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Predictors of poor response during asthma therapy differ with definition of outcome

Angela J Rogers[†],

Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Kelan G Tantisira,

Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Anne L Fuhlbrigge,

Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Augusto A Litonjua,

Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Jessica A Lasky-Su,

Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Stanley J Szefer,

National Jewish Health and University of Colorado Health Sciences Center, CO, USA

Robert C Strunk,

Washington University School of Medicine and St Louis Children's Hospital, MO, USA

Robert S Zeiger, and

University of San Diego, CA, USA and Kaiser Permanente San Diego, CA, USA

Scott T Weiss

Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

for the Childhood Asthma Management Program (CAMP) Research Group

Abstract

Aims—To evaluate phenotypic and genetic variables associated with a poor long-term response to inhaled corticosteroid therapy for asthma, based independently on lung function changes or asthma exacerbations.

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[†]Author for correspondence: Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA Tel.: +1 617 525 2045; Fax: +1 617 525 0958; reagr@channing.harvard.edu.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Materials & methods—We tested 17 phenotypic variables and polymorphisms in *FCER2* and *CRHR1* in 311 children (aged 5–12 years) randomized to a 4-year course of inhaled corticosteroid during the Childhood Asthma Management Program (CAMP).

Results—Predictors of recurrent asthma exacerbations are distinct from predictors of poor lung function response. A history of prior asthma exacerbations, younger age and a higher IgE level ($p < 0.05$) are associated with recurrent exacerbations. By contrast, lower bronchodilator response to albuterol and the minor alleles of RS242941 in *CRHR1* and T2206C in *FCER2* ($p < 0.05$) are associated with poor lung function response. Poor lung function response does not increase the risk of exacerbations and vice versa ($p = 0.72$).

Conclusion—Genetic and phenotypic predictors of a poor long-term response to inhaled corticosteroids differ markedly depending on definition of outcome (based on exacerbations vs lung function). These findings are important in comparing outcomes of clinical trials and in designing future pharmacogenetic studies.

Keywords

asthma; corticosteroid; exacerbation; lung function; pharmacogenetics

The National Asthma Education and Prevention Program guidelines, initially published in 1991 and updated in 2007, established inhaled corticosteroid (ICS) therapy as the cornerstone of treatment for children with asthma [1,2]. ICS therapy has been associated with myriad positive effects, including improvements in forced expiratory volume in 1 second (FEV₁), more symptom-free days and reductions in asthma exacerbations and hospitalizations [2,3]. However, response to ICS varies considerably among individuals. In a 12-week study of ICS therapy for adults with asthma, FEV₁ improved by a mean of 13% from baseline, but the range of change varied from 30% decline to more than 50% improvement [4]. Szeffler and colleagues found that only 40% of children achieved a 7.5% improvement in FEV₁ during an 8-week course of ICS therapy [5]. Similarly, while a reduction in asthma exacerbations is one of the major benefits of treatment with ICS, a significant proportion of subjects have exacerbations despite therapy [6].

Identifying subjects at risk for poor response to ICS therapy would be helpful, as they would be candidates for close monitoring and consideration of alternate therapies. Several investigators have identified phenotypic variables associated with a response to ICS as defined by improved lung function or a reduction in asthma exacerbations, though most focus on short-term outcomes. High exhaled nitric oxide, high bronchodilator reversibility, and a low FEV₁:force vital capacity ratio have each been associated with greater lung function improvement during ICS therapy in children [7,8]. Sputum eosinophils and airways hyper-responsiveness have been shown to predict exacerbations during ICS taper [9], and a history of past exacerbations predicted exacerbations during a 48-week trial [10]. Genetic factors are also important modulators of the response to ICS. We have previously published an association between SNPs in the low-affinity IgE receptor (*FCER2*) gene and severe exacerbations [11] and SNPs in the corticotropin-releasing hormone receptor 1 (*CRHR1*) gene and 8-week lung function response among Childhood Asthma Management Program (CAMP) subjects taking ICS [12]. We note that none of the phenotypic and genetic predictors of lung function appear to overlap the predictors of exacerbations in these studies, though each focused on a single outcome definition. No assessment of long-term failure to respond has been attempted, nor have any groups attempted to incorporate both genetic and phenotypic variables in a single model.

The Childhood Asthma Management Program was a multicentered North American clinical trial designed to investigate the long-term effects of inhaled anti-inflammatory medications in

children with mild-to-moderate asthma [6,13]. Subjects were followed for 4–6 years while randomized to therapy. The richness of CAMP data-set allows us to identify subjects who consistently fail to respond to ICSs over time, not simply at a single or short-term time point, and allows us to focus on both lung function and exacerbations as independent outcomes in response to ICS. We hypothesized that genetic polymorphisms and phenotypic variables at baseline (prior to initiation of ICS) are associated with a long-term response, in terms of either recurrent asthma exacerbations or lung function. We further hypothesized that subjects with a poor lung function response would be likely to have recurrent exacerbations and vice versa.

Materials & methods

Population

In the CAMP clinical trial, a diagnosis of asthma was based on methacholine hyper-responsiveness provocative concentration causing a 20% fall in FEV₁ (PC₂₀) no greater than 12.5 mg/ml and one or more of the following criteria for at least 6 months in the year before recruitment: asthma symptoms at least two-times per week, at least two uses per week of an inhaled bronchodilator or daily asthma medication. Protocols for collection of baseline phenotypic data have been described in detail elsewhere [13,14]. Each subject's parent or guardian signed a consent statement, with each child providing assent. Institutional review board approval was obtained for all participating CAMP centers and the data coordinating center.

Of the 1041 children enrolled in the original trial, 311 were randomized to ICS therapy (200 µg twice daily budesonide) and followed for a mean of 4.3 years. Analysis is limited to those 311 subjects and to the first 48 months of follow-up. Subjects were evaluated for 13 follow-up visits after randomization (four-times in year one and then three-times yearly). Spirometry pre-and post-albuterol was performed and parents or subjects were asked about interval exacerbations at each visit. Subjects who missed an entire year of follow-up were excluded from analysis.

Definition of response

We used two definitions of a poor long-term response to ICS: one based on exacerbations and the other based on change in lung function. An asthma exacerbation was defined as any Emergency Department visit, hospitalization or oral prednisone burst. Recurrent exacerbators were those who had at least four exacerbations during the trial. Because of our focus on consistently poor response over the 4-year period, this definition required at least two exacerbations during the first 2 years and two during the last 2 years. These were compared with rare exacerbators, those subjects who had 0–1 exacerbations over the entire 4-year trial period. Based on these definitions, subjects with a total of two to three exacerbations or those without at least two exacerbations during both the first and last 2 years of the study were excluded from analysis.

A poor lung function response to ICS was defined as consistent failure to improve pre-bronchodilator percentage predicted FEV₁. A 7.5% change in absolute FEV₁ was used by Szeffler *et al.* to denote therapeutic success over 8 weeks [5]; the 7.5% threshold for clinically meaningful response was chosen because it reflects approximately half of the median maximum bronchodilator responsiveness (BDR) to albuterol in subjects in the Childhood Asthma Research and Education (CARE) network and was greater than the median 5% improvement in prebronchodilator FEV₁ noted at 2 months in ICS-treated subjects in CAMP [5,6]. We focused on the percentage of predicted change because of lung growth in children over the 4-year follow-up period. Subjects who never improved by 7.5% predicted from baseline at any of the 13 follow-up visits over 4 years were designated poor lung function

responders. This group was compared with subjects who at least once improved by 7.5% predicted over baseline.

Phenotypic & genetic predictors

A total of 17 phenotypic predictors were evaluated based on their role in asthma severity or association with short-term steroid responsiveness: subject age, race/ethnicity, gender, household income, BMI, smoking exposure, intrauterine smoke exposure, baseline percentage of predicted FEV₁, BDR to albuterol, PC₂₀ response to methacholine (log-transformed), serum IgE (log-transformed), eosinophil count (log-transformed), family history of atopy, personal history of a positive skin test, age at onset of asthma, history of asthma exacerbations (Emergency Department visit or hospitalization) in the year prior to study entry and family history of asthma. Baseline values (at randomization, off controller medication) were used for all variables.

We also tested two SNPs for association with long-term ICS response, RS242941 in *CRHR1* and T2206C in *FCER2*; we chose the SNP within each gene that was most significantly associated with short-term outcomes during ICS therapy in prior work by our group [11,12]. The SNPs were genotyped in 267 and 270 of the subjects, respectively, using a Sequenom MassARRAY® MALDI-TOF mass spectrometer (Sequenom, CA, USA). We used the very short extension method [15], in which sequencing products are extended by a single base for three of the four nucleotides and by several additional bases for the fourth nucleotide (representing an allele of the SNP), allowing separation of the two variants at a given locus using mass spectrometry.

Statistical methodology

All statistical analysis was performed using SAS version 9.1 (SAS, NC, USA). Each phenotypic variable was evaluated as a univariate predictor for poor ICS response using t-test, Wilcoxon test or Fisher's exact test as appropriate. The two SNPs were assessed in an additive model using logistic regression; univariate genetic analyses were limited to Caucasians because of concern for population stratification. All variables were tested in a multivariate model using forward stepwise logistic regression, with a threshold for significance of 0.05. Age, gender and race were forced into both models; height and baseline FEV₁ were additionally forced into the model for lung function response. All significant univariate predictors were evaluated as potential confounders, with those that changed effect estimates by more than 20% to be included in the final multivariable model. We also performed a sensitivity analysis by stratifying by baseline FEV₁ to evaluate whether baseline FEV₁ level modifies the association between BDR and albuterol and lung function.

Results

Poor response: recurrent exacerbations

Of the 311 CAMP participants randomized to ICS therapy, the present study compared the 66 recurrent exacerbators (at least two exacerbations in both the first and last 2 years of the study) with the 136 rare exacerbators (0–1 exacerbation over the entire 4-year follow-up period). The 109 participants not meeting the above criteria were omitted from these analyses. As shown in Figure 1, using these definitions, recurrent exacerbators had a mean of 9.5 (±0.5) exacerbations, with a range of 4–21.

A total of 17 phenotypic variables and two genetic variables were tested for association with a poor response to ICS based on exacerbations. In univariate analysis, a history of an asthma exacerbation in the prior year ($p = 0.008$) and a low baseline BMI ($p = 0.02$) were the two phenotypic variables associated with recurrent exacerbations during ICS therapy. A trend

toward an association of recurrent exacerbations with a higher level of IgE did not reach statistical significance ($p = 0.06$, Table 1). The minor allele of T2206C in *FCER2* was also associated with recurrent exacerbations (odds ratio [OR]: 1.9 for minor allele, $p < 0.05$) in white CAMP subjects. When all variables were evaluated in a forward stepwise logistic regression model, younger age, higher IgE level, and a past history of exacerbations were significantly associated with recurrent exacerbations (with $p < 0.05$, Table 2). IgE was assessed on a linear scale, with each $\log_{10}$ increase in IgE associated with a 1.8-fold risk of recurrent exacerbations. T2206C in *FCER2* did not reach significance in multivariate analysis (OR: 1.4, $p = 0.18$), though this may relate in part to collinearity with IgE (OR: 1.6, $p = 0.07$ when IgE removed) and a history of past exacerbations (OR: 1.7, $p = 0.04$ when exacerbations additionally excluded from the model).

Poor response: lung function

The second asthma outcome was based on a failure to improve FEV₁ by at least 7.5% at any of the 13 evaluations during the study despite ICS therapy ($n = 76$). Figure 2 demonstrates the wide range of change in percentage of predicted FEV₁ responses at four representative visits. Poor lung function responders ($n = 76$) were compared with the 213 subjects (responders) who improved by 7.5% at least once during follow-up. The 22 subjects missing lung function data for an entire year were excluded from analysis.

The baseline characteristics of subjects in the two lung function groups are noted in Table 1. A higher percentage of predicted FEV₁, less responsiveness to bronchodilators (BDR to albuterol) and methacholine (higher PC₂₀) and the minor allele of both RS242941 in *CRHR1* and T2206C in *FCER2* were significantly associated with poor lung function response in univariate analysis. After adjustment for baseline percent predicted FEV₁, the two SNPs and BDR to albuterol were significant in multivariable forward stepwise logistic regression (Table 3). We note that the directionality of RS242941 in *CRHR1* was unexpected, as the minor allele (T) confers an OR of poor response of 1.9 in this analysis, while TT homozygotes had been previously noted to have the most improved lung function at 8 weeks [12].

The only significant phenotypic predictor of poor lung function response was BDR to albuterol, with a 1% increase in BDR associated with a reduced risk of poor lung function response, with an OR of 0.87 (95% CI: 0.82–0.93; $p < 0.0001$). We performed a sensitivity analysis to assess whether baseline FEV₁ modifies the association of BDR and lung function response, by stratifying poor lung function responders by baseline level of lung function (FEV₁ percentage predicted of $\leq 100\%$, $\leq 90\%$ and $\leq 85\%$) and comparing them to the 213 responders. As shown in Table 4, a low bronchodilator response to albuterol was strongly associated with failure to improve lung function across groups, no matter how low the baseline FEV₁. This suggests that a ‘ceiling effect’ is not the etiology of this association. We note that while a single visit with greater than or equal to 7.5% improvement was used to define the 213 responders, this group improved by greater than or equal to 7.5% at an average of 49% (standard deviation: 33%) of follow-up visits. Defining responders as those whose FEV₁ increased by greater than or equal to 7.5% at least twice or four-times did not substantially change our results (data not shown).

Comparison of the two outcomes

Variables associated with poor response in terms of lung function show remarkably little overlap with those that predict recurrent exacerbations. The phenotypic variable that predicts a poor response in terms of lung function (low bronchodilator response to albuterol) is not associated with a poor response in terms of asthma exacerbations. On the contrary, as shown in Table 1, while low bronchodilator response is associated with a poor lung function response, there is a nonsignificant trend toward higher bronchodilator response among recurrent exacerbators ($p = 0.14$). Similarly, subjects with a history of an asthma exacerbation in the year

prior to enrollment were more likely to have recurrent exacerbations, but experienced no increased risk of a poor lung function response. The only variable that is associated with both poor response outcomes in univariate testing is T2206C in *FCER2*, with the minor allele increasing the odds of being a poor lung function responder by 1.8 ($p = 0.04$) and recurrent exacerbator by 1.9 ($p = 0.046$).

Poor responders based on FEV₁ did not tend to be poor responders based on exacerbations and vice versa. A total of 194 subjects were included in both case definitions of poor response. A total of 45 subjects (23%) had a poor FEV₁ response: 22% of rare exacerbators and 25% of recurrent exacerbators ($p = 0.72$ by Fisher's exact test, Figure 3).

Discussion

Comparison of the variables that predict a poor long-term response to ICS therapy based on lung function versus recurrent exacerbations has not been reported in the literature to date. We are able to address this question because of the frequent and detailed visit structure inherent in the 4-year follow-up period in CAMP, far longer than the vast majority of asthma clinical trials. We found that the phenotypic and genetic variables associated with a poor long-term response to ICSs depend entirely on the definition of response, with little overlap between predictors of lung function and exacerbations.

A history of exacerbations prior to study entry most strongly predicted recurrent exacerbations during long-term ICS therapy. Subjects with a history of a previous exacerbation were 2.5-times as likely to be recurrent exacerbators during follow-up. While this relationship has been well-documented in previous studies for asthma in general [16,17], the importance of this variable in predicting a long-term poor response to ICS therapy is worth emphasizing. Higher IgE levels were also associated with increased exacerbations in this cohort, with each log₁₀ increase in IgE associated with a 1.8-fold higher risk of recurrent exacerbations. This is consistent with multiple prior studies supporting the association of IgE and specific aeroallergen sensitization with asthma exacerbations [18–20]. We note that our analysis complements the recent work of Covar *et al.*, who also found that past exacerbations are the most important predictor of future exacerbations during therapy; younger age and higher IgE levels (significant in our analysis) trended in the same direction in that report but were not significant in multivariate analysis [10].

Alternatively, if one defines poor response as a consistent failure to improve lung function during ICS therapy, the outcome is strongly associated with a low BDR to albuterol and variation in *CRHR1* and *FCER2*. For each 1% increase in BDR, the odds of poor response are 0.87; thus, a subject who meets American Thoracic Society criteria for bronchodilator responsiveness of 12% is five-times less likely to have a poor lung function response than someone who does not bronchodilate at all (0%). Half of all subjects with two copies of the minor allele of RS242941 in *CRHR1* are poor lung function responders versus only 20% of subjects with two copies of the major allele.

Comparing predictors of the two outcomes reveals remarkably little overlap. The most recent Expert Panel Report guidelines incorporate multiple asthma phenotypes (based on exacerbations, symptoms and lung function) into their definition of asthma control [21]. Our work supports these distinctions, and highlights the importance of careful definition of asthma outcome when designing pharmacogenetic studies. Our predictors of recurrent exacerbators (high level of IgE and history of exacerbations) were not at all associated with poor FEV₁ response. On the contrary, there was a trend toward lower IgE and less history of past exacerbations in poor lung function responders (Table 1). The best marker of poor lung function response (low BDR to albuterol) likewise trended in the opposite direction in recurrent

exacerbators. Persistent exacerbators were no more likely to have a poor lung function response than those who were rare exacerbators (Figure 3). Failure to distinguish outcome phenotypes or grouping of poor response outcomes in a composite score may limit the development of clinical and pharmacogenetic models associated with ICS response.

Among all 19 variables studied, only variation in *FCER2* appears to contribute to the pathophysiology of both outcomes, as the minor allele conferred risk of both poor lung function response and recurrent exacerbations in univariate analysis among white subjects. Subjects who are homozygous for the T2206C mutant allele are 3.3-times more likely to be recurrent exacerbators and 3.9-times more likely to be poor lung function responders than those who are homozygous wild-type. *FCER2* encodes the low-affinity IgE receptor (CD23), which is involved in downregulation of IgE [22,23]. High levels of IgE are associated with numerous adverse outcomes in asthma, including exacerbations [20], emergency room visits [18,19], and hospitalizations [24,25] and, as demonstrated in this work, recurrent exacerbations during ICS treatment. While corticosteroid treatment has multiple beneficial effects in asthma, these are not achieved via a reduction in IgE levels; in fact, multiple studies have shown systemic corticosteroids may increase IgE levels [22–24], and targeted monoclonal anti-IgE therapy with omalizumab has been shown to improve lung function and reduce exacerbations in steroid-refractory adult asthmatics. Thus, it is plausible that mutations in the *FCER2* receptor alter the ability of a subject to downregulate the IgE pathway, which is itself inherently relatively resistant to downregulation via steroids, leading to poorer long-term outcomes in both lung function and exacerbations. We note that *FCER2* did not meet inclusion in our multivariate model; thus the importance of this finding is unclear.

A potential limitation of our study is a lack of power, as our dichotomous poor responder outcomes increase interpretability at the expense of power. In addition, our main focus was to identify baseline variables that predict a durable response – choosing not to use repeated measures again reduces our power. We may thus have been underpowered to pick up other variables that are in fact associated with our outcomes. For example, Fuhlbrigge *et al.* found low FEV₁ measurements to be significantly associated with increased exacerbations during the 4 months following that measurement in the placebo arm of CAMP, using a repeated measures analysis [25]. While our method did not demonstrate this association, a trend toward an association between lower FEV₁ and increased exacerbations is suggested using our definitions in both the placebo and ICS arms of CAMP (Table 1 for ICS subgroup; placebo data not shown).

Low statistical power does not invalidate our results, however. Not only do the significant predictors not overlap for the two definitions of response to ICS, but the directionality of most predictors is exactly opposite (Table 1). While not all statistically significant in both analyses, higher BDR to albuterol, lower IgE values, and lack of history of severe asthma exacerbations were more common in those with poor FEV₁ response in univariate analyses; on the contrary, recurrent exacerbators tended to have a lower BDR to albuterol, higher IgE levels and more have had severe asthma exacerbations. Similarly, the minor allele of *CRHR1* is associated with poor lung function response (OR: 1.5), yet shows no signal of influencing exacerbations (OR: 0.95). The divergent directionality for most variables suggests that our major conclusion (that variables associated with lung function response are distinct from those associated with recurrent exacerbations) would not have changed appreciably with greater sample size and power.

We caution that these results may not be generalizable to adult asthmatics – other studies have demonstrated that variables associated with response to ICS differ between children and adults [5,21]. Another potential limitation is a lack of accurate measure of adherence in the cohort – failure to adhere to ICS therapy would be a major unmeasured confounder. We note that the

mutant allele of RS242941 in *CRHR1* conferred increased risk of being a poor lung function responder in this study, but was associated with an improved FEV₁ at 8 weeks in previous work by our group [12]. This discrepancy likely reflects differences in analytic strategy (8 weeks vs 4 years, distinct inclusion criteria) though a false-positive result in one study is also possible. Further investigation is needed to clarify the role of *CRHR1* in asthma. We note that we focused this work on those subjects randomized to ICS; some of the variables that predict long-term outcomes during ICS therapy are also associated with long-term asthma outcomes in nontreated subjects (data not shown). The importance of our long-term ICS response phenotypes will be best assessed by testing for replication in other asthma cohorts in whom long-term follow-up data is available. Finally, we assessed variation in only two genes (*CRHR1* and *FCER2*), chosen because they were associated with short-term ICS outcomes. While we confirmed that SNPs in the two genes are also associated with long-term response to ICS, numerous other genes no doubt contribute to the pharmacogenetic response and will need to be incorporated in future pharmacogenetic models in asthma.

Conclusion

We found that variables associated with a poor long-term ICS response differ when the outcome is defined based on lung function or exacerbations, although one genetic predictor (T2206C in *FCER2*) appears important in the modulation of both. Subjects with a poor lung function response were not more commonly recurrent exacerbators, and vice versa, providing further evidence that the two outcome phenotypes reflect distinct aspects of asthma control. Our results support the latest Expert Panel Report guidelines, which define asthma control based on three phenotypes – exacerbations, symptoms and lung function [21] – and suggest that disparate mechanisms underlie the phenotypes. Pharmacogenetic studies aimed at determining an individual's response to asthma therapy will likely require incorporation of phenotypic, laboratory and genetic information. Meticulous definition of outcomes will be critical to the success of such investigations.

Executive summary

Poor response: exacerbations

- Predictors of recurrent asthma exacerbations despite inhaled corticosteroid treatment include history of prior asthma exacerbations, younger age and a higher IgE level.

Poor response: lung function

- By contrast, poor lung function response is associated with lower bronchodilator response to albuterol and variation in two genes studied: RS242941 in *CRHR1* and T2206C in *FCER2*.

Comparison of the two outcomes

- Subjects who have a poor response based on lung function do not tend to have recurrent exacerbations and vice versa, further suggesting a distinction in phenotypes.
- The one factor associated with both ICS outcomes in univariate analysis is *FCER2*; the lack of further overlap in predictors suggests disparate mechanisms underlie these asthma phenotypes.

Conclusion

- Genetic and phenotypic predictors of a poor long-term response to ICS therapy in asthma differ markedly when the outcome is based on recurrent exacerbations versus lung function.
- Pharmacogenetic studies and clinical trials in asthma must be designed with a careful focus on definition of outcome.

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Figure 1. Number of exacerbations among rare versus recurrent exacerbators in response to inhaled corticosteroid in The Childhood Asthma Management Program

Recurrent exacerbators are those with two or more exacerbations in both years 1–2 and years 3–4 (n = 66). Rare exacerbators had at most one exacerbation over the 4-year trial period (n = 136). Subjects with two to three exacerbations (n = 68), missing follow-up visits for at least 1 year (n = 10) and those with greater than or equal to four exacerbations but only during one 2-year period (n = 31) were excluded from analysis.

Figure 2. Change in percentage of predicted FEV₁ from baseline at four representative follow-up visits

FEV₁ response to inhaled corticosteroids demonstrates substantial variability at each measured time point.

FEV₁: Forced expiratory volume in 1 second.

Figure 3. Proportion of rare and recurrent exacerbators with poor lung function response

Of the 131 rare exacerbators, 22% had a poor FEV₁ response (never improved by 7.5% during follow-up); similarly, of the 63 recurrent exacerbators, 25% had a poor FEV₁ response (Fisher's exact p-value = 0.72). The proportion of nonresponders is similar, suggesting that these are independent phenotypes.

FEV₁: Forced expiratory volume in 1 second.

Table 1
Univariate analysis of recurrent versus rare exacerbations and poor versus good lung function improvement.

Baseline values (prior to ICS therapy)	Exacerbations*		Lung function*	
	Recurrent exacerbators (n = 66)	Rare exacerbators (n = 136)	Nonresponders (n = 76)	Responders (n = 213)
				<i>p</i> -value
<i>Demographics</i>				
Age, years	8.7 ± 2	9.2 ± 2	8.6 ± 1.9	9.2 ± 2.1
				0.08
Race (% each race)	White (68%) Black (17%) Hispanic (5%) Other (11%)	White (63%) Black (15%) Hispanic (13%) Other (9%)	White (66%) Black (12%) Hispanic (11%) Other (12%)	White (66%) Black (15%) Hispanic (10%) Other (9%)
				0.36
Gender (% male)	56	57	57	59
				0.76
Household income over US\$30,000 (%)	70	79	71	78
				0.29
BMI	17.6 ± 2.8	18.6 ± 3.5	18.4 ± 3.8	18.5 ± 3.7
				0.02
Smoking exposure (%)	43	38	38	41
				0.54
Intrauterine smoke exposure (%)	15	8	8	13
				0.18
<i>Lung function parameters</i>				
Prebronchodilator FEV ₁ (% predicted)	91 ± 16	94 ± 13	102.7 ± 12.7	90.1 ± 13
				0.14
Bronchodilator response to albuterol	10.6 ± 7.8	8.9 ± 7.4	4.7 ± 4.4	11.2 ± 7.9
				0.14
Methacholine PC ₂₀	0.9 (0.4, 2.1)	1.1 (0.5, 3.1)	1.5 (0.7, 4.3)	0.9 (0.4, 2)
				0.19
				0.002

Baseline values (prior to ICS therapy)	Exacerbations [*]		Lung function [*]	
	Recurrent exacerbators (n = 66)	Rare exacerbators (n = 136)	p-value	p-value
<i>Measures of atopy</i>				
IgE	683 (324, 1176)	399 (140, 1068)	0.06	0.34
Eosinophils	422 (246, 730)	400 (205, 562)	0.35	0.05
Family history of atopy (%)	67	71	0.63	0.77
Any positive skin test (%)	94	89	0.22	0.41
<i>Asthma history</i>				
Age at onset of asthma (years)	2.9 ± 2.4	3.2 ± 2.2	0.42	0.93
History of asthma exacerbations in year prior to enrollment (%)	41	23	0.008	0.56
Family history of asthma (%)	68	55	0.17	0.1
<i>Genetic factors[‡]</i>				
T2206C (MAF) (%)	33	22	0.046	0.03
RS242941 (MAF) (%)	27	28	0.9	0.02

± values are means ± standard deviation. Methacholine PC20, IgE level and eosinophil count were log-transformed for normality; median (IQR) values are shown here. Count data expressed as 'percentage yes' as appropriate. Variables associated with a p-value <0.05 are in bold. We used Fisher's exact and t-test or Wilcoxon test for phenotypic variables.

^{*} Recurrent exacerbators are those with greater than or equal to two exacerbations in both the first and last 2 years, rare exacerbators have less than or equal to one over the 4 years. Lung function nonresponders had less than 7.5% FEV₁ percentage predicted improvement from baseline at every follow-up visit, while responders had greater than or equal to 7.5% improvement at least once.

[‡] Genetic factors assessed in white subjects only, using logistic regression in an additive model.

FEV₁: Forced expiratory volume in 1 second; ICS: Inhaled corticosteroid; IQ: Interquartile; MAF: V-maf musculoaponeurotic fibrosarcoma oncogene homolog; PC20: Provocative concentration causing a 20% fall in FEV₁.

Table 2

Multivariable logistic regression model: variables associated with recurrent exacerbator status.

Variable	Odds ratio	95% CI	p-value
Log ₁₀ IgE	1.8	1.1–2.9	0.02
Prior Emergency Department visit or hospitalization	2.4	1.2–4.6	0.01
Age	0.85	0.73–0.998	0.047

After adjustment for race and gender.

Table 3

Multivariable logistic regression model: variables associated with poor lung function response.

Variable	OR	95% CI	p-value
T2206C (G allele)	2.1	1.2–3.5	0.006
RS242941 (T allele)	1.6	1–2.7	0.05
BDR to albuterol	0.89	0.83–0.94	<0.0001

After adjustment for age, race, gender and baseline lung function.

BDR: Bronchodilator response; OR: Odds ratio.

Table 4

Decreased bronchodilator response to albuterol increases risk of poor lung function response to inhaled corticosteroid across all levels of baseline FEV₁*.

Baseline FEV ₁	n poor responder	OR	CI	p-value
Baseline FEV ₁ >100%	41	0.87	0.83–0.94	<0.0001
Baseline FEV ₁ ≤100%	35	0.83	0.76–0.9	<0.0001
Baseline FEV ₁ ≤90%	17	0.76	0.67–0.87	<0.0001
Baseline FEV ₁ ≤85%	7	0.75	0.62–0.91	0.004

* Effect estimate of bronchodilator response to albuterol in forward selection logistic regression model, after adjustment for age, race, height, gender and baseline percentage of predicted FEV₁, each strata was compared with 213 good responders.

FEV₁: Forced expiratory volume in 1 second; OR: Odds ratio.