

Polymorphisms in the 5' region of the CD14 gene are associated with eczema in young children

Augusto A. Litonjua, MD, MPH,^{a,b,c} Kathleen Belanger, PhD,^d Juan C. Celedón, MD, PhD,^{a,b,c} Donald K. Milton, MD,^{c,e} Michael B. Bracken, PhD,^d Peter Kraft, PhD,^e Elizabeth W. Triche, PhD,^d Diane L. Sredl, MPH,^a Scott T. Weiss, MD, MS,^{a,c,f} Brian P. Leaderer, PhD,^d and Diane R. Gold, MD, MPH^{a,c} Boston, Mass, and New Haven, Conn

Background: Variants in the CD14 gene (*CD14*) are hypothesized to be associated with atopic disorders. However, most studies have only investigated one polymorphism in this gene.

Objective: We sought to study the association of 5 single nucleotide polymorphisms (SNPs) in the 5' flanking region of *CD14* with eczema and serum IgE levels in young children.

Methods: We genotyped 5 SNPs in an approximately 6.5-kb region in the 5' region of *CD14* in 344 2-year-old white children from 2 birth cohorts in the northeastern United States. We examined the relation of both single SNPs and haplotypes in *CD14* with the atopic outcomes.

Results: Two SNPs were significantly associated with eczema. In dominant models adjusted for potential confounders, SNP rs2569193 was associated with significantly decreased risk for eczema (odds ratio [OR] for CT/TT vs CC, 0.5; 95% CI, 0.3-0.8), whereas SNP rs2569190 (also reported as the C-159T) was associated with significantly increased risk for eczema (OR for CT/TT vs CC, 2.3; 95% CI, 1.4-3.8). The CT/TT genotypes of SNP rs2569190 also had higher geometric means of serum IgE

than the CC genotype (24.6 vs 15 IU/mL, $P = .025$). Haplotype analyses provided results similar to those of the single SNP analyses.

Conclusions: Our results contradict previous reports that have found a protective effect of the T allele of SNP rs2569190 (C-159T) against atopic disorders. Nevertheless, these results confirm the importance of polymorphisms in *CD14* in the development of atopy, and future studies of this gene region will need to account for linkage disequilibrium and environmental exposures unique to the study population. (J Allergy Clin Immunol 2005;115:1056-62.)

Key words: Eczema, polymorphism, genetic, IgE

In 1999, Baldini et al¹ reported on an association between a CD14 promoter single nucleotide polymorphism (SNP) and both soluble CD14 levels and serum IgE levels in a cohort of children from Tucson, Arizona. Subsequently, reports from other groups have shown that this polymorphism, C-159T, was also associated with either serum IgE levels or other atopic phenotypes²⁻⁴ in other populations. However, others have not found an association of this polymorphism with atopy phenotypes.⁵⁻⁸

Although other polymorphisms in the 5' region of the gene have been reported,⁹ most of these previous association studies have considered only one polymorphism in this region of the gene. Thus linkage disequilibrium (LD) of the C-159T polymorphism with other SNPs in the 5' region or other regions of the gene is one explanation for the discrepant results.¹⁰ Another explanation that has been put forth is that *CD14* might have different effects, depending on the background environment.¹¹ In support of this, a recent report showed that the risk associated with the C-159T polymorphism was modified by the presence of a dog in the first year of life.¹²

In the current analysis we sought to determine whether this and other polymorphisms in the 5' flanking region of *CD14* are associated with the atopic phenotypes of eczema and total serum IgE in a sample of children at risk for asthma and allergies from 2 birth cohorts from the same region of the United States. We also sought to determine whether these SNPs interacted with the presence of a pet dog in the first year of life in the development of eczema.

From ^athe Channing Laboratory, the Department of Medicine, Brigham and Women's Hospital, Boston; ^bthe Section of Pulmonary and Critical Care Medicine, Beth Israel Deaconess Medical Center, Boston; ^cHarvard Medical School, Boston; ^dthe Center for Perinatal, Pediatric and Environmental Epidemiology, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven; ^eHarvard School of Public Health, Boston; and ^fHarvard Partners Center for Genetics and Genomics, Boston.

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Reprint requests: Augusto A. Litonjua, MD, MPH, 181 Longwood Ave, Boston, MA 02115. E-mail: augusto.litonjua@channing.harvard.edu.

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Abbreviations used

FDR: False discovery rate
LD: Linkage disequilibrium
OR: Odds ratio
SNP: Single nucleotide polymorphism

METHODS

Populations and study sample

The children in this study are participants in 2 birth cohort studies in the northeastern United States. The first birth cohort is the Epidemiology of Home Allergens and Asthma (hereafter referred as the Boston cohort), an ongoing longitudinal family and birth cohort study the primary aim of which is to examine the role of indoor home allergen exposure in the development of asthma-wheeze and allergic sensitization during early childhood in children whose parents have asthma or allergy. Recruitment and exclusion criteria have been published previously.¹³ In brief, 499 families were recruited between 1994 and 1996 within 48 hours of the birth of the index child at a tertiary hospital in Boston. If either parent had a history of physician-diagnosed asthma, hay fever, or allergies, a screening questionnaire was administered, and if either parent was allergic to house dust or house dust mites, cockroaches, pollens, animals, or mold, then they were eligible for inclusion in the cohort. The study was approved by the Institutional Review Board of the Brigham and Women's Hospital.

The second birth cohort is the Connecticut Childhood Asthma Study (hereafter referred as the Connecticut cohort). Between 1996 and 1998, 1002 families were recruited. Details of the recruitment and design of the study have previously been published.^{14,15} To be eligible, a family had to have a newborn infant (index child) and a child less than 12 years old with physician-diagnosed asthma (asthmatic sibling). Mothers were approached after delivery at 5 Connecticut hospitals (Bridgeport, Danbury, Hartford, St Francis, and Yale-New Haven) and one hospital in southwestern Massachusetts (Baystate). The study was approved by the Institutional Review Board of the Yale University School of Medicine. The current study was approved by institutional review boards from both institutions.

There was a total of 543 children (252 in the Boston cohort and 291 in the Connecticut cohort) for whom we had available genetic material for genotyping. For this analysis, we restricted the subjects to the 379 white children. Each child in this analysis came from unique households, and thus no siblings were included in this analysis. To avoid misclassification bias in our control group, we excluded 35 children who had eczema after the second year of life. This left a total number of 344 (173 in the Boston cohort and 171 in the Connecticut cohort) for the current analysis. Further details of each cohort and a comparison between them are available in the Journal's Online Repository at www.mosby.com/jaci. Briefly, the associations between the predictors of interest and eczema were similar in each group. More importantly, genotype frequencies for each SNP and the LD patterns between each SNP were the same in each cohort.

Eczema

Information on eczema was obtained from a parental report of the condition. In the Boston cohort this was ascertained by using questionnaires administered every 2 months to ask the following question: "Has a doctor or nurse ever said that (child) had eczema?" In the Connecticut cohort this was ascertained by using question-

naires administered every 3 months to ask the following question: "Has (child) had eczema since our last interview?" A child was identified as a case if he or she was reported to have had eczema within the first 2 years of life. From the 379 white children, a total of 154 children had eczema within the first 2 years of life. From follow-up questionnaires, 35 children were found to have eczema after age 2 years and were excluded from the analysis to avoid misclassification in the control group. This left 190 children who did not have eczema, and these children served as control subjects for the analysis.

Pets in the home and other predictor variables

Information on pets in the home in the first year of life was obtained from the bimonthly questionnaires in the Boston cohort and the quarterly questionnaire in the Connecticut cohort. In the Boston cohort participants were asked the following: "Do you have any of the following pets?" In the Connecticut cohort, participants were asked the following: "Since our last interview, have you kept pets inside your home?" In either case dog or cat ownership in the first year of life was determined on the basis of affirmative responses. Similarly, information for the first year of life on daycare attendance, breast-feeding, and parental smoking were obtained from these follow-up questionnaires. From screening questionnaires, information regarding parental asthma and hay fever, along with the number of older siblings, was obtained. Information on maternal age and birth weight were obtained from birth records; season of birth was derived from birth dates. The definitions of these variables are detailed in the Journal's Online Repository.

Measurement of total serum IgE

Serum samples from a subset of children from both cohorts were analyzed for total IgE levels by using an enzyme immunoassay based on the sandwich technique (UNICAP system; Pharmacia Diagnostics, Kalamazoo, Mich). A total of 272 children had available serum IgE values for this analysis. All IgE values were converted to the log-natural scale for analysis.

SNP selection and genotyping

We selected SNPs in the region 5' to *CD14*. One SNP, rs2569190, mapped precisely to the previously reported C-159T promoter polymorphism (Genbank accession no. AF097335).¹ This same SNP is also reported as C-260T in the literature.¹⁶ From our sequencing and genotyping effort in the Innate Immunity Program for Genomic Applications (<http://innateimmunity.net>), we chose an additional 4 SNPs, and together, these 5 SNPs span an area that is approximately 6.5 kb in the 5' flanking region of the gene (Fig 1).^{17,18} Flanking sequences of all 5 of the SNPs can be found in Table E1 in the Journal's Online Repository at www.mosby.com/jaci.

Genomic DNA was isolated from venous blood samples according to standard protocols. Genotyping was performed by using unlabeled minisequencing reactions and mass spectrometry analysis (Sequenom, San Diego, Calif). Multiplex PCR and minisequencing assays were designed by using SpectroDESIGNER software (Sequenom). Protocol details are available at <http://innateimmunity.net>, and primer data are posted in the Journal's Online Repository. Secondary multiplex single-primer minisequencing reactions were performed and analyzed by using the Bruker Bi-flex MALDI-TOF mass spectrometer (Bruker Daltonics, Billerica, Mass). Spectral output was analyzed by using SpectroTYPER-RT software (Sequenom) and by means of manual review. Duplicate genotyping was performed on approximately 50% of the samples to assess genotype reproducibility. Genotype discordance rates ranged from 0% to 1.7%.

To assess for evidence of population stratification among the participants, we genotyped a panel of 41 SNPs obtained through the

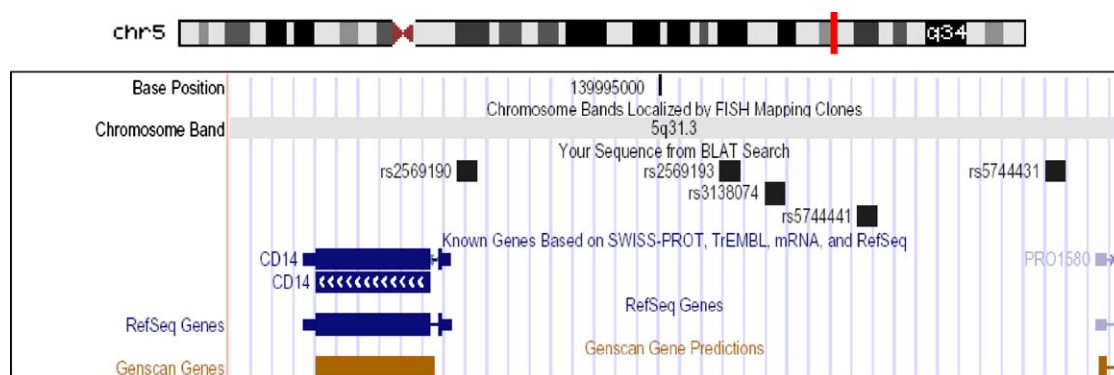


FIG 1. Positions of the 5 *CD14* SNPs. From UCSC Genome Browser (<http://genome.ucsc.edu>), May 2004, Human Reference Sequence Assembly (position chr5:139,990,780-139,999,496 size 8717 bp).^{17,18}

SNP Consortium database. All of these SNPs were located in noncoding regions of genes that were not known to be associated with asthma or atopy phenotypes and were located on autosomal chromosomes. Under the null hypothesis of identical allele frequencies among cases and control subjects at each locus, contingency tables were constructed for each locus, and χ^2 statistics were computed (see Fig E1 in the Journal's Online Repository at www.mosby.com/jaci). The test statistics from each locus were summed as follows: $X_s^2 = \sum_{i=1}^L X_i^2$, where X_i^2 is the χ^2 statistic computed at the i th marker locus, and L is the set of unlinked marker loci typed in all individuals. Under H_0 , X_s^2 is χ^2 distributed, with df equaling the sum of the df of individual loci (in this case $df = 41$). On the basis of our results, $X_s^2, 41df = 45.18$ ($P = .37$), and thus there was no evidence of population stratification in this study population.

Statistical analysis

We conducted univariate analyses of the association between potential predictor variables and eczema in the first 2 years of life by using χ^2 tests for categorical variables and 2-tailed t tests for continuous variables. Logistic regression, as implemented in the LOGISTIC Procedure in SAS (SAS Institute, Inc, Cary, NC), was used to assess the association between individual SNPs and eczema while adjusting for potential confounders and examining interactions. Genotypes for each SNP were coded as either a 3-level categorical variable for the number of minor alleles (additive genetic model) or dichotomous variables for the presence of any minor allele (dominant genetic model). Linear regression (REG Procedure in SAS) was used to assess the association between individual SNPs and log-transformed total serum IgE while controlling for the age and sex of the child.

Haplotype analyses were conducted with the software haplo.score,¹⁹ a suite of S-PLUS routines that computes score statistics to test associations between imputed haplotypes and a wide variety of traits. In this method score tests derived from generalized linear models were used for global tests of association, as well as haplotype-specific tests. All analyses included only haplotypes that had a frequency of at least 5.0%. Multiple testing was addressed by controlling the false discovery rate (FDR) with the method of Benjamini and Liu (FDR tool available at <https://innateimmunity.net/IIPGA2/Bioinformatics/>).^{20,21} Control of the FDR was set at the 0.05 threshold.

RESULTS

The baseline characteristics are shown in Table I. The presence of a dog in the home in the first year of life was

TABLE I. Baseline characteristics and genotype frequencies of the 344 white children by eczema at 2 years of age

	Eczema (n = 154)	No eczema (n = 190)	P value
Male sex, n (%)	91 (59)	101 (53)	.3
Birth weight, g (mean $\pm$ SD)	3552.0 $\pm$ 498.7	3519.2 $\pm$ 521.2	.5
Season of birth, n (%)			.4
Fall	43 (28)	38 (20)	
Winter	33 (21)	41 (22)	
Spring	38 (25)	52 (27)	
Summer	40 (26)	59 (31)	
Dog in the home in the first year, n (%)	36 (23)	62 (33)	.05
Cat in the home in the first year, n (%)	52 (34)	59 (31)	.6
Maternal asthma, n (%)	52 (34)	48 (25)	.08
Maternal allergic rhinitis, n (%)	89 (58)	102 (54)	.5
Maternal age, y (mean $\pm$ SD)	34.2 $\pm$ 4.1	34.0 $\pm$ 4.3	.5
Paternal asthma, n (%)	35 (23)	31 (17)	.1
Paternal allergic rhinitis, n (%)	79 (53)	83 (45)	.1
<i>CD14</i> promoter polymorphisms			
rs5744431			.3
AA	152 (99)	182 (98)	
AG	1 (1)	4 (2)	
rs5744441			.3
CC	93 (60)	107 (58)	
CT	57 (37)	66 (36)	
TT	4 (3)	11 (6)	
rs3138074			.6
AA	90 (59)	105 (57)	
AT	57 (38)	69 (38)	
TT	5 (3)	10 (5)	
rs2569193			.01
CC	89 (60)	83 (45)	
CT	52 (35)	81 (44)	
TT	8 (5)	21 (11)	
rs2569190			.002
CC	31 (20)	70 (38)	
CT	78 (51)	79 (42)	
TT	43 (28)	37 (20)	

TABLE II. Association of individual *CD14* SNPs with eczema at 2 years of age in white children*

	Additive model			Dominant model		
	OR (95% CI)	P value	FDR thresholds†	OR (95% CI)	P value	FDR thresholds†
rs5744431	0.3 (0.0-2.6)	.25	0.016	—	—	—
rs5744441	0.9 (0.6-1.2)	.4	0.028	0.9 (0.6-1.4)	.6	0.02
rs3138074	0.9 (0.6-1.3)	.5	0.05	0.9 (0.6-1.4)	.6	0.05
rs2569193	0.6 (0.4-0.8)	.003	0.01	0.5 (0.3-0.8)	.005	0.0125
rs2569190	1.7 (1.2-2.3)	.001	0.007	2.3 (1.4-3.8)	.001	0.008

*Results are from individual logistic regression models. All models are adjusted for maternal asthma, sex, and the presence of a pet dog in the home in the first year of life.

†FDR thresholds using the procedure of Benjamini and Liu.^{20,21}

associated with a lower proportion of children who had eczema by 2 years of age (23% for having a pet dog vs 33% for not having a pet dog, $P = .05$), whereas maternal asthma was associated with a higher proportion (34% for maternal asthma vs 25% for no maternal asthma, $P = .08$). None of the other characteristics were associated with eczema. A comparison of the characteristics of the children in each cohort is shown in Table E2 in the Journal's Online Repository at www.mosby.com/jaci.

The genotype frequencies of the 5 SNPs are shown in Table I. Genotype frequencies of the 5 SNPs in the children in each cohort were identical with each other (see Table E2 in the Journal's Online Repository at www.mosby.com/jaci). Linkage disequilibrium patterns between each of the SNPs in each cohort were also identical with each other (see Fig E2 and Table E3 in the Journal's Online Repository at www.mosby.com/jaci). Among control subjects, there was no evidence for deviation from Hardy-Weinberg equilibrium (P values ranged from .09 to 1.0 for the 5 SNPs). Two SNPs were significantly associated with eczema: the T allele of rs2569193 was inversely associated with eczema, and the T allele of rs2569190 was positively associated with eczema. In models adjusted for maternal asthma, sex, and the presence of a dog, these univariate associations were confirmed (Table II). In both additive and dominant genetic models, the T allele of rs2569193 was significantly protective against eczema, whereas the opposite was true for the T allele of rs2569190. Table II also presents the FDR thresholds to account for multiple testing. By using this method, the P values for both SNPs rs2569193 and rs2569190 remained less than the FDR threshold and thus remained statistically significant. Additional control for paternal asthma, season of birth, and the presence of a cat did not change these observed relationships.

We reran these multivariable models in the children from each cohort separately and obtained the same results. For SNP rs2569190, the ORs were 0.7 (95% CI, 0.4-1.1) in the Boston cohort and 0.5 (95% CI, 0.3-0.8) in the Connecticut cohort, whereas for SNP rs2569190, the ORs were 1.5 (95% CI, 1.0-2.2) in the Boston cohort and 1.9 (95% CI, 1.2-3.1) in the Connecticut cohort for additive genetic models (Table E4 in the Journal's Online Repository at www.mosby.com/jaci).

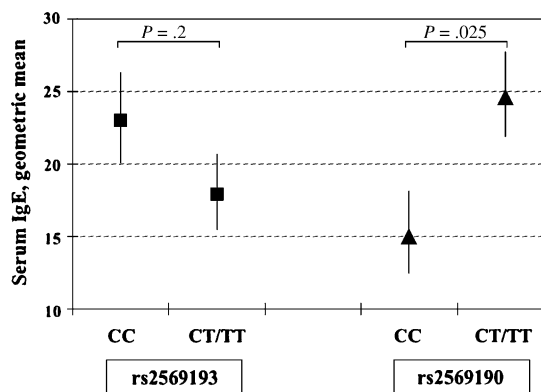


FIG 2. The association between 2 *CD14* SNPs and serum IgE in children. Values are geometric means of age- and sex-adjusted serum IgE.

We next investigated whether the presence of a pet dog in the first year of life modified the effect of these SNPs on eczema in dominant genetic models. The association of rs2569193 with eczema was protective irrespective of whether a pet dog was present in the home (OR of 0.5 [95% CI, 0.3-0.8] for those without a pet dog vs OR of 0.6 [95% CI, 0.3-1.5] for those with a pet dog, P value for interaction = .6). In similar fashion, rs2569190 was associated with increased risks for eczema, regardless of the presence or absence of a pet dog (OR of 2.6 [95% CI, 1.4-4.8] for those without a pet dog vs OR of 1.8 [95% CI, 0.7-4.4] for those with a pet dog, P value for interaction = .6).

In the subset of 272 children with total serum IgE measurements, children who were either heterozygous (CT) or homozygous TT at rs2569190 had significantly higher geometric means of serum IgE than children who were homozygous CC (Fig 2). For rs2569193, children who were either heterozygous CT or homozygous TT had lower serum IgE levels than children who were homozygous CC, although this was not statistically significant.

We next investigated the association between haplotypes defined by these 5 SNPs and eczema. There was a total of 7 haplotypes that were imputed from the data, although 3 of these haplotypes accounted for more than 98% of the observations. Table III shows the results of

TABLE III. Association of *CD14* 5' flanking SNP haplotypes with eczema at 2 years of age in white children*

	Haplotypes					Frequency	Score statistic	P value
	rs5744431	rs5744441	rs3138074	rs2569193	rs2569190			
1	A	C	T	T	C	0.28964	-2.70493	.023
2	A	T	A	C	C	0.22764	-1.08731	.28
3	A	C	T	C	T	0.46618	2.86852	.004

Global score statistic = 8.9132, $df = 3$, $P = .03$.

*From Haplo.score analysis, with minimum haplotype frequency set at 0.05. The analysis is adjusted for maternal asthma, sex, and the presence of a dog in the home in the first year of life.

a Haplo.score analysis. Haplotype 1, which contained rs2569193(T) and rs2569190(C), was inversely associated with eczema, whereas haplotype 3, which contained rs2569193(C) and rs2569190(T), was positively associated with eczema. The frequencies of these haplotypes were similar in the children from each cohort, and the haplotype analyses for each cohort yielded similar results (Table E5 in the Journal's Online Repository at www.mosby.com/jaci).

DISCUSSION

We have found an association between 2 SNPs in the 5' flanking region of *CD14* and eczema and total serum IgE levels among 2-year-old children at risk for asthma and atopic disorders. This is the first report of an association of one SNP (rs2569193) with eczema. The other SNP, rs2569190, has variably been reported in the literature as C-159T or C-260T, and previous studies have reported that the C allele is associated with lower CD14 levels, higher serum IgE levels, and increased risks for atopy. However, we found that in our cohort of children from the northeastern United States, the T allele is associated with eczema and higher serum IgE levels.

In the initial report of an association, Baldini et al¹ showed that the TT homozygotes of rs2569190 had higher circulating soluble CD14 levels than CC homozygotes in a subset of 109 children with a mean $\pm$ SD age of 10.8 ± 0.6 years. They also found that TT homozygotes had lower serum IgE levels than other genotypes but only among children who had positive skin test responses. Similarly, Leung et al⁴ found that TT homozygotes for this SNP had lower serum IgE levels than other genotypes only in the group of 261 10-year-old children with positive RAST results from Hong Kong. Koppelman et al²² found similar associations between this SNP and both serum IgE and number of skin tests among atopic subjects from the Netherlands.

Although our results appear to contradict those of these previous studies, they are consistent with a population-based study that found the T allele was associated with nonatopic asthma and food allergy.²³ In addition, several studies have not found an association with this SNP.⁵⁻⁸ Several reasons might account for these discrepant findings, and these include deviation from Hardy-Weinberg equilibrium, the presence of population stratification,

differences in phenotype definitions, different environmental exposures, and LD of the SNP with other SNPs in *CD14* or in other genes.

Although many of the previous studies had tested for deviation from Hardy-Weinberg equilibrium, to date, no other population-based study tested for population stratification. We tested and found no evidence of population stratification in our cohort. In addition, a family-based study (a study design resistant to the effects of population stratification) of a 15-generation pedigree of Hutterites²⁴ found that the T allele was overtransmitted to atopic individuals by using the transmission disequilibrium test. Our results therefore are consistent with the results of this family-based study.

Differences in definition of atopic disorders and gene-environment interactions might also contribute to the discrepant results between our study and others. We used a report of a diagnosis of eczema by 2 years, which has been validated against both clinical examination²⁵ and clinical chart-recorded diagnosis.²⁶ However, differences in phenotype definition are not likely to explain the discrepant results with regard to serum IgE levels, where we found that the TT homozygotes also had higher levels of IgE. There are also significant age differences between our cohort of children and others. Although we investigated children who were all 2 years of age, all of the previous studies that have been cited have investigated either adults or older children (about 10 years of age). Recently, O'Donnell et al²⁷ demonstrated age-specific effects of the rs2569190 SNP with atopic phenotypes in a cohort of children assessed between 8 and 25 years of age. In the only other study to assess this SNP using a cohort of comparable age, Gern et al¹² studied a birth cohort from Wisconsin and found that the T allele of the rs2569190 SNP was protective against atopic dermatitis but only among those with a pet dog in the home. In our cohort of children from Massachusetts and Connecticut, we did not find a significant interaction between SNPs in the 5' region of *CD14* and dog ownership in the first year of life. It is likely that dog ownership might represent a different exposure (or group of exposures) in this region of the United States where type and age of housing, allergen exposure, and other background exposures differ from the rest of the country.^{14,28,29} Although the presence of a pet dog has been linked to endotoxin levels in the home,³⁰ it is also likely that determination of dog ownership is not sensitive enough to capture the relevant

exposures (eg, varying exposure dose of endotoxin). Better assessment of the exposure (eg, measurement of endotoxin levels) might help clarify this issue in future studies.

SNP rs2569190 has been shown to alter the transcriptional activity of *CD14*.³¹ Thus it is likely that interactions of this SNP with different background environmental exposures could further modulate gene expression and lead to different effects on IgE production and expression of atopic disorders.¹¹ Finally, because asthma and atopy are complex disorders, unstudied interactions between SNPs (or between genes) are also likely to contribute to the inconsistencies of results when only one SNP (or gene) at a time is investigated.

LD of the rs2569190 SNP with the true susceptibility variant on *CD14* is another potential explanation of the discrepancies between results from different studies. In support of this notion, Ober et al²⁴ found that the T allele of rs2569190 (−159T) was only overtransmitted to atopic subjects when it was on a haplotype with one particular allele from another marker but not on other haplotypes. Although this SNP was not in strong LD with the other SNPs that we investigated in our cohort, LD with other SNPs in other regions of the gene cannot be ruled out, and future association studies will need to account for these SNPs. A few studies have looked at other SNPs in the promoter region of *CD14*.^{3,9} However, none of these SNPs were associated with any atopic phenotype. We genotyped 4 other SNPs that were farther upstream in the 6.5-kb region 5′ to *CD14*. We found one SNP, rs2569193, to be associated with eczema. In this case the T allele of this SNP was inversely associated with eczema and serum IgE. This SNP was not in tight LD with rs2569190 in our cohort ($r^2 = 0.34$; see Fig E2 and Table E3 in the Journal's Online Repository at www.mosby.com/jaci), suggesting independent associations. The 3 other SNPs that we studied were not associated with eczema. Results of the haplotype analyses were consistent with our single SNP results in that the haplotype that included the T allele of rs2569193 and the C allele of rs2569190 was inversely associated with eczema, whereas the haplotype that included the C allele of rs2569193 and the T allele of rs2569190 was positively associated with eczema. Haplotype analyses for IgE were also consistent with these findings but did not reach statistical significance (data not shown).

A limitation of our study is that these children were drawn from 2 separate cohorts, with some differences in recruitment and in ascertaining exposures and the outcome. Before combining these subsets of children for this analysis, however, we confirmed that the data were consistent across each cohort (see the Journal's Online Repository for the comparison between each cohort). Additionally, genotype frequencies of each SNP and LD patterns across the region of interest were similar for each subset, giving us reasonable confidence to combine these subsets for genetic association analyses. Finally, we accounted for the multiple testing issue by controlling for FDR, and our results remained significant.

In summary, we have found associations between 2 SNPs in the 5′ flanking region and eczema in the first 2

years of life. Associations have been reported previously with SNP rs2569190, but this is the first report of an association with SNP rs2569193. Haplotype analyses were consistent with the single SNP analyses. Although our results are different from the results of other population-based studies, they are consistent with the only published family-based analysis of *CD14*. Taken together with previous studies, our results confirm that *CD14* plays a role in the genesis of atopic disorders, but future studies will need to address gene-environment effects, as well as gene-gene interactions.

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