

inhaled steroids). By using a human IL-33 ELISA kit (Cytoset; Invitrogen, Carlsbad, Calif), we detected increased IL-33 levels in the BALF supernatants from subjects with moderate asthma (average of 120.8 ± 22.4 pg/mL) compared with those with mild asthma (89.8 ± 26.4 pg/mL) or controls without asthma (89.4 ± 12.4 pg/mL; FEV₁, 110.0 ± 5.2), respectively (Fig 2, B). This suggests that bronchial epithelium and other airway resident cells express elevated levels of IL-33 in asthma^{1,4} and may also be subjected to conditions favoring its release. In asthma, several reports documented intense epithelial cell turnover caused by cell damage/death and aberrant repair leading to thickening of epithelium.⁸ Recent studies on IL-33-expressing endothelial cells reported significant release of IL-33 in supernatants of damaged and/or necrotic endothelial cells compared with supernatants from live cells.⁹ It is therefore tempting to speculate that increased epithelial damage caused by chronic inflammation of the asthmatic bronchi contributes to the release of IL-33. However, discrepancies observed between the epithelial IL-33 immunoreactivity in subjects with moderate versus mild asthma (Fig 1, E) and the increased IL-33 levels in BALF from subjects with moderate versus mild asthma (Fig 2) suggest other cell types, like smooth muscle,⁴ may also be significant IL-33 sources in asthma.

Aside from the literature describing IL-33 as an "alarmin"-type cytokine with proallergic properties, there is a lack of studies regarding the sources of this cytokine and the regulation of its release in airway diseases. This study proposes that bronchial epithelium is an important IL-33 reservoir in the lung and that its expression is elevated in bronchial asthma. Histologic observations support the intracellular and nuclear localization of IL-33 in epithelial cells, whereas we also document the increasing release of this cytokine in the airway lumen along with asthma severity (moderate > mild asthma and controls). This study sheds light on the relevance of further using IL-33 BALF levels and studying epithelial cells' IL-33 expression as potential biomarkers in moderate and severe asthma, respectively.

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Polymorphisms of chitinases are not associated with asthma

To the Editor:

One of the most exciting findings recently in the pathophysiology of asthma is that mammalian chitinases might play an important role in the pathogenesis of asthma. Some researchers hypothesize that mammalian chitinases and a chitinase homologue might contribute to the pathogenesis of type 2 helper immune responses, which play an important role in asthma.^{1,2} Chitinases are enzymes that cleave chitin, a polysaccharide that is present in fungal cells, crustaceans, insects, and parasitic nematodes.³ Although chitin does not exist in human subjects, 2 chitinases, acidic mammalian chitinase (*CHIA*) and chitotriosidase (*CHIT1*), have been described in human subjects.³ A third protein, chitinase-like protein YKL-40 (also known as human cartilage glycoprotein 39 and chitinase 3-like 1 [*CHI3L1*]), also appears to be important in asthma.¹

The objectives of this study were to assess whether single nucleotide polymorphisms (SNPs) in *CHIT1*, *CHIA*, and *CHI3L1* and one *CHIT1* duplication are associated with asthma, changes in lung physiology that are associated with asthma, or allergy-related phenotypes. We used data from the Childhood Asthma Management Program (CAMP), a multicenter trial that enrolled children between the ages of 5 and 12 years with mild-to-moderate persistent asthma and their parents.⁴ Subjects were followed every 2 to 4 months for 4 years to study the long-term use of budesonide, nedocromil, and placebo.⁴

SNPs in *CHIT1*, *CHIA*, and *CHI3L1* (see Fig E1 in this article's Online Repository at www.jacionline.org for linkage disequilibrium plots) were genotyped by using the Infinium HumanHap550 genotyping at Illumina (San Diego, Calif). Genotyping quality was evaluated by using the program PLINK (version 1.01). SNPs with low Illumina GenCall scores, poor completion rates, or 4 or more parent-offspring genotyped inconsistencies were dropped. Using the Basic Local Alignment Search Tool, SNPs

TABLE I. Demographics (n = 422)

Age (y [range])	8.7 (2.1 [5.2-13.2])
Treatment group	
Budesonide	28% (118)
Nedocromil	29% (122)
Placebo	43% (182)
Sex, n = 422	
Male	63% (266)
Female	37% (156)
Weight at baseline (kg), n = 419	31.87 (10.56)
Height at baseline (cm), n = 417	132.45 (13.50)
Total number of hospitalization and ED visits over 4-y period, n = 422	
0	69% (291)
1	14% (60)
2	7% (31)
≥3	9.5% (40)
Baseline pre-FEV ₁ , n = 421	1.694 (0.473)
Baseline bronchodilator Response, n = 421	0.104 (0.098)
Baseline FEV ₁ percent predicted, n = 416	93.370 (13.954)
Baseline lnPC ₂₀ , n = 420	0.025 (1.153)
Baseline log ₁₀ IgE level, n = 417	2.616 (0.671)
Baseline log ₁₀ eosinophil count, n = 414	2.561 (0.488)

Values are presented as means (SDs) or percentages (numbers), where shown.
ED, Emergency department.

were further limited to those whose flanking sequences were reliably mapped to unique autosomal locations in the hg17 reference genome sequence. The *CHIT1* fragment analysis⁵ was performed by using the Applied Biosystems (Foster City, Calif) 3100 Genetic Analyzer platform. Primers CHIT1_A1FGTCTGGATGAGGGGGTATCG-FAM and CHIT1_A1RGTTCCTCCCTGCACAGGTCAGCTATC were used to PCR amplify the region containing the 24-bp duplication, and peaks were analyzed with Applied Biosystems GeneMapper software. The genotyping completion rate was 94%.

Family-Based Association Test–Principal Components (FBAT-PC) is a method that has the ability to use genetic data from family members to assess associations between a disease phenotype and a gene allele while maximizing the genetic information when multiple phenotypes are tested.⁶ We performed association analyses for each SNP and each phenotype using the FBAT-PC approach. FBAT-PC uses principal components analysis to construct an overall phenotype that amplifies the trait heritability by aggregating the genetic components of all measurements into a single univariate phenotype with maximal heritability.⁶

After the univariate phenotype is generated at each SNP, FBAT-PC uses a screening procedure to select the SNPs to be tested by using a univariate quantitative FBAT statistic, the FBAT-PC statistic. For each SNP, the power to detect the association with the generated univariate phenotype is calculated, a group of SNPs with their associated phenotypes are selected based on the power to detect a genetic association, and then the FBAT-PC statistic is calculated on the SNPs and their

associated phenotypes. In the analysis for this study, the additive genetic model was used, and a minimum of 20 informative families were required. We used an FBAT approach with generalized estimating equations⁷ for our outcomes, which were assessed at one time point.

Power calculations were conducted by using the FBAT Power Calculator (HelixTree version 6.4.2, 2008; see Table E1 in this article's Online Repository at www.jacionline.org). Assuming a significance level of .05, we had an 80% or greater power to detect an association between each SNP and a single continuous measure for a heritability of 4% or greater. We had greater power to detect smaller effect sizes for our outcomes with repeated measures. For example, we had an 80% or greater power to detect an association for a heritability of 4% or greater for the outcomes FEV₁ and FEV₁ percent predicted, which had 16 repeated measures.

Table I provides the baseline demographic characteristics measured in our study population of 422 children. None of the polymorphisms were associated with asthma after Bonferroni correction. We found no associations between the SNPs and the total number of hospitalizations and emergency department visits over 4 years (Table II). The results were not significantly different after adjusting for age, sex, and treatment group.

Although there is increasing evidence that chitinases play a role in asthma, our analysis suggests that variations in chitinase genes are not associated with asthma. Our study found no associations between SNPs in the genes *CHIT1*, *CHIA*, and *CH13L1* and any of the outcomes studied: asthma, changes in lung physiology, or allergy-related phenotypes in subjects with mild-to-moderate asthma. Another strength of our study was the use of repeated measures of the asthma- and allergy-related phenotypes using a family-based design that accounts for these repeated measures, thus providing greater power to detect associations than a single measurement of the outcome.

Our finding that SNPs in *CHIT1* and *CH13L1* are not associated with asthma is consistent with the findings of other studies.^{8,9} On the other hand, our study findings are in contrast to previous studies that found that polymorphisms in *CHIA* are associated with asthma and IgE levels^{10,11} and a previous study that concluded that *CH13L1* is associated with asthma.¹² One potential reason for the discrepant findings might be that the studies that found positive associations used a case-control design, did not evaluate for population stratification, or did not adjust for multiple testing. Alternatively, environmental exposures in our cohort interacting with these genes might be different than in other cohorts.

Despite the strengths of our study, we were limited by our relatively small sample size of 422 subjects. Nevertheless, our power calculations suggest we had adequate power to detect small-to-moderate effect sizes.

The human chitinases and chitinase-like proteins have received attention in recent years because of their potential role in the pathogenesis of asthma. Nevertheless, polymorphisms in *CHIT1*, *CHIA*, and *CH13L1* are not associated with asthma, changes in lung physiology, or allergy-related phenotypes, suggesting that the effects of variation in these genes alone are weak without the appropriate environmental exposure.

We thank Brooke Schuemann, MPH, for her assistance with preparation of the phenotype data. We thank all subjects for their ongoing participation in this study. We acknowledge the CAMP investigators and research team, supported by the National Heart, Lung, and Blood Institute, for collection of CAMP Genetic Ancillary Study data. All work on data collected from the CAMP

TABLE II. FBAT-PC results from the SNPs using the PBAT Power Screen

Gene	Marker	Minor allele frequency	No. of informative families	Unadjusted FBAT-PC <i>P</i> value*					Total no. of hospitalizations and ED visits
				Pre-FEV ₁	BDR	lnPC ₂₀	log ₁₀ Eosinophil count	log ₁₀ IgE level	
<i>CHIT1</i>	rs4950934	0.108	161	.036	.526	.879	.221	.715	.144
	rs2486953	0.473	341	.403	.483	.080	.175	.084	.646
	rs2486954	0.196	251	.233	.570	.590	.776	.117	.299
	rs12141375	0.197	252	.221	.621	.573	.774	.107	.282
	rs4950936	0.474	341	.443	.524	.083	.170	.121	.640
	rs4950937	0.280	276	.697	.854	.752	.089	.699	.668
	rs872583	0.195	253	.262	.728	.694	.796	.050	.239
	rs1417149	0.471	340	.441	.609	.079	.106	.096	.679
	rs3831317†	0.174	273	.913	.693	.799	.490	.420	.922
	rs2486958	0.492	340	.570	.753	.102	.935	.872	.591
	rs1556854	0.485	341	.516	.697	.087	.560	.815	.556
	rs2486959	0.174	235	.263	.775	.837	.702	.244	.265
	rs946257	0.309	290	.387	.913	.372	.860	.325	.951
	rs2486068	0.171	234	.275	.875	.724	.868	.223	.253
	rs2297950	0.308	289	.456	.886	.676	.746	.233	.984
	rs2486070	0.171	233	.312	.840	.702	.799	.209	.269
	rs3766537	0.192	241	.218	.148	.842	.117	.106	.957
	rs1417150	0.467	331	.781	.970	.177	.237	.077	.305
	rs2486072	0.353	323	.703	.533	.784	.471	.098	.844
	rs12747110	0.014	28	.774	.567	.427	.405	.896	.798
<i>CHIA</i>	rs2494287	0.128	177	.149	.937	.348	.602	.529	.999
	rs4240529	0.283	222	.256	.622	.538	.594	.331	.589
	rs4272622	0.190	167	.126	.900	.369	.018	.049	.178
	rs11102233	0.258	208	.052	.839	.101	.167	.466	.550
	rs12401737	0.460	264	.979	.078	.764	.992	.028	.172
	rs10857871	0.212	188	.847	.514	.787	.493	.091	.146
	rs3806448	0.481	261	.844	.293	.891	.930	.527	.666
	rs10494132	0.221	208	.449	.263	.378	.234	.257	.072
	rs3806446	0.450	270	.590	.651	.868	.891	.510	.331
	rs7411387	0.401	239	.978	.319	.775	.018	.018	.064
	rs11584291	0.313	243	.940	.502	.691	.144	.191	.636
	rs4240530	0.288	245	.533	.779	.777	.060	.213	.758
	rs12127313	0.136	149	.487	.477	.625	.870	.261	.214
	rs10494133	0.143	159	.188	.417	.528	.036	.039	.362
	rs3818822	0.101	124	.547	.714	.592	.395	.930	.906
	rs12034576	0.326	242	.567	.007	.610	.860	.566	.524
	rs10494134	0.463	269	.058	.000	.204	.807	.631	.805
	rs2275253	0.288	236	.603	.692	.577	.028	.501	.751
	rs2275254	0.396	261	.679	.011	.400	.493	.645	.718
	rs2256721	0.286	225	.708	.764	.593	.050	.432	.787
<i>CH13LI</i>	rs2820093	0.102	126	.663	.857	.515	.457	.716	.877
	rs2282290	0.469	267	.576	.119	.767	.077	.253	.268
	rs12034177	0.328	241	.562	.007	.597	.858	.558	.534
	rs10776724	0.454	262	.815	.232	.958	.088	.560	.156
	rs12137697	0.128	141	.840	.724	.594	.935	.075	.105
	rs7542294	0.145	168	.953	.616	.171	.985	.257	.797
	rs880633	0.485	254	.130	.436	.007	.560	.272	.903
	rs10399805	0.126	149	.448	.999	.047	.757	.060	.192
	rs946261	0.401	252	.200	.687	.010	.811	.291	.970

ED, Emergency department.

*The results were not significantly different, even after adjusting for age, sex, and treatment group.

†rs3831317 is a 24-bp duplication in *CHIT1*.

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Evidence for neuronal expression of functional Fc (ε and γ) receptors

To the Editor:

The Fc receptor family plays a key role in adaptive immunity through the binding of immunoglobulin antibodies that recognize an immune insult and elicit an inflammatory response leading to its clearance. Dysregulation of this receptor family may have untoward consequences that result in autoimmune and allergic diseases. Many of these diseases seem to involve the nervous system and are exacerbated by stress or other neurologic challenges. Recently, the presence of Fc receptors was uncovered on dorsal root ganglion neurons and suggested an IgG and possibly

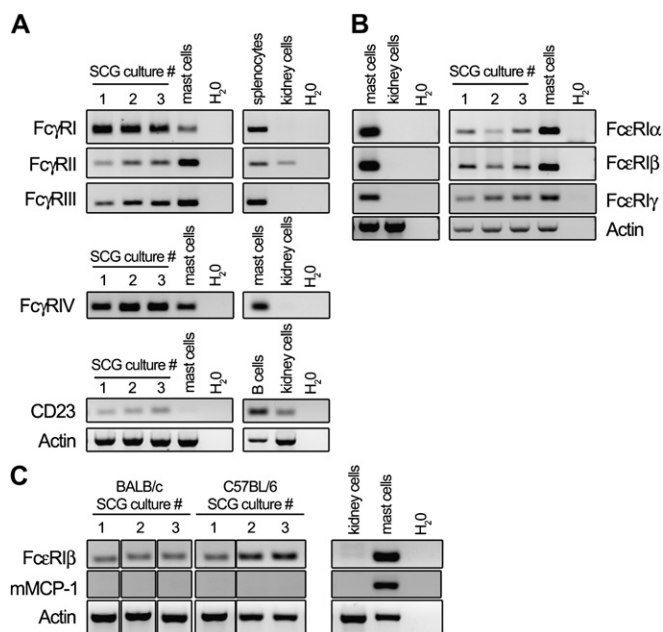


FIG 1. mRNA expression of the subunits of FcεRI, FcγRI-IV, and CD23 in SCG neurons. mRNA was collected from three (1-3) SCG neuronal cultures, and expression of the indicated mRNA was measured by RT-PCR. **A**, Expression of the α subunit of the low-affinity receptors for IgG (FcγRI-IV) and for IgE (CD23). **B and C**, Expression of the subunits of FcεRI and of mMCP-1 (**C**) in SCG neurons derived from Balb/c (**A-C**) or C57BL/6 (**C**) mice. Spleen cDNA and mRNA from bone marrow-derived mouse mast cells or from B cells were used as positive controls. The mRNA of the mouse IMCD-3 kidney epithelial cell line from the inner medulla collective duct was a negative control for FcεRI, mMCP-1, and FcγRI, III, and IV expression. A control for PCR contamination was performed by using H₂O.

IgE-mediated activation of neurons.¹⁻³ We set out to explore more extensively which Fc receptors might be expressed in neurons, and whether they were functional and able to transmit signals to interconnected neurites *in vitro* and *in vivo*.

Messenger RNA was isolated from a highly pure culture of mouse superior cervical ganglion (SCG) neurons⁴ and expression of Fc receptor transcripts assessed by RT-PCR using specific primers for Fcγ and Fcε family members. **Fig 1, A**, demonstrates the presence of transcripts for the immunoglobulin-binding α chain of FcγRI, II, III, and IV in 3 individual SCG neuron mRNA preparations. A small amount of the transcript for the low-affinity IgE receptor (FcεRII or CD23) was also detected relative to that seen in B cells, known to express this receptor. FcγRI transcripts were detected in bone marrow-derived mouse mast cells, but these levels were less than seen in the neurons. This observation and the inability to detect mouse mast cell protease (mMCP)-6 mRNA in either Balb/c or Bl6 mice together with the absence of CD23 transcripts in both neurons and mast cells provided confidence that the observed Fc receptor transcripts in neurons was not a result of mast cell contamination of cultures.

We also unexpectedly observed the presence of transcripts for the α, β, and γ chains of the high-affinity IgE receptor (FcεRI; **Fig 1, B**). Although the trimeric form (αγ₂) of this receptor has been described in cells other than mast cells or basophils (such as in human Langerhans cells⁵), the expression of the tetrameric form (αβγ₂) was previously thought to be limited to these proinflammatory cells. The trimeric FcεRI shows weak calcium signals

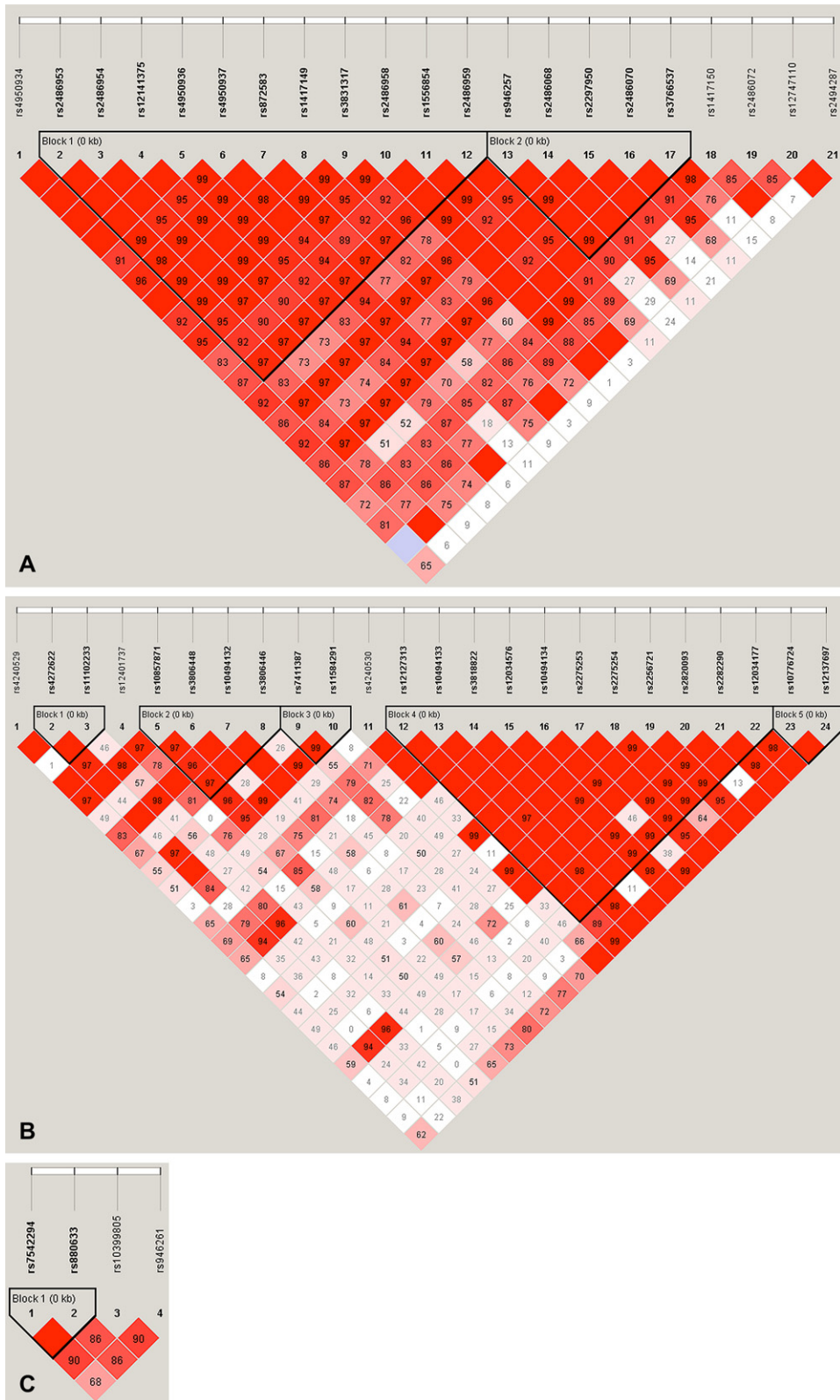


FIG E1. The following figures depict the linkage disequilibrium patterns of SNPs in *CHIT1* (A), *CHIA* (B), and *CHI3L1* (C) of subjects in CAMP. Numbers in the individual blocks represent r^2 values for each pair of SNPs (blank values, 100%), with the colors corresponding the D' values. Plots were created with the program Haploview 4.1 (<http://www.broad.mit.edu/mpg/haploview/>).

TABLE E1. Power for varying numbers of repeated measures and heritability

Power	Heritability				
	2%	3%	4%	6%	10%
No. of repeated measures					
1	0.52	0.69	0.81	0.94	1.00
2	0.65	0.81	0.91	0.98	1.00
(log ₁₀ IgE level and log ₁₀ eosinophil count had 2 repeated measures)					
5	0.96	1.00	1.00	1.00	1.00
(lnPC ₂₀ had 5 repeated measures)					
10	1.00	1.00	1.00	1.00	1.00
(BDR had 10 repeated measures)					
16	1.00	1.00	1.00	1.00	1.00
(FEV ₁ had 16 repeated measures)					

Calculations assume an allele frequency of 10% and an α value of .05.