The role of genetic variants in *FCGR2A* on the risk of rheumatoid arthritis in the Han Chinese population

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Abstract

Background: Rheumatoid arthritis (RA) is the most common inflammatory arthritis and is characterized by irreversible joint damage and deformities, which is largely caused by genetic factors. The aim of this study was to explore the role of *FCGR2A* polymorphisms with the susceptibility to RA in the Han Chinese cohort.

Methods: We enrolled 506 RA patients and 509 healthy controls, with four single nucleotide polymorphisms (SNPs) successfully genotyped using Agena MassARRAY. Genetic models, haplotype analyses were applied to assess the association between *FCGR2A* polymorphisms and RA. And we evaluated the relative risk by odds ratios (ORs) and 95% confidence intervals (95% CIs) using logistic regression analysis.

Results: The results revealed that *FCGR2A* rs6668534 was significantly related to an increased risk of RA in the overall (OR = 1.24, 95%CI = 1.04 – 1.48, $p = 0.014$). There was no any association found between the polymorphisms and RA risk at age > 54 years, while the two (rs6671847 and rs1801274) of the four SNPs possibly contributed to the susceptibility to RA at age ≤ 54 years. And the rs6668534 polymorphism conferred the increased susceptibility to RA in the male population. The haplotypes in the *FCGR2A* gene was significantly associated with the RA risk.

Conclusions: Our research have demonstrated that the *FCGR2A* gene polymorphisms (rs6671847, rs1801274 and rs6668534) were implicated in RA susceptibility in the Han Chinese population.

Introduction

Rheumatoid arthritis (RA), considered as an autoimmune disease, is characterized by multiple joints, symmetry and invasive inflammation of hand and foot facet joints. Furthermore, the involvement of extra-articular organs may occur, including vasculitis, pericarditis or interstitial lung disease¹. These symptoms are the consequences of long-term activation of the immune system. It affects approximately 1% of the population worldwide and 5–50 per 100 000 new cases annually. The occurrence rate is 2 to 3 times more frequently in women than in men². The pathogenic autoimmune process associated with RA is very complicated, involving several different stages that ultimately lead to the onset of RA³. Unfortunately, until today, there is no preventive treatment or cure for RA. The disability associated with RA has a significant impact on the quality of life and socio-economic status of patients, families and society as a whole⁴.

To date, the precise mechanism of RA which genetic factors has not been fully explained. It is believed that the development of RA is triggered by complex interactions between genetic and environmental factors⁵. The common environmental factors include smoking, female, and oral contraceptive use⁶. Moreover, previous studies have suggested that genetic factors may account for approximately one-half to two-thirds of the risk of RA⁷. Genome-wide association analysis studies have identified ~ 100 gene loci that are linked with the disease. And the strongest association to RA is human leukocyte antigen (HLA), which is contribute to about 30% of genetic factors⁸. In addition, the non-HLA also have been proved to be significantly related to RA¹.

Previous studies have reported that human FC-gamma receptors (FcγRs), a family of cell-surface receptors, have a pivotal role in many immunological process^{8–9}. Based on their affinity for IgG, they can be divided into two types, low- and high-affinity receptors¹⁰. In human, five low-affinity FcγRs (including FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, and FcγRIIIb) are encoded by the Fc receptors for IgG immunoglobulins (FCGRs) genes (*FCGR2A*, *FCGR2B*, *FCGR2C*, *FCGR3A*, and *FCGR3B*). Among them, *FCGR2A* is located on chromosome 1q23 and consists of 7 exons mapping to approximately 18.58 kb of genomic DNA¹⁰. It encodes a member of a family of Fc γ receptors for immunoglobulin G. And it is also widely used to explore the correlation with the response to anti-TNF therapy in RA management¹¹, but there are few researches on association between *FCGR2A* variants and risk of RA.

In our study, the results showed that the *FCGR2A* polymorphisms were also related to the risk of RA in overall. In addition, we conducted stratified association analysis about the influence of *FCGR2A* variants on age and gender. We aimed to analyze the genetic association of *FCGR2A* and RA among the Chinese population of Shaanxi Han.

Methods And Materials

Study subjects

This case-control study was conducted in accordance with the Declaration of Helsinki. And the protocol was approved by the Ethics Committee of the Affiliated Hospital of Xizang Minzu University. Briefly, 506 RA patients and 509 unrelated healthy controls in a large cohort of Han Chinese population were enrolled to explore whether the *FCGR2A* variants had influence on the development of RA. All cases were recruited from the October 2016 to January 2019 from the Affiliated Hospital of Xizang Minzu University. And they were diagnosed as RA based on the American College of Rheumatology 1987 classification criteria and routine biochemical blood analysis (including C-reaction protein [CRP], erythrocyte sedimentation rate [ESR], rheumatoid factor (RF), anti-cyclic citrulline antibody [CCP])¹². Patients with any other immune and tumor diseases were excluded from this

study. At the same period, the 509 healthy controls, without any immune disease or other diseases were also selected from the same hospital. Written informed consents were obtained from all individuals.

SNP selection and genotyping

Four variants (rs6671847, rs1801274, rs17400517, and rs6668534) in *FCGR2A* gene were selected for the study to evaluate the effect on RA risk in the 1000 Genomes Project (<http://www.1000genomes.org/>) with minor allele frequency (MAF) > 5%. Strictly following the manufacturer's guidelines, we extracted genomic DNA from the blood samples using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag. Co. Ltd., Xi'an, China). And the DNA concentration and purity were measured by spectrophotometer (NanoDrop 2000; Thermo Fisher Scientific, Waltham, MA, USA) ¹³. The Agena Bioscience Assay Design Suite V2.0 software (<https://agenacx.com/online-tools/>) was performed to design amplification and extension primers (**Supplementary Table 1**) ¹⁴. The Agena MassARRAY platform (Agena Bioscience, San Diego, CA, USA) and Agena Bioscience TYPER version 4.0 were used for the SNPs genotyping and data analysis, respectively ¹⁵.

Statistical analysis

We used the SPSS 19.0 (SPSS, Chicago, IL, USA) software for statistical analysis in this study ¹⁶. The Pearson's Chi-square test and independent sample Student's t-test were applied to evaluate the differences in the distribution of age and gender between cases and controls, respectively. The genotype frequencies among the controls were calculated to evaluate departure from Hardy-Weinberg Equilibrium (HWE) using the Chi-square test. And based on the four genetic model (codominant, dominant, recessive, and log-additive), the correlation between SNPs and RA risk was estimated with the values of odd ratios (ORs) and 95% confidence intervals (CIs) using the logistic regression analysis on PLINK software (version 1.07) ¹⁷. In addition, Haploview software (version 4.2) was used to assess linkage disequilibrium (LD), haplotype construction and genetic association of polymorphism loci. All *p* values were two-sided, and *p* < 0.05 was considered to be statistically significant.

Results

Characteristics of cases and controls

We recruited 506 RA patients consisting of 135 males and 371 females (mean age 54.35 ± 11.69 years). And 509 unrelated healthy individuals consisting of 134 males and 375 females were used as the controls (mean age 54.39 ± 12.02 years). There was no statistically significant difference on distribution of gender between the case and control group (*p* > 0.958). However, the distribution of age was significant difference (*p* = 0.038). In addition, we analyzed the clinical parameters in the cases. The mean ± SD of CRP and RF among 506 cases were 31.05 ± 40.25 mg/L and 164.09 ± 147.21 KIU/L, respectively. And the mean ± SD of ESR and CCP in the cases were 44.28 ± 30.86 mm/h and 75.11 ± 60.78 RU/ml. The detailed characteristics of cases and controls were showed in **Table 1**.

Association between *FCGR2A* variations and RA risk

The basic information of four *FCGR2A* polymorphisms is shown in **Table 2**. The genotype distribution of all SNPs in the control group was in accordance with HWE (*p* > 0.05). The minor allele "A" of rs6668534 was significantly related to an increased risk of RA in the Han Chinese population (OR = 1.24, 95% CI = 1.04 – 1.48, *p* = 0.014). Genetic models (including the codominant, the dominant, the recessive, and the log-additive model) were applied for further exploration of the relationship between *FCGR2A* variations and RA risk in this study (**Table 3**). Our result showed that the rs6668534 was associated with a 1.51-fold increased risk of RA in the codominant model (adjusted, 95% CI = 1.07 – 2.12, *p* = 0.018 for the "A/A" genotype), 1.35 - fold increased risk of RA in the recessive model (adjusted, 95% CI = 1.02 – 1.78, *p* = 0.034 for the "A/A" genotype), and 1.23 - fold increased risk of RA in the log-additive model (adjusted, 95% CI = 1.04 – 1.46, *p* = 0.018), respectively. However, we had not found that any correlation between other three SNPs and RA risk with or without adjustment by age and gender.

Stratification analysis by gender and age

The stratification analysis by gender and age between the four SNPs and RA risk were displayed in **Table 4**. After the stratification analysis by gender adjusted for age, we found only rs6668534 was correlated with improved risk of RA in males in the allele model (OR = 1.50, 95% CI = 1.07 – 2.10, *p* = 0.020), the codominant model (adjusted, OR = 2.33, 95% CI = 1.29 – 4.22, *p* = 0.005 for the "G/A" genotype; OR = 2.16, 95% CI = 1.10 – 4.24, *p* = 0.026 for the "A/A" genotype), the dominant model (adjusted, OR = 2.27, 95% CI = 1.30 – 3.95, *p* = 0.004), and the log-additive model (adjusted, OR = 1.47, 95% CI = 1.05 – 2.06, *p* = 0.023). However, there was no significant differences between the female subgroup in any genetic model.

Then, we conducted stratification analysis by age of 54 years old adjusted for age and gender. There was no significant association between SNPs and RA risk at age > 54 years old. But two SNPs (rs6671847 and rs1801274) were observed to be associated with the risk of RA at age ≤ 54 years old based on the results of the allele model (rs6671847, OR = 0.72, 95% CI = 0.55 – 0.94, *p* = 0.014; rs1801274, OR = 0.73, 95% CI = 0.56 – 0.94, *p* = 0.017), the codominant model (rs6671847, OR = 0.50, 95% CI = 0.27 – 0.90, *p* = 0.020; rs1801274, OR = 0.50, 95% CI = 0.28 – 0.90, *p* = 0.022), and the log-additive model (rs6671847, OR = 0.72, 95% CI = 0.55 – 0.94, *p* = 0.016; rs1801274, OR = 0.73, 95% CI = 0.56 – 0.95, *p* = 0.019).

Furthermore, the relationship between genotypes at different loci and clinical parameters among patients were analyzed, as listed in **Table 5**. Our results showed that RA patients with different genotype of rs6671847 and rs1801274 had significantly different RF and CCP level (rs6671847, $p = 0.003$, $p = 0.015$; rs1801274, $p = 0.002$, $p = 0.014$, respectively). Similarly, the genotypes of rs6668534 in the RA patients showed significantly different CRP and CCP level ($p = 0.029$, $p = 0.028$, respectively).

LD and Haplotype analysis

We further performed the LD analysis among the four SNPs (rs6671847, rs1801274, rs17400517, and rs6668534) in *FCGR2A*. A strong linkage in block 1 between rs6671847 and rs1801274 was found (**Figure 1**). Unfortunately, there was no statistically difference between the cases and controls among the *FCGR2A* haplotypes (**Table 6**).

Discussion

Rheumatoid arthritis, one of the most typical autoimmune disease, is determined by various genetic and environmental interactions. It is widely recognized that genetic factors can lead prominently to the susceptibility to the RA and multiple genes and SNPs have been identified to be related to the RA⁷. However, the contribution of the SNPs in *FCGR2A* gene to RA still remains unclear. Take these into account, we designed a case-control study to clarify the correlation between *FCGR2A* polymorphisms and RA susceptibility in the Han Chinese population. Our results revealed that three (rs6671847, rs1801274, and rs6668534) of four candidate SNPs were significantly associated with RA risk. And when stratified analysis by clinical parameters, the three mentioned above were also found to be related with RA.

FcγRs, as a kind of glycoproteins, bind the Fc region of immunoglobulin G (IgG) and are expressed by various immune cell types. It provides a pivotal link between the humoral and the cellular compartments of the immune system¹⁸. Three FcγRs types (FcγR1, FcγR2, and FcγR3) have been acknowledged in humans and mice. And the mice arthritis model suggested FcγR2 is essential in autoantibody dependent arthritis¹⁹. And the dysregulation of FcγRs is important in many different inflammatory diseases, including rheumatoid arthritis²⁰. The FcγRs proteins encoded by *FCGR* genes are involved in the process of phagocytosis and the clearing of immune complexes. Several studies demonstrated various genetic polymorphisms of these receptors were related to many autoimmune disease, one of which is the variants in *FCGR2A*²¹. *FCGR2A* protein plays an important and protective role by removing antigen-antibody complexes in the circulation and transduces activated signals to cells via immune receptors when ligated with immune complexes²². Upon binding of antibodies and autoantibodies, *FCGR2A* activates immune cell function and the release of inflammatory mediators, which is related to the pathogenic consequences caused by autoantibodies or immune complexes in a variety of immune diseases²³.

For *FCGR2A* gene, rs1801274 was a missense variant resulting in an amino-acid substitution of histidine by arginine at position 131. This variant, proved to interact differently with certain IgG subclasses, and related to the development of multiple autoimmune diseases. And rs1801274 (A > G) could bind to and mediate phagocytosis with IgG2, which result in altered immune response and the activation of B cells and overproduction of cytokines²⁴. In addition, several studies have proved that it was significantly related to the risk of many autoimmune diseases, including systemic lupus erythematosus (SLE), diabetes mellitus type 1 (T1D), and RA²⁵. MDC et al²² genotyped the *FCGR2A* (A > G) (rs1801274) genetic variant and evaluated the clinical response at 24 weeks with the use of the 28-joint disease activity score criteria (DAS28). They confirmed that *FCGR2A* (A > G) (rs1801274) variants could be used for genetic marker of tocilizumab efficacy in RA patients. Chatzikiriakidou et al²⁶ found that absence of association of *FCGR2A* gene polymorphism rs1801274 with Kawasaki disease in Greek patients. Meziani R et al²⁷ indicated that *FCGR2A* was identified as a candidate common risk factor in Japanese and European populations. However, we found few reports on the relationship between the other three loci (rs6671847, rs17400517 and rs6668534) and susceptibility to RA. In a word, there were few evidence for the role of heredity between *FCGR2A* polymorphisms and risk of RA, especially in a Han Chinese population.

In our results, the results showed that *FCGR2A* gene was involved in the progress of the RA. Our current study subjects were enrolled from hospital with small number of samples, which may limit the statistical power. And the overall information about association between *FCGR2A* and RA is few. Despite the limitations mentioned above, our current study shed novel light on *FCGR2A* as potential contributors for RA development in the Han Chinese population, which provides new insights into the pathogenesis of this disease. Further research is needed to explore the potential mechanism by which the above-mentioned polymorphisms affect RA.

Declarations

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Declaration of interest

The authors declared no conflicts of interest. The authors alone are responsible for the content of this manuscript.

Funding

Not applicable.

Data Availability

All relevant data are within the manuscript.

Ethical Approval and Consent to participate

This study was performed in accordance with the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of Xi'an 630 Hospital. Written informed consent was obtained from all of the subjects before participating.

Consent for publication

Not applicable

Authors' contributions

YH Y and LN P completed genotyping and performed the manuscript. CJ H, SS X, DD L and TB J participated in the statistical analysis of the data and modified the manuscript. LW designed the study, co-supervised the work and modified the manuscript. All the authors have read and approved the final manuscript.

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Tables

Table 1 Basic characteristics of both cases and controls

Variables	Case (n = 508)	Controls (n = 494)	p-value
Gender			> 0.05
Male	134 (26%)	124 (25%)	
Female	374 (74%)	370 (75%)	
Age, years (Mean $\pm$ SD)	54.34 $\pm$ 12.01	54.03 $\pm$ 8.83	< 0.001
> 54	261 (51%)	253 (51%)	
$\leq$ 54	247 (49%)	241 (49%)	

p-value was calculated by Student's *t*-test. $p < 0.05$ indicates statistical significance.

Table 2 The distribution of allele frequencies of *IL1R1/IL1R2* SNPs in case and control

Gene	SNP-ID	Chromosome position	Alleles	MAF		O (HET)	E (HET)	p-HWE	OR (95%CI)	p*
			(minor/major)	Control	Case					
IL1R2	rs11674595	Chr2:101994530	C/T	0.204	0.227	0.311	0.325	0.333	1.14 (0.92-1.42)	0.223
IL1R2	rs4851527	Chr2:102005914	A/G	0.326	0.297	0.453	0.439	0.539	0.87 (0.72-1.06)	0.166
IL1R2	rs719250	Chr2:102007256	A/G	0.296	0.258	0.397	0.416	0.282	0.83 (0.68-1.01)	0.064
IL1R2	rs3218896	Chr2:102015190	C/T	0.137	0.123	0.229	0.236	0.451	0.88 (0.68-1.15)	0.356
IL1R2	rs3218977	Chr2:102024739	A/G	0.234	0.257	0.358	0.358	1.000	1.13 (0.92-1.39)	0.230
IL1R2	rs2072472	Chr2:102026557	C/T	0.197	0.230	0.298	0.317	0.200	1.22 (0.98-1.51)	0.072
IL1R1	rs10490571	Chr2:102100877	A/G	0.178	0.204	0.292	0.293	0.879	1.18 (0.94-1.48)	0.145
IL1R1	rs956730	Chr2:102141656	A/G	0.242	0.231	0.370	0.367	0.903	0.94 (0.77-1.16)	0.574
IL1R1	rs3917225	Chr2:102152842	A/G	0.359	0.363	0.472	0.460	0.626	1.02 (0.85-1.22)	0.877
IL1R1	rs3917318	Chr2:102176300	A/G	0.490	0.475	0.469	0.500	0.176	0.94 (0.79-1.12)	0.516

95% CI: 95% confidence interval, HWE: Hardy- Weinberg equilibrium, MAF: Minor allele frequency, OR: Odds ratio, SNP: Single-nucleotide polymorphism, p*: Calculated by Pearson χ^2 test

Table 3 Association between IL1R1/IL1R2 genetic variants and rheumatoid arthritis risk

Gene	SNP	Model	Genotype	Case N (%)	Control N (%)	OR (95% CI)	<i>p</i>
IL1R2	rs11674595						
		Codominant	T/T	298 (59.01)	315 (64.02)	1	
			T/C	185 (36.63)	153 (31.10)	1.28 (0.98-1.67)	0.072
			C/C	22 (4.36)	24 (4.88)	0.97 (0.53-1.77)	0.921
		Dominant	T/T	298 (59.01)	315 (64.02)	1	
			T/C-C/C	207 (40.99)	177 (35.98)	1.24 (0.96-1.60)	0.105
		Recessive	T/C-T/T	483 (95.64)	468 (95.12)	1	
			C/C	22 (4.36)	24 (4.88)	0.89 (0.49-1.61)	0.699
		Log-additive	-	-	-	1.14 (0.92-1.42)	0.224
	rs4851527						
		Codominant	G/G	244 (48.03)	221 (44.74)	1	
			A/G	226 (44.49)	224 (45.34)	0.91 (0.70-1.18)	0.481
			A/A	38 (7.48)	49 (9.92)	0.70 (0.44-1.12)	0.136
		Dominant	G/G	244 (48.03)	221 (44.74)	1	
			A/G-A/A	264 (51.97)	273 (55.26)	0.87 (0.68-1.12)	0.288
		Recessive	A/G-G/G	470 (92.52)	445 (90.08)	1	
			A/A	38 (7.48)	49 (9.92)	0.74 (0.47-1.15)	0.177
		Log-additive	-	-	-	0.87 (0.71-1.06)	0.154
	rs719250						
		Codominant	C/C	279 (55.25)	250 (50.61)	1	
			C/T	191 (37.82)	196 (39.68)	0.87 (0.67-1.13)	0.307
			T/T	35 (6.93)	48 (9.72)	0.66 (0.41-1.05)	0.078
		Dominant	C/C	279 (55.25)	250 (50.61)	1	
			C/T-T/T	226 (44.75)	244 (49.39)	0.83 (0.65-1.06)	0.142
		Recessive	C/T-C/C	470 (93.07)	446 (90.28)	1	
			T/T	35 (6.93)	48 (9.72)	0.70 (0.44-1.10)	0.118
		Log-additive	-	-	-	0.84 (0.69-1.02)	0.070
	rs3218896						
		Codominant	T/T	396 (77.95)	369 (74.85)	1	
			T/C	99 (19.49)	113 (22.92)	0.81 (0.60-1.10)	0.183
			C/C	13 (2.56)	11 (2.23)	1.12 (0.49-2.53)	0.792
		Dominant	T/T	396 (77.95)	369 (74.85)	1	
			T/C-C/C	112 (22.05)	124 (25.15)	0.84 (0.63-1.13)	0.241
		Recessive	T/C-T/T	495 (97.44)	482 (97.77)	1	
			C/C	13 (2.56)	11 (2.23)	1.17 (0.52-2.63)	0.712
		Log-additive	-	-	-	0.89 (0.69-1.15)	0.368
	rs3218977						

		Codominant	A/A	271 (53.35)	290 (58.70)	1	
			A/G	213 (41.93)	177 (35.83)	1.29 (0.99-1.67)	0.056
			G/G	24 (4.72)	27 (5.47)	0.94 (0.53-1.68)	0.842
		Dominant	A/A	271 (53.35)	290 (58.70)	1	
			A/G-G/G	237 (46.65)	204 (41.30)	1.24 (0.97-1.60)	0.090
		Recessive	A/G-A/A	484 (95.28)	467 (94.53)	1	
			G/G	24 (4.72)	27 (5.47)	0.85 (0.48-1.5)	0.574
		Log-additive	-	-	-	1.14 (0.92-1.40)	0.225
	rs2072472						
		Codominant	A/A	296 (58.27)	323 (65.38)	1	
			A/G	190 (37.40)	147 (29.76)	1.41 (1.08-1.84)	0.011
			G/G	22 (4.33)	24 (4.86)	1.00 (0.55-1.82)	1.000
		Dominant	A/A	296 (58.27)	323 (65.38)	1	
			A/G-G/G	212 (41.73)	171 (34.62)	1.35 (1.05-1.75)	0.021
		Recessive	A/G-A/A	486 (95.67)	470 (95.14)	1	
			G/G	22 (4.33)	24 (4.86)	0.89 (0.49-1.60)	0.688
		Log-additive	-	-	-	1.22 (0.98-1.51)	0.073
IL1R1	rs10490571						
		Codominant	C/C	318 (62.60)	334 (67.61)	1	
			C/T	173 (34.06)	144 (29.15)	1.26 (0.96-1.65)	0.096
			T/T	17 (3.35)	16 (3.24)	1.11 (0.55-2.24)	0.773
		Dominant	C/C	318 (62.60)	334 (67.61)	1	
			C/T-T/T	190 (37.40)	160 (32.39)	1.24 (0.96-1.61)	0.103
		Recessive	C/T-C/C	491 (96.65)	478 (96.76)	1	
			T/T	17 (3.35)	16 (3.24)	1.03 (0.51-2.07)	0.934
		Log-additive	-	-	-	1.18 (0.94-1.48)	0.149
	rs956730						
		Codominant	G/G	292 (57.71)	283 (57.29)	1	
			A/G	194 (38.34)	183 (37.04)	1.02 (0.79-1.33)	0.863
			A/A	20 (3.95)	28 (5.67)	0.69 (0.38-1.25)	0.224
		Dominant	G/G	292 (57.71)	283 (57.29)	1	
			A/G-A/A	214 (42.29)	211 (42.71)	0.98 (0.76-1.26)	0.868
		Recessive	A/G-G/G	486 (96.05)	466 (94.33)	1	
			A/A	20 (3.95)	28 (5.67)	0.68 (0.38-1.23)	0.206
		Log-additive	-	-	-	0.94 (0.76-1.16)	0.547
	rs3917225						
		Codominant	A/A	201 (39.72)	200 (40.49)	1	
			A/G	243 (48.02)	233 (47.17)	1.04 (0.80-1.36)	0.772
			G/G	62 (12.25)	61 (12.35)	1.02 (0.68-1.52)	0.943
		Dominant	A/A	201 (39.72)	200 (40.49)	1	

		A/G-G/G	305 (60.28)	294 (59.51)	1.04 (0.80-1.33)	0.790
	Recessive	A/G-A/A	444 (87.75)	433 (87.65)	1	
		G/G	62 (12.25)	61 (12.35)	0.99 (0.68-1.45)	0.972
	Log-additive	-	-	-	1.02 (0.84-1.22)	0.859
rs3917318						
	Codominant	A/A	140 (27.61)	136 (27.59)	1	
		A/G	252 (49.70)	231 (46.86)	1.06 (0.79-1.43)	0.682
		G/G	115 (22.68)	126 (25.56)	0.89 (0.63-1.26)	0.501
	Dominant	A/A	140 (27.61)	136 (27.59)	1	
		A/G-G/G	367 (72.39)	357 (72.41)	1.00 (0.76-1.32)	0.991
	Recessive	A/G-A/A	392 (77.32)	367 (74.44)	1	
		G/G	115 (22.68)	126 (25.56)	0.85 (0.64-1.14)	0.286
	Log-additive	-	-	-	0.95 (0.80-1.12)	0.529

95%CI: 95% confidence interval, HWE: Hardy- Weinberg equilibrium, MAF: Minor allele frequency, OR: Odds ratio, SNP: Single-nucleotide polymorphism, *p*-value was calculated by unconditional logistic regression adjusted by age and gender, *p* < 0.05 indicates statistical significance.

Table 4 Association between IL1R1/IL1R2 genetic variants and rheumatoid arthritis risk based on the gender stratification

Gene/SNP-ID	Model	Genotype	males				females			
			Case	control	OR (95% CI)	<i>p</i>	Case	control	OR (95% CI)	<i>p</i>
IL1R2/rs11674595	Allele	T	203 (75.75%)	199 (80.24%)	1		578 (77.90%)	584 (79.35%)	1	
		C	65 (24.25%)	49 (19.76%)	1.30 (0.86-1.98)	0.219	164 (22.10%)	152 (20.65%)	1.09 (0.85-1.40)	0.497
	Codominant	T/T	75 (55.97%)	80 (64.52%)	1		223 (60.11%)	235 (63.86%)	1	
		C/T	53 (39.55%)	39 (31.45%)	1.46 (0.87-2.46)	0.156	132 (35.58%)	114 (30.98%)	1.22 (0.89-1.66)	0.211
		C/C	6 (4.48%)	5 (4.03%)	1.28 (0.37-4.37)	0.695	16 (4.31%)	19 (5.16%)	0.89 (0.45-1.77)	0.736
	Dominant	T/T	75 (55.97%)	80 (64.52%)	1		223 (60.11%)	235 (63.86%)	1	
		C/T-C/C	59 (44.03%)	44 (35.48%)	1.44 (0.87-2.38)	0.157	148 (39.89%)	133 (36.14%)	1.17 (0.87-1.58)	0.296
	Recessive	T/T-T/C	128 (95.52%)	119 (95.97%)	1		355 (95.69%)	349 (94.84%)	1	
		C/C	6 (4.48%)	5 (4.03%)	1.11 (0.33-3.75)	0.862	16 (4.31%)	19 (5.16%)	0.83 (0.42-1.64)	0.589
	Log-additive	–	–	–	1.32 (0.86-2.03)	0.208	–	–	1.09 (0.85-1.40)	0.501
IL1R2/rs4851527	Allele	G	191 (71.27%)	175 (70.56%)	1		523 (69.92%)	491 (66.35%)	1	
		A	77 (28.73%)	73 (29.44%)	0.97 (0.66-1.41)	0.860	225 (30.08%)	249 (33.65%)	0.85 (0.68-1.06)	0.140
	Codominant	G/G	65 (48.51%)	60 (48.39%)	1		179 (47.86%)	161 (43.51%)	1	
		G/A	61 (45.52%)	55 (44.35%)	1.02 (0.62-1.70)	0.936	165 (44.12%)	169 (45.68%)	0.82 (0.30-2.28)	0.710
		A/A	8 (5.97%)	9 (7.26%)	0.82 (0.30-2.28)	0.710	30 (8.02%)	40 (10.81%)	1.02 (0.62-1.70)	0.936
	Dominant	G/G	65 (48.51%)	60 (48.39%)	1		179 (47.86%)	161 (43.51%)	1	
		G/A-A/A	69 (51.49%)	64 (51.61%)	0.99 (0.61-1.62)	0.978	195 (52.14%)	209 (56.49%)	0.99 (0.61-1.62)	0.978
	Recessive	G/G-G/A	126 (94.03%)	115 (92.74%)	1		344 (91.98%)	330 (89.19%)	1	
		A/A	8 (5.97%)	9 (7.26%)	0.82 (0.30-2.19)	0.688	30 (8.02%)	40 (10.81%)	0.82 (0.30-2.19)	0.688
	Log-additive	–	–	–	0.96 (0.65-1.44)	0.853	–	–	0.96 (0.65-1.44)	0.853
IL1R2/rs719250	Allele	C	204 (76.12%)	168 (67.74%)	1		545 (73.45%)	528 (71.35%)	1	
		T	64 (23.88%)	80 (32.26%)	0.66 (0.45-	0.034	197 (26.55%)	212 (28.65%)	0.90 (0.72-	0.366

					0.97)			1.13)		
	Codominant	C/C	76 (56.72%)	58 (46.77%)	1		203 (54.72%)	192 (51.89%)	1	
		C/T	52 (38.81%)	52 (41.94%)	0.76 (0.46-1.26)	0.288	139 (37.47%)	144 (38.92%)	0.91 (0.67-1.24)	0.559
		T/T	6 (4.48%)	14 (11.29%)	0.33 (0.12-0.91)	0.032	29 (7.82%)	34 (9.19%)	0.81 (0.47-1.38)	0.430
	Dominant	C/C	76 (56.72%)	58 (46.77%)	1		203 (54.72%)	192 (51.89%)	1	
		C/T-T/T	58 (43.28%)	66 (53.23%)	0.67 (0.41-1.09)	0.109	168 (45.28%)	178 (48.11%)	0.89 (0.67-1.19)	0.441
	Recessive	C/T-C/C	128 (95.52%)	110 (88.71%)	1		342 (92.18%)	336 (90.81%)	1	
		T/T	6 (4.48%)	14 (11.29%)	0.37 (0.13-0.99)	0.049	29 (7.82%)	34 (9.19%)	0.84 (0.50-1.41)	0.503
	Log-additive	–	–	–	0.66 (0.44-0.97)	0.036	–	–	0.90 (0.72-1.13)	0.377
IL1R2/rs3218896	Allele	T	237 (88.43%)	208 (83.87%)	1		654 (87.43%)	643 (87.13%)	1	
		C	31 (11.57%)	40 (16.13%)	0.68 (0.41-1.13)	0.133	94 (12.57%)	95 (12.87%)	0.97 (0.72-1.32)	0.860
	Codominant	T/T	106 (79.10%)	86 (69.35%)	1		290 (77.54%)	283 (76.69%)	1	
		T/C	25 (18.66%)	36 (29.03%)	0.56 (0.31-1.01)	0.054	74 (19.79%)	77 (20.87%)	0.94 (0.65-1.34)	0.717
		C/C	3 (2.24%)	2 (1.61%)	1.31 (0.20-8.50)	0.776	10 (2.67%)	9 (2.44%)	1.08 (0.43-2.70)	0.868
	Dominant	T/T	106 (79.10%)	86 (69.35%)	1		290 (77.54%)	283 (76.69%)	1	
		C/T-C/C	28 (20.90%)	38 (30.65%)	0.60 (0.34-1.05)	0.076	84 (22.46%)	86 (23.31%)	0.95 (0.68-1.34)	0.774
	Recessive	C/T-T/T	131 (97.76%)	122 (98.39%)	1		364 (97.33%)	360 (97.56%)	1	
		C/C	3 (2.24%)	2 (1.61%)	1.50 (0.23-9.67)	0.670	10 (2.67%)	9 (2.44%)	1.10 (0.44-2.73)	0.844
	Log-additive	–	–	–	0.68 (0.41-1.13)	0.139	–	–	0.97 (0.73-1.31)	0.855
IL1R2/rs3218977	Allele	A	194 (72.39%)	185 (74.60%)	1		561 (75.00%)	572 (77.30%)	1	
		G	74 (27.61%)	63 (25.40%)	1.12 (0.76-1.66)	0.570	187 (25.00%)	168 (22.70%)	1.14 (0.89-1.44)	0.299
	Codominant	A/A	67 (50.00%)	71 (57.26%)	1		204 (54.55%)	219 (59.19%)	1	
		A/G	60 (44.78%)	43 (34.68%)	1.37 (0.94-2.00)	0.104	153 (40.91%)	134 (36.22%)	1.31 (0.90-1.90)	0.155
		G/G	7 (5.22%)	10 (8.06%)	0.45(0.20-1.00)	0.052	17 (4.55%)	17 (4.59%)	0.44 (0.90-	0.081

										6.63)
	Dominant	A/A	67 (50.00%)	71 (57.26%)	1		204 (54.55%)	219 (59.19%)	1	
		A/G-G/G	67 (50.00%)	53 (42.74%)	1.17(0.82- 1.68)	0.383	170 (45.45%)	151 (40.81%)	1.38 (0.96- 1.98)	0.081
	Recessive	A/G-A/A	127 (94.78%)	114 (91.94%)	1		357 (95.45%)	353 (95.41%)	1	
		G/G	7 (5.22%)	10 (8.06%)	0.40 (0.18- 0.88)	0.023	17 (4.55%)	17 (4.59%)	2.18 (0.81- 5.84)	0.123
	Log-additive	–	–	–	0.97 (0.73- 1.30)	0.843	–	–	1.39 (1.01- 1.90)	0.041
IL1R2/rs2072472	Allele	A	206 (76.87%)	201 (81.05%)	1		576 (77.01%)	592 (80.00%)	1	
		G	62 (23.13%)	47 (18.95%)	1.29 (0.84- 1.97)	0.245	172 (22.99%)	148 (20.00%)	1.19 (0.93- 1.53)	0.160
	Codominant	A/A	78 (58.21%)	82 (66.13%)	1		218 (58.29%)	241 (65.14%)	1	
		A/G	50 (37.31%)	37 (29.84%)	1.43 (0.84- 2.42)	0.184	140 (37.43%)	110 (29.73%)	1.41 (1.03- 1.92)	0.031
		G/G	6 (4.48%)	5 (4.03%)	1.26 (0.37- 4.30)	0.712	16 (4.28%)	19 (5.14%)	0.93 (0.47- 1.85)	0.834
	Dominant	A/A	78 (58.21%)	82 (66.13%)	1		218 (58.29%)	241 (65.14%)	1	
		A/G-G/G	56 (41.79%)	2 (33.87%)	1.41 (0.85- 2.34)	0.185	156 (41.71%)	129 (34.86%)	1.34 (0.99- 1.80)	0.056
	Recessive	A/G-A/A	128 (95.52%)	119 (95.97%)	1		358 (95.72%)	351 (94.86%)	1	
		G/G	6 (4.48%)	5 (4.03%)	1.11 (0.33- 3.75)	0.862	16 (4.28%)	19 (5.14%)	0.82 (0.42- 1.63)	0.577
	Log-additive	–	–	–	1.30 (0.84- 1.99)	0.238	–	–	1.19 (0.93- 1.53)	0.164
IL1R1/rs10490571	Allele	C	203 (75.75%)	120 (82.66%)	1		606 (81.02%)	607 (82.03%)	1	
		T	65 (24.25%)	43 (17.34%)	1.53 (0.99- 2.35)	0.065	142 (18.98%)	133 (17.97%)	1.07 (0.82- 1.39)	0.615
	Codominant	C/C	77 (57.46%)	86 (69.35%)	1		241 (64.44%)	248 (67.03%)	1	
		C/T	49 (36.57%)	33 (26.61%)	1.66 (0.97- 2.84)	0.065	124 (33.16%)	111 (30.00%)	1.14 (0.84- 1.57)	0.398
		T/T	8 (5.97%)	5 (4.03%)	1.84 (0.57- 5.97)	0.307	9 (2.41%)	11 (2.97%)	0.84 (0.34- 2.06)	0.698
	Dominant	C/C	77 (57.46%)	86 (69.35%)	1		241 (64.44%)	248 (67.03%)	1	
		C/T-T/T	57 (42.54%)	38 (30.65%)	1.68 (1.01- 2.81)	0.047	133 (35.56%)	122 (32.97%)	1.12 (0.82- 1.51)	0.477
	Recessive	C/T-C/C	126 (94.03%)	119 (95.97%)	1		365 (97.59%)	359 (97.03%)	1	

		T/T	8 (5.97%)	5 (4.03%)	1.56 (0.49-4.97)	0.454	9 (2.41%)	11 (2.97%)	0.80 (0.33-1.96)	0.624
	Log-additive	–	–	–	1.52 (0.99-2.33)	0.056	–	–	1.07 (0.82-1.40)	0.630
IL1R1/rs956730	Allele	G	200 (75.19%)	184 (74.19%)	1		578 (77.48%)	565 (76.35%)	1	
		A	66 (24.81%)	64 (25.81%)	0.95 (0.64-1.41)	0.796	168 (22.52%)	175 (23.65%)	0.94 (0.74-1.20)	0.606
	Codominant	G/G	75 (56.39%)	64 (51.61%)	1		217 (58.18%)	219 (59.19%)	1	
		G/A	50 (37.59%)	56 (45.16%)	0.76 (0.46-1.26)	0.288	144 (38.61%)	127 (34.32%)	1.14 (0.84-1.55)	0.388
		A/A	8 (6.02%)	4 (3.23%)	1.70 (0.49-5.91)	0.406	12 (3.22%)	24 (6.49%)	0.50 (0.24-1.03)	0.061
	Dominant	G/G	75 (56.39%)	64 (51.61%)	1		217 (58.18%)	219 (59.19%)	1	
		G/A-A/A	58 (43.61%)	60 (48.39%)	0.82 (0.50-1.35)	0.434	156 (41.82%)	151 (40.81%)	1.04 (0.78-1.40)	0.785
	Recessive	G/A-G/G	125 (93.98%)	120 (96.77%)	1		365 (97.59%)	359 (97.03%)	1	
		A/A	8 (6.02%)	4 (3.23%)	1.92 (0.56-6.54)	0.298	9 (2.41%)	11 (2.97%)	0.48 (0.24-0.97)	0.042
	Log-additive	–	–	–	0.94 (0.62-1.43)	0.777	–	–	0.94 (0.73-1.2)	0.596
IL1R1/rs3917225	Allele	A	167 (62.78%)	166 (66.94%)	1		478 (64.08%)	467 (63.11%)	1	
		G	99 (37.22%)	82 (33.06%)	1.20 (0.83-1.73)	0.325	268 (35.92%)	273 (36.89%)	0.96 (0.78-1.19)	0.699
	Codominant	A/A	52 (39.10%)	57 (45.97%)	1		149 (323.91%)	143 (38.65%)	1	
		A/G	63 (47.37%)	52 (41.94%)	1.33 (0.79-2.25)	0.285	180 (48.00%)	181 (48.92%)	0.95 (0.70-1.30)	0.766
		G/G	18(13.53%)	15 (12.10%)	1.34 (0.61-2.94)	0.471	46 (12.27%)	46 (12.43%)	0.92 (0.57-1.47)	0.724
	Dominant	A/A	52 (39.10%)	57 (45.97%)	1		149 (39.95%)	143 (38.65%)	1	
		A/G-G/G	81(60.90%)	67 (54.03%)	1.33 (0.81-2.19)	0.258	224 (60.05%)	227 (61.35%)	0.95 (0.71-1.27)	0.717
	Recessive	A/G-A/A	115 (86.47%)	109 (87.90%)	1		361 (96.78%)	346 (93.51%)	1	
		G/G	18 (13.53%)	15(12.10%)	1.15 (0.55-2.41)	0.708	12 (3.22%)	24 (6.49%)	0.94 (0.61-1.47)	0.792
	Log-additive	–	–	–	1.21 (0.84-1.73)	0.314	–	–	0.96 (0.77-1.19)	0.692
IL1R1/rs3917318	Allele	G	113 (42.16%)	127 (51.21%)	1		377 (50.54%)	382 (51.76%)	1	

	A	155 (57.84%)	121 (48.79%)	1.44 (1.02-2.04)	0.040	369 (49.46%)	356 (48.24%)	1.05 (0.86-1.29)	0.637
Codominant	G/G	26 (19.40%)	38 (30.65%)	1		93 (24.93%)	101 (27.37%)	1	
	G/A	61 (45.52%)	51 (41.13%)	1.97 (1.01-3.83)	0.045	191 (51.21%)	180 (48.78%)	1.15 (0.81-1.63)	0.427
	A/A	47 (35.07%)	35 (28.23%)	1.76 (0.94-3.27)	0.077	89 (23.86%)	88 (23.85%)	1.10 (0.73-1.65)	0.651
Dominant	G/G	26 (19.40%)	38 (30.65%)	1		93 (24.93%)	101 (27.37%)	1	
	G/A-A/A	108 (80.60%)	86 (69.35%)	1.84 (1.04-3.27)	0.037	280 (75.07%)	268 (72.63%)	1.13 (0.81-1.57)	0.452
Recessive	G/A-G/G	87 (64.93%)	89 (71.77%)	1		329 (88.20%)	324 (87.57%)	1	
	A/A	47 (35.07%)	35 (28.23%)	1.38 (0.81-2.33)	0.237	44 (11.80%)	46 (12.43%)	1.00 (0.71-1.40)	0.992
Log-additive	–	–	–	1.39 (1.00-1.93)	0.053	–	–	1.00 (0.86-1.29)	0.636

95%CI: 95% confidence interval, HWE: Hardy- Weinberg equilibrium MAF: Minor allele frequency,

OR: Odds ratio, SNP:Single-nucleotide polymorphism, *p*-value was calculated by unconditional logistic regression adjusted by age and gender,

p < 0.05 indicates statistical significance.

Table 5 Association between IL1R1/IL1R2 genetic variants and rheumatoid arthritis risk.

Gene / SNP-ID	Model	Genotype	age>54 years				age ≤54 years			
			Case	Control	OR (95% CI)	<i>p</i>	Case	Control	OR (95% CI)	<i>p</i>
IL1R2/rs11674595	Allele	T	402 (77.91%)	399 (79.17%)	1		379 (76.72%)	384 (80.00%)	1	
		C	114 (22.09%)	105 (20.83%)	1.08 (0.80-1.45)	0.624	115 (23.28%)	96 (20.00%)	1.21 (0.89-1.65)	0.214
	Codominant	T/T	151 (58.53%)	161 (63.89%)	1		147 (59.51%)	154 (64.17%)	1	
		C/T	100 (38.76%)	77 (30.56%)	1.43 (0.98-2.10)	0.064	85 (34.41%)	76 (31.67%)	1.16 (0.79-1.70)	0.461
		C/C	7 (2.71%)	14 (5.56%)	0.48 (0.19-1.25)	0.134	15 (6.07%)	10 (4.17%)	1.60 (0.69-3.71)	0.271
	Dominant	T/T	151 (58.53%)	161 (63.89%)	1		147 (59.51%)	154 (64.17%)	1	
		C/T-C/C	107 (41.47%)	91 (36.11%)	1.28 (0.89-1.84)	0.189	100 (40.49%)	86 (35.83%)	1.21 (0.83-1.75)	0.317
	Recessive	T/T-T/C	251 (97.29%)	238 (94.44%)	1		232 (93.93%)	230 (95.83%)	1	
		C/C	7 (2.71%)	14 (5.56%)	0.42 (0.17-1.09)	0.075	15 (6.07%)	10 (4.17%)	1.52 (0.67-3.49)	0.319
	Log-additive	–	–	–	1.08 (0.79-1.47)	0.627	–	–	1.21 (0.89-1.64)	0.231
IL1R2/rs4851527	Allele	G	360 (68.97%)	344 (67.98%)	1		354 (71.66%)	322 (66.80%)	1	
		A	162 (31.03%)	162 (32.02%)	0.96 (0.73-1.24)	0.735	140 (28.34%)	160 (33.20%)	0.80 (0.61-1.05)	0.100
	Codominant	G/G	113 (43.30%)	119 (47.04%)	1		131 (53.04%)	102 (42.32%)	1	
		G/A	134 (51.34%)	106 (41.90%)	1.32 (0.91-1.91)	0.148	92 (37.25%)	118 (48.96%)	0.63 (0.43-0.93)	0.019
		A/A	14 (5.36%)	28 (11.07%)	0.47 (0.23-0.96)	0.039	24 (9.72%)	21 (8.71%)	0.93 (0.49-1.78)	0.831
	Dominant	G/G	113 (43.30%)	119 (47.04%)	1		131 (53.04%)	102 (42.32%)	1	
		G/A-A/A	148 (56.70%)	134 (52.96%)	1.13 (0.79-1.62)	0.490	116 (46.96%)	139 (57.68%)	0.68 (0.47-0.97)	0.035
	Recessive	G/G-G/A	247 (94.64%)	225 (88.93%)	1		223 (90.28%)	220 (91.29%)	1	
		A/A	14 (5.36%)	28 (11.07%)	0.41 (0.21-0.82)	0.011	24 (9.72%)	21 (8.71%)	1.16 (0.62-2.17)	0.641
	Log-additive	–	–	–	0.92 (0.69-1.22)	0.558	–	–	0.82 (0.62-1.08)	0.156
IL1R2/rs719250	Allele	C	373 (72.29%)	359 (70.95%)	1		376 (76.11%)	337 (69.92%)	1	
		T	143 (27.71%)	147 (29.05%)	0.94 (0.71-1.23)	0.635	118 (23.89%)	145 (30.08%)	0.73 (0.55-0.97)	0.029

	Codominant	C/C	132 (51.16%)	129 (50.99%)	1		147 (59.51%)	121 (50.21%)	1	
		C/T	109 (42.25%)	101 (39.92%)	1.11 (0.76-1.61)	0.589	82 (33.20%)	95 (39.42%)	0.68 (0.46-1.01)	0.054
		T/T	17 (6.59%)	23 (9.09%)	0.89 (0.45-1.77)	0.739	18 (7.29%)	25 (10.37%)	0.54 (0.28-1.05)	0.070
	Dominant	C/C	132 (51.16%)	129 (50.99%)	1		147 (59.51%)	121 (50.21%)	1	
		C/T-T/T	126 (48.84%)	124 (49.01%)	1.07 (0.75-1.53)	0.709	100 (40.49%)	120 (49.79%)	0.65 (0.45-0.94)	0.022
	Recessive	C/T-C/C	241 (93.41%)	230 (90.91%)	1		229 (92.71%)	216 (89.63%)	1	
		T/T	17 (6.59%)	23 (9.09%)	0.85 (0.44-1.66)	0.633	18 (7.29%)	25 (10.37%)	0.63 (0.33-1.20)	0.162
	Log-additive	–	–	–	1.01 (0.76-1.34)	0.927	–	–	0.71 (0.54-0.95)	0.019
IL1R2/rs3218896	Allele	T	447 (85.63%)	429 (85.12%)	1		444 (89.88%)	422 (87.55%)	1	
		C	75 (14.37%)	75 (14.88%)	0.96 (0.68-1.36)	0.816	50 (10.12%)	60 (12.45%)	0.79 (0.53-1.18)	0.251
	Codominant	T/T	194 (74.33%)	184 (73.02%)	1		202 (81.78%)	185 (76.76%)	1	
		T/C	59 (22.61%)	61 (24.21%)	0.95 (0.62-1.45)	0.813	40 (16.19%)	52 (21.58%)	0.68 (0.43-1.08)	0.105
		C/C	8 (3.07%)	7 (2.78%)	1.46 (0.51-4.19)	0.478	5 (2.02%)	4 (1.66%)	0.80 (0.20-3.17)	0.747
	Dominant	T/T	194 (74.33%)	184 (73.02%)	1		202 (81.78%)	185 (76.76%)	1	
		C/T-C/C	67 (25.67%)	68 (26.98%)	1.00 (0.67-1.49)	0.990	45 (18.22%)	56 (23.24%)	0.69 (0.44-1.08)	0.105
	Recessive	C/T-T/T	253 (96.93%)	245 (97.22%)	1		242 (97.98%)	237 (98.34%)	1	
		C/C	8 (3.07%)	7 (2.78%)	1.48 (0.52-4.22)	0.462	5 (2.02%)	4 (1.66%)	0.86 (0.22-3.42)	0.835
	Log-additive	–	–	–	1.04 (0.74-1.47)	0.817	–	–	0.74 (0.50-1.10)	0.134
IL1R2/rs3218977	Allele	A	396 (75.86%)	382 (75.49%)	1		359 (72.67%)	375 (77.80%)	1	
		G	126 (24.14%)	124 (24.51%)	0.98 (0.74-1.30)	0.891	135 (27.33%)	107 (22.20%)	1.32 (0.98-1.77)	0.064
	Codominant	A/A	145 (55.56%)	150 (59.29%)	1		126 (51.01%)	140 (58.09%)	1	
		A/G	106 (40.61%)	82 (32.41%)	1.37 (0.94-2.00)	0.104	107 (43.32%)	95 (39.42%)	1.00 (0.90-1.90)	0.155
		G/G	10 (3.83%)	21 (8.30%)	0.45 (0.20-1.01)	0.052	14 (5.67%)	6 (2.49%)	2.44 (0.90-6.63)	0.081

	Dominant	A/A	145 (55.56%)	150 (59.29%)	1		126 (51.01%)	140 (58.09%)	1	
		A/G-G/G	116 (44.44%)	103 (40.71%)	1.17 (0.82-1.68)	0.383	121 (48.99%)	101 (41.91%)	1.38 (0.96-1.98)	0.081
	Recessive	A/G-A/A	251 (96.17%)	232 (91.70%)	1		233 (94.33%)	235 (97.51%)	1	
		G/G	10 (3.83%)	21 (8.30%)	0.40 (0.18-0.88)	0.023	14 (5.67%)	6 (2.49%)	2.18 (0.81-5.84)	0.123
	Log-additive	–	–	–	0.97 (0.73-1.30)	0.843	–	–	1.39 (1.01-1.91)	0.041
IL1R2/rs2072472	Allele	A	404 (77.39%)	407 (80.43%)	1		378 (76.52%)	386 (80.08%)	1	
		G	118 (22.61%)	99 (19.57%)	1.20 (0.89-1.62)	0.232	116 (23.48%)	96 (19.92%)	1.23 (0.91-1.68)	0.177
	Codominant	A/A	150 (57.47%)	168 (66.40%)	1		146 (59.11%)	155 (64.32%)	1	
		A/G	104 (39.85%)	71 (28.06%)	1.67 (1.14-2.45)	0.009	86 (34.82%)	76 (31.54%)	1.18 (0.80-1.74)	0.391
		G/G	7 (2.68%)	14 (5.53%)	0.51 (0.20-1.32)	0.163	15 (6.07%)	10 (4.15%)	1.77 (0.76-4.09)	0.185
	Dominant	A/A	150 (57.47%)	168 (66.40%)	1		146 (59.11%)	155 (64.32%)	1	
		A/G-G/G	111 (42.53%)	85 (33.60%)	1.47 (1.02-2.12)	0.039	101 (40.89%)	86 (35.68%)	1.25 (0.86-1.81)	0.238
	Recessive	A/G-A/A	254 (97.32%)	239 (94.47%)	1		232 (93.93%)	231 (95.85%)	1	
		G/G	7 (2.68%)	14 (5.53%)	0.42 (0.16-1.09)	0.075	15 (6.07%)	10 (4.15%)	1.67 (0.73-3.82)	0.228
	Log-additive	–	–	–	1.20 (0.88-1.63)	0.262	–	–	1.25 (0.92-1.69)	0.155
IL1R1/rs10490571	Allele	C	407 (77.97%)	411 (81.23%)	1		402 (81.38%)	401 (83.20%)	1	
		T	115 (22.03%)	95 (18.77%)	1.22 (0.90-1.66)	0.196	92 (18.62%)	81 (16.80%)	1.13 (0.82-1.58)	0.457
	Codominant	C/C	154 (59.00%)	165 (65.22%)	1		164 (66.40%)	169 (70.12%)	1	
		C/T	99 (37.93%)	81 (32.02%)	1.30 (0.89-1.89)	0.169	74 (29.96%)	63 (26.14%)	0.98 (0.37-2.57)	0.962
		T/T	8 (3.07%)	7 (2.77%)	1.32 (0.46-3.81)	0.602	9 (3.64%)	9 (3.73%)	1.23 (0.82-1.84)	0.319
	Dominant	C/C	154 (59.00%)	165 (65.22%)	1		164 (66.40%)	169 (70.12%)	1	
		C/T-T/T	107 (41.00%)	88 (34.78%)	1.30 (0.90-1.88)	0.156	83 (33.60%)	72 (29.88%)	1.20 (0.81-1.76)	0.364
	Recessive	C/T-C/C	253 (96.93%)	246 (97.23%)	1		238 (96.36%)	232 (96.27%)	1	
		T/T	8	7	1.20	0.728	9	9	0.92	0.861

			(3.07%)	(2.77%)	(0.42-3.43)		(3.64%)	(3.73%)	(0.35-2.40)	
	Log-additive	–	–	–	1.25 (0.91-1.73)	0.174	–	–	1.13 (0.81-1.57)	0.477
IL1R1/rs956730	Allele	G	391 (75.48%)	375 (74.11%)	1		387 (78.34%)	374 (77.59%)	1	
		A	127 (24.52%)	131 (25.89%)	0.93 (0.70-1.23)	0.613	107 (21.66%)	108 (22.41%)	0.96 (0.71-1.30)	0.778
	Codominant	G/G	138 (53.28%)	138 (54.55%)	1		154 (62.35%)	145 (60.17%)	1	
		G/A	115 (44.40%)	99 (39.13%)	1.19 (0.83-1.72)	0.342	79 (31.98%)	84 (34.85%)	0.86 (0.58-1.26)	0.434
		A/A	6 (2.32%)	16 (6.32%)	0.40 (0.15-1.06)	0.065	14 (5.67%)	12 (4.98%)	1.28 (0.57-2.89)	0.549
	Dominant	G/G	138 (53.28%)	138 (54.55%)	1		154 (62.35%)	145 (60.17%)	1	
		G/A-A/A	121 (46.72%)	115 (45.45%)	1.08 (0.76-1.55)	0.660	93 (37.65%)	96 (39.83%)	0.91 (0.63-1.31)	0.601
	Recessive	G/A-G/G	253 (97.68%)	237 (93.68%)	1		233 (94.33%)	229 (95.02%)	1	
		A/A	6 (2.32%)	16 (6.32%)	0.37 (0.14-0.97)	0.043	14 (5.67%)	12 (4.98%)	1.35 (0.61-3.02)	0.462
	Log-additive	–	–	–	0.95 (0.70-1.28)	0.720	–	–	0.98 (0.72-1.32)	0.881
IL1R1/rs3917225	Allele	A	336 (64.62%)	337 (66.60%)	1		309 (62.80%)	296 (61.41%)	1	
		G	184 (35.38%)	169 (33.40%)	1.09 (0.84-1.41)	0.503	183 (37.20%)	186 (38.59%)	0.94 (0.73-1.22)	0.654
	Codominant	A/A	104 (40.00%)	110 (43.48%)	1		97 (39.43%)	90 (37.34%)	1	
		A/G	128 (49.23%)	117 (46.25%)	1.17 (0.81-1.71)	0.406	115 (46.75%)	116 (48.13%)	0.93 (0.63-1.38)	0.721
		G/G	28 (10.77%)	26 (10.28%)	1.21 (0.66-2.24)	0.533	34 (13.82%)	35 (14.52%)	0.93 (0.53-1.63)	0.806
	Dominant	A/A	104 (40.00%)	110 (43.48%)	1		97 (39.43%)	90 (37.34%)	1	
		A/G-G/G	156 (60.00%)	143 (56.52%)	1.18 (0.82-1.69)	0.367	149 (60.57%)	151 (62.66%)	0.93 (0.64-1.35)	0.707
	Recessive	A/G-A/A	232 (89.23%)	227 (89.72%)	1		212 (86.18%)	206 (85.48%)	1	
		G/G	28 (10.77%)	26 (10.28%)	1.12 (0.63-1.99)	0.711	34 (13.82%)	35 (14.52%)	0.97 (0.58-1.62)	0.908
	Log-additive	–	–	–	1.13 (0.86-1.48)	0.391	–	–	0.96 (0.74-1.25)	0.744
IL1R1/rs3917318	Allele	G	241 (46.17%)	253 (50.20%)	1		251 (51.02%)	252 (52.28%)	1	
		A	281	251	1.18	0.197	241	230	1.05	0.693

			(53.83%)	(49.80%)	(0.92-1.50)		(48.98%)	(47.72%)	(0.82-1.35)	
	Codominant	G/G	55 (21.07%)	70 (27.78%)	1		65 (26.42%)	67 (27.80%)	1	
		G/A	131 (50.19%)	113 (44.84%)	1.45 (0.93-2.26)	0.105	121 (49.19%)	118 (48.96%)	1.07 (0.70-1.65)	0.757
		A/A	75 (28.74%)	69 (27.38%)	1.45 (0.88-2.37)	0.143	60 (24.39%)	56 (23.24%)	1.12 (0.67-1.85)	0.672
	Dominant	G/G	55 (21.07%)	70 (27.78%)	1		65 (26.42%)	67 (27.80%)	1	
		G/A-A/A	206 (78.93%)	182 (72.22%)	1.45 (0.95-2.19)	0.083	181 (73.58%)	174 (72.20%)	1.09 (0.72-1.63)	0.693
	Recessive	G/A-G/G	186 (71.26%)	183 (72.62%)	1		186 (75.61%)	185 (76.76%)	1	
		A/A	75 (28.74%)	69 (27.38%)	1.13 (0.76-1.68)	0.534	60 (24.39%)	56 (23.24%)	1.07 (0.70-1.63)	0.762
	Log-additive	–	–	–	1.19 (0.93-1.53)	0.157	–	–	1.06 (0.82-1.36)	0.669

95%CI: 95% confidence interval, HWE: Hardy- Weinberg equilibrium, MAF: Minor allele frequency,

OR: Odds ratio, SNP:Single-nucleotide polymorphism, p -value was calculated by unconditional logistic regression adjusted by age and gender,

$p < 0.05$ indicates statistical significance.

Table 6 The haplotype frequencies of *IL1R1/IL1R2* polymorphisms and their associations with rheumatoid arthritis risk

Gene	SNP	Haplotype	Frequency		Without adjusted		Adjusted	
			Case	Control	OR (95% CI)	p	OR (95% CI)	p
IL1R2	rs3218977 rs2072472	AG	0.77	0.80	0.82 (0.66-1.02)	0.073	0.82 (0.66-1.02)	0.073
		GA	0.26	0.23	1.14 (0.93-1.41)	0.218	1.14 (0.92-1.40)	0.225
		AA	0.51	0.57	0.79 (0.65-0.94)	0.010	0.79 (0.65-0.94)	0.010

p -value was calculated by Wald test with and without adjusted by age and gender.

Figures

Figure 1

The linkage disequilibrium (LD) of four SNPs in the FCGR2A gene.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable1.docx](#)