

**TABLE I.** Immunoglobulin levels at diagnosis

|                        | Patient 1<br>(1973)  | Patient 2<br>(1976) | Patient 3<br>(1999)  |
|------------------------|----------------------|---------------------|----------------------|
| IgG (g/L)              | 0.32<br>(6.67-11.79) | 0.29<br>(2.41-6.13) | 0.03<br>(4.42-8.80)  |
| IgA (g/L)              | 0.33<br>(0.79-1.69)  | <0.05<br>(0.1-0.46) | <0.05<br>(0.19-0.55) |
| IgM (g/L)              | 0.02<br>(0.4-0.9)    | 0.02<br>(0.26-0.60) | <0.02<br>(0.31-0.77) |
| IgE (U/mL)             | 270<br>(<155)        | 2<br>(<7.2)         | <2<br>(<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 C<sub>4</sub> synthase A<sub>-444</sub>C promoter polymorphism in a Spanish population

To the Editor:

In a recent study, Kedda et al<sup>1</sup> analyzed the A<sub>-444</sub>C polymorphism in the leukotriene C<sub>4</sub> 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<sub>-444</sub>C polymorphism, firstly described by Sanak et al,<sup>2</sup> 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<sub>-444</sub> allele and the asthma phenotype, we have detected a discrete increase of C<sub>-444</sub> 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.<sup>3</sup> In aspirin-intolerant asthma (AIA), Sanak et al<sup>2</sup> have described an association between C<sub>-444</sub> 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<sub>-444</sub> allele (Table I). These results are in agreement with those of Kedda et al<sup>1</sup> and other authors. In conclusion, we have not detected any association between the C<sub>-444</sub> allele and asthma phenotype, degree of severity, or AIA in our population. Nevertheless, we have observed a slight increase of carriers of C<sub>-444</sub> allele in the group of patients with asthma compared with controls, particularly in patients with

**TABLE I.** Genotype and allele frequencies of leukotriene C<sub>4</sub> synthase A<sub>-444</sub>C promoter polymorphism

| Phenotype                 | N   | Genotype |      |      | Allele |      | Hardy-Weinberg equilibrium<br>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                                   |

severe asthma. This is the first study of the A<sub>444</sub>C polymorphism of the *LTC4S* gene performed in a population of southern Europe with asthma and confirms the results obtained in American, Dutch, Japanese, and Australian populations.

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The authors of the referenced article declined the opportunity to reply.

#### Nasal nitric oxide in experimental rhinovirus infection

To the Editor:

We read with interest the article by Sanders et al<sup>1</sup> that appeared in the April issue of the Journal. In their interesting study, the authors reported that experimentally induced rhinovirus (human rhinovirus) infection in human beings is associated with an increase in nitric oxide (NO) production from both the lower and upper airways. The latter, in turn, was positively correlated to the expression of NO synthase-2 in the nasal epithelium and inversely correlated to the cold symptoms score. Because the authors included lower airway NO in the nasal measurement, they used the extrapolated NO values at zero flow on the basis of the existing linear relationship between exhaled NO concentrations measured at different constant expiratory air flow rates for data analysis. A large variability in exhaled NO was found, and in contrast with NO from the lower airway, nasal NO concentrations were not significantly increased on any single day.

We think that the paranasal sinuses' contribution to nasal NO measurements should be taken in account,

because it is known that the common cold is frequently associated with anatomical involvement of the upper airways, such as occlusion and other abnormalities in the NO-rich sinus cavities.<sup>2</sup> This may result in a reduced passage of NO from the sinuses to the nasal cavity, where it is measured, as recently pointed out.<sup>3,4</sup> In fact, this might in part explain the interindividual spread in nasal NO and the negative correlation between nasal NO levels and the symptoms score found by the authors.

In addition, we believe that the assessment of the actual nasal output would have better characterized changes in upper airway NO production. Thus, by using a nasal-mask method as the authors did, the large variability in nasal and oral NO values could be significantly reduced if oral NO was subtracted from the mean level of nasal NO air.<sup>5</sup>

Finally, although nasal NO in healthy subjects is more dependent on airflow dynamics than the concentration gradient between luminal air and airway mucosa, it is likely that human rhinovirus infection could have induced variations of nasal luminal volume and/or submucosal area. It may potentially affect the slope of nasal NO concentration–flow rate relationship representing the diffusing capacity for NO in the nose,<sup>6</sup> which could have been included in the data analysis.

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#### Reply

To the Editor:

We thank Drs Maniscalco and Sofia<sup>1</sup> for their comment and interest in our article. We certainly recognize that nitric oxide (NO) from the paranasal sinuses contributes to the nasal NO measurement, and that rhinovirus infection may affect sinus NO production and/or flow of sinus gases into the exhaled nasal gases measured. We agree that enhanced sinus contribution to nasal NO as the cold is