The Assessment of TNF-α Gene Polymorphism Association with the Risk of Allergic Rhinitis in the Chinese Han Population

Qianbo Cui1,2,* Jing Li1,* Jing Wang2
1Department of Otorhinolaryngology-Head and Neck Surgery, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, 430000, People’s Republic of China; 2Department of Otorhinolaryngology-Head and Neck Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, Hubei Province, People’s Republic of China

*These authors contributed equally to this work

Background: Allergic rhinitis (AR) is a non-infectious chronic inflammatory disease of the nasal mucosa that is mainly mediated by IgE after exposure to allergens. Tumor necrosis factor-α has been found to be involved in inflammation response. In the present study, we screened several SNPs of TNF-α gene and analyzed the associations between target SNPs polymorphism and AR.

Methods: Using an unmatched case-control design, 600 AR patients and 600 healthy controls were enrolled. General characteristics were collected including IgE expression. Univariate and multivariate logistic regression were used to estimate the odds ratio (OR) and 95% confidence interval (CI) of TNF-α gene for AR in dominant model, additive model, recessive model and allele model. The haplotype analyses were performed using rs1799964, rs1800630 and rs769178. Stratified analyses were also performed in gender, age, overweight, smoking, drinking, family history, and asthma history.

Results: Our multivariate logistic regression indicated that rs1799964, rs1800630 and rs769178 locus polymorphisms are not associated with AR. For rs769178, the GT (OR=2.35, 95% CI:1.82–3.03, P<0.001) and GT+TT (OR=1.89, 95% CI: 1.50–2.38, P<0.001) genotypes present an increased risk for AR compared to GG. The C-G-A-T (OR=2.04, 95% CI: 1.21–3.44, P=0.007) and C-G-C-T (OR=1.29, 95% CI: 1.04–1.62, P=0.024) haplotypes are associated with the increased risk of AR, and the C-G-C-G haplotypes decreased risk of AR (OR=0.75, 95% CI: 0.63–0.88, P=0.001). Stratified analyses shown a significant association between recessive model of rs769178 locus and AR risk in the subgroup of age≤60, overweight and smoking. Cross-over analysis indicated that the effects of TT+GT of genotype combined with smoking or drinking related with AR were associated with AR risk.

Conclusion: The rs769178 locus polymorphism of TNF-α was associated with an increased risk of AR. The haplotypes (C-G-A-T and C-G-C-T) of TNF-α can significantly increase the risk of AR, and C-G-C-G haplotype decreased the risk of AR. There are interactions between rs769178 polymorphism and smoking/drinking for AR risk.

Keywords: allergic rhinitis, tumor necrosis factor-α, gene polymorphism, interaction

Introduction

Allergic rhinitis (AR) is a chronic inflammatory disease that affects approximately 10–20% of the global population.1 In recent years, the incidence of AR is increasing year by year worldwide. AR is part of a systemic inflammatory disease and is associated with other inflammatory disorders, including asthma, sinusitis, and allergic conjunctivitis.2 AR reduces the quality of life of a patient and can affect sleep, school
work, work productivity, and social life.3,4 AR has been classified as a chronic respiratory disease due to its high morbidity and its impact on life quality. The mechanism of AR still remains unclear. The present findings have shown that inflammation plays an important role in AR.5 Previous studies had identified some risk factors of AR such as family history, dust exposure history, drug allergy history and pollen allergy.6,7 Brozek et al showed that the interaction between the genetic susceptibility and environmental factors are the fundamental cause of AR.8 Genetic factors play an equally important role in the risk factors related to the incidence of AR as same as and environmental factors.9,10 The emergence of gene polymorphism changes the coding sequence or changes the process of transcription and translation, which are involved in the occurrence and development of the disease by regulating the character, activity and dose of protein expressed by gene.11 Therefore, it is one of the important ways for researchers to discover the genetic mechanism of human complex diseases and to prevent and treat complex diseases by searching for the gene loci closely related to human complex diseases.

Tumor necrosis factor α (TNF-α) is a kind of mononuclear pro-inflammatory cytokine produced mainly by macrophages and monocytes.12 Previous studies showed that expression of TNF-α could be associated with some pulmonary diseases.13,14 Recently, the highly expressed TNF-α was observed in nasal mucosal mast and epithelial cells.15 Similarly, the highly expressed cytokine of TNF receptors is also found in patients with AR.16 The vivo suggested that inhibition of TNF-α delayed the development of AR.17 These results indicated that TNF-α may be involved in AR. TNF-α is regulated by TNF-α gene. Several single nucleotide polymorphisms (SNP) of TNF-α gene have been reported, and studies have identified several SNP of TNF-α gene promoter regions 308 G/A locus were associated with asthma.18 Recent several studies also explored the between TNF-α gene 308 G/A locus polymorphism and AR.19–21 However, the results are inconsistent. TNF-α gene has multiple variants. In the present study, we screened several SNPs of TNF-α gene and analyzed the associations between target SNPs polymorphism and AR, and we also investigated the effects of interactions between gene-environment factors on AR risk.

Methods

Study Population

Using an unmatched case-control study design, we enrolled 600 patients with allergic rhinitis and 600 healthy controls from the Tongji Hospital, Tongji Medical College. The AR diagnosis is in accordance with the allergic rhinitis and its impact on asthma (ARIA, 2010) recommended by World Health Organization (WHO) and guidelines for the diagnosis and treatment of allergic rhinitis established by Chinese Medicine Association (2018).8,22 (1) persistent runny nose, sneezing nasal congestion and nasal itching; (2) The nasal mucosa is pale and edema; (3) at least one inhales allergen is positive, including skin prick test 2++ and/or serum IgE≥0.35kU/L; All patients were confirmed by advanced experienced clinicians. The control population is selected according to the following criteria: (1) The control group is from the healthy population who participate in the healthy examination during the same period; (2) No symptoms and history of AR or other nasal diseases; (3) No symptoms and history of allergic dermatitis, or other allergic diseases; (4) Total serum IgE < 200kU/L; (5) Serum specific IgE screening test (PHADIA) <0.35 kU/L; (5) No history of AR or other allergic diseases in the immediate relatives; The results of blood biochemical examination were normal. The following population are excluded: patients with autoimmune diseases, severe mental diseases or other systemic diseases; (2) patients with acute upper respiratory tract infection, severe nasal septum deviation, suppurative sinusitis, nasal polyps and nasosinus tumors; (3) Usage history of glucocorticoids within 4 weeks or usage of antihistamines, leukotriene receptor antagonists within 2 weeks. This study was approved by the Ethics Committee of Central Hospital of Wuhan, Tongji Medical College, and study was in accordance with the Declaration of Helsinki. Study subjects provided written informed consent prior to participation.

Data Collection

The data are mainly from the medical records and questionnaire investigation. The following information is collected: age, sex, height and weight for body mass index (BMI=weight/(height)^2 kg/m^2), BMI<24 for normal, and BMI≥24 for overweight according to the Chinese body mass criteria), smoking (defined by one stick each day for lasting at least month), drinking (at least three times one month), family history, and asthma history. The IgE is detected using enzyme-linked immunosorbent assay.

SNP Selection

For our study, we selected four single nucleotide polymorphisms of TNF-α: rs1799964, rs1800629, rs1800630 and rs769178. The selection criteria are as follows: minor
The number and frequency of genotypes are obtained by Equilibrium of four SNPs locus among control group.

**DNA Extraction and Genotyping**

The peripheral venous blood was extracted and stored in an anticoagulant vacuum sampling vessel and placed in the ultra-low temperature refrigerator for preparation. DNA was extracted using the TIANamp Blood DNA kit (Tiangen Biotech, Beijing, China) by following the manufacturer’s instructions. DNA concentration and purity were measured using a UV spectrophotometer (Pharmacia Biotech). Genotyping was performed using matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS) using the MassARRAY system (Sequenom, San Diego, CA, USA). Duplicate samples and negative controls were included to ensure accuracy. The Primers were designed using the Primer Premier software version 6. The primers of four SNPs are as follows: rs1800629 (F: 5’-AGGCAAATGTTTTGAGGGCCAT -3’; R: 5’-TCTCTCCTGCTCCGATTCCG -3’), rs1800630 (F: 5’-GGGGCTAGGAAGTGGATAGTGG -3’, R: CCGCCTACGTGGCCCTGTTCT -3’), rs1799964 (F: GGAAGCCAGGAGCAGGATGGAATGTA-3’, R: 5-GAA AAACCGATGCCCCACTTA -3’).

**Statistical Analysis**

The Chi-square test is used for Hardy-Weinberg Equilibrium of four SNPs locus among control group. The number and frequency of genotypes are obtained by counting and percent. The allele frequencies of patients and control groups were analyzed by using Chi-square test, and the odd ratios and 95% confidence interval were calculated in the dominant model (TT vs CC), recessive model (TT + TC vs CC) and allele model (C vs T). High frequency alleles and genotypes were used as reference genes to compare other alleles and genotypes. Chi-square test was used to analyze the differences in genotyping rate, mean age, sex BMI, smoking, drinking, family history, and t-test was used to compare the differences of asthma, and IgE levels between the two groups of subjects. Logical regression was used to analyze allele frequency and statistical differences using age, sex, BMI, smoking, drinking, family history, and asthma. The Bonferroni correction is used for multiple comparisons of SNPs (corrected α=α/n, n=number of tests). Haplotype data analyzed using programs and online software platforms (http://analysis.bio-x.cn/). High frequency haplotypes were used as reference genes for statistical comparison with other haplotype genotypes. Stratified analyses were performed among the subgroup of age, gender, BMI, smoking, drinking, family history, asthma. The interactions between gene locus and environments were analyzed using cross-over methods. These analyses are finished using SPSS 23.0. P<0.05 is the threshold of significant difference unless being specifically defined.

**Results**

**General Characteristics of Case Group and Control Group**

Table 1 presents the comparisons of general characteristics between allergic rhinitis group and healthy control. Compared with control group, the ratio of male is higher in the case group as compared to control group (69.2% vs 60.3%, P=0.002). The case group and control are close in age (P=0.055). The BMI or overweight rate is higher in the case group than that in the control group (P=0.030, P=0.003). The smoking rate is also higher in the case group than that in the control group (29.2% vs 23.2%, P=0.022), but no significant difference is observed in drinking rate between two groups (23.5% vs 26.8%, P=0.206). Furthermore, the case group tends to have a family history (35.7% vs 21.7%, P<0.001) and asthma history (36.7% vs 4.3%, P<0.001), and the IgE level is also higher in the case group than that in the control group (131.3±18.7 vs 33.3±12.7, P<0.001).

**The Association of TNF Gene and Allergic Rhinitis**

We identified four SNPs of TNF-α according to the screening criteria (rs1799964, rs1800629, rs1800630, and rs769178). The Hardy-Weinberg equilibrium test indicates no genetic bias in the control group (P>0.05). The univariate analysis indicates that rs1800630, rs769178 and rs1799964 are significantly associated with allergic rhinitis. Specifically, compared with control, the TC (OR=1.31, 95% CI: 1.01–1.69, P=0.042) and TC+CC (OR=1.29, 95% CI: 1.02–1.64, P=0.031) genotypes of rs179964 have
higher frequencies in the case group. The C allele is also associated with an increased risk AR (OR=1.23, 95% CI: 1.01–1.49, \( P=0.036 \)). The CA (OR=1.34, 95% CI:1.03–1.75, \( P=0.031 \) and CA+AA (OR=1.31, 95% CI:1.01–1.68, \( P=0.039 \) genotypes of rs1800630 also shown the increased risk of AR compared to CC genotypes. For rs769178, the GT (OR=2.35, 95% CI:1.82–3.03, \( P<0.001 \) and GT+TT (OR=1.89, 95% CI: 1.50–2.38, \( P<0.001 \) genotypes present in increased risk for AR. In the allele model, the T allele is associated with the increased risk of AR (OR=1.37, 95% CI: 1.14–1.65, \( P=0.001 \). The Bonferroni correction indicates that only rs769178 polymorphism is still significantly associated with AR (GT and GT+TT: \( P<0.001 \). The multivariate logistic regression suggests the GT (\( P<0.001 \)) and GT+TT (\( P<0.001 \)) genotypes of rs769178 polymorphism is still associated with the increased risk of AR compared to TT. The rs1799964, rs1800629 and rs1800630 locus polymorphisms are not associated with AR susceptibility. Table 2 shows the results details. We also compared the IgE expression level among gene polymorphisms of four SNPs, the results indicated a significant difference among three genotypes of rs769178, the IgE is higher in the TT genotype than that in the GG genotype (\( P<0.010, \) Figure 1). The rs1800630, rs1800629 and rs1799964 were not associated with IgE expression.

The haplotypes analysis indicates that the C-G-A-T and C-G-C-T haplotypes have higher frequencies in the case group than in the control group, and the C-G-C-G haplotype shows lower frequency in the case group. The C-G-A-T (OR=2.04, 95% CI: 1.21–3.44, \( P=0.007 \) and C-G-C-T (OR=1.29, 95% CI: 1.04–1.62, \( P=0.024 \) haplotypes are associated with the increased risk of AR, and the C-G-C-G haplotypes decreased risk of AR (OR=0.75, 95% CI: 0.63–0.88, \( P=0.001 \). Table 3 presents other haplotypes effect for AR risk.

### Stratified Analyses

Furthermore, we performed the stratified analyses according to gender, age, smoking, drinking, family history and asthma to evaluate the effect of rs769178 polymorphism AR risk. We noted a significant association between recessive model of rs769178 locus and AR risk in the subgroup of age≤60, overweight and smoking. Both heterozygous model and dominant model show similar significant effects on AR risk in these subgroups. The Homozygous model shows no significant effect on AR risk. Table 4 presents all details.

### Interaction Effects

We also perform the interactions analyses between TT+GT genotype of rs769178 and these positive risk factors for AR risk. The effects of TT+GT genotype combined with smoking or drinking related with AR was associated with increased risk of AR, which confirmed the gene-environment interaction. Similarly, when children with TT +GT model and gender of male or overweight, or history of family or asthma will have increased risk of AR compared to those without these factors and TT+GT model. More details can be seen in Table 5.

### Discussion

In the present study, we identified the rs769178 locus polymorphism of TNF-α gene was associated with the increased risk of AR, and others (rs1799964, rs1800629, rs1800630) may be not related to AR. The rs769178 locus polymorphism was also associated with IgE expression level. The haplotypes indicated that C-G-A-T and C-G-C-T could increase the risk of AR, and

| Factors          | Level | Control Group | Case Group | \( P \) |
|------------------|-------|---------------|------------|--------|
| Sex (%)          | Female Male | 238 (39.7) | 185 (30.8) | 415 (69.2) | 0.002 |
| Age (mean (SD))  | –     | 49.9 (18.24) | 47.9 (17.62) | 0.055 |
| BMI (mean (SD))  | –     | 22.9 (2.93)  | 23.3 (3.40)  | 0.030 |
| Overweight (%)   | ≤24   | 436 (72.7)  | 388 (64.7)  | 212 (35.3) | 0.003 |
|                  | >24   | 164 (27.3)  | 425 (70.8)  | 175 (29.2) | 0.022 |
| Smoking (%)      | No    | 461 (76.8)  | 459 (76.5)  | 141 (23.5) | 0.206 |
|                  | Yes   | 139 (23.2)  | 388 (64.7)  | 212 (35.3) | 0.001 |
| Drinking (%)     | No    | 439 (73.2)  | 161 (26.8)  | 141 (23.5) | 0.001 |
|                  | Yes   | 131.3(18.7) | 23.3 (3.40) | 461 (76.5) | 0.036 |
| Age group (%)    | ≤60   | 139 (23.2)  | 459 (76.5)  | 141 (23.5) | 0.169 |
|                  | >60   | 403 (67.2)  | 426 (71.0)  | 174 (29.0) | 0.001 |

| Table 2 | Comparisons of General Characteristics Between Case Group and Control Group |

**Table 1** Comparisons of General Characteristics Between Case Group and Control Group
and smoking/drinking for AR risk. There are interactions between rs769178 polymorphism and smoking. The cross-over analysis also indicated that increased the risk in the subgroup of age≤60, overweight.

Table 2 Logistic Regression Analysis of Associations Between Gene Polymorphism and Allergic Rhinitis

| Genotype | Case | Control | OR | 95% CI | P | OR | 95% CI* | P |
|----------|------|---------|----|--------|---|----|---------|---|
| rs1799964 |      |         |    |        |   |    |         |   |
| TT       | 361  | 60.2%   | 397| 66.2%  | 1.00|    | 1.00   |    |
| TC       | 184  | 30.7%   | 155| 25.8%  | 1.31| 1.01| 1.69    | 0.042|
| CC       | 55   | 9.2%    | 48 | 8.0%   | 1.26| 0.83| 1.90    | 0.271|
| TC+CC    | 239  | 39.8%   | 203| 45.9%  | 1.29| 1.02| 1.64    | 0.031|
| TT+TC    | 545  | 90.8%   | 552| 92.0%  | 1.00|    |         |    |
| CC       | 55   | 9.2%    | 48 | 8.0%   | 1.16| 0.77| 1.74    | 0.471|
| T        | 906  | 75.5%   | 949| 79.1%  | 1.00|    |         |    |
| C        | 294  | 24.5%   | 251| 20.9%  | 1.23| 1.01| 1.49    | 0.036|
| rs1800629 |      |         |    |        |   |    |         |   |
| GG       | 535  | 89.2%   | 515| 85.8%  | 1.00|    |         |    |
| GA       | 54   | 9.0%    | 75 | 12.5%  | 0.69| 0.48| 1.00    | 0.051|
| AA       | 11   | 1.8%    | 10 | 1.7%   | 1.06| 0.45| 2.51    | 0.897|
| AA+AA    | 65   | 10.8%   | 85 | 56.7%  | 0.74| 0.52| 1.04    | 0.081|
| GG+GA    | 589  | 98.2%   | 590| 98.3%  | 1.00|    |         |    |
| AA       | 11   | 1.8%    | 10 | 1.7%   | 1.10| 0.46| 2.61    | 0.826|
| G        | 1124 | 93.7%   | 1105| 92.1%  | 1.00|    |         |    |
| A        | 76   | 6.3%    | 95 | 7.9%   | 0.79| 0.58| 1.08    | 0.132|
| rs1800630 |      |         |    |        |   |    |         |   |
| CC       | 418  | 69.7%   | 450| 75.0%  | 1.00|    |         |    |
| CA       | 163  | 27.2%   | 131| 21.8%  | 1.34| 1.03| 1.75    | 0.031|
| AA       | 19   | 3.2%    | 19 | 3.2%   | 1.08| 0.56| 2.06    | 0.824|
| CA+AA    | 182  | 30.3%   | 150| 45.2%  | 1.31| 1.01| 1.68    | 0.039|
| CC+CA    | 581  | 96.8%   | 581| 96.8%  | 1.00|    |         |    |
| AA       | 19   | 3.2%    | 19 | 3.2%   | 1.00| 0.52| 1.91    | 0.999|
| C        | 999  | 83.3%   | 1031| 85.9%  | 1.00|    |         |    |
| A        | 201  | 16.8%   | 169| 14.1%  | 1.23| 0.98| 1.53    | 0.070|
| rs769178 |      |         |    |        |   |    |         |   |
| GG       | 301  | 50.2%   | 393| 65.5%  | 1.00|    |         |    |
| GT       | 252  | 42.0%   | 140| 23.3%  | 2.35| 1.82| 3.03    | <0.001|
| TT       | 47   | 7.8%    | 67 | 11.2%  | 0.92| 0.61| 1.37    | 0.668|
| GT+TT    | 299  | 49.8%   | 207| 40.9%  | 1.89| 1.50| 2.38    | 0.000|
| GG+GT    | 533  | 92.2%   | 533| 88.8%  | 1.00|    |         |    |
| TT       | 47   | 7.8%    | 67 | 11.2%  | 0.68| 0.46| 1.00    | 0.049|
| T        | 854  | 71.2%   | 926| 77.2%  | 1.00|    |         |    |
| G        | 346  | 28.8%   | 274| 22.8%  | 1.37| 1.14| 1.65    | 0.001|

Notes: *Adjusting for age, sex, BMI, smoking, drinking, family history, asthma.

C-G-C-G haplotype decreased the risk of AR. The stratified analyses suggested that the recessive of rs769178 increased the risk in the subgroup of age≤60, overweight and smoking. The cross-over analysis also indicated that there are interactions between rs769178 polymorphism and smoking/drinking for AR risk.

Previous studies also investigated the associations between TNF-α gene and AR risk. Nasiri et al evaluated the association between various single-nucleotide polymorphisms (SNPs) of the TNF and AR risk in a case-control study. They identified two SNPs (rs1800629 and rs361525) were associated with AR risk. Minhas et al explored the genetic associations between TNF-alpha polymorphism G-308A (rs1800629) and AR in patients of Pakistani origin using a case-control study with 153 AR patients and 116 healthy controls. They identified a positive association between TNF-308A allele and AR. Another study also evaluated the effect of TNF-α
gene on AR in two population setting including Greenland and Denmark. No significant associations were found between rhinitis and any SNPs of TNF-α for Inuit residing in either Greenland or Denmark. Our results are completely different from previous studies. Similarly, we did not identify the significant associations between SNPs (rs1799964, rs1800629, rs1800630) and AR. However, a significant association between rs769178 polymorphism

---

**Table 3 Haplotype Analysis of Four SNPs of TNF Gene for the Risk of Allergic Rhinitis**

| Haplotype  | Case(Frequency) | Control(Frequency) | P   | OR [95% CI] |
|------------|-----------------|--------------------|-----|------------|
| C-A-A-G    | 10.00(0.008)    | 10.78(0.009)       | –   | –          |
| C-A-T      | 2.16(0.002)     | 3.04(0.003)        | –   | –          |
| C-A-C-G    | 31.71(0.026)    | 44.09(0.037)       | 0.141 | 0.71 [0.44–1.12] |
| C-A-C-T    | 14.25(0.012)    | 20.94(0.017)       | –   | –          |
| C-G-A-G    | 90.48(0.075)    | 95.40(0.080)       | 0.675 | 0.94 [0.70–1.27] |
| C-G-A-T    | 43.18(0.036)    | 21.49(0.018)       | 0.007 | 2.04 [1.21–3.44] |
| C-G-C-G    | 509.60(0.425)   | 589.46(0.491)      | 0.001 | 0.75 [0.63–0.88] |
| C-G-C-T    | 204.62(0.171)   | 163.79(0.136)      | 0.024 | 1.29 [1.04–1.62] |
| T-A-A-G    | 2.66(0.002)     | 0.12(0.000)        | –   | –          |
| T-A-C-G    | 8.43(0.007)     | 15.23(0.013)       | –   | –          |
| T-A-C-T    | 0.72(0.001)     | 0.80(0.001)        | –   | –          |
| T-G-A-G    | 36.88(0.031)    | 28.41(0.024)       | 0.299 | 1.30 [0.79–2.14] |
| T-G-A-T    | 9.56(0.008)     | 9.75(0.008)        | –   | –          |
| T-G-C-G    | 164.23(0.137)   | 142.50(0.119)      | 0.202 | 1.17 [0.92–1.49] |
| T-G-C-T    | 65.44(0.055)    | 54.19(0.045)       | 0.307 | 1.21 [0.84–1.76] |

---

**Figure 1** Four target SNPs of TNF-α affect the IgE expression level using Kruskal–Wallis test: (A) rs1800630, (B) rs769178, (C) rs1799964, (D) rs1800629. **P<0.01.**
**Table 4** Stratified Analysis Between rs769178 Polymorphisms and Allergic Rhinitis

| SNP          | Case/Control | Heterozygous Model | Homozygous Model | Recessive Model | Dominant Model |
|--------------|--------------|--------------------|------------------|-----------------|---------------|
| **rs2228570** |              |                    |                  |                 |               |
| **Gender**   |              |                    |                  |                 |               |
| **Females**  | 96/162       | 75/51              | 14/25            | 2.48(1.60–3.48) | <0.001        |
| **Males**    | 205/231      | 177/89             | 33/42            | 2.24(1.63–3.08) | <0.001        |
| **Age**      |              |                    |                  |                 |               |
| ≤60          | 213/255      | 179/98             | 34/50            | 1.06(0.63–1.79) | 0.825         |
| >60          | 88/138       | 73/42              | 13/17            | 3.87(2.80–5.36) | <0.001        |
| **Overweight** |            |                    |                  |                 |               |
| Yes          | 114/102      | 85/40              | 13/22            | 1.90(1.20–3.02) | 0.006         |
| No           | 187/291      | 167/100            | 34/45            | 2.60(1.91–3.54) | <0.001        |
| **Smoking**  |              |                    |                  |                 |               |
| Yes          | 91/92        | 74/28              | 10/19            | 2.50(1.49–4.20) | <0.001        |
| No           | 210/301      | 178/112            | 37/48            | 2.30(1.72–3.08) | <0.001        |
| **Drinking** |              |                    |                  |                 |               |
| Yes          | 71/104       | 58/34              | 12/23            | 2.50(1.49–4.20) | <0.001        |
| No           | 230/289      | 194/106            | 35/44            | 2.30(1.72–3.08) | <0.001        |
| **Family history** |        |                    |                  |                 |               |
| Yes          | 109/81       | 87/31              | 18/15            | 2.09(1.26–3.44) | 0.004         |
| No           | 192/312      | 165/109            | 29/52            | 2.46(1.82–3.33) | <0.001        |
| **Asthma**   |              |                    |                  |                 |               |
| Yes          | 104/18       | 98/18              | 18/2             | 2.83(1.08–7.41) | 0.029         |
| No           | 197/375      | 154/134            | 29/65            | 2.19(1.64–2.92) | <0.001        |
Table 5 Interactions Between rs769178 Polymorphisms and Risk Factors for the Risk of Allergic Rhinitis

| G              | E     | Cases(n) | Controls | OR   | 95% CI   | $\chi^2$ | P     |
|---------------|-------|----------|----------|------|----------|----------|-------|
| TT+GT/GG      | Male  |          |          |      |          |          |       |
| – –           |       | 96       | 162      | 62.8%| 1.00     |          |       |
| – +           |       | 205      | 231      | 53.0%| 1.50     | 1.09     | 2.05  |
| + –           |       | 89       | 76       | 46.1%| 1.98     | 1.33     | 2.94  |
| + +           |       | 210      | 131      | 38.4%| 2.71     | 1.94     | 3.78  |
| TT+GT/GG      | Overweight |       |          |      |          |          |       |
| – –           |       | 187      | 291      | 60.9%| 1.00     |          |       |
| – +           |       | 114      | 102      | 47.2%| 1.74     | 1.26     | 2.41  |
| + –           |       | 201      | 145      | 41.9%| 2.16     | 1.53     | 3.04  |
| + +           |       | 98       | 62       | 38.8%| 2.46     | 1.70     | 3.55  |
| TT+GT/GG      | Smoking |        |          |      |          |          |       |
| – –           |       | 210      | 301      | 58.9%| 1.00     |          |       |
| – +           |       | 91       | 92       | 50.3%| 1.42     | 1.01     | 1.99  |
| + –           |       | 215      | 160      | 42.7%| 1.93     | 1.35     | 2.75  |
| + +           |       | 84       | 47       | 35.9%| 2.56     | 1.72     | 3.81  |
| TT+GT/GG      | Family history |        |          |      |          |          |       |
| – –           |       | 192      | 312      | 61.9%| 1.00     |          |       |
| – +           |       | 109      | 81       | 42.6%| 2.19     | 1.55     | 3.069 |
| + –           |       | 194      | 158      | 44.9%| 2.00     | 1.39     | 2.849 |
| + +           |       | 105      | 49       | 31.8%| 3.48     | 2.37     | 5.111 |
| TT+GT/GG      | Asthma |        |          |      |          |          |       |
| – –           |       | 197      | 375      | 65.6%| 1.00     |          |       |
| – +           |       | 104      | 18       | 14.8%| 11.00    | 6.48     | 18.67 |
| + –           |       | 183      | 199      | 52.1%| 1.75     | 1.34     | 2.28  |
| + +           |       | 116      | 8        | 6.5% | 27.60    | 13.21    | 57.67 |

and AR risk. We also identified potential interactions between gene and environment factors and possible haplotypes associated with AR. As far as we know, this is the first study that reports the significant association between rs769178 polymorphism and AR. Besides, the present study also included a large sample size with 600 AR patients and 600 healthy controls.

At present, the pathogenesis of allergic rhinitis with IgE regulated type I allergy as the core link is the most convincing and well-recognized mechanism. This process is as follows: Firstly, with the participation of HLA, antigen-presenting cell (APC) was delivered to T cells, and the differentiation of T cells was biased, and the Th2 cytokine products such as TNF, IL-3, IL-4, IL-5, etc., were significantly increased. They play an important role in the occurrence and development of AR. HLA is a highly polymorphic gene group on human chromosome 6, which plays an important role in immune system, especially in immune recognition and genetic regulation. The gene of TNF is located in the MHCIII locus, and its first intron contains gene polymorphism caused by single base point mutation. The most common is that the guanine nucleotide G at the downstream site of transcription start site −308 is replaced by adenine nucleotide A, which changes the recognition sequence of restriction enzyme NCOI. The gene in which guanine nucleotide G exists by NCOI. The gene in which guanine nucleotide G exists is called TNF-308. Due to the important biological role of TNF and the special position of the gene, the relationship between TNF gene polymorphism and disease has been widely paid attention. TNF has been found to be involved in immune regulation and inflammation.

Although TNF-α is primarily involved in Th1-mediated inflammation, it has recently been shown to be necessary for the production of Th2-type cytokines and
their movement to the site of inflammation. It is produced and released mainly by macrophages and mast cells in the immune response through IgE-dependent mechanisms.\textsuperscript{28} Okano et al found that IL-4 is necessary for the production of Th2 cell-related antibodies, especially IgE antibodies, and TNF-α can enhance the induction of IL-4 on IgE production.\textsuperscript{29} The migration of eosinophils mainly depends on cytokines, chemo cytokines and adhesion molecules, which play an important role in AR and IgE mediated allergic reactions. TNF-α can induce the expression of adhesion molecules in epithelial cells, promote the infiltration and activation of inflammatory cells, and stimulate the synthesis of inflammatory mediators such as platelet activating factor, prostaglandin, leukotriene, etc. TNF-α can increase the production and release of IL-5 and IL-8. IL-5 can promote eosinophils to enter inflammatory sites, and eosinophils and mast cells play a central role in the pathogenesis of AR, while TNF-α can increase the expression of eosinophils, mast cells and T cells.\textsuperscript{30,31} TNF-α can also induce the synthesis of vasodilator, which is derived from endothelial cells, leading to vasodilation.\textsuperscript{15} The levels of TNF-α and adhesion molecules in serum of patients with AR and asthma were significantly higher than those in normal population, and the levels of TNF-α and adhesion molecules in patients with asthma were also significantly higher than those in remission stage, and the increased degree was positively correlated with the severity of the disease.\textsuperscript{32,33} Our study also found that TNF-α gene polymorphism was related to IgE expression level. This may be the mechanism of TNF-α gene regulating the occurrence of AR.

There are several study limitations. Firstly, this is a case-control study, and the cause-effect degree is very limited. Secondly, the present study is performed in the Chinese population, results should be cautious when being applied in other population setting. Third, the gene-gene interaction should be considered in the future. Finally, the present study did not explore the molecular mechanism. Anyway, this is an epidemiology study, which means the results is still far from the clinical practice. But, Correct recognition of the combined effects of the risk factors is of important significance for the primary prevention and making up the public health policies. If anything for clinical practice, that would be that the clinicians can tell patients not to smoke or drink or other behaviors that may aggravating illness. The clinicals also can take some measure to treat the AR.\textsuperscript{34,35}

**Conclusion**

In conclusion, the rs769178 locus polymorph of TNF-α was associated with an increased risk of AR. The haplotypes (C-G-A-T and C-G-C-T) of TNF-α can significantly increase the risk of AR, and C-G-C-G haplotype decreased the risk of AR. There are interactions between rs769178 polymorphism and smoking/drinking for AR risk. Further research is required for specific molecular mechanisms.

**Data Sharing Statement**

Please contact the correspondence author for original data.

**Funding**

There is no funding to report.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**

1. Tan R, Cvetkovski B, Kritikos V, et al. Identifying the hidden burden of allergic rhinitis (AR) in community pharmacy: a global phenomenon. *Asthma Res Pract*. 2017;3:8. doi:10.1186/s40733-017-0036-z
2. Incorvaia C, Barbera S, Makri E, Mauro M. Allergic rhinitis: pathology of general interest. *Recenti Prog Med*. 2013;104(3):116–119.
3. Meltzer EO. Allergic rhinitis: burden of illness, quality of life, comorbidities, and control. *Immunol Allergy Clin North Am*. 2016;36(2):235–248. doi:10.1016/j.iac.2015.12.002
4. Schoenwetter WF, Dupclay LJ, Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin*. 2004;20(3):305–317. doi:10.1185/030079903125003053
5. Zhou B, Xu G. [The mechanism and treatment of nasal obstruction in allergic rhinitis]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2019;33(8):780–785. Chinese.
6. Ho CL, Wu WF. Risk factor analysis of allergic rhinitis in 6–8 year-old children in Taipei. *PLoS One*. 2021;16(4):e249572. doi:10.1371/journal.pone.0249572
7. Ahn Y, An SY, Won TB, et al. Nasal polyps: an independent risk factor for bronchial hyperresponsiveness in patients with allergic rhinitis. *Am J Rhinol Allergy*. 2010;24(5):359–363. doi:10.2500/ajra.2010.24.3502
8. Brozek JL, Bouquet J, Baena-Cagnani CE, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126(3):466–476. doi:10.1016/j.jaci.2010.06.047
9. Li ZP, Yin LL, Wang H, Liu LS. Association between promoter polymorphisms of interleukin-4 gene and allergic rhinitis risk: a meta-analysis. *J Huazhong Univ Sci Technolog Med Sci*. 2014;34(3):306–313. doi:10.1007/s11596-014-1275-3
10. Wang H, Song J, Yao Y, et al. Angiotensin-converting enzyme II expression and its implication in the association between COVID-19 and allergic rhinitis. *Allergy*. 2021;76(3):906–910. doi:10.1111/all.14569
11. Davila I, Mullol J, Ferrer M, et al. Genetic aspects of allergic rhinitis. *J Invest Allergol Clin Immunol*. 2009;19(Suppl 1):25–31.
12. Saha P, Smith A. TNF-α (tumor necrosis factor-α). *Arterioscler Thromb Vasc Biol*. 2018;38(11):2542–2543. doi:10.1161/ATVBAHA.118.311660
24. T amari M, T anaka S, Hirota T. Genome-wide association studies of tumor necrosis factor-alpha and its receptors in diesel exhaust particle-induced pulmonary inflammation. *Sci Rep*. 2017;7(1):11508. doi:10.1038/s41598-017-11991-7

25. Senechal H, Geny S, Desvaux FX, et al. Genetics and specific immune response in allergy to birch pollen and food: evidence of a strong, positive association between atopy and the HLA class II allele HLA-DR7. *J Allergy Clin Immunol*. 1999;104(2 Pt 1):395–401. doi:10.1016/S0091-6749(99)70384-2

26. Falvo JV, Tsytyskova AV, Goldberg AE. Transcriptional control of the TNF gene. *Curr Dir Autoimmun*. 2010;11:27–60.

27. Zhang Y, Zhang F, Lin H, et al. Nucleotide polymorphism of the TNF gene cluster in six Chinese populations. *J Hum Genet*. 2010;55(6):350–357. doi:10.1038/jhg.2010.33

28. Gomez D, Correa PA, Gomez LM, Cadena J, Molina JF, Anaya JM. Th1/Th2 cytokines in patients with systemic lupus erythematosus: is tumor necrosis factor alpha protective? *Semin Arthritis Rheum*. 2004;33(6):404–413. doi:10.1016/j.semarthrit.2003.11.002

29. Okano M, Satoskar AR, Abe M, et al. Interleukin-4-independent production of Th2 cytokines by nasal lymphocytes and nasal eosinophilia in murine allergic rhinitis. *Allergy*. 2000;55(8):723–731. doi:10.1034/j.1398-9995.2000.00429.x

30. Hamid QA, Minshall EM. Molecular pathology of allergic disease: I: lower airway disease. *J Allergy Clin Immunol*. 2000;105(1 Pt 1):20–36. doi:10.1067/mai.2003.1554

31. Christodouloupolus P, Cameron L, Durham S, Hamid Q. Molecular pathology of allergic disease. II: upper airway disease. *J Allergy Clin Immunol*. 2000;105(2 Pt 1):211–223. doi:10.1067/mai.2003.1554

32. Gentile DA, Doyle WJ, Zeevi A, Howe-Adams J, Treeki J, Skoner DP. Association between TNF-α and TGF-β genotypes in infants and parental history of allergic rhinitis and asthma. *Hum Immunol*. 2004;65(4):347–351. doi:10.1016/j.humimm.2004.01.014

33. Krasznai M, Szaniszlo K, Kraxner H, et al. Association of TLR-4 and TNF-alpha polymorphisms with clinical symptoms and cytokine levels in patients with allergic rhinitis. *Eur Arch Otorhinolaryngol*. 2011;268(4):561–567. doi:10.1007/s00405-010-1424-7

34. Zhang H, Li H, Zhang Q. Comprehensive intervention in treatment of allergic rhinitis patients with sublingual drug administration. *Nurs Res*. 2016;35(8):960–961.

35. Li H, Zhang Q, Zhang X, Zhang H. Nursing intervention of children with allergic rhinitis treated by immunotherapy. *J Nurs Sci*. 2016;31(6):28–30.