Atopy Can Be an Interfering Factor in Genetic Association Studies of ß-Lactam Allergy

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Genetic and environmental factors are involved in immediate hypersensitivity reactions to ß-lactam antibiotics. Several genes have been associated with immediate hypersensitivity reactions to ß-lactams, including those encoding cytokines and receptors involved in the synthesis of IgE (*FCER1*), as well as signal transduction proteins and products released by mast cells. Nevertheless, analysis of publications reporting on genetic association studies in patients allergic to ß-lactams reveals that most were performed in 3 main populations and, in most cases, by the same groups of investigators, who progressively increased the population sample in successive studies. Most of the publications reported a series of concerns, namely, the diagnosis was not always based on skin or challenge tests, tolerance to ß-lactams in controls was not proved, and atopy was not taken into account.

The first group of studies was conducted in a Chinese population [1-3], among whom some patients were diagnosed based on the clinical history, and immediate and nonimmediate reactions were mixed. The number of patients and controls increased with the successive studies, although samples were not generally large. Controls did not usually have proven tolerance to penicillin but were included because they had a negative history of allergy to ß-lactams, negative questionnaire result, or negative specific IgE or skin test results. The

percentages of atopy were not taken into consideration in patients or controls. The genes involved were *IL4, IL13, IL4RA, IFNR1, IL18*, and *STAT6*.

The second group of studies were conducted in a Korean population. In one study [4], types of reaction (urticaria, angioedema, maculopapular rash, and exudative erythema) and antibiotics (eg, ß-lactams, quinolones) were assessed using a database of adverse drug reactions; however, the controls were from a previous study on the PGE2 receptor, and their characteristics were not described. Another study [5] evaluated patients occupationally exposed to cephalosporins and unexposed nonatopic controls with negative skin test results to 3 frequently prescribed cephalosporins. However, only 4 patients reported work-related symptoms, and only 1 patient had positive skin test results and symptoms upon exposure to a cephalosporin. Although atopy was considered in 1 of the studies, it was not taken into account in the genetic analyses. The genes involved were *FCERB1* and *CD40*.

The third group of studies were conducted in European populations, initially in Italian patients, who were evaluated in collaboration with French researchers [6,7]. Later, a Spanish population was analyzed [8]. In the first of the studies [6], patients were diagnosed according to whether they had a clinical history compatible with an immediate reaction and positive skin test or specific IgE results, while controls were selected from age-matched volunteers in a query from an allergist on the basis of absence of drug reactions (tolerance was not confirmed). Although atopy was not considered, total IgE levels were higher in patients than in controls. In the study involving Italian and Spanish patients [8], immediate and delayed reactions were evaluated simultaneously. Patients were diagnosed according to the recommendations of the European Network for Drug Allergy (ENDA); however, the controls were from a preventive care clinic. In these studies, total IgE levels were higher in patients than in controls. In another Spanish study [9], patients were diagnosed based on positive results in skin or controlled drug exposure tests, and controls were selected on the basis of not having reported a history of ß-lactam allergy. A significantly higher percentage of atopy was also observed in ß-lactam–allergic patients, according to total IgE levels and specific IgE to prevalent allergens, which were significantly more frequent than in controls. The genes involved were *IL4RA, IL13, TNFA*, and *NOD*.

In short, the review of these studies suggests that larger populations are needed, diagnostic criteria must be homogeneous and not based only on the clinical history, tolerance to ß-lactams should be verified in control groups, different reactions should be analyzed separately, and atopy should be considered as a possible confounding factor.

We evaluated whether atopy could be a confounding factor in genetic studies on ß-lactam allergy. Following the ENDA protocol, we evaluated 98 patients diagnosed with immediate hypersensitivity to ß-lactams and 104 controls who had a negative result and tolerated a full dose of a ß-lactam (see the methods section in Supplementary material). Skin tests with a locally adapted battery of common aeroallergens were performed in both patients and controls. Atopy was defined as the presence of at least 1 positive skin test result with allergens from the test series. No statistically significant differences were observed between patients and controls regarding age, sex, atopy, or total IgE levels (Supplementary table 1).

By analyzing 22 polymorphisms in patients with ß-lactam hypersensitivity compared with controls, the only statistically significant differences identified were for the *TGFB1* single-nucleotide polymorphism (SNP) c25, with the C allele at codon 25 being significantly more frequent in ß-lactam–positive patients (11.8%) than in controls (4.5%) (P=.029) (see Supplementary material). When patients were classified according to atopy, irrespective of ß-lactam sensitization, statistically significant differences were found between controls and patients for the following SNPs: *IL1R* pst1 +1970, *IFNG* +874, and *IL4* –33 (Table). To confirm whether these differences were due to ß-lactam hypersensitivity or to atopy, we compared atopic and nonatopic patients with ß-lactam allergy and found the same statistically significant differences mentioned above. In addition, we found an association with the SNP *IL4RA* +1902 (Supplementary table 3). No differences were found between ß-lactam–allergic and ß-lactam–tolerant patients when only nonatopic patients were evaluated, irrespective of ß-lactam sensitization.

In summary, in our study, in which proven tolerance to ß-lactams and atopic status were taken into account, we detected statistically significant differences between atopic and nonatopic ß-lactam–allergic patients, as well as between atopic ß-lactam–allergic patients and controls, although not between nonatopic patients. Therefore, we suggest that atopy

Table. Allelic and Genotypic Frequencies of Statistically Significant Polymorphisms: Comparison Between Atopic Patients With Hypersensitivity to ß-Lactams and Nonatopic Controls

		Genotype				Allele		
IL1R pst1+1970	Number	CC	TC	TT	*P* Value	C	T	*P* Value
Controls	77	0.456	0.465	0.079		0.689	0.311	
Patients	19	0.326	0.435	0.239	.017	0.543	0.457	.014
IFNG +874		AA	AT	TT	*P* Value	A	T	*P* Value
Controls	77	0.324	0.353	0.324		0.500	0.500	
Patients	19	0.571	0.286	0.143	.15	0.714	0.286	.027
IL4 –33	No.	CC	CT	TT	*P* Value	C	T	*P* Value
Controls	77	0.692	0.280	0.028		0.832	0.168	
Patients	18	0.909	0.091	0.000	.017	0.955	0.045	.004

is a confounding factor that is overrepresented in ß-lactam–allergic patients and that the previously described associations could have been due to atopy.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Qiao HL, Yang J, Zhang YW. Relationships between specific serum IgE, cytokines and polymorphisms in the IL-4, IL-4Ralpha in patients with penicillin allergy. Allergy. 2005;60:1053-9.
2. Ming L, Wen Q, Qiao HL, Dong ZM. Interleukin-18 and IL18 -607A/C and -137G/C gene polymorphisms in patients with penicillin allergy. J Int Med Res. 2011;39:388-98.
3. Huang CZ, Zou D, Yang J, Qiao HL. Polymorphisms of STAT6 and specific serum IgE levels in patients with penicillin allergy. Int J Clin Pharmacol. 2012;50:461-7.
4. Kim SH, Lee JE, Kim SH, Jee YK, Kim YK, Park HSm, et al. Allelic variants of CD40 and CD40L genes interact to promote antibiotic-induced cutaneous allergic reactions. Clin Exp Allergy. 2009;39:1852-6.
5. Nam YH, Kim JE, Kim SH, Jin HJ, Hwang EK, Shin YS, et al. Identifying genetic susceptibility to sensitization to cephalosporins in health care workers. J Korean Med Sci. 2012;27:1292-9.
6. Guéant-Rodriguez RM, Romano A, Béri-Dexheimer M, Viola M, Gaeta F, Guéant JL. Gene-gene interactions of IL13 and IL4RA variants in immediate allergic reactions to betalactam antibiotics. Pharmacogenet Genomics. 2006;16(10):713-9.
7. Guéant-Rodriguez RM, Guéant JL, Viola M, Tramoy D, Gaeta F, Romano A. Association of tumor necrosis factor-alpha -308G>A polymorphism with IgE-mediated allergy to betalactams in an Italian population. Pharmacogenomics J. 2008;8:162-8.
8. Bursztejn AC, Romano A, Guéant-Rodriguez RM, Cornejo JA, Oussalah A, Chery C, et al. Allergy to betalactams and nucleotide-binding oligomerization domain (NOD) gene polymorphisms. Allergy. 2013;68:1076-80.
9. Cornejo-García JA, Guéant-Rodriguez RM, Torres MJ, Blanca-Lopez N, Tramoy D, Romano A, et al. Biological and genetic determinants of atopy are predictors of immediate-type allergy to betalactams, in Spain. Allergy. 2012;67:1181-5.

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