IL-7R gene polymorphisms among patients with rheumatoid arthritis: A case–control study

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Abstract

**Background:** Rheumatoid arthritis (RA) is the most common inflammatory disease which refers to bony erosions and joint destruction largely caused by genetic factors. Our study aimed to explore whether interleukin-7 receptor (IL-7R) gene polymorphisms influenced RA risk in the Han Chinese population.

**Methods:** Five single nucleotide polymorphisms (SNPs) in IL-7R gene were successfully genotyped using Agena MassARRAY platform. The associations between IL-7R polymorphisms and RA were evaluated by the Chi-squared test, T test, genetic model analysis, and haplotype analysis. We calculated odds ratios (ORs) and 95% confidence intervals (95% CIs) using logistic regression analysis.

**Results:** Rs969129 and rs6451231 in the IL-7R gene were associated with an increased risk of RA in the allele model (OR = 1.25, 95% CI = 1.05–1.49, p = 0.013; OR = 1.23, 95% CI = 1.03–1.48, p = 0.023), respectively. In the genetic models, rs969129 and rs6451231 were associated with an increased risk of RA. After stratification analysis by age, rs969129 and rs6451231 were associated with an increased risk of RA in patients (age <54). After stratification analysis by gender, rs6451231 was associated with an increased risk of RA in males, while rs969129 was found to be associated with an elevated risk of RA in females. And there was a strong linkage disequilibrium among the four SNPs (rs969129, rs118137916, rs10053847, and rs6451231).

**Conclusion:** These results suggested rs969129 and rs6451231 in the IL-7R gene were associated with an increased risk of RA in the Han Chinese population.

**KEYWORDS**
case–control study, Han Chinese population, interleukin-7 receptor (IL-7R), rheumatoid arthritis, single nucleotide polymorphisms (SNPs)

1 INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, and autoimmune disease that occurs at any age. The clinical presentation of RA is characterized by inflammation of the joint synovium, progressive articular destruction, and other comorbidities such as cardiovascular disease, lung disease, infections, and some malignancies (Metsios, Stavropoulos-Kalinoglou, & Kitas, 2015), which usually contribute to declining life expectancy, early unemployment, and severe disability even death (Sokka et
The interleukin-7 receptor (IL7R; OMIM: 146661) encodes a receptor protein that plays an important role in the development of immune cells (Galarza-Munoz et al., 2017). Previous studies have confirmed that the IL-7R gene may be associated with a variety of autoimmune diseases, mainly including multiple sclerosis, Type 1 diabetes (T1D), and so on (Galarza-Munoz et al., 2017; Santiago et al., 2008; Todd et al., 2007). While studies on the association between IL-7R gene polymorphisms and susceptibility to RA. We designed a case–control study including 507 RA patients and 499 healthy controls for association analysis and further tried to find new IL-7R susceptibility loci for RA among the Han Chinese population. Finally, we hope that we can further clarify their relationship with RA risk among the Han Chinese population.

This study was to explore the relationship between IL-7R gene polymorphisms and susceptibility to RA. We designed a case–control study including 507 RA patients and 499 healthy controls for association analysis and further tried to find new IL-7R susceptibility loci for RA among the Han Chinese population. Finally, we hope that we can further clarify their relationship with RA risk among the Han Chinese population.

2 | MATERIALS AND METHODS

2.1 | Ethics compliance

This case–control study was conducted in accordance with the ethical standards of the Declaration of Helsinki and following international guidelines. The study protocol was approved by the ethics committee of the Affiliated Hospital of Xizang Minzu University. Informed consents were obtained from all participants. The experimental protocol was implemented in accordance with the approved guidelines.

2.2 | Subjects

The Han Chinese population-based case–control study containing 507 RA patients diagnosed from September 2015 to February 2018 from the Affiliated Hospital of Xizang Minzu University was conducted. In the meantime, we undertook rigorous screening for RA patients based on American College of Rheumatology 1987 classification criteria (Arnett et al., 1988). RA patients were diagnosed by routine biochemical blood analysis (including C-reactive protein [CRP], rheumatoid factor, erythrocyte sedimentation rate [ESR], anti-cyclic citrulline antibody [CCP]) and X-rays of small joints. Patients with other autoimmune and tumor diseases were excluded from the study. At the same time, the 499 healthy controls were randomly selected from the Affiliated Hospital of Xizang Minzu University and were diagnosed without immune disease or other diseases. All subjects were unrelated individuals and at least three generations of Han ancestors.

2.3 | Sample collection

Peripheral venous blood samples were collected from each participant in an anti-coagulation tube and stored at −80°C freezer for DNA extraction. According to the manufacturer’s instructions to the GoldMag-Mini Purification Kit (GoldMag Co.Ltd. Xi’an city, China), we isolated genomic DNA from whole blood samples. And the concentration and purity of the DNA were measured using the NanoDrop 2000 (Thermo Fisher Scientific, Waltham, Massachusetts, USA) to ensure accurate and uniform concentration.

2.4 | Single nucleotide polymorphisms selection and genotyping

A total of five single nucleotide polymorphisms (SNPs) (rs10213865, rs969129, rs118137916, rs10053847, rs6451231) in IL-7R (NG_009567.1) were selected with a minor allele frequency >0.05 in the 1000 Genomes Project (http://www.internationalgenome.org/) for further genotyping. The primers for amplification and extension reactions were designed with Agena MassARRAY Assay Design 3.0 Software (Data S1) (Gabriel, Ziaugra, & Tabbaa, 2009). Agena MassARRAY RS1000 was used to perform the SNP genotyping according to the manufacturer’s instruction, and we used Agena Typer 4.0 software for data management and analysis (Gabriel et al., 2009; Thomas et al., 2007).

2.5 | Statistical analysis

The SPSS 19.0 (SPSS, Chicago, IL, USA) and Microsoft Excel were used to perform statistical analyses. The gender distribution between the cases and the controls was compared by two-sided Chi-square tests, and the age distribution was evaluated by Student’s t tests. The genotype frequencies of the control group were tested for departure from the Hardy–Weinberg equilibrium (HWE) using
Chi-square test. We calculated the allele frequencies of the cases and controls with Chi-squared test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between *IL-7R* gene polymorphisms and the RA risk using logistic regression analysis with adjustment for age and gender (Bland & Altman, 2000). The multiple genetic models analyses were applied using PLINK software (Version 1.07) to evaluate the associations between SNPs and the RA risk (Clarke et al., 2011). Then, we conducted stratification analysis on age and gender. Finally, we performed linkage disequilibrium (LD) and haplotype analysis using the Haploview software package (version 4.2). All *p* values of statistical tests in this study were two-sided, and *p* < 0.05 indicated statistical significance.

### RESULTS

#### 3.1 Characteristics of study population

A total of 507 patients (135 males and 372 females) with RA and 499 healthy individuals (135 males and 364 females) were enrolled for this study. Their demographic and clinical data were described in Table 1. The age at diagnosis of the two groups were 54.34 ± 12.03 years in the case group and 53.89 ± 9.56 years in the control group. No significant difference was found in the distribution differences of age and gender between RA patients and healthy controls. The proportion of male and female in the case group and control group was the same (27% and 73%, respectively). In addition, we analyzed the clinical indicators in the case group. The Mean ± SD of CRP and ESR among 507 cases

| Variable | Cases (n = 507) | Controls (n = 499) | p-Value |
|----------|----------------|-------------------|---------|
| Gender   |                |                   | 0.879a  |
| Male     | 135 (27%)      | 135 (27%)         |         |
| Female   | 372 (73%)      | 364 (73%)         |         |
| Age, year| 54.34 ± 12.03  | 53.89 ± 9.56      | 0.508b  |
| ≥54      | 261 (51%)      | 221 (44%)         |         |
| <54      | 246 (49%)      | 278 (56%)         |         |

### Table 2 Basic information of selected SNPs in this study

| SNP      | Gene | Chr | position | Alleles A/B | Genotype Frequency | p-HWE | OR (95% CI) |
|----------|------|-----|----------|-------------|--------------------|-------|-------------|
| rs10213865 | *IL7R* | 5    | 35857748 | A/C         | 0.195              | 0.199 | 1.21 (0.96–1.52) |
| rs969129    | *IL7R* | 5    | 35861166 | G/T         | 0.480              | 0.647 | 1.25 (1.05–1.49) |
| rs118137916 | *IL7R* | 5    | 35863436 | A/G         | 0.074              | 0.786 | 0.81 (0.59–1.11) |
| rs10053847  | *IL7R* | 5    | 35878038 | A/G         | 0.154              | 0.864 | 1.00 (0.79–1.28) |
| rs6451231   | *IL7R* | 5    | 35878825 | C/T         | 0.410              | 0.628 | 1.23 (1.03–1.48) |

Abbreviations: A/B, Minor/major alleles; CI, Confidence interval; HWE, Hardy–Weinberg equilibrium; MAF, Minor allele frequency; OR, Odds ratio; SNP, Single-nucleotide polymorphism.

*p* values were calculated using two-sided Chi-squared test (the major allele of each SNP was a reference allele).

Bold values represents a positive result.

*p* < 0.05 indicates statistical significance.
### TABLE 3  Relationships between IL7R polymorphisms and RA risk

| SNP       | Model         | Genotype | Case (%)  | Control (%) | Before adjusted | After adjusted |
|-----------|---------------|----------|-----------|-------------|-----------------|----------------|
|           |               |          | OR (95% CI) | p\(^a\)-Value | OR (95% CI) | p\(^b\)-Value |
| rs969129  | Codominant    | T/T      | 134 (26.4%) | 162 (32.5%) | 1.25 (0.94–1.67) | 1.58 (1.10–2.27) | 0.012\(^c\) | 0.012\(^c\) |
|           |               | G/T      | 259 (51.1%) | 250 (50.1%) |                 |                 |               |               |
|           |               | G/G      | 114 (22.5%) | 87 (17.4%)  | 1.58 (1.10–2.27) | 1.59 (1.11–2.28) |               |               |
|           | Dominant      | T/T      | 134 (26.4%) | 162 (32.5%) | 1.58 (1.10–2.27) | 1.59 (1.11–2.28) | 0.036\(^c\) | 0.037\(^c\) |
|           |               | G/T      | 259 (51.1%) | 250 (50.1%) |                 |                 |               |               |
|           |               | G/G      | 114 (22.5%) | 87 (17.4%)  | 1.58 (1.10–2.27) | 1.59 (1.11–2.28) |               |               |
|           | Recessive     | T/T-G/T  | 373 (73.6%) | 337 (67.5%) | 1.34 (1.02–1.76) | 1.34 (1.02–1.76) |               |               |
|           |               | G/G      | 114 (22.5%) | 87 (17.4%)  | 1.58 (1.10–2.27) | 1.59 (1.11–2.28) |               |               |
|           | Log-additive  | —        | —         | —           | 1.26 (1.05–1.50) | 1.26 (1.05–1.51) | 0.012\(^c\) | 0.011\(^c\) |
|           |               |          |           |             |                 |                 |               |               |
| rs6451231 | Codominant    | T/T      | 174 (34.4%) | 201 (40.3%) | 1.22 (0.93–1.60) | 1.38 (1.01–1.88) | 0.027\(^c\) | 0.026\(^c\) |
|           |               | C/T      | 249 (49.2%) | 236 (47.3%) |                 |                 |               |               |
|           |               | C/C      | 83 (16.4%)  | 62 (12.4%)  | 1.55 (1.05–2.28) | 1.55 (1.05–2.29) |               |               |
|           | Dominant      | T/T      | 174 (34.4%) | 201 (40.3%) | 1.22 (0.93–1.60) | 1.38 (1.01–1.88) | 0.054 | 0.052 |
|           |               | C/T-C/C  | 332 (65.6%) | 298 (59.7%) |                 |                 |               |               |
|           |               | C/C      | 83 (16.4%)  | 62 (12.4%)  | 1.38 (0.97–1.97) | 1.39 (0.97–1.98) |               |               |
|           | Log-additive  | —        | —         | —           | 1.24 (1.03–1.49) | 1.24 (1.03–1.49) | 0.022\(^c\) | 0.021\(^c\) |

Abbreviations: CI, Confidence interval; OR, Odds ratio; SNP, Single-nucleotide polymorphism.

\(^a\) p-Values were calculated from logistic regression analysis.

\(^b\) p-Values were calculated by logistic regression analysis with adjustments for age and gender.

\(^c\) p < 0.05 indicates statistical significance.

Bold values represent a positive result.
were 30.88 ± 40.25 mg/L and 44.14 ± 30.73 mm/hr, respectively. The Mean ± SD of RF among 497 cases were 165.10 ± 147.36 KIU/L. In addition, the Mean ± SD of CCP among 260 cases were 75.18 ± 60.95 RU/ml.

3.2 The association analysis between IL7R SNPs and RA susceptibility

The basic information on the five SNPs examined in this study was summarized in Table 2. Those SNPs were in accordance with HWE in the controls (p > 0.05). The two-sided Chi-squared test was used to compare the differences in frequency distributions of alleles between RA cases and controls. The frequency of the minor allele “G” of rs969129 was significantly higher in RA cases than that in controls (48.0% vs. 42.5%), which suggested that “G” allele of rs969129 was a non-protective allele against risk of RA (OR = 1.25, 95% CI: 1.05–1.49, p = 0.013). Similarly, we found the frequency of the minor allele “C” of rs6451231 was significantly higher in RA case group than that in control group (41.0% vs. 36.1%). And it was a risk factor for RA (OR = 1.23, 95% CI: 1.03–1.48, p = 0.023). In a word, rs969129 and rs6451231 were associated with an increased risk of RA in allele model.

Next, we hypothesized that the minor allele of each SNP was a risk factor and analyzed the associations between each variant and RA risk under four genetic models by unconditional logistic regression analysis with adjustments for age and gender. As shown in Table 3, our analyses showed that rs969129 in IL7R gene was associated with a 1.34-fold increase in the risk of RA in the co-dominant model (adjusted, OR = 1.59; 95% CI: 1.11–2.28; p = 0.012) for the ‘G/G’ genotype, 1.34-fold increase the risk of RA in the dominant model (adjusted, OR = 1.34, 95% CI: 1.02–1.76, p = 0.037 for the ‘G/T’ genotype, and 1.38-fold increase the risk of RA in the recessive model (adjusted, OR = 1.38, 95% CI: 1.01–1.89, p = 0.043 for the ‘G/G’ genotype), and 1.26-fold increase the risk of RA in the log-additive model (adjusted, OR = 1.26, 95% CI: 1.05–1.51, p = 0.011), respectively. The rs6451231 in IL7R gene was associated with a 1.55-fold increase the risk of RA in the co-dominant model (adjusted, OR = 1.55, 95% CI: 1.05–2.29, p = 0.026 for the ‘C/C’ genotype), and 1.24-fold increase the risk of RA in the log-additive model (adjusted OR = 1.24, 95% CI: 1.03–1.49, p = 0.021), respectively.

Then, we analyzed the association between selected SNPs and RA risk with stratified age and gender in Table 4. After the stratification analysis by age adjusted by age and gender, there was no significant differences between selected SNPs and risk of RA in patients who were over 54 years old. However, in patients who were under the age of 54 years, the rs969129 (IL7R) was associated with an increased risk of RA in the dominant model (OR = 1.54, 95% CI: 1.05–2.27, p = 0.029), log-additive model (OR = 1.31, 95% CI = 1.02–1.69, p = 0.036). The rs6451231 (IL7R) was associated with the elevated risk of RA in the co-dominant model (OR = 1.48, 95% CI: 1.01–2.18, p = 0.044), dominant model (OR = 1.51, 95% CI: 1.05–2.18, p = 0.027), log-additive model (OR = 1.32, 95% CI: 1.02–1.72, p = 0.038). After the stratification analysis of gender adjusted by age, we observed that rs6451231 was significantly associated with an increased risk of RA in males under the dominant model (OR = 1.67, 95% CI: 1.01–2.75, p = 0.046), log-additive model (OR = 1.47, 95% CI: 1.01–2.14, p = 0.042). Rs969129 was found to be associated with an increased risk of RA in females under log-additive model (OR = 1.25, 95% CI: 1.01–1.53, p = 0.036).

Furthermore, we analyzed the relationship between genotypes at different loci and clinical parameters, as displayed in Table 5. Our results demonstrated that RA patients with different genotype of rs10213865 had significantly different CCP level (p = 0.011). Similarly, the genotypes of rs10053847 in the RA patients showed significantly different CRP and ESR level (p = 0.027, p = 0.017, respectively).

3.3 Haplotype association

Finally, we used allele frequency data from all subjects to perform the LD block (Figure 1). LD block in IL7R gene on chromosome 5 was constructed by rs969129, rs118137916, rs10053847, rs6451231 and there was a significant linkage. The association analysis results between haplotypes and RA risk were shown in Table 6. The haplotype “GAGC” was associated with an increased risk of RA after the adjustment (OR = 1.35; 95% CI: 1.09–1.67; p = 0.006).

4 DISCUSSION

Rheumatoid arthritis is a multifactorial disease caused by environmental and genetic factors and their interactions. In this hospital-based case–control study, we evaluated the association between the five selected SNPs (rs10213865, rs969129, rs118137916, rs10053847, and rs6451231) in IL-7R gene and the risk of RA in the Han Chinese population. We found rs969129 and rs6451231 in this gene were significantly associated with an increased risk of RA. And there was a strong LD between the four SNPs (rs969129, rs118137916, rs10053847, and rs6451231). Those results indicated the IL-7R gene may be a risky gene for RA in the Han Chinese population.

IL-7 receptor is made up of a heterodimer consisting of two subunits, the IL-7R α chain and the γc chain. It is involved in the regulation of IL-7 signaling pathway (Rose et al., 2010), which plays an important role in the growth, reproduction and differentiation of immature thymus cells, and acts as an irreplaceable decisive role in maintaining
| SNP       | Model            | Genotype | >54  | Male | Female | <54  | Male | Female |
|-----------|------------------|----------|------|------|--------|------|------|--------|
| rs969129  | Allele T         | T        | 1    | 0.146| 1      | 0.042*| 1    | 0.166  | 1      | 0.038* |
|           | G                | G        | 1.21 (0.94–1.56) | 1.29 (1.01–1.65) | 1.27 (0.91–1.79) | 1.24 (1.01–1.53) |
|           | Codominant       | T/T      | 1    | 0.185| 1      | 0.042*| 1    | 0.083  | 1      | 0.038* |
|           | G/T              | G/T      | 1.15 (0.75–1.75) | 1.49 (0.99–2.25) | 1.52 (0.87–2.65) | 1.17 (0.83–1.63) |
|           | G/G              | G/G      | 1.64 (0.96–2.79) | 1.67 (1.00–2.78) | 1.62 (0.78–3.38) | 1.57 (1.04–2.38) |
|           | Dominant         | T/T      | 1    | 0.252| 1      | 0.029*| 1    | 0.111  | 1      | 0.134  |
|           | G/T-G/G          | G/T-G/G  | 1.26 (0.85–1.89) | 1.54 (1.05–2.27) | 1.54 (0.91–2.63) | 1.27 (0.93–1.75) |
|           | Recessive        | T/T-G/T  | 1    | 0.085| 1      | 0.246 | 1    | 0.511  | 1      | 0.051  |
|           | G/G              | G/G      | 1.50 (0.95–2.37) | 1.30 (0.84–2.02) | 1.24 (0.65–2.34) | 1.43 (1.00–2.04) |
|           | Log-additive     | —        | 1.26 (0.97–1.65) | 1.31 (1.02–1.69) | 1.31 (0.91–1.87) | 1.147 | 1.25 (1.01–1.53) | 0.036* |
| rs6451231 | Allele T         | T        | 1    | 0.236| 1      | 0.046 | 1    | 0.05   | 1      | 0.14   |
|           | C                | C        | 1.17 (0.90–1.52) | 1.29 (1.00–1.66) | 1.42 (1.00–2.01) | 1.17 (0.95–1.44) |
|           | Codominant       | T/T      | 1    | 0.22 | 1      | 0.044*| 1    | 0.115  | 1      | 0.285  |
|           | C/T              | C/T      | 1.09 (0.73–1.61) | 1.48 (1.01–2.18) | 1.60 (0.95–2.69) | 1.11 (0.81–1.52) |
|           | C/C              | C/C      | 1.64 (0.93–2.88) | 1.61 (0.92–2.81) | 2.02 (0.90–4.53) | 1.43 (0.92–2.22) |
|           | Dominant         | T/T      | 1    | 0.35 | 1      | 0.027*| 1    | 0.046  | 1      | 1      |
|           | C/T-C/C          | C/T-C/C  | 1.20 (0.82–1.74) | 1.51 (1.05–2.18) | 1.67 (1.01–2.75) | 1.18 (0.87–1.59) | 0.279 |
|           | Recessive        | T/T-C/T  | 1    | 0.091| 1      | 0.338 | 1    | 0.261  | 1      | 1      |
|           | C/C              | C/C      | 1.56 (0.93–2.62) | 1.28 (0.77–2.14) | 1.54 (0.73–3.26) | 1.18 (0.95–1.45) | 0.130 |

Abbreviations: CI, Confidence interval; OR, Odds ration; SNP, Single-nucleotide polymorphism. Bold values represents a positive result. \( *p < 0.05 \) indicates statistical significance.
the balance of T cells in human peripheral blood (Hong, Luckey, & Park, 2012; Jiang et al., 2007; Walsh, 2010). According to the binding state of IL-7R, IL-7R can be divided into membrane-bound receptor (mIL-7R) and soluble.

### TABLE 5
The relationship between genotypes at different loci and clinical parameters

| SNP-ID    | Variable | Genotype | Mean ± standard deviation | p-Value |
|-----------|----------|----------|---------------------------|---------|
| rs10213865 | CRP      | AA       | 38.48 ± 38.48             | 0.164   |
|           |          | CA       | 43.85 ± 43.85             |         |
|           |          | CC       | 37.41 ± 37.41             |         |
|           | RF       | AA       | 161.91 ± 150.89           | 0.487   |
|           |          | CA       | 175.07 ± 144.50           |         |
|           |          | CC       | 139.86 ± 106.11           |         |
|           | ESR      | AA       | 43.31 ± 31.51             | 0.601   |
|           |          | CA       | 46.15 ± 29.91             |         |
|           |          | CC       | 41.95 ± 23.76             |         |
|           | CCP      | AA       | 82.20 ± 62.72             | 0.011†  |
|           |          | CA       | 62.90 ± 55.87             |         |
|           |          | CC       | 28.83 ± 7.00              |         |
| rs969129   | CRP      | TT       | 28.67 ± 35.15             | 0.716   |
|           |          | GT       | 32.15 ± 45.07             |         |
|           |          | GG       | 30.58 ± 33.98             |         |
|           | RF       | TT       | 151.49 ± 131.73           | 0.473   |
|           |          | GT       | 170.02 ± 157.01           |         |
|           |          | GG       | 169.70 ± 142.13           |         |
|           | ESR      | TT       | 45.15 ± 33.23             | 0.837   |
|           |          | GT       | 44.20 ± 30.03             |         |
|           |          | GG       | 42.82 ± 29.43             |         |
|           | CCP      | TT       | 87.56 ± 66.16             | 0.052   |
|           |          | GT       | 67.25 ± 55.21             |         |
|           |          | GG       | 82.98 ± 67.58             |         |
| rs118137916| CRP      | AA       | 30.64 ± 40.19             | 0.939   |
|           |          | GA       | 32.56 ± 42.28             |         |
|           |          | GG       | 30.93 ± 25.08             |         |
|           | RF       | AA       | 161.26 ± 144.19           | 0.248   |
|           |          | GA       | 194.58 ± 167.80           |         |
|           |          | GG       | 146.12 ± 147.41           |         |
|           | ESR      | AA       | 43.74 ± 30.38             | 0.168   |
|           |          | GA       | 44.73 ± 32.17             |         |
|           |          | GG       | 67.50 ± 37.30             |         |
|           | CCP      | AA       | 72.64 ± 60.60             | 0.173   |
|           |          | GA       | 94.14 ± 62.14             |         |
|           |          | GG       | 109.00 ± 0.00             |         |
| rs10053847 | CRP      | AA       | 0.22 ± 0.16               | 0.027†  |
|           |          | GA       | 36.99 ± 42.99             |         |
|           |          | GG       | 28.80 ± 39.01             |         |
|           | RF       | AA       | 82.26 ± 32.09             | 0.165   |
|           |          | GA       | 180.59 ± 151.16           |         |
|           |          | GG       | 159.89 ± 146.24           |         |

Abbreviations: CCP, Anti-cyclic citrullinated peptide; CRP, C-reaction protein; ESR, Erythrocyte sedimentation rate; RF, Rheumatoid factor; SD, Standard deviation.

Bold values represents a positive result.

* p < 0.05 indicates statistical significance.

### TABLE 5 (Continued)

| SNP-ID    | Variable | Genotype | Mean ± standard deviation | p-Value |
|-----------|----------|----------|---------------------------|---------|
| ESR       | AA       | 47.85 ± 30.95 | 0.017†       |
|           | GA       | 43.07 ± 30.54 |           |
|           | GG       | 44.14 ± 30.73 |           |
| CCP       | AA       | 74.28 ± 56.95 | 0.453       |
|           | GA       | 74.63 ± 61.98 |           |
|           | GG       | 75.18 ± 60.95 |           |
| rs6451231 | CRP      | TT       | 31.54 ± 41.11           | 0.847   |
|           | TC       | 31.28 ± 41.97 |           |
|           | CC       | 28.61 ± 33.03 |           |
|           | RF       | TT       | 152.57 ± 134.05          | 0.356   |
|           | TC       | 168.53 ± 155.00 |           |
|           | CC       | 179.01 ± 16.56 |           |
|           | ESR      | TT       | 45.75 ± 33.48           | 0.501   |
|           | TC       | 44.16 ± 29.33 |           |
|           | CC       | 40.92 ± 28.96 |           |
|           | CCP      | TT       | 82.86 ± 65.73           | 0.119   |
|           | TC       | 67.60 ± 54.82 |           |
|           | CC       | 84.10 ± 68.79 |           |

### FIGURE 1
Linkage disequilibrium (LD) plots containing five SNPs from IL7R

(Continues)
receptor (sIL-7R). The latter can enhance the biological activity of IL-7 and promote the proliferation of self-reactive T cells, which may be correlated with the autoimmune diseases (Boyman, Ramsey, Kim, Sprent, & Surh, 2008; Corfe & Paige, 2012; Lundstrom et al., 2013), including RA (van Roon et al., 2005), T1D (Harrison, 2012) and systemic lupus erythematosus (Badot et al., 2013) etc. In a published article about T1D, IL-7Rα monoclonal antibody can prevent the occurrence of diabetes, and can also alleviate the new occurrence of nonobese diabetic mice model, which showed that IL-7R may be involved in the pathogenesis of T1D (Penaranda et al., 2012). Studies have shown that the nonsynonymous rs6897932 in IL-7R gene may affect the subtype, expression, and function of IL-7R (Kreft et al., 2012; Lundstrom, Fewkes, & Mackall, 2012). Therefore, the variants in IL-7R gene may be associated with the occurrence and development of other immune diseases. However, studies based on the association between IL-7R polymorphisms and RA have rarely been reported. In our result, rs969129 and rs6451231 in IL-7R gene firstly exhibited an increased risk of RA, suggesting that these IL-7R variants were likely to be susceptible loci for RA in the Han Chinese population.

Although this study had sufficient statistical power, some potential limitations should be considered when decipher the results. First, the sample size of our study was relatively small when compared with previous GWAS studies. Second, our subjects were all Han Chinese people, so the results cannot be extrapolated to other people. Despite the limitations mentioned above, our present results provided scientific evidence of IL-7R gene with RA in the future studies.

In a conclusion, there is a great desire for more case–control to find the genetic basis of RA. Fortunately, our study enriched this field. This study demonstrated that rs969129 and rs6451231 in IL-7R gene were associated with an increased risk of RA, which has not previously been reported. Combined with the previous studies, we believe that the IL-7R gene may be a new insight into the treatment of RA. Larger well-designed epidemiological studies with more diverse populations and functional evaluations should be conducted.

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## CONFLICTS OF INTEREST

We declare that we have no potential conflicts of interest.

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## REFERENCES

Arnett, F. C., Edworthy, S. M., Bloch, D. A., Mcshane, D. J., Fries, J. F., Cooper, N. S., …Hunder, G. G. (1988). The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and Rheumatism, 31*(3), 315–324. https://doi.org/10.1002/art.1780310302

Badot, V., Luijten, R. K. M. A. C., van Roon, J. A., Depresseux, G., Aydin, S., Van den Eynde, B. J., … Lauwerys, B. R. (2013). Serum soluble interleukin 7 receptor is strongly associated with lupus nephritis in patients with systemic lupus erythematosus. *Annals of the Rheumatic Diseases, 72*(3), 453–456. https://doi.org/10.1136/annrheumdis-2012-202364

Bland, J. M., & Altman, D. G. (2000). Statistics notes. The odds ratio. *BMJ, 320*(7247), 1468.

Boyman, O., Ramsey, C., Kim, D. M., Sprent, J., & Surh, C. D. (2008). IL-7/anti-IL-7 mAb complexes restore T cell development and induce homeostatic T Cell expansion without lymphopenia. *The Journal of Immunology, 180*(11), 7265–7275. https://doi.org/10.4049/jimmunol.180.11.7265

| Table 6 | The haplotype of four SNPs in IL7R and the RA risk |
| SNP-ID | rs969129 | rs118137916 | rs10053847 | rs6451231 | Haplotype | Frequency | Case | Control | OR (95% CI) | p |
|---------|-----------|-------------|-------------|------------|-----------|----------|------|---------|-------------|---|
| rs969129 | G         | A           | A           | C          | GAAC      | 0.846    | 0.847 | 1.00    | (0.78–1.28) | 0.985 |
| rs118137916 | G       | A           | G           | C          | GAGC      | 0.256    | 0.206 | 1.35    | (1.09–1.67) | 0.006* |
| rs10053847 | T         | G           | G           | T          | TGGT      | 0.926    | 0.910 | 1.23    | (0.90–1.69) | 0.198 |
| rs6451231 | G         | A           | G           | T          | GAGT      | 0.930    | 0.935 | 0.92    | (0.65–1.31) | 0.665 |
| rs6451231 | T         | A           | G           | T          | TAGT      | 0.554    | 0.516 | 1.17    | (0.98–1.40) | 0.077 |

Note: p values were calculated by Wald test adjusted by gender and age.
Abbreviations: CI, Confidence interval; OR, Odds ration; SNP, Single-nucleotide polymorphism.
Bold values represents a positive result.

*p < 0.05 indicates statistical significance.
between interleukin-7 and its receptor. *Biochemistry, 49*(40), 8766–8778. https://doi.org/10.1021/bi101050h

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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