

Original article

FCER2: A pharmacogenetic basis for severe exacerbations in children with asthma

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Background: Although inhaled corticosteroids (ICSs) generally protect against severe exacerbations in asthma, they may result in elevated IgE levels, which are associated with exacerbations. **Objective:** To determine whether variation in the low-affinity IgE receptor gene, *FCER2*, is associated with severe exacerbations defined as emergency department visits and/or hospitalizations in patients with asthma on ICSs.

Methods: We resequenced, then genotyped 10 *FCER2* single nucleotide polymorphisms (SNPs) in 311 children randomized to inhaled budesonide as part of the Childhood Asthma Management Program. We evaluated the association of *FCER2* variants with IgE levels and presence or absence of severe exacerbations over the 4-year clinical trial. We also evaluated differences in cellular expression of the novel *FCER2* SNP, T2206C.

Results: In white subjects, 3 *FCER2* SNPs were significantly associated ($P < .05$) with elevated 4-year IgE level; each was also associated with increased severe exacerbations. Final multivariable models demonstrated associations between T2206C and severe exacerbations in both white and African American children (hazard ratio, 3.95; 95% CI, 1.64-9.51; and hazard ratio, 3.08; 95% CI, 1.00-9.47), despite ICS use.

Interaction models supported a true gene-environment effect in white subjects (interaction $P = .004$). T2206C was also associated with decreased *FCER2* expression ($P = .02$).

Conclusion: *FCER2* predicts the likelihood of treatment protocol success in asthma. The associations of T2206C with IgE level, severe exacerbations, and *FCER2* expression may provide a mechanistic basis for the observed findings.

Clinical implications: Genetic variation in *FCER2* may help form a prognostic model for ICS response in asthma. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, CD23, *FCER2*, exacerbation, corticosteroid, pharmacogenetic, hospitalization

Asthma, the most common chronic disease of children, affects an estimated 300 million individuals worldwide.¹ Of concern are the recent increases in asthma prevalence,¹⁻³ exacerbations requiring hospitalization,⁴ and mortality attributed to asthma. In fact, asthma is the leading cause of childhood hospitalizations and emergency department visits. In the United States, between 1980 and 1999, annual physician office visits for asthma in children increased from 38.1 to 61.4 per 1000 (a 61% increase). Similarly, hospitalizations for asthma in children increased from 21.6 to 31.7 (47%) per 1000 between 1980 and 1995, with marked increases in hospitalizations noted in ethnic minorities and young (age 0-4 years) children.⁵ Of the major classes of asthma therapy, inhaled corticosteroids (ICSs) are the most effective and commonly used drugs for the chronic treatment of asthma.⁶ Although usage of ICSs significantly decreases severe exacerbations, a substantial proportion of emergency visits and hospitalizations occur despite optimal asthma management.⁷

The link between atopy and asthma is well established. The majority of subjects with asthma, including more than 85% of children with asthma, have evidence of IgE-mediated hypersensitivity to airborne allergens.^{8,9} In turn, elevated IgE levels in individuals with asthma are associated with increased frequency of exacerbations,¹⁰ emergency visits,^{11,12} and hospitalizations.^{13,14} Anti-IgE therapy is now available for use in patients with asthma with frequent exacerbations despite high doses of ICSs.^{15,16} A key regulator in the biologic actions of IgE in asthma is the low-affinity IgE receptor, CD23.¹⁷ Activation of this receptor results in downregulation of IgE-mediated immune responses. CD23 is encoded for by the Fc fragment of IgE, low-affinity II receptor

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Supported by National Institutes of Health grants HL U01 65899 and HG K23 3983. The Childhood Asthma Management Program Genetics Ancillary Study was supported by the National Heart, Lung, and Blood Institute, NO1-HR-16049. Additional support for this research came from grants NO1 HR16044, HR16045, HR16046, HR16047, HR16048, HR16049, HR16050, HR16051, and HR16052 from the National Heart, Lung and Blood Institute.

Disclosure of potential conflict of interest: L. J. Rosenwasser has consulting arrangements with Biogen Idec Corp. A. L. Fuhlbrigge has consulting arrangements with GlaxoSmithKline and Merck; has received grant support from Boehringer Ingelheim, Merck, and GlaxoSmithKline; and is on the speakers' bureau for GlaxoSmithKline and Merck. The rest of the authors have declared that they have no conflict of interest.

Received for publication March 16, 2007; revised August 16, 2007; accepted for publication September 5, 2007.

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0091-6749/\$32.00

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doi:10.1016/j.jaci.2007.09.005

Abbreviations used

CAMP: Childhood Asthma Management Program
FCER2: Fc fragment of IgE, low-affinity II receptor gene
 (the gene encoding for CD23)
 ICS: Inhaled corticosteroid
 OR: Odds ratio
 SNP: Single nucleotide polymorphism

(*FCER2*) gene. Interestingly, IgE levels do not seem to be lowered by corticosteroid therapy. Instead, IgE levels may increase in children treated with inhaled¹⁴ and oral¹⁸ corticosteroids. This may be explained by the effects of corticosteroids on CD23¹⁹; studies have demonstrated that corticosteroids decrease *FCER2* expression,¹⁹⁻²¹ CD23 production,^{19,21,22} and resultant CD23 actions.²³ Conversely, CD23 may be a specific marker for corticosteroid resistance.²⁴

Pharmacogenetics is defined as the study of the variability in the response to medications caused by heredity. The overall goal of the field of pharmacogenetics is to provide a genetic basis for individualized therapy with an individual's DNA used prognostically to determine the likelihood of treatment response and/or adverse events, including the need for emergency visits and hospitalizations. As part of our pharmacogenetics of asthma therapy program, we are interested in genetic influences on differential responses to ICSs, including the risk of severe exacerbations. Because IgE level predicts health care utilization and may be augmented by corticosteroid usage via corticosteroid influences on *FCER2* expression and CD23 production, we hypothesized that single nucleotide polymorphisms (SNPs) in *FCER2* would be associated with increased severe exacerbations requiring emergency care and/or hospitalization in patients with asthma on ICSs. We tested this hypothesis within a clinical trial population of 1041 children participating in the Childhood Asthma Management Program (CAMP).

METHODS

Study population and outcomes

CAMP was a multicenter, randomized, double-blind clinical trial testing the safety and efficacy of inhaled budesonide versus nedocromil versus placebo in 1041 children over a mean period of 4.3 years. Trial design and methodology have been published.^{25,26} Self-reported classification of race was used. Entry criteria included asthma symptoms and/or medication use for ≥ 6 months in the previous year and airway responsiveness with $PC_{20} \leq 12.5$ mg/mL. Exclusion criteria included $FEV_1 < 65\%$ of predicted when off β -agonists for > 4 hours, other active pulmonary disease, and the inability to perform acceptable spirometry or to complete the study protocol requirements.

DNA was collected from 951 probands. Our primary focus was on the CAMP children randomized to the corticosteroid group, evaluated over the course of their 4-year follow-up visits. These children were comparable at baseline to the children not randomized to inhaled steroids. Although we evaluated the association of IgE levels obtained during the run-in period and at the 4-year follow-up visit, our primary outcome of interest was the presence of either emergency

department visits or hospitalizations for asthma. Because CAMP did not initially distinguish between emergency visits and hospitalizations, we examined these as a single "severe exacerbations" outcome variable. The CAMP Genetics Ancillary Study was approved by each individual study center's Internal Review Board, and informed consent/assent was obtained from all participants and their parents.

Resequencing and genotyping

Amplified genomic fragments of all *FCER2* exons and their immediate (at least 50 bp) perioxonic sequences were resequenced at the Whitehead Institute (Cambridge, Mass). A panel of 32 multiethnic in-house Coriell cell lines was used for SNP discovery. Primer3 (http://frodo.wi.mit.edu/primer3/primer3_code.html) was used for primer design. Resequencing was performed on 32 multiethnic in-house Coriell cell lines. Detailed information about the resequencing is available on the PharmGKB Web site (www.pharmgkb.org) and our internal Web site (www.pharmgat.org).

From the resequencing efforts, we identified 10 SNPs with minor allele frequency > 0.15 to genotype. Genotyping was performed by using the SEQUENOM MassARRAY MALDI-TOF mass spectrometry platform (Sequenom, San Diego, Calif). We used the very short extension method,²⁷ whereby sequencing products are extended by only 1 base for 3 of the 4 nucleotides and by several additional bases for the fourth nucleotide (representing 1 of the alleles), permitting clearly delineated mass separation of the 2 allelic variants at a given locus. Primers were designed by using a semiautomated program (SpectroDESIGNER; Sequenom). To assess for possible population stratification, we also genotyped a random panel of 49 SNPs across the genome.²⁸ Quality control of the genotyping consisted of at least 90% of successful calls in the genotyping reactions, regenotyping of approximately 10% of genotypes, and documentation of presence of Hardy-Weinberg equilibrium for each of the SNPs.

FCER2 T2206C functional analysis

Using in-house Coriell lymphoblastoid cell lines, we performed RT-PCR assays on a novel *FCER2* SNP located 7 bp 3' of exon 9, T2206C (rs28364072). Because of the proximity of this SNP to the exon, it was postulated that *FCER2* expression may be affected by alternative splicing. RT-PCR was performed by using 2 biologic replicates for each individual. Each biologic replicate was run 4 times for technical replication, and all RT-PCR assays were normalized to GAPDH. Normalized expression levels for cells homozygous at the T2206C locus were compared with the heterozygous and wild-type expression levels by using Student *t* tests.

Statistical methodology

We initially dichotomized the severe exacerbations outcome to any versus none over the course of the clinical trial follow-up period. Temporal coding permitted subsequent time to first event analyses. IgE levels were log-transformed and analyzed as a continuous variable. To test for main, within treatment group effects, all initial and confirmatory analyses were performed only on CAMP probands randomized to the ICS group. Generalized linear models using analysis of covariance were initially run in white subjects to assess the association between *FCER2* genotypic status and 4-year log IgE levels, assuming an additive genetic model. The multivariable analysis adjusted for age, sex, and baseline IgE level. We then explored the relationships between each *FCER2* SNP and our severe exacerbations outcome in white subjects by using univariate and multivariable logistic regression analyses, assuming an additive genetic model. We subsequently performed confirmatory analyses of the main effects of the T2206C SNP in the white and African American subjects by using time-to-event analyses. Proportional hazards assumptions were tested. All multivariable analyses were adjusted for age, sex,

TABLE I. Population characteristics

	ICS exacerbation,* no	ICS exacerbation,* yes	No ICS exacerbation,* no	No ICS exacerbation,* yes
n	219	92	461	269
Age (y)†	9.1 ± 2.0	8.8 ± 2.2	9.1 ± 2.2	8.5 ± 2.0
Sex, n (%)				
Male	135 (61.6)	46 (50.0)	275 (60.0)	165 (61.3)
Female	84 (38.4)	46 (50.0)	186 (40.0)	104 (38.7)
Race, n (%)‡				
White	148 (67.6)	53 (57.6)	343 (74.4)	167 (62.1)
African American	22 (10.1)	22 (23.9)	49 (10.6)	45 (16.7)
Hispanic	24 (11.0)	8 (8.7)	38 (8.2)	28 (10.4)
Other	25 (11.4)	9 (9.8)	31 (6.7)	29 (10.8)
Baseline FEV ₁ (% predicted)†	94.2 ± 14.1	92.0 ± 14.9	94.4 ± 13.4	92.8 ± 15.5

*Severe exacerbation as defined by any emergency department visit or hospitalization over the 4-year clinical trial period.

†Means ± SDs.

‡ $P < .05$ for intergroup differences in exacerbations.

baseline IgE level, and baseline level of lung function (FEV₁ as a percent predicted). After the main effects analyses, we concluded with analyses for steroid-genotype interaction including terms for steroid usage, genotype, and their interaction in the models. All analyses were performed by using SAS (Version 8; Cary, NC).

RESULTS

Study population

The characteristics of the 311 CAMP participants randomized to the ICS group are shown in Table I. These subjects form the basis of our primary, within treatment group analyses. Population characteristics are shown stratified by presence or absence of severe exacerbations. Approximately 65% of the subjects identified themselves as white, forming the primary analytic subgroup. Baseline level of lung function, expressed as FEV₁, was similar between the groups. Both the white and African American subjects randomized to ICSs in CAMP formed the basis of our confirmatory analysis. Characteristics of the 730 CAMP participants not randomized to ICSs (*No ICS*) are also shown in Table I. After the within treatment group confirmatory analyses, these subjects were used in our gene-environment interaction analyses.

IgE and exacerbations

Our hypothesis postulated a relationship between IgE and severe exacerbations. For the CAMP subjects included in our genetic analyses, baseline IgE levels (log-transformed) were associated with severe exacerbations during the 4-year follow-up (odds ratio [OR], 1.27; 95% CI, 1.03-1.58) after adjusting for age, sex, and baseline level of lung function.

Association of *FCER2* variants with IgE and severe exacerbations

Because we were analyzing relatively rare outcomes, we chose to genotype only those 10 SNPs with high minor allele frequencies (>.15) based on resequencing. Detailed results from the resequencing effort are available on the PharmGKB Web site (www.pharmgkb.org), and all SNPs

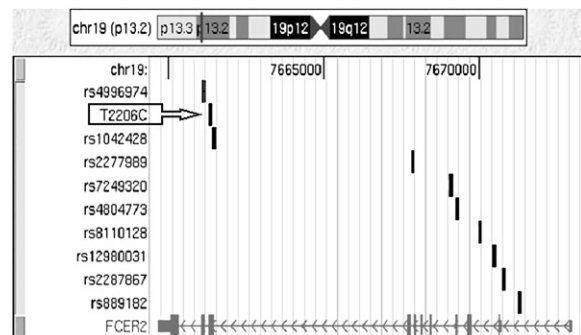


FIG 1. Coverage of *FCER2* by genotyped SNPs. As a novel SNP, T2206C is highlighted. Figure obtained from SNP sequence BLAT to the Human Genome Browser <http://genome.ucsc.edu>, March 2006 Assembly. Accessed March 1, 2007.

identified have now been incorporated into dbSNP (www.ncbi.nlm.nih.gov/SNP). Of the 42 variants identified via the resequencing efforts, 1, T2206C, was novel and of high allele frequency. Physical locations of the genotyped SNPs are shown in Fig 1. As anticipated, given our screening criteria, 9 of the 10 SNPs had a minor allele frequency of >.15 in the white CAMP subjects (Table II). The remaining SNP (rs1042428) was present in only 2.7% of the white subjects. All of the SNPs were in Hardy-Weinberg equilibrium (P values, 0.26-1.0).

The multivariable association of the *FCER2* SNPs with IgE levels in white subjects on ICSs is shown on Table II. Not surprisingly, genetic variations in the low-affinity IgE receptor were associated with IgE levels at the 4-year follow-up visit, after adjusting for age, sex, and baseline IgE level. Variation in 3 of the 10 SNPs, including T2206C, were significantly associated with increases in IgE levels at 4 years.

We next explored the association of *FCER2* SNPs with severe exacerbations in white subjects, as defined by any emergency visits or hospitalizations (Table II). In the multivariate analysis, the 3 SNPs associated with increased IgE levels were also associated with an increased risk of severe exacerbations while on ICSs over the course of

TABLE II. *FCER2* SNP associations with IgE levels and severe exacerbations in white subjects*

SNP	Minor allele frequency	4-Year log IgE†		Exacerbation‡
		β§	P	OR (95% CI)
rs889182	0.27	−0.01 ± 0.04	.80	1.18 (0.70-1.97)
rs2287867	0.44	−0.01 ± 0.04	.86	0.93 (0.56-1.52)
rs12980031	0.22	−0.01 ± 0.05	.76	1.26 (0.71-2.26)
rs8110128	0.47	−0.02 ± 0.04	.62	0.66 (0.40-1.11)
rs4804773	0.17	0.05 ± 0.05	.35	1.80 (0.95-3.43)
rs7249320	0.22	0.09 ± 0.05	.04	1.69 (0.98-2.93)
rs2277989	0.46	−0.06 ± 0.04	.14	0.81 (0.50-1.32)
rs1042428	0.03	−0.15 ± 0.12	.21	1.26 (0.28-5.63)
T2206C	0.26	0.13 ± 0.05	.006	1.85 (1.04-3.26)
rs4996974	0.27	0.14 ± 0.04	.002	1.73 (1.01-2.94)

*Analyses in this table performed under the assumption of an additive genetic model.

†Adjusted for age, sex, and baseline IgE.

‡Any severe exacerbation as in Table I. Adjusted for age, sex, baseline IgE, and baseline FEV₁.

§±SE.

the 4-year clinical trial (OR, 1.69-1.85; Table II). One additional SNP (rs4804773) that was marginally associated with severe exacerbations outcomes in these children but not with IgE levels encodes for a common nonsynonymous amino acid change (Arg62Trp).

Confirmatory analyses

Given the associations of 3 SNPs with both increased IgE levels and with increased exacerbations in white CAMP subjects on ICSs, we sought to confirm the principal genotypic associations in the CAMP African American probands on ICSs by using time to first severe exacerbation event analyses. Because T2206C represented a novel variant that was common (minor allele frequency, 0.26 in white subjects and 0.44 in African American subjects), and because this SNP demonstrated the highest OR for severe exacerbations in our exploratory analysis, we focused all subsequent analyses exclusively on this SNP.

Kaplan-Meier curves stratified by genotype demonstrate similar patterns in both the white and African American subjects taking ICSs, with a markedly increased propensity for severe exacerbations in those homozygous for the mutant T2206C allele (see this article's Fig E1 in the Online Repository at www.jacionline.org). Wild-type homozygotes and heterozygous individuals experienced similar overall levels of severe exacerbations, supporting a recessive genetic model. We therefore encoded the final Cox proportional hazards models using a recessive model. Table III demonstrates the relative hazard of severe exacerbations in white and African American subjects. T2206C was associated with a 3-fold to 4-fold increase risk of severe exacerbations (hazard ratio, 3.95; 95% CI, 1.64-9.51; and hazard ratio, 3.08; 95% CI, 1.00-9.47 for white and African American subjects, respectively).

Evidence for a pharmacogenetic gene-environment interaction

To evaluate whether the associations represented a pharmacogenetic gene-treatment group interaction, we evaluated T2206C for association with severe

TABLE III. T2206C relative risk of severe exacerbations while on ICSs*

	Univariate	Multivariate†
White	3.88 (1.64-9.21)	3.95 (1.64-9.51)
African American	3.20 (1.23-8.31)	3.08 (1.00-9.47)
Overall	3.62 (2.02-6.49)	3.70 (1.99-6.91)

*All analyses show relative risk expressed as hazard ratios (95% CIs) for those homozygous for the T2206C mutant allele compared with all other T2206C genotypes.

†Adjusted for age, sex, baseline IgE, and baseline FEV₁. Overall analysis also adjusted for race.

exacerbations in the 730 CAMP subjects not randomized to ICSs. T2206C was not associated with severe exacerbations in subjects with asthma not taking ICSs (recessive model multivariable hazard ratios of 0.68; 95% CI, 0.32-1.42; and 1.05; 95% CI, 0.38-2.91 for white and African American subjects, respectively). Kaplan-Meier curves demonstrate that individuals wild-type or heterozygous for the T2206C allele while on ICSs tended to do better than subjects of any genotype not on ICSs (supporting general benefit from ICSs), whereas T2206C homozygous CC individuals on ICSs fared worse, on average, than subjects not on ICSs (supporting a pharmacogenetic risk; Fig 2). For the white subjects, there was a significant interaction between ICS use and genotype in the risk of severe exacerbations (interaction $P = .004$). There was no significant interaction for the African American subjects (interaction $P = .22$). However, the trend for association for treatment group versus nontreatment group was similar in African American and white subjects, suggesting that the lack of a significant interaction was likely a result of sample size considerations (Fig 2).

Given our biologic hypothesis, we also investigated the potential for a pharmacogenetic interaction of T2206C with ICS use in the context of IgE levels. Whereas T2206C was significantly associated with higher 4-year IgE level in white subjects taking ICSs (Table II), no significant difference related to genotype was noted in those

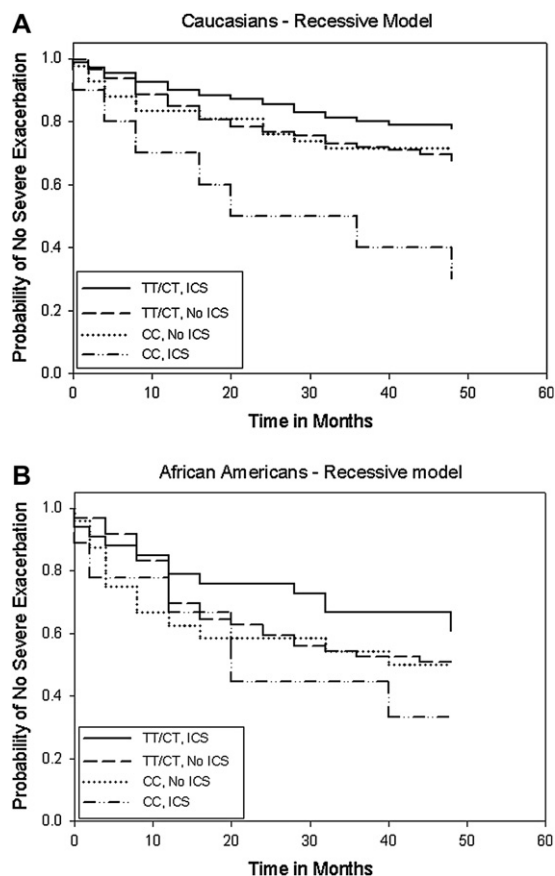


FIG 2. Treatment-specific association of T2206C with severe exacerbations in white subjects (A) and African American subjects (B). Under a recessive model, the risk for severe exacerbations for subjects homozygous for the T2206C mutant allele on ICSs is significantly greater than the wild-type and heterozygotes for the T2206C allele on ICSs in both white subjects (A) and African American subjects (B). There is no difference in relative risk for any of the T2206C alleles in those subjects not taking ICSs. There was a significant interaction between genotype and ICS use in the white subjects (interaction $P = .004$). Although there was no significant interaction between genotype and ICS use for African American subjects, the similarities in the Kaplan-Meier curves suggest that this is likely a result of sample size considerations.

not taking ICSs ($P = .09$), yielding a significant pharmacogenetic effect of T2206C on IgE levels (interaction $P = .02$). Given sample size considerations, there was no significant interaction between T2206C and corticosteroid use in the determination of IgE levels in the African American subjects (interaction $P = .28$). However, the highest 4-year IgE levels in both white and African American subjects occurred in subjects both homozygous for T2206C and taking ICSs.

Expression of *FCER2* by T2206C genotype

Given the proximity of T2206C to exon 9, we postulated that this SNP may influence *FCER2* expression by, among other things, its potential to influence splicing. We therefore compared expression across genotypic cell types. By using in house lymphoblastoid cell lines, we identified 9 wild-type TT, 10 heterozygous CT, and 3

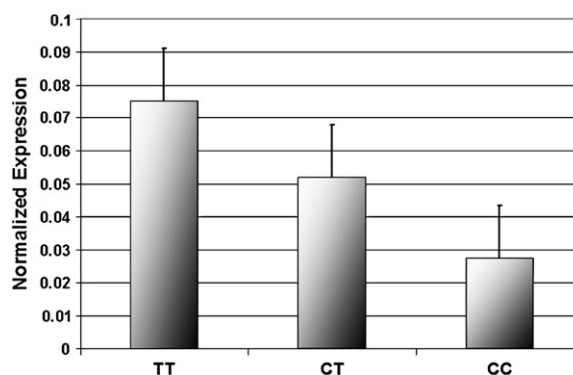


FIG 3. *FCER2* expression by T2206C genotype. Expression was measured in 9 TT, 10 CT, and 3 CC lymphoblastoid cell lines and normalized to GAPDH. Normalized expression is significantly lower in those homozygous for the mutant CC allele compared with the other 2 groups ($P = .02$).

homozygous mutant CC cell lines. By using RT-PCR, we measured cDNA expression of these cell lines and normalized expression levels for glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*). Fig 3 depicts that when *FCER2* expression levels were stratified by genotypic group, the least expression was noted for the CC homozygotes. Using the assumption of a recessive model, there was significantly less expression for the mutant CC genotype group compared with the other 2 genotypic groups combined ($P = .02$).

DISCUSSION

In CAMP, use of the ICS budesonide was associated with significant decreases in severe exacerbations.²⁶ Despite these protective effects, we have demonstrated that variation in *FCER2*, the gene encoding for the low-affinity IgE receptor, is associated with severe exacerbations in children with asthma taking ICSs. In addition to prominent within ICS group associations, there appears to be a true pharmacogenetic gene-environment interaction, in that there was no association in those children not taking ICSs, but there was a significant interaction between genotype and steroid use. Moreover, this association appears valid across multiple ethnic subgroups, with a 3-fold to 4-fold increased risk of emergency visits or hospitalizations noted for the same SNP, T2206C, in both white and African American subjects. The combination of a reasonably large clinical trial population and long duration of follow-up makes CAMP an ideal population in which to study genetic predictors of health care utilization outcomes. To our knowledge, this is the first detailed report of an association of a pharmacogenetic predictor of severe exacerbations in asthma, as well as one of the few demonstrations of a pharmacogenetic gene-environment interaction in asthma.

It should be reiterated that the minor allele frequency of the T2206C SNP was substantially greater in African American subjects (0.44) than white subjects (0.26).

Given similar genotypic relative risks for severe exacerbations, the increased frequency of T2206C in African American children may provide a genetic basis to help explain the increased incidence of asthma-related hospitalizations consistently attributed to that racial group.^{5,29,30}

That the novel SNP, T2206C, is associated with functional differences related to degree of cellular gene expression provides a potential mechanistic basis for the observed association. The low-affinity IgE receptor, CD23, in its native form functions in the downregulation of T-cell-regulated IgE mediated immune responses. This is evidenced by the CD23 knockout mouse, which demonstrates exaggerated IgE responses and increased airways responsiveness compared with wild-type.³¹⁻³³ CD23 physiology is complex; animal model studies demonstrate that airways responsiveness and eosinophilia are reduced on administration of neutralizing antibodies to CD23. However, this may be a result of IgE-independent processes³² or transduction of CD23 signaling via the antibody.³³ In human beings, proteolytic cleavage of CD23 in cultured B cells by the dust mite, Der p 1, leads to decreased cellular binding of IgE, thereby disrupting the negative regulatory feedback mechanism. The net result is the promotion of IgE synthesis, potentially explaining the allergenic nature of Der p 1.³⁴ In a manner similar to the mouse and cellular models of CD23 inhibition, decreased genetic expression of CD23, as noted with T2206C (Fig 3), would be expected to result in higher serum IgE levels. Our data support increases in IgE related to genotypic differences in *FCER2*, including the polymorphism, T2206C, that influences expression (Table II). This expands on a previous study that noted a haplotypic association of microsatellite variants in and around *FCER2* with elevations in IgE levels.³⁵ The effect of *FCER2* genetic variation on increasing IgE levels may be further augmented by the decreases in CD23 expression associated with corticosteroid administration.¹⁹⁻²² We have substantiated this by noting that the highest IgE levels were found in subjects both homozygous for the T2206C variant and taking ICSs, including the demonstration of a significant steroid-genotype interaction in white subjects.

Elevations in IgE, in turn, are associated with increased frequency of exacerbations,¹⁰ emergency visits,^{11,12} and hospitalizations^{13,14} in children with asthma. In addition, in a study limited to inpatients hospitalized for asthma, higher IgE levels were associated with a greater likelihood of admission to an intensive care unit.³⁶ Previous CAMP data,³⁷ as well as those presented in our results section, suggest that the associations of IgE with hospitalizations extend to our cohort of children with asthma as well. Use of ICSs in asthma is associated with decreased risk of urgent care visits and hospitalization.^{7,26} However, our data clearly demonstrate that, even in this low-risk group, there is an independent association of genetic variation in *FCER2* with severe exacerbations. As noted, this may be directly related to corticosteroid-induced decrements in CD23 expression.

To date, although a few studies have described genetic predictors of exacerbations in childhood asthma,^{38,39}

almost none have done so with respect to therapeutic intervention. We have previously detailed the association of variants in the leukotriene pathway with exacerbations in adults with asthma taking montelukast.⁴⁰ However, exacerbations were broadly defined to include any increase in therapy or symptoms, and the study was insufficiently powered to evaluate emergency visits or hospitalizations specifically. A recent investigation reported the observation that *IL13* variants may be related to exacerbations in children taking corticosteroids.⁴¹ However, this observation was part of a larger exploration of the association of *IL13* with asthma phenotypes, limited to white subjects, and contained no formal interaction analyses or detailed risk assessments. We now report a novel association of a pharmacogenetic predictor, *FCER2*, with severe exacerbations in both white and African American subjects in the context of a large clinical trial population of children with asthma taking ICSs.

There are several potential limitations to our study. First, CAMP consisted of children with mild to moderate asthma.²⁶ Therefore, it is unknown whether one can specifically extrapolate our results to more severe asthma or to other age groups. Next, ideally one replicates findings from genetic studies in a second, independent population. However, no such population was available to us. We therefore examined the association of T2206C within the CAMP African American subjects, which was a relatively limited sample size. Nevertheless, the associations noted in the African American subjects closely paralleled those of the white subjects (Figs 2 and E1; Table III). In addition, the high minor allele frequency of the T2206C SNP in the African American subjects (0.44) provides additional power for association in that racial group. Moreover, T2206C was also associated with changes in *FCER2* expression; this functional effect is unlikely to vary by racial group. Finally, we identified only 3 homozygous mutant CC cell lines, so the precision of the normalized expression may be low, possibly explaining why the expression values appeared to follow an additive rather than a recessive model. However, despite these small numbers, the variability of the CC normalized expression was quite low (Fig 3) and significantly different from the other groups ($P = .02$).

In conclusion, *FCER2* is a pharmacogenetic predictor associated with marked increased risk of emergency visits and hospitalizations in children with asthma on ICSs. Increased frequency of *FCER2* genetic variants may also help explain the increased incidence of asthma-related hospitalizations consistently noted in African American children. Furthermore, the novel *FCER2* SNP, T2206C, is associated with altered level of expression of the gene and may provide a mechanistic basis for the observed associations with severe exacerbations. Noting that a major indication for consideration of anti-IgE therapy in asthma is frequent exacerbations despite the use of ICSs, confirmation of our findings may be incorporated into a prognostic model to assist with the determination of high-risk subjects with asthma who may benefit from therapies in addition to ICSs.

We thank all of the families for their enthusiastic participation in the CAMP Genetics Ancillary Study. We also 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 from the CAMP Genetics Ancillary Study was conducted at the Channing Laboratory of the Brigham and Women's Hospital under appropriate CAMP policies and human subject protections.

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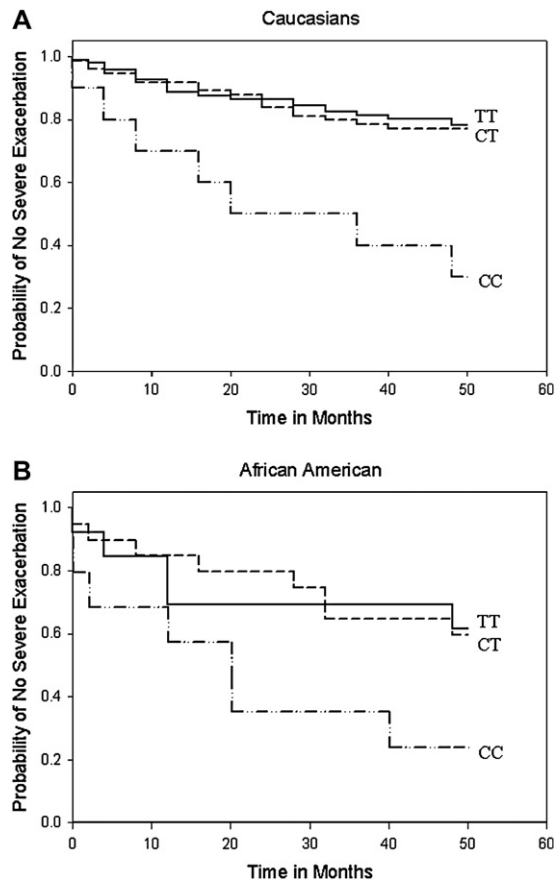


FIG E1. T2206C genotype-stratified risk of severe exacerbations in white subjects (**A**) and African American subjects (**B**). Kaplan-Meier curves demonstrate the T2206C genotype-stratified risk of severe exacerbations over time in white subjects (*A*) and African American subjects (*B*). Significant differences in genotypic risk of severe exacerbations are noted for both white subjects ($P = .003$) and African American subjects ($P = .03$). Subjects homozygous T2206C for the mutant allele demonstrate a marked increase in risk, supporting a recessive genetic model.