

Relationships between specific serum IgE, IgG, IFN- γ level and IFN- γ , IFNR1 polymorphisms in patients with penicillin allergy

Na Gao · Hai-Ling Qiao · Lin-Jing Jia · Xin Tian ·
Yue-Wen Zhang

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Abstract

Objective The findings of numerous studies have suggested that both genetic and environmental influences are involved in the pathogenesis of allergic disease and atopy. We studied the polymorphisms in the interferon (IFN)-gamma (γ) and IFN- γ receptor 1 (IFNR1) gene with the aim of clarifying the relationships among these polymorphisms, penicillin allergy and anti-penicillin antibodies.

Methods A restriction endonuclease fragment length polymorphism (RFLP)-PCR analysis and sequencing were used to study the IFNR1 and IFN- γ polymorphisms. The presence and level of eight specific immunoglobulin (Ig)E and IgG antibodies were determined by the radioallergo-sorbent test (RAST) and enzyme-linked immunosorbent assay (ELISA), respectively.

Results The positive rates of specific IgE and IgG were 61.11 and 53.92%, respectively. There was no significant difference in the whole-allele of IFN- γ distribution between patients with a penicillin allergy and control subjects. Allele 7 (18CA repeat) was significantly less frequent in the urticaria group (3.19 vs. 11.93%) than in the controls. There was no difference in IFN- γ production among different alleles in IFN- γ . The frequency of G/A (Val/Met) in the IFNR1 gene in allergic patients was significantly less than that in the controls ($P < 0.05$). There were no significant differences in the positive rate of IgE among different alleles of IFN- γ . The same was true for the positive rate of IgG.

Conclusions The Met/Val allele in IFNR1 gene may have a protective role in the non-penicillin allergic population. The

allele 18CA repeat in IFN- γ gene may be associated with urticaria.

Keywords Genetic polymorphism · IFNR1 · IgE · IgG · Interferon-gamma · Penicillin allergy

Introduction

Penicillins are a group of highly effective antibiotics of a relatively low cost. Although they are generally nontoxic, they are one of the classes of drugs most frequently associated with allergy [1–3], with between 10 and 20% of hospitalized individuals reporting an allergic reaction to penicillin. This adverse drug reaction to penicillin has often resulted in its replacement by other drugs [4]. However, while allergic reactions to penicillins represent a serious threat to health, the mechanisms underlying this allergic response are as yet poorly understood.

A considerable body of experimental evidence indicates that penicillin allergy is associated with high serum levels of immunoglobulin E (IgE) and with an imbalance in cellular and humoral immunity. Although the pathogenic role of IgE in allergic diseases is well established, in earlier studies about 40% of patients with penicillin allergy also presented normal IgE levels [5–7]. IgE-mediated penicillin allergy represents only a fraction of these adverse reactions. Consequently, IgE antibodies to penicillin are indicative for—but not conclusive proof of—penicillin allergy [8, 9], suggesting that the IgE system is not the only one activated during an allergic reaction to penicillin. The T-cell system must also be involved because IgE production is strongly, if not absolutely, dependent on T-cell mediation.

T helper (Th) cells play an important role in the development of allergy. Although allergic diseases have

N. Gao · H.-L. Qiao (✉) · L.-J. Jia · X. Tian · Y.-W. Zhang
Department of Clinical Pharmacology, School of Medicine,
Zhengzhou University,
Zhengzhou 450052, People's Republic of China
e-mail: qiaohl@zzu.edu.cn

been linked to an enhanced Th2 immune response associated with high levels of interleukin (IL)-4, IL-5 and IL-13, accumulating evidence demonstrates that a decreased Th1 immune response is also important in the pathogenesis of these diseases and that interferon-gamma (IFN- γ) could act as a central regulator in this process [10]. IFN- γ , produced by activated T lymphocytes cells and NK cells, directly suppresses IgE synthesis and inhibits the Th2 cell developmental process. IFN- γ exerts its various biologic effects through its binding to the cell-surface ligand-binding chain IFN- γ receptor 1 (IFNR1) in combination with its signaling chain, IFN- γ receptor 2 (IFNR2) [11, 12]. Receptor binding of IFN- γ activates the intracellular signaling pathway, which induces the expression of various genes, including the IFN- γ regulatory factor 1 (IRF-1). Western blotting has also revealed that the prototype β -lactam benzylpenicillin conjugates to human IFN- γ but not to IL-4 [13].

Although environmental factors are important in the development of any allergy, there is also a strong genetic predisposition. Genome-wide searches have linked chromosome loci of the IFN- γ , IFNR1, IFNR2 and IRF1 genes to a predisposition for atopy and asthma [12, 14–17]. A CA repeat microsatellite polymorphism in intron 1 of the IFN- γ gene has been associated with atopic asthma in Japanese children [18]. Khani-Hanjani et al. [19] reported a strong association between the microsatellite polymorphism of the IFN- γ gene and susceptibility to, and severity of, rheumatoid arthritis, but Constantin et al. [20] failed to confirm the association. Tanaka et al. [21] demonstrated that the genetic polymorphism found within the IFNR1 gene (Val14Met) may result in a shift to Th2, and this shift may increase susceptibility to systemic lupus erythematosus.

IFN- γ and its associated genes may be responsible for an inherited predisposition to a penicillin allergic reaction. To study this possibility in a Chinese population, we measured IFN- γ levels in serum of Chinese patients with an allergy to penicillin and control subjects (from the general population) and analysed the polymorphisms of two genes, a CA repeat polymorphism within the first intron of the IFN- γ gene and single nucleotide polymorphisms (SNPs) in codon 14 Val/Met in the IFNR1 gene. Our aim was to determine a possible association between these two genes and the allergic reaction to penicillin.

Materials and methods

Subjects studied

A total of 144 patients with a penicillin allergy (81 males and 63 females; mean age 24.05 years; range 15–80 years) and 88 healthy volunteers (48 males and 40 females; mean

Table 1 The clinical data and positive rates of anti-penicillins' antibodies in patients with penicillin allergy

Group	IgE		IgG	
	<i>n</i>	Positive rate (%)	<i>n</i>	Positive rate (%)
Patients	144 ^a	61.11	102	53.92
According to gender				
Male	81	67.90	53	47.17
Female	63	52.38	49	61.22
According to the result of skin test				
Positive skin test (PST)	35	77.14	16	56.25
Negative skin test (NST) ^b	109	55.96	86	53.49
According to allergic symptoms				
Anaphylactic shock	40	57.50	35	54.28
Urticaria	47	55.32	41	58.54
Other symptoms ^c	22	54.54	10	30.00
According to the time interval between drug administration and the onset of symptoms				
Immediate reaction (IR)	67	52.24	56	48.21
Non-immediate reaction (NIR)	42	61.90	30	63.33

^a Immunoglobulin (Ig)E was determined in serum samples taken from 144 patients; of these, 102 patients were determined to have IgG

^b NST, Patients with typical clinical symptoms after penicillin administration when skin tests were negative

^c "Other symptoms" refer to all allergic symptoms except anaphylactic shock and urticaria (e.g. angioedema, bronchospasm and maculopapular eruption, among others)

age 24.86 years; range 16–60 years) were enrolled in the study. The patients were mainly recruited from the first affiliated hospital of Zhengzhou University. A questionnaire was developed and used to obtain information on their illnesses and the time and nature of the drug reactions. The patient cohort could be divided into two major groups. One group (109) consisted of patients who developed typical clinical symptoms after penicillin administration even

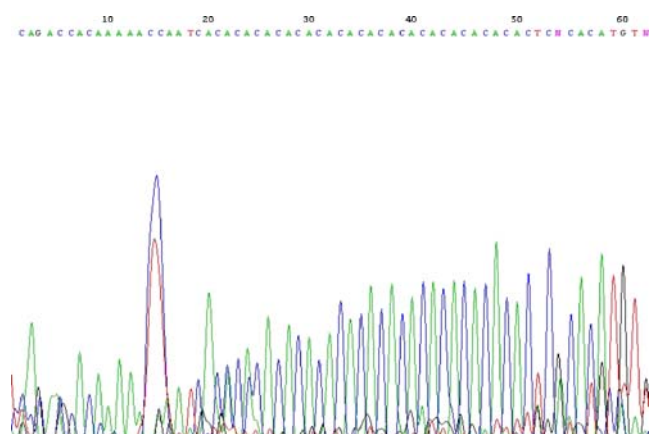


Fig. 1 DNA sequence of the 16CA repeat polymorphism within the first intron of the interferon-gamma (IFN- γ) gene (corresponding to the 129-bp PCR product)

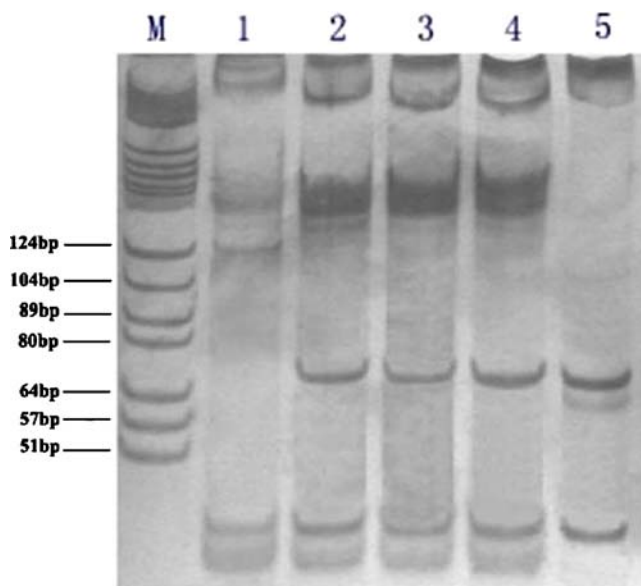


Fig. 2 PCR-restriction fragment length polymorphism (RFLP) analysis with *FokI* for the IFN- γ receptor 1 (IFNR1) 88 G/A polymorphism. Lanes 1–4 PCR products digested with *FokI*: 1 G/G88 homozygote, 2, 3, 4 G/A88 heterozygote, 5 PCR product, M marker

through the skin tests were negative (these patients were divided into those with immediate reactions and those with non-immediate reactions according to the time interval between drug intake and the appearance of clinical manifestation). Based on the allergic symptom, the patients of this group could be divided into an urticaria group (47 patients), an anaphylactic shock group (40) and an "other symptoms" group (22). The second major group (35 patients) comprised patients with positive skin tests. The skin test was performed by testing penicillin G (PG) intradermally on the inner side of the forearms. The PG sodium salt was diluted in saline solution until a concentration of 200 U/ml was reached. Approximately 0.1 ml (20 U) of reagent was injected for intradermal testing. The diameter of the wheal that developed was measured after

20 min, and the reaction was considered to be positive when the diameter was >5 mm with a surrounding area of erythema (Table 1).

The control group comprised 88 individuals recruited from the general population who answered a screening questionnaire on allergy. All individuals of the control group had no history of allergic diseases, cancer, cardiovascular disease or other atopic diseases.

Fetal cord sera samples were obtained from the third affiliated hospital of Zhengzhou University and used as negative control in the radioallergosorbent tests (RAST). Blood samples were drawn from each subject at the time of the clinical manifestations and/or at the time of a positive skin test. Informed consent was obtained from all participants or their guardians, and the study was approved by the Ethics Committee, Zhengzhou University.

RAST for detection of IgE against penicillin

We developed determinant paper disks for major antigenic determinants, such as benzylpenicilloyl-polylysine (BPO-PLL), ampicilloyl (APO)-PLL, amoxicilloyl (AXO)-PLL and phenoxymethylpenicilloyl (PVO)-PLL, and for minor antigenic determinants, such as benzylpenicillanyl (BPA)-PLL, ampicillanyl (APA)-PLL, amoxicillanyl (AXA)-PLL and phenoxomethylpenicillanyl (PVA)-PLL. The tests were performed as previously reported [5]. The RAST results reflected the uptake of the radiolabeled substance, expressed as a percentage of the maximum counts per minute (cpm). Values over the mean + 2.33 SD of the results in the control group were considered to be a positive result against the allergen being tested.

ELISA for detection of IgG against penicillins

Major and minor antigenic determinants were BPO-human serum albumin (HSA), BPA-HSA, APO-HSA, APA-HSA,

Table 2 Genotype and allele distribution of the interferon (IFN)- γ polymorphism in control and allergy subjects

IFN- γ polymorphism	Number of CA repeats	Control subjects [n=88; 176 alleles (%)]	Patients [n=144; 288 alleles(%)]	NST ^a [n=109; 218 alleles (%)]		
				Shock (n=40; 80 alleles)	Urticaria (n=47; 94 alleles)	Other symptoms (n=22; 44 alleles)
Allele 1	12 repeat	29 (16.48)	33 (11.46)	7 (8.75)	15 (15.96)	7 (15.91)
Allele 2	13 repeat	42 (23.86)	90 (31.25)	24 (30.00)	33 (35.11)	11 (25.00)
Allele 3	14 repeat	8 (4.55)	14 (4.86)	4 (5.00)	2 (2.13)	3 (6.82)
Allele 4	15 repeat	51 (28.98)	77 (26.73)	22 (27.5)	20 (21.28)	10 (22.72)
Allele 5	16 repeat	18 (10.23)	40 (13.89)	12 (15.00)	14 (14.89)	9 (20.45)
Allele 6	17 repeat	7 (3.98)	11 (3.82)	0 (0.00)	7 (7.45)	1 (2.27)
Allele 7	18 repeat	21 (11.93)	23 (7.99)	11 (13.75)	3 (3.19)*	3 (6.82)

* $P < 0.05$ vs control

^a Patients with typical clinical symptoms after penicillin administration when skin tests were negative

Table 3 Genotype and allele distribution of the IFN- γ receptor 1 (IFNR1) polymorphism in control and allergy subjects

Group	<i>n</i>	Genotype frequency		Allele frequency	
		GG (%)	GA (%)	G (%)	A (%)
Control	88	84 (95.45)	4 (4.55)	172 (97.73)	4 (2.27)
Patients	144	144 (100)	0 (0)*	288 (100)	0 (0)*

* $P < 0.05$ vs control

AXO-HSA, AXA-HSA, PVO-HSA and PVA-HSA. The penicilloylation of HSA was carried out following the method of Zhao [22]. An enzyme-linked immunosorbent assay (ELISA) was performed according to a published procedure [23]. Absorbance (*A*) was read at 490 nm using EIA Reading. Values over the mean + 2.33 SD of the results in the control group were considered to be a positive result against the allergen being tested.

Detection of the CA repeat polymorphism within the IFN- γ gene [18]

Genomic DNA was isolated from peripheral blood by standard phenol–chloroform extraction followed by ethanol precipitation. The region containing a CA repeat polymorphism within the first intron of the IFN- γ gene was amplified using the PCR method with primer pair 5'-GCT GTC ATA ATA ATA TTC AGA C-3' (upstream primer) and 5'-CGA GCT TTA AAA GAT AGT TCC-3' (downstream primer). The PCR analysis was carried out in a total volume of 25 μ l containing 20 ng of genomic DNA, 10 pmol of each primer, 1 U *Taq* polymerase and 200 μ mol/L of each deoxynucleotide triphosphate. The PCR amplification profile consisted of an initial denaturation at 95°C for 5 min, followed by 30 cycles of 95°C for 30 s, 52°C for 30 s and 72°C for 1 min, with a final extension of 72°C for 5 min. A number of PCR products

were purified and analyzed by means of direct sequencing; the remainder were run on a polyacrylamide gel (8%, 1 $\times$ TBE). The sizes of the PCR products ranged from 121 bp to 133 bp. The 129-bp product corresponded to the 16CA repeat (Fig. 1).

Detection of the SNPs in the codon 14 Val/Met polymorphism within the IFNR1 gene [21]

Mismatched PCR was performed with primers 5'-TGA GGA CGG CCC CAG ATC C-3' (downstream primer) and 5'-CTC CTA CCC CTT GTC ATG CAG GAT-3' (upstream primer; 1-bp mismatch shown in bold). Thus, the 69-bp amplified product incorporated a restriction site for the endonuclease *FokI* in the presence of G88, but not in the presence of A88. *FokI* digestion of the PCR amplicon produced 34- and 35-bp products for the G88 allele and an intact 69-bp product for the A88 allele (Fig. 2).

Cytokine assays

The levels of IFN- γ , IL-4 and IL-13 were measured using a human IFN-gamma ELISA kit, human IL-4 ELISA kit and human IL-13 ELISA kit, respectively, according to the manufacturer's instructions (Zhengzhou Xintiandi Co, China). Concentrations of unknown samples were determined from a curve obtained with the standards.

Statistical techniques

Comparisons for statistical significance were performed using the Mann–Whitney *U* (two-tailed *P* value) and Kruskal–Wallis *H* tests. The chi-square test or Fisher's exact test were used to test for a significant association between penicillin allergy and alleles or genotypes. A *P* value of <0.05 was considered to be statistically significant.

Table 4 Positive rate of IgG in different alleles of IFN- γ

Allele (<i>n</i>)	Positive rate of IgG [<i>n</i> (%)]								
	BPO	BPA	APO	APA	AXO	AXA	PVO	PVA	Total
12CA (25)	7 (28.0)	0 (0)	6 (24.0)	0 (0)	5 (20.0)	0 (0)	4 (16.0)	0 (0)	13 (52.0)
13CA (62)	13 (21.0)	0 (0)	13 (21.0)	1 (1.6)	10 (16.1)	2 (3.2)	7 (11.3)	0 (0)	33 (53.2)
14CA (9)	2 (22.2)	0 (0)	1 (11.1)	0 (0)	1 (11.1)	0 (0)	1 (11.1)	0 (0)	3 (33.3)
15CA (52)	12 (23.1)	0 (0)	11 (21.2)	0 (0)	11 (21.2)	1 (1.9)	5 (9.6)	0 (0)	30 (57.7)
16CA (29)	7 (24.1)	0 (0)	6 (20.7)	1 (3.4)	6 (20.7)	2 (6.9)	3 (10.3)	0 (0)	17 (58.6)
17CA (7)	2 (28.6)	0 (0)	5 (71.4)	0 (0)	4 (57.1)	0 (0)	3 (42.8)	0 (0)	5 (71.4)
18CA (19)	3 (15.8)	0 (0)	4 (21.0)	0 (0)	3 (15.8)	1 (5.3)	1 (5.3)	0 (0)	9 (47.4)

BPO, Benzylpenicilloyl; PVO, phenoxomethylpenicilloyl; APO, ampicilloylampicilloyl; BPA, benzylpenicillanyl; APA, ampicillanyl; AXO, amoxicilloyl; AXA, amoxicillanyl; PVA, phenoxomethylpenicillanyl

Table 5 Positive rate of IgE in different allele of IFN- γ

Allele (<i>n</i>)	Positive rate of IgE [<i>n</i> (%)]								Total
	BPO	BPA	APO	APA	AXO	AXA	PVO	PVA	
12CA (33)	9 (27.3)	4 (12.1)	7 (21.2)	2 (6.1)	6 (18.2)	4 (12.1)	6 (18.2)	3 (9.1)	20 (60.6)
13CA (88)	30 (34.1)	13 (14.8)	18 (20.4)	17 (19.3)	17 (19.3)	17 (19.3)	14 (15.9)	18 (20.4)	56 (63.6)
14CA (14)	2 (14.3)	1 (7.1)	0 (0)	0 (0)	4 (28.6)	1 (7.1)	2 (14.3)	2 (14.3)	7 (50.0)
15CA (77)	17 (22.1)	10 (13.0)	12 (15.6)	10 (13.0)	7 (9.1)	12 (15.6)	7 (9.1)	14 (18.2)	44 (57.1)
16CA (40)	12 (30.0)	8 (20.0)	8 (20.0)	7 (17.5)	9 (22.5)	7 (17.5)	10 (25.0)	7 (17.5)	25 (62.5)
17CA (11)	5 (45.4)	4 (36.4)	3 (27.3)	0 (0)	4 (36.4)	2 (18.2)	3 (27.3)	0 (0)	8 (72.7)
18CA (23)	5 (21.7)	4 (17.4)	5 (21.7)	3 (13.0)	4 (17.4)	2 (8.7)	3 (13.0)	5 (21.7)	16 (69.6)

Results

Profile of patients with penicillin allergy

The clinical data and positive rates of antipenicillin antibodies in patients participating in the study are presented in Table 1. The diagnosis of hypersensitivity to penicillins was based on clinical symptoms or a positive skin test. According to the time interval between drug administration and the onset of symptoms, reactions to beta-lactams were classified as immediate ($n=67$) and non-immediate reactions ($n=42$). Immediate reactions occurred within the first hour of penicillin administration. The positive rates of a specific IgE and IgG reaction were 61.11 (88/144) and 53.92% (55/102) (Table 1).

Association study for gene polymorphisms and penicillin allergy

As shown in Table 2, we detected seven types of the dinucleotide CA repeat polymorphism, with the repeat number varying from 12 to 18, in our Chinese population. A comparison of allele frequencies between patients with penicillin allergy and control subjects showed no differences in terms of whole-allele distribution. There was also no difference between patients with a history of penicillin allergy and those with positive skin test. When the frequency of each allele was compared between patients and the controls, allele 7 was found to be significantly less frequent in the urticaria group (3.19 vs. 11.93%, $P<0.05$). Based on allergic reaction types, there was also no difference between patients with immediate reaction (IR) and those with non-immediate reactions (NIR). The same was true for gender (data not shown).

The distribution of IFNR1 genotypes is presented in Table 3. Based on our results, we determined that the frequency of G/A (Val/Met) was significantly lower in allergic patients than the controls ($P<0.05$).

Association study for IFN- γ gene polymorphism and anti-penicillin antibodies

Among the different alleles of IFN- γ , there were no significant differences in the positive rate of IgE and IgG. The data are presented in Tables 4 and 5.

Association study for cytokine, penicillin allergy and IFN- γ polymorphism

In our study, all levels of IFN- γ , IL-4 and IL-13 were detected in the sera of 61 patients who were positive to IgE. The Spearman test did not reveal any significant correlations between IFN- γ and IL-4 or between IFN- γ and IL-13. There was, however, a significant association between IL-4 and IL-13 levels (correlation coefficient=0.95, $P<0.01$).

Based on the Mann–Whitney U test, the levels of IFN- γ , IL-4 and IL-13 were not significantly different between allergic patients with positive IgG and allergic patients with negative IgG ($P>0.05$). In terms of allergic symptoms,

Table 6 The levels of IFN- γ , IL-4 and IL-13 in patients allergic to penicillins ($n=61$)

Group	n	Level of cytokine Median (ng/L)		
		IFN- γ	IL-4	IL-13
Patients	61	24.47	78.00	11.10
According to the results of ELISA				
Patients with positive IgG	30	28.02	114.00	15.48
Patients with negative IgG	31	20.40	74.00	8.60
According to allergic symptoms				
Shock	12	28.73	49.00	6.88
Urticaria	16	28.29	54.50	8.10
Other symptoms	8	17.96	60.00	7.30

IL, Interleukin; ELISA, enzyme-linked immunosorbent assay

there was no difference among the anaphylactic shock group, urticaria group and “other symptoms” group (Table 6).

To evaluate the effect of the IFN- γ polymorphism on levels of IFN- γ , we performed association studies between them and did not find differences in IFN- γ levels among patients with different alleles.

Discussion

Although IgE- and T-cell-dependent responses are the main mechanisms involved in a penicillin allergic reaction, other immunological mechanisms can also play a role, such as cytokines and their polymorphisms. Linkage and association studies have identified a number of putative atopy genes, and some of these, including the IL-4R and IL-10 genes, have been shown to be associated with penicillin allergy or serum IgE levels [6, 23].

The secretion of IgG4 (spontaneous and IL-4-induced) has been reported to be suppressed by IFN- γ among cells from most donors [24]. IFN- γ significantly suppressed the production of IgG1, whereas IgG2 secretion was spontaneously enhanced, thus demonstrating the specificity of IFN- γ for IgG2 [25]. However, our results suggest that the level of IFN- γ is independent of IgG. Human IgG is divided into four subclasses based on the antigenicity of the heavy chains. Research on the relationships between IFN- γ and IgG subclass will be the subject of a future investigation.

The results of an earlier study from our laboratory suggest that IFN- γ , IL-4 and IL-13 play important roles in the penicillin allergic reaction [6]. These results showed that IFN- γ , IL-4 and IL-13 were present at significantly higher levels in allergic patients with positive specific IgE levels and lower levels of IFN- γ , in addition, IL-4 were observed in allergic patients with negative specific IgE compared with the control subjects. By comparing the IL-4/IFN- γ cytokine ratios, we found that the Th1/Th2 balance in the patients with positive IgE was significantly skewed towards a Th2-like response. In investigation reported here, we found that there was a significant association between IL-4 and IL-13 levels in the patients.

The gene for human IFN- γ is located on chromosome 12q24.1. It has four exons and three intervening sequences and contains a tissue non-specific enhancer element within the first intron [26]. Pravica et al. [27] demonstrated that a 12-CA repeat microsatellite allele is associated with a higher level of IFN- γ production in vitro. However, we did not find this association in our study cohort of patients allergic to penicillin. Our results showed that the distribution of IFN- γ alleles in the allergic patients was not different from that of the healthy control population. The fact that the polymorphism locates within the intron—not

exons or the promoter region—suggests that the CA repeat polymorphism is not linked with functional ones in the coding or promoter region of the IFN- γ gene [18]. Our results did show that allele 18CA in the IFN- γ gene was associated with urticaria.

We detected the genetic polymorphism of 88G/88A within IFNR1, which leads to an amino acid substitution, methionine for valine, within the signal peptide of IFNR1. A study to determine whether this polymorphism has any effect on the level of expression of IFNR1 on the cell surface revealed that there was no difference in the level of expression between the peripheral blood mononuclear cells, Val14/Val14, and Met14/Val14 [21]. We analyzed the association between this polymorphism and penicillin allergy and found that the frequency of the Met14/Val allele in allergic patients was significantly lower than that in the healthy controls, which supports the theory that the Met/Val allele may have a protective role in the non-penicillin allergic population.

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