

Polymorphisms in *IL13*, total IgE, eosinophilia, and asthma exacerbations in childhood

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Background: It is unclear whether single nucleotide polymorphisms (SNPs) in the gene for IL-13 (*IL13*) influence asthma severity and/or asthma morbidity.

Objectives: To examine the relation between *IL13* SNPs and asthma-related phenotypes in 2 independent populations.

Methods: We used family-based methods to test for association between SNPs in *IL13* and asthma-related phenotypes in Costa Rican children with asthma. We attempted to reproduce significant findings in white (non-Hispanic) children with asthma in the Childhood Asthma Management Program (CAMP).

Results: In Costa Rica and in CAMP, the A allele (Gln) of *IL13* coding SNP (rs20541) was significantly associated with increased eosinophil count ($P < .011$ in both studies) and increased serum total IgE ($P < .054$ in both studies). The T allele of *IL13* promoter SNP (rs1800925) was inversely associated with asthma exacerbations in Costa Rica ($P = .069$). Although this SNP (rs1800925) was not associated with asthma exacerbations among all white children in CAMP, it was associated with increased risk of asthma exacerbations among children on inhaled corticosteroids ($P = .02$).

Conclusion: Polymorphisms in *IL13* were significantly associated with serum total IgE and eosinophil count in 2

populations. *IL13* polymorphisms may also be associated with asthma exacerbations, and this effect may be dependent on medication use. Our study is the first to report a potential negative interaction between a genetic polymorphism and response to inhaled corticosteroids.

Clinical implications: Polymorphisms in *IL13* are associated with serum total IgE and eosinophil count and may be associated with asthma exacerbations. (J Allergy Clin Immunol 2007;120:84-90.)

Key words: IL13, asthma, IgE, eosinophil, severity, exacerbations, Costa Rica, CAMP

IL-13 is a critical cytokine in the pathogenesis of allergic asthma in mouse models.¹ In human beings, CD4⁺ T cells,² eosinophils, mast cells, basophils,³ and natural killer T cells⁴ produce IL-13, which induces IgG₄ and IgE synthesis in cultured B cells.⁵ Levels of IL-13 mRNA and protein are increased in sputum of subjects with asthma, and these levels have been significantly correlated with increased eosinophil count⁶ and airway responsiveness.⁷ IL-13 has been shown to inhibit monocyte and macrophage production of IL-1B, TNF- α , and nitric oxide.⁸ IL-4 and IL-13 share a common signaling pathway in binding to a heterodimer of the IL-4 receptor and the IL-13 receptor α -1.⁹ IL-13 binds with even greater affinity to IL-13 receptor α -2,¹⁰ which may primarily serve as a decoy receptor but in some instances could lead to upregulation of TGF- β .¹¹

Variants in the gene for IL-13 (*IL13*) have been frequently associated with asthma. *IL13* maps to chromosome 5q, a region frequently linked to asthma,¹²⁻¹⁴ total serum IgE,^{15,16} airway responsiveness,¹⁶ and other asthma-related phenotypes.¹⁷ Two of the best characterized single nucleotide polymorphisms (SNPs) in *IL13* include a promoter SNP (-1111, rs1800925) and a coding SNP in exon 4 (Arg130Gln, rs20541). Functional studies support a regulatory role for the -1111 variant (ie, enhanced *IL13* promoter activity in CD4⁺ T_H2 lymphocytes)¹⁸ and suggest that the 130Gln substitution results in signal transducer and activator of transcription 6 phosphorylation in monocytes, decreased affinity of IL-13 for IL-13 receptor α -2, and increased expression of IL-13 in patients with asthma.^{19,20} These polymorphisms have been associated with asthma and/or its intermediate phenotypes in some studies^{21,22} but not in others.^{23,24} The most consistent association has been with total serum IgE.²⁵⁻²⁸

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Supported by grants HL04370 and HL66289 from the National Institutes of Health. The CAMP Genetics Ancillary Study is supported by the National Heart, Lung, and Blood Institute, N01-HR-16049. Additional support for this research came from grants P50 HL67664 and T32 HL07427 from the National Institutes of Health and the National Heart, Lung, and Blood Institute.

Disclosure of potential conflict of interest: E. K. Silverman has consulting arrangements with GlaxoSmithKline; has received grant support from GlaxoSmithKline; has received money for a talk on chronic obstructive pulmonary disease genetics from Wyeth; and has received honoraria from Bayer. The rest of the authors have declared that they have no conflict of interest.

Received for publication March 23, 2007; revised April 23, 2007; accepted for publication April 24, 2007.

Available online June 13, 2007.

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0091-6749/\$32.00

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doi:10.1016/j.jaci.2007.04.032

Abbreviations used

CAMP: Childhood Asthma Management Program
FBAT: Family-based association test
FVC: Forced vital capacity
SNP: Single nucleotide polymorphism

Of interest, it is unclear whether polymorphisms in *IL13* influence the morbidity and/or severity of asthma. Variants in *IL13* have been previously associated with airway responsiveness²² but not with asthma exacerbations.²⁹ We performed a family-based analysis of association between 2 SNPs in *IL13* and asthma and asthma-related phenotypes in the Genetics of Asthma in Costa Rica Study. To account for the issue of multiple testing and correlated phenotypes, we attempted to replicate significant findings in families of white (non-Hispanic) children with asthma in the Childhood Asthma Management Program (CAMP). Our group previously analyzed the coding SNP in exon 4 (Arg130Gln, rs20541) by using restriction fragment length polymorphism technology in CAMP²⁶ and in another smaller cohort in Costa Rica.²⁴ This study differs significantly from the previous studies in terms of sample size,²⁴ inclusion of additional SNPs, genotyping technology, analyses of additional traits,²⁶ and use of a test replication design.

METHODS

Costa Rica

Subject enrollment and phenotypic assessment for the Genetics of Asthma in Costa Rica Study have been presented previously³⁰ and are presented in detail in this article's [Online Repository](#) at www.jacionline.org. Briefly, Costa Rican schoolchildren age 6 to 14 years were recruited from February 2001 to March 2005. Index children were eligible for inclusion in the study (along with their parents) if they had asthma and a high probability of having at least 6 great-grandparents born in the Central Valley of Costa Rica. There was no significant difference in sex or grade in school for children who did and did not agree to participate in the study.

Study participants completed a protocol that included a questionnaire, spirometry, allergy skin testing, measurement of serum total and allergen-specific IgE, peripheral blood eosinophil count, and (on a separate visit) assessment of airway responsiveness to methacholine. Written parental consent was obtained for participating children, for whom written assent was also obtained. The study was approved by the Institutional Review Boards of the Hospital Nacional de Niños (San José, Costa Rica) and Brigham and Women's Hospital (Boston, Mass).

Questionnaire. Each participant completed a slightly modified version of the questionnaire used in the Collaborative Study on the Genetics of Asthma,³¹ which was translated into Spanish.

Pulmonary function tests. Spirometry was conducted with a Survey Tach Spirometer (Warren E. Collins, Braintree, Mass) following American Thoracic Society recommendations.³² The best FEV₁ and forced vital capacity (FVC) were selected for data analysis of FEV₁ and FEV₁/FVC.

Methacholine challenge testing. After completion of baseline spirometry, subjects whose FEV₁ was at least 65% of predicted

underwent methacholine challenge testing by using a slightly modified version of the Chatham protocol.³³

Serum total IgE and peripheral blood eosinophil count. Serum total and allergen-specific IgE levels were determined by the UniCAP 250 system (Pharmacia & Upjohn, Kalamazoo, Mich) with samples measured in duplicate. Total serum IgE levels were transformed to a log₁₀ scale for data analysis. Eosinophil count was measured in peripheral blood by Coulter-counter techniques and then transformed to a log₁₀ scale for data analysis.

CAMP

Phenotypic data were collected at baseline and during the course of the clinical trial as previously described.^{34,35} CAMP was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the other CAMP study centers.

Pulmonary function and methacholine challenge testing. Prebronchodilator and postbronchodilator spirometry was performed according to American Thoracic Society recommendations with a volume-displaced spirometer, and airway responsiveness was assessed by methacholine challenge with the Wright nebulizer tidal breathing technique.³⁴ Testing was performed at least 4 hours after the participant's last use of a short-acting bronchodilator and at least 24 hours after the participant's use of a long-acting bronchodilator.

Serum total IgE and peripheral blood eosinophil count. Total serum IgE and peripheral blood total eosinophil counts were measured by the radioimmunosorbent assays from blood samples collected during the screening sessions of CAMP. Both IgE and eosinophil counts were transformed to the log₁₀ scale for analysis.

Genotyping

We genotyped 2 SNPs in *IL13*, 1 in the promoter region (rs1800925) and 1 in exon 4 (Arg130Gln or rs20541), in Costa Rican children with asthma and their parents. Among families of white children with asthma in CAMP, we genotyped the same SNPs as in Costa Rica plus 3 additional SNPs (1 in the promoter [rs1881457], 1 in exon 4 [rs848], and 1 in the intergenic region between *IL13* and *IL4* [rs2243204]). SNPs were assessed in both TaqMan (Applied Biosystems, Foster City, Calif)³⁶ and the Illumina (San Diego, Calif) Sentrix bead-array systems. Genotype data quality control was assessed by several methods. Duplicate genotyping was performed on approximately 10% of the sample to assess genotype reproducibility. In samples run with TaqMan, there were no discordant genotypes observed. Genotype completion rates were at least 95% for all loci. In Illumina, 4 samples were repeated on 17 plates resulting in less than 0.1% discordance. The genotypic pass rate was >99% for all loci.

Statistical analysis

Hardy-Weinberg equilibrium was tested in parental data by using a χ^2 goodness-of-fit test, and deviations from mendelian inheritance were tested with PedCheck.³⁷ Genotypes of families with mendelian inconsistencies were set to missing. Estimates of D' and r² were obtained from Haploview v3.11 (<http://www.broad.mit.edu/mpg/haploview/>).³⁸ Phenotypes were analyzed in 6 categories, including asthma diagnosis, allergy, airway responsiveness, bronchodilator responsiveness, pulmonary function, and asthma exacerbations. All analyses were performed assuming an additive genetic model, with the exception of the promoter rs1800925, which we also evaluated assuming a recessive effect on the basis of previous functional data,³⁹ and to facilitate comparison of our results with those of previous publications.³⁹⁻⁴¹ In both cohorts, SNPs and haplotypes were tested for association with asthma and its intermediate phenotypes by using the family-based association test (FBAT) statistic implemented in PBAT version v3.2 (<http://www.biostat.harvard.edu/~clange/default.htm>).⁴²

TABLE I. Baseline characteristics of children with asthma in Costa Rica and white (non-Hispanic) children with asthma in CAMP

Variable	Median (interquartile range) or count (%)	
	Costa Rican subjects n = 417	White subjects n = 503
Age, y	8.7 (7.7-10.4)	8.6 (7.0-10.5)
Sex, female	157 (37.7%)	192 (38.2%)
Total serum IgE, IU/mL	414 (117-962)	399 (159-1066)
Eosinophil count, cells/mL ³	530 (290-805)	402 (211-700)
FEV ₁ /FVC %*	86.1 (82.0-90.0)	86.0 (82.0-90.0)
ED visits for asthma†	399 (95.7%)	149 (29.6%)
Hospitalized for asthma‡	184 (44.1%)	45 (9.0%)
On anti-inflammatory medications§	138 (33.1%)	138 (27.4%)

*Postbronchodilator.

†In Costa Rica, "emergency department (ED) visits for asthma" refers to having ever visited the ED for an asthma exacerbation. Among white subjects in CAMP, "ED visits for asthma" refers to having visited the ED for asthma at least once during the first 4 years of the CAMP trial.

‡In Costa Rica, "hospitalized for asthma" refers to having ever been hospitalized for an asthma exacerbation. Among white subjects in CAMP, "hospitalized for asthma" refers to having been hospitalized for asthma at least once during the first 4 years of the CAMP trial.

§In Costa Rica, "on anti-inflammatory medications" refers to use of either inhaled corticosteroids or leukotriene inhibitors in the year before enrollment. Among white subjects in CAMP, "on anti-inflammatory medications" refers to treatment assignment to inhaled corticosteroids during the course of the CAMP trial.

RESULTS

Baseline characteristics for both children with asthma in Costa Rica and white (non-Hispanic) children with asthma in the CAMP study are presented in Table I. Of the 426 participating families in Costa Rica, 9 were excluded from this analysis because of mendelian inconsistencies. Of the 483 white families in the CAMP study, 13 were removed from this analysis because of mendelian inconsistencies, leaving 470 families (and 503 probands). Parental genotypes were in Hardy-Weinberg equilibrium for all SNPs in Costa Rica and in European Americans in the CAMP study. The minor allele frequencies observed in both cohorts were similar to those reported in other populations (see this article's Table E1 in the Online Repository at www.jacionline.org).

Table II shows the results of the family-based analysis of association between SNPs in *IL13* and asthma and airway responsiveness. Although we found no significant association between polymorphisms in *IL13* and asthma in Costa Ricans, 1 SNP in the promoter of *IL13* (rs1800925) was associated with asthma in white subjects in the CAMP study under a recessive genetic model (the TT genotype was overtransmitted to offspring with asthma). The TT genotype of SNP rs1800925 was inversely associated with a continuous measure of airway responsiveness ($P = .025$) in Costa Rican children but not

in white children in CAMP. We found no association between any SNP in *IL13* and bronchodilator responsiveness in Costa Rican or white children.

Table III shows the results of the family-based analysis of association between variants in *IL13* and peripheral blood eosinophil count and serum total IgE. The minor allele (A) of Arg130Gln (rs20541) was significantly associated with increased eosinophil count and increased total serum IgE in Costa Rican and in white children in CAMP. A SNP that was only genotyped in the CAMP (rs848) and that was in strong linkage disequilibrium ($D' = 1.0$; $r^2 = 0.94$) with SNP rs20541 was also associated with increments in eosinophil count and serum total IgE in white (non-Hispanic) children.

The analysis of association between SNPs in *IL13* and pulmonary function is shown in this article's Table E2 in the Online Repository at www.jacionline.org. Although we observed significant findings in both cohorts, the results were not replicable at the SNP level. The minor allele (T) of the promoter polymorphism (rs1800925) of *IL13* was significantly associated with an increase in postbronchodilator FEV₁/FVC ratio in Costa Rican children ($P = .005$) but not in white children in CAMP. Among white subjects, there was marginal evidence for an inverse association between 3 additional SNPs in *IL13* and FEV₁/FVC.

Table IV shows the results of the analysis of association between variants in *IL13* and asthma exacerbations. Among Costa Ricans, the minor allele (T) of the promoter SNP (rs1800925) was undertransmitted to offspring with asthma who had been hospitalized for asthma (compared with those who had not been hospitalized for asthma), under both additive ($P = .069$) and recessive ($P = .056$) models, but these results did not reach statistical significance. Among white children in CAMP, this effect on asthma exacerbation was not present. In analyses stratified by randomized treatment group in the CAMP study, there was evidence that the T allele of SNP rs1800925 was overtransmitted to those with an asthma exacerbation (compared with those who had not had an asthma exacerbation) on inhaled corticosteroids. There was a statistically significant interaction between use of inhaled corticosteroids and SNP rs1800925 ($P = .049$) in models for asthma exacerbations in white (non-Hispanic) children with asthma in CAMP.

Analysis of family-based association between haplotypes of *IL13* and asthma and related phenotypes demonstrated additional nominally significant findings (presented for peripheral blood eosinophil count and total serum IgE in this article's Table E3 in the Online Repository at www.jacionline.org). However, findings for asthma and related phenotypes were not reproducible at the haplotypic level across studies.

DISCUSSION

We found that polymorphisms in *IL13* were significantly associated with serum total IgE and eosinophil count in 2 well characterized, ethnically and geographically

TABLE II. Family-based analysis of association between *IL13* SNPs and asthma and airway responsiveness among children with asthma in Costa Rica and white (non-Hispanic) children with asthma in CAMP

rs Number	Chromosome 5 position	Alleles	Location	Model	Costa Ricans		White subjects	
					n‡	FBAT	n‡	FBAT
					P value		P value	
Asthma*								
rs1881457	132020308	A>C	5' genomic	Additive			203	.295
rs1800925	132020708	C>T	Promoter	Additive	155	1.000	222	.444
				Recessive	35	.638	59	(+).001§
rs20541	132023863	G>A	Arg130Gln	Additive	198	.796	231	.682
rs848	132024399	G>T	3' UTR	Additive			238	.529
rs2243204	132027393	C>T	3' genomic	Additive			132	.812
Airway responsiveness†								
rs1881457	132020308	A>C	5' genomic	Additive			196	.791
rs1800925	132020708	C>T	Promoter	Additive	187	.265	216	.903
				Recessive	41	(-).025	58	.752
rs20541	132023863	G>A	Arg130Gln	Additive	241	.948	223	.202
rs848	132024399	G>T	3' UTR	Additive			230	.265
rs2243204	132027393	C>T	3' genomic	Additive			132	.255

UTR, Untranslated region.

*Asthma in Costa Rica is defined as having a doctor's diagnosis of asthma, wheeze in the last year, and either airway responsiveness to methacholine ≤ 16.81 μ mol or bronchodilator responsiveness (an increment of at least 12% and at least 200 mL in baseline FEV₁ after administration of albuterol). Asthma in CAMP is defined as having a doctor's diagnosis of asthma and airway responsiveness to methacholine ≤ 12.5 mg/mL. All analyses are adjusted for age and sex.

†Airway responsiveness in Costa Rica and CAMP is defined as the dose response slope to methacholine.

‡Number of informative families.

§Positive and negative signs refer to the direction of association between the minor allele and the outcome.

TABLE III. Family-based analysis of association between SNPs in *IL13* and allergy-related phenotypes among children with asthma in Costa Rica and white (non-Hispanic) children with asthma in CAMP

					Costa Ricans		White subjects	
rs Number	Chromosome 5 position	Alleles	Location	Model	n†	FBAT	n†	FBAT
					P value		P value	
Eosinophil count*								
rs1881457	132020308	A>C	5' genomic	Additive			199	.475
rs1800925	132020708	C>T	Promoter	Additive	204	.294	218	.590
				Recessive	43	.755	57	.591
rs20541	132023863	G>A	Arg130Gln	Additive	265	(+).010‡	226	(+).011
rs848	132024399	G>T	Exon 4	Additive			233	(+).003
rs2243204	132027393	C>T	3' UTR	Additive			127	.523
Serum total IgE*								
rs1881457	132020308	A>C	5' genomic	Additive			201	.845
rs1800925	132020708	C>T	Promoter	Additive	205	.290	222	.954
				Recessive	44	.595	59	.607
rs20541	132023863	G>A	Arg130Gln	Additive	266	(+).017	231	(+).054
rs848	132024399	G>T	3' UTR	Additive			238	(+).026
rs2243204	132027393	C>T	3' genomic	Additive			132	.105

*All analyses are adjusted for age and sex.

†Number of informative families.

‡Positive and negative signs refer to the direction of association between the minor allele and the outcome.

distinct groups of children with asthma. Associations with measures of pulmonary function were not consistent at the SNP level. In CAMP, our results suggest that a promoter polymorphism (rs1800925) in *IL13* may influence asthma exacerbations, and that this effect is dependent on inhaled corticosteroid use. To our knowledge, this is the first report of a significant negative interaction between a genetic polymorphism and response to inhaled corticosteroids.

Major concerns regarding association studies of complex diseases include false-positive results secondary to multiple testing, false-negative results because of conservative correction in the setting of correlated markers and correlated phenotypes, small sample size, population stratification, and association without evidence of function.⁴³ To address these issues, we genotyped more than 1200 individuals in ~400 families in each of

TABLE IV. Family-based analysis of association between SNPs in *IL13* and acute exacerbations among children with asthma in Costa Rica and European-American children with asthma in CAMP

rs Number	Chromosome 5 position	Alleles	Location	Model	Costa Ricans				European Americans			
					n§	FBAT	All subjects		On P/N†		On ICS‡	
							n§	FBAT	n§	FBAT	n§	FBAT
Asthma exacerbations*												
rs1881457	132020308	A>C	5' genomic	Additive			203	.127	153	.620	55	(+).019
rs1800925	132020708	C>T	Promoter	Additive	205	(-).069	222	.213	168	.862	60	(+).018
				Recessive	44	(-).056	59	.511	47	.973	13	(+).143
rs20541	132023863	G>A	Arg130Gln	Additive	266	.453	231	.635	171	.685	66	.800
rs848	132024399	G>T	3' UTR	Additive			238	.847	175	.964	69	.612
rs2243204	132027393	C>T	3' genomic	Additive			132	.745	102	.612	34	.074

*In Costa Rica, "asthma exacerbations" refers to having ever been hospitalized for asthma. In CAMP, "asthma exacerbations" refers to having had an emergency department visit or having been hospitalized for asthma during the first 4 years of the CAMP trial.

†Children randomized to receive either placebo or nedocromil.

‡Children randomized to receive inhaled corticosteroids (budesonide).

§Number of informative families.

||Positive and negative signs refer to the direction of association between the minor allele and the outcome.

TABLE V. Summary of asthma and intermediate phenotype associations with *IL13* in distinct populations

Trait	IL-13 SNP	Association	No association	Level of replication		
				Phenotype	Direction*	Majority
Asthma	rs1800925	3	5	Yes	Yes	Negative
	rs20541	4	11	Yes	Yes	Negative
Total IgE	rs1800925	3	8	Yes	Yes	Negative
	rs20541	12	6	Yes	Yes	Positive
Eosinophil count	rs1800925	0	2	No	—	Negative
	rs20541	2	0	Yes	Yes	Positive
Pulmonary function	rs1800925	1	2	No	—	Negative
	rs20541	1	4	No	—	Negative
Airway hyperresponsiveness	rs1800925	2	1	Yes	No	Opposing effects
	rs20541	0	4	No	—	Negative
Exacerbations	rs1800925	2	1	Yes	No	Opposing effects
	rs20541	0	3	No	—	Negative

*Has the effect of the minor allele been consistent in direction for replicated phenotypes?

2 populations, presented results from family-based association analyses (which are not affected by population stratification), and confirmed any significant findings in Costa Ricans in an independent cohort of white children. The expected probability of a false-positive finding given 2 independent type I errors (at an α of 0.05) is .0025. Our study includes the analysis of 2 functional SNPs in both populations.^{19,20,39}

Many studies have reported an association between the Arg130Gln (rs20541) SNP of *IL13* and an elevated serum total IgE.^{26,28,29} Although other studies (including a previous study from our group in Costa Rica) did not confirm this association,^{21,22,24} they were limited because of small sample size^{22,24} or nonconsideration of serum total IgE as a quantitative trait.²¹ Although the Arg130Gln polymorphism of *IL13* was associated with an elevated eosinophil count in a previous analysis in CAMP,²⁶ our results from Costa Rica are the first replication of this finding. As reviewed in Table V, associations with the Arg130Gln

(rs20541) SNP and total IgE and eosinophil count are the most consistent in effect and direction in the literature on *IL13* to date. This suggests that the predominant genetic effect of the Arg130Gln (rs20541) polymorphism is on allergy and not asthma *per se*.

The observed inverse association between the promoter polymorphism (rs1800925) of *IL13* and asthma exacerbations in Costa Rica may be mediated by the effects of this SNP on airway responsiveness. However, IL-13 levels might be independently important in the response to respiratory viral infection, the most frequently implicated cause of acute asthma exacerbations.^{44,45} In the Childhood Origins of Asthma Study (a birth cohort study), phytohemagglutinin-induced IL-13 responses from cord blood cells were significantly increased in children who did not develop wheezing with respiratory syncytial virus, with similar results noted for rhinovirus.⁴⁶ In mice, increased expression of IL-13 has been shown to decrease 4 day respiratory syncytial virus titers⁴⁷ and may be associated with the

prevention of postviral airway inflammation.⁴⁸ Although articles on *IL13* polymorphisms and the severity of respiratory syncytial virus infection suggest contrary effects of these polymorphisms in children,^{49,50} the reports are limited by lack of phenotypic information in control subjects,^{49,50} marked differences in age between cases and control subjects,⁴⁹ lack of reproducibility at the SNP level across studies,^{49,50} and limited data (11 subjects) on which to base inference.⁵⁰

We found the opposite effect of the promoter polymorphism (rs1800925) of *IL13* in white children using inhaled corticosteroids. In multiple experimental models, corticosteroids appear to blunt IL-13 secretion.^{51,52} A recent study on the functional effect of SNP rs1800925 suggests that although the minor allele enhances promoter activity in polarized human and murine CD4⁺ T_H2 lymphocytes, this polymorphism may have the opposite effect on nonpolarized CD4⁺ lymphocytes.¹⁸ This suggests that inhaled corticosteroids and the underlying T_H2 predisposition may influence the functional effect of this polymorphism, making contrasting population-based effects plausible. We stress the importance of replicating our findings, both to exclude false-positive results and to assess the possibility of inadequate response to inhaled corticosteroids for those with the minor allele of the *IL13* promoter polymorphism (rs1800925). Lack of information about medication use before hospitalization in retrospective data in children with asthma in Costa Rica precludes a similar comparative analysis.

We cannot exclude true ethnic-specific effects of particular polymorphisms of *IL13*. For example, the TT genotype of the promoter polymorphism rs1800925 has been associated with asthma and airway responsiveness in other populations of European descent.^{22,27,39} Additional study limitations include the inability to exclude differential linkage disequilibrium (LD) with unevaluated variants in *IL13* and LD with variants in nearby genes as potential explanations for our findings. Differences in LD patterns (see this article's Fig E1 in this article's Online Repository at www.jacionline.org), gene-by-gene interactions, and/or environmental exposures between Costa Ricans and whites in CAMP may explain replication of some findings at the gene level but not at the SNP level (eg, for postbronchodilator FEV₁/FVC, airway responsiveness, and asthma exacerbations). However, most studies of variants in *IL13* have not replicated initial associations with asthma (Table V; see this article's Table E4 in the Online Repository at www.jacionline.org), again suggesting that *IL13* primarily influences the pathogenesis of atopy.

In summary, we have shown that a coding polymorphism (rs20541) of *IL13* is associated with increased total serum IgE and eosinophil count in 2 populations. We demonstrated contrasting effects of the promoter polymorphism (rs1800925) on asthma exacerbations and present data suggesting that inhaled corticosteroid use may influence this difference. Elucidating polymorphisms that influence asthma exacerbations among diverse asthmatic populations might provide a more immediately clinically

applicable use to the expanding technologies of genetic epidemiology.

We thank all families for their invaluable participation in the Genetics of Asthma in Costa Rica Study and in the CAMP Genetics Ancillary Study. All work on data from the CAMP Genetics Ancillary Study was conducted at the Channing Laboratory and the Brigham and Women's Hospital under appropriate CAMP policies and human subjects protections.

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