

tolerated sesame. Given that the predictive values depend on the prevalence of sesame allergy, these values were recalculated with a presumed prevalence of sesame allergy of 1% (Table II).

We have conducted the first study to evaluate the diagnostic value of sesame-specific IgE. We were unable to establish a threshold, in our population, with a 95% positive predictive value. At a sesame-specific IgE threshold of 7 kU_A/L, the positive predictive value was 74.1% and did not increase monotonically at higher thresholds. The significance of lower positive predictive values at higher thresholds is uncertain because these were based on a small number of cases. Of the 5 of 17 patients with sesame-specific IgE ≥ 20 kU_A/L who tolerated sesame, all were allergic to peanut. Because one of the major sesame allergens, Ses I 3, has 80% homology with a major peanut allergen, Ara h 1,⁴ it is possible that the peanut-specific IgE in these patients was falsely detected as sesame-specific IgE.

Our study does demonstrate, however, that a sesame-specific IgE <0.35 kU_A/L is useful in excluding a diagnosis of sesame allergy. Although patients with a sesame-specific IgE exceeding this value may not have sesame allergy, none of our patients with a value <0.35 kU_A/L had sesame allergy.

Although our study is limited by a small sample of cases, the sample size is similar to that in the study by Sampson⁵ of wheat and soy IgE, which also did not predict allergy. It is possible that a larger sample would be successful in establishing a threshold. Another potential limitation of our study is that allergy or tolerance to sesame was usually determined by history rather than the gold standard food challenge. Although history is subject to recall and reporting bias, we applied strict inclusion and exclusion criteria. Furthermore, other studies have relied on clinical history to define their allergic cohort.⁶⁻⁸ The several year delay between convincing reaction and measurement of sesame-specific IgE is also a limitation of our study because it raises the concern that the sesame allergy may have resolved at the time of the IgE measurement. However, this delay was unavoidable because measurement of sesame-specific IgE was not available at our institution until several years after the children's reactions in some cases. At the time of the IgE measurement, all children were still considered by their treating allergist to have sesame allergy because they had had a recent positive SPT to sesame (23 of the children with sesame allergy) or a recent reaction, either accidental or during a food challenge (5 children). In the 23 with a persistently positive SPT in the context of a convincing history, a challenge was considered too risky. It should be noted that the potential misclassification as allergic of a child who may have a resolved sesame allergy would not change the conclusion of our research—that is, a sesame-specific IgE <0.35 kU_A/L is useful in excluding a diagnosis of sesame allergy.

Considering our relatively small sample, a sesame-specific IgE <0.35 kU_A/L should still be interpreted in the context of the history and SPT. With the exception of individuals with convincing histories of sesame allergy, we suggest that challenges should be offered to all patients to confirm the diagnosis of sesame allergy, irrespective of SPT or sesame-specific IgE values. In those with a sesame-specific IgE level <0.35 kU_A/L, the risk of an allergic reaction is low. Further, the clinician should be aware of the potential for patients with peanut allergy to be falsely labeled as having sesame allergy if this diagnosis is solely based on the sesame-specific IgE. We suggest that if a patient clearly tolerates sesame, it is not warranted to obtain a sesame-specific IgE. Alternatively, if the patient's history is truly convincing of a significant

allergic reaction to sesame, regardless of the SPT result or sesame-specific IgE level, the patient should be considered allergic, because anaphylaxis to sesame has been described with negative SPT and IgE levels.^{7,9}

We thank Aileen Frew, Duncan Lejtenyi, Joanna Priestly, and Nathalie Gautier for data collection, Kim Allan for secretarial support, and Somagen Diagnostics for providing support through the provision of kits to measure sesame-specific IgE.

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Supported by internal funding from the Montreal Children's Hospital Research Institute and the Montreal Children's Hospital Foundation.

Disclosure of potential conflict of interest: R. Kagan has consulting arrangements with Genentech. The rest of the authors have declared that they have no conflict of interest.

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doi:10.1016/j.jaci.2008.04.012

Pharmacogenomics and outcome of asthma: No clinical application for long-term steroid effects by *CRHR1* polymorphisms

To the Editor:

Worldwide, millions of patients are affected by asthma, an inflammatory airway disease. Corticosteroids suppress virtually every step of the inflammatory cascade and constitute the cornerstone of asthma treatment. Their beneficial effects on a group level are well accepted, but the individual response to inhaled corticosteroids (ICSs) varies widely. The latter might be due to an underlying genetic background, as suggested by Tantisira and colleagues.^{1,2} They have shown that 3 haplotype-tagging single nucleotide polymorphisms (SNPs) in the corticotropin-releasing hormone receptor 1 gene (*CRHR1*) are associated with lung function improvement after 8 weeks' treatment with ICSs in patients

with asthma.^{1,2} If this association would last over many years, it might open avenues for pharmacogenetic long-term management of asthma.

We assessed, in an asthma cohort followed for 22 years, whether the effects of ICS treatment on the immediate improvement in lung function and long-term decrease in lung function were associated with the 3 previously described *CRHR1* SNPs.

We evaluated 281 patients given diagnoses of symptomatic asthma who were initially studied in 1962 through 1975 and re-examined in 1991 through 1999.³ All were younger than 45 years and had airway hyperresponsiveness to histamine.³ After initial testing, participants had routine check-ups for asthma at least once a year. Lung function tests were performed with the same type of water-sealed spirometer throughout follow-up (Lode Spirograph D53; Lode Instruments, Groningen, The Netherlands). Data on lung function and corticosteroid use during check-ups were extracted from medical records, excluding lung function data during asthma exacerbations and pregnancies. The Medical Ethics Committee of the University Hospital Groningen approved this study. All participants provided written informed consent.

We genotyped the 3 *CRHR1* SNPs described by Tantisira et al¹: rs1876828, rs242939, and rs242941 (TaqMan Universal PCR Master Mix and ABI prism 7900 HT, Applied Biosystems TaqMan SNP Genotyping Assays, Nieuwekerk aan de IJssel, The Netherlands).

Linear mixed-effects models were used to investigate the effect of *CRHR1* SNPs on annual decrease in FEV₁. The age of 30 years was the starting point for analyses of the decrease in FEV₁. Subjects had to have more than 2 FEV₁ measurements over more than 2 years to be included in the analyses. Annual FEV₁ decrease was estimated for the different genotypes by including genotype, time, and their interaction in the analyses. Individual variation in these decreases was accounted for by estimating random effects for this variable. Only subjects who started ICSs during follow-up were analyzed. To minimize potential bias by subjects stopping ICSs or using ICSs intermittently, we included only data on lung function in the first period with continuous ICS use. Interactions between SNPs and the use of ICSs were included in the model to investigate whether the effects of ICSs on the change in level of FEV₁ (immediate effect), rate of decline in FEV₁ (long-term effect), or both differed between the genotypes. Explanatory variables were sex, height, the first available FEV₁ measurement after age 30 years (centered at 2.8 L), pack-years smoking, and oral corticosteroid and ICS use over time and their interaction with time. Oral steroid use was accounted for only on the FEV₁ level (as a time-varying variable) because oral steroids were often used intermittently, which makes it impossible to estimate their effect on FEV₁ decrease.

Of the 281 individuals, 68 were excluded from analyses because they had insufficient data on FEV₁ or missing lung function records, incomplete or unknown data on smoking history, or intermittent ICS use. Of the remaining 213 patients, 164 had data on *CRHR1* genotyping (Table I), and the median number of FEV₁ measurements per individual was 25 (interquartile range [IQR], 8-43). There existed no demographic differences between subjects with different *CRHR1* genotypes.

Within the period of analysis on the course of FEV₁, 98 of the 164 included subjects started using ICSs. The median time period without and with ICSs was 11.2 (IQR, 7-22) and 13.0 (IQR, 7-19) years, respectively. There was no significant association of the *CRHR1* polymorphisms with FEV₁ decrease, neither in all subjects before the start of ICS use (results not shown) nor

TABLE I. Population characteristics

Male/female sex (n)	96/72	
No. of corticosteroid users (n [%])	98 (60)	
Age of onset of symptoms (y)	6 (3-21)	
Mean daily dose of ICSs (μg/d)*	749 (426-1152)	
Duration of use of ICSs (y)	13.0 (7-19)	
	Visit 1962-1975	Visit 1990-1999
Age (y)	27 (20-35)	53 (46-60)
FEV ₁ % predicted after BD (%)	89 (70-99)	82 (66-100)
Reversibility (% predicted)	23 (16-31)	12 (7-17)
AHR ≤16.0 mg/mL (%)†	87	79
≥1 Positive skin test result (%)	91	80
Blood eosinophils (× 10 ⁷ /L)	35 (22-54)	12 (7-21)
Smoking		
Pack-years smoking	0.3 (0.0-6.3)	4.5 (0.0-15.6)
Nonsmoker/exsmoker/current smoker (%)	51/10/40	42/34/25

Data are presented as median values (IQR) unless stated otherwise.

BD, Bronchodilator; AHR, airway hyperresponsiveness to histamine.

*Calculated for individuals who ever used ICSs only. The dose of ICSs was calculated to an equivalent daily dose of beclomethasone, with 500 μg of fluticasone, 1000 μg of budesonide, and 500 μg of budesonide administered through a Turbuhaler being equipotent to 1000 μg of beclomethasone.

†Percentage of all subjects with an airway hyperresponsiveness of less than 16 mg/mL histamine. All subjects had airway hyperresponsiveness (≤32 mg/mL histamine).

during ICS use. The effect of ICS use was not significantly different between *CRHR1* genotypes with respect to both the immediate effect on FEV₁ level (effect within 3-6 months) and the long-term effect of ICSs on the decrease in FEV₁ (Fig 1). Estimates and 95% CIs of the differences between genotypes in the effect of ICSs on the change in FEV₁ decrease are presented in Table II.

The rs242939 SNP showed the largest difference in effect of ICS use on the change in FEV₁ decrease. Pooling the heterozygous and homozygous subjects for this SNP is justified given the absence of change in FEV₁ decrease by ICS use in patients having at least 1 mutant allele. The estimated difference in this change in FEV₁ decrease compared with the wild-type was -34.1 mL/y (95% CI, -73.1 to 4.9 mL/y), which is almost significant ($P = .087$).

Corticotropin-releasing hormone binds to *CRHR1*, which exerts indirect anti-inflammatory effects through ACTH-induced cortisol production and direct proinflammatory effects through, for example, mast cell degranulation.^{4,5} SNPs in this gene might thus affect airway inflammation and treatment effects of ICSs in asthma. Three variants in *CRHR1* have been previously shown to be associated with improvement in FEV₁ after 8 weeks' ICS treatment in childhood and adult asthma.^{1,2} We investigated adult asthmatic subjects who were followed for more than 20 years, a population in which we previously have shown that ICS treatment could reduce long-term lung function decrease in a dose-dependent way.⁶ We found no association of the 3 *CRHR1* variants with long-term lung function decrease (both with and without the use of ICSs). Importantly, there was also no significant association with the immediate effects of ICS treatment on lung function in the same asthmatic patients. These findings suggest that variability of long-term improvement and preservation of lung function with corticosteroid treatment cannot simply be predicted by genotyping *CRHR1* variants in asthmatic patients.

Our study seems to contradict the work of Tantisira and colleagues.^{1,2} However, Tantisira and colleagues showed

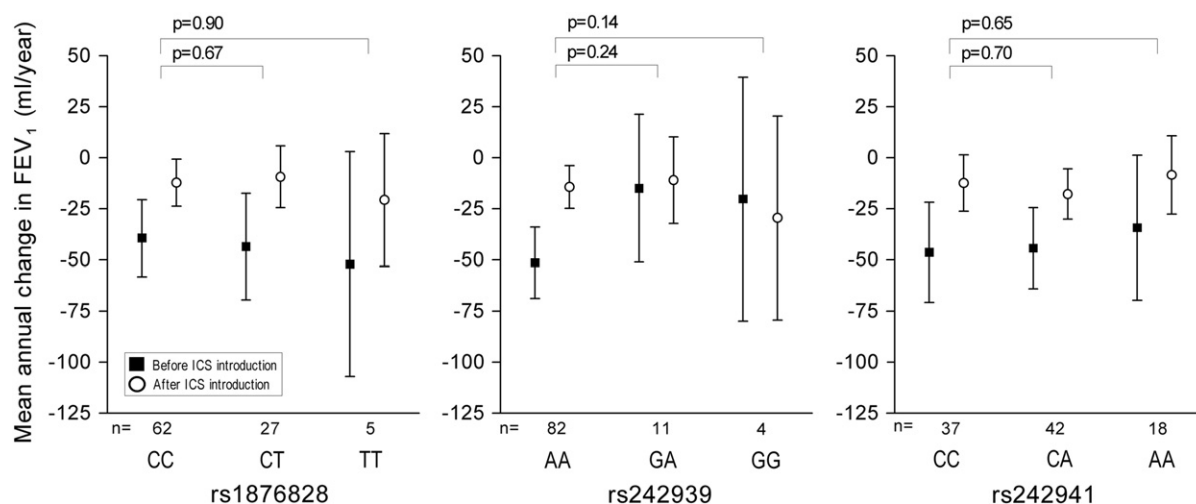


FIG 1. Differences in ICS-associated mean annual change (long-term effect) in lung function and association with human *CRHR1* polymorphisms in subjects using corticosteroids. *P* values over differences in ICS-associated changes in mean annual change in FEV₁ decrease in the genotypes compared with the reference genotype are shown as follows: CC in rs1876828, AA in rs242939, and CC in rs242941.

TABLE II. The effect of ICS use per genotype on the mean annual change in lung function (long-term effect) compared with no ICS use and differences in these effects between genotypes in human *CRHR1* polymorphisms

		Mean annual FEV ₁ change (mL/y), 95% CI	
		Change in annual FEV ₁ during ICS use compared with no ICS use	Differences in these effects between genotypes*
<i>CRHR1</i> polymorphisms			
rs1876828	CC	27.2 (4.9 to 49.4)	
	CT	34.1 (4.0 to 64.1)	7.0 (–25.5 to 39.6)
	TT	31.4 (–32.8 to 95.5)	4.4 (–60.8 to 69.5)
rs242939	AA	37.1 (17.0 to 57.2)	
	GA	4.0 (–37.6 to 45.7)	–33.0 (–77.3 to 11.3)
	GG	–9.3 (–86.2 to 67.5)	–46.4 (–124.2 to 31.4)
rs242941	CC	33.9 (5.9 to 61.9)	
	CA	26.4 (3.3 to 49.6)	–7.4 (–40.0 to 25.1)
	AA	25.9 (–14.4 to 66.1)	–8.1 (–50.1 to 33.8)

*Wild-type as the reference.

significant effects of *CRHR1* variants on the short-term increase in FEV₁ level with ICS use and demonstrated the greatest effects in their pediatric cohort. We did not find this effect in our adult asthmatic subjects and extend these observations by investigating long-term effects of ICS use on FEV₁ decrease, which can only be investigated in adults.

We are aware that our study is observational in nature and that there is a possibility that the lack of significance of *CRHR1* variants on corticosteroid response can be spurious. However, we believe the outcome to be of relevance given the large number of FEV₁ measurements per individual and hence accurate analyses of longitudinal FEV₁ decrease. Moreover, our previous analyses on a disintegrin and metalloprotease gene (*ADAM33*) variants in association with FEV₁ decrease in the same asthmatic patients contained even fewer subjects with a homozygous *ADAM33* genotype, and these findings were replicated in the general population.^{7,8} Therefore we believe that the lack of significance might not be due to inadequate power.

We studied the same 3 SNPs as Tantisira et al¹ that were positively associated with lung function improvement in interaction with ICS treatment. Because the SNPs cover about 10% of the total variation in *CRHR1*, we cannot rule out that other SNPs in *CRHR1* or genes in the vicinity are associated with ICS effects on lung function improvement in our patients. However, the magnitude of pharmacogenetic effects of scarce variants in genes, such as the *CRHR1* variants, are likely small or less common and therefore would not have sufficient magnitude to affect our clinical approach to individual asthma therapy.⁹

It would be of interest to analyze the effect of homozygosity of the GAT haplotype described by Tantisira and colleagues.^{1,2} In our study only 9 subjects had 2 GAT copies, and these subjects showed the largest reduction in FEV₁ decrease with ICS use (44.5 mL/y less decline than without ICS use (95% CI, –7.3 to 96.3 mL/y). Subjects with 1 or 0 GAT copies had smaller and non-significant effects.

Our data suggest that *CRHR1* polymorphisms are not associated with immediate or long-term improvement in FEV₁ by ICSs or with prevention of accelerated FEV₁ decrease in adult asthma.

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Supported by the Netherlands Asthma Foundation (AF 3.2.00.38).

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

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doi:10.1016/j.jaci.2008.04.015

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