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

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Research

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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 disease. 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 men. The pathogenic autoimmune process associated with RA is very complicated, involving several different stages that ultimately lead to the onset of RA. 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 whole.

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 factors. The common environmental factors include smoking, female, and oral contraceptive use. Moreover, previous studies have suggested that genetic factors may account for approximately one-half to two-thirds of the risk of RA. 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 factors. In addition, the non-HLA also have been proved to be significantly related to RA.

Previous studies have reported that human FC-gamma receptors (FcγRs), a family of cell-surface receptors, have a pivotal role in many immunological process. Based on their affinity for IgG, they can be divided into two types, low- and high-affinity receptors. In human, five low-affinity FcγRs (including FcγRI, FcγRIIb, FcγRIIc, FcγRIIIa, and FcγRIIIb) are encoded by the Fc receptors for IgG immunoglobulins (FCγRs) 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 DNA. It encodes a member of a family of Fcγ receptors for immunoglobulin G. And it is also widely used to explore the correlation with the response to anti-TNF therapy in RA management, 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-reactive protein [CRP], erythrocyte sedimentation rate [ESR], rheumatoid factor [RF], anti-cyclic citrulline antibody [CCP]). 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) 

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). 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.

**Statistical analysis**

We used the SPSS 19.0 (SPSS, Chicago, IL, USA) software for statistical analysis in this study. 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). 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 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.

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 RA. 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 system. Three FcγRs types (FcγRI, FcγRII, and FcγRIII) have been acknowledged in humans and mice. And the mice arthritis model suggested FcγRI is essential in autoantibody dependent arthritis. And the dysregulation of FcγRs is important in many different inflammatory diseases, including rheumatoid arthritis. 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. 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 complexes. 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 diseases.

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 cytokines. 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 RA. MDC et al 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. Chatzikyriakidou et al found that absence of association of FCGR2A gene polymorphism rs1801274 with Kawasaki disease in Greek patients. Meziani R et al 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 ± SD) | 54.34 ± 12.01 | 54.03 ± 8.83 | < 0.001
> 54 | 261 (51%) | 253 (51%) | |
≤ 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* |
|---|---|---|---|---|---|---|---|---|---|
| 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 X² test

Table 3 Association between IL1R1/IL1R2 genetic variants and rheumatoid arthritis risk
| Gene  | SNP     | Model     | Genotype | Case N (%) | Control N (%) | OR (95% CI) | p     |
|-------|---------|-----------|----------|------------|---------------|-------------|-------|
| 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/T-C/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/T  | 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/T-C/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 |
| Genotype | rs2072472 | Codominant | 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 (0.48-1.68) | 0.574 |
| Log-additive | -      | -           | -           | 1.14 (0.92-1.40) | 0.225 |

| Genotype | rs2072472 | Codominant | 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 |

| Genotype | rs10490571 | Codominant | 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 |

| Genotype | rs956730  | Codominant | 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 |

| Genotype | rs3917225 | Codominant | 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 |

Page 9/21
|                  | A/G-G/G | A/G-A/A | G/G | Log-additive | 95% CI       | p-value   |
|------------------|---------|---------|-----|--------------|--------------|-----------|
| Recessive        | 305 (60.28) | 294 (59.51) | 1.04 (0.80-1.33) | 0.790        |
|                  | 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) | p  | Case | control | OR (95% CI) | p  |
| IL1R2/rs11674595 | Allele     | T        | 203 (75.75%) | 199 (80.24%) | 1.30 (0.86-1.98) | 0.219 | 578 (77.90%) | 584 (79.35%) | 1.09 (0.85-1.40) | 0.497 |
|            |             | C        | 65 (24.25%) | 49 (19.76%) | 1.14 (0.74-1.74) | 0.295 | 164 (22.10%) | 152 (20.65%) | 1.23 (0.85-1.77) | 0.236 |
|            | Codominant  | T/T      | 75 (55.97%) | 80 (64.52%) | 1.07 (0.69-1.66) | 0.784 | 223 (60.11%) | 235 (63.86%) | 1.09 (0.85-1.40) | 0.501 |
|            |             | C/T      | 53 (39.55%) | 39 (31.45%) | 1.46 (0.87-2.46) | 0.156 | 132 (35.58%) | 114 (30.98%) | 1.11 (0.87-1.46) | 0.211 |
|            |             | C/C      | 6 (4.48%) | 5 (4.03%) | 1.30 (0.86-1.98) | 0.219 | 16 (4.31%) | 19 (5.16%) | 0.89 (0.45-1.77) | 0.736 |
|            | Dominant    | T/T      | 75 (55.97%) | 80 (64.52%) | 1.23 (0.51-3.00) | 0.621 | 223 (60.11%) | 235 (63.86%) | 1.13 (0.85-1.51) | 0.296 |
|            |             | C/T-C/C  | 59 (44.03%) | 44 (35.48%) | 1.22 (0.87-1.70) | 0.222 | 133 (36.14%) | 148 (39.89%) | 1.09 (0.85-1.40) | 0.501 |
|            | Recessive   | T/T-T/C  | 128 (95.52%) | 119 (95.97%) | 1.07 (0.87-1.35) | 0.581 | 349 (94.84%) | 355 (95.69%) | 1.14 (0.87-1.51) | 0.296 |
|            |             | C/C      | 6 (4.48%) | 5 (4.03%) | 1.22 (0.87-1.70) | 0.222 | 133 (36.14%) | 148 (39.89%) | 1.09 (0.85-1.40) | 0.501 |
|            | Log-additive| –        | –        | –        | 0.96 (0.65-1.44) | 0.853 | –        | –        | 0.96 (0.65-1.44) | 0.853 |
| IL1R2/rs4851527 | Allele     | G        | 191 (71.27%) | 175 (70.56%) | 1.07 (0.87-1.35) | 0.581 | 523 (69.92%) | 491 (66.35%) | 1.14 (0.87-1.51) | 0.296 |
|            |             | A        | 77 (28.73%) | 73 (29.44%) | 0.86 (0.66-1.14) | 0.353 | 225 (30.08%) | 249 (33.65%) | 0.85 (0.68-1.06) | 0.140 |
|            | Codominant  | G/G      | 65 (48.51%) | 60 (48.39%) | 1.04 (0.80-1.36) | 0.732 | 179 (47.86%) | 161 (43.51%) | 1.05 (0.81-1.35) | 0.591 |
|            |             | G/A      | 61 (45.52%) | 55 (44.35%) | 1.00 (0.80-1.25) | 0.977 | 165 (44.12%) | 169 (45.68%) | 1.04 (0.80-1.35) | 0.591 |
|            |             | A/A      | 8 (5.97%) | 9 (7.26%) | 0.94 (0.60-1.44) | 0.853 | 30 (8.02%) | 40 (10.81%) | 1.07 (0.62-1.70) | 0.366 |
|            | Dominant    | G/G      | 65 (48.51%) | 60 (48.39%) | 1.04 (0.80-1.36) | 0.732 | 179 (47.86%) | 161 (43.51%) | 1.05 (0.81-1.35) | 0.591 |
|            |             | G/A-A/A  | 69 (51.49%) | 64 (51.61%) | 0.99 (0.61-1.62) | 0.978 | 195 (52.14%) | 209 (56.49%) | 0.97 (0.61-1.62) | 0.501 |
|            | Recessive   | G/G-A/A  | 126 (94.03%) | 115 (92.74%) | 1.00 (0.80-1.25) | 0.977 | 344 (91.98%) | 330 (89.19%) | 1.04 (0.80-1.35) | 0.591 |
|            |             | A/A      | 8 (5.97%) | 9 (7.26%) | 0.94 (0.60-1.44) | 0.853 | 30 (8.02%) | 40 (10.81%) | 1.07 (0.62-1.70) | 0.366 |
|            | 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%) | 1.04 (0.80-1.36) | 0.732 | 545 (73.45%) | 528 (71.35%) | 1.05 (0.81-1.35) | 0.591 |
|            |             | T        | 64 (23.88%) | 80 (32.26%) | 1.04 (0.80-1.36) | 0.732 | 197 (26.55%) | 212 (28.65%) | 1.05 (0.81-1.35) | 0.591 |
### IL1R2/rs3218896

| Allele | Codominant | T/T | C/T | T/C | C/C |
|--------|------------|-----|-----|-----|-----|
|        |            |     |     |     |     |
| C/C    | 76 (56.72%) | 58 (46.77%) | 58 (41.94%) | 52 (38.81%) | 0.97 |
|        | 203 (54.72%) | 192 (51.89%) | 139 (37.47%) | 144 (38.92%) | 1.13 |
|        | 1.00         | 1.00         | 0.81         | 0.90         |     |

### Log-additive

| Allele | Codominant | T/T | C/T | T/C | C/C |
|--------|------------|-----|-----|-----|-----|
|        |            |     |     |     |     |
| C/C    | 76 (56.72%) | 58 (46.77%) | 58 (41.94%) | 52 (38.81%) | 0.97 |
|        | 203 (54.72%) | 192 (51.89%) | 139 (37.47%) | 144 (38.92%) | 1.13 |
|        | 1.00         | 1.00         | 0.81         | 0.90         |     |

### IL1R2/rs3218977

| Allele | Codominant | T/T | C/T | T/C | C/C |
|--------|------------|-----|-----|-----|-----|
|        |            |     |     |     |     |
| A/A    | 67 (50.00%) | 71 (57.26%) | 67 (50.00%) | 57 (47.06%) | 0.97 |
|        | 204 (54.55%) | 196 (59.19%) | 153 (40.91%) | 153 (40.91%) | 0.97 |
|        | 1.00         | 1.00         | 1.14         | 1.00         |     |

### Log-additive

| Allele | Codominant | T/T | C/T | T/C | C/C |
|--------|------------|-----|-----|-----|-----|
|        |            |     |     |     |     |
| A/A    | 67 (50.00%) | 71 (57.26%) | 67 (50.00%) | 57 (47.06%) | 0.97 |
|        | 204 (54.55%) | 196 (59.19%) | 153 (40.91%) | 153 (40.91%) | 0.97 |
|        | 1.00         | 1.00         | 1.14         | 1.00         |     |
| 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) |
| 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) |
| Log-additive | – | – | – | 0.97 (0.73-1.30) | 0.843 | – | – | 1.39 (1.01-1.90) |

| 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) |
| 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) |
| 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) |
| 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) |
| 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) |
| Log-additive | – | – | – | 1.30 (0.84-1.99) | 0.238 | – | – | 1.19 (0.93-1.53) |

| 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) |
| 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) |
| 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) |
| 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) |
| Recessive | C/T-C/C | 126 (94.03%) | 119 (95.97%) | 1 | 365 (97.59%) | 359 (97.03%) | 1 |
| Allele | T/T | Log-additive | IL1R1/rs396730 |
|-------|-----|-------------|----------------|
|       |     |             |                |
|       | 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 |
|       | 57 (14.3) | 14 (3.23%) | 1.52 (0.99-2.33) | 0.056 | 5 (1.73) | 10 (2.97%) | 1.07 (0.82-1.40) | 0.630 |
| 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 |
| A/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     | 1 (0.95) | 217 (58.18%) | 2 (2.69) | 0.50 (0.24-1.03) | 0.061 |
| G     | 200 (75.19%) | 184 (74.19%) | 1 | 578 (77.48%) | 565 (76.35%) | 1 | 127 (48.39%) | 40 (15.62%) | 0.042 |
| G/A   | 21 (8.42) | 21 (8.42) | 0.94 (0.62-1.43) | 0.777 | 365 (97.59%) | 359 (97.03%) | 0.94 (0.73-1.2) | 0.596 |
| A/A   | 166 (66.94%) | 166 (66.94%) | 1 | 478 (64.08%) | 467 (63.11%) | 1 | 117 (45.52%) | 23 (8.78%) | 0.042 |
| A     | 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 |
| G     | 57 (45.97) | 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 |
| A/G   | 63 (47.37) | 52 (41.94) | 1.34 (0.61-2.94) | 0.471 | 46 (12.27) | 46 (12.43) | 0.92 (0.57-1.47) | 0.724 |
| A/A   | 149 (39.95) | 143 (38.65) | 1 | 149 (39.95) | 143 (38.65) | 1 | 66 (25.81) | 12 (4.44) | 0.042 |
| A     | 81 (60.9%) | 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 |
| A/G/A/G/G | 115 (86.47) | 109 (87.90) | 1 | 361 (96.78) | 346 (93.51) | 1 | 66 (25.81) | 12 (4.44) | 0.042 |
| A/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 |
| G     | 113 (42.16) | 127 (51.21) | 1 | 377 (50.54) | 382 (51.76) | 1 | 66 (25.81) | 12 (4.44) | 0.042 |
|                  | 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) | p       | Case         | Control      | OR (95% CI) | p       |
| IL1R2/rs11674595 | Allele  | T        | 402 (77.91%) | 399 (79.17%) | 1           | 0.624 | 379 (76.72%) | 384 (80.00%) | 1.21 (0.89-1.65) | 0.214 |
|              |         | 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) | 0.624 | 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) | 0.624 | 15 (6.07%) | 10 (4.17%) | 1.21 (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) | 0.624 | 100 (40.49%) | 86 (35.83%) | 1.21 (0.83-1.75) | 0.317 |
|              |         | C/C     | 251 (97.29%) | 238 (94.44%) | 1           | 232 (93.93%) | 230 (95.83%) | 1           |
|              | Recessive     | T/T-T/C | 113 (43.30%) | 119 (47.04%) | 1           | 131 (53.04%) | 102 (42.32%) | 1           |
|              |         | C/C     | 134 (51.34%) | 106 (41.90%) | 1.32 (0.91-1.91) | 0.624 | 92 (37.25%) | 118 (48.96%) | 1.21 (0.89-1.64) | 0.231 |
|              | Log-additive       | –     | –           | –           | 1.08 (0.79-1.47) | 0.624 | –           | –           | 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) | 0.624 | 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) | 0.624 | 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) | 0.624 | 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) | 0.624 | 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) | 0.624 | 24 (9.72%) | 21 (8.71%) | 1.16 (0.62-2.17) | 0.641 |
|              | Log-additive       | –     | –           | –           | 0.92 (0.69-1.22) | 0.624 | –           | –           | 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) | 0.624 | 118 (23.89%) | 145 (30.08%) | 0.73 (0.55-0.97) | 0.029 |
| Allele         | Codominant | C/C          | C/T          | T/T          | Dominant | C/C          | C/T-T/T       | Recessive | C/T-C/C       | T/T          | Log-additive | IL1R2/rs3218896 | Allele | T           | C           | 1 | 147 | 121 | 1 | 1 |
|----------------|------------|--------------|--------------|--------------|-----------|--------------|---------------|------------|---------------|--------------|--------------|----------------|---------|--------------|--------------|---|-----|-----|---|---|
|                |            |              |              |              |           |              | 1.07 (0.75-1.53) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Codominant | C/T-T/T      |              |              |           |              | 1.00 (0.67-1.49) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Recessive  | C/T-C/C      |              |              |           |              | 1.00 (0.67-1.49) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Log-additive |              |              |              |           |              | 1.00 (0.67-1.49) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| IL1R2/rs3218896 | Allele     | T/A          |              |              |           |              | 0.927 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Codominant | C/T-T/T      |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Recessive  | C/T-C/C      |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Log-additive |              |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| IL1R2/rs3218977 | Allele     | A/G          |              |              |           |              | 0.927 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Codominant | A/A          |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Recessive  | A/G          |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Log-additive |              |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Codominant | G/G          |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Recessive  | G/G          |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Log-additive |              |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Codominant | G/G          |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Recessive  | G/G          |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Log-additive |              |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Codominant | C/T-T/T      |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Recessive  | C/T-C/C      |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele         | Log-additive |              |              |              |           |              | 1.00 (0.76-1.34) |           |              |              |              |                |         |              |              |   |     |     |   |   |
| Allele                  | Genotype | Dominant | Recessive | Log-additive |
|------------------------|----------|----------|-----------|--------------|
|                        |          | A/A      | A/G-G/G   | G/G          | A/G          | G                  |
| IL1R2/rs2072472        |          | 145 (55.56%) | 116 (44.44%) | 10 (3.83%)   | 118 (22.61%) | 118 (22.61%)   |
|                        |          | 150 (59.29%) | 103 (40.71%) | 21 (8.30%)   | 99 (19.57%)  | 99 (19.57%)    |
|                        |          | 1         | 1.17 (0.82-1.68) | 0.40 (0.18-0.88) | 1.20 (0.89-1.62) | 1.67 (1.14-2.45) |
|                        |          | 126 (51.01%) | 121 (48.99%) | 14 (5.67%)   | 116 (23.48%) | 86 (34.82%)    |
|                        |          | 140 (58.09%) | 101 (41.91%) | 6 (2.49%)    | 96 (19.92%)  | 76 (31.54%)    |
|                        |          | 1         | 0.383 (0.16-2.12) | 0.023 (0.01-1.91) | 0.232 (0.16-2.32) | 0.023 (0.15-1.91) |
|                        |          | 1         | 0.156 (0.04-1.07) | 0.039 (0.01-1.91) | 0.163 (0.12-2.32) | 0.075 (0.04-1.07) |
|                        |          | 1         | 1.84 (0.88-1.63) | 0.026 (0.01-1.91) | 1.20 (0.88-1.63) | 1.20 (0.88-1.63) |
|                        |          | 1         | 1.23 (0.91-1.66) | 0.185 (0.09-1.45) | 1.77 (0.76-4.09) | 1.77 (0.76-4.09) |
|                        |          | 1         | 0.177 (0.08-1.74) | 0.391 (0.19-2.14) | 1.18 (0.80-1.74) | 1.18 (0.80-1.74) |
|                        |          | 1         | 0.238 (0.09-1.81) | 0.228 (0.09-1.81) | 1.25 (0.86-1.81) | 1.25 (0.86-1.81) |
| IL1R1/rs10490571       |          | 150 (57.47%) | 150 (57.47%) | 7 (2.68%)    | 150 (57.47%) | 150 (57.47%)   |
|                        |          | 168 (66.40%) | 168 (66.40%) | 14 (5.53%)   | 168 (66.40%) | 168 (66.40%)   |
|                        |          | 1         | 1.47 (1.02-2.12) | 0.163 (0.12-2.32) | 1.67 (1.14-2.45) | 1.67 (1.14-2.45) |
|                        |          | 1         | 0.89 (0.52-1.54) | 0.075 (0.05-1.54) | 1.47 (1.02-2.12) | 1.47 (1.02-2.12) |
|                        |          | 1         | 1.84 (0.88-1.63) | 0.262 (0.15-1.84) | 1.20 (0.88-1.63) | 1.20 (0.88-1.63) |
|                        |          | 1         | 1.25 (0.92-1.69) | 0.155 (0.08-1.58) | 1.25 (0.92-1.69) | 1.25 (0.92-1.69) |
|                        |          | 1         | 1.457 (0.82-2.58) | 0.457 (0.25-2.68) | 1.457 (0.82-2.58) | 1.457 (0.82-2.58) |
|                        |          | 1         | 0.962 (0.37-2.57) | 0.319 (0.18-0.58) | 0.962 (0.37-2.57) | 0.962 (0.37-2.57) |
|                        |          | 1         | 0.457 (0.25-2.68) | 0.319 (0.18-0.58) | 0.457 (0.25-2.68) | 0.457 (0.25-2.68) |
|                        |          | 1         | 0.319 (0.18-0.58) | 0.319 (0.18-0.58) | 0.319 (0.18-0.58) | 0.319 (0.18-0.58) |
|                        |          | 1         | 0.319 (0.18-0.58) | 0.319 (0.18-0.58) | 0.319 (0.18-0.58) | 0.319 (0.18-0.58) |
## Log-additive

| IL1R1/rs956730 | Allele | G | 391 (75.48%) | 375 (74.11%) | 1 | Log-additive | 2.58 (0.91-1.73) | 0.174 | 1 | 1.13 (0.81-1.57) | 0.477 |
|----------------|--------|---|--------------|--------------|---|--------------|------------------|-------|---|------------------|------|
| A              |        | 127 (24.52%) | 131 (25.89%) | 0.93 (0.70-1.23) | 0.613 | 107 (21.66%) | 2.40 (11.66%) | 0.174 | 1 | 1.13 (0.81-1.57) | 0.477 |

## Codominant

| G/G            |        | 138 (53.28%) | 138 (54.55%) | 1 | G/A          | 115 (44.40%) | 99 (39.13%) | 1.19 (0.83-1.72) | 0.342 | 79 (31.98%) | 45 (34.85%) | 0.86 (0.58-1.26) | 0.434 |
|----------------|--------|--------------|--------------|---|--------------|--------------|-------------|------------------|-------|-----------|-------------|------------------|------|
| A/G            |        | 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          |        | 253 (97.68%) | 237 (93.68%) | 1 | 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 |
|----------------|--------|--------------|--------------|---|--------------|------------|-------------|------------------|-------|-----------|-------------|------------------|------|
| 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 |

## Log-additive

| IL1R1/rs3917225 | Allele | A | 336 (64.62%) | 337 (66.60%) | 1 | Log-additive | 0.95 (0.70-1.28) | 0.720 | 1 | 1.35 (0.61-3.02) | 0.462 |
|-----------------|--------|---|--------------|--------------|---|--------------|------------------|-------|---|------------------|------|
| 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 | A/G          | 128 (49.23%) | 117 (46.25%) | 1.17 (0.81-1.71) | 0.406 | 115 (46.75%) | 116 (48.13%) | 0.93 (0.63-1.31) | 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 |

## Recessive

| A/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 |
|----------------|--------|--------------|--------------|---|--------------|--------------|-------------|------------------|-------|-----------|-------------|------------------|------|
| 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

| IL1R1/rs3917318 | Allele | G | 241 (46.17%) | 253 (50.20%) | 1 | Log-additive | 1.13 (0.86-1.48) | 0.391 | 1 | 0.96 (0.74-1.25) | 0.744 |
|-----------------|--------|---|--------------|--------------|---|--------------|------------------|-------|---|------------------|------|
| A               |        | 281 | 251 | 1.18 | 0.197 | 241 | 230 | 1.05 | 0.693 |
| Gene | SNP        | Haplotype | Frequency | Without adjusted | Adjusted |
|------|------------|-----------|-----------|------------------|----------|
|      |            |           | Case      | Control          |          |
| IL1R2| rs3218977  | AG        | 0.77      | 0.80             | 0.82     |
|      | rs2072472  | GA        | 0.26      | 0.23             | 1.14     |
|      |            | AA        | 0.51      | 0.57             | 0.79     |

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

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

**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