Correlation between IL-7R gene variants and breast cancer susceptibility in Chinese Han women

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Abstract

Introduction

IL-7R is involved in the occurrence and development of breast cancer by binding to its ligand IL-7. This study aimed to explore the potential relationships of IL-7R polymorphisms with breast cancer susceptibility in Chinese Han women.

Methods

Five polymorphisms (rs969129, rs10213865, rs10053847, rs118137916, and rs6451231) of IL-7R gene were genotyped in 553 patients and 550 healthy individuals from the Chinese Han women using the Agena MassARRAY platform. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated used to evaluate the relationship.

Results

IL-7R rs10213865, rs969129 and rs6451231 was correlated with an increased the risk of breast cancer in multiple genetic models. Age stratified analysis revealed that rs6451231 was correlated with an increased breast cancer risk at age > 52 years. Additionally, rs10213865 was correlated with tumor site and ER expression, rs969129 was related to tumor size and Ki67 expresses status, and rs6451231 was related to tumor size. Haplotype CGAG (rs969129, rs10213865, rs10053847 and rs118137916) were observed to a decrease breast cancer risk.

Conclusions

IL-7R polymorphism were significantly correlated with an increased breast cancer susceptibility in Chinese Han women.

Introduction

Breast cancer, with about 2.1 million new cases and 0.6 million deaths in GLOBOCAN 2018 data, has been recognized as the most common type of cancer and a main cause of cancer death among women worldwide [1]. The data from China's urban cancer registration institutions showed that the incidence of breast cancer has increased by 20–30%, and the annual growth rate was 35% in the past 30 years. It is estimated that by 2021, the number of breast cancer cases in Chinese women aged 35 and 49 will reach 2.2 million [2]. Although the current development of medical technology has contributed to reduce the death rate of breast cancer, the specific cause of breast cancer has not been clarified. In addition to environmental factors, including radiation exposure and lifestyle, genetic factors are also crucial to the development of breast cancer. These genetic factors include single nucleotide polymorphism (SNPs) in the genome, and genetic variations in susceptible genes resulting in about 5–10% breast cancer [3, 4].

Interleukin 7 receptor (IL-7R) is one of the γ type cytokines receptors family members secreted by stromal cells, and its coding protein is interleukin-7 (IL-7) receptor [5]. Previous studies have shown that IL-7 binds to IL-7R can was essential for inflammatory or the immune response [6, 7]. Recently, increasing studies have shown that IL-7R influences the occurrence of various tumors, such as breast cancer, by forming signal complexes with its ligand IL-7 [8]. Binding IL-7R to IL-7 triggers a cascade of phosphorylation induced by signaling molecules that also participated in cell behavior such as cell division, cell adhesion, and cell differentiation [9, 10]. Rawi et al. pointed out the abnormal expression of IL-7R and IL-7 in breast cancer, and also found that IL-7 could accelerated the growth of breast cancer cells through wortmannin-sensitive pathway [11, 12]. These studies suggested that IL-7R is closely related to the occurrence of breast cancer. Moreover, a large amount of evidence has been explored that single nucleotide polymorphisms (SNPs) affect an individual's risk of breast cancer [13, 14]. However, the relationship between IL-7R polymorphisms and breast cancer risk remains unclear.

Therefore, we conducted an association study based on Chinese Han population to clarify the correlation between IL-7R SNPs and the risk of breast cancer, which is of great significance for the early molecular diagnosis of breast cancer.

Materials And Methods

Ethics statement

Our research was approved by the First Affiliated Hospital of Xi'an Jiaotong University and conducted in accordance with the ethical standards of the Helsinki declaration and national and international norms. All subjects signed informed consent forms after full understanding of the purpose of this research, agreeing to provide personal and relevant clinical information.

Participates statement

The study finally included 681 cases and 756 controls recruited from the the First Affiliated Hospital of Xi'an Jiaotong University. All subjects of cases were confirmed as breast cancer by pathology, excluding those who had received radiotherapy, chemotherapy, and other types of cancers. Data on the patient's clinicopathological characteristics (such as tumor location, tumor size, progesterone receptor (PR) status, estrogen receptor (ER) status, and Ki-67 status etc) were obtained from the patient's medical records. The control groups were healthy women with no disease and no

history of any disease who were recruited from the same hospital for physical examination at the same time. All the participants were Chinese Han population and were not related to each other.

SNP selection and genotyping

In this study, five IL-7R SNPs (rs10213865, rs969129, rs118137916, rs10053847 and rs6451231) with minor allele frequency (MAF) value > 0.05 were selected in present study based on 1000 Genomes Project (<http://www.1000genomes.org/>) and dbSNP database (<https://www.ncbi.nlm.nih.gov/projects/SNP/>). Participants' blood samples were stored at -80°C in a test tube containing EDTA reagent until analyzed. Whole-blood genomic DNA extraction was performed using the GoldMag whole-blood genomic DNA purification kit (GoldMag Co. Ltd., Xi an, China), and its quality was detected by NanoDrop 2000C spectrophotometer (Thermo Scientific, Waltham, MA, USA) according to the manufacturer's guidelines. Primer design was conducted with Agena MassARRAY Assay Design 3.0 Software (San Diego, California, USA) [15]. The corresponding primers of the selected SNPs in this study were listed in Supplementary Table S1. The SNPs genotyping was performed by two professionals using the Agena MassARRAY system (Agena, San Diego, CA, U.S.A.) software in a double-blind manner [16].

Statistical analysis

This study used SPSS 20.0 version and Microsoft Excel to analyze all relevant data, and $P < 0.05$ was considered statistically significant. The variation frequency of the controls was evaluated by the Hardy Weinberg-equilibrium (HWE) calculated by Fisher's exact test. The frequency of alleles and genotypes in cases and controls was assessed by the Pearson's χ^2 test, and the relationship between IL-7Rs SNPs and breast cancer risk was analyzed using Odds ratios (OR) and 95% confidence intervals (CI) in multiple genetic model (allele, co-dominant, dominant, recessive and log-additive). Linkage disequilibrium and haplotype analysis were performed using the 4.2 version of the Haploview software package.

Results

The Basic information about the subject

Basic clinical information of the cases and the control groups were summarized in Table 1. Our study containing 553 patients with an average age of 52.00 ± 9.83 years and 550 controls with an average age of 52.11 ± 9.51 years. There was no statistically significant difference in age distribution between the case group and the control group, and they were matched by age ($P = 0.884$).

Table 1
The general characteristics of study subjects

Variable	Cases (553)	Control (550)	P
Age			0.844
Age (Mean $\pm$ SD, years)	52.00 $\pm$ 9.83	52.11 $\pm$ 9.51	
Age > 52	263 (48%)	271 (49%)	
Age $\leq$ 52	290 (52%)	279 (51%)	
LN metastasis			
Positive	268 (48.5%)		
Negative	258 (46.7%)		
Unavailable	27 (4.9%)		
T stage			
T1 + T2	361 (65.3%)		
T3 + T4	156 (28.2%)		
Unavailable	36 (6.5%)		
PR status			
Positive	334 (60.4%)		
Negative	209 (37.8%)		
Unavailable	10 (1.8%)		
ER status			
Positive	371 (67.1%)		
Negative	159 (28.8%)		
Unavailable	23 (4.2%)		
Tumor size			
> 2 cm	311 (56.2%)		
$\leq$ 2 cm	105 (19.0%)		
Unavailable	137 (24.8%)		
Tumor site			
Left	224 (40.5%)		
Right	215 (38.9%)		
Unavailable	114 (20.6%)		
Ki-67 expresses state			
Overexpression (Ki67 > 25%)	360 (65.1%)		
Low expression (Ki67 < 25%)	134 (24.2%)		
Unavailable	59 (10.7%)		
Abbreviations: LN, lymph node; ER estrogen receptor, RP progesterone receptor;			
Notes: P value was calculated by independent samples t test. P < 0.05 in bold indicates a statistically significant difference.			

Information about the IL7R SNPs locus

The specific information of the IL-7R polymorphisms were shown in Table 2. All SNPs in the control group were complied with Hardy-Weinberg equilibrium (HWE). In addition, we used the HaploRegv4.1 database to predict the function of IL-7R polymorphisms, and found that the SNPs sites were involved in the Proteins bound, DNase, and motifs changed etc., suggesting that these SNPs sites had potential biological functions.

Table 2
Basic information of candidate SNPs in all the individuals examined in this study

SNPs	Chr	Position	Gene(s)	Role	Alleles (A/B)	Frequency (MAF)		P - HWE	HaploReg
						Cases	Controls		
rs10213865	5	35857748	IL7R	intronic	A/C	237	198	0.772	DNase, Proteins bound, Motifs changed, GRASP QTL hits, Selected eQTL hits
rs969129	5	35861166	IL7R	intronic	G/T	541	482	1.000	Promoter histone marks, Enhancer histone marks, DNase, Motifs changed, Selected eQTL hits
rs118137916	5	35863436	IL7R	intronic	A/G	82	88	0.770	Promoter histone marks, Enhancer histone marks, DNase, Proteins bound, Motifs changed
rs10053847	5	35878038	IL7R	UTR3	A/G	168	166	0.136	Motifs changed, GRASP QTL hits, Selected eQTL hits
rs6451231	5	35878825	IL7R	UTR3	C/T	457	404	0.854	Enhancer histone marks, DNase, Motifs changed, Selected eQTL hits
Abbreviations: SNP: single nucleotide polymorphism, Alleles A/B: minor/major alleles, MAF: minor allele frequency, HWE: Hardy-Weinberg equilibrium, OR: odds ratio, 95% CI: 95% confidence interval;									

Table 3

Genotypes frequencies of the SNPs and their associations with risk of breast cancer under multiple models of inheritance

SNP	Model	Genotype	Control (N, %)	Case (N, %)	With adjustment	
					OR (95% CI)	P-value
rs10213865	Allele	A	900 (82.0%)	869 (78.6%)	1	
		C	198 (18.0%)	237 (21.4%)	1.24 (1.00-1.53)	0.045
	Co-dominant	A/A	370 (67.4%)	340 (61.5%)	1	
		A/C	160 (29.1%)	189 (34.2%)	1.37 (0.74–2.55)	0.317
		C/C	19 (3.5%)	24 (4.3%)	1.29 (1-1.67)	0.054
	Dominant	A/A	370 (67.4%)	340 (61.5%)	1	
		A/C-C/C	179 (32.6%)	213 (38.5%)	1.30 (1.01–1.66)	0.040
	Recessive	A/A-A/C	530 (96.5%)	529 (95.7%)	1	
		C/C	19 (3.5%)	24 (4.3%)	1.26 (0.68–2.34)	0.455
	Log-additive	—	—	—	1.24 (1.00-1.53)	0.045
rs969129	Allele	T	616 (56.1%)	565 (51.1%)	1	
		G	482 (43.9%)	541 (48.9%)	1.22 (1.04–1.45)	0.018
	Co-dominant	T/T	173 (31.5%)	148 (26.8%)	1	
		T/G	270 (49.2%)	269 (48.6%)	1.50 (1.07–2.10)	0.017
		G/G	106 (19.3%)	136 (24.6%)	1.17 (0.88–1.54)	0.277
	Dominant	T/T	173 (31.5%)	148 (26.8%)	1	
		T/G-G/G	376 (68.5%)	405 (73.2%)	1.26 (0.97–1.64)	0.082
	Recessive	T/T-T/G	443 (80.7%)	417 (75.4%)	1	
		G/G	106 (19.3%)	136 (24.6%)	1.37 (1.02–1.82)	0.034
	Log-additive	—	—	—	1.22 (1.03–1.44)	0.019
rs118137916	Allele	A	1008 (92%)	1022 (92.6%)	1	
		G	88 (8%)	82 (7.4%)	0.92 (0.67–1.26)	0.597
	Co-dominant	A/A	464 (84.7%)	471 (85.3%)	1	
		A/G	80 (14.6%)	80 (14.5%)	0.25 (0.03–2.21)	0.210
		G/G	4 (0.7%)	1 (0.2%)	0.99 (0.7–1.38)	0.933
	Dominant	A/A	464 (84.7%)	471 (85.3%)	1	
		A/G-G/G	84 (15.3%)	81 (14.7%)	0.95 (0.68–1.32)	0.764
	Recessive	A/A-A/G	544 (99.3%)	551 (99.8%)	1	
		G/G	4 (0.7%)	1 (0.2%)	0.25 (0.03–2.21)	0.211
	Log-additive	—	—	—	0.92 (0.67–1.26)	0.596
rs10053847	Allele	G	932 (84.9%)	938 (84.8%)	1	
		A	166 (15.1%)	168 (15.2%)	1.01 (0.8–1.27)	0.963
	Co-dominant	G/G	400 (72.9%)	405 (73.2%)	1	
		G/A	132 (24.0%)	128 (23.1%)	1.17 (0.6–2.26)	0.651
		A/A	17 (3.1%)	20 (3.6%)	0.96 (0.72–1.27)	0.765

Abbreviations: SNP: single nucleotide polymorphism, OR: odds ratio, 95% CI: 95% confidence interval;

Notes: P values were calculated using two-sided Chi-squared test; P < 0.05 in bold indicates a statistically significant difference.

SNP	Model	Genotype	Control (N, %)	Case (N, %)	With adjustment	
					OR (95% CI)	P-value
rs6451231	Dominant	G/G	400 (72.9%)	405 (73.2%)	1	
		G/A-A/A	149 (27.1%)	148 (26.8%)	0.98 (0.75–1.28)	0.892
	Recessive	G/G-G/A	532 (96.9%)	533 (96.3%)	1	
		A/A	17 (3.1%)	20 (3.6%)	1.18 (0.61–2.27)	0.627
	Log-additive	—	—	—	1.01 (0.80–1.26)	0.959
	Allele	T	688 (63%)	633 (58.1%)	1	
		C	404 (37%)	457 (41.9%)	1.23 (1.04–1.46)	0.018
	Co-dominant	T/T	218 (39.9%)	187 (34.3%)	1	
		T/C	252 (46.2%)	259 (47.5%)	1.52 (1.07–2.18)	0.021
		C/C	76 (13.9%)	99 (18.2%)	1.20 (0.92–1.56)	0.175
	Dominant	T/T	218 (39.9%)	187 (34.3%)	1	
		T/C-C/C	328 (60.1%)	358 (65.7%)	1.27 (1.00–1.63)	0.054
	Recessive	T/T-T/C	470 (86.1%)	446 (72.8%)	1	
		C/C	76 (13.9%)	99 (18.2%)	1.38 (0.99–1.91)	0.055
	Log-additive	—	—	—	1.23 (1.03–1.46)	0.019
Abbreviations: SNP: single nucleotide polymorphism, OR: odds ratio, 95% CI: 95% confidence interval;						
Notes: P values were calculated using two-sided Chi-squared test; P < 0.05 in bold indicates a statistically significant difference.						

Association of IL7R SNPs with breast cancer susceptibility

Pearson's χ^2 test was used to assess the effect of IL-7R SNPs on breast cancer risk in a variety of genetic models. In the overall analysis, IL-7R - rs10213865 was related to an increased breast cancer risk in allele (C vs A: OR = 1.24, 95% CI = 1.00–1.53, P = 0.045), dominant (A/C-C/C vs A/A: OR = 1.30, 95% CI = 1.01–1.66, P = 0.040), and log-additive models (OR = 1.24, 95% CI = 1.00–1.53, P = 0.029). As for polymorphism rs969129, an increased risk of breast cancer was found in the allele (G vs T: OR = 1.22, 95% CI = 1.04–1.45, P = 0.018), co-dominant (T/G vs T/T: OR = 1.50, 95% CI = 1.07–2.1, P = 0.017), recessive (G/G vs T/T-T/G: OR = 1.37, 95% CI = 1.02–1.82, P = 0.034), and additive models (OR = 1.22, 95% CI = 1.03–1.44, P = 0.019). Rs6451231 was related to an increased breast cancer risk under allele (C vs T: OR = 1.23, 95% CI = 1.04–1.46, P = 0.018), co-dominant (T/C vs T/T: OR = 1.52, 95% CI = 1.07–2.18, P = 0.021), and log-additive models (OR = 1.23, 95% CI = 1.03–1.46, P = 0.019). The other two SNPs rs118137916 and rs10053847 were not related to breast cancer susceptibility (P > 0.05).

Stratification analysis of IL7R polymorphisms and breast cancer risk by age

To further investigate the impact of age on the potential breast cancer risk of selected IL7R polymorphisms, we stratified analysis by age under multiple genetic, we performed a stratified analysis according to age under multiple genetic models (Table 4). The results showed that rs6451231 was a breast cancer risk SNP locus at age > 52 years under allele (C vs T: OR = 1.30, 95% CI = 1.02–1.66, P = 0.034), co-dominant (T/C vs. T/T: OR = 1.69, 95% CI = 1.03–2.79, P = 0.039) and log-additive models (OR = 1.30, 95% CI = 1.02–1.65, P = 0.036).

Table 4
Association analysis of the IL7R polymorphisms and risk of breast cancer stratified by age

SNP	Model	Genotype	Age (years) ≤ 52				Age (years) > 52			
			Control	Case	OR (95% CI)	P-value	Control	Case	OR (95% CI)	P-value
rs6451231	Allele	T	354 (64.1%)	346 (60.5%)	1.00		335 (61.8%)	287 (55.4%)	1.00	
		C	198 (35.9%)	226 (39.5%)	1.17 (0.92–1.49)	0.208	207 (38.2%)	231 (44.6%)	1.30 (1.02–1.66)	0.034
	Co-dominant	T/T	113 (40.9%)	105 (36.7%)	1.00		105 (38.7%)	82 (31.7%)	1.00	
		T/C	128 (46.4%)	136 (47.6%)	1.38 (0.83–2.32)	0.217	125 (46.1%)	123 (47.5%)	1.69 (1.03–2.79)	0.039
		C/C	35 (12.7%)	45 (15.7%)	1.14 (0.8–1.64)	0.465	41 (15.1%)	54 (20.8%)	1.27 (0.87–1.86)	0.220
	Dominant	T/T	113 (40.9%)	105 (36.7%)	1.00		105 (38.7%)	82 (31.7%)	1.00	
		T/C-C/C	163 (57.1%)	181 (63.3%)	1.2 (0.85–1.68)	0.305	166 (71.3%)	313 (76.3%)	1.38 (0.96–1.97)	0.082
	Recessive	T/T-T/C	241 (87.3%)	241 (84.3%)	1.00		230 (84.9%)	205 (79.2%)	1.00	
		C/C	35 (12.7%)	45 (15.7%)	1.29 (0.8–2.07)	0.301	41 (15.1%)	54 (20.8%)	1.48 (0.94–2.31)	0.089
	Log-additive	—	—	—	1.17 (0.92–1.49)	0.209	—	—	1.30 (1.02–1.65)	0.036
Abbreviations: SNP: single nucleotide polymorphism, OR: odds ratio, 95% CI: 95% confidence interval;										
Notes: P values were calculated using two-sided Chi-squared test; P < 0.05 in bold indicates a statistically significant difference.										

Table 5
Association analysis of the IL7R polymorphisms and risk of breast cancer stratified by Clinical features (tumor site)

SNP	Model	Genotype	Tumor site-left				Tumor site-right			
			Control	Case	OR (95% CI)	P-value	Control	Case	OR (95% CI)	P-value
rs10213865	Allele	A	900(82.0%)	339(75.7%)	1.00		900(82%)	354(82.3%)	1.00	
		C	198(18.0%)	109(24.3%)	1.46(1.12–1.91)	0.005	198(18%)	76(17.7%)	0.98(0.73–1.31)	0.870
	Co-dominant	A/A	370(67.4%)	128(57.1%)	1.00		370(67.4%)	145(67.4%)	1.00	
		A/C	160(29.1%)	83(37.1%)	1.95(0.94–4.07)	0.075	160(29.1%)	64(29.8%)	0.81(0.32–2.06)	0.651
		C/C	19(3.5%)	13(5.8%)	1.51(1.08–2.11)	0.015	19(3.5%)	6(2.8%)	1.02(0.72–1.45)	0.907
	Dominant	A/A	370(67.4%)	128(57.1%)	1.00		370(67.4%)	145(67.4%)	1.00	
		A/C-C/C	179(32.6%)	96(42.9%)	1.56(1.13–2.15)	0.006	179(32.6%)	70(32.6%)	1(0.71–1.4)	0.991
	Recessive	A/A-A/C	530(96.5%)	201(94.2%)	1.00		530(96.5%)	209(97.2%)	1.00	
		C/C	19(3.5%)	13(5.8%)	1.69(0.82–3.49)	0.154	19(3.5%)	6(2.8%)	0.8(0.32–2.03)	0.639
	Log-additive	—	—	—	1.46(1.12–1.9)	0.005	—	—	0.98(0.73–1.31)	0.870
rs969129	Allele	T	616(56.1%)	219(48.9%)	1.00		616(56.1%)	234(54.4%)	1.00	
		G	482(43.9%)	229(51.1%)	1.34(1.07–1.67)	0.010	482(43.9%)	196(45.6%)	1.07(0.86–1.34)	0.551
	Co-dominant	T/T	173(31.5%)	64(28.6%)	1.00		173(31.5%)	59(27.4%)	1.00	
		T/G	270(49.2%)	91(40.6%)	1.78(1.15–2.74)	0.009	270(49.2%)	116(54.0%)	1.16(0.7–1.91)	0.574
		G/G	106(19.3%)	69(30.8%)	0.88(0.62–1.25)	0.462	106(19.3%)	40(18.6%)	1.36(0.96–1.92)	0.084
	Dominant	T/T	173(31.5%)	64(28.6%)	1.00		173(31.5%)	59(27.4%)	1.00	
		T/G-G/G	376(68.5%)	160(71.4%)	1.08(0.79–1.49)	0.623	376(68.5%)	156(72.6%)	1.31(0.94–1.83)	0.110
	Recessive	T/T-T/G	343(80.7%)	155(69.2%)	1.00		443(80.7%)	175(81.4%)	1.00	
		G/G	106(19.3%)	69(30.8%)	1.90(1.28–2.83)	0.001	106(19.3%)	40(18.6%)	0.97(0.61–1.54)	0.897
	Log-additive	—	—	—	1.25(1.01–1.56)	0.044	—	—	1.14(0.9–1.43)	0.280
rs6451231	Allele	T	688(63.0%)	256(57.4%)	1.00		688(63%)	257(60%)		
		C	404(37.0%)	190(42.6%)	1.26(1.01–1.58)	0.041	404(37%)	171(40%)	1.13(0.9–1.43)	0.285
	Co-dominant	T/T	218(39.9%)	85(38.1%)	1.00		218(39.9%)	72(33.6%)	1.00	
		T/C	252(46.2%)	86(38.6%)	1.78(1.17–2.71)	0.007	252(46.2%)	113(52.8%)	1.11(0.69–1.77)	0.672
		C/C	76(13.9%)	52(23.3%)	0.92(0.63–1.33)	0.655	76(13.9%)	29(13.6%)	1.26(0.87–1.82)	0.217

Abbreviations: SNP: single nucleotide polymorphism, OR: odds ratio, 95% CI: 95% confidence interval;

Notes: P values were calculated using two-sided Chi-squared test; P < 0.05 in bold indicates a statistically significant difference.

SNP	Model	Genotype	Tumor site-left				Tumor site-right			
			Control	Case	OR (95% CI)	P-value	Control	Case	OR (95% CI)	P-value
	Dominant	T/T	218(39.9%)	85(38.1%)	1.00		218(39.9%)	72(33.6%)	1.00	
		T/C-C/C	328(60.1%)	138(61.9%)	1.16(0.82–1.63)	0.393	328(60.1%)	142(37.2%)	1.22(0.86–1.73)	0.271
	Recessive	T/T-T/C	470(76.1%)	171(76.7%)	1.00		470(86.1%)	185(86.4%)	1.00	
		C/C	76(13.9%)	52(23.3%)	1.87(1.31–2.67)	0.001	76(13.9%)	29(13.6%)	0.96(0.64–1.43)	0.824
	Log-additive	—	—	—	1.32(1.07–1.64)	0.011	—	—	1.07(0.85–1.35)	0.546
Abbreviations: SNP: single nucleotide polymorphism, OR: odds ratio, 95% CI: 95% confidence interval;										
Notes: P values were calculated using two-sided Chi-squared test; P < 0.05 in bold indicates a statistically significant difference.										

Relationship of IL7R SNPs with clinicopathological features of breast cancer

The effect of IL7R SNPs on the clinical characteristics of breast cancer was also investigated. In subgroups stratified by tumor site, we found that rs10213865 significantly increases the risk of tumors on the left side in allele (C vs A: OR = 1.46, 95% CI = 1.12–1.91, P = 0.005), co-dominant (C/C vs AA: OR = 1.51, 95% CI = 1.08–2.11, P = 0.015), dominant (A/C-C/C vs A/A: OR = 1.56, 95% CI = 1.13–2.15, P = 0.006), and log-additive models (OR = 1.46, 95% CI = 1.12–1.90, P = 0.005). Rs969129 significantly increases the risk of tumors on the left side in allele (C vs A: OR = 1.34, 95% CI = 1.07–1.67, P = 0.010), dominant (A/C-C/C vs A/A: OR = 1.78, 95% CI = 1.15–2.74, P = 0.009), recessive (G/G vs T/T-T/G: OR = 1.90, 95% CI = 1.28–2.83, P = 0.001) and log-additive genetic models (OR = 1.25, 95% CI = 1.01–1.56, P = 0.044). Rs6451231 was correlated with an increased the risk of tumor on the left in allele (C vs T: OR = 1.24, 95% CI = 1.01–1.58, P = 0.041), co-dominant (T/C vs T/T: OR = 1.78, 95% CI = 1.17–2.71, P = 0.007), recessive (C/C vs T/T-T/C: OR = 1.87, 95% CI = 1.31–2.67, P = 0.001), and log-additive genetic models (OR = 1.32, 95% CI = 1.07–1.64, P = 0.011).

As shown in Table 6, we observed that individuals with rs10213865 mutational genotype had a higher risk of breast cancer in ER positive patients than in ER negative patients in allele model (C vs A: OR = 0.69, 95% CI = 0.51–0.92, P = 0.012), co-dominant model (C/C vs A/A: OR = 0.62, 95% CI = 0.43–0.90, P = 0.011), dominant model (A/C-C/C vs A/A: OR = 0.62, 95% CI = 0.43–0.88, P = 0.008) and log-additive model (OR = 0.68, 95% CI = 0.50–0.92, P = 0.011). The mutation genotype frequency of rs969129 in patients with high expression of Ki-67 was significantly increased (co-dominant model, G/G vs T/T: OR = 0.56, 95% CI = 0.34–0.92, P = 0.023).

Table 6

Association analysis of the IL7R polymorphisms and risk of breast cancer stratified by Clinical features (ER status and Ki67 expresses status)

Clinical features	SNP	Model	Genotype	Control (N, %)	Case (N, %)	With adjustment	
						OR (95% CI)	P-value
ER status (positive vs. negative)	rs10213865	Allele	A	313(74.9%)	543(81.3%)	1.00	
			C	105(25.1%)	125(18.7%)	0.69(0.51–0.92)	0.012
	Co-dominant	A/A	115(55%)	222(66.5%)	1.00		
		A/C	83(39.7%)	99(29.6%)	0.59(0.26–1.37)	0.219	
	Dominant	C/C	11(5.3%)	13(3.9%)	0.62(0.43–0.90)	0.011	
		A/A	115(55.0%)	222(66.5%)	1.00		
	Recessive	A/C-C/C	94(45.0%)	112(33.5%)	0.62(0.43–0.88)	0.008	
		A/A-A/C	198(94.7%)	312(33.5%)	1.00		
	Log-additive	C/C	11(5.3%)	13(3.9%)	0.7(0.31–1.61)	0.406	
		—	—	—	0.68(0.50–0.92)	0.011	
Ki67 expresses status (Ki67 > 25% vs. Ki67 < 25%)	rs969129	Allele	T	136(50.7%)	373(51.8%)	1.00	
			G	132(49.3%)	347(48.2%)	0.96(0.72–1.27)	0.767
	Co-dominant	T/T	28(20.9%)	104(28.9%)	1.00		
		T/G	80(59.7%)	165(45.8%)	0.95(0.52–1.74)	0.868	
	Dominant	G/G	26(19.4%)	91(25.3%)	0.56(0.34–0.92)	0.023	
		T/T	28(20.9%)	104(28.9%)	1.00		
	Recessive	T/G-G/G	106(79.1%)	256(70.1%)	0.66(0.41–1.06)	0.084	
		T/T-T/G	108(90.6%)	269(74.7%)	1.00		
	Log-additive	G/G	26(19.4%)	91(25.3%)	1.41(0.86–2.3)	0.175	
		—	—	—	0.96(0.73–1.28)	0.793	
Abbreviations: SNP: single nucleotide polymorphism, OR: odds ratio, 95% CI: 95% confidence interval;							
Notes: P values were calculated using two-sided Chi-squared test; P < 0.05 in bold indicates a statistically significant difference.							

Associations between haplotype analyses and the risk of breast cancer

Finally, haplotype analysis was performed to explore the relationship between interactions of the IL-7R SNPs and breast cancer risk. As shown in Fig. 1, rs10213865, rs969129, rs118137916 and rs10053847 consisted of one block in IL-7R gene. As shown in Table 7, haplotype CGAG was observed to prominently reduce the risk of breast cancer through χ^2 test analysis (OR = 0.80, 95% CI, 0.65–0.99; P = 0.043).

Table 7
Haplotype frequencies of IL7R gene and the association with breast cancer risk

SNPs	Haplotype	Freq (Case)	Freq (Control)	Without adjusted		With adjusted	
				OR (95% CI)	P	OR (95% CI)	P
rs10213865 rs969129 rs118137916 rs10053847	AGAA	0.848	0.849	0.99(0.79–1.24)	0.95	0.99(0.79–1.24)	0.945
rs10213865 rs969129 rs118137916 rs10053847	ATGG	0.926	0.92	1.09(0.79–1.49)	0.602	1.09(0.79–1.49)	0.604
rs10213865 rs969129 rs118137916 rs10053847	CGAG	0.785	0.82	0.80(0.65–0.99)	0.043	0.80(0.65–0.99)	0.043
rs10213865 rs969129 rs118137916 rs10053847	AGAG	0.877	0.893	0.85(0.65–1.11)	0.243	0.85(0.65–1.11)	0.243
rs10213865 rs969129 rs118137916 rs10053847	ATAG	0.436	0.481	0.83(0.7–0.99)	0.034	0.83(0.7–0.99)	0.033
Abbreviations: SNP: single nucleotide polymorphism, OR: odds ratio, 95% CI: 95% confidence interval;							
Notes: P values were calculated using two-sided Chi-squared test; P < 0.05 in bold indicates a statistically significant difference.							

Discussion

Genetic variations, including single nucleotide polymorphism, were closely related to the occurrence of breast cancer. Genome-wide association studies (GWAS) have detected many SNPs were related to breast cancer susceptibility in tumor-related genes such as PD-1, FGFR2, ESR1, PTEN, and MAP3K1 [17–19]. The effect of IL-7R SNPs on breast cancer susceptibility in Chinese Han population is not clear at present. In this present work, we revealed that the allele and genotype frequency distribution of IL-7R SNPs (rs969129, rs10213865 and rs6451231) was significantly different between the case and control groups, and they increased the risk of breast cancer. In the age stratified analysis subgroup, IL-7R-rs6451231 significantly increased breast cancer risk among those older than 50 years. Rs10213865, rs969129 and rs6451231 were also significantly correlated with some clinical parameters, such as tumor size, ER status and Ki67 stress status. We have also observed that haplotype CGAG increases breast cancer susceptibility. These results provided some support for the impact of genetic variation of IL-7R on breast cancer risk among Chinese Han population.

IL-7R, located on chromosome 5p13, is a heterodimer consisting of two strands (IL-7R α and common γ chain). The binding of IL-7R and IL-7 leads to the activation of tumor-related signaling pathways, including PEDF Induced Signaling and Interleukin-7 signaling pathway, etc [20, 21]. At present, there are many studies on the relevant mechanism of IL-7R in lung cancer. Researchs have reported that IL-7/IL-7R can affect the production level of vascular endothelial growth factor in lung cancer and the formation of lymphatic vessels through the c-fos/c-jun pathway [22]. It can also affect the production of cyclin D1 by activating the AP1 pathway, thus accelerating the proliferation of breast cancer cells [23]. However, there are few researchs has been done on the mechanism of IL-7R in breast cancer. Only studies reported the expression levels of IL-7 and IL-7R have been observed to increase significantly in breast cancer [8, 11], and IL-7 can affect the proliferation rate of breast cancer cells [12]. Therefore, further studies on the mechanism of IL-7R and breast cancer are still needed.

Genetic variation polymorphisms of IL-7R has been reported to affect the occurrence of many diseases. Sinha et al. [24] found that polymorphisms of IL-7R (rs1494555 and rs6897932) were associated with asthma in the northern Indian population. IL-7R-rs6897932 (C/T) was related to the susceptibility of systemic lupus erythematosu [25]. In our study, we explored the influence of IL-7R SNPs (rs6451231, rs10213865, rs118137916, rs969129, and rs10053847) on breast cancer susceptibility in Chinese Han population. Bai et al. [26] that IL-7R SNPs (rs6451231 and rs969129) were significantly correlated with an increased rheumatoid arthritis (RA) susceptibility under multiple genetic model, and the haplotype GAGC constructed by IL-7R SNPs (rs118137916, rs969129, rs6451231 and rs10053847) also increased the RA risk.

Zhang et al. [27] explored the effect of IL-7R polymorphism on lung cancer risk. The rs10053847 and rs10213865 variant was observed to be correlated with a decreased breast cancer risk under multiple genetic model, and AGAA haplotypes (rs10213865, rs969129, rs118137916, and rs10053847) also increased breast cancer risk. However, our study observed that IL-7R SNPs (rs969129, rs10213865 and rs6451231) were significantly increased breast cancer risk, and haplotype CGAG (rs10213865, rs118137916, rs969129 and rs10053847) significantly increased breast cancer susceptibility. As far as we know, our study is the first to explore the relationship between IL-7R polymorphism and susceptibility to breast cancer.

There are some limitations to this study that cannot be ignored. First, this was a hospital-based case-control study involving only Han women, and the applicability of our conclusions should be explored in other ethnic populations. Second, our sample size was relatively small, and false negative results cannot be excluded. Despite the above limitations, the results of this study provide a scientific basis for future research on IL-7R gene and breast cancer.

In conclusion, our study was the first to found that IL-7R SNPs (rs6451231, rs10213865 and rs969129) were significantly increased breast cancer risk, which provides a basis for further mechanism research of IL-7R and breast cancer.

Abbreviations

IL-7: Interleukin 7; SNPs: single nucleotide polymorphisms; OR: Odds ratio; CIs: 95% confidence intervals.

Declarations

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Consent for publication

Written informed consent was obtained from the patient for publication of this report.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Miao Li and Chenli Yue: analyzed the data. Xiaoxiao Zuo and Guoquan Jin: performed the experiments. Guanying Wang, Hulin Guo and Fang Wu: contributed reagents/materials/analysis tools. Xinhan Zhao and Shangke Huang: conceived and designed the experiments. All authors contributed significantly to the final draft of the paper and agreed to submit the manuscript for publication.

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Figures

Figure 1

rs10213865, rs969129, rs118137916 and rs10053847 consisted of one block in IL-7R gene.

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