

Uncertain biologic relevance of polymorphisms of leukotriene C₄ synthase in asthma

To the Editor:

The study by Kedda et al¹ provides some evidence that polymorphisms of leukotriene C₄ synthase, a key enzyme in the biosynthesis of cysteinyl leukotrienes, have little relationship to markers of asthma severity.

In this study the authors define asthma severity according to clinical parameters, such as FEV₁, inhaled corticosteroid dose, and symptoms. However, it is important to be aware that symptoms and lung function tend to be downstream consequences of the asthmatic inflammatory process. Moreover, many patients with persistent asthma have normal lung function, despite demonstrating marked airway hyperresponsiveness (AHR),^{2,3} which in turn is often the driving force behind episodic airflow obstruction with subsequent perception of symptoms. In view of this, it would have been of interest if the relationship between polymorphisms of leukotriene C₄ synthase and surrogate biomarkers of inflammation, such as AHR to adenosine monophosphate and airway eosinophils, had also been evaluated.

A retrospective analysis evaluated whether polymorphisms of leukotriene C₄ synthase were related to response to leukotriene receptor antagonists (LTRAs) in asthmatic patients.⁴ This study demonstrated that LTRAs did not preferentially attenuate the primary outcome of AHR to either direct or indirect stimuli between patients with the variant (C) and wild-type (A) alleles. There were also no treatment differences between genotypes (A/A vs A/C or CC) in terms of effects on other surrogate biomarkers of inflammation or lung function. In turn, it would have been of interest if Kedda et al¹ had prospectively examined whether a response to leukotriene antagonism, in terms of both surrogate biomarkers of inflammation and clinical parameters, was related to genotypes containing the variant allele.

Thus whether polymorphisms of leukotriene C₄ synthase are truly related to fundamental components driving the asthma inflammatory process remains uncertain. Further prospective data are also required to definitely determine whether clinical response to LTRAs are determined by polymorphisms (or combinations of polymorphisms) of leukotriene C₄ synthase in asthmatic patients.

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Kinase activity and XLA phenotypic variability

To the Editor:

In reference to the phenotypic variability and the apparent lack of genotype-phenotype correlation in XLA reported by Morwood et al,¹ we present data from our series of 60 patients that show several cases of heterogeneity. One family presents the R288W mutation as in the report by Morwood et al.¹ The index case (patient 1; Table I) presented at age 7 years with lymphocytic meningitis and pneumonia, and intramuscular gamma globulin replacement was started. Despite refusing intravenous administration, he has only catarrhal episodes. Patient 2, a cousin of patient 1, presented with otitis and pneumonia at age 4 months and lymphocytic meningitis at age 2 years. Treated with intramuscular gamma globulin he switched to intravenous administration at 7 years old. Later he presented with infectious meningoencephalitis with hemiparesia, from which he recovered. Patient 3, a cousin of patients 1 and 2, started at 7 months with neutropenia and *Pseudomonas* spp sepsis. He received intravenous gamma globulin from the beginning with favorable evolution.

All 3 patients show normal Btk expression by Western blot and flow cytometry. The mutant protein maintains autokinase activity assayed by a phosphotyrosine specific immunoblot. Patient 1 presented with normal IgA and IgE levels at diagnosis (Table I), currently maintained. Thus, leaky phenotypes can be identified in this family, reinforcing the findings of Morwood et al¹ and others^{2,3} associated with the R288W. Nevertheless, we do not agree with the suggestion of Morwood et al¹ of the lower importance of Btk interactions through the Src-homology domain 2 (SH2). Two brothers of our group present another mutation in the SH2, K374N. Btk expression and kinase activity are normal. In contrast, these patients have a classic phenotype. If SH2 interactions were not fully necessary, a leaky phenotype would also be expected. In

TABLE I. Immunoglobulin levels at diagnosis

	Patient 1 (1973)	Patient 2 (1976)	Patient 3 (1999)
IgG (g/L)	0.32 (6.67-11.79)	0.29 (2.41-6.13)	0.03 (4.42-8.80)
IgA (g/L)	0.33 (0.79-1.69)	<0.05 (0.1-0.46)	<0.05 (0.19-0.55)
IgM (g/L)	0.02 (0.4-0.9)	0.02 (0.26-0.60)	<0.02 (0.31-0.77)
IgE (U/mL)	270 (<155)	2 (<7.2)	<2 (<12.7)
B lymphocytes (%)	0	0	0
Initiation of symptoms	7 y	4 mo	7 mo

our opinion, missense mutations in less sensible residues could contribute to the genetic component of XLA variability, but other genetic and ambient factors account for the greatest proportion.

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Analysis of the leukotriene C₄ synthase A₋₄₄₄C promoter polymorphism in a Spanish population

To the Editor:

In a recent study, Kedda et al¹ analyzed the A₋₄₄₄C polymorphism in the leukotriene C₄ synthase (*LTC4S*) gene in an Australian population. They concluded that this polymorphism was weakly associated with the asthma phenotype but was not related to aspirin intolerance or disease severity. We have analyzed this polymorphism in a Spanish population of 226 individuals: 123 patients with asthma and 103 controls without asthma from the Allergy Department of the University Hospital of Salamanca. The allergic status was based on a positive skin test to at least 1 allergen of a battery of common aeroallergens. Lung function was measured by spirometry, and asthma was diagnosed according to the criteria of the American Thoracic Society and classified following the Global Initiative for Asthma guidelines. The A₋₄₄₄C polymorphism, firstly described by Sanak et al,² was analyzed by PCR-RFLP by using *MspI* restriction endonuclease. Allelic and genetic frequencies are shown in Table I. Although we have not found a statistically significant association between the C₋₄₄₄ allele and the asthma phenotype, we have detected a discrete increase of C₋₄₄₄ allele in patients with asthma. This trend was clearer observed in patients with severe asthma, but these data were not statistically significant. Association of this allele with severe asthma has been previously reported by Sampson et al.³ In aspirin-intolerant asthma (AIA), Sanak et al² have described an association between C₋₄₄₄ allele and AIA in a Polish population. We considered positive those patients who had undergone a formal aspirin challenge or who reported more than 3 episodes with characteristic symptoms. We have not found any association between AIA and C₋₄₄₄ allele (Table I). These results are in agreement with those of Kedda et al¹ and other authors. In conclusion, we have not detected any association between the C₋₄₄₄ allele and asthma phenotype, degree of severity, or AIA in our population. Nevertheless, we have observed a slight increase of carriers of C₋₄₄₄ allele in the group of patients with asthma compared with controls, particularly in patients with

TABLE I. Genotype and allele frequencies of leukotriene C₄ synthase A₋₄₄₄C promoter polymorphism

Phenotype	N	Genotype			Allele		Hardy-Weinberg equilibrium P value
		AA	AC	CC	A	C	
Nonasthma controls	103	0.53	0.40	0.07	0.73	0.27	.86
All asthma	123	0.47	0.44	0.09	0.69	0.31	.75
Intermittent asthma	57	0.53	0.42	0.05	0.74	0.26	.52
Mild asthma	27	0.48	0.37	0.15	0.67	0.33	.39
Moderate asthma	26	0.42	0.50	0.08	0.67	0.33	.49
Severe asthma	12	0.33	0.50	0.17	0.58	0.42	.92
Aspirin-intolerant asthma	43	0.51	0.47	0.02	0.74	0.26	.15
Aspirin-tolerant asthma	76	0.45	0.45	0.10	0.67	0.33	.91