

Letter to the Editor

Association of thromboxane A1 synthase (TBXAS1) gene polymorphism with acute urticaria induced by nonsteroidal anti-inflammatory drugs

To the Editor:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs all over the world and represent the second most frequent cause of drug-induced hypersensitivity reactions (0.5% to 1.9% of the general population).¹ In some circumstances an underlying disease, such as chronic urticaria or bronchial asthma, accompanies the clinical expression of this hypersensitivity.^{1,2} According to the pattern of reactivity among different NSAIDs, these reactions can be classified into cross-reactive or multiple hypersensitivity (MR), with cross-reactivity among different nonstructurally related NSAIDs, and selective (SR), in which a unique specific NSAID is the culprit drug.¹⁻³

Either MR or SR could be related to some genetic background. Thus knowledge of possible genetic variations in patients with NSAID hypersensitivity might provide information about individual susceptibility to these side effects (both detrimental and beneficial). In this setting the present study was aimed at investigating the search for 1 or more polymorphisms associated with isolated acute cutaneous NSAID hypersensitivity, both the MR and SR types, in a Spanish population with no underlying chronic or recurrent urticaria or respiratory disease.

Nineteen allergy departments throughout Spain participated in the study. A total of 563 adult patients (mean age, 43.6 years; range, 18-86 years; 58.8% male) given a diagnosis of acute urticaria, angioedema, or both because of NSAID hypersensitivity and 551 healthy control subjects (mean age, 38.2 years; range, 18-77 years; 68.6% male) without a history of NSAID hypersensitivity were enrolled from December 2009 to August 2011. Cutaneous NSAID hypersensitivity was classified into MR (n = 314, 57.8%) and SR (n = 249, 45.8%) types, depending on oral challenge test results, skin test (when necessary), and the pattern of reactivity. A total of 217 single nucleotide polymorphisms (SNPs) in 48 genes were studied. Detailed information on

the methods used can be found in this article's Online Repository at www.jacionline.org.

From the initial dataset of 1114 subjects, 41 samples were discarded because of a low genotyping rate (<80%). Sample quality was 96.4% and 96.1% for cases and control subjects, respectively. Finally, 303 patients in the MR group, 240 patients in the SR group, and 530 healthy control subjects were enrolled for genotype-phenotype analysis. Patients in the SR group were older (mean age, 48.3 ± 15.9 years) than those in the MR group (mean, 40.0 ± 14.4 years; $P < .0001$). Patients in the SR group were more frequently women (67.1%) than those in the MR group (52.2%, $P = .0004$). The prevalence of atopy (skin prick test [SPT] response positivity) was significantly higher in the MR group than in the SR group (66.2% vs 37.8%, respectively; $P < .0001$). The prevalence of atopy (as assessed by means of Phadia-top positivity) in the control group was 36.7%. The quality control procedure discarded 10 SNPs, and statistical analyses were finally performed on 207 SNPs.

Table I shows the top associated SNPs ($P < .005$) after adjusting for age and sex for the MR group. The most significant association was found for rs6962291 (thromboxane A synthase 1 [TBXAS1]) under the log-additive genetic model ($P = 1.6 \times 10^{-5}$), which remained significant after correction for multiple comparisons (false discovery rate-adjusted P value [Q value] = .0158). The minor allele (AA) seems to have a protective effect. Other SNPs from TBXAS1 and 1 SNP from 5-lipoxygenase (ALOX5) also show suggestive probabilities ($Q < .2$).

As can be seen in Table II, no SNPs achieved a significant association in the SR group. However, 3 independent SNPs belonging to ALOX5 appear to be associated with this kind of hypersensitivity (nominal $P < .005$ and $Q < .2$), and the other 2 (rs2291427 and rs901681) also showed suggestive nominal probabilities ($P = .008$ and $P = .006$, respectively; see Table E1 in this article's Online Repository at www.jacionline.org). The linkage disequilibrium coefficients (D') among the SNPs of the ALOX5 gene were calculated for all the study subjects. As can be seen in Fig E1 in this article's Online Repository at www.jacionline.org, associated SNPs belong to different blocks of linkage,

TABLE I. Results of the top associated SNPs ($P < .005$) after adjusting for age and sex for the MR hypersensitivity group

SNP	Gene	Model	Genotype	Control subjects	Cases	OR	95% CI	P value	Q value
				No. (%)	No. (%)				
rs4948672	ALOX5	Rec	GG/CG	434 (85.1)	231 (77.3)	1	—	—	
			CC	76 (14.9)	68 (22.7)	1.82	1.25-2.65	.00664	.1199
rs2938392	PPARG	Rec	CC/CT	399 (77.3)	256 (84.8)	1	—	—	
			TT	117 (22.7)	46 (15.2)	0.58	0.39-0.85	.00452	.3310
rs11147439	ALOX5AP	Log-add*	CC	116 (23.5)	98 (32.7)				
			AT	260 (52.6)	151 (50.3)	0.73	0.59-0.91	.00466	.3310
			AA	118 (23.9)	51 (17.0)				
rs10487667	TBXAS1	Dom	TT	231 (44.5)	172 (57.9)	1	—	—	
			GT/GG	288 (55.5)	125 (42.1)	0.58	0.44-0.79	.00034	.1177
rs6962291	TBXAS1	Log-add*	TT	171 (33.3)	139 (46.5)				
			AT	254 (49.4)	136 (45.5)	0.62	0.49-0.77	1.6×10^{-5}	.0158
			AA	89 (17.4)	24 (8.0)				

Dom, Dominant; Log-add, log-additive; OR, odds ratio; Rec, recessive.

*The log-additive model assumes that on a log scale, each additional copy of the minor allele increases the effect (risk or protective) by the same amount. Genotypes are coded as 0, 1, and 2, and the calculated ORs summarize the effect of the minor allele.

TABLE II. Results for SR hypersensitivity after adjusting for age and sex

SNP	Gene	Model	Genotype	Control subjects	Cases	OR	95% CI	P value	Q value
				No. (%)	No. (%)				
rs1565096	ALOX5	Dom	AA	326 (63.2)	122 (51.5)	1	—	—	—
			AG/GG	190 (36.8)	115 (48.5)	1.83	1.28-2.62	.00086	.1423
rs4948672	ALOX5	Rec	GG/CG	434 (85.1)	181 (76.7)	1	—	—	—
			CC	76 (14.9)	55 (23.3)	2.22	1.41-3.49	.00061	.1199
rs7894352	ALOX5	Dom	GG	326 (62.6)	129 (55.4)	1	—	—	—
			AG/AA	195 (37.4)	104 (44.6)	1.78	1.24-2.57	.00170	.1813

Dom, Dominant; OR, odds ratio; Rec, recessive.

pointing to a possible role of this gene in the risk of this selective allergy.

In this study we have showed, for the first time, a significant role of the minor allele rs6962291 of *TBXAS1* in patients with MR NSAID acute cutaneous hypersensitivity. Up to 46 different SNPs of the same gene have been analyzed (see Fig E2 in this article's Online Repository at www.jacionline.org), and rs10487667 also showed a suggestive probability, pointing out that the *TBXAS1* gene could be related to this condition. For both SNPs, the allele frequency was higher within control subjects than patients, suggesting a protective role of this minor allele. *TBXAS1* catalyzes the conversion of prostaglandin H₂ to thromboxane A₂, and thromboxane A₂ induces platelet aggregation and smooth muscle contraction.^{4,5} This SNP has been recently described as having a protective role in relation to aspirin intolerance in asthmatic patients. Expression analyses have demonstrated that this polymorphism encodes for a nonfunctional isoform of *TBXAS1* because of the synthesis of a truncated *TBXAS1* mRNA, which affects the heme-binding domain, reducing its catalytic activity.⁶ The same authors showed a significant contribution of *TBXA2R* in the pathogenesis of MR NSAID acute urticaria but did not study the possible role of *TBXAS1* in this clinical form of the disease.⁷ We have analyzed rs3786989 and rs4523, 2 different *TBXA2R* polymorphisms, but we were not able to show any relationship with MR or SR.

Despite no SNPs achieving a significant association in patients with SR NSAID hypersensitivity, a certain relationship could be suggested for *ALOX5*. A complementary analysis stratified according to the specific drug involved showed that our results might be mainly due to pyrazolones, but further studies are needed to truly prove this association (data not shown).

The high prevalence of atopy detected in patients in the MR group (66.2%) is remarkable and in accordance with previous data from other investigators.⁸ One limitation of the study is that we used a serum assay for IgE to common allergens instead of SPTs to characterize the atopic status in control subjects (overall accuracy of 85%, with the SPT as the gold standard),⁹ but the associations between specific SNPs and NSAID hypersensitivity remain similar with or without atopy as a covariate.

As far as the power of the study is concerned, considering our actual sample size, the number of cases and control subjects, and a *P* value threshold of less than 5×10^{-5} , we had 80% power to detect an odds ratio of 0.32/2.2 to 0.46/2.03 for SNPs showing a frequency of the risk genotype in control subjects and 0.2 to 0.4 for the MR group. In the SR group we had some power limitations because of the smaller population size. In fact, we had a power of 61% to detect as significant the odds ratio we found for rs4948672 (*ALOX5*). We would have needed to study at least

312 cases and 690 control subjects to be able to identify this effect as statistically significant with a power of 80%.

In conclusion, our findings suggest a role of the *TBXAS1* and *ALOX5* genes in MR and SR NSAID hypersensitivity, respectively, when no underlying disease is present.

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