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Association of interleukin-4 receptor I75V, Q576R and S503P polymorphisms and haplotypes with risk of allergic rhinitis in a population of China.

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Abstract

Objective: We carried out a study to investigate the association of IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) polymorphisms with the development of AR in a Chinese population.

Methods: Between October 2012 and May 2015, 326 patients with AR and 412 healthy control participants were recruited. IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) were amplified and genotyped by polymerase chain reaction coupled with restriction fragment length polymorphism method. Multivariate unconditional logistic regression analysis was employed to evaluate the association between IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) polymorphisms and AR risk.

Results: This study included 184 females and 142 males in AR patients, and 209 females and 203 males in controls. The mean ages of AR patients and controls were 35.82 ± 11.24 and 37.22 ± 12.07 y, respectively. We observed that the GG genotype of IL-4R Q576R (rs1801275) was associated with a reduced risk of AR when compared with the AA genotype of Q576R (rs1801275) (OR=0.43, 95% CI=0.26-0.71, P=0.001). A significant linkage disequilibrium was found between rs1805010 and rs1801275 (D=0.79, r^2=0.02). The G-A-T (OR=0.32, 95% CI=0.24-0.42) and G-G-T (OR=0.18, 95% CI=0.12-0.27) haplotypes showed a decreased risk of AR, while the A-A-T revealed an increased risk (OR=4.07, 95% CI=3.25-5.09).

Conclusion: Our study suggests that the IL-4R Q576R (rs1801275) genetic polymorphism is associated with the development of AR, and the G-A-T, G-G-T and A-A-T haplotypes contribute to the susceptibility to AR. The nurses and doctors would provide health education to these high risk individuals.

Keywords: IL-4R, Polymorphism, Haplotype, Allergic rhinitis.

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Introduction

Allergic Rhinitis (AR) is defined as an IgE-mediated nasal inflammation disease, and this disease is caused by allergens and regulated by T lymphocytes [1,2]. AR is characteristics by unpleasant symptoms, such as paroxysmal sneezing, watery nose, nasal congestion, itchy nose, and rhinorrhea [3-5]. This disease contributes to the development of asthma, nasosinusitis, nasal polyposis and sleep disorders [3-5]. The root causes of allergic rhinitis are still unclear. Epidemical studies have revealed that many environmental factors contribute to the development of allergic rhinitis, such as house dust mites, dust mites, pollen and animal dander [5,6]. Increasing studies have revealed that hereditary factors, such as Single Nucleotide Polymorphisms (SNPs), and have a vital role in the risk of developing allergic rhinitis [7-12].

IL-4 is a typical cytokine of Th2 cells, which has the inhibition effect on the inflammation and transplant rejection caused by the cytokine network to the Th1, and has a strong and broad biological activity [13]. Interleukin 4 (IL-4) was discovered in 1982, and it is mainly secreted by activated T cells and mononuclear cells [14]. IL-4 is also the strongest regulatory factor of IgE, and its biological function should be mediated through the IL-4 receptors (IL-4R) in effector cell [15]. A few previous studies have reported the association between polymorphisms in *IL-4R* gene and development of several allergic diseases, but the results are inconsistent [16-18]. IL-4R rs1801275, rs1805010, and rs1805015 are three common missense mutations of *IL-4R* gene, and these genetic polymorphisms could enhance signaling function and change the biological activity of the protein [19]. Therefore, we carried out a case-control study to investigate the role of IL-4R I75V

(rs1805010), Q576R (rs1801275) and S503P (rs1805015) polymorphisms and haplotypes in the development of AR in a Chinese population.

Material and Methods

Subjects

A hospital-based case-control design was used. Between October 2012 and May 2015, three hundred and twenty six patients with AR were collected from the Houjie Hospital. All patients were newly diagnosed and did not receive any treatment before. The AR was diagnosed based on patients' medical history, clinical manifestation of AR, and positive skin prick tests with a series of common allergens defined by the Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update from World Health Organization [20]. The positive skin prick test was diagnosed according to the guidelines from European Academy of Allergy and Clinical Immunology. The inclusion criteria for patients with accompanying systemic diseases. There were 184 females and 142 males in patients, and the mean age was 35.82 ± 11.24 y.

Simultaneously, 412 subjects, designated as controls, were randomly selected from the physical examination center at the Houjie Hospital. These controls were healthy participants. These healthy participants were confirmed to have no history of any allergic diseases. There were 209 females and 203 males in patients, and the mean age was 37.22 ± 12.07 y.

The demographic and clinical variables of participants were collected from their medical records, comprising of age, gender, occupation and allergen classification. Signed consent forms were obtained from each study participant. The protocol of this study was approved from the ethics committee of Houjie Hospital.

DNA extraction and genotyping

Five separate ml peripheral blood, obtained from each participant after study enrollment, were stored in tubes with 10.0~12.5 IU/ml Ethylenediaminetetraacetic acid (EDTA). Genomic DNA was extracted from the blood sample using the Tiangen Blood DNA Kit (Tiangen Biotech Co., LTD. Beijing, China) according to manufacturer' protocol. Amplification and genotyping of IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) were performed by the polymerase chain reaction coupled with restriction fragment length polymorphism method. The primers of the three SNPs were designed by MassARRAY Sequenom Assay Design 3.1. The 25 μL polymerase chain reaction mixture consisted of 2.0 μL of 40 ng genomic DNA, l U Taq enzyme, 2.5 μL 10X PCR mix, 2.0 μL 2.0 M deoxynucleotidemixture, and 20 μM forward and reverse primers. The reaction process included an initial denaturation at 94°C for 5 min, 30 cycles of denaturation at 94°C for 15 s, annealing at 62°C for 30 s, extension at 72°C for 1 min, and a final cycle of 72°C for 10 min. The enzyme-digested products were separated by 3% agarose gel electrophoresis, and was visualized using 300 nm Ultra Violet light.

Statistical analysis

The differences in the demographic and genotype variables of patients with AR and control subjects were determined using chi-square test or student's t-test. Deviation from Hardy-Weinberg equilibrium (HWE) of genotype frequencies of IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) in controls was evaluated using chi-square test. Multivariate unconditional logistic regression analysis was employed to evaluate the association between IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) polymorphisms and AR risk. Odds Ratios (ORs), 95% Confidence Intervals (95% CI), and their corresponding P-values were used to evaluate the relationship between IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) polymorphisms and AR risk. The linkage disequilibrium and haplotype analysis of IL-4R rs1805010, rs1801275 and rs1805015 were evaluated by SHEsis software. The statistical analyses were made by the SPSS statistical software, version 20.0 (SPSS Inc., Chicago, IL, USA). A probability value<0.05 were considered as a statistically significant difference.

Results

This study included 184 females and 142 males in AR patients, and 209 females and 203 males in controls (Table 1). The mean ages of AR patients and controls were 35.82 ± 11.24 and 37.22 ± 12.07 y, respectively. There were significant differences in age (t=4.23, P=0.04) and occupation (chi-square=9.82, P=0.002) between patients with AR and controls. 141 (43.25%) patients were allergic to house dust mite, 61 (18.71%) were allergic to pollens, and 124 (38.04%) were allergic to mixed allergens.

The genotype distributions of IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) between allergic rhinitis patients and controls were showed in Table 2. We observed the QQ, QR and RR genotype frequencies of IL-4R Q576R (rs1801275) showed significant difference between the two investigated groups (chi-square=11.48, P=0.003). The genotype distributions of IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) did not deviate from the HWE in controls.

Using multivariate unconditional logistic regression analysis, we found that the GG genotype of IL-4R Q576R (rs1801275) was associated with a reduced risk of AR when compared with the AA genotype of Q576R (rs1801275) (OR=0.43, 95% CI=0.26-0.71, P=0.001) (Table 3). A significant linkage disequilibrium was found between rs1805010 and rs1801275 (D=0.79, r^2=0.02). The G-A-T (OR=0.32, 95% CI=0.24-0.42) and G-G-T (OR=0.18, 95% CI=0.12-0.27) haplotypes showed

a decreased risk of AR, while the A-A-T revealed an increased risk (OR=4.07, 95% CI=3.25-5.09) (Table 4).

Table 1. *Demographic variables of patients with AR and controls.*

Variables	Patients (N=326)	%	Controls (N=412)	%	Chi-square test or student t test	P value
Sex						
Female	184	56.44	209	50.73		
Male	142	43.56	203	49.27	2.39	0.12
Age, years	35.82 ± 11.24		37.22 ± 12.07		4.23	0.04
Occupation						
Indoor	185	56.75	280	67.96		
Outdoor	141	43.25	132	32.04	9.82	0.002
Allergen category						
House dust mite	141	43.25				
Pollens	61	18.71				
Mixed allergens	124	38.04				

Table 2. *Genotype distributions of IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) between patients with AR and controls.*

IL-4	Patients (N=326)	%	Controls (N=412)	%	Chi-square value	P value	Chi-square value for HWE	P value for HWE
I75V (rs1805010)								
AA	151	46.32	191	46.36				
AG	133	40.8	181	43.93				
GG	42	12.88	40	9.71	2.07	0.36	0.09	0.76
Q576R (rs1801275)								
AA	154	47.24	169	41.02				
AG	144	44.17	173	41.99				
GG	28	8.59	70	16.99	11.48	0.003	0.49	0.48
S503P (rs1805015)								
TT	317	97.24	391	94.9				
TC	9	2.76	21	5.1				
CC	0	0	0	0	2.55	0.11	0.28	0.6

Table 3. *Relationship between IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) polymorphisms and AR risk.*

Variable		B	S.E	wald	P value	OR (95% CI)
Age		-0.01	0.01	2.38	0.12	0.99 (0.97-1.01)
Sex	Female					1.0 (Ref.)
	Male	0.79	0.17	21.71	<0.001	2.20 (1.58-3.07)
Occupation	Indoor					1.0 (Ref.)
	Outdoor	0.47	0.16	8.97	0.003	1.60 (1.18-2.18)
I75V (rs1805010)	AA			1.37	0.51	1.0 (Ref.)
	AG	-0.14	0.16	0.72	0.4	0.87 (0.63-1.20)
	GG	0.13	0.25	0.25	0.62	1.14 (0.69-1.86)
Q576R (rs1801275)	AA			11.22	0.004	1.0 (Ref.)
	AG	-0.1	0.16	0.38	0.54	0.91 (0.66-1.24)

	GG	-0.85	0.26	11.01	0.001	0.43 (0.26-0.71)
S503P (rs1805015)	TT					1.0 (Ref.)
	TC	0.69	0.41	2.83	0.09	0.50 (0.22-1.12)

Table 4. *Haplotype analysis of IL-4R rs1805010- rs1801275-rs1805015 with allergic rhinitis risk.*

Haplotype	Patients	%	Controls	%	OR (95% CI)	P value
A-A-T	370	56.75	193	23.42	4.07 (3.25-5.09)	<0.001
A-G-T	180	27.61	208	25.24	1.08 (0.85-1.36)	0.52
G-A-T	71	10.89	222	26.94	0.32 (0.24-0.42)	<0.001
G-G-T	31	4.75	171	20.75	0.18 (0.12-0.27)	<0.001
Global χ^2=220.44, P value<0.001						

Discussion

Current genome-wide association studies have indicated that many genetic loci contribute to the onset of allergic rhinitis [21,22]. In the current study, we investigated the association of IL-4R I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015) polymorphisms with AR risk in a Chinese population, and our study discovered that the AA genotype of IL-4R Q576R (rs1801275) was associated with risk of AR in the Chinese population.

IL-4R Q576R is located in the 9th exon of *IL-4R*, and the gene mutation of Q576R is alteration of G of A. Previous studies have reported the association of IL-4R Q576R polymorphism with the development of allergic diseases [16,23-26]. Rogala et al. carried out a study with 44 atopic patients with pollen and house dust mite allergy, and discovered that the R576 allele might be associated with the risk of developing allergic diseases in patients with elevated IgE serum level [24]. Cui et al. have indicated that IL-4R 576R/R genotype is correlated with an elevated risk of allergic asthma in Chinese in comparison to the 576Q/Q genotype [16]. Zhang et al. carried out a study with 94 children with asthma and 68 healthy children, and have reported that mutant R576 allele of *IL-4R* is associated with the susceptibility to asthma in a Chinese population [24]. Zheng et al. made a study with 160 asthmatic children and 143 healthy children, and have revealed that IL-4R Q576R and I75V polymorphisms are associated with the pathogenesis of asthma in a Chinese population [25]. Huang et al. carried out a study comprising of 2077 asthma patients and 1589 controls, and have indicated that IL-4R Q576R polymorphism is related to the risk of asthma in the Chinese population [26]. The polymorphism in IL-4R Q576R could promote the production of specific IgE which is involved in type I allergic reaction, and thus increases the risk of allergic diseases. Our results also found that the AA genotype of IL-4R Q576R (rs1801275) influence the susceptibility to AR, which are similar with previous studies. Moreover, we firstly reported significant linkage disequilibrium between rs1805010 and rs1801275, and the G-A-T, G-G-T and A-A-T haplotypes were associated with risk of AR. Therefore, the haplotypes could be a genetic marker for AR, and there may be mutation linked to the haplotypes of IL-4, which may change the activity of IL-4 and consequently influence the susceptibility to AR.

With the development of urbanization and industrialization construction, the incidence of AR increasing rapidly, and the results of our study could help to early find the high risk individuals. Moreover, the nurses and doctors would provide health education to these high risk individuals. AR is associated with many complications, such as venous hemorrhage, thrombosis and phlebitis. It is necessary to prevent the high risk individuals to expose allergens, and nurses and doctors should provide psychological nursing [27,28], dietary nursing and health education for individuals carrying the AA genotype of IL-4R Q576R.

The first limitation of this study was that the investigated subjects were only recruited from only one hospital in China, which may not be good on behalf of the general population of other parts of China. The selection bias is unavoidable. Second, due to the small sample size, the statistical power for finding differences between groups would be reduced. Therefore, further studies are greatly needed to verify our findings.

Conclusions

Our study suggests that the IL-4R Q576R (rs1801275) genetic polymorphism is associated with the development of AR, and the G-A-T, G-G-T and A-A-T haplotypes contribute to the susceptibility to AR. The nurses and doctors would provide health education to these high risk individuals.

Conflict of Interest Statement

The authors declare no conflict of interest in preparing this article.

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