RESEARCH ARTICLE

Association analysis of interleukin-18 gene promoter region polymorphisms and susceptibility to sporadic breast cancer in Chinese Han women

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Background: Interleukin-18-137G/C, -607G/T polymorphisms play multiple roles in various cancers. However, studies focused on its involvement in breast cancer remain controversial, and no study has taken the interaction between interleukin-18 (IL-18) gene polymorphism and body mass index (BMI), menopause into consideration. The study investigated the association between IL-18-137, -607 polymorphisms and risk of breast cancer and a possible interaction between the 2 single nucleotide polymorphisms (SNPs) and BMI, menopause in Chinese Han woman.

Methods: A total of 488 participants, including 178 patients with breast cancer, 150 patients with benign breast disease and 160 healthy controls were recruited for this study. Polymerase chain reaction (PCR)-direct sequencing technology was used to identify the genotypes.

Results: 137 G/C genotype can decrease the risk of breast cancer (OR = 0.54, 95% CI: 0.31-0.93; $P = .025$). In benign group, subjects with G/C genotype of IL-18-137G/C polymorphism had a 1.89-fold increased risk of developing breast cancer (95% CI = 1.05-3.41; $P = .032$). Among postmenopausal subjects, people with G/T genotype of IL-18-607 polymorphism had a 7.97-fold increased risk of lymph node metastasis compared with those with T/T homozygotes (95% CI = 1.95-32.65; $P = .0045$). Among Overweight and obese patients with breast cancer (BMI ≥ 24), people with G/T genotype of IL-18-607 polymorphism had a 5.45-fold increased risk of lymph node metastasis compared with those with T/T homozygotes (95% CI = 1.74-17.06; $P = .034$).

Conclusions: IL-18-137 G/C genotype may be a protective factor for healthy group, but a risk factor for benign group. IL-18-607 G/T genotype have an interaction with menopausal and BMI. The synergetic effect can further increase the risk of lymph node metastasis for breast cancer patients.

KEYWORDS

breast cancer, interleukin-18, polymorphism, susceptibility

Our study analyzed the relationship of the SNPs at the IL-18-137 and -607 sites with the susceptibility to sporadic breast cancer, and a possible interaction of the IL-18 gene with menopause, BMI in Chinese Han women.

1 | INTRODUCTION

Interleukin-18 (IL-18) gene is located on chromosome 11q22.2-22.3,¹ and it contains many single nucleotide polymorphisms (SNPs), especially in the promoter region. The IL-18-607 (rs1946518) site and the IL-18-137 (rs187238) site in the IL-18 gene promoter region are the binding sites for the c-AMP-responsive element binding protein and H4TF-1 nuclear factor, respectively. It is predicted that IL-18 gene promoter region SNP-137G/C and -607G/T can influence expression and activity of IL-18, respectively.² Arimitsu et al³ found that the production capability of IL-18 by monocytes from volunteers with -137G/G genotype was significantly higher than that with -137G/C genotype. Research showed that IL-18 can suppress antitumor immunity in a programmed death-1 (PD-1)-dependent manner, PD-1 is a co-inhibitory receptor and one of the major checkpoints.⁴ Furthermore, the association was verified between the 2 SNPs and the susceptibility to many cancers.⁵⁻¹⁴ However, studies focus on the role of IL-18 polymorphisms on the risk of breast cancer remain controversial. To the best of our knowledge, only 3 studies have estimated the impact of IL-18 polymorphisms -137G/C and/or -607A/C on breast cancer susceptibility.¹⁵⁻¹⁷ Khalili et al recruited 200 breast cancer patients and 206 healthy controls to examine the effect of -607A/C and -137G/C gene polymorphism of IL-18 on breast cancer risk. They found that CC homozygote of -137G/C polymorphism will reduce breast cancer risk, but IL-18 -607A/C polymorphism is not associated with the susceptibility to breast cancer.¹⁵ Taheri et al recruited 72 patients with breast cancer and 93 healthy controls to investigate the association of IL-18 gene polymorphisms -607A/C with breast cancer in a sample of Iranian population. And no meaningful association was found.¹⁶ Back et al recruited 154 breast cancer patients and 118 healthy controls to evaluate the association of -607A/C and -137G/C gene polymorphism with breast cancer risk. Their result suggested that IL-18-607A/C and -137G/C polymorphism contribute to increase the breast cancer risk.¹⁷ No study has taken the interaction between the 2 SNPs and body mass index (BMI), menopause in the course of the development of breast cancer into consideration. The current study first analyzed the possible role of the 2 SNPs on the susceptibility to female sporadic breast cancer and benign breast diseases in Chinese Han women, and further analyzed the interaction of the IL-18 gene with menopause, BMI in the course of the development of breast cancer. Finally, this study conducted a comparative analysis, according to the difference of immunohistochemical results.

2 | METHODS

2.1 | Data acquisition

The study was approved by the Beijing meitan general hospital Ethical Review Board. The 488 research subjects included unrelated Chinese Han women who were either patients treated at the Peking Union Medical College Hospital between June 30th, 2014

and October 30th, 2017 or healthy subjects. Of the 488 subjects, 178 cases were malignant breast tumor patients (malignant group), 150 cases were benign breast disease patients (benign group) and 160 cases were healthy subjects (healthy group). Inclusion criteria for the malignant group and benign group were as follows: (i) All patients received surgical and pathological diagnosis. (ii) No family history of cancer. (iii) No other organ tumor history. (iv) Newly diagnosed breast diseases patients. The healthy subjects were randomly selected from the health examination department of Peking Union Medical College Hospital, without any malignant, other serious illness, family tumor history or autoimmune disease. The basic information is shown in Table 1.

2.2 | Specimen processing

About 3 mL of EDTA-K2 anticoagulant fasting venous blood was collected. DNA was extracted from peripheral blood leukocytes using a TIANamp Blood DNA Kit (Tiagen Biotech Co., Ltd., Beijing, China). The extracted DNA was stored at -80°C until use.

Amplification of the target DNA was performed by polymerase chain reaction (PCR) with the following primers: upstream primer sequence, 5'-CTA GGG CAA TGG AAG TCG AA-3'; downstream primer sequence, 5'-TCC CTC TCC CCA AGC TTA CT-3'. The length of the amplified product was 601 bp, and it encompassed the -607 and -137 SNP sites in the IL-18 promoter region. A 20-μL PCR was set up with the following components: 10 μL of Taq Mix (Shanghai Hao Ran Biotechnology Co., Ltd., Shanghai, China); 1.5 μL of each forward and reverse primers; 1 μL of extracted DNA sample; and 6 μL of nucleic acid-free redistilled water. The reaction conditions were as follows: 94°C preheat for 5 minutes; and 35 cycles of 94°C for 30 seconds, 60°C for 30 seconds and 72°C for 1 minutes. The PCR product were electrophoresed to determine the size in each batch, then subjected to direct sequencing (sequencing of double deoxy end terminating method). A portion of the samples (5%) was randomly selected to perform a blinded retest. A 100% concordance rate was achieved.

2.3 | Statistical method

Pairwise comparison analysis was performed with the breast cancer, benign breast disease and healthy control groups to observe whether there was an association of the 2 selected SNP sites with disease susceptibility. Online analysis software (<http://bioinfo.iconcologia.net/snpstats>) and SPSS 16.0 (SPSS Inc., Chicago, IL, USA) were used for statistical analysis. The SNP analysis included the following tests: Hardy-Weinberg equilibrium analysis; association strength analysis of the genotype frequency and allele frequency with the disease; linkage disequilibrium analysis; and haplotype analysis. The Chi-square test was used to compare univariate count data, and unconditional logistic regression analysis was used to compare multivariate count data. The odds ratio OR value and 95% confidence intervals (95% CI) were calculated to assess the association strength of the SNP with the risk of breast disease and lymph node metastasis in breast cancer.

TABLE 1 General information of populations included in each group

Clinical information	Benign group	Malignant group	Healthy group
Menopause status (%)			
Premenopausal	116/150 (77.3)	89/178 (50.0)	-
Postmenopausal	29/150 (19.3)	78/178 (43.8)	-
Unknown	5/150 (3.3)	11/178 (6.2)	-
BMI (%)			
<18.5	12/150 (8.0)	5/178 (2.8)	-
18.5-23.9	97/150 (64.7)	86/178 (48.3)	-
24.0-27.9	27/150 (18.0)	57/178 (32.0)	-
>28	8/150 (5.3)	16/178 (8.9)	-
Unknown	6/150 (4.0)	14/178 (7.9)	-
Initial diagnosis age (y)			
Average age	41	50	42.67
Median age	39.97	50.45	42
Tissue type			
Malignant (%)			
Invasive ductal carcinoma	-	118/178 (66.3)	-
Intraductal carcinoma	-	19/178 (10.7)	-
Lobular carcinoma	-	19/178 (10.7)	-
Unknown	-	13/178 (7.3)	-
Benign			
Intraductal papilloma	9/150 (6.0)	-	-
Adenopathy	32/150 (21.3)	-	-
Adenoma, adenopathy	12/150 (8.0)	-	-
Adenoma	97/150 (64.7)	-	-
Malignant group (%)			
Immunohistochemistry staining result			
Luminal B type		130 (73.0)	-
Luminal A type		28 (15.7)	-
Basal-like type		9 (5.1)	-
Her-2 overexpression type		4 (2.2%)	-
Unknown		7 (3.9)	-

BMI, body mass index.

Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to select the best SNP inheritance model. A *P* value <.05 was considered significant.

3 | RESULTS

3.1 | Hardy-Weinberg equilibrium test

The Hardy-Weinberg equilibrium goodness of fit test for the -137G/C and -607G/T sites of the IL-18 gene was performed for the 3 groups, and the result is shown in Table 2. In our recruited 3 groups, the frequencies of genetic polymorphisms were all in the Hardy-Weinberg equilibrium.

3.2 | Association strength analysis of the -137G/C and -607G/T genotypes and alleles with breast diseases

3.2.1 | Analysis comparison of the malignant and healthy groups

A case-control study with a healthy population serving as a control group was performed to observe the correlation of genotypes of 2 SNP sites and the allele frequency distribution with malignant breast tumors. The logistic regression analysis after adjusting the initial diagnosis age showed that -137 G/C genotype can decrease the risk of breast cancer (OR = 0.54, 95% CI: 0.31-0.93; *P* = .025) and that

TABLE 2 Hardy-Weinberg equilibrium test

	-137G/C site (P value)	-607G/T site (P value)
Benign group (n = 150)	.42	.14
Malignant group (n = 178)	.21	.37
Healthy group (n = 160)	1	1

the best inheritance model was Overdominant C/C-G/G vs G/C (The smallest AIC = 424.8, The smallest BIC = 436.2). The distribution difference of the CG allele between the malignant and healthy control groups did not have statistical significance ($P = .096$). However, there was no significant association between genetic polymorphisms of IL-18 -607 G/T and breast cancer susceptibility (Table 3).

3.2.2 | Analysis comparison of the benign and malignant groups

A case-control study with a benign breast disease population as the control group was performed to analyze the association of the SNP at the 2 sites with breast cancer susceptibility. The unconditional logistic regression model results after adjusting the initial diagnosis age showed that people with G/C genotype of IL-18-137G/C polymorphism had a 1.89-fold increased risk of developing breast cancer (95% CI = 1.05-3.41; $P = .032$), the best inheritance model was overdominant C/C-G/G vs G/C (The smallest AIC = 380.4, The smallest BIC = 391.6). However, there was no significant association between IL-18-607G/T polymorphism and breast cancer susceptibility (Table 4). In addition, no interactions between the 2 SNPs and menopause or BMI were found (Table 5).

3.2.3 | Analysis of the benign and healthy groups

Healthy individuals were used as the control group to observe the correlation between the 2 SNPs and the risk of benign breast diseases. Logistic regression analysis showed that there was no association between the 2 SNPs and benign breast disease susceptibility.

3.3 | Analysis of the lymph node metastatic breast cancer group and the non-metastatic breast cancer group

According to lymph node metastasis condition, the breast cancer patients were divided into the lymph node metastasis group and the lymph node non-metastasis group to perform unconditional logistic regression analysis. The analysis results showed that there was no significant association between the 2 SNPs and the risk of lymph node metastasis.

The interaction analysis found that the IL-18-607 G/T genotype have an interaction with menopausal and BMI. Among postmenopausal subjects, people with G/T genotype of IL-18-607 polymorphism had a 7.97-fold increased risk of lymph node metastasis compared with those with T/T homozygotes (95% CI = 1.95-32.65; $P = .0045$). Among overweight and obese patients (BMI ≥ 24), people with G/T genotype of IL-18-607 polymorphism had a 5.45-fold increased risk of lymph node metastasis compared with those with T/T homozygotes (95% CI = 1.74-17.06; $P = .034$) (Table 6). However, no interaction was found between the -137G/C site and menopause status or BMI.

TABLE 3 -607G/T and -137G/C association with breast cancer susceptibility (Malignant vs Healthy)

Mode	-607G/T	Malignant (%)	Healthy (%)	OR (95% CI)	P value	OR* (95% CI)	P* value	AIC	BIC
Condominant	T/T	50 (29.6)	41 (25.6)	1.00		1.00		473	484.5
	G/T	80 (47.3)	80 (50)	1.22 (0.73-2.04)	.522	1.12 (0.65-1.92)	.534		
	G/G	39 (23.1)	39 (24.4)	1.15 (0.63-2.09)	.758	1.16 (0.62-2.20)	.626		
Allele		Malignant (%)	Healthy (%)	Chi-square test	P value				
	T	187 (53)	162 (51)	χ^2					
	G	169 (47)	158 (49)	0.244	.621				
	-137G/T	Malignant (%)	Healthy (%)	OR (95% CI)	P value	OR* (95% CI)	P* value	AIC	BIC
Overdominant	C/C-G/G	122 (72.6)	131 (81.9)	1.00	.063	1.00			
	G/C	46 (27.4)	29 (18.1)	0.61 (0.36-1.03)		0.54 (0.31-0.93)	.025	424.8	436.2
Allele		Malignant (%)	Healthy (%)	Chi-square test	P value				
	C	305 (86)	289 (90)	χ^2					
	G	49 (14)	31 (10)	2.773	.096				

The odds ratios (OR) with their 95% confidence intervals (CI) were estimated by logistic regression models. The adjusted odds ratios (OR*) and P^* were estimated by multiple logistic regression models, after adjusting age of first diagnosis. Best model according to the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC).

TABLE 4 -607G/T and -137G/C association with breast cancer susceptibility (Benign vs Malignant)

Mode	-607G/T	Benign (%)	Malignant (%)	OR (95% CI)	P value	OR* (95% CI)	P* value	AIC	BIC
Condominant	T/T	38 (25.3)	52 (29.2)	1.00		1.00			
	G/T	66 (44)	83 (46.6)	0.92 (0.54-1.56)	0.858	1.13 (0.63-2.04)	0.883		
	G/G	46 (30.7)	43 (24.2)	0.68 (0.38-1.23)	0.263	0.78 (0.40-1.52)	0.196	456.5	467.9
Allele		Benign (%)	Malignant (%)	Chi-square test	P value				
	T	142 (47)	187 (53)	χ^2					
	G	158 (53)	169 (47)	1.757	.185				
	-137G/T	Benign (%)	Malignant (%)	OR (95% CI)	P value	OR* (95% CI)	P* value	AIC	BIC
Overdominant	C/C-G/G	121 (80.7)	130 (73.5)	1.00		1.00			
	G/C	29 (19.3)	47 (26.6)	1.51 (0.89-2.55)	.12	1.89 (1.05-3.41)	.032	380.4	391.6
Allele		Benign (%)	Malignant (%)	Chi-square test	P value				
	C	265 (88)	305 (86)	χ^2					
	G	35 (12)	49 (14)	0.407	.407				

The odds ratios (OR) with their 95% confidence intervals (CI) were estimated by logistic regression models. The adjusted odds ratios (OR*) and P* were estimated by multiple logistic regression models, after adjusting age of first diagnosis. Best model according to the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC).

TABLE 5 Interaction analysis between single nucleotide polymorphisms (SNPs) and menopausal state

	Premenopausal			Postmenopausal			Interaction <i>P</i> value
Genotype	Benign	Malignant	OR (95% CI)	Benign	Malignant	OR (95% CI)	
-607G/T							
T/T	25	22	1.00	12	26	0.58 (0.19-1.72)	.68
G/T	52	44	0.98 (0.47-2.06)	10	33	0.87 (0.29-2.60)	
G/G	37	20	0.63 (0.27-1.44)	7	17	0.66 (0.19-2.27)	
-137G/C							
C/C	89	60	1.00	24	55	1.00	.59
G/C	23	26	1.78 (0.89-3.55)	4	19	1.88 (0.55-6.36)	
G/G	2	0	0	1	1	0.5 (0.03-8.74)	

The odds ratios (OR) with their 95% confidence intervals (CI) were estimated by logistic regression models.

3.4 | Analysis of linkage disequilibrium

To perform haplotype analysis, we first performed a pairwise linkage disequilibrium test among the 3 established groups. The r^2 values of the linkage disequilibrium test were as follows: benign group vs malignant group (.135); malignant group vs healthy group (.104); benign group vs healthy group (.112); and lymph node metastasis group vs non-metastasis group of the malignant breast tumor patients (.124). These data indicated that both of the SNP sites, -137G/C and -607G/T, had no linkage disequilibrium in each population group included in this study.

3.5 | Comparison of histochemical staining groups

According to the results of the histochemical staining, the patients in the malignant group were divided into the following 4 groups: luminal A type group, luminal B type group, Her-2 overexpression

type group and Basal-Like type group. Pairwise comparison analysis was conducted. However, no significant results were found.

4 | DISCUSSION

Breast cancer is one of the major threats to female health, worldwide. Currently, breast cancer is treated with surgery, followed by chemotherapy or radiation therapy, or both. However, a substantial proportion of breast cancer patients might have a risk for recurrence and metastasis.¹⁸ Therefore searching for new and potential strategies for risk prediction and treatment of breast cancer remains necessary. Immunotherapy as an attractive and promising approach, has gradually become the focus of many studies.¹⁸⁻²¹

Interleukin-18 was first discovered as an inducible factor of interferon-gamma.²² Research showed that IL-18 can suppress anti-tumor immunity in a PD-1-dependent manner, PD-1 is a co-inhibitory

TABLE 6 Interaction analysis between -607G/T polymorphism and menopausal or BMI

-607G/T	Genotype	Non-metastasis	Metastasis	OR (95% CI)	Interaction P value
Postmenopausal	T/T	20	3	1.00	.0045
	G/T	14	17	7.97 (1.95-32.65)	
	G/G	14	3	1.43 (0.25-8.14)	
BMI $\geq$ 24	T/T	13	4	1.00	.034
	G/T	13	20	5.45 (1.74-17.06)	
	G/G	10	5	1.66 (0.35-8.01)	

BMI, body mass index.

The odds ratios (OR) with their 95% confidence intervals (CI) were estimated by logistic regression models.

receptor and one of the major checkpoints.⁴ Furthermore, the association was verified between the 2 SNPs and the susceptibility to many cancers, including hepatocellular carcinoma,⁵ non-small-cell lung cancer,⁶ papillary thyroid carcinoma,⁷ chronic leukemia,²³ oral squamous cell carcinoma.²⁴ Although there have been reports on the association analysis of the IL-18 -137, and -607 sites with susceptibility to breast cancer, but the conclusions are not consistent.¹⁵⁻¹⁷ These controversial results may due to the genetic differences between various populations. However, there is no report on the association between IL-18 and susceptibility to breast cancer according to a stratified analysis of menopause, BMI and other factors.

In the present study, when the malignant group was compared with the healthy control group, the result showed that IL-18 -137G/C genotype was a protective factor for breast cancer. But, the comparative analysis between the benign group and the malignant group showed that IL-18 -137G/C genotype was a risk factor for benign group. So, -137 G/C genotype may be a protective factor for healthy group, but a risk factor for benign group. One of the possible explanations for the controversial effect of IL-18 -137 G/C polymorphism in breast cancer susceptibility and clinical progression is that IL-18 has dual effects on cancer development and progression.^{25,26}

When the benign group was compared with the healthy control group, the result showed that there was no significant association between genetic polymorphisms of IL-18 -607G/T and -137G/C and benign breast diseases susceptibility.

When the lymph node metastasis breast cancer group was compared with the non-metastasis breast cancer group, result showed that IL-18-607 G/T genotype have an interaction with menopausal and BMI. IL-18-607 G/T genotype can increase the risk of lymph node metastasis for the postmenopausal and overweight or obese subjects. This means that the causes of breast cancer may include heredity, endocrine, and external environment.

The results of the linkage disequilibrium test showed that the -137G/C and -607G/T sites had no linkage disequilibrium in the present study.

In summary, IL-18-137 G/C genotype may be a protective factor for healthy group, but a risk factor for benign group. IL-18-607 G/T genotype have an interaction with menopausal and BMI. The synergistic effect can further increase the risk of lymph node metastasis for breast cancer patients.

Our results and conclusions should be verified because of several limitations. Firstly, the present study just focused on Chinese Han women. Secondly, the case number of each study group was limited. Thirdly, the association was not investigated between the 2 IL-18 SNPs and IL-18 serum levels in our study, since serum IL-18 levels may be affected by various factors, some of these may mask the gene polymorphism effects. Fourthly, we just controlled age, menopausal and BMI, however, other possible confounding factors (living habits, smoking, and alcohol consumption) may cause some bias.²⁷

AUTHORS' CONTRIBUTIONS

Concepts, Design: XQ, WC; Definition of intellectual content, Literature search, Clinical studies, Manuscript editing, Manuscript review: XQ; Experimental studies: XQ, DX, DS; Data acquisition: XQ, DX, DS, SS; Data analysis: XQ, ZH; Statistical analysis, Manuscript preparation: XQ, ZH; Guarantor: WC.

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