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Polymorphisms of STAT6 and specific serum IgE levels in patients with penicillin allergy

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Key words
penicillin allergy –
STAT6 – polymorphism

Abstract. **Objective:** Signal transducer and activator of transcription (STAT) 6 signaling pathway is required for mediating the biologic functions of interleukin (IL)-4 which is proved to play an important role in the pathogenesis of allergic diseases and the induction of specific immunoglobulin (Ig) E synthesis. The current studies are conducted to evaluate the relationship between polymorphisms of STAT6, specific IgE and penicillin allergy. **Materials and methods:** In 242 patients with penicillin allergy and 220 controls, polymorphisms of STAT6 in2SNP3 and 3'UTR SNP3 were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Eight kinds of specific IgE to penicillins were detected with radioallergosorbent test (RAST). **Results:** For STAT6 in2SNP3, the frequency of the CC genotype was significantly higher in all patients than in controls (60 vs. 47%, $p = 0.005$). A similar result was observed between patients of the urticaria group and controls (70 vs. 47%, $p = 0.005$). With respect to allele frequency, the C-allele occurred more frequently in all patients and in the urticaria group than in controls (78 vs. 69%, $p = 0.002$; 83 vs. 69%, $p = 0.007$). **Conclusions:** Our finding suggests that STAT6 in2SNP3 is associated with penicillin allergy, but has no effect on the specific IgE levels of patients with penicillin allergy.

tions are still not fully understood. In order to study further mechanisms of penicillin allergy, many researches [1, 7, 9], including our own [4, 10, 16, 17, 18, 27], have been performed, which involve the relationship between penicillin allergy and total or specific serum IgE, cytokines, and related gene polymorphisms, e.g., polymorphisms of IL-4, IL-10, IL-13, IL-4- α receptor, interferon (IFN)- γ 1 receptor, IFN- γ 2 receptor and signal transducer and activator of transcription (STAT) 6. Of these genes, STAT6 polymorphisms located in intron 2 (C2892T) and the 3'untranslated region (UTR) (T12888C) are reported to contribute significantly to elevated total serum IgE levels [6, 20, 23], meanwhile STAT6 C2892T is thought to increase an individual's susceptibility to asthma and contribute to the pathogenesis of asthma [24]. Another STAT6 polymorphism located in 3'UTR (G2964A) displays inconsistent result in allergic disease [11, 12, 25].

STAT6, one of the protein family of signal transducer and activators of transcription (STATs), is required for mediating the biologic functions of IL-4. Our group has carried out some researches in the field of single nucleotide polymorphisms (SNPs) of regulative genes in the Th2 signaling pathway, such as IL-4, IL-13 and IL-4- α receptor, and has evidenced that IL-4 and IL-4 receptor genes are linked to penicillin allergy [10, 18, 27]. Similar conclusions are observed in the field of asthma and atopy [2, 19]. In order to study pharmacogenetics of penicillin allergy, adverse reaction of penicillins, and following on our previous researches, we chose STAT6 in2SNP3 (C2892T, NCBI SNP CLUSTER ID: rs324011) and 3'UTR SNP3 (T12888C, NCBI SNP CLUSTER ID: rs1059513) to detect polymorphisms in 242 penicillin-allergic patients and 220 controls in this study.

Introduction

Penicillins have a long history in clinical practice, but the high prevalence of penicillin allergy limits their application. It is reported that 10% of hospitalized patients have penicillin allergy, and allergic prevalence is as frequent as 2% in patients treated with penicillin [1]. In the pathogenesis of penicillin allergy, IgE, cytokines regulating IgE synthesis (mainly interleukin (IL)-4 and IL-13) and related IL-4/IL-13 signaling pathway play important roles [8], but their exact func-

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Table 1. The clinical data of controls and penicillin-allergic patients.

Groups	Controls	Patients
All patients	220	242
Age (Mean $\pm$ SD, range)	20.35 $\pm$ 2.14 (16 – 24)	20.13 $\pm$ 2.09 (16 – 24)
Gender (%)		
Male	125 (57)	133 (55)
Female	95 (43)	109 (45)
Skin test ^a		
Positive skin test	0	185
Negative skin test	220	57
Allergic symptoms ^b		
Shock		12
Urticaria		44
Other symptoms		16
Allergic type ^c		
Immediate reactions		46
Non-immediate reaction		26

^aOf a total of 242 allergic patients 185 patients were recruited because of positive skin test. Other 57 patients presented typical allergic symptoms after penicillins administration but showed negative reaction of skin test. ^bA total of 72 patients presented allergic symptoms. Other patients just presented positive skin test but no systemic symptom. ^cPatients with allergic symptoms were categorized as immediate group (≤ 1 h) and non-immediate group (> 1 h) according to the onset of allergic symptoms.

At the same time, we determine the levels of specific serum IgE, and investigate gene-antibody association in penicillin allergy. To the best of our knowledge, there is still no report on the relationship between these polymorphisms of STAT6 and specific serum IgE levels in patients with penicillin allergy.

Materials and methods

Subjects and grouping

We prospectively studied 242 consecutive patients with penicillin allergy in the first affiliated hospital of Zhengzhou University. The clinical characteristics are summarized in Table 1. All patients were interviewed by allergists and our group. We used a detailed questionnaire that was designed by our group and had been applied in our previous studies [4, 16, 17, 18, 27]. The questionnaire included full history of penicillin allergy (penicillin G, phenoxymethyl penicillin, ampicillin, amoxicillin, etc.), other drug allergy, allergic diseases (including anaphylactic shock, urticaria, asthma, allergic rhinitis, etc.) and allergic family history.

Of a total of 242 allergic patients, 185 patients were recruited because of positive skin

test (see the method in the section of skin test). Other 57 patients presented typical allergic symptoms after penicillin administration but showed negative reaction in the skin test. Meanwhile, of patients with positive skin test, 15 patients presented systemic allergic symptom (shock or urticaria) shortly after skin test administration. Combined with patients with negative skin test, a total of 72 patients with typical symptoms were subdivided into three symptom groups: shock group, urticaria group and other symptoms (pruritus, dyspnea, angioedema, bronchospasm, and other allergic symptoms expect for shock and urticaria) group. Besides, patients with allergic symptoms were also categorized as immediate group and non-immediate group according to the initiation time of allergic symptoms. The immediate group was defined as allergic symptoms occurring within 1 h (including 1 h) after drug administration and non-immediate group was defined as allergic symptoms occurring later than 1 h.

A total of 220 controls was recruited (Table 1). These controls, who had used penicillins previously without any reported reactions, presented negative results of skin test. They were excluded if they had experienced any 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 this study and this study was carried out under the approval of the Ethics Committee, Zhengzhou University.

Blood samples

Blood samples were drawn and clotted for 2 h at room temperature. Then 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 standard phenol chloroform extraction followed by ethanol precipitation.

Skin test

Skin test was performed in all enrolled subjects. The method of skin test has been described in detail in our previous studies [18]. Briefly, Penicillin G sodium salt was di-

luted in saline solution until reaching a concentration of 200 U/ml as reagent. The volume of 0.1 ml (20 U) of reagent was injected for intradermal testing on the inner side of the forearm. The diameter of wheal was measured after 20 min of skin test. Positive reaction of skin test was defined as the diameter of erythema area greater than 5 mm.

Genotyping

Genotypes and alleles of STAT6 in2SNP3 and 3'UTRSNP3 polymorphisms were detected by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP).

The amplification of in2SNP3 and 3'UTRSNP3 were carried out with the following primers respectively: 5'-AAC TAA ATC CTC TGC CAC TC-3' and 5'-TCC CAT AGA TAG CCC TCC -3'; 5'-GGA CGG ATA GGC AGG AAC ATA CA -3' and 5'-ACG AAG AAT CTC AGC CCT TGG AC -3'. The program was accomplished by 36 cycles at 95 °C for 30 s, 52 °C (in2SNP3) or 58 °C (3'UTRSNP3) for 30 s, 72 °C for 50 s, and a final 8 min extension at 72 °C. The negative (water) control was set in every amplification cluster. If the negative control showed to be amplified, the amplification cluster perhaps was polluted and should be forsaken. The successful rate of amplification was 85 – 100%. Random repetition was enforced to detect the repeatability of experiment.

PCR product for in2SNP3 was 217 bp long and was digested with BmgT120I restriction enzyme. The 217-bp DNA product from CC homozygous individuals was digested into 192- and 25-bp fragments, that from CT heterozygous individuals showed 217-, 192-, and 25-bp fragments, and that from TT homozygous individuals only showed 217-bp fragment. PCR product for 3'UTRSNP3 was 259 bp long, which included a site, besides site of polymorphism, can be digested with EcoT141 restriction enzyme. So, the 259-bp DNA product from TT homozygous individuals was digested into 168-, 20- and 71-bp fragments, that from CT heterozygous individuals was digested into 188-, 168-, 20- and 71-bp fragments, and that from CC homozygous individuals should show 188- and 71-bp fragments, but had not been detected in the

study. Digested fragments were separated on 3% agarose gel. Random repetition was performed in the procedure of enzyme digestion to verify the correctness of genotyping.

Radioallergosorbent test (RAST)

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) [28]. The test was performed according to the method of our previous report [17].

Statistical analysis

Descriptive variables for quantitative and qualitative values were given by means and absolute numbers or frequencies, respectively. Descriptive statistics was performed using SPSS 13.0. The deviation from the Hardy-Weinberg equilibrium was tested with Pearson's χ^2 -test for any of the SNPs under consideration. Comparisons of statistical significance were performed using Mann-Whitney U-test (two-tailed p value) and Kruskal-Wallis H-test. The alleles frequencies of STAT6 in2SNP3 polymorphism between controls and patients were compared using Pearson's two-tailed χ^2 -test or Fisher's exact test. Comparisons of the means of specific IgE were performed using one-way analysis of variance. A p value less than 0.05 was considered statistically significant. Logistic regression was used to evaluate the relationship of alleles with penicillin allergy.

Results

Genetic polymorphism in controls and penicillin-allergic patients

We detected genotypes and alleles of STAT6 in2SNP3 and 3'UTRSNP3 polymorphisms. For STAT6 in2SNP3 (Table 2), the

Table 2. Genotype and allele distribution of STAT6 in2SNP3 polymorphism in penicillin-allergic patients.

STAT6 in2SNP3	n	Genotype frequency (%)			p value ^a	Allele frequency (%)		p value ^a
		CC(%)	CT (%)	TT (%)		C (%)	T (%)	
Controls	220	104 (47)	94 (43)	22 (10)		302 (69)	138 (31)	
All patients	242	144 (60)	88 (36)	10 (4)	0.005	376 (78)	107 (22)	0.002
Skin test								
Positive	185	108 (58)	70 (38)	7 (4)	0.026	286 (78)	83 (22)	0.005
Negative	57	36 (63)	18 (32)	3 (5)	0.033	90 (79)	24 (21)	0.031
p value ^a					0.52			0.74
Symptoms								
Shock	12	7 (58)	4 (34)	1 (8)	0.46	18 (75)	6 (25)	0.51
Urticaria	44	31 (70)	11 (25)	2 (5)	0.005	73 (83)	15 (17)	0.007
Others	16	9 (56)	6 (38)	1 (6)	0.49	24 (75)	8 (25)	0.45
p value ^b					0.51			0.25
Allergic type								
IR ^c	46	30 (65)	15 (33)	1 (2)	0.027	75 (82)	17 (18)	0.013
NIR ^d	26	17 (65)	6 (23)	3 (12)	0.081	40 (77)	12 (23)	0.22
p value ^b					0.99			0.51

^ap value of comparison between controls and patients in each group; ^bp value of comparison inside each classification; ^cIR = immediate reactions; ^dNIR = non-immediate reactions.

frequency of the CC genotype was significantly higher in all patients than in controls (60 vs. 47%, $p = 0.005$). A similar result was observed between patients of the urticaria group and controls (70 vs. 47%, $p = 0.005$). With respect to allele frequency, the C-allele occurred more frequently in all patients and the urticaria group than in controls (78 vs. 69%, $p = 0.002$; 83 vs. 69%, $p = 0.007$). The comparisons were performed in each group (group of positive skin test vs. group of negative skin test, shock group vs. urticaria group vs. other symptom group, group of immediate reactions vs. group of non-immediate reactions). No statistically significant difference was found in these comparisons. For STAT6 3'UTR SNP3, we detected genotypes in 64 patients and 22 controls at first, but most of them were TT genotype except 3 patients who were TC genotype. As the frequency of T-allele was about 88% according to the report [20, 23], 242 patients in this research were perhaps not enough. So the research of STAT6 3'UTR SNP3 polymorphism was stopped ahead of schedule.

Specific IgE antibodies in controls and penicillin-allergic patients

Eight types of penicillin-related specific serum IgE were determined in all patients

and controls (Table 3). Every mean value of specific IgE in patients was higher than that in controls. Statistically significant differences were found in seven types of specific IgE except APO-IgE. Next, patients with CC genotype, CT genotype and TT genotype were compared with controls, respectively. A novel result was found, that 6, 4 and 3 kinds of specific IgE in CC-patients, CT-patients and TT-patients, respectively, were significant higher than in controls ($p < 0.01$). In other words, patients with more C-allele displayed more types of elevated specific IgE. At last, because we had drawn a preliminary conclusion that CC genotype had relationship with penicillin allergy from preceding study, comparisons between patients with CC genotype and patients with other genotypes were performed. However, no statistically significant difference was observed.

Discussion

This study detected STAT6 in2SNP3 polymorphism in 242 penicillin-allergic patients and 220 controls, and STAT6 3'UTR SNP3 polymorphism in 64 penicillin-allergic patients and 22 controls. We found that CC genotype of STAT6 in2SNP3 was associated with penicillin allergy, which to our knowledge is the first report on this association, and then presumed that CC genotype

Table 3. Specific IgE levels in radioallergosorbent test (RAST) in controls and patients according to STAT6 in2SNP3 polymorphism.

Group	n	Specific IgE (RAST value, mean $\pm$ SD) ^a							
		BPO	PVO	APO	AXO	BPA	PVA	APA	AXA
Controls	220	0.53 $\pm$ 0.52	0.48 $\pm$ 0.58	0.57 $\pm$ 0.53	0.45 $\pm$ 0.23	0.79 $\pm$ 0.46	0.75 $\pm$ 0.30	0.74 $\pm$ 0.52	0.57 $\pm$ 0.41
All patients	242	0.69 $\pm$ 0.50	1.03 $\pm$ 0.72	0.60 $\pm$ 0.73	0.54 $\pm$ 0.41	1.15 $\pm$ 0.85	0.94 $\pm$ 0.47	0.89 $\pm$ 0.39	0.88 $\pm$ 0.46
p value ^b		0.011	0.000	0.72	0.053	0.000	0.001	0.006	0.000
CC	145	0.71 $\pm$ 0.51	1.1 $\pm$ 0.78	0.62 $\pm$ 0.78	0.57 $\pm$ 0.43	1.09 $\pm$ 0.67	0.97 $\pm$ 0.51	0.91 $\pm$ 0.42	0.88 $\pm$ 0.46
p value ^c		0.009	0.000	0.62	0.02	0.000	0.001	0.008	0.000
CT	87	0.65 $\pm$ 0.47	0.94 $\pm$ 0.64	0.58 $\pm$ 0.67	0.47 $\pm$ 0.37	1.10 $\pm$ 0.64	0.90 $\pm$ 0.37	0.84 $\pm$ 0.33	0.89 $\pm$ 0.45
p value ^c		0.11	0.000	0.93	0.61	0.000	0.006	0.15	0.000
TT	10	0.74 $\pm$ 0.50	1.06 $\pm$ 0.46	0.55 $\pm$ 0.30	0.75 $\pm$ 0.44	2.30 $\pm$ 2.58	0.90 $\pm$ 0.58	1.14 $\pm$ 0.38	0.80 $\pm$ 0.48
p value ^c		0.23	0.003	0.90	0.001	0.000	0.20	0.02	0.10
CT+TT	97	0.66 $\pm$ 0.48	0.95 $\pm$ 0.62	0.58 $\pm$ 0.64	0.50 $\pm$ 0.39	1.22 $\pm$ 1.06	0.90 $\pm$ 0.39	0.87 $\pm$ 0.35	0.88 $\pm$ 0.45
p value ^d		0.39	0.15	0.62	0.17	0.19	0.19	0.44	0.97

CC, CT and TT represent patients with CC, CT and TT genotype, respectively. ^aBPO = benzylpenicilloyl; PVO = phenoxomethylpenicilloyl; APO = ampicilloyl; AXO = amoxicilloyl; BPA = benzylpenicillanyl; PVA = phenoxomethylpenicillanyl; APA = ampicillanyl; AXA = amoxicillanyl; ^bp value: controls vs. all patients; ^cp value: controls vs. patients with CC, CT or TT genotype, respectively; ^dp value: patients with CC genotype vs. patients with CT and TT genotypes.

of this site might influence initiation of penicillin allergy through elevating specific serum IgE. In order to check this presumption, we determined penicillin-related specific IgE in all patients and controls, and analyzed the relationship between specific IgE and genotypes of STAT6 in2SNP3. However, specific IgE levels in different genotypes showed no statistically significant difference.

STAT6 is one of the important proteins in the IL-4/IL-13 pathway. The pathway is triggered from IL-4 and IL-13 binding with interleukin-4 receptor- α (IL-4- α receptor). It leads to the activation of members of the Janus family of protein kinases (Jaks), which are associated with the cytoplasmic tails. Activated Jaks initiate intracellular signaling cascade, then make STAT6 become tyrosyl phosphorylated at its C-terminus. The factor by tyrosine phosphorylation dimerizes and migrates to the nucleus, where it binds to specific DNA sequence motif within promoters of IL-4- and IL-13-responsive genes, and activates the transcription of them [13]. STAT6 plays a critical role in gene regulation and IL-4- and IL-13-responsive allergic reaction, including Th2 differentiation and IgE production.

Human STAT6 gene is located at a region on chromosome 12q13.3-q24.1 which is 19 kb in length and contains 23 exons [14]. Screening all 23 exons and parts of the neighboring introns in STAT6, Duetsch [3] reported 13 single nucleotide polymorphisms (SNPs) which were all non-coding sequence. Another

screening research also identified the highly conserved exon structure of STAT6 [15, 22].

Although no coding variants can lead to amino acid change, the STAT6 gene was concerned because it plays a crucial role in the IL-4/IL-13 signaling pathway. Recently, Guglielmiet al. [9] reported, in 44 patients with immediate β -lactam allergy and 44 control subjects, that no difference was revealed in the distribution of a STAT6 SNP of intron 18. Except this, no other report was found regarding relationship between penicillin allergy and STAT6 SNPs, but there were several studies focusing on total serum IgE levels and SNPs inside intron 2 of STAT6 [3, 15, 20, 23]. One study, based on cohort of 1,407 German adults, revealed that in2SNP3 (the third SNP of intron 2) polymorphism of STAT6 influenced total serum IgE levels [23]; the other study, including 1,120 German school-children, was in consistence with this [20]. However, another research reported by Pykalainen [15], based on 245 asthmatic patients and 405 population-based controls, showed that STAT6 SNPs, including in2SNP3, had no significant association with asthma or serum total IgE levels. In our study, the incidence of the in2SNP3-CC genotype was significantly higher in the penicillin-allergic patients than in the controls (60 vs. 47%, $p = 0.005$), but specific IgE levels had no significant difference between CC and other genotypes of STAT6 in2SNP3, which was in accordance with Pykalainen [15] and differed from German researches [20, 23]. These novel findings may

partly be explained by the following reason: both of the German large sample size studies were based on normal subjects, however, our study, enforced in penicillin-allergic patients, focused on the relationship among penicillin allergy, gene polymorphism and specific IgE levels. Most of the patients, no matter which genotype they were, showed high specific IgE levels, so genotypes appeared to have a minor effect on specific IgE levels.

Besides, SNPs inside intron 2 of STAT6, polymorphisms in 3'UTR of STAT6 were concerned. 3'UTR SNP1 (another name is G2964A) polymorphism was reported to show a strong association with mild atopic asthma in the Japanese population by Gao [5]. In the next research on different allergic diseases, there were discordant results [11, 15, 26, 29]. From five SNPs in the 3'UTR of STAT6, we chose 3'UTR SNP3 (another name is T12888C) and studied it because a research in 1,120 German schoolchildren reported that 3'UTR SNP3 significantly and consistently contributed to elevated total serum IgE levels [20], and the other two large sample researches which involved 1,407 German adults [23] and 6,819 participants from the Framingham Heart [6], respectively, observed similar result. At first, we detected genotypes in 64 patients and 22 controls, but all of them were TT genotype except 3 patients who were TC genotype. So we stopped the research of 3'UTR SNP3 polymorphism ahead of schedule because of insufficient cases and the minor frequency of C-allele according to the report [20, 23].

In conclusion, our study indicates that STAT6 in2SNP3 is related to penicillin allergy, but has no effect on the specific IgE levels of patients with penicillin allergy. STAT6 in2SNP3 is located in the center of a NFkB transcription factor binding site [21], further researches should be done to find out how it influences penicillin allergy. In the future, once the field of candidate gene is identified to be narrowed, we will be able to use genetic tests to screen the potential patients with high risk of penicillin allergy and avoid the occurrence of skin test related allergic reactions.

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