

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

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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 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.

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

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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 shown 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 *in 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 ≥ 0.35 kU_A/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 < 200 kU/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 ($BMI = \text{weight}/(\text{height})^2$ kg/m², $BMI < 24$ for normal, and $BMI \geq 24$ 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

allele frequency >0.05 ; (2) location: promoter, exon or 3'-UTR; (3) The linkage disequilibrium coefficient $r^2 > 0.8$ and (4) these SNPs have been studied in other diseases, but not in AR.

DNA Extraction and Genotyping

The peripheral venous blood was extracted and stored in the anticoagulant vacuum sampling vessel and placed in the ultra-low temperature refrigerator for prepare. DNA was extracted using the TIANamp Blood DNA kit (Tiagen 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 by 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'-AGGCAATAGTTTGGAGGGCCAT -3', R: 5'-TCCTCCCTGCTCCGATTCCG -3'), rs1800630 (F: 5'-GGGCTA TGGAAGTCGAGTATGG-3', R: CCCTCTACATGGCCCTGTCT-3'), rs1799964 (F: GGAAGCAAAGGAGAAGCTGAGAAGA-3', R: 5-GAAGGAAAAGTCAGGGTC TGGAGGG -3'), rs769178 (F: 5-ACTGGGAGCCCCACTGAGTT -3', R: 5-GGAA 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 in dominant model (TC +CC vs TT), additive model (TT vs TC 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, asthma. The multivariate logistic regressions (AR or not AR as i) were performed in models (TC+CC vs TT,

CC vs TT+TC, CC vs TT, TC vs TT) by adjusting the following variables: age, sex, BMI, smoking, drinking, family history, asthma. The Bonferroni correction is used for multiple comparisons of SNPs (corrected $\alpha' = \alpha/n$, 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 haploid genotypes. Stratified analyses are 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 rs1799964 have

Table 1 Comparisons of General Characteristics Between Case Group and Control Group

Factors	Level	Control Group	Case Group	P
Sex (%)	Female	238 (39.7)	185 (30.8)	0.002
	Male	362 (60.3)	415 (69.2)	
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)	0.003
	>24	164 (27.3)	212 (35.3)	
Smoking (%)	No	461 (76.8)	425 (70.8)	0.022
	Yes	139 (23.2)	175 (29.2)	
Drinking (%)	No	439 (73.2)	459 (76.5)	0.206
	Yes	161 (26.8)	141 (23.5)	
Family history (%)	No	470 (78.3)	386 (64.3)	<0.001
	Yes	130 (21.7)	214 (35.7)	
Asthma (%)	No	574 (95.7)	380 (63.3)	<0.001
	Yes	26 (4.3)	220 (36.7)	
Age group (%)	≤60	403 (67.2)	426 (71.0)	0.169
	>60	197 (32.8)	174 (29.0)	
IgE (mean (SD))	–	33.3(12.7)	131.3(18.7)	<0.001

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

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

Genotype	Case		Control		OR	95% CI		P	OR	95% CI*		P
	n	%	n	%								
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	1.26	0.94	1.68	0.119
CC	55	9.2%	48	8.0%	1.26	0.83	1.90	0.271	1.51	0.96	2.38	0.077
TC+CC	239	39.8%	203	45.9%	1.29	1.02	1.64	0.031	1.31	1.01	1.71	0.042
TT+TC	545	90.8%	552	92.0%	1.00				1.00			
CC	55	9.2%	48	8.0%	1.16	0.77	1.74	0.471	1.41	0.90	2.20	0.134
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				1.00			
GA	54	9.0%	75	12.5%	0.69	0.48	1.00	0.051	0.67	0.44	1.02	0.061
AA	11	1.8%	10	1.7%	1.06	0.45	2.51	0.897	1.40	0.56	3.54	0.474
GA+AA	65	10.8%	85	56.7%	0.74	0.52	1.04	0.081	0.75	0.51	1.10	0.144
GG+GA	589	98.2%	590	98.3%	1.00				1.00			
AA	11	1.8%	10	1.7%	1.10	0.46	2.61	0.826	1.46	0.58	3.69	0.422
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				1.00			
CA	163	27.2%	131	21.8%	1.34	1.03	1.75	0.031	1.35	1.01	1.82	0.045
AA	19	3.2%	19	3.2%	1.08	0.56	2.06	0.824	1.32	0.66	2.66	0.437
CA+AA	182	30.3%	150	45.2%	1.31	1.01	1.68	0.039	1.35	1.02	1.79	0.038
CC+CA	581	96.8%	581	96.8%	1.00				1.00			
AA	19	3.2%	19	3.2%	1.00	0.52	1.91	0.999	1.22	0.61	2.45	0.574
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				1.00			
GT	252	42.0%	140	23.3%	2.35	1.82	3.03	<0.001	2.17	1.63	2.87	0.000
TT	47	7.8%	67	11.2%	0.92	0.61	1.37	0.668	0.89	0.57	1.41	0.625
GT+TT	299	49.8%	207	40.9%	1.89	1.50	2.38	0.000	1.76	1.36	2.28	<0.001
GG+GT	553	92.2%	533	88.8%	1.00				1.00			
TT	47	7.8%	67	11.2%	0.68	0.46	1.00	0.049	0.68	0.44	1.06	0.087
G	854	71.2%	926	77.2%	1.00							
T	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.²¹ 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.¹⁹ Another study also evaluated the effect of TNF- α

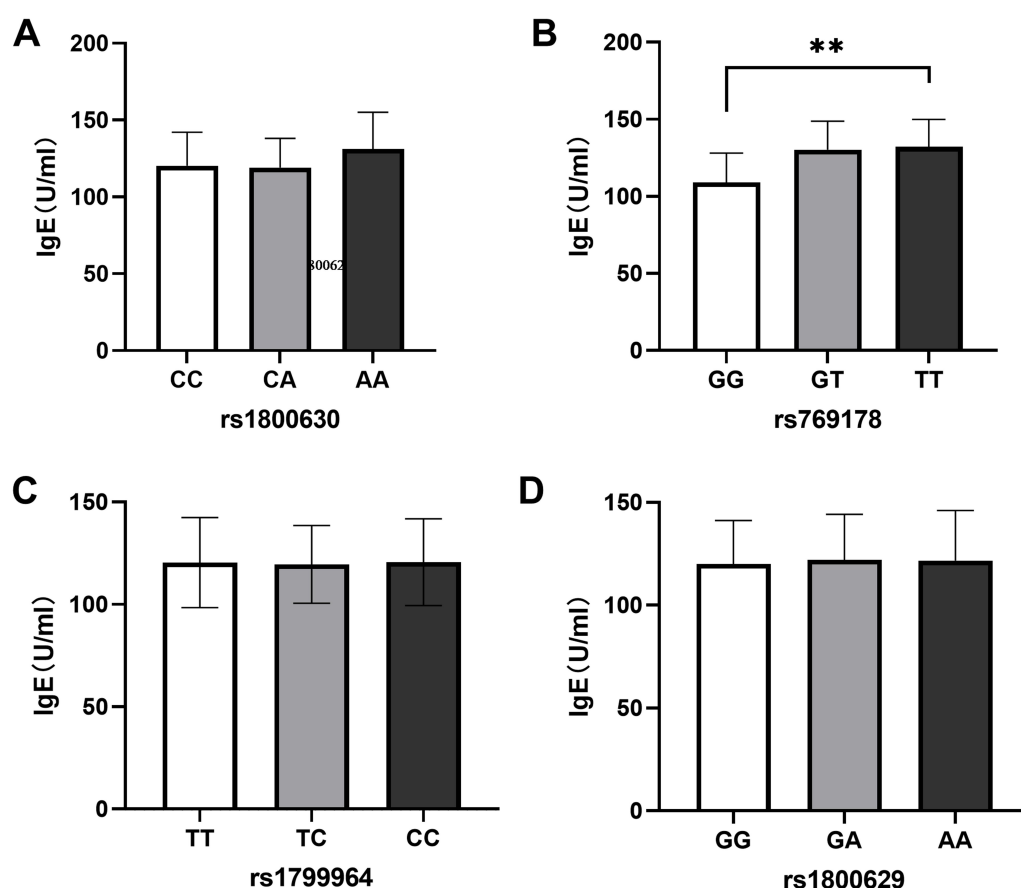


Figure 1 Four target SNPs of TNF- α affect the IgE expression level using Kruskal–Wallis test: (A) rs1800630, (B) 769178, (C) rs1799964, (D) rs1800629; ** $P < 0.01$.

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.²³ 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-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]

Table 4 Stratified Analysis Between rs769178 Polymorphisms and Allergic Rhinitis

SNP	Case/Control			Heterozygous Model		Homozygous Model		Recessive Model		Dominant Model	
	GG	GT	TT	GT vs GG	P	TT vs GG	P	TT vs GT+GG	P	TT+GT vs GG	P
rs2228570											
Gender											
Females	96/162	75/51	14/25	2.48(1.60–3.48)	<0.001	0.95(0.47–1.91)	0.874	0.70(0.35–1.38)	0.300	1.98(1.33–2.94)	0.001
Males	205/231	177/89	33/42	2.24(1.63–3.08)	<0.001	0.89(0.54–1.45)	0.628	0.66(0.41–1.06)	0.086	1.81(1.35–2.41)	<0.001
Age											
≤60	213/255	179/98	34/50	1.06(0.63–1.79)	0.825	0.81(0.51–1.31)	0.393	0.61(0.39–0.97)	0.035	1.72(1.31–2.27)	<0.001
>60	88/138	73/42	13/17	3.87(2.80–5.36)	<0.001	1.20(0.56–2.59)	0.644	0.85(0.40–1.81)	0.683	2.29(1.49–3.50)	<0.001
Overweight											
Yes	114/102	85/40	13/22	1.90(1.20–3.02)	0.006	0.53(0.25–1.10)	0.086	0.42(0.21–0.87)	0.016	1.41(0.93–2.14)	0.101
No	187/291	167/100	34/45	2.60(1.91–3.54)	<0.001	1.18(0.73–1.90)	0.510	0.83(0.52–1.33)	0.448	2.16(1.63–2.86)	<0.001
Smoking											
Yes	91/92	74/28	10/19	2.50(1.49–4.20)	<0.001	0.53(0.23–1.21)	0.127	0.38(0.17–0.85)	0.016	1.81(1.14–2.86)	0.011
No	210/301	178/112	37/48	2.30(1.72–3.08)	<0.001	1.10(0.69–1.76)	0.673	0.82(0.52–1.29)	0.389	1.93(1.47–2.52)	<0.001
Drinking											
Yes	71/104	58/34	12/23	2.50(1.49–4.20)	<0.001	0.76(0.36–1.63)	0.487	0.56(0.27–1.17)	0.118	1.80(1.13–2.85)	0.012
No	230/289	194/106	35/44	2.30(1.72–3.08)	<0.001	1.00(0.62–1.61)	0.998	0.74(0.47–1.18)	0.205	1.92(1.47–2.51)	<0.001
Family history											
Yes	109/81	87/31	18/15	2.09(1.26–3.44)	0.004	0.89(0.42–1.87)	0.762	0.69(0.33–1.41)	0.305	1.70(1.08–2.66)	0.021
No	192/312	165/109	29/52	2.46(1.82–3.33)	<0.001	0.91(0.56–1.48)	0.693	0.66(0.41–1.06)	0.082	1.96(1.49–2.58)	<0.001
Asthma											
Yes	104/18	98/18	18/2	2.83(1.08–7.41)	0.029	1.56(0.33–7.30)	0.571	1.07(0.23–4.89)	0.931	2.51(1.06–6.01)	0.034
No	197/375	154/134	29/65	2.19(1.64–2.92)	<0.001	0.85(0.53–1.36)	0.496	0.65(0.41–1.02)	0.061	1.75(1.34–2.28)	<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		χ^2	P
TT+GT/GG	Male									
–	–	96	37.2%	162	62.8%	1.00				
–	+	205	47.0%	231	53.0%	1.50	1.09	2.05	6.350	0.012
+	–	89	53.9%	76	46.1%	1.98	1.33	2.94	11.447	0.001
+	+	210	61.6%	131	38.4%	2.71	1.94	3.78	34.920	<0.001
TT+GT/GG	Overweight									
–	–	187	39.1%	291	60.9%	1.00				
–	+	114	52.8%	102	47.2%	1.74	1.26	2.41	11.297	0.001
+	–	201	58.1%	145	41.9%	2.16	1.53	3.04	28.993	<0.001
+	+	98	61.3%	62	38.8%	2.46	1.70	3.55	23.750	<0.001
TT+GT/GG	Smoking									
–	–	210	41.1%	301	58.9%	1.00				
–	+	91	49.7%	92	50.3%	1.42	1.01	1.99	4.087	0.043
+	–	215	57.3%	160	42.7%	1.93	1.35	2.75	22.847	<0.001
+	+	84	64.1%	47	35.9%	2.56	1.72	3.81	22.271	<0.001
TT+GT/GG	Family history									
–	–	192	38.1%	312	61.9%	1.00				
–	+	109	57.4%	81	42.6%	2.19	1.558	3.069	20.869	<0.001
+	–	194	55.1%	158	44.9%	2.00	1.398	2.849	24.244	<0.001
+	+	105	68.2%	49	31.8%	3.48	2.372	5.111	43.118	<0.001
TT+GT/GG	Asthma									
–	–	197	34.4%	375	65.6%	1.00				
–	+	104	85.2%	18	14.8%	11.00	6.48	18.67	105.676	<0.001
+	–	183	47.9%	199	52.1%	1.75	1.34	2.28	17.328	<0.001
+	+	116	93.5%	8	6.5%	27.60	13.21	57.67	143.871	<0.001

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.²⁴ 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.²⁵ 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, so that the sequence replaced by adenine nucleotide A cannot be recognized and cut off by NCOI. The gene in which guanine nucleotide G exists is called TNF-308.²⁶ 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.²⁷ 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.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.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.^{30,31} TNF- α can also induce the synthesis of vasodilator, which is derived from endothelial cells, leading to vasodilation.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.^{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.^{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.

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Disclosure

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