

Polymorphisms and haplotype analysis of IL-4R α Q576R and I75V in patients with penicillin allergy

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Abstract

Background The interleukin (IL)-4 and IL-4R genes are linked to allergic diseases and atopy and elevated serum IgE levels closely follow the presentation of penicillin allergy. We have evaluated the association between specific immunoglobulin (Ig)E, polymorphisms of IL-4R α , and penicillin allergy.

Methods Eight types of specific IgE to penicillins were detected with the radioallergosorbent test (RAST) in 242 patients with penicillin allergy and 220 control subjects. Polymorphisms of IL-4R α Q576R and IL-4R α I75V were genotyped by PCR–restriction fragment length polymorphism (RFLP). The polymorphisms and haplotype of IL-4R α Q576R and I75V were analyzed.

Results For IL-4R α Q576R, the frequency of the AA genotype was higher in patients with penicillin allergy (76 vs. 64%, $P=0.005$). The A allele occurred more frequently in the penicillin-allergic patients than in the controls (87 vs. 80%, $P=0.003$). For IL-4R α I75V, the AA genotype was more likely to be detected in the urticaria group than in the control group (32 vs. 19%, $P=0.049$). Haplotype analysis revealed that Q576/I75 was more frequently found in patients with penicillin allergy than in controls (42 vs. 35%, $P=0.037$).

Conclusions The IL4R α Q576 allele is related to penicillin allergy, and the IL-4R α I75 allele is associated with the symptom of urticaria. The Q576/I75 haplotype may be related with an allergy to penicillin.

Key words Allergy · Gene polymorphisms · IL-4R α · Penicillins

Introduction

Penicillins have been widely used in clinical practice, but penicillin allergy is a relatively common occurrence among the general population and is a cause of great concern in terms of drug security. A number of serious adverse reactions of penicillin allergy can lead to allergic shock or even death [1]. Following the initiation of penicillin allergy, specific immunoglobulin (Ig)E antibodies form and the total level of serum IgE is elevated [2]. The IgE antibody is considered to be the key mediator of allergic diseases through direct formatting and regulating the course of allergic reactions. In addition, many cytokines [3–5], especially interleukin-4 (IL-4), are known to play important roles in the pathogenesis of allergic diseases and the induction of IgE synthesis [6]. Interleukin-4 can stimulate the differentiation of B-cells and regulate the switching of immunoglobulin to IgE [7].

The biologic effect of IL-4 is realized through adherence to the target IL-4 receptor (IL-4R) [8]. The IL-4R complexes are classified into two types. Type I IL-4R complexes are composed of an IL-4R α chain (IL-4R α) and a common γ c chain and are predominant in hematopoietic cells. Type II IL-4R complexes consist of IL-4R α and the interleukin-13 receptor α 1 chain (IL-13R α 1), binding IL-4 and IL-13, and are present on both hematopoietic and non-hematopoietic cells [9].

Many studies have been conducted to study the functional consequences of specific polymorphisms in the IL-4R α gene [10–12] with the aim of evaluating the relation between these variants and asthma or other allergic

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diseases. In comparison, there have been relatively few studies on the genetic risk factors associated with penicillin allergy in Western countries [13–16]. In China, such research is rare. Our group has carried out some work in this field and has recognized the importance of IL-4R α gene in penicillin allergy [17]. Following on our earlier research, the aim of the study reported here was to investigate not only single nucleotide polymorphisms (SNPs) but also linkage disequilibrium and haplotype analysis of the IL-4R α gene in order to evaluate in depth the role of the IL-4R α gene in penicillin allergy.

Materials and methods

Subjects and grouping

For the purposes of calculating sample size, it is assumed that 60% of the controls will present a susceptible genotype. It is also assumed that during the initial procedure, 75% of patients with penicillin allergy will present a susceptible genotype (i.e., 15% difference in efficacy) [17]. If the chi-square test is used with a 0.05 two-tailed significance level and 80% power, a sample size of at least 167 patients is required in each group. Therefore, if we assume a study dropout rate of approximately 10% for

each group, a total of 184 patients in each group will be needed.

We prospectively studied 242 consecutive patients with penicillin allergy in the first affiliated hospital of Zhengzhou University from 2002 to 2006. The clinical characteristics of the patients are summarized in Table 1. All patients were interviewed by allergists and by the members of our research group. The patients were asked to complete a detailed questionnaire that was designed by our group and had been used in our previous studies [2–5, 17]. The questionnaire included a full history of penicillin allergy (penicillin G, phenoxymethyl penicillin, ampicillin, amoxicillin, etc), other drug allergies, allergic diseases (including anaphylactic shock, urticaria, asthma, allergic rhinitis, etc), and an allergic family history.

Of the 242 penicillin-allergic patients who were enrolled in the study, 185 were recruited based on a positive skin test; the remaining 57 patients presented typical allergic symptoms after penicillin administration but had a negative skin test. Of the patients with a positive skin test, 15 presented systemic allergic symptoms (shock or urticaria) shortly after the administration of the skin test. In total, the 72 patients that presented allergic symptoms [positive skin test/systemic allergic symptoms (15) + with typical allergic symptoms/negative skin test (57)] were subdivided into three symptom groups: shock group, urticaria group, and

Table 1 Clinical data and the results of the specific immunoglobulin E test in penicillin-allergic patients

Groups	Controls	Patients	IgE-positive patients (%)
All patients (<i>n</i>)	220	242	146 (60)
Age (mean $\pm$ SD, range)	20.35 $\pm$ 2.14 (16~24)	20.13 $\pm$ 2.09 (16~24)	
Gender (%; 95%CI)			
Male	125 (57, 50~64)	133 (55, 49~61)	83 (62)
Female	95 (43, 36~50)	109 (45, 39~51)	63 (58)
Skin test ^a			
Positive skin test		185	109 (59)
Negative skin test		57	37 (65)
Allergic symptoms ^b			
Shock		12	8 (67)
Urticaria		44	27 (61)
Other symptoms		16	8 (50)
Allergic type ^c			
Immediate reactions		46	28 (61)
Non-immediate reaction		26	15 (58)

SD, Standard deviation; CI, confidence interval; Ig, immunoglobulin

^a Of the 242 allergic patients, 185 were recruited based on a positive skin test; the remaining 57 patients presented typical allergic symptoms after penicillin administration but had a negative skin test

^b A total of 72 patients presented allergic symptoms. Other patients just presented positive skin test but no systemic symptom

^c Patients with allergic symptoms were categorized as immediate group (≤ 1 h) and non-immediate group (> 1 h) according to the initiation time of allergic symptoms

other symptoms (pruritus, dyspnoea, angioedema, bronchospasm, and other allergic symptoms expect for shock and urticaria) group. Patients with allergic symptoms were also categorized as immediate group and non-immediate group according to the initiation time of the allergic symptoms. The immediate group was defined as presenting allergic symptoms within ≤ 1 h after drug administration, and the non-immediate group was defined as presenting allergic symptoms at >1 h after drug administration. In order to investigate the relationship between specific antibodies and the IL-4R α gene, we assayed for specific IgE antibody using the radioallergosorbent test (RAST) and divided patients into a positive IgE group and a negative IgE group.

A total of 220 controls were recruited (Table 1). These controls, who had used penicillins previously without any reported reactions, tested negative for the skin test and specific IgE. They were also tested negative for other allergic reactions (including other drugs, foods, pollen, etc) and allergic diseases (atopic dermatitis, allergic rhinitis, etc).

Informed consent was obtained from all participants in the study, and the study was carried out with the approval of the Ethics Committee, Zhengzhou University.

Blood samples

Blood samples were drawn and allowed to clot for 2 h at room temperature. The sera were separated and stored at -20°C until the *in vitro* tests were performed. DNA was extracted from the surplus whole blood by a standard phenol chloroform extraction method followed by ethanol precipitation.

Skin test

The skin test was performed on all enrolled subjects according to the method described in detail in our previous study [17]. Briefly, Penicillin G sodium salt was diluted in saline solution until a final concentration of 200 U/ml as reagent. A 0.1-ml (20 U) of reagent was injected for intradermal testing on the inner side of the forearm, and the diameter of the wheal was measured after 20 min. The formation of erythema with a diameter >5 mm was taken as a positive reaction.

Radioallergosorbent test

Eight kinds of penicillin-related specific serum IgE were detected, including benzylpenicilloyl-polylysine (BPO-PLL), phenoxomethylpenicilloyl-polylysine (PVO-PLL), ampicilloyl-polylysine (APO-PLL), amoxicilloyl-polylysine (AXO-PLL), benzylpenicillanyl-polylysine (BPA-PLL), phenoxomethylpenicillanyl-polylysine (PVA-PLL), ampicillanyl-polylysine (APA-PLL) and

amoxicillanyl-polylysine (AXA-PLL)[18]. The test and the positive criteria of specific IgE are according to the method described in our previous report [2].

Genotyping

Genotypes and alleles of the IL-4R α Q576R and IL-4R IL-4R α I75V polymorphisms were detected by PCR–restriction fragment length polymorphism (RFLP).

The amplification of Q576R and I75V was carried out with the following primers [17, 19]: 5'-GCC CCCACCAGTGGCTACC-3' and 5'-GAGGTCT TGGAAAGGCTTATAC-3'; 5'-GGCAGGTGT GAGGAGCATCC-3' and 5'-GCCTCCGTTGTTCTCAGG TA-3'. The amplification program consisted of 38 cycles at 95°C for 30 s, 58°C (Q576R) or 52°C (I75V) for 30 s, and 72°C for 50 s, and a final 8-min extension at 72°C . There was a negative (water) control in each amplification cluster. If the negative control was amplified, the amplification cluster may have been contaminated and was therefore discarded. The successful rate of amplification was 85~100%. Random repetition was enforced to determine the repeatability of experiment.

The PCR product for Q576R was 204 bp long and was digested with the *MspI* restriction enzyme; that for I75V was 273 bp long and was digested with the *AfaI* restriction enzyme. Digested fragments were separated on a 3% agarose gel. The results of genotyping are shown in Figs. 1 and 2. Random repetition was performed as described for enzyme digestion to verify the correctness of genotyping.

Statistical analysis

Descriptive variables for quantitative and qualitative values are given by median and absolute numbers or frequencies, respectively. Descriptive statistics was performed using SPSS ver. 13.0 (SPSS, Chicago, IL). Comparisons of statistical significance were performed using the Mann–Whitney *U* test (two-tailed *P* value) and the Kruskal–Wallis *H* test. The alleles frequencies of the IL-4R polymorphisms between controls and patients were compared using Pearson's two-tailed chi-square test or Fisher's exact test. A *P* value <0.05 was considered to be statistically significant. Using logistic regression, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the relationship of alleles and haplotypes with penicillin allergy. The deviation from the Hardy–Weinberg equilibrium was tested with Pearson's chi-square test for any of the SNPs under consideration. Linkage disequilibrium and frequencies of haplotypes in the controls and patients were estimated using SHEsis software[20].

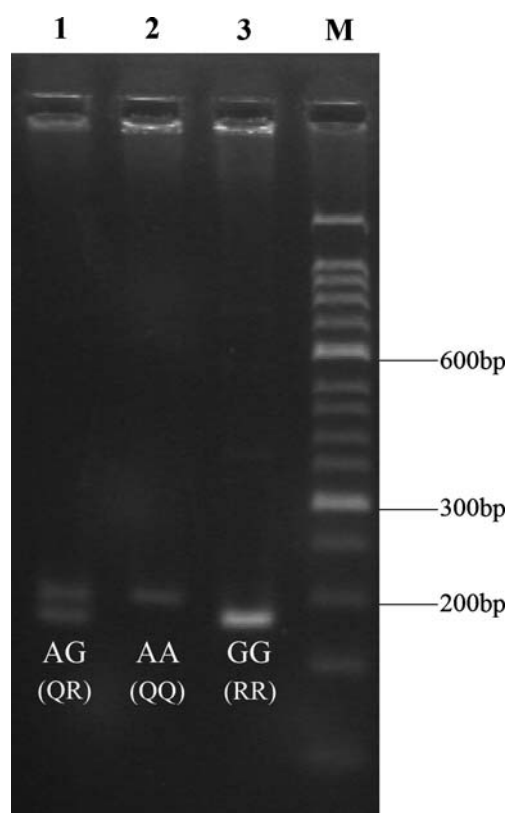


Fig. 1 Genotyping of the interleukin-4R α Q576R polymorphism by a PCR–restriction fragment length polymorphism (RFLP) method. AG, AA, GG Genotype according to single nucleotide polymorphism (SNP) analysis. QR, QQ, RR Amino acid substitutions in the mature protein caused by genotype according to the SNP analysis. Lanes: M 50-bp ladder, 1 Q576R heterozygote, 2 Q576 homozygote, 3 R576 homozygote. *MspI* digests the 204-bp DNA product from Q576 homozygous individuals into 186- and 18-bp fragments. DNA from Q576R heterozygous individuals shows the expected 204-, 186-, and 18-bp fragments

Results

Specific serum IgE

A total of 242 patients with penicillin allergy and 220 controls were enrolled in this study (Table 1). Of the 242 patients, 185 tested positive for the skin test. Of the 72 patients that presented allergic symptoms, 12, 44, and 16 were classified in the shock, urticaria, and other symptoms group, respectively, and 46 and 26 were enrolled in the immediate and non-immediate group. The incidence of positivity for specific IgE was 60% among the 242 allergic patients (Table 1). There was no significant difference between controls and each group.

IL-4R α Q576R and I75V polymorphisms

For IL-4R α Q576R (Table 2), the frequency of the AA genotype was significantly higher in allergic patients than

in the controls (76 vs. 64%, $P=0.005$). Based on the RAST results, allergic patients were divided into those testing positive for the specific IgE group and those testing negative. The frequency of the IL-4R α Q576R-AA genotype was higher in the positive and negative specific IgE group than in the controls (76 vs. 64%, $P=0.020$; 77 vs. 64%, $P=0.028$). Similar results were observed between patients with a positive skin test and controls (77 vs. 64%, $P=0.007$). With respect to allele frequency, the A allele occurred more frequently in allergic patients than in the controls (87 vs. 80%, $P=0.003$).

For IL-4R α I75V (Table 3), the AA genotype was more frequent detected in urticaria group than control group (32% vs 19%, $P=0.049$).

Linkage disequilibrium and haplotype analysis of IL-4R α SNPs

Multiple testing with a two-side significance level of 5% revealed a non-significant deviation of polymorphism from the Hardy–Weinberg equilibrium.

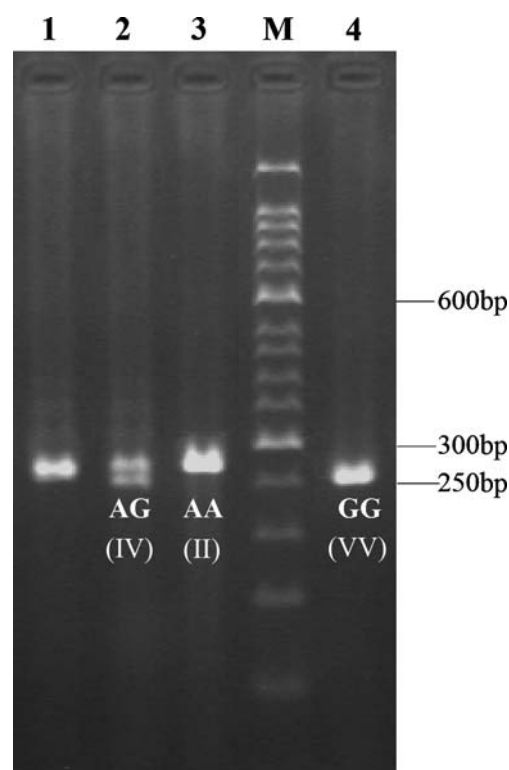


Fig. 2 Genotyping the IL-4R α I75V polymorphism by a PCR-RFLP method. AG, AA, GG Genotype according to SNP analysis. IV, II, VV Amino acid substitutions in the mature protein caused by genotype according to SNP analysis. Lanes: M 50-bp ladder, 1, 3 I75 heterozygote, 2 I75V homozygote, 4 V75 homozygote. *AfaI* digests the 273-bp DNA product from I75 homozygous individuals into 254- and 19-bp fragments. DNA from I75V heterozygous individuals shows the expected 273-, 254-, and 19-bp fragments

Table 2 Genotype and allele distribution of the IL-4R α Q576R polymorphism in penicillin-allergic patients

IL-4R α Q576R	<i>n</i>	Genotype frequency (%)			<i>P</i> value AA vs. AG+GG	Allele frequency (%)		<i>P</i> value
		AA (%) (QQ)	AG (%) (QR)	GG (%) (RR)		A (%) (Q)	G (%) ([®])	
Controls	220	142 (64)	68 (31)	10 (5)		352 (80)	88 (20)	
Patients	242	185 (76)	52 (22)	5 (2)	0.005	422 (87)	62 (13)	0.003 ^a
Specific IgE								
Positive	146	111 (76)	33 (23)	2 (1)	0.020	255 (87)	37 (13)	0.010
Negative	96	74 (77)	19 (20)	3 (3)	0.028	167 (87)	25 (13)	0.035
Skin test								
Positive	185	142 (77)	38 (20)	5 (3)	0.007	322 (87)	48 (13)	0.008
Negative	57	43 (75)	14 (25)	0 (0)	0.12	100 (88)	14 (12)	0.017
Symptoms								
Shock	12	9 (75)	3 (25)	0 (0)	0.46	21 (87)	3 (13)	0.37
Urticaria	44	32 (73)	12 (27)	0 (0)	0.30	76 (86)	12 (14)	0.16
Others	16	12 (75)	4 (25)	0 (0)	0.40	28 (87)	4 (13)	0.30
Allergic type								
Immediate reaction	46	34 (74)	12 (26)	0 (0)	0.22	80 (87)	11 (13)	0.078
Non-immediate reaction	26	19 (73)	7 (27)	0 (0)	0.39	45 (87)	7 (13)	0.26

^a Association of allele frequency with penicillin allergy in patients and controls

Odds ratio=1.67; 95% CI=1.17~2.38

Table 3 Genotype and allele distribution of IL-4R α I75V polymorphism in penicillins allergic patients

IL-4R α I75V	<i>n</i>	Genotype frequency (%)			<i>P</i> value II vs. IV+VV	Allele frequency (%)		<i>P</i> value
		AA (%) (II)	AG (%) (IV)	GG (%) (VV)		A (%) (I)	G (%) (V)	
Controls	220	41 (19)	121 (55)	58 (26)		203 (46)	237 (54)	
Patients	242	58 (24)	128 (53)	56 (23)	0.16	244 (50)	240 (50)	0.19 ^a
Specific IgE								
Positive	146	37 (25)	75 (52)	34 (23)	0.13	149 (51)	143 (49)	0.20
Negative	96	20 (21)	54 (56)	22 (23)	0.65	94 (49)	98 (51)	0.51
Skin test								
Positive	185	42 (23)	101 (54)	42 (23)	0.31	185 (50)	185 (50)	0.27
Negative	57	15 (26)	28 (49)	14 (25)	0.20	58 (51)	56 (49)	0.37
Symptoms								
Shock	12	3 (25)	9 (75)	0 (0)	0.58	15 (62)	9 (38)	0.12
Urticaria	44	14 (32)	15 (34)	15 (34)	0.049	43 (49)	45 (51)	0.64
Others	16	2 (13)	10 (62)	4 (25)	0.43	14 (44)	18 (56)	0.79
Allergic type								
Immediate reaction	46	12 (26)	21 (46)	13 (28)	0.25	45 (49)	47 (51)	0.63
Non-immediate reaction	26	7 (27)	13 (50)	6 (23)	0.31	27 (52)	25 (48)	0.43

^a Association of allele frequency with penicillin allergy in patients and controls

Odds ratio=1.21; % 95 CI=0.93~1.57

Table 4 Haplotype frequencies of Q576R and I75V in penicillin-allergic patients

Haplotype	Allele		Patients (%)	Controls (%)	<i>P</i> value	Odds ratio (95%CI)
	Q576R	I75V				
Q576/I75	A	A	201 (42)	154 (35)	0.037	1.33 (1.02~1.73)
Q576/V75	A	G	220 (45)	198 (45)	0.092	1.01 (0.78~1.31)
R576/I75	G	A	42 (9)	49 (11)	0.32	0.80 (0.52~1.24)
R576/V75	G	G	21 (4)	39 (9)	0.002	0.44 (0.26~0.75)

Analyzed with SHEsis software, the score of D' is 0.223 ($D' < 0.5$, no linkage disequilibrium; $0.8 > D' \geq 0.5$, existing linkage disequilibrium; $D' \geq 0.8$, strong linkage disequilibrium), which implies that there was no linkage disequilibrium between the two genetic sites of IL-4R α Q576R and I75V.

Haplotypes of IL-4R α Q576R and I75V were also analyzed with SHEsis software. Four haplotypes of IL-4R α comprised two alleles of each of two polymorphism sites. The haplotype Q576I75 was more frequent in allergic patients than in the controls (42 vs. 35%, $P=0.037$; Table 4), indicating that the haplotype Q576I75 was associated with penicillin allergy.

To check the result of haplotype analysis, we divided the 242 allergic patients and 220 controls into nine groups according to the genotypes of Q576R and I75V. The genotypes of Q576R-AA and I75V-AA were more frequently observed in allergic patients than in controls (17 vs. 10%, $P=0.041$, Table 5), implying that the genotypes of Q576R-AA and I75V-AA are associated with penicillins allergy.

Discussion

Penicillins are used to treat numerous infectious diseases, but the high incidence of latent allergic reaction among patients is a major clinical concern [21]. The classic mechanism of the immediate allergic reaction to penicillins is characterized by the induction and formation of IgE [22]. Interleukin-4 is the major cytokine formed during the process of IgE synthesis through the adhesion of IL-4R alpha onto the target cell surface [8]. There is an abundant body of empirical evidence demonstrating the association of IL-4R genetic polymorphisms and atopic disease, thereby implying that the specific genetic markers may be limited to specific traits and groups of patients [23–25]. More recently, studies on IL-4R SNPs and haplotypes in association with penicillin allergy have been carried out in a number of research departments of Europe and America [13–16]. Our group has also done some work in this field [2–5, 17]. Following on earlier work, in this study, we enlarged the sample size, subdivided the patient groups according to different indexes, and studied not only SNPs but also linkage disequilibrium and haplotypes of IL-4R in order to evaluate its association with penicillin allergy.

IL4R α Q576R and penicillin allergy

As IL-4 exerted its biological function through its receptor, the IL-4R α gene may be a candidate gene for allergic disease. However, this possibility is the subject of much debate. Mitsuyasu et al. concluded that IL4R α Q576R was not related to asthma [26]; however, Rosa-Rosa, based on a study of 149 patients, came to the conclusion that the IL4R α R576 allele was correlated with the allergic reaction [19]. In contrast, we determined that the IL4R α Q576 allele was closely related to penicillin allergy (87 vs. 80%, $P=0.003$). We also found that the AA genotype of IL-4R α Q576R was more frequently present in penicillin-allergic patients than in the controls (76 vs. 64%, $P=0.005$). A similar result was also observed between patients with a positive skin test and the controls (77 vs. 64%, $P=0.007$). These novel findings may partly be explained by the following reason. Although both are allergic reactions, the underlying mechanisms of asthma and penicillin allergy are partly different. Whether the activation of the allergen and the chain reaction of allergy are the same is as yet undetermined. In addition, with the individual variance of allergic populations, these research findings defined in a Chinese population may be different to the results from

Table 5 Genotype frequencies of Q576R and I75V in penicillin-allergic patients and controls

Genotype		Patients (%)	Controls (%)
Q576R	I75V		
AA	AA	40 (17) ^a	22 (10)
AA	AG	97 (40)	79 (36)
AA	GG	48 (20)	41 (19)
AG	AA	15 (6)	16 (7)
AG	AG	29 (12)	37 (17)
AG	GG	8 (3)	15 (7)
GG	AA	2 (1)	3 (1)
GG	AG	3 (1)	5 (2)
GG	GG	0 (0)	2 (1)

^a $P=0.041$ vs. controls

Western countries. Recently, focusing on the relationship of beta-lactams with IL-4R α , Gueant-Rodriguez et al. reported that the IL4R α Q576 allele is associated with the risk of beta-lactam allergy ($P=0.0152$) [13]. This results is similar ours and supports our first explanation.

IL-4R α I75V and penicillin allergy

An interesting finding of our study was the association between the AA genotype of IL-4R α I75v and the symptoms of urticaria. Previous research revealed that the variant IL-4R α I50 (another name of I75) was associated with elevated total serum IgE and enhanced signaling [27]. Recently, Apter et al., based on a study of 23 self-reported penicillin-allergic patients, reported that the IL-4R α I75V polymorphism had no relationship with penicillin allergy [14]. However, another recent study by Gueant et al. showed that the IL-4R α I75V of the AA genotype was more significantly associated with the risk of penicillin allergy than with the risk of cephalosporin allergy and that a difference in the AA genotype frequency of IL-4R α I75V existed between two Europeans populations [15]. In our study, the incidence of the I75V-AA genotype was significantly higher in the urticaria group than in the controls (73 vs. 64%, $P=0.049$). One of the possible explanations for this is that there was a difference in the AA genotype frequency of IL-4R α I75V between the different populations. This explanation is supported by the research of Gueant et al. [15]. The other possible explanation is that I75V was possibly not involved causally in contributing to penicillin allergy, but was in linkage disequilibrium with a locus in the IL-4R α gene or a nearby gene in chromosome 16p. This possibility is supported by the research of Hackstein et al. which showed that I50V is significantly associated with the polymorphism of S478P [28]. These two alternative explanations indicate that the relationship between IL-4R α I75V and penicillin allergy needs to be further researched.

Haplotype of IL-4R α gene and penicillin allergy

In the haplotype analysis of the IL-4R α gene, we found that the frequency of the haplotype Q576I75 in penicillin-allergic patients was higher than that in the controls (42 vs. 35%, $P=0.037$), indicating that the haplotype Q576I75 is associated with penicillin allergy in the Chinese population. The aim of our haplotype analysis was to confirm the SNP association. The association of the Q576 and I75 combination with penicillin allergy was not greater than that of the Q576 allele alone, suggesting that the haplotype analysis did not add provide any more information than the single SNP analyses.

Conclusion

Our results have a certain clinical implication. The identification of genetic risk factors may improve the diagnosis and understanding of the pathophysiology of penicillin allergy. The genetic test for IL-4R α may provide a tool by which to screen potential patients with a high risk of penicillin allergy and to predict the severity of the allergic reaction, if it can be applied to general clinical practice. This genetic test may also help patients to avoid severe allergy—even death—caused by the skin test; this is especially true for hypersensitive patients. In the future, once the field of candidate genes has been narrowed down, we will be better able to understand the mechanism of penicillin allergy and to target therapies. The main findings of our study are: (1) the IL4R α Q576 allele is related to penicillin allergy; (2) the IL-4R α I75 allele is associated with the symptom of urticaria; (3) the haplotype of IL-4R α Q576I75 may be related somehow with penicillin allergy. Our observations warrant further research aimed at exploring and identifying the mechanism of penicillin allergy.

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