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Correlation analysis of gene polymorphisms and β-lactam allergy*

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Abstract: A total of 64 patients with β-lactam allergy and 30 control subjects were enrolled in a case-control study. This study is aimed to analyze the relationship between β-lactam allergy and 10 single nucleotide polymorphisms (SNPs) in interleukin-10 (*IL-10*), *IL-13*, *IL-4Rα*, high-affinity immunoglobulin E-receptor β chain (*FcεRIβ*), interferon γ receptor 2 (*IFNGR2*), and *CYP3A4*, and within the Han Chinese population of Northwest China. Genotyping for the SNPs was conducted using the Sequenom MassARRAY® platform. SPSS 17.0 was employed to analyze the statistical data and SHEsis was used to perform the haplotype reconstruction and analyze linkage disequilibrium of SNPs of *IL-10* and *IL-13*. The results showed that the genotype distribution of *CYP3A4* rs2242480/CT differed significantly between case and control groups of males (P=0.022; odds ratio (OR)=0.167, 95% confidence interval (CI): 0.032–0.867). Further analysis showed that CCA, CCG, and TAA haplotypes of *IL-10* had no significant correlation in patients with β-lactam allergy. The correlation between CCT and CAC haplotypes of *IL-13* and β-lactam allergy needs to be further studied. The analysis did not reveal any differences in the distribution of others gene polymorphisms between cases and controls.

Key words: Allergy, β-Lactam, Interleukin (IL), Pharmacogenomics, Single nucleotide polymorphism (SNP)
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1 Introduction

β-Lactams are widely used in clinical practice worldwide. However, it is difficult to prevent adverse reactions of the drug (Prematta *et al*., 2012; Torres *et al*., 2014). Penicillin G presented the most serious allergic reactions with an incidence of 0.7%–10%, and anaphylactic shock with an incidence of 0.004%–0.018%, within which there was a 10%–20% mortality rate. The incidence of skin rash as a result of using ampicillin is greater than 10%. Urticaria, angioneurotic edema, gastrointestinal reactions, and aplastic anemia are the most common allergic symptoms, which may lead to anaphylactic shock and death (Bousquet *et al*., 2009; Comte *et al*., 2012; Lee, 2014). However, the mechanism of β-lactam antibiotics inducing the allergic reactions remains unclear (Comte *et al*., 2012).

The present study attempts to identify the underlying genetic mechanisms involved in the allergic reactions caused by β-lactam antibiotics. The correlation between β-lactam allergy and the single nucleotide polymorphisms (SNPs) of genes such as interleukin-10 (*IL-10*) rs1800871, *IL-10* rs1800872, *IL-10* rs1800896, *IL-13* rs20541, *IL-13* rs1881457, *IL-13* rs1800925, *IL-4Rα* rs1801275, high-affinity immunoglobulin E-receptor β chain (*FcεRIβ*) rs569108, interferon γ receptor 2 (*IFNGR2*) rs9808753, and *CYP3A4* rs2242480 was assessed within the Han Chinese population of Northwest China by performing multiplex polymerase chain reaction (PCR) using iPLEX single-base extension technology from

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Sequenom MassARRAY® (Bo'ao Biotechnology Co., Beijing, China) and matrix-assisted laser desorption/ ionization-time of flight (MALDI-TOF). The relationship between the haplotype and β-lactam allergy was also further analyzed. This study provides data concerning the genetic diagnosis for patients with β-lactam allergy, and further clarifies the relationship between pharmacogenomics and the efficacy and safety of drugs. These findings also provide evidence that several new genetic targets can be utilized in the diagnosis and prevention of the adverse drug reactions to antibiotics and that treatment can be provided for a specific target gene with polymorphic variation.

2 Materials and methods

2.1 Subjects

The subjects for this study were recruited from the outpatient department of Lanzhou University Second Hospital (Lanzhou, China) between Jan. 2010 and Apr. 2013. The allergic work-up was performed according to the European Network for Drug Allergy guidelines (Torres *et al*., 2002; 2003). The case group had to have a history compatible with an immediate reaction to β-lactam and with a positive result of skin tests. Skin tests were made with major and minor determinants of benzyl penicillin (penicilloyl-polylysine and minor determinant mixture (MDM) containing benzyl-penicillin, sodium benzyl-penicilloate, and benzyl-penicilloic acid at a final concentration of 1.5 mmol/L) (Torres *et al*., 2003; Guéant *et al*., 2015). The control group included the patients who presented negative skin test to β-lactam and had no history of allergic, dermatologic, or respiratory diseases, or autoimmune diseases such as asthma, eczema, allergic rhinitis, and urticaria. All the subjects were selected from the Han Chinese population of Northwest China and matched for age, race, and gender. Of the 94 patients enrolled, 64 (33 males and 31 females) were included in the case group (mean age: (42.04±14.4) years) and 30 (15 males and 15 females) were included in the control group (mean age: (41.73±6.06) years). There was no significant differences in the average age or gender between the two groups (P=0.888).

The study protocol and medical informed consent were approved by the ethical committee of Lanzhou University Second Hospital (Lanzhou, China). In accordance with the medical informed consent, 3 ml of whole blood was drawn in ethylene diamine tetraacetic acid (EDTA) tubes from all subjects, and was stored at −20 °C whilst awaiting analysis.

2.2 Genomic DNA extraction

Genomic DNA was extracted from 200 μl of venous blood anticoagulated with EDTA using the QuickGene DNA whole blood kit (Shenggong, Shanghai, China) as per the manufacturer's instructions. All DNA samples were tested using the NanoDrop 2000 spectrophotometer (Thermo Scientific, USA) for evaluation of template quality and quantity, and then adjusted to a concentration of 20 ng/μl and stored at −40 °C.

2.3 Gene polymorphism analysis of the SNPs

The following 10 SNPs of six genes that might increase the susceptibility to β-lactam allergy were selected: *IL-10* rs1800871, *IL-10* rs1800872, *IL-10* rs1800896, *IL-13* rs20541, *IL-13* rs1881457, *IL-13* rs1800925, *IL-4Rα* rs1801275, *FcεRIβ* rs569108, *IFNGR2* rs9808753, and *CYP3A4* rs2242480. The primers were synthesized by Invitrogen Co. (Shanghai, China; Table 1). The iPLEX® Gold Reagent kit (SEQUENOM Co., USA) was used for SNP genotyping. MassARRAY Nanodispenser RS1000 (SEQUENOM Co., USA) was used for chip spotting. MassARRAY Analyzer Compact (SEQUENOM Co., USA) was used for mass spectrometry detection and analysis.

2.4 Plex PCR

Plex PCR was performed with a total volume of 5 μl, and the reaction mixture contained 10 ng DNA, 0.5 U Hotstar Taq, 0.5 pmol of each primer, and 0.1 μl of 25 mmol/L dNTP. The PCR reaction conditions were as follows: 94 °C for 4 min; 45 cycles of 94 °C for 20 s, 56 °C for 30 s, and 72 °C for 1 min; final 3 min extension at 72 °C, and then kept at 4 °C.

2.5 Purification of the PCR product

Firstly, the remanent dNTP was removed by adding 0.5 U shrimp alkaline phosphatase (SAP) into the PCR product. The reaction mixture that contained 5 μl PCR product and 2 μl SAP buffer (0.5 U SAP, 0.17 μl buffer) was incubated at 37 °C for 20 min and 85 °C for 5 min and then kept at 4 °C.

Table 1 Primer sequences for β-lactam allergy-related SNPs

SNP	Primer sequence (5'→3')	
	Forward	Reverse
rs1800871	ACGTTGGATGGGTGTACCCTTGTACAGGTG	ACGTTGGATGGACCCCTACCGTCTCTATTT
rs1800872	ACGTTGGATGAAGCAGCCCTTCCATTTTAC	ACGTTGGATGCCTGGAACACATCCTGTGAC
rs1800896	ACGTTGGATGGACAACACTACTAAGGCTTC	ACGTTGGATGTGGATAGGAGGTCCCTTACT
rs20541	ACGTTGGATGTGATGCTTTCGAAGTTTCAG	ACGTTGGATGCCAGTTTGTAAAGGACCTGC
rs1881457	ACGTTGGATGGGCCCTCTACTACAGATTAG	ACGTTGGATGTGCCTGGAGTGCCGCTACTT
rs1800925	ACGTTGGATGGGGTTTCTGGAGGACTTCTA	ACGTTGGATGTGCAGCCATGTCGCCTTTTC
rs1801275	ACGTTGGATGAAATGTCCTCCAGCATGGG	ACGTTGGATGACCCTGCTCCACCGCATGTA
rs569108	ACGTTGGATGTTACAGTGAGTTGGAAGACC	ACGTTGGATGCTGGACACGTGATTCTTATA
rs9808753	ACGTTGGATGCAGTGGCCCTGAGCAATAG	ACGTTGGATGGATCCAACAGAAATACCGGC
rs2242480	ACGTTGGATGGCAGGAGGAAATTGATGCAG	ACGTTGGATGTAAGGTTTCACCTCCTCCCT

2.6 Single-base extension and resin purification

In total, 7 μl SAP-treated PCR product, 0.804 μl primer mixture, 0.041 μl iPLEX, and 0.2 μl extension mixture were combined in an Eppendorf tube. The reaction conditions were as follows: 94 °C for 30 s; 40 cycles of 94 °C for 5 s, 52 °C for 5 s, 80 °C for 5 s, and 94 °C for 5 s; and final 3 min extension at 72 °C. Each extension product was purified using 6 mg Clean Resin (SEQUENOM Co., USA).

2.7 Chip spotting and mass spectrometric examination

The purified product was examined by SpectroCHIP (SEQUENOM Co., USA). SpectroCHIP was analyzed by MALDI-TOF, and the results were exported using TYPER Version 4.0 (SEQUENOM Co., USA).

2.8 Statistical analysis

All data were analyzed using statistical software SPSS 17.0. The relationships between the nine SNPs and β-lactam allergy susceptibility were assessed using chi-square test for estimation of the odds ratio (OR) and 95% confidence interval (CI) for each SNP genotype. Hardy-Weinberg equilibriums of each SNP in the control group were tested using chi-square test. All the statistics were inspected using bilateral probability, and statistical significance was determined as being below the conventional level of P=0.05. Moreover, the online SHEsis software (http://analysis2.bio-x.cn/myAnalysis.php) (Shi and He, 2005) was used to analyze the linkage disequilibrium (LD) and haplotype construction. D' and r^2 were calculated for LD analysis.

3 Results

3.1 SNPs associated with β-lactam allergy

In order to increase statistical power, homozygous mutant genotypes were merged into heterozygous genotypes to conduct statistical analysis. For gender and age, no significant statistical difference was found between the trial group and the control group. The results showed that the nine SNPs such as rs1800871, rs1800872, rs1800896, rs20541, rs1881457, rs1800925, rs1801275, rs569108, and rs9808753 were not significantly correlated with β-lactam allergy in the Han Chinese population of Northwest China between the case and control groups (P>0.05; Table 2). The rs2242480/CT genotype of *CYP3A4* gene was significantly correlated with β-lactam allergy in the male patients (P=0.022, OR=0.167, 95% CI: 0.032–0.867; Table 3).

3.2 LD analysis

Three SNPs of *IL-10* such as rs1800871, rs1800872, and rs1800896 were located at the promoter region of *IL-10* (separation distance <100 bp). The LD analysis was performed to study the relationships between these three SNPs and β-lactam allergy. For patients with β-lactam allergy in the Han Chinese population of Northwest China, rs1800872 and rs1800871 showed complete linkage; rs1800896 and rs1800872, rs1800896 and rs1800871, respectively, showed strong linkage (Table 4).

The LD analysis on three SNPs of *IL-13* showed that rs1881457 and rs1800925 had strong linkage, rs1800925 and rs20541 had strong linkage. However, rs1881457 and rs20541 did not show LD (Table 5).

Table 2 Genotype and allele frequencies of SNPs from the case and control groups

Genotype	*n*/percentage (%)		*P*-value	OR (95% CI)	Allele	*n*/percentage (%)		*P*-value	OR (95% CI)
	Case	Control				Case	Control		
rs1800871					rs1800871				
CC	11/17.2	6/20.0			C	58/42.3	22/36.7		
CT	27/42.2	10/33.3	0.537	0.679 (0.198–2.326)	T	79/57.7	38/63.3	0.456	1.268 (0.679–2.369)
TT	26/40.6	14/46.7	0.983	0.987 (0.301–3.239)					
rs1800872					rs1800872				
AA	26/41.3	14/46.7			A	84/63.0	38/63.3		
AC	26/41.3	10/33.3	0.499	0.714 (0.269–1.897)	C	50/37.0	22/36.7	0.931	0.973 (0.517–1.828)
CC	11/17.4	6/20.0	0.983	1.103 (0.309–3.323)					
rs1800896					rs1800896				
AA	57/86.4	26/86.7			A	121/91.7	56/93.3		
AG	7/10.6	4/13.3	1.000	1.253 (0.337–4.657)	G	11/8.3	4/6.7	0.913	0.786 (0.240–2.576)
GG	2/3.0	0/0	1.000	0.966 (0.921–1.013)					
rs20541					rs20541				
CC	28/44.4	13/43.3			C	87/69.0	39/62.8		
CT	31/49.3	11/36.7	0.579	0.764 (0.295–1.980)	T	39/31.0	23/37.2	0.400	1.316 (0.694–2.492)
TT	4/6.3	6/20.0	0.196	3.231 (0.776–13.446)					
rs1881457					rs1881457				
AA	39/60.9	14/46.7			A	99/77.3	39/65.0		
AC	21/32.8	11/36.7	0.435	1.459 (0.564–3.778)	C	29/22.7	21/35.0	0.074	1.838 (0.938–3.602)
CC	4/6.3	5/16.6	0.173	3.482 (0.817–14.84)					
rs1800925					rs1800925				
CC	46/73	17/56.7			C	108/85.7	45/75.0		
CT	16/25.4	11/36.7	0.196	1.860 (0.721–4.801)	T	18/14.3	15/25.0	0.074	2.000 (0.928–4.313)
TT	1/1.6	2/6.6	0.406	5.412 (0.460–63.602)					
rs1801275					rs1801275				
AA	40/63.5	20/66.7			A	99/78.6	50/83.3		
AG	19/30.2	10/33.3	0.914	1.053 (0.413–2.682)	G	27/21.4	20/16.7	0.447	0.733 (0.329–1.634)
GG	4/6.3	0/0	0.300	0.909 (0.828–0.998)					
rs569108					rs569108				
CC	1/1.6	2/6.9			C	25/19.8	15/25.9		
CT	23/36.5	11/37.9	0.574	0.239 (0.020–2.930)	T	101/80.2	43/74.1	0.358	0.710 (0.341–1.477)
TT	39/61.9	16/55.2	0.466	0.205 (0.017–2.425)					
rs9808753					rs9808753				
AA	20/31.8	12/31.5			A	68/54.0	42/55.2		
AG	28/44.4	18/47.4	0.884	1.071 (0.423–2.712)	G	58/46.0	34/44.8	0.858	0.949 (0.536–1.682)
GG	15/23.8	8/21.1	0.836	0.889 (0.291–2.717)					
rs2242480					rs2242480				
CC	31/48.4	19/65.6			C	94/73.4	26/81.1		
CT	32/50.0	9/31.0	0.099	0.459 (0.180–1.168)	T	34/26.6	4/18.9	0.198	0.425 (0.138–1.308)
TT	1/1.6	1/3.4	1.000	1.632 (0.096–27.648)					

Table 3 Genotype and allele frequencies of rs2242480 of *CYP3A4* gene in male patients from case and control groups

Genotype	*n*/percentage (%)		*P*-value	OR (95% CI)
	Case	Control		
CC	16/48.5	12/80.0		
CT	16/48.5	2/13.3	0.022	0.167 (0.032–0.867)
TT	1/3.0	1/6.7	0.844	1.333 (0.076–23.542)
C	48/72.8	26/86.6		
T	18/27.2	4/13.4	0.132	0.410 (0.126–1.340)

Table 4 Linkage disequilibrium (LD) analysis among rs1800872, rs1800871, and rs1800896

IL-10 SNP	*D*'	r^2
rs1800872, rs1800871	1.000	1.000
rs1800872, rs1800896	1.000	0.125
rs1800871, rs1800896	1.000	0.122

D' and r^2 were used to represent LD; *D*'=0, r^2=0: no LD; *D*'=1, r^2=1: complete LD; 0.5≤*D*'<0.8: moderate LD; *D*'>0.8: strong LD

Table 5 Linkage disequilibrium (LD) analysis among rs1881457, rs1800925, and rs20541

IL-13 SNP	*D*'	r^2
rs1881457, rs1800925	1.000	0.620
rs1881457, rs20541	0.441	0.134
rs1800925, rs20541	0.890	0.342

D' and r^2 were used to represent LD; *D*'=0, r^2=0: no LD; *D*'=1, r^2=1: complete LD; 0.5≤*D*'<0.8: moderate LD; *D*'>0.8: strong LD

Table 6 Major haplotype frequencies of *IL-10* and *IL-13* genes in the case and control groups

Genotype	Haplotype	Frequency		χ^2	*F*-value*	OR (95% CI)
		Case	Control			
IL-10 rs1800871 rs1800872 rs1800896	CCA	39.00 (0.310)	18.00 (0.300)	0.017	0.895169	1.046 (0.536–2.042)
	CCG	9.00 (0.071)	4.00 (0.067)	0.014	0.905296	1.077 (0.318–3.648)
	TAA	78.00 (0.619)	38.00 (0.633)	0.035	0.850875	0.941 (0.498–1.778)
IL-13 rs20541 rs1881457 rs1800925	CAC	78.03 (0.619)	28.69 (0.478)	3.311	0.068864	1.775 (0.954–3.305)
	CCC	8.97 (0.071)	6.00 (0.100)	0.454	0.500449	0.690 (0.234–2.038)
	CCT	0.00 (0.000)	2.31 (0.038)	4.904	0.026841	
	TAC	20.97 (0.166)	10.31 (0.172)	0.008	0.928295	0.963 (0.425–2.183)
	TCT	18.00 (0.143)	12.69 (0.212)	1.391	0.238336	0.621 (0.280–1.377)
	TCC	0.03 (0.000)	0.00 (0.000)			

* Statistical *F*-value from Fisher's exact probability of haplotype

3.3 Haplotype analysis

Three SNPs of *IL-10* and *IL-13* exhibited LD. The haplotype was constructed to analyze the effect of the LD on β-lactam allergy in the Chinese Han population of Northwest China.

The SNPs such as rs1800871, rs1800872, and rs1800896 showed complete linkage. Three haplotypes were found in the three SNPs of *IL-10* gene: CCA, CCG, and TAA, respectively. These haplotypes were observed in the case and control groups (*F*=0.895, 0.905, and 0.851, respectively). None of the three haplotypes correlated with β-lactam allergy in the Han Chinese population of Northwest China (Table 6).

Six haplotypes were observed in rs20541, rs1881457, and rs1800925 of *IL-13*. Four of them were observed in the case and control groups that included CAC, CCC, TAC, and TCT (*F*=0.069, 0.500, 0.928, and 0.238, respectively). Hence, these four haplotypes were not correlated with the β-lactam allergy in the Han Chinese population of Northwest China. Among these six haplotypes, CCT was only observed in the control group (*F*=0.026). The *F*-value of CAC was a marginal value of 0.069 (Table 6).

4 Discussion

4.1 Relationship between genetic polymorphisms of T cell-related cytokine and β-lactam allergy

T cells play an important role in β-lactam allergy. They are reported to be involved in various types of hypersensitivity (Kim *et al*., 2005; Rubio *et al*., 2010). T helper (Th) 1 and Th2 cells are the two types of T cells. Th2 cells can be involved in immunoglobulin E (IgE)-mediated immediate hypersensitivity as they promote the secretion of cytokines such as *IL-4*, *IL-5*, *IL-6*, *IL-10*, and *IL-13* (Palomares, 2013).

IL-10 can inhibit the clonal expansion of Th0, Thl, and Th2 cells (Jiang, 2015), and it plays an important role in the occurrence and development of allergy. This study selected rs1800871, rs1800872, and rs1800896, which directly affected the expression of *IL-10*. Apter *et al*. (2008) reported that there was no significant correlation between *IL-10* genetic polymorphism and β-lactam allergy. Guglielmi *et al*. (2006) suggested that *IL-10* promoter and *IL-4Rα* genetic polymorphisms were related to immediate β-lactam allergy in female patients. The results of present study show that rs1800872 of *IL-10* was not correlated with β-lactam allergy in the Han Chinese

population of Northwest China. Additionally, three types of haplotype, CCA, CCG, and TAA of *IL-10*, were not found to be correlated with β-lactam allergy in the Han Chinese population. The study data were consistent with the findings of Apter *et al*. (2008); however, it was not consistent with that of Guglielmi *et al*. (2006). The reason might be that because our SNP chip is based on Sequenom MassARRAY® technology which is used to perform high-throughput sequencing. The chip presented high sensitivity and specificity, so the results are more reliable. The researchers have utilized different technologies including classic sequencing and high-sensitive PCR. The threshold for the detection of gene expression might be further explored using such procedures. Guglielmi *et al*. (2006) and Apter *et al*. (2008) have proved that other important factors, such as race, region, and environmental conditions, can also influence the distribution of genotype.

The *IL-4Rα* gene was located on chromosome 16p11–16p12. It is a subunit that plays a key role in allergic disease by promoting the IgE production (Wu and Scheerens, 2014). The present study showed that the distribution frequency of rs1801275 of *IL-4Rα* was not significantly different between the groups (P>0.05), and the same results were obtained when the patients were stratified by gender (P>0.05).

IL-13 was mainly involved in the allergic reactions through inducing the B lymphocytes to secrete IgE antibodies (Ford *et al*., 2001). *IL-13* and *IL-4* were isogenous, because of their chromosomal localization and the molecular composition of proteins. Additionally, the sharing receptor structure presented the same signal pathway, and it also demonstrated similar physiological functions. *IL-13* can indirectly play a role in eosinophils by upregulating the expression of eotaxin, and the effect of *IL-13* was greater than that of *IL-4* (Levine and Wenzel, 2010). The present study results showed that the distribution frequencies of three SNPs of *IL-13* gene such as rs20541, rs1881457, and rs1800925 were not significantly different between the case and control groups (P>0.05). The same results were obtained when the patients were stratified by gender (P>0.05). Six haplotypes were constructed on these three SNPs of *IL-13* gene, in which CCT was only one observed in the control group (F=0.026) but not in the case group. The F-value of CAC was 0.069. Therefore, the relationship between these two haplotypes and β-lactam allergy in the Han Chinese population of Northwest China requires further study.

4.2 Relationship between β-lactam allergy and other genetic polymorphisms

The study of SNPs of *FcεRIβ* and *IFNGR2* mainly focused on their relationships with allergic diseases such as asthma (Kim and Park, 2006; Sanak *et al*., 2007) and allergic rhinitis (Nagata *et al*., 2001), and was used to treat malignant tumors such as non-Hodgkin lymphoma (Purdue *et al*., 2007; Chen *et al*., 2011) and gastric cancer (Hou *et al*., 2007). *IFNGR1* was reported to correlate with β-lactam allergy, however, the relationship between SNP of *IFNGR2* and β-lactam allergy was not clear. The study showed that the SNPs of both *FcεRIβ* and *IFNGR2* were not correlated with β-lactam allergy.

4.3 Relationship between *CYP3A4* gene polymorphism and β-lactam allergy

Cytochrome P450 is widely distributed across all living organisms including vertebrates, invertebrates, plants, fungi, and bacteria. It was one of the most widely distributed enzymes of phase I drug metabolism, and it presented the richest natural content and the broadest substrate spectrum. Furthermore, CYP is distributed in various organs and tissues of the human body. CYP3A subfamily was one of the major rate-limiting enzymes in drug metabolism (Gellner *et al*., 2001). Four genotypes were involved in drug metabolism in humans including *CYP3A4*, *CYP3A5*, *CYP3A7*, and *CYP3A43* (Gibson *et al*., 2002).

The correlation between the SNPs of *CYP3A4* and β-lactam allergy was not reported in the past, and we found that the rs2242480 of *CYP3A4* gene was correlated to β-lactam allergy in male patients. The frequency of genotype CT was significantly different between the case and control groups when compared with the wild-type gene CC (P=0.022; OR=0.167, 95% CI: 0.032–0.867).

5 Conclusions

The study provides evidence about the genetic diagnosis for patients with β-lactam allergy in the Han Chinese population of Northwest China. *CYP3A4*

polymorphism was found to correlate with β-lactam allergy in male patients. The relationships between β-lactam allergy and haplotypes CCT and CAC from rs20541, rs1881457, and rs1800925 of *IL-13* need to be further studied using a larger sample. The roles of these sites in the pathogenesis of β-lactam allergy require further clarification.

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Compliance with ethics guidelines

Jing LI, Xin-yue LIU, Lin-jing LI, Chong-ge YOU, Lei SHI, Shang-di ZHANG, Qian LIU, Jun WANG, Ze-jing LIU, and Ting-hong LV declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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中文概要

题　目：基因多态性与β-内酰胺类抗生素过敏的关联性分析

目　的：探讨*IL-10*、*IL-13*、*IL-4Rα*、*FcεRIβ*、*IFNGR2*、*CYP3A4*基因多态性与中国西北地区汉族人群β-内酰胺类抗生素过敏易感性的关联性。

创新点：首次在甘肃地区汉族人群中探讨10个单核苷酸多态性位点与β-内酰胺类抗生素过敏易感性的关联性，为该地区人群β-内酰胺类抗生素过敏患者提供了基因组学水平的诊断数据。

方　法：以β-内酰胺类抗生素过敏者为研究对象进行病例对照研究，采用Sequenom MassARRAY®分子量阵列技术平台定制单核苷酸多态性（SNP）芯片检测10个单核苷酸多态性与甘肃地区汉族人群β-内酰胺类抗生素过敏易感性的关联性。应用SHEsis软件完成*IL-10*及*IL-13*的连锁不平衡分析及单倍型构建。

结　论：*CYP3A4* rs2242480基因多态性与男性患者β-内酰胺类抗生素过敏有显著的相关性（P=0.022；OR=0.167，95% CI：0.032–0.867）。*IL-13*的CCT及CAC单倍型与中国西北地区汉族β-内酰胺类抗生素过敏的相关性有待进一步研究。

关键词：过敏；β-内酰胺类抗生素；白细胞介素；药物基因组学；单核苷酸多态性