

Correspondence

Gene variants of *IL13*, *IL4*, and *IL4RA* are predictors of β -lactam allergy

To the Editor:

The article by Apter et al¹ adds interesting evidence that penicillin allergy (PA) is influenced by genetic factors. They showed an association between self-reported PA and genetic polymorphisms of the *IL4* gene but no association with a gene variant of *IL4RA* (rs1805010).

Despite its limited size, this study confirms that genetic factors in PA are in relation with the *IL4* pathway.^{2,3} In a previous study on 210 patients (with clinical report, skin testing, and specific IgE measurement) and 265 paired control subjects from Italy, we evidenced associations between β -lactam allergy (BA) and *IL4RA* variants (rs1805010 and rs1801275).² The discrepancy between both studies was not related with the type of β -lactam involved in the reaction. When evaluating BA risk of *IL4RA* rs1805010 according to either cephalosporin allergy or PA, the association of the AA genotype with PA risk was even more significant than with cephalosporin allergy (Table I). Another explanation could be the distinct allele frequencies and gene-environment interactions among control populations. The National Center for Biotechnology Information database shows a difference in AA genotype frequency of *IL4RA* rs1805010 between 2 populations of European origin, which is confirmed between our Italian control group and control subjects from southern Spain (Table I). *IL13* gene variants (rs20541 and rs1800925) were more potent predictors of BA than *IL4RA* polymorphisms in our series.² In addition, our most significant finding was an interaction between *IL13* and the 3 polymorphisms of *IL4RA*. The combination of the less frequent allele of *IL13* polymorphisms with any of the predominant homozygous genotypes of the 3 polymorphisms of *IL4RA* was more significantly connected with the risk of BA and with the total serum IgE level than any polymorphism considered alone.² In regard to our data and those of Apter et al,¹ it would be of interest to evaluate the gene-gene interactions between *IL4RA* and *IL4* in BA by using a population size that avoid a type II error.

Taken together, the several studies reported in Europe, China, and the United States on the association of BA with genetic

predictors converge in showing that immediate allergic reactions to β -lactams are influenced by genes of the *IL13* and *IL4* pathways.¹⁻⁶ Because these genes are involved in IgE class switching and atopy, this suggests that we should evaluate atopy and its gene predictors as risk factors of BA in contrasted populations, taking into account worldwide variations of allele frequencies, gene-gene interactions, contrasted situations of environmental exposure, and influence on IgE production.

Jean-Louis Guéant, MD, PhD, AGAF^{a,b}

Rosa-Maria Guéant-Rodriguez, MD, PhD^a

Jose-Antonio Cornejo-Garcia, PhD^{a,d}

Marinella Viola, MD^c

Miguel Blanca, MD^{a,d}

Antonino Romano, MD^{b,c}

From ^aInserm U-724, Cellular and Molecular Pathology in Nutrition, Faculty of Medicine, University Henry Poincaré and University Hospital Center (CHU) of Nancy, Vandœuvre lès Nancy, France; ^bIRCCS Oasi Maria SS, Troina, Italy; ^cUnità di Allergologia, Complesso Integrato Columbus, Rome, Italy; and ^dthe Allergy Service, Carlos Haya Hospital, Malaga, Spain. E-mail: jean-louis.gueant@medecine.uhp-nancy.fr.

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TABLE I. *IL4RA* rs1805010 among Italian patients with BA and nonallergic subjects from Italy and Spain

		Alleles				Genotype				P value, AA vs AG+GG			
		A		G		P value		AA				AG	
Population													
Our study	White Italian subjects												
Patients with PA		140	(56.4)	108	(44.6)	.3986*	43	(34.7)	54	(43.5)	27	(21.8)	.0032*
Patients with cephalosporin allergy		94	(54.6)	78	(45.4)	.2501†	29	(33.7)	36	(41.9)	21	(24.4)	.0143‡
Control subjects		257	(59.7)	173	(40.3)		55	(20.7)	147	(55.5)	63	(27.8)	
Spain	White Spanish patients												
Control subjects		228	(60.0)	152	(40.0)		70	(36.9)	88	(46.3)	32	(16.8)	.0007‡

*Versus control subjects.

†Versus control subjects.

‡Italian vs Spanish control subjects.