ORIGINAL RESEARCH

The Assessment of *TLR1* Gene Polymorphism Association with the Risk of Allergic Rhinitis in the Chinese Han Population from Northern China

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Background: Environmental factors and genetic predisposition can influence the occurrence and development of AR. Toll-like receptor 1 (TLR1) belongs to the TLR receptor family, which plays a fundamental role in the activation of innate immunity. This study aimed to explore the association between *TLR1* genetic loci and AR susceptibility in the Han Chinese from northern China.

Methods: Genotyping of three SNPs in the *TLR1* has proceeded using the Agena MassARRAY platform. Odds ratio (OR) and 95% confidence interval (CI) were used to assess the correlation between candidate SNPs and AR susceptibility. Using FPRP (false-positive report probability analysis) to detect whether the positive results are noteworthy findings. The SNP-SNP interactions were detected by multifactor dimensionality reduction (MDR).

Results: *TLR1*-rs72493538 (Allele "G": OR=0.77, $p = 0.034$) and -rs76600635 (Allele "G": OR=0.75, $p = 0.024$) were associated with reducing the risk of AR among Han Chinese in northern China. In addition, we found evidence that *TLR1*-rs72493538 (males, participants with aging > 43 years, or coming from the wind-blown sand region) and -rs76600635 (males, participants with BMI ≤ 24 kg/m^2, or coming from the wind-blown sand region) were associated with AR risk in stratified analyses. FPRP showed that all positive results are noteworthy findings. MDR analysis showed that a two-loci genetic model composed of rs72493538 and rs76600635 can be chosen as the best genetic model to predict the risk of AR.

Conclusion: *TLR1*-rs72493538 and -rs76600635 have a close association with reducing the risk of AR.

Keywords: allergic rhinitis, *TLR1*, susceptibility, case-control study

Introduction

Allergic rhinitis (AR) is a chronic non-infectious disease characterized by occasional nasal congestion, nasal itching, sneezing, and runny nose, which can occur at all stages.[1] Epidemiological surveys in recent years have shown that the incidence of AR in the United States is 10%-20%, and the global prevalence is about 10%-25%.[2] AR not only triggers a significant decline in the quality of life but also imposes a heavy social and economic burden on individuals, families, communities, and countries.[3] Therefore, it is necessary to investigate the etiology of AR.

Previous studies have demonstrated that environmental factors (air pollutants, aeroallergens) and genetic predisposition promote the occurrence and development of AR.[4] The heritability of AR has been estimated to be over 0.65, indicating a strong genetic component in AR.[5] Moreover, Noguchi et al have proposed that when both parents have allergies, the prevalence of AR in children is as high as 75%; when one parent has allergies, the prevalence is 50%.[6] In addition, single nucleotide polymorphisms (SNPs) are important genetic factors for AR.[7,8] Numerous investigations have indicated that SNPs in *ADAM33, IL-18, FOXP3*, and *IL13* have been implicated in susceptibility to AR.[9–11]

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Toll-like receptor 1 (*TLR1*) belongs to the *TLR* receptor family which plays a fundamental role in the activation of innate immunity. It has been reported that *TLRs* are involved in the pathogenesis of AR.[12,13] Renkonen et al have found the protein expression levels of *TLR1* and *TLR6* are down-regulated in the allergic group after allergen stimulation.[14] Another study has also revealed that the expression levels of *TLR2* and *TLR4* are increased in patients with AR compared with controls.[15] Aoi et al have indicated that *TLR2* signaling participates in the development of AR through regulating OK-432-induced anti-T helper 2 (Th2) immunity.[16] Moreover, the allele *TLR4*-rs1927911 contributes to a higher risk of AR in children.[17] In general, these findings emphasize the critical impact of *TLRs* on AR development. However, there are relatively few studies on the correlation between *TLR1* and allergic rhinitis. Based on the above studies, it is necessary to further explore the *TLR1* polymorphism related to AR susceptibility, which will provide a theoretical basis for the study of the mechanism of *TLR1* in the AR and then further supplement the mechanism research of TLR family genes in allergic rhinitis.

The purpose of this study is to explore the relationship between TLR1 polymorphism and AR risk, which is helpful to further understand the pathogenesis of AR at the genetic level. This study will provide a new research direction and theoretical basis for the early prevention and treatment of AR and the development of individualized treatment programs.

Materials and Methods

Study Population

A total of 982 patients with AR and 984 healthy controls were recruited from Daliuta Town, Jinjie Town, Langanbao Town, Hejiachuan Town, and central urban area (including Linzhou Street and Yingbin Road Street) of Shenmu city, Shaanxi province, China. AR patients were diagnosed based on clinical features (sneezing, nasal congestion, nasal itching, and runny nose), clinical examination, and serum-specific IgE detection. The inclusion criteria for patients were positive history of AR, positive physical examination, and positive serum IgE. Patients with possible chronic systemic disorder, atopic or allergic disease, family history of asthma, airway diseases, malignant disease, auto-immune disease, any diffuse dermatitis, or respiratory tract infection before recruitment were excluded from the study. The inclusion criteria for controls were no history of AR and no treatment with antihistamine drugs.

The Ethics Committee of Shenmu Hospital approved the study. The experimental procedures of this study were in accordance with Declaration of Helsinki and informed consent was signed by all subjects.

Selection of Candidate SNPs and Genotyping

Through an online tool, we found that the physical position of TLR1 was on Chromosome 4: 38,790,677–38,856,817 (e!Ensmbl Human GRCh38.p13: https://asia.ensembl.org/Homo_sapiens/Gene/Summary?db=core;g=ENSG00000174125;r=4:38790677-38856817). There were 33,914 variants in TLR1. In order to narrow the research scope, we conducted the following screening steps: First, we used "Ensembl Tools: VCF to PED conversion window" to download *TLR1* gene variants files (CHB and CHS populations). Then, putting the above files into Haploview software to further narrow the scope of the study after setting specific conditions (MAF> 0.05, Min Genotype > 75%, Tagger r2 > 0.8, and HWE> 0.01). Finally, rs72493538, rs76600635, and rs17616434 of *TLR1* were randomly selected as the candidate genetic variants for this study.

We collected venous blood from each subject and stored it in EDTA-treated tubes. Genomic DNA was isolated by an extraction kit (GoldMag Co. Ltd, Xi'an, China) and its concentration was quantified by NanoDrop 2000. Genotyping of SNPs was proceeded using the Agena MassARRAY platform (Agena Bioscience, USA). All primers were designed through the MassARRAY platform (https://support.agenabio.com/s/online-tools). All primer sequences can be found in Supplemental Table 1. Agena Typer 4.0 software was utilized to analyze and manage data.

Data Analysis

We performed Student's *t*-test to compare differences in age and BMI between the case and control groups. In addition, the gender distribution and *p*-values for Hardy-Weinberg equilibrium (HWE) were assessed by χ^2 test. Odds ratio (OR) and 95% confidence interval (CI) were used to assess the correlation between SNPs and AR susceptibility. Then, performing false-positive report probability analysis (FPRP) to detect whether the positive results obtained in this study

are noteworthy findings.[18] The SNP-SNP interactions were detected by multifactor dimensionality reduction (MDR). A *p*-value of 0.05 or less was considered statistically significant.

Results
Characteristics of Subjects
There were 982 AR patients (357 males and 625 females) and 984 healthy controls (344 males and 640 females) in this study. The mean ages of the case group and the control group were 42.43 ± 10.39 years and 43.62 ± 8.05 years, respectively (Table 1).

Rs72493538, rs76600635, and rs17616434 in *TLR1* were selected as candidate SNPs. The HWE *P*-values of these SNPs were all greater than 0.05 (Table 2).

AR Risk Assessment
The results demonstrated (Table 3) that Allele "G" (OR=0.77; $p = 0.034$) and heterozygous genotype "AG" (OR=0.70; $p = 0.011$) of *TLR1*-rs72493538 were protective genetic factors of susceptibility to AR. And *TLR1*-rs72493538 has a significant association with decreasing risk of AR under dominant ($p = 0.019$), and additive ($p = 0.044$) genetic models. Similarly, Allele "G" (OR=0.75; $p = 0.024$) and heterozygous genotype "AG" (OR=0.71; $p = 0.014$) of *TLR1*-rs76600635 were protective genetic factors of susceptibility to AR. And *TLR1*-rs76600635 has a significant association with decreasing risk of AR under dominant ($p = 0.017$), and additive ($p = 0.028$) genetic models. No evidence has been found that *TLR1*-rs17616434 was associated with susceptibility to AR in overall analysis.

Next, we conducted a stratified analysis based on gender, age, BMI, and region. Figure 1 showed the positive results obtained in stratified analysis. *TLR1*-rs72493538 had significant associations with susceptibility of AR in males (Allele:

Table 1 Characteristics of the AR Patients and Healthy Controls

Variables	Cases (n = 982)	Control (n = 984)
Age (mean ± SD, years)	42.43 ± 10.39	43.62 ± 8.05
> 43	486(49.5%)	561(57.0%)
≤ 43	496(50.5%)	423(43.0%)
Gender		
Male	357(36.4%)	344(35.0%)
Female	625(63.6%)	640(65.0%)
BMI (kg/m^2)	24.78 ± 3.61	24.87 ± 3.66
> 24	495(50.4%)	520(52.8%)
≤ 24	487(49.6%)	464(47.2%)
Region		
Wind beach region	245(24.9%)	270(27.4%)
Loess hilly region	737(75.1%)	714(72.6%)

Abbreviations: SD, standard deviation; AR, allergic rhinitis; BMI, body mass index.

Table 2 Basic Information of the SNPs in *TLR1* Gene

SNP	Gene	Chromosome	Allele (minor/major)	MAF		HWE	HaploReg
				Case	Control	P	
rs72493538	*TLR1*	4p14	A/G	0.061	0.078	0.507	SiPhy cons; Enhancer histone marks
rs76600635	*TLR1*	4p14	G/A	0.059	0.077	0.650	Enhancer histone marks; Motifs changed
rs17616434	*TLR1*	4p14	T/C	0.365	0.350	0.079	Enhancer histone marks; Motifs changed; NHGRI/ EBI GWAS hits; Selected eQTL hits

Note: *P* values were calculated by χ^2 test.
Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Table 3 Associations Between *TLR1* Polymorphisms and AR Susceptibility

SNP	Model	Genotype	Control	Case	OR (95% CI)	*p*-value
rs72493538	Allele	A	1812 (96.2%)	1844 (93.9%)	1.00	
		G	154 (3.8%)	120 (6.1%)	0.77 (0.60–0.98)	**0.034**
	Codominant	G/G	833 (84.7%)	869 (88.5%)	1.00	
		A/G	146 (14.8%)	106 (10.8%)	0.70 (0.54–0.92)	**0.011**
		A/A	4 (0.4%)	7 (0.7%)	1.67 (0.48–5.74)	0.418
	Dominant	G/G	833 (84.7%)	869 (88.5%)	1.00	
		A/G-A/A	150 (15.3%)	113 (11.5%)	0.73 (0.56–0.95)	**0.019**
	Recessive	G/G-A/G	979 (99.6%)	975 (99.3%)	1.00	
		A/A	4 (0.4%)	7 (0.7%)	1.75 (0.51–6.02)	0.375
	Additive	—	—	—	0.78 (0.61–0.99)	**0.044**
rs76600635	Allele	A	1815 (92.3%)	1845 (94.1%)	1.00	
		G	151 (7.7%)	115 (5.9%)	0.75 (0.58–0.96)	**0.024**
	Codominant	A/A	836 (85%)	870 (88.8%)	1.00	
		A/G	143 (14.6%)	105 (10.7%)	0.71 (0.54–0.93)	**0.014**
		G/G	4 (0.4%)	5 (0.5%)	1.17 (0.31–4.36)	0.821
	Dominant	A/A	836 (85%)	870 (88.8%)	1.00	
		A/G-G/G	147 (14.9%)	110 (11.2%)	0.72 (0.56–0.94)	**0.017**
	Recessive	A/A-A/G	979 (99.6%)	975 (99.5%)	1.00	
		G/G	4 (0.4%)	5 (0.5%)	1.22 (0.33–4.56)	0.771
	Additive	—	—	—	0.75 (0.58–0.97)	**0.028**
rs17616434	Allele	C	1274 (65.0%)	1246 (63.5%)	1.00	
		T	686 (35%)	716 (36.5%)	1.07 (0.94–1.22)	0.329
	Codominant	C/C	401 (40.9%)	401 (40.9%)	1.00	
		C/T	472 (48.2%)	444 (45.3%)	0.93 (0.77–1.13)	0.474
		T/T	107 (10.9%)	136 (13.9%)	1.26 (0.95–1.69)	0.113
	Dominant	C/C	401 (40.9%)	401 (40.9%)	1.00	
		C/T-T/T	579 (59.1%)	580 (59.1%)	0.99 (0.83–1.19)	0.946
	Recessive	C/C-C/T	873 (89.1%)	845 (86.1%)	1.00	
		T/T	107 (10.9%)	136 (13.9%)	1.31 (1.00–1.72)	0.050
	Additive	—	—	—	1.06 (0.93–1.21)	0.362

Notes: *p* values were calculated by χ^2 test after adjustment for age, gender, and BMI. Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

OR = 0.34, $p < 0.0001$; Codominant: OR = 0.30, $p < 0.0001$; Dominant: OR = 0.31, $p < 0.0001$; Additive: OR = 0.34, $p < 0.0001$), participants with aging > 43 years old (Codominant: OR = 0.66, $p = 0.030$; Dominant: OR = 0.67, $p = 0.032$; Additive: OR = 0.69, $p = 0.039$), or coming from wind beach region (Allele: OR = 0.57, $p = 0.038$). Similarly, *TLR1*-rs76600635 was significant associated with susceptibility of AR in males (Allele: OR = 0.41, $p = 0.001$; Codominant: OR = 0.40, $p = 0.001$; Dominant: OR = 0.40, $p = 0.001$; Additive: OR = 0.42, $p = 0.001$), participants with BMI ≤ 24 kg/m^2 (Allele: OR = 0.66, $p = 0.027$; Codominant: OR = 0.65, $p = 0.031$; Dominant: OR = 0.64, $p = 0.025$; Additive: OR = 0.65, $p = 0.024$), or coming from wind beach region (Allele: OR = 0.52, $p = 0.048$; Additive: OR = 0.56, $p = 0.048$).

TLR1-rs17616434 was not associated with susceptibility to AR in all stratified analyses. There was no association between all candidate genetic loci (rs72493538, rs76600635, and rs17616434) and susceptibility to AR in females, participants with aging ≤ 43 years old, BMI > 24 kg/m^2, or coming from loess hilly region.

In addition, FPRP analysis showed (Supplemental Table 2) that all positive results found in this study are noteworthy at a probability level of 0.25 and FPRP cutoff value of 0.2.

MDR Analysis

MDR analysis showed (Table 4) that two-loci genetic model composed of rs72493538 and rs76600635 can be chose as the best model to predict the risk of AR, which with the highest Bal. Acc. Testing (0.536) and perfect CVC (10/10). The Fruchterman-Region of SNP-SNP interactions is shown in Figure 2.
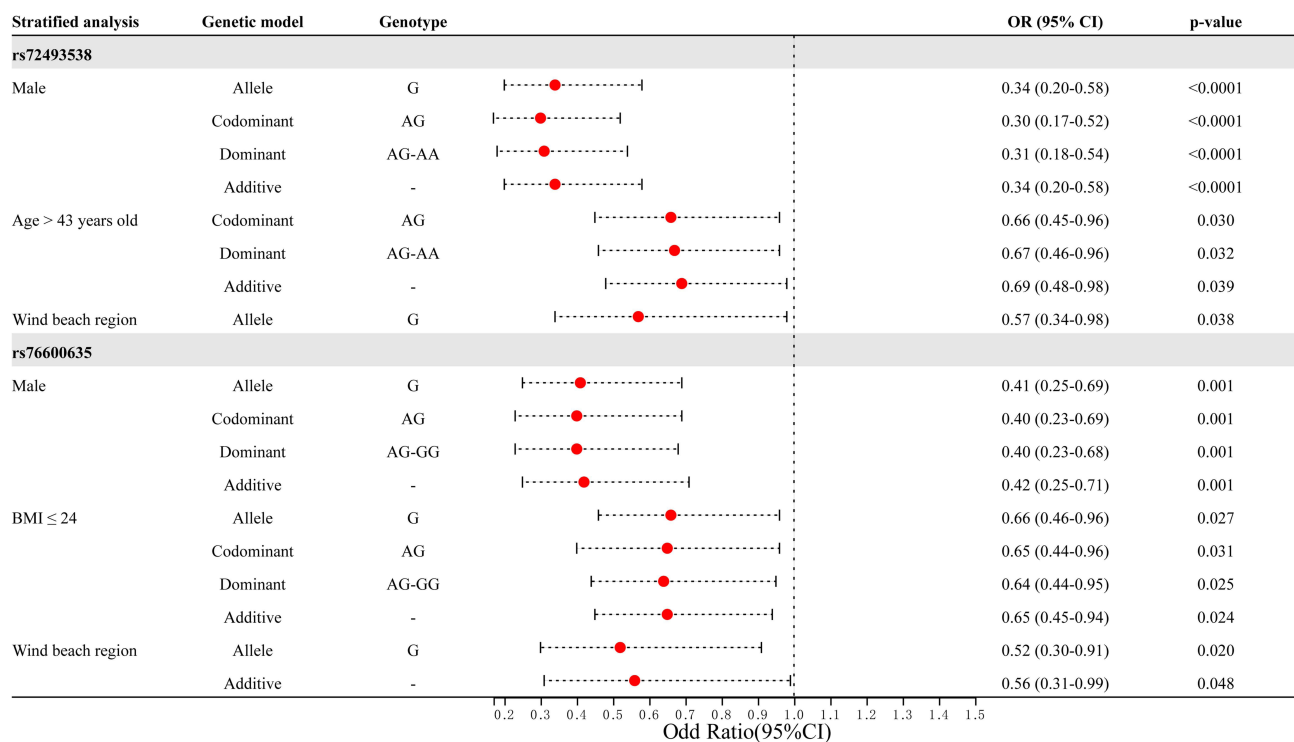
Stratified analysis	Genetic model	Genotype		OR (95% CI)	p-value
rs72493538					
Male	Allele	G		0.34 (0.20-0.58)	<0.0001
	Codominant	AG		0.30 (0.17-0.52)	<0.0001
	Dominant	AG-AA		0.31 (0.18-0.54)	<0.0001
	Additive	-		0.34 (0.20-0.58)	<0.0001
Age > 43 years old	Codominant	AG		0.66 (0.45-0.96)	0.030
	Dominant	AG-AA		0.67 (0.46-0.96)	0.032
	Additive	-		0.69 (0.48-0.98)	0.039
Wind beach region	Allele	G		0.57 (0.34-0.98)	0.038
rs76600635					
Male	Allele	G		0.41 (0.25-0.69)	0.001
	Codominant	AG		0.40 (0.23-0.69)	0.001
	Dominant	AG-GG		0.40 (0.23-0.68)	0.001
	Additive	-		0.42 (0.25-0.71)	0.001
BMI ≤ 24	Allele	G		0.66 (0.46-0.96)	0.027
	Codominant	AG		0.65 (0.44-0.96)	0.031
	Dominant	AG-GG		0.64 (0.44-0.95)	0.025
	Additive	-		0.65 (0.45-0.94)	0.024
Wind beach region	Allele	G		0.52 (0.30-0.91)	0.020
	Additive	-		0.56 (0.31-0.99)	0.048

0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5
Odd Ratio(95%CI)

Figure 1 Positive results about *TLR1*-rs72493538 and -rs76600635 found in stratified analysis are shown in forest map.

Discussion

In this research, we found *TLR1*-rs72493538 and –rs76600635 reduced the susceptibility to AR among Han Chinese in northern China. In addition, we found evidence that *TLR1*-rs72493538 and -rs76600635 were associated with AR risk in stratified analyses. These results highlight the importance of *TLR1* polymorphisms in AR development and may provide potential biological targets for the treatment of AR.

Koponen and his colleagues have confirmed that *TLR1*-rs5743618 is involved in the development of allergy and asthma.[19] Furthermore, it has been reported that *TLR1*-rs76600635 is correlated with poor outcomes of melioidosis in Thais populations.[20] A targeted sequencing study has identified *TLR1*-rs72493538 as a novel genetic variant associated with asthma risk in the Chinese Han population.[21] *TLR1*-rs76600635 has been reported to be significantly associated with the occurrence, presentation and adverse drug reactions of tuberculosis in adults in western China.[22] Based on the above researches, it can be concluded that *TLR1* gene polymorphism may play a potential role in the occurrence and development of nose-related diseases or allergic diseases. All the above studies were conducted on populations with other genetic backgrounds. However, there are relatively few studies on the association between *TLR1* gene polymorphism and disease risk in the Chinese population. Our study is the first to investigate the association between TLR1 gene polymorphism and susceptibility to allergic rhinitis in the Chinese population, and noteworthy results have been found. It

Table 4 SNP-SNP Interactions of *TLR1* Gene Analyzed by MDR Method

Model	Bal. Acc. Training	Bal. Acc. Testing	CVC	OR (95% CI)	*p*
rs72493538	0.522	0.507	8/10	1.45 (1.11–1.90)	**0.006**
rs72493538, rs76600635	0.538	0.536	10/10	1.85 (1.43–2.40)	**< 0.0001**
rs72493538, rs76600635, rs17616434	0.542	0.524	10/10	2.46 (1.81–3.35)	**< 0.0001**

Notes: *p* values were calculated using χ^2 tests. *p* < 0.05 and bold text indicate there are statistical significance.
Abbreviations: MDR, multifactor dimensionality reduction; Bal. Acc., balanced accuracy; CVC, cross–validation consistency; OR, odds ratio; CI, confidence interval.
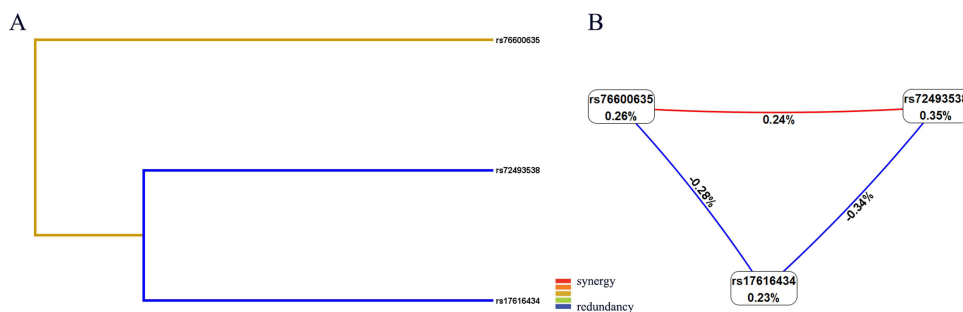
Figure 2 Multifactor dimensionality reduction (MDR) analysis of interaction between the four SNPs of TLR1 (rs72493538, rs76600635, and rs17616434). (**A**) The color represents the degree of redundancy or synergy between SNP-SNP; the closer the color is to red, the more synergy, and the closer to blue, the more redundancy; (**B**) The Fruchterman-Region of SNP-SNP interactions. Each SNP is reported in per cent the value of Information Gain (IG), while numbers in the connections indicate the entropy-based IG for the SNP pairs. Red bar indicates high-level synergies on the phenotype, while blue connections with negative IG values indicate redundancy or lack of synergistic interactions between the markers.

is worth noting that this study is the first to find that *TLR1*-rs72493538 and -rs76600635 are associated with the susceptibility to AR in the northern Chinese Han population.

Previous study has reported that *TLR1*-rs17616434 is associated with susceptibility to asthma and rhinoconjunctivitis in a cohort of Sicilian children,[23] but not with the genetic susceptibility of milk allergy in Chinese children.[24] More importantly, no evidence was found in our study that *TLR1*-rs17616434 is associated with AR susceptibility. We speculate that why *TLR1*-rs17616434 is not associated with allergic diseases in Chinese population may be influenced by the genetic background of the study population, which further indicates that genetic loci play different genetic roles in different populations. In our study, *TLR1*-rs72493538 has a significant association with AR risk in males, participants with aging > 43 years, or coming from wind-blown sand region. Similarly, *TLR1*-rs76600635 is significantly associated with the decreasing risk of AR in males, participants with BMI ≤ 24 kg/m^2, or coming from wind-blown sand region. Studies have found that the clinical symptoms of allergic rhinitis vary with age and gender.[25] In general, the symptoms of allergic rhinitis will slowly improve with age, and the skin test reactivity tends to weaken.[26] Environment is also one of the important factors in the pathogenesis of AR.[27] Different regions of China may have different environmental factors, climate factors and economic levels, which will cause prevalence of AR may be different. More importantly, many epidemiological studies have found significant differences in AR incidence in different regions of China.[28,29] Combined with previous studies and the results of this study, it is necessary to identify the genetic loci associated with AR susceptibility in a specific population, which will provide valuable reference for individualized treatment and diagnosis.

The *TLR1* gene is located on chromosome 4p14 and contains seven exons. It plays a critical role in the innate immune system and inflammatory diseases.[30] Some research has illustrated that *TLR1* participates in the development of nasal diseases.[14,31] For example, Kaczmarek et al have observed an upregulated expression of *TLR1* in nasal polyps of patients with chronic rhinosinusitis, further suggesting an important role of *TLR1* in the formation and maintenance of nasal polyp.[31] Moreover, another study has reported that the protein expression level of *TLR1* is decreased in nasal epithelium of AR patients.[14] Combined with the results of previous studies and this study, we hypothesized that *TLR1*-rs72493538 and rs76600635 might affect the AR susceptibility of the Han population from northern China by affecting the expression level of *TLR1* in AR patients. However, the above is only a speculation, and further design function studies for *TLR1*-rs72493538 and -rs76600635 will help to better understand the specific molecular mechanism of the above SNPs in AR. In any case, this study provides a new idea for studying the pathogenesis of AR.

However, this study has some limitations that must be faced. Firstly, the research scope is further expanded in the following research to further verify the results of this study. Secondly, further designing functional studies based on the positive results of this study will help to better understand the mechanism of candidate SNPs in the development of AR. In any case, this study is the first to find *TRL1* genetic loci associated with reducing AR risk in the Han population in northern China, which will provide a new idea for clinical monitoring of AR risk, as well as early prevention and treatment of AR.

Conclusions

TLR1-rs72493538 and -rs76600635 have closely association with reducing risk of AR. Our study provides a theoretical basis for the treatment and prevention of AR.

Abbreviations

TLR1, Toll-like receptor 1; SNPs, single nucleotide polymorphisms; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; 95% CI, 95% confidence interval; MDR, multifactor dimensionality reduction.

Data Sharing Statement

All data generated or analyzed during this study are included in this manuscript.

Ethics Statement

This research received approval from the Shenmu Hospital, and conformed to the Declaration of Helsinki.

Consent to Participate

Informed consent was obtained from each participant in recruitment after a full understanding of our research.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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