

Lack of association of *GPRA* (G protein-coupled receptor for asthma susceptibility) haplotypes with high serum IgE or asthma in a Korean population

To the Editor:

The identification of genetic loci conferring susceptibility to the development of asthma is important for our understanding of disease progress and for the ultimate design of new therapies.

Recently, haplotype tagged by one single-nucleotide polymorphism in *GPRA* (G protein-coupled receptor for asthma susceptibility) was reported to be associated with high serum IgE levels or asthma in 3 cohorts from Finland and Canada. They found that *GPRA*, alternatively called vasopressin receptor-related receptor 1, showed distinct distribution of protein isoforms between bronchial biopsy specimens from healthy and asthmatic individuals. By means of phylogenetic analysis of haplotypes (haplotypes 1-7) with 13 markers within a 77-kb segment, they found that risk-associated haplotypes (haplotypes 2, 4, 5, and 7) were tagged by *SNP522363**C, and nonrisk haplotypes (haplotype 1, 3, and 6) were tagged by the alternative allele, *SNP522363**G. They also provided additional evidence of involvement of *GPRA* and that the murine ortholog of *GPRA* was upregulated in a mouse model of ovalbumin-induced inflammation.¹

SNP522363G>C was genotyped in a Korean asthma cohort (439 patients and 374 control subjects) in which several genetic associations had been detected, to test

the genetic effects of *GPRA* in a Korean population²⁻⁵; in addition, 311 normal samples from a type 2 diabetes mellitus cohort⁶ were used as population controls. *SNP522363G>C* in *GPRA* was genotyped with TaqMan.⁷ The sequences for the TaqMan assay were as follows: *GPRA-SNP522363G>C-F*, 5'-ggcttgagagtaac-taagtatctgttcaaa-3'; *SNP522363G>C-R*, 5'-ggtagctg-tattttgtcactctattct-3', 5'-cctcattacgtttctc-3' (VIC probe), and 5'-cctcattacgtttctc-3' (FAM probe). Genotype distribution of *SNP522363G>C* among patients with bronchial asthma versus healthy subjects, atopic subjects versus nonatopic subjects, and high IgE responders (IgE >100 kU/L) versus low IgE responders (IgE ≤100 kU/L) was analyzed with logistic regression models, controlling for age (continuous value), sex (male, 0; female, 1); and smoking status (nonsmoker, 0; exsmoker, 1; smoker, 2) as covariates.

The frequency of *GPRA-SNP522363G>C* in the Korean population was found to be higher (frequency = 0.478) than those in the Finnish (frequency = 0.333) and Canadian (frequency = 0.386) populations.¹ Association analyses of *GPRA-SNP522363G>C* with the risk of asthma, atopy, total serum IgE level, and log-transformed PC₂₀ value in the Korean population revealed no significant association. Furthermore, no significant difference in allele frequency among population controls (n = 311) was observed (Table I).

There are a number of factors that could explain the observed differences between the 2 studies. First, it is possible that *GPRA-SNP522363G>C* is not tagging the

TABLE I. Association analysis of *GPRA-SNP522363G>C* with the risk of asthma, atopy, total serum IgE level, and PC₂₀ value in a Korean population

Phenotype	Subgroup	Diagnosis	Genotype			Frequency	P value*
			G	CG	C		
Asthma	All	BA	122	221	96	0.470	.63
		NC	96	195	83	0.483	
		PC†	83	155	73	0.484	
	Atopy	BA	82	155	68	0.477	.65
		NC	31	61	20	0.451	
	Nonatopy	BA	40	65	28	0.455	.47
NC		63	117	57	0.487		
Atopy	All	Atopy	113	216	88	0.470	.53
		Nonatopy	103	182	85	0.476	
	Asthmatic patients	Atopy	82	155	68	0.477	.8
		Nonatopy	40	65	28	0.455	
	Nonasthmatic patients	Atopy	31	61	20	0.451	.36
		Nonatopy	63	117	57	0.487	
Total serum IgE	Asthmatic patients	High IgE	77	150	64	0.478	.50
		Low IgE	45	71	32	0.456	
	Atopic asthmatic patients	High IgE	67	134	53	0.472	.91
		Low IgE	15	21	15	0.500	
	Nonatopic asthmatic patients	High IgE	10	16	11	0.514	.27
		Low IgE	30	49	17	0.432	
Log (initial PC ₂₀)	Asthmatic patients		111 (0.03 ± 0.59)	196 (0.06 ± 0.61)	79 (0.09 ± 0.55)		.75
	Atopic asthmatic patients		74 (0.001 ± 0.54)	137 (0.07 ± 0.62)	55 (0.12 ± 0.51)		.62
	Nonatopic asthmatic patients		37 (0.10 ± 0.68)	59 (0.04 ± 0.58)	24 (0.02 ± 0.63)		.52

*P values of codominant models by means of logistic regression analyses controlling for smoking, age, and sex as covariates.

†Population controls from a type 2 diabetes mellitus cohort.⁶ Population controls were not included in the analysis.

Numbers of subjects, means ± SD of each value, and P values of codominant models for regression analyses are shown.

risk-associated haplotype because of the different genetic background among white and Asian populations. Second, the relatively small sample size in the Korean asthma study (439 patients and 374 control subjects) might not have allowed detection of the genetic effects revealed in the larger previous study. Finally, certain genes might lead to the development of asthma in specific ethnic-geographic populations because of different genetic background, environmental interaction, or both. Further studies are required to determine the genetic effect of haplotypes tagged by *GPRA-SNP522363G>C* in other studies.

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Occupational asthma caused by shark cartilage dust

To the Editor:

Allergic occupational asthma can be caused by a large number of high-molecular-weight substances, mostly proteins derived from animals, plants, food, and enzymes.¹ Recently, the increasing use of traditional and

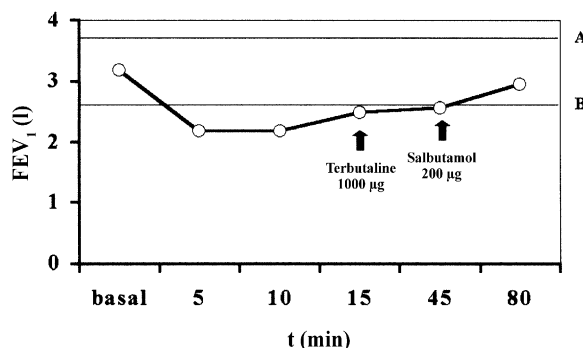


FIG 1. Bronchial challenge test with shark cartilage extract at 1/100 dilution. Line A, FEV₁ 100% of predicted. Line B, PC₂₀ FEV₁.

herbal remedies and dietary supplements has caused an outbreak of new potential allergens.²

We report a case of occupational asthma caused by shark cartilage dust. A 29-year-old man without a personal history of asthma or other respiratory disorders, a never-smoker, was admitted to the hospital for dyspnea. He worked in a dietetic product industry for 7 years, where he was in contact with plant extracts, amino acids, and vitamins, among other substances. The most significant exposure to dust was during the encapsulating process of the products contained in sacks. After a latent period of 2 years, he developed chest tightness, cough, and dyspnea, requiring bronchodilators and hospital admissions on several occasions. He also had moderate oculonasal symptoms. Initially, he improved on weekends and holidays, but subsequently he needed days off from work to become asymptomatic.

Physical examination in the hospital was normal. Skin prick tests to common aeroallergens were positive to several pollens and negative to dust mites, mold, cat, and dog epithelia. Skin prick-by-prick tests with products handled by the patient at work (*Hamamelis virginiana*, shark cartilage, *Aesculus hippocastanum*, *Melilotus officinalis*, and lemon flavor) were positive only to shark cartilage (8-mm wheal diameter) with a control wheal for histamine of 8 mm. Spirometric values were in the normal range. Serial determinations of peak expiratory flow rate were seen to drop by more than 20% during work periods, showing normal values on weekends. Methacholine challenge showed nonspecific airways hyperresponsiveness (PC₂₀, 0.06 mg/mL). Specific bronchial challenge test was performed with shark cartilage extract (10% wt/vol in PBS) and showed an immediate response at 1/100 dilution with a FEV₁ decrease of 31% at 5 minutes (Fig 1). A placebo-bronchial challenge test with PBS was negative. Immunoblotting with shark cartilage extract was positive, with a strong recognition of nonresolved antigens (Fig 2, A, lane 2). Treatment with urea and 2-mercaptoethanol had no result (results not shown). Therefore, a digestion with pepsin was performed, as previously described,^{3,4} obtaining several defined protein bands with molecular weights higher than 10 kd, as shown in Fig 2, B, lane 2. A study with 39 randomly selected, unexposed