Association between *IL1RL1* gene polymorphisms and allergic rhinitis risk in the Chinese Han population

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Abstract

**Background:** Although it has been confirmed that *IL1RL1* is involved in the occurrence of allergic rhinitis (AR), the role of *IL1RL1* gene single nucleotide polymorphisms (SNPs) in AR is still unclear.

**Methods:** We performed a case–control study including 1000 AR patients and 1000 healthy controls. The four SNPs rs72823628 G > A, rs950881 G > T, rs72823641 T > A and rs3771175 T > A in *IL1RL1* were chosen and genotyped using Agena MassARRAY platform. The relationship between *IL1RL1* SNPs and AR risk was analyzed by logistic regression and assessed with odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs).

**Results:** Overall analysis revealed that *IL1RL1* gene rs72823628, rs950881 and rs3771175 were associated with a reduced AR risk. Stratified analysis showed that the three SNPs (rs72823628, rs950881 and rs3771175) were obviously linked to a reduced risk of AR in males. Moreover, no correlation was observed between haplotypes and reduced AR risk after the false discovery rate (FDR) correction. The false positive report probability (FPRP) analysis was used to further validate significant findings.

**Conclusion:** Our study is the first to indicate that *IL1RL1* gene polymorphisms (rs72823628, rs950881 and rs3771175) may be correlated with decreased risk of AR in the Chinese Han population.

**KEYWORDS**

allergic rhinitis, Chinese Han population, *IL1RL1*, polymorphisms, risk
1 | INTRODUCTION

Allergic rhinitis (AR) is an atopic disease characterized by nasal congestion, runny nose, sneezing, post-nasal drip and nasal pruritus. As one of the most common forms of chronic allergic diseases, AR has become a global health problem with heavy economic burden, affecting approximately 40% of the world’s total population. Although AR does not cause death, its clinical symptoms can have serious effects on patients’ daily activities (e.g., sleep habits, cognitive function, work, etc.) and overall quality of life. AR is usually accompanied by asthma, atopic disease, sinusitis, conjunctivitis and otitis media, thus complicating the treatment and management of patients. Modern researches have revealed that the pathogenesis of AR is affected by multiple factors, including genetic, environmental and epigenetic factors. Among them, genetic factors, such as single nucleotide polymorphisms (SNPs), have become one of the important causes of AR. At present, relevant studies have defined several AR risk loci, such as TNF-α, IL-4 and TLR4, and these identifications are helpful in deepening the understanding of AR pathogenesis. Therefore, more SNPs in genes involved in AR development remain to be revealed.

Interleukin 1 receptor-like 1 (IL1RL1), also known as suppression of tumorigenicity 2 (ST2) and located on chromosome 2, exists in two forms, namely, transmembrane receptor and soluble decoy receptor. It is also identified as a receptor for interleukin 33 (IL-33), which is highly expressed in immune cells (macrophages, eosinophils, dendritic cells, mast cells, basophils, NK cells, type 2 innate lymphoid cells, Th2 lymphocytes, B cells, endothelial cells, epithelial cells and fibroblasts). Besides, IL1RL1 is implicated in the pathogenesis of various diseases as a critical mediator that can regulate immune cell function, participate in the process of antigen presentation and promote immune responses. The study found that IL1RL1 may contribute to the occurrence of AR. While patients are exposed to an allergic environment, allergens will stimulate endothelial and epithelial cells and mainly promote the secretion of IL-33, and elevated levels of IL-33 will increase IL1RL1 expression and induce the secretion of Th2 cytokines (IL-4, IL-5 and IL-13), leading to B cell activation, IgE secretion, enhanced mast cell degranulation and histamine release, ultimately leading to a greater allergic reaction in AR patients. Hence, we have reason to trust that IL1RL1 participates in the pathogenesis of AR, but, the detailed mechanism remains unknown. Taken together, there is a need to broaden the focus on the association between IL1RL1 polymorphisms and AR.

In this study, we aimed to determine the role of IL1RL1 gene polymorphisms in AR risk in the Chinese Han population through genotyping and association analysis. Based on the 1000 Genomes Project database and Haploview software, combined with Hardy–Weinberg equilibrium (HWE) test and primer design principles, we selected four SNPs (rs72823628, rs950881, rs72823641 and rs3771175) of the IL1RL1 gene in the Chinese Han population for further study. Finally, the relationship between SNPs of IL1RL1 gene and AR risk were analyzed, which can help provide new references and methods for AR prevention and treatment.

2 | MATERIALS AND METHODS

2.1 | Study population

A case-control study of 1000 AR patients and 1000 controls was designed. A total of 1000 randomly selected AR patients were admitted to the otolaryngology department of Shenmu Hospital, and they were mainly from five towns in Shenmu City (Daliuta, Jinjie, Langanbao, Hejiachuan and a central distinct of Shenmu City).

| Parameter       | AR group (n = 1000) | Control group (n = 1000) | p     |
|-----------------|---------------------|--------------------------|-------|
| Age (years, Mean ± SD) | 42.70 ± 10.42       | 43.79 ± 8.18             | 0.009a|
| Age > 43        | 508 (50.8%)         | 572 (57.2%)              |       |
| Age ≤ 43        | 492 (49.2%)         | 428 (42.8%)              |       |
| BMI (kg/m², Mean ± SD) | 24.84 ± 3.63       | 25.49 ± 14.25            | 0.168a|
| BMI > 24        | 509 (50.9%)         | 530 (53.0%)              |       |
| BMI ≤ 24        | 491 (49.1%)         | 470 (47.0%)              |       |
| Sex, n (%)      |                     |                          | 0.163b|
| Male            | 376 (37.60%)        | 346 (34.60%)             |       |
| Female          | 624 (62.40%)        | 654 (65.40%)             |       |
| Region, n (%)   |                     |                          | 0.762b|
| Eolian-beach region | 264 (49.40%)        | 270 (50.60%)             |       |
| Loess hilly region | 736 (50.20%)        | 730 (49.80%)             |       |

Note: p<sup>a</sup>-value was calculated by Student’s t-test. p<sup>b</sup>-value was calculated by Pearson’s χ<sup>2</sup> test. Bold values indicated that the p-value was statistically significant.

Abbreviations: AR, allergic rhinitis; BMI, body mass index.
People in the control group were healthy without clinical symptoms of AR, allergic diseases, autoimmune history and family history of allergy, and participated in the physical examination at the same period as cases. The diagnosis of AR refers to the guidelines for the diagnosis and treatment of AR issued by the Chinese Medical Association. (1) Clinical symptoms: two or more symptoms must be present, including sneezing, runny nose, itchy nose, stuffy nose and so on, and the symptoms continue or accumulate for more than one hour a day; (2) Nasal symptoms: pale and swollen bilateral nasal mucosa, inferior turbinate edema, and watery nasal discharge; Ocular symptoms: conjunctival hyperemia, edema, and sometimes papilla-like reactions in eyes; (3) Allergen testing: test results for at least one allergen should be positive. Exclusion criteria for AR group were: No any history of asthma, no comprehensive diseases such as lung, liver or kidney diseases, and no infectious diseases such as hepatitis or tuberculosis. This study was approved by the Ethics Committee of Shenmu Hospital, and complied with the Declaration of Helsinki. Subjects provided written informed consent prior to participation.

2.2 | SNP selection and genotyping

Four SNPs (rs72823628, rs950881, rs72823641 and rs3771175) in IL1RL1 gene were screened by the following processes. Firstly, all mutation loci in IL1RL1 were downloaded from the Global Population 1000 Genomes Project. Secondly, Haploview software was performed to set parameters (Hardy–Weinberg equilibrium (HWE)>0.01 and minor allele frequency (MAF)>0.05) to filter SNPs. Finally, combined with the principle of primer design, the non-specific primers were excluded, and the screening of SNP in this study was completed. Meanwhile, 5-ml peripheral blood was collected from each subject and DNA was extracted using GoldMag Genomic DNA Purification Kit (GoldMag Co. Ltd. Xi’an, China). DNA concentration was estimated by NanoDrop 2000 (Thermo Scientific, Waltham, Massachusetts, USA). Genotyping of four SNPs was performed using matrix-assisted laser desorption ionization time-of-flight mass spectrometry on Agena MassARRAY iPLEX (Agena Bioscience, San Diego, CA, USA) platform. Genotyping was performed in a double-blind manner and results were generated using Agena Bioscience TYPER version 4.0.

2.3 | Statistical analyses

All statistical analyses were performed by SPSS 22.0 and Microsoft Excel, and all statistical tests were two-sided. p < 0.05 was considered statistically significant. Chi-square test was carried out to investigate whether the four SNPs in IL1RL1 in the control group conformed to HWE. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression. In addition, PLINK software was utilized to perform association analysis of SNPs and AR risk under four genetic models (co-dominant, dominant, recessive and log-additive). At the same time, PLINK software was used to perform haplotype analysis and intragenic epistatic effect...
LI et al. analysis. Finally, false discovery rate (FDR) analysis was used to correct multiple testing, while false positive reporting probability (FPRP) analysis was used to test whether significant results were credible.

### RESULTS

#### 3.1 Characteristics of the study sample

The basic characteristics of 1000 AR patients and 1000 controls in the study are presented in **Table 1**. As shown, the mean ages of cases and controls were 42.70 ± 10.42 years and 43.79 ± 8.18 years, respectively. There were significant differences in age distribution between the AR and healthy control groups (p < 0.05), by contrast, there was no significant difference in body mass index (BMI), sex and region distribution.

| SNP-ID          | Model       | Genotypes | AR group | Control group | OR (95% CI) | p      | FDR-p   |
|-----------------|-------------|-----------|----------|---------------|-------------|--------|---------|
| rs72823628      | Co-dominant | GG        | 854 (85.49%) | 815 (81.66%) | Reference   | 0.014  | 0.027   |
|                 |             | GA        | 134 (13.41%) | 174 (17.44%) | 0.74 (0.58–0.94) | 0.734  | 1.467   |
|                 |             | AA        | 11 (1.10%)  | 9 (0.90%)    | 1.17 (0.49–0.94) | 1.22 (0.51–2.96) | 2.621   |
| Dominant        |             | GG        | 854 (85.49%) | 815 (81.66%) | Reference   | 0.021  | 0.043   |
|                 |             | AA+GA     | 145 (14.51%) | 183 (18.34%) | 0.76 (0.60–0.96) | 0.655  | 2.621   |
| Recessive       |             | GA+GG     | 988 (98.90%) | 989 (99.10%) | Reference   | 0.046  | 0.061   |
|                 |             | AA        | 11 (1.10%)  | 9 (0.90%)    | 1.22 (0.51–2.96) | 0.655  | 2.621   |
| Log-additive    |             | –         | –         | –            | 0.80 (0.64–1.00) | 0.046  | 0.061   |
| rs950881        | Co-dominant | GG        | 852 (85.29%) | 810 (81.08%) | Reference   | 0.009  | 0.036   |
|                 |             | GT        | 138 (13.81%) | 181 (18.12%) | 0.73 (0.57–0.92) | 0.891  | 1.187   |
|                 |             | TT        | 9 (0.90%)   | 8 (0.80%)    | 1.07 (0.41–2.79) | 0.47 (0.21–1.09) | 3.65    |
| Dominant        |             | GG        | 852 (85.29%) | 810 (81.08%) | Reference   | 0.012  | 0.049   |
|                 |             | TT+GT     | 147 (14.71%) | 189 (19.22%) | 0.74 (0.58–0.94) | 0.828  | 1.077   |
| Recessive       |             | GT+GG     | 990 (99.10%) | 991 (99.20%) | Reference   | 0.12   | 0.497   |
|                 |             | TT        | 9 (0.90%)   | 8 (0.80%)    | 1.13 (0.43–2.93) | 0.808  | 1.077   |
| Log-additive    |             | –         | –         | –            | 0.78 (0.66–1.00) | 0.023  | 0.093   |
| rs72823641      | Co-dominant | TT        | 961 (96.10%) | 960 (96.00%) | Reference   | 0.996  | 0.999   |
|                 |             | TA        | 39 (3.90%)  | 39 (3.90%)   | 1.00 (0.64–1.57) | 0.996  | 0.999   |
|                 |             | AA        | 0 (0.00%)   | 1 (0.10%)    | 6.184E-10 (0–/) | 0.999  | 0.999   |
| Dominant        |             | TT        | 961 (96.10%) | 960 (96.00%) | Reference   | 0.909  | 0.909   |
|                 |             | AA+TA     | 39 (3.90%)  | 40 (4.00%)   | 0.97 (0.62–1.53) | 0.999  | 0.999   |
| Recessive       |             | TA+TT     | 1000 (100%) | 999 (99.90%) | Reference   | 0.999  | 0.999   |
|                 |             | AA        | 0          | 1 (0.10%)    | 6.18E-10 (0–/) | 0.999  | 0.999   |
| Log-additive    |             | –         | –         | –            | 0.78 (0.66–1.00) | 0.822  | 0.822   |
| rs3771175       | Co-dominant | TT        | 865 (86.50%) | 827 (83.03%) | Reference   | 0.032  | 0.043   |
|                 |             | TA        | 128 (12.80%) | 161 (16.17%) | 0.76 (0.59–0.98) | 0.832  | 2.926   |
|                 |             | AA        | 7 (0.70%)   | 8 (0.80%)    | 0.84 (0.30–2.32) | 0.731  | 2.926   |
| Dominant        |             | TT        | 865 (86.50%) | 827 (83.03%) | Reference   | 0.031  | 0.042   |
|                 |             | AA+TA     | 135 (13.50%) | 169 (16.77%) | 0.76 (0.60–0.98) | 0.790  | 1.579   |
| Recessive       |             | TA+TT     | 993 (99.30%) | 988 (99.20%) | Reference   | 0.039  | 0.079   |
|                 |             | AA        | 7 (0.70%)   | 8 (0.80%)    | 0.87 (0.32–2.41) | 0.790  | 1.579   |
| Log-additive    |             | –         | –         | –            | 0.79 (0.63–0.99) | 0.039  | 0.079   |

Note: p-value was calculated by logistic regression analysis. Bold values indicated that the p-value was statistically significant.

Table 2: The association between IL1RL1 polymorphisms and allergic rhinitis risk

3.2 Basic information on SNPs

The basic information and allele frequencies of rs72823628, rs72823641 and rs3771175 loci in IL1RL1 are shown in Table 2. The genotype frequency distributions of the four SNPs in the control group were all in line with HWE. The distribution of allele frequencies of rs72823628 (p = 0.042), rs950881 (p = 0.022) and rs3771175 (p = 0.038) differed between the two groups. Logistic regression analysis showed rs72823628 A allele (OR = 0.80, 95%
CI = 0.64–0.99), rs950881 T allele (OR = 0.77, 95% CI = 0.62–0.97) and rs3771175 A allele (OR = 0.78, 95% CI = 0.62–0.99) was associated with a reduced risk of AR. After FDR correction, the results indicated no association between the minor alleles of the three SNPs and AR risk (FDR-p = 0.057; FDR-p = 0.089; FDR-p = 0.075).

### 3.3 Relationship between IL1RL1 gene polymorphisms and AR risk

Overall analyses showed that three-quarters of SNPs were significantly associated with a reduced AR risk (Table 3): rs72823628 (heterozygous: \( p = 0.014, \) OR = 0.74, 95% CI = 0.58–0.94; dominant: \( p = 0.021, \) OR = 0.76, 95% CI = 0.60–0.96; additive: \( p = 0.046, \) OR = 0.80, 95% CI = 0.64–1.00), rs950881 (heterozygous: \( p = 0.009, \) OR = 0.73, 95% CI = 0.57–0.92; dominant: \( p = 0.012, \) OR = 0.74, 95% CI = 0.58–0.94; additive: \( p = 0.023, \) OR = 0.78, 95% CI = 0.66–1.00), and rs3771175 (heterozygous: \( p = 0.032, \) OR = 0.76, 95% CI = 0.59–0.98; dominant: \( p = 0.031, \) OR = 0.76, 95% CI = 0.60–0.98; additive: \( p = 0.039, \) OR = 0.79 95% CI = 0.63–0.99). After FDR correction, these three SNPs remained significantly associated with reduced AR risk. Conversely, no correlation was observed between rs72823641 and AR risk.

### 3.4 Stratified analysis

Stratified analysis of the cases and controls was performed by age, BMI, sex and region. Precisely, after age stratification, the selected SNPs bore no relationship to AR risk (Table S1). After BMI stratification, as shown in Table S2, rs950881 in a co-dominant heterozygous model was linked to a reduced risk of AR among people with BMI ≤ 24. After stratification for sex, rs72823628, rs950881 and rs3771175 were significantly associated with a reduced risk of AR in men (Table 4). What is more, along with the stratified analysis based on region, rs72823628, rs950881 and rs3771175 in additive model, rs72823628 and rs950881 in dominant model, and rs72823628 in co-dominant heterozygote model were all associated with a reduced risk of AR in people in the eolian-beach region (Table 5). After FDR correction, rs72823628, rs950881 and rs3771175 were still significantly associated with reduced AR risk in men, suggesting that sex differences may affect the relationship between IL1RL1...
gene polymorphisms and AR risk. However, after FDR correction, rs72823628, rs950881 and rs3771175 were no longer relevant to a reduced risk of AR in people in the eolian-beach region, indicating that the impact of geographical region on AR risk may need to be further studied by expanding samples.

### 3.5 Haplotypes and the risk of AR

In the haplotype model analysis, a block of linkage disequilibrium (LD) was detected in the IL1RL1 gene SNPs (rs72823628-rs950881; Figure 1; Table 6). Haplotype rs72823628 A - rs950881 T was significantly associated with a reduced risk of AR compared with the reference haplotype rs72823628 G - rs950881 G (OR = 0.78, 95% CI = 0.63–0.98, p = 0.032). After FDR correction, the haplotype rs72823628 A - rs950881 T was not related to the reduction of AR risk (FDR-p = 0.064).

### 3.6 Intragenic epistasis effect in IL1RL1 to AR risk

To explore whether there was a potential genetic epistatic effect among the four SNPs in the IL1RL1 gene to affect the risk of AR, we performed a pairwise epistatic effect test using logistic regression. However, no epistatic association between pairwise SNPs and AR risk was observed in this study (p > 0.05), as shown in Table 7.

### 3.7 FPRP analysis

To avoid false-positive results, FPRP analysis was used to further investigate the reliability of associations between selected SNPs and AR risk (Table 8). A pre-specified FPRP value below 0.2 was considered noteworthy for each association. When the prior probability was 0.25, all results for rs72823628, rs950881 and rs3771175 were deserving of attention, except for eolian-beach region subgroup (rs72823628 AG vs GG, rs950881 TT+TG vs GG and rs3771175 log-additive). When a prior probability of 0.1 was adopted, the significant association for rs72823628 (GA vs GG and AA+GA vs GG) remained noteworthy, so were results for the male subgroup. Noteworthy results were also found for the rs950881 (GT vs GG, TT+GT vs GG and male subgroup) and the rs3771175 (male subgroup).

### 4 DISCUSSION

AR is a health problem of global concern, and especially with the development of society in recent years, its incidence has been
increasing sharply year by year. A survey has shown that the standardized prevalence rate of AR in the Chinese adults has increased by 6.5% in the past six years, imposing a considerable economic burden on both societies and individuals. Therefore, it is worthwhile to study the key risk factors for AR. Notably, the pathogenesis of common allergic diseases (e.g., asthma, atopic dermatitis, and AR) influenced by genetic and environmental factors is complex. Interestingly, it has been reported that IL1RL1 polymorphisms have been found in both asthma and atopic dermatitis, however, little is known about it in AR. Therefore, we first studied the relationship between IL1RL1 gene polymorphisms and AR risk from a genetic perspective, in order to provide a reference for individualized treatment of AR patients. The results demonstrated that rs72823628, rs950881 and rs3771175 polymorphisms in the IL1RL1 gene were significantly associated with a reduced risk of AR, and subjects heterozygous or homozygous for at least one polymorphism allele were less likely to develop AR than subjects who were homozygous for main alleles.

The data regarding the IL1RL1 gene polymorphisms have revealed that rs3771175 is located on human chromosome 2, and the variant type is single nucleotide variation (SNV). So far, only two literatures have researched rs3771175 polymorphism. Colin L Robinson has reported that IL1RL1 is an asthma-related candidate gene and determined rs3771175 with genotyping results T > A. These results were consistent with ours. Another study has reported the relationship between rs3771175 and obesity, showing that the allele and genotype frequencies of rs3771175 were significantly different between obese people and control groups, and genotypes carrying minor alleles are significantly associated with an increased risk of obesity. In our study, we explored the association of rs3771175 with AR, and the results showed that rs3771175 was associated with a reduced risk of AR. It has been speculated that these different results may have a great correlation with differences in disease. However, for the IL1RL1 genes rs72823628, rs950881 and rs72823641, there are no related reports so far.

**TABLE 6** The haplotype frequencies of IL1RL1 polymorphisms and their association with the risk of AR

| SNP-ID                  | Haplotypes | Fre-AR | Fre-control | OR (95% CI) | p      | FDR-p |
|-------------------------|------------|--------|-------------|-------------|--------|-------|
| rs72823628-rs950881     | GG         | 0.919  | 0.899       | 1           |        |       |
|                         | AT         | 0.075  | 0.094       | 0.78 (0.63–0.98) | 0.032  | 0.064 |

Note: Adjust OR (95%CI) were calculated by logistic regression analysis. p < 0.05 was considered to be significant. Bold values indicated that the p-value was statistically significant.

Abbreviations: AR, allergic rhinitis; CI, confidence interval; FDR, false discovery rate; Fre, frequency; OR, odds ratio; SNP, single nucleotide polymorphism.

**TABLE 7** Pairwise epistatic interacting results amongst three independent variants in IL1RL1

| gene      | SNP-1   | SNP-2   | OR     | \(\chi^2\) | p     |
|-----------|---------|---------|--------|-------------|-------|
| IL1RL1    | rs72823628 | rs950881 | 1.358  | 1.476       | 0.224 |
| rs72823628 | rs72823641 | rs950881 | 1.219  | 0.069       | 0.792 |
| rs72823628 | rs3771175 | rs72823641 | 1.246  | 0.699       | 0.403 |
| rs950881  | rs72823641 | rs3771175 | 1.228  | 0.078       | 0.780 |
| rs950881  | rs3771175 | rs72823641 | 1.510  | 2.278       | 0.131 |
| rs72823641 | rs3771175 | rs72823641 | 1.151  | 0.027       | 0.869 |

Note: \(p < 0.05\) was considered to be significant.

Abbreviations: OR, odds ratio; SNP, single nucleotide polymorphism; \(\chi^2\), Chi-squared.
### TABLE 8  Results of FPRP analysis for significant findings

| Genotype and variables | Crude OR (95% CI) | \( p \) | Statistical power | Prior probability |
|------------------------|-------------------|--------|-------------------|-------------------|
|                        |                   |        |                   | 0.25  | 0.1  | 0.01 | 0.001 | 0.0001 |
| rs72823628             |                   |        |                   |       |     |     |       |       |
| Overall analysis       |                   |        |                   |       |     |     |       |       |
| A vs G                 | 0.80 (0.64–0.99)  | 0.040  | 0.953             | 0.112 | 0.275 | 0.806 | 0.977 | 0.998  |
| GA vs GG               | 0.74 (0.58–0.94)  | 0.014  | 0.804             | 0.048 | 0.132 | 0.627 | 0.944 | 0.994  |
| AA+GA vs GG            | 0.76 (0.60–0.96)  | 0.021  | 0.864             | 0.069 | 0.182 | 0.709 | 0.961 | 0.996  |
| Log-additive           | 0.80 (0.64–1.00)  | 0.049  | 0.945             | 0.137 | 0.322 | 0.840 | 0.981 | 0.998  |
| Male                   |                   |        |                   |       |     |     |       |       |
| GA vs GG               | 0.46 (0.29–0.73)  | <0.001 | 0.058             | 0.049 | 0.133 | 0.628 | 0.944 | 0.994  |
| AA+GA vs GG            | 0.47 (0.30–0.73)  | <0.001 | 0.060             | 0.037 | 0.105 | 0.562 | 0.928 | 0.992  |
| Log-additive           | 0.54 (0.36–0.79)  | 0.002  | 0.139             | 0.031 | 0.089 | 0.517 | 0.915 | 0.991  |
| Eolian-beach region    |                   |        |                   |       |     |     |       |       |
| AG vs GG               | 0.23 (0.03–2.10)  | 0.193  | 0.173             | 0.770 | 0.909 | 0.991 | 0.999 | 1.000  |
| AA+AG vs GG            | 0.59 (0.37–0.92)  | 0.020  | 0.295             | 0.168 | 0.378 | 0.870 | 0.985 | 0.999  |
| Log-additive           | 0.59 (0.39–0.79)  | 0.014  | 0.285             | 0.131 | 0.311 | 0.832 | 0.980 | 0.998  |
| rs950881               |                   |        |                   |       |     |     |       |       |
| Overall analysis       |                   |        |                   |       |     |     |       |       |
| T vs G                 | 0.77 (0.62–0.97)  | 0.027  | 0.889             | 0.082 | 0.212 | 0.747 | 0.968 | 0.997  |
| GT vs GG               | 0.73 (0.57–0.92)  | 0.008  | 0.779             | 0.029 | 0.081 | 0.493 | 0.908 | 0.990  |
| TT+GT vs GG            | 0.74 (0.58–0.94)  | 0.014  | 0.804             | 0.048 | 0.132 | 0.627 | 0.944 | 0.994  |
| Log-additive           | 0.78 (0.66–1.00)  | 0.049  | 0.892             | 0.144 | 0.335 | 0.847 | 0.982 | 0.998  |
| Male                   |                   |        |                   |       |     |     |       |       |
| GT vs GG               | 0.42 (0.27–0.67)  | <0.001 | 0.026             | 0.030 | 0.085 | 0.506 | 0.912 | 0.990  |
| TT+GT vs GG            | 0.42 (0.27–0.65)  | <0.001 | 0.019             | 0.015 | 0.045 | 0.339 | 0.838 | 0.981  |
| Log-additive           | 0.45 (0.30–0.68)  | <0.001 | 0.031             | 0.014 | 0.042 | 0.324 | 0.829 | 0.980  |
| BMI ≤24                |                   |        |                   |       |     |     |       |       |
| GT vs GG               | 0.70 (0.19–0.99)  | 0.043  | 0.609             | 0.177 | 0.393 | 0.877 | 0.986 | 0.999  |
| Eolian-beach region    |                   |        |                   |       |     |     |       |       |
| TT+TG vs GG            | 0.63 (0.40–0.97)  | 0.036  | 0.399             | 0.213 | 0.448 | 0.899 | 0.989 | 0.999  |
| Log-additive           | 0.62 (0.41–0.95)  | 0.028  | 0.369             | 0.186 | 0.407 | 0.883 | 0.987 | 0.999  |
| rs3771175              |                   |        |                   |       |     |     |       |       |
| Overall analysis       |                   |        |                   |       |     |     |       |       |
| A vs T                 | 0.78 (0.62–0.99)  | 0.041  | 0.902             | 0.120 | 0.291 | 0.819 | 0.979 | 0.998  |
| TA vs TT               | 0.76 (0.59–0.98)  | 0.034  | 0.844             | 0.109 | 0.268 | 0.801 | 0.976 | 0.998  |
| AA+TA vs TT            | 0.76 (0.60–0.98)  | 0.034  | 0.844             | 0.109 | 0.268 | 0.801 | 0.976 | 0.998  |
| Log-additive           | 0.79 (0.63–0.99)  | 0.041  | 0.930             | 0.116 | 0.282 | 0.812 | 0.978 | 0.998  |
| Male                   |                   |        |                   |       |     |     |       |       |
| TA vs TT               | 0.45 (0.28–0.73)  | 0.001  | 0.056             | 0.062 | 0.164 | 0.684 | 0.956 | 0.995  |
| AA+TA vs TT            | 0.44 (0.28–0.71)  | <0.001 | 0.044             | 0.050 | 0.135 | 0.632 | 0.946 | 0.994  |
| Log-additive           | 0.48 (0.31–0.73)  | <0.001 | 0.062             | 0.028 | 0.080 | 0.488 | 0.906 | 0.990  |
| Eolian-beach region    |                   |        |                   |       |     |     |       |       |
| Log-additive           | 0.64 (0.41–0.98)  | 0.040  | 0.426             | 0.220 | 0.459 | 0.903 | 0.989 | 0.999  |
| Haplotypes             |                   |        |                   |       |     |     |       |       |
| rs72823628-rs950881(AT vs GG) | 0.80 (0.64–1.00) | 0.049  | 0.945             | 0.137 | 0.322 | 0.840 | 0.981 | 0.998  |

Note: While the false-positive report probability threshold at 0.2, noteworthy findings are presented. The bold values were statistically significant results and noteworthy findings.

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
At present, association studies of \textit{IL1RL1} gene SNPs are mainly based on studies under different genetic models, and the haplotypes and intragenic epistatic effects of SNPs have not been deeply understood. In our study, haplotype analysis of the \textit{IL1RL1} gene SNPs was performed in the Chinese Han population, and we found that the combination of the risk alleles rs72823628 (A) and rs950881 (T) might increase the risk of AR. This may indicate that haplotype rs72823628-rs950881 tended to be inherited as a whole to offspring and played an integral role in the progression of AR. On the other hand, we found that potential genetic epistatic effects amongst the four SNPs in \textit{IL1RL1} gene may not affect the risk of AR. This likely indicated that epistatic effects between SNPs may not work in the pathogenesis of AR.

Although our study is the first to confirm \textit{IL1RL1} polymorphisms as the possible protective genetic factor for AR, the study has several limitations. First, we only explored statistical associations, so further investigation of the underlying mechanisms is required. Second, this study was conducted in the Chinese population, and the results should be applied to other populations with caution. Additionally, this is a basic research, which means the results are far from clinical practice. In the future, we will investigate the relationship between \textit{IL1RL1} polymorphisms and AR risk by expanding the sample size to include populations from different regions and ethnic groups, and animal experiments will be employed for further potential mechanistic studies.

5 | CONCLUSION
This study is the first to find that rs72823628, rs950881 and rs3771175 polymorphisms in the \textit{IL1RL1} gene appear to be associated with a reduced risk of AR in the Chinese Han population. Also, the findings provide a theoretical basis for the role of \textit{IL1RL1} gene in AR. In summary, a correct understanding of the joint roles of risk factors for AR has important implications for primary prevention and public health policymaking.

AUTHOR CONTRIBUTIONS
Zhengqing Li conceived the idea; Jiajia Ren carried out the experiment; Jirong Zhang performed the literature search and wrote the manuscript; Xing Wang conducted quality assessment and data analysis; Qiang Wang contributed to the analysis and interpretation of descriptive data; Yonglin Liu contributed to the research concept and design as well as key revisions. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST
The authors have declared that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT FOR PUBLICATION
All authors agree to publicize the paper.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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