 2).

Nijmegen Breakage Syndrome 1

The tSNPs rs2735385 and rs6999227 of NBS1 were both associated with decreased risks of breast cancer (OR = 0.72, 95% CI: 0.57-0.91 for the C/A genotype and OR = 0.59, 95% CI: 0.42-0.81 for the A/A genotype of rs2735385; OR = 0.73, 95% CI: 0.57-0.92 for the C/G genotype and OR = 0.61, 95% CI: 0.44-0.84 for the C/C genotype of rs6999227) compared to common homozygotes C/C ($P = .002$) and G/G ($P = .003$), respectively, in unselected cases under the codominant model (Table 1). There were also significant associations of the 2 tSNPs under both the dominant model and the recessive model in unselected cases (Table 2). At the rs2735385 locus, OR = 0.69 (95% CI: 0.55-0.86) for the C/A and A/A genotypes to C/C genotype under the dominant model ($P = .001$) and OR = 0.71 (95% CI: 0.53-0.95) for the A/A genotype to C/C and C/A genotypes under the recessive model ($P = .023$; Table 2). At the rs6999227 locus, OR = 0.70 (95% CI: 0.56-0.87) for the C/G and C/C genotypes to the G/G genotype under the dominant model ($P = .001$) and OR = .74 (95% CI: 0.56-0.98) for the C/C genotype to the G/G and C/G genotypes under the recessive model ($P = .034$; Table 2). The status of sporadic cases was the same as the unselected cases at these 2 tSNP loci, but the recessive model of rs6999227 was not significant ($P = .081$; Tables 3 and 4). In contrast, there was only 1 significant association of rs6999227 under the dominant model in familial and early-onset cases ($P = .043$), although the other models showed decreased risks of breast cancer with no significance (Tables 3 and 5).

The tSNP rs1805812 showed a significant association with breast cancer under the codominant model in unselected cases (OR = 0.73, 95% CI: 0.57-0.93 for the C/T genotype and OR = 1.01, 95% CI: 0.51-1.99 for the C/C genotype compared to the T/T genotype, $P = .037$; Table 1). The trend of sporadic cases was the same for unselected cases but with a marginal significance (OR = 0.72, 95% CI: 0.55-0.94 for the C/T genotype and OR = 1.03, 95% CI: 0.49-2.13 for the C/C genotype compared to the T/T genotype, $P = .053$; Table 3). Under the dominant model in both the unselected group and the sporadic group, the C/T and C/C genotypes were associated with a decreased risk of breast cancer compared to the common homozygote T/T (OR = 0.75, 95% CI: 0.59-0.95, $P = .017$; and OR = 0.74, 95% CI: 0.57-0.96, $P = .025$, respectively; Table 2 and

Table 3. Summary Data for Correlation of 11 tSNPs Under the Codominant Model in Sporadic and Familial and Early-Onset Cases.

			Control	Sporadic Cases			Familial and Early-Onset Cases		
Gene	SNP	Genotype	n	n	OR[a] (95% CI)	*P* Value[b]	n	OR[a] (95% CI)	*P* Value[b]
TP53	rs12951053	AA	331	227	1	.073	81	1	.079
		CA	273	248	1.32 (1.04-1.69)		98	1.47 (1.05-2.05)	
		CC	67	52	1.13 (0.76-1.69)		19	1.16 (0.66-2.04)	
	rs1042522	CC	227	154	1	.22	51	1	.07
		GC	327	273	1.23 (0.95-1.60)		113	1.54 (1.06-2.23)	
		GG	117	101	1.27 (0.91-1.78)		35	1.33 (0.82-2.16)	
NBS1	rs1061302	TT	190	183	1	.048	63	1	.60
		CT	349	251	0.75 (0.58-0.97)		100	0.86 (0.60-1.24)	
		CC	132	90	0.71 (0.51-0.99)		35	0.80 (0.50-1.28)	
	rs1805812	TT	470	401	1	.053	151	1	.29
		CT	184	113	0.72 (0.55-0.94)		44	0.74 (0.51-1.08)	
		CC	16	14	1.03 (0.49-2.13)		5	0.97 (0.35-2.70)	
	rs2735385	CC	210	213	1	.003	77	1	.086
		CA	345	246	0.70 (0.55-0.90)		97	0.77 (0.54-1.08)	
		AA	116	69	0.59 (0.41-0.84)		25	0.59 (0.35-0.97)	
	rs6999227	GG	200	201	1	.008	75	1	.063
		CG	344	247	0.71 (0.55-0.92)		98	0.76 (0.54-1.08)	
		CC	126	79	0.62 (0.44-0.88)		27	0.57 (0.35-0.94)	
PTEN	rs2299941	AA	268	258	1	.003	91	1	.21
		GA	314	224	0.74 (0.58-0.94)		90	0.84 (0.60-1.18)	
		GG	85	44	0.54 (0.36-0.80)		18	0.62 (0.36-1.09)	
PALB2	rs513313	TT	434	356	1	.13	133	1	.26
		CT	203	156	0.94 (0.73-1.20)		61	0.98 (0.69-1.39)	
		CC	34	15	0.54 (0.29-1.00)		5	0.48 (0.18-1.25)	
BRIP1	rs11871753	GG	473	381	1	.25	140	1	.039
		GA	177	123	0.86 (0.66-1.13)		45	0.86 (0.59-1.25)	
		AA	20	23	1.43 (0.77-2.64)		14	2.36 (1.16-4.80)	
	rs16945628	CC	271	236	1	.19	86	1	.006
		CT	313	218	0.80 (0.63-1.02)		72	0.72 (0.51-1.03)	
		TT	86	71	0.95 (0.66-1.36)		41	1.50 (0.96-2.34)	
	rs7220719	GG	429	352	1	.10	127	1	.044
		GA	217	146	0.82 (0.64-1.06)		56	0.87 (0.61-1.24)	
		AA	25	29	1.41 (0.81-2.46)		16	2.16 (1.12-4.17)	

Abbreviations: CI, confidence interval; NBS, Nijmegen breakage syndrome; OR, odds ratio; SNP, single-nucleotide polymorphisms; tSNPs, tagging single-nucleotide polymorphisms.
[a]Compared with common homozygote by logistic regression analysis.
[b]Genotype frequency *P* value.

Table 4). However, we have not found significant associations under the recessive model in any groups or under any models in the familial and early-onset group (Tables 2-5).

The tSNP rs1061302 was associated with a decreased risk of breast cancer under the codominant model in sporadic cases (OR = 0.75, 95% CI: 0.58-0.97 for the C/T genotype; and OR = 0.71, 95% CI: 0.51-0.99 for the C/C genotype compared to the T/T genotype, $P = .048$; Table 3). The trend of unselected cases was the same as that of sporadic cases but with no significant difference ($P = .063$; Table 1). There was also a significant association between the C/T and C/C genotypes and the common homozygote T/T under the dominant model in both the unselected cases and the sporadic cases (OR = 0.76, 95% CI: 0.61-0.96, $P = .02$; and OR = 0.74, 95% CI: 0.58-0.94, $P = .015$, respectively; Tables 2 and 4). However, we did not find any significant associations under any of the models in the familial and early-onset cases (Tables 3 and 5).

We did not find any significant associations in the other 6 tSNPs under any of the models (rs13312986, rs14448, rs16893166, rs1805835, rs709816, and rs7830738; Supplementary Tables S1-S5).

PTEN

The tSNP rs2299941 was associated with decreased risks of breast cancer under the codominant model in both unselected cases and sporadic cases (OR = 0.77, 95% CI: 0.61-0.96 for the G/A genotype, and OR = 0.56, 95% CI: 0.39-0.81 for the G/G genotype, $P = .0027$ in unselected cases; and OR = 0.74, 95% CI: 0.58-0.94 for the G/A genotype and OR = 0.54, 95% CI: 0.36-0.80 for the G/G genotype, $P = .0026$ in sporadic cases, compared to the A/A genotype; Tables 1 and 3). When we analyzed both groups in the dominant and recessive models, we also found significant associations (OR = 0.72, $P = .003$

Table 4. Risk Estimates Calculated Using the Dominant and Recessive Inheritance Models of 12 tSNPs in Sporadic Cases.[a]

		Dominant[b]		Recessive[c]	
Gene	SNP	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
TP53	rs1042522	1.24 (0.97-1.59)	.084	1.12 (0.83-1.50)	.45
	rs12951053	1.29 (1.02-1.62)	.031	0.99 (0.67-1.45)	.95
	rs8064946	1.21 (0.96-1.52)	.10	0.97 (0.65-1.45)	.88
NBS1	rs1061302	0.74 (0.58-0.94)	.015	0.85 (0.63-1.14)	.27
	rs1805812	0.74 (0.57-0.96)	.025	1.11 (0.54-2.30)	.77
	rs2735385	0.67 (0.53-0.86)	.001	0.72 (0.52-0.99)	.043
	rs6999227	0.69 (0.54-0.88)	.003	0.76 (0.56-1.04)	.081
PTEN	rs2299941	0.70 (0.55-0.88)	.002	0.63 (0.43-0.92)	.015
	rs2735343	1.12 (0.86-1.45)	.40	1.26 (0.96-1.65)	.091
PALB2	rs513313	0.88 (0.69-1.12)	.30	0.55 (0.30-1.02)	.05
BRIP1	rs11871753	0.92 (0.71-1.18)	.52	1.48 (0.81-2.73)	.20
	rs7220719	0.88 (0.69-1.12)	.30	1.50 (0.87-2.60)	.14

Abbreviations: CI, confidence interval; NBS, Nijmegen breakage syndrome; OR, odds ratio; SNP, single-nucleotide polymorphisms; tSNPs, tagging single-nucleotide polymorphisms.
[a]A/A as common homozygote.
[b]Dominant model: B/B + A/B versus A/A.
[c]Recessive model: B/B versus A/B +A/A.

Table 5. Risk Estimates Calculated Using the Dominant and Recessive Inheritance Models of 13 tSNPs in Familial and Early-Onset Cases.[a]

		Dominant[b]		Recessive[c]	
Gene	SNP	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
TP53	rs1042522	1.48 (1.04-2.12)	.027	1.01 (0.67-1.53)	.96
	rs12951053	1.41 (1.02-1.94)	.036	0.96 (0.56-1.64)	.87
	rs8064946	1.33 (0.97-1.83)	.077	1.20 (0.71-2.02)	.51
NBS1	rs1061302	0.85 (0.60-1.19)	.34	0.88 (0.58-1.32)	.53
	rs1805812	0.76 (0.53-1.10)	.14	1.05 (0.38-2.90)	.93
	rs2735385	0.72 (0.52-1.00)	.053	0.69 (0.43-1.09)	.10
	rs6999227	0.71 (0.51-0.99)	.043	0.67 (0.43-1.06)	.076
PTEN	rs2299941	0.80 (0.58-1.10)	.16	0.68 (0.40-1.16)	.15
	rs2735343	1.16 (0.80-1.67)	.43	1.44 (1.01-2.07)	.049
PALB2	rs513313	0.91 (0.65-1.27)	.57	0.48 (0.19-1.25)	.10
BRIP1	rs11871753	1.01 (0.72-1.43)	.95	2.46 (1.22-4.96)	.015
	rs7220719	1.01 (0.72-1.40)	.98	2.26 (1.18-4.32)	.018
	rs16945628	0.89 (0.65-1.23)	.49	1.76 (1.17-2.66)	.008

Abbreviations: CI, confidence interval; NBS, Nijmegen breakage syndrome; OR, odds ratio; SNP, single-nucleotide polymorphisms; tSNPs, tagging single-nucleotide polymorphisms.
[a]A/A as common homozygote.
[b]Dominant model: B/B + A/B versus A/A.
[c]Recessive model: B/B versus A/B +A/A.

and OR = 0.64, $P = .011$ in the unselected group, and OR = 0.70, $P = .002$ and OR = 0.63, $P = .015$ in the sporadic group). Although the same trend was found in familial and early-onset cases, this did not reach significance (Tables 3 and 5).

Although the tSNP rs2735343 showed increased risk of breast cancer under the codominant model in unselected cases, this did not reach significance ($P = .096$; Supplementary Table 1). However, under the recessive model, it had significant associations in both unselected cases and familial and early-onset cases (OR = 1.31, 95% CI: 1.02-1.68, $P = .032$; and OR = 1.44, 95% CI: 1.01-2.07, $P = .049$, respectively, for the G/G genotype compared with the C/C and G/C genotypes; Tables 2 and 5). Neither of the other 2 tSNPs (rs17107001 and rs2299939) showed any significant associations under any of the models (Supplementary Tables S1-S5).

BRCA1-Interacting Protein 1

The tSNPs rs16945628 and rs7220719 had significant associations with breast cancer under the codominant model in unselected cases or familial and early-onset cases. At the rs16945628 locus, OR = 0.78 (95% CI: 0.62-0.98) and OR = 0.72 (95% CI: 0.51-1.03) for the C/T genotype, and OR = 1.10 (95% CI: 0.79-1.52) and OR = 1.50 (95% CI: 0.96-2.34) for the T/T genotype compared to the C/C genotype in unselected cases or familial and early-onset cases, respectively ($P = .037$ and $P = .006$; Tables 1 and 3). The tSNP rs7220719 exhibited the same trend as rs16945628 (Tables 1 and 3). Under the recessive model, the A/A genotype showed increased risk of breast cancer compared to the G/G and G/A genotypes in both unselected cases and familial and early-onset cases at the rs7220719 locus (OR = 1.71, 95% CI: 1.04-2.82, $P = .033$ and OR = 2.26, 95% CI: 1.18-4.32, $P = .018$, respectively; Tables 2 and 5). At the rs16945628 locus, the T/T genotype also showed increased risk of breast cancer compared to the C/C and C/T genotypes but only in familial and early-onset cases under the recessive model (OR = 1.76, 95% CI: 1.17-2.66, $P = .008$; Table 5). We have not found any significant associations with breast cancer under the dominant model in any groups (Tables 2 and 5). Furthermore, the data for sporadic cases did not show any significant associations with breast cancer in any of the models (Tables 3 and 4).

The tSNP rs11871753 exhibited the same trend as rs7220719 under the codominant model in familial and early-onset cases (OR = 0.86, 95% CI: 0.59-1.25 for the G/A genotype and OR = 2.36, 95% CI: 1.16-4.80 for the A/A genotype compared to the common G/G genotype, $P = 0.039$; Table 3), but there was no significant association in unselected cases ($P = .065$; Supplementary Table 1). Under the recessive model, the A/A genotype showed increased risk of breast cancer compared to the G/G and G/A genotypes in unselected cases or familial and early-onset cases (OR = 1.75, 95% CI: 1.00-3.04, $P = .044$ and OR = 2.46, 95% CI: 1.22-4.96, $P = .015$, respectively; Tables 2 and 5). We have also found no significant associations with breast cancer under the dominant model in any of the groups (Tables 2 and 5).

The data for the other 8 tSNPs showed no significant association with breast cancer in any of the groups (Supplementary Tables S1-S5).

PALB2/ATM/RAD50/CHEK2

We have found no significant associations with breast cancer in the tSNPs of the other 4 genes, except for the tSNP rs513313 of *PALB2* (Supplementary Tables S1-S5). Under the recessive model, the C/C genotype of rs513313 showed a decreased risk of breast cancer compared to the G/G and G/A genotypes in unselected cases (OR = 0.53, 95% CI: 0.30-0.93, $P = .025$; Table 2) as well as in sporadic cases with a marginal significance (OR = 0.55, 95% CI: 0.30-1.02, $P = .05$; Table 4). However, we did not find any significant associations of breast cancer under the codominant and dominant models in any groups (Table 1-5).

Discussion

Ten genes for inherited breast cancer have been found to be associated with an increased breast cancer risk and are all directly or indirectly involved in the monoubiquitinated FANCD2–DNA damage repair pathway.[13] In this study, we have analyzed 48 tSNPs of the 10 genes, with the exception of *BRCA1* and *BRCA2*, to estimate the breast cancer risk conferred by individual SNPs in sporadic and familial and early-onset breast cancer cases in Chinese women. We have found that 13 tSNPs of 5 genes (*PALB2*, *TP53*, NBS1, *PTEN*, and *BRIP1*) were significantly associated with breast cancer risk.

TP53 encodes transcription factors with multiple antiproliferative functions that respond to various forms of cell stress.[22] More than 20 000 *TP53* alterations have been found in human tumors, and 30% of breast cancers are estimated to contain *TP53* mutations.[23,24] Inherited *TP53* mutations predispose individuals to a wide spectrum of early-onset cancers (eg, Li-Fraumeni syndrome).[25] However, studies on the association between *TP53* polymorphisms and breast cancer risk have yielded conflicting results. Many studies focused on SNP rs1042522, which is located in codon 72 on exon 4, leading to arginine–proline substitution, which in turn results in a structural alteration of the protein.[26] A recent meta-analysis showed that codon 72 polymorphism may not be associated with breast cancer risk in the Caucasian population but was associated with a decreased risk of breast cancer in a stratified analysis of the Indian population.[27]

On the one hand, we have found that the tSNP rs12951053 of *TP53* was associated with an increased risk of breast cancer (OR = 1.36, C/A vs A/A) in unselected cases, but this was not significant in the sporadic group or the familial and early-onset group under the codominant model. On the other hand, under the dominant model, the unselected group and the other 2 groups showed increased risks of breast cancer (OR = 1.32, OR = 1.29, and OR = 1.41, respectively, C/A and C/C vs A/A). Here, the C allele appeared to play an adverse role in relation to breast cancer in the rs12951053 locus. The SNP rs12951053 is located in intron 8 of the *TP53* gene, and its function is uncertain.

The tSNP rs1042522 of *TP53* was also associated with an increased risk of breast cancer in the unselected group and the familial and early-onset group under the dominant model (OR = 1.30 and OR = 1.48, respectively, G/C and G/G vs C/C). However, under the codominant model, we have only found a marginal significance in the unselected group (OR = 1.31, C/G vs C/C, $P = .074$). Thus, the G allele appeared to play an adverse role in relation to breast cancer in the rs1042522 locus, especially in familial and early-onset cases. This result is similar to that of a study that showed a marginal increased risk of breast cancer under the dominant model.[28] However, a published pooled analysis that included data from 9 studies indicated no overall association of rs1042522 with breast cancer risk, and similar results were found in another meta-analysis.[29,30] Nevertheless, another study showed the opposite result, where proline homozygosity at *TP53* on codon 72 was associated with a decreased risk of breast cancer in Arab women.[31]

We have found that tSNP rs8064946 was associated with an increased risk of breast cancer in unselected cases under the dominant model (OR = 1.24, 95% CI: 1.01-1.53 for G/C and C/C vs G/G) but not in the other 2 groups. The SNP rs8064946 is located in intron 2 of the *TP53* gene, and its function is also uncertain.

The protein NBS1 encoded by the NBS1 gene, together with its partners MRE11 and *RAD50*, needs DNA DSBs to repair.[32,33] The mutation of NBS1 is associated with the autosomal recessive disorder, NBS, characterized by small head deformity, growth retardation, immunodeficiency, X-ray hypersensitivity, and cancer susceptibility.[34] Although 2 meta-analyses showed that NBS1 8360G>C (rs1805794) polymorphism is associated with breast cancer,[35,36] the results were quite different in previous studies from different regions, which did not find significant risks in the Chinese population.[37-44] The mutations in 657del5, I171 V, and R215 W of NBS1 were found to have the same results as 8360G>C.[6,45-52]

The tSNPs rs2735385 and rs6999227 of NBS1 were both associated with significant decreased risks of breast cancer in unselected cases and sporadic cases under the codominant, dominant, and recessive model, except for rs6999227 under the recessive model, which exhibited no significant association in sporadic cases. In contrast, there was only 1 significant association of rs6999227 under the dominant model in familial and early-onset cases ($P = .043$), although the other models showed the same trend with no significance. Thus, the A allele and C allele appear to play a protective role against breast cancer in the rs2735385 and rs6999227 loci, especially in sporadic cases. The 2 SNPs are both located in intron 15 of the NBS1 gene, and their functions are uncertain.

The tSNP rs1805812 of NBS1 showed significant association with breast cancer under the codominant model in unselected cases (OR = 0.73, C/T vs T/T). The trend for sporadic cases was the same as that of unselected cases but with a marginal significance ($P = .053$). Under the dominant model in both the unselected group and the sporadic group, the C/T and C/C genotypes were also associated with a decreased risk of breast cancer compared to the common homozygote T/T (OR = 0.75 and OR = 0.74, respectively). Thus, the C/T genotype in rs1805812 appears to play a protective role

against breast cancer, especially in sporadic cases. SNP rs1805812 is located in intron 12 of NBS1 gene, and its function is also uncertain.

The tSNP rs1061302 of NBS1 was associated with a decreased risk of breast cancer under the codominant model in sporadic cases (OR = 0.75, C/T vs T/T and OR = 0.7, C/C vs T/T). The trend for unselected cases was the same as that of sporadic cases but with a marginal significance ($P = .063$). There was also significant association between the C/T and C/C genotypes and common homozygote T/T under dominant model in both unselected cases and sporadic cases (OR = .76 and OR = .74, respectively). However, we have not found any significant associations under any models in familial and early-onset cases. Thus, the C allele also appeared to play a protective role against breast cancer in the rs1061302 locus, especially in sporadic cases. The tSNP rs1061302 is located on exon 13 of NBS1, which is a synonymous-codon mutation like Pro672Pro and represents rs1063045 (3816 G>A) and rs1805794 (8360 G>C), whose associations with breast cancer are quite different in individuals from different geographical areas or ethnic backgrounds. Thus, their function needs to be identified further.

Germ line mutations in *PTEN*, a tumor suppressor gene that is commonly altered in a variety of somatic cancers, have been identified in families with Cowden syndrome.[53,54] Patients with Cowden syndrome and *PTEN* mutation have higher risk of developing breast carcinomas,[55,56] and the risk of breast cancer in Cowden disease associated with mutations in the *PTEN* gene has been estimated to be 30% to 50% by age 70.[57] However, the mutation rate was not as high in sporadic breast cancer and was not common in familial cases as some studies have found.[7,58-60] In contrast, a study of the Chinese population showed that the incidence of *PTEN* mutations is relatively high in patients with sporadic breast cancer in the region of Yunnan, People's Republic of China, and these exist at the early stage of breast cancer development.[61] In our study, we have found 2 significant tSNPs associated with breast cancer.

The tSNP rs2299941 of *PTEN* was associated with decreased risk of breast cancer under the codominant model in both unselected cases and sporadic cases (OR = 0.77 and OR = 0.74 for G/A vs A/A, respectively; OR = 0.56 and OR = 0.54 for G/G vs A/A, respectively). When we analyzed both groups in the dominant and recessive models, we have also found significant associations (OR = 0.72 and OR = 0.64 in the unselected group and OR = 0.70 and OR = 0.63 in the sporadic group). Although the same trend was found in familial and early-onset cases, this did not reach significance. Thus, the G allele appeared to play a protective role against breast cancer in the rs2299941 locus, especially in sporadic cases. The SNP rs2299941 is located in intron 5 of the *PTEN* gene, and its function is also uncertain.

Although the tSNP rs2735343 of *PTEN* showed increased risk of breast cancer under the codominant model in unselected cases, this did not reach significance ($P = .096$). However, under the recessive model, it had significant associations in both unselected cases and familial and early-onset cases (OR = 1.31 and OR = 1.44, respectively, for G/G vs C/C and G/C). Thus, the G/G genotype may play an adverse role in breast cancer at the rs2735343 locus, especially in familial and early-onset cases. The SNP rs2735343 is also located in intron 5 of the *PTEN* gene, and its function is also uncertain.

BRCA1-interacting protein 1, also called *BRCA1*-associated C-terminal helicase-1 (BACH1) and FANCJ, belongs to the DEAH helicase family and directly binds the BRCT-motif containing domain of *BRCA1*, thus likely contributing to its DNA repair and tumor suppressor functions.[16,62,63] *BRCA1-interacting protein 1* deficiency has been described as the cause of cancer-predisposing Fanconi anemia, which is a chromosome instability disorder characterized by developmental abnormalities, bone marrow failure, and a predisposition to cancer.[16,64,65] A previous study has identified constitutional truncating *BRIP1* mutations to confer susceptibility to breast cancer.[9]

In our study, under the recessive model, the tSNP rs7220719 of *BRIP1* showed increased risk of breast cancer in unselected cases and familial and early-onset cases (OR = 1.71 and OR = 2.26 for A/A vs G/G and G/A, respectively). However, rs16945628 showed an increased risk of breast cancer only in familial and early-onset cases (OR = 1.76 for T/T vs C/C and C/T). Thus, the T/T genotype of the rs16945628 and the A/A genotype of the rs7220719 appeared to play an adverse role in relation to breast cancer, especially in familial and early-onset cases. The SNPs rs7220719 and rs16945628 are located in intron 17 and intron 11, respectively, of the *BRIP1* gene, and their functions are uncertain.

The tSNP rs11871753 of *BRIP1* showed an increased risk of breast cancer under the codominant model in familial and early-onset cases (OR = 2.36 for A/A vs G/G). Like rs7220719, under the recessive model, the A/A genotype showed increased risk of breast cancer compared to G/G and G/A genotypes in unselected cases and familial and early-onset cases (OR = 1.75 and OR = 2.46, respectively). Thus, the A/A genotype also appeared to play an adverse role in relation to breast cancer at the rs11871753 locus, especially in familial and early-onset cases. The SNP rs11871753 is located in intron 14 and its function is also uncertain.

Although a kin-cohort study has shown a strong correlation between Pro919Ser (rs4986764) of *BRIP1* in premenopausal women and a 4.5- to 6.9-fold familial breast cancer risk,[66] we have found no significant association between this SNP and breast cancer risk; this is in accord with previously published data.[67-70]

PALB2 (*BRCA2*'s nuclear mate and locator) is essential for the localization and stability of *BRCA2* in the nucleus and realizes its functional in the error-free DNA DSB repair by means of homologous recombination and checkpoint control during the DNA damage process of the DNA S phase.[15] In previous researches, *PALB2* mutations are risk factors for moderate penetrance of breast cancer. Nonetheless, these mutations only occur in less than 1% of general breast cancers and in less than 3% of familial breast cancers.[11,71-73]

In our study, we have only found that the C/C genotype of the rs513313 of *PALB2* showed decreased risk of breast cancer compared to the G/G and G/A genotypes in unselected cases under the recessive model (OR = 0.53, $P = .025$). However, we did not find any significant associations with breast cancer under the codominant and dominant models in any groups at this locus. SNP rs513313 is located in intron 5 of the *PALB2* gene, and its function is uncertain. The C/C genotype may play a protective role against breast cancer at the rs513313 locus in unselected cases. The study by Chen *et al* did not show a significant association in this locus.[74] Thus, further analysis is needed to validate this finding. Moreover, there were no significant associations with breast cancer in the other 2 tSNPs (rs249954 and rs16940342). However, these 2 tSNPs were found to be associated with an increased risk of breast cancer under the dominant model in the study by Chen et al.[74]

Although mutations of the other 3 genes (*ATM*, *CHEK2*, and *RAD50*) were found in previous studies to have ORs for heterozygosity between 2.0 and 4.3 in breast cancer,[8,10,12] we did not find significant tSNPs in the 3 genes. The abovementioned conflicting results may be ascribed to the fact that the prevalence of breast cancer susceptibility genes varies widely among populations from different geographical areas or ethnic backgrounds.

There were some potential limitations in our study. Firstly, our patients came from the Hunan and Sichuan provinces, which are in central and western China, respectively, and incorporate multiple nationalities; thus, the patients may not have been completely representational of the Chinese ethnicities. Furthermore, the normal controls only came from Hunan Province. Secondly, the inclusion criteria for the familial and early-onset group were somewhat lenient since cases that had a first-degree relative with a malignant tumor other than breast cancer or ovarian cancer were included. Thirdly, we did not include any variables like living habits for further analysis. Thus, when comparing results, consideration should be taken of the aforementioned limitations.

Conclusions

In this hospital-based case–control study of breast cancer risk conferred by individual SNPs, we have found that 13 tSNPs of 5 genes (*PALB2*, *TP53*, NBS1, *PTEN*, and *BRIP1*) were significantly associated with a risk of breast cancer. Among these, 5 tSNPs (rs2299941 of *PTEN*, rs2735385, rs6999227, rs1805812, and rs1061302 of NBS1) were especially associated breast cancer risk in sporadic cases and another five tSNPs (rs1042522 of *TP53*, rs2735343 of *PTEN*, rs7220719, rs16945628, and rs11871753 of *BRIP1*) were especially associated with breast cancer risk in familial and early-onset cases. These results may represent the risk of breast cancer in central south and Southwestern China. The majority of the tSNPs are located in the intron domain, and their functions are unknown. Furthermore, because of the limitations of the study, larger and multicentric national studies are needed to verify these findings and research the functions of these genes further.

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Supplemental Material

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