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Association between Interleukin-27 gene polymorphisms and susceptibility to allergic rhinitis

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ABSTRACT

Objectives: Allergic rhinitis (AR) is an inflammatory disorder of the upper airway. Interleukin-27 (IL-27), a novel IL-12 family member, has recently been reported to play a role in some immune-related disorders. This study was performed to evaluate the potential association of IL-27 polymorphisms with AR in a Chinese Han population.

Design and Methods: A case-control study was performed in 445 Chinese AR patients and 691 healthy controls. Three SNPs in the IL-27p28 gene, including rs153109, rs17855750 and rs181206, were detected using a polymerase chain reaction–restriction fragment length polymorphism assay (PCR–RFLP).

Results: A significantly increased prevalence of the rs153109 TT genotype and the T allele was found in AR patients, while a decreased prevalence of the CT and CC genotypes and the C allele was found. For rs153109, the TT genotype and the T allele were significantly associated with the risk of AR, but the CT and CC genotypes and the C allele decreased the risk of AR; for rs17855750, the TT genotype and T allele were risk factors for AR, and the GT genotype and G allele provided protection. TTT and TTC haplotypes in the IL-27p28 gene were positively correlated with AR, while CGT, CTC and CTT haplotypes were associated with a significantly decreased risk of AR.

Conclusion: This study indicates that IL-27p28 polymorphisms rs153109 and rs17855750 are likely involved in AR susceptibility, making them potentially useful genetic biomarkers for AR susceptibility in the Chinese Han population.

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1. Introduction

Allergic rhinitis (AR) is an IgE-mediated inflammation of the upper airway, which is induced by allergens and regulated by T cells. AR has an estimated worldwide incidence rate of 10–20% [1]. Our previous epidemiological investigations showed that in western China, the prevalence of self-reported AR was 32.30% (Chongqing), 34.3% (Chengdu), 37.9% (Urumqi), and 30.3% (Nanning) [2]. AR has a major impact on quality of life by causing unpleasant symptoms such as sneezing, nasal congestion, nasal pruritus, rhinorrhea and the obstruction of the nasal passages.

Furthermore, AR is a known risk factor for comorbid conditions such as asthma, rhinosinusitis, nasal polyposis, and sleep disorders, resulting in important medical and social problems [3,4]. Over the last two decades, the pathogenesis of AR has been widely studied and genetic factors are thought to be major players affecting the development, severity and treatment of AR [5,6]. It has been reported that numerous loci and candidate genes show associations with AR [7,8]. In spite of this, the details of the underlying pathogenic mechanisms remain unclear.

IL-27 is a novel IL-12 family member produced early after activation by antigen-presenting cells, and it promotes both anti- and pro-inflammatory immune responses [9,10]. IL-27 is formed by the dimerization of the Epstein-Barr virus-induced gene 3 protein (EBI3) and p28, a novel IL-12 p35-related polypeptide [11]. Recently, IL-27 has been shown to be an important immunoregulatory cytokine involved in the immune response as well as in the development of inflammation. It appears to act as an early

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mediator of naive T-cell proliferation and is a potent inducer of interferon gamma (IFN- γ) production, particularly in synergy with IL-12 [12]. Thus, IL-27 is thought to promote Th1-mediated immune responses and may be an important cytokine in the pathogenesis of immune-related disorders. Indeed, recent studies have confirmed the role of IL-27 in uveitis, asthma and postinfluenza pneumococcal pneumonia [13–15].

Single nucleotide polymorphisms (SNPs) include coding sequences of genes, non-coding regions of genes, and intergenic regions between genes. The polymorphisms of important cytokine or molecule genes might predict susceptibility to certain diseases or clinical features. For example, Masoud Movahedi et al. reported that gene polymorphisms of IL-4 were associated with AR and its clinical phenotypes [16], and our recent study demonstrated an important association between polymorphisms in IL-23R and AR in the Han Chinese population [17]. Furthermore, several SNPs in the IL-27 gene have been found to be involved in immune-related diseases, including uveitis, inflammatory bowel disease and tuberculosis [18–20], although there are some contradictory reports [21–24]. However, to date, no studies have examined the role of SNPs within the IL-27 gene in the development of AR. In this study, we attempted to gain a better understanding of the genetic influences of IL-27 on AR. We have identified three possible variation sites of IL-27p28, including two exons and one promoter sequence. To determine whether these IL-27p28 SNPs are associated with susceptibility to AR, we have analyzed their frequencies in genomic DNAs isolated from AR patients and healthy controls.

2. Materials and methods

2.1. Subjects

Overall, 445 patients (205 men, 240 women) between 6 and 81 years of age were recruited from April 2012 to April 2013. All patients were identified by and treated at the outpatient clinic of the Department of Otolaryngology Head and Neck Surgery at the First Affiliated Hospital of Chongqing Medical University, Chongqing, China. The diagnosis of AR was based on the patients' medical history, symptoms and the presence of a positive skin prick test (SPT, Allergopharma, Hamburg, Germany) in response to a panel of common allergens defined by the ARIA 2008 guidelines [25]. The SPT results were diagnosed in accordance with the recommendations of the Subcommittee on Allergen Standardization and Skin Tests of the European Academy of Allergy and Clinical Immunology [26]. A positive SPT result was defined as the formation of a wheal larger than or equal to one half the diameter of the histamine control wheal, and at least 3 mm larger than the diameter of the negative control wheal. A total of 18 inhaled allergens were tested, including house dust, grass, tree, mold, food, and cat and dog dander.

In contrast, patients with accompanying systemic disease were excluded from the study. 691 healthy volunteers of the same ethnicity as the patients were recruited as the control group.

2.2. Ethics statement

The local ethics authorities (the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China) provided permission and helped to obtain informed consent from all participants. Written informed consent was obtained from all participants. Informed consent was obtained from the next of kin, caretakers, or guardians of any minors participating in this study.

2.3. DNA extraction

Genomic DNA was extracted from EDTA-anticoagulated peripheral blood leukocytes using the Wizard® Genomic DNA Purification Kit method. briefly, 300 μ l of blood was mixed with cell lysis solution. Leucocytes were spun down and lysed with Nuclei Lysis Solution. The pellet was separated out by Protein Precipitation Solution. Precipitated proteins were removed by centrifugation. Then, two-filar DNA was separated out by methyl alcohol. The DNA on the EP tube was dissolved in 100 μ l DNA Rehydration Solution.

2.4. Determination of the IL-27p28 genotype

We selected the rs153109, rs17855750 and rs181206 SNPs in IL-27p28 gene as candidate sites, which have been demonstrated to be associated with certain immune-related diseases. SNP rs153109 lies in the promoter region, while SNPs rs17855750 and rs181206 lie on exon 2 and exon 4, respectively. These three SNPs were genotyped using the polymerase chain reaction–restriction fragment length polymorphism method (PCR–RFLP). The primer sequences and reaction conditions used in this study are shown in Table 1. The PCR products were incubated with restriction enzymes for 1 or 1–16 h. The obtained digestion products were visualized on a 4% agarose gel and stained with Gold View (SBS Genentech, Beijing, China). To confirm the genotyping results, PCR-amplified DNA samples were examined by direct sequencing (20% of all the blood samples), and the results were 100% concordant (Figs. 1 and 2).

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 18.0 software (SPSSInc., Chicago, Illinois, USA). P values of less than 0.05 were considered statistically significant. To evaluate the quality of the genotyping data, the Hardy–Weinberg equilibrium (HWE) for SNP genotype frequencies was tested using a chi-square test (χ^2 test). Allelic and genotypic frequencies between patients with AR and the control patients were compared by χ^2 test. The online software platform SHEsis (<http://analysis2.bio-x.cn/myanalysis.php>) was used to analyze the haplotype and probabilities. The association between genotypes/alleles and the AR risk was estimated by calculating odds ratios (OR) and 95% confidence intervals (CI).

Table 1
Primer sequences, PCR conditions, and restriction enzymes used for PCR–RFLP analysis of the IL-27p28 polymorphisms.

Reference SNP ID	Primer sequence	Annealing temperature ($^{\circ}$ C)	Restriction enzyme
rs1531093	F:5'TCAGTCAGTGACCAAGATCG3' R:5'ACCAAGAAACCCATCCTCT3'	58	PaeR7I
rs17855750	F:5'ATCTCGCCAGGAAGCTGCGC3' R:5'CTGTTAGTGGGGCCAGAGGGA3'	62	Bstul
rs181206	F:5'GCTTCAGCCCTTCATGCC3' R:5'TCTACCTGGAAGCGAGGTGCC3'	64	FauI

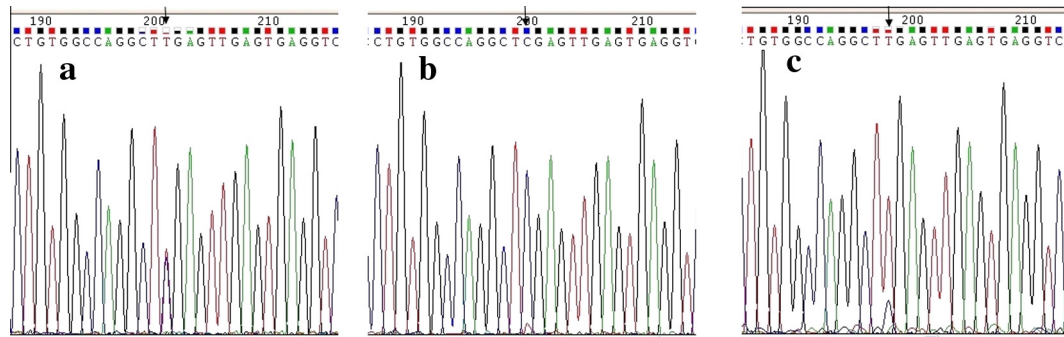


Fig. 1. Sequencing map of the genotype for IL-27p28 gene rs153109 polymorphisms. The arrows in panels a, b and c show the CT, CC and TT genotypes, respectively.

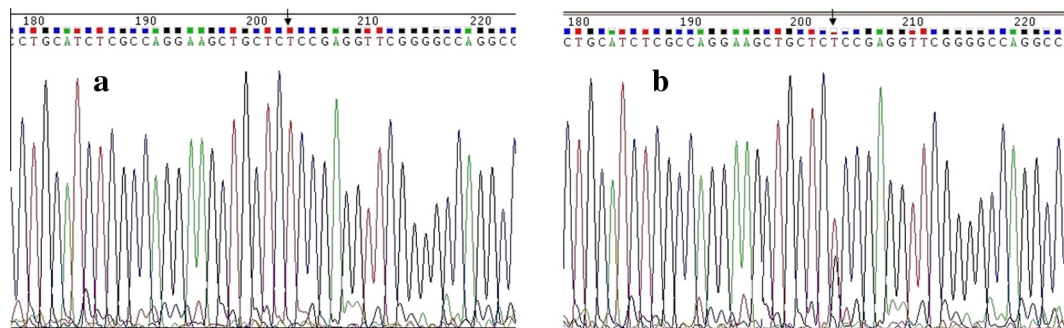


Fig. 2. Sequencing map of the genotype for IL-27p28 gene rs17855750 polymorphisms. The arrows in panels a and b show the TT and GT genotypes, respectively.

3. Results

3.1. Clinical characteristics of the study participants

The demographics of the cases and controls enrolled in this study are shown in Table 2. There were no significant differences between the cases and controls in terms of the mean age and gender distribution. 242 (54.4%) patients were sensitive to house dust mite, 61 (13.7%) were sensitive to tree pollen and 142 (31.9%) were sensitive to multiple allergens.

3.2. Genotype distribution of the IL-27p28 polymorphisms

Our results showed that IL-27p28 SNPs rs153109, rs17855750 and rs181206 were in Hardy–Weinberg equilibrium in the cases and controls ($P > 0.01$). The genotype and allele frequencies of the three tested IL-27p28 polymorphisms are shown in Table 3. The call rate for the examined three SNPs was 100%.

The results showed that there were obvious differences between the AR patients and control patients concerning the frequencies of rs153109 and rs17855750. A significantly increased prevalence of the rs153109 TT genotype and T allele was found in the AR patients compared to the controls ($P = 7.72 \times 10^{-10}$, OR

2.26, 95% CI 1.76–2.90; $P = 2.79 \times 10^{-11}$, OR 1.187, 95% CI 1.13–1.24, respectively). The frequencies of the CT and CC genotype and the C allele were significantly lower in the AR patients than in the controls ($P = 7.46 \times 10^{-5}$, OR 0.57, 95% CI 0.44–0.73; $P = 9.54 \times 10^{-5}$, OR 0.24, 95% CI 0.12–0.48; $P = 2.79 \times 10^{-11}$, OR 0.57, 95% CI 0.48–0.67, respectively).

For rs17855750, a higher frequency of the TT genotype ($P = 1.10 \times 10^{-13}$, OR 1.15, 95% CI 1.12–1.19) and the T allele ($P = 4.24 \times 10^{-13}$, OR 1.07, 95% CI 1.05–1.09), and a lower frequency of the GT genotype ($P = 1.10 \times 10^{-13}$, OR 0.05, 95% CI 0.02–0.15) and the G allele ($P = 4.24 \times 10^{-13}$, OR 0.05, 95% CI 0.02–0.15) were found in AR patients compared with the controls. No differences in the genotype frequency of the rs181206 SNP were observed between the AR cohort and the control group.

3.3. Haplotype analysis of the IL-27 p28 gene

Haplotype analyses were performed using the Haploview V3.32 program and the online software platform SHEsis. The eight possible haplotype frequencies are shown in Table 4. The major TTT haplotype, constructed by SNPs including rs153109, rs17855750 and rs181206, accounted for 78.0% and 65.5% of these eight haplotypes in the cases and the controls, respectively. We found that the distribution rate of the TTT and TTC haplotypes were notably increased in the AR patients compared to the control patients and that the distribution rate of the CGT, CTC and CTT haplotypes was significantly reduced. The TTT and TTC haplotypes in the IL-27p28 gene were positively correlated with AR, while the CGT, CTC and CTT haplotypes were associated with a significantly decreased risk of AR.

4. Discussion

In this study, we investigated the IL-27 gene polymorphisms in AR and demonstrated a novel association between SNPs

Table 2

Selected clinical features and demographic characteristics of study population and controls.

Characteristics	AR (N = 445)	Control (N = 691)
Gender[male/female]	205/240	337/354
Age[mean(range)]years	32.39 (6–81)	30.61 (10–78)
Allergen		
House dust mite	242	–
Pollen	61	–
Multiple allergens	142	–

Table 3
The genotype and allele frequencies of IL-27p28 polymorphisms in AR patients and controls.

SNP	Genotype allele	AR (%) (N = 445)	Control (%) (N = 691)	χ^2	P	Unadjusted OR (95%CI)
rs153109	TT	301 (67.6)	332 (48.0)	42.121	7.72×10^{-10}	2.26 (1.76–2.90)
	CT	134 (30.1)	299 (43.3)	19.87	7.46×10^{-5}	0.57 (0.44–0.73)
	CC	10 (2.2)	60 (8.7)	19.39	9.54×10^{-5}	0.24 (0.12–0.48)
	T	736 (82.7)	963 (69.7)	48.62	2.79×10^{-11}	1.187 (1.13–1.24)
	C	154 (17.3)	419 (30.3)	48.62	2.79×10^{-11}	0.57 (0.48–0.67)
rs17855750	TT	442 (99.3)	596 (86.3)	58.70	1.10×10^{-13}	1.15 (1.12–1.19)
	GT	3 (0.7)	95 (13.7)	58.70	1.10×10^{-13}	0.05 (0.02–0.15)
	T	887 (99.7)	1287 (93.1)	56.05	4.24×10^{-13}	1.07 (1.05–1.09)
	G	3 (0.3)	95 (6.9)	56.05	4.24×10^{-13}	0.05 (0.02–0.15)
rs181206	TT	396 (89.0)	596 (86.3)	1.83	1.08	1.03 (0.99–1.08)
	TC	49 (11.0)	95 (13.7)	1.83	1.08	0.80 (0.58–1.11)
	T	841 (94.5)	1287 (93.1)	1.71	1.14	1.02 (0.99–1.04)
	C	49 (5.5)	95 (6.9)	1.71	1.14	0.80 (0.57–1.12)

Table 4
Haplotype frequencies of the IL-27p28 gene in AR patients and controls.

Haplotype	AR (%)	Control (%)	χ^2	P	Odds ratio (95%CI)
C G C	0.00 (0.0)	1.43 (0.1)	–	–	reference
C G T	0.48 (0.1)	58.88 (4.3)	37.651	8.72×10^{-10}	0.012 [0.002 ~ 0.087]
C T C	9.50 (1.1)	68.64 (5.0)	25.718	4.03×10^{-7}	0.201 [0.102 ~ 0.399]
C T T	144.02 (16.2)	290.05 (21.0)	9.678	1.873×10^{-3}	0.705 [0.565 ~ 0.879]
T G C	0.00 (0.0)	1.51 (0.1)	–	–	–
T G T	2.52 (0.3)	33.18 (2.4)	–	–	–
T T C	39.50 (4.4)	23.42 (1.7)	14.352	1.53×10^{-4}	2.630 [1.566 ~ 4.417]
T T T	693.98 (78.0)	904.89 (65.5)	31.603	1.94×10^{-8}	1.748 [1.437 ~ 2.126]

rs17855750 and rs153109 in the IL-27p28 gene and AR in a Chinese Han population. For rs153109, the TT genotypes and the T allele significantly increased the risk of AR, but the CT, CC genotypes and the C allele decreased the risk of AR. For rs17855750, the TT genotype and the T allele were risk factors for AR, but the GT genotype and the G allele provided protection. Furthermore, we found that the TTT and TTC haplotypes in IL-27p28 gene were positively correlated with AR, while the CGT, CTC and CTT haplotypes were negatively correlated with AR. To the best of our knowledge, this is the first study to evaluate an association between IL-27p28 SNPs rs153109 and rs17855750 and AR in a Chinese Han population.

AR, a common inflammatory disorder of the upper airway, is the result of a complex interplay between multiple genetic and environmental factors resulting in the dysregulation of the immune system [27]. To explore the genetic influences of IL-27 on AR, we chose rs153109, rs17855750 and rs181206 in the IL-27p28 gene as candidate sites, based on the results of some previous studies. The rs153109, rs17855750 and rs181206 polymorphisms of IL-27p28 were recently identified, and a relationship between the rs153109 polymorphism and risk for asthma has been found [28]. Meanwhile, Huang et al. [29] reported a significant difference in the genotype and allele frequencies of rs153109 and rs17855750 between patients with chronic obstructive pulmonary disease (COPD) and controls. In this study, our data demonstrated an association between SNPs rs153109 and rs17855750 in the IL-27p28 gene and AR. However, no significant association was observed between rs181206 polymorphisms and AR. These results are consistent with those reported in the above studies and suggest that the rs153109 and rs17855750 polymorphisms of the IL-27p28 gene may be associated with AR susceptibility. Furthermore, the results suggest that the genetic background of AR might be similar to those of asthma and COPD.

IL-27 is a critical cytokine that functions as a mediator between the innate and adaptive immune system. It plays an important role in the down-regulation of airway hyper-reactivity and lung

inflammation through its suppressive effect on cytokine production [30]. Our haplotype analysis indicated that the TTT and TTC haplotypes in the IL-27p28 gene were positively correlated with AR, but that the CGT, CTC and CTT haplotypes were negatively correlated with AR. It is therefore likely that people with the TTT and TTC haplotypes in rs153109, rs17855750 and rs181206 of IL-27p28 are at a higher risk of developing AR than people with the other haplotypes. Conversely, people with the haplotypes CGT, CTC and CTT would be more resistant to AR, suggesting that these three haplotypes may play a protective role in the development of AR.

As for rs153109, which lies within the promoter region of the IL-27p28 gene, we think that it is directly involved in AR susceptibility. Our data show that the TT genotype of rs153109 increases the risk of AR by 2.26-fold, while the T allele of rs153109 is associated with a 1.187-fold increase in the risk of AR. However, the CC genotype and the C allele decreased the risk of AR by 0.24-fold and 0.57-fold, respectively. These results suggest that the T allele may lead to AR susceptibility, and that people with the T allele in the rs153109 SNP of the IL-27p28 gene are more likely to develop AR. In contrast, the C allele may protect against AR development. Recent studies have shown that in asthma, COPD and esophageal cancer diseases [28,29,31], the T allele of rs153109 in the IL-27p28 gene might be correlated with the up-regulated expression of IL-27, which participates in disease pathogenesis. Based on these studies, we speculate that the change between the T and C alleles in rs153109 most likely influences AR susceptibility. This change might affect gene splicing, transcription factor binding, or the non-coding RNA sequence, and might thereby influence the expression of certain proteins.

In the present study, we made many efforts to decrease the influence of confounding factors on the results. We selected the AR patients and controls using strict guidelines and confirmed the genotyping results by direct sequencing. We observed a novel association between SNPs rs17855750 and rs153109 of IL-27p28 and AR in a Chinese Han population. However, it is worth mentioning that there are some limitations to our study. First, we did not

detect the protein level of IL-27 in the peripheral blood and perform a functional analysis study, so we could not draw a certain conclusion about the influence of these polymorphisms on the cytokine levels. Second, as it is well known that environmental factors are critical for the development of AR, further studies will be needed to clarify the genetic influence of IL-27 in AR pathogenesis, including gene-gene and gene-environment interactions.

In summary, we have demonstrated an association between IL-27 gene polymorphisms and susceptibility to AR. Our results suggest that rs17855750 and rs153109, but not rs181206, are susceptibility genes for the development of AR in the Chinese Han population. However, more intensive studies are required to further clarify the molecular mechanisms and the complex interaction between environmental factors and IL-27 gene polymorphisms in AR. Generally, we hope that our study can provide a deeper insight into AR pathogenesis.

Disclosure statement

The authors declare no financial or other conflicts of interest regarding the content of this article

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