

Factors predicting inhaled corticosteroid responsiveness in African American patients with asthma

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Background: African American patients disproportionately experience uncontrolled asthma. Treatment with an inhaled corticosteroid (ICS) is considered first-line therapy for persistent asthma.

Objective: We sought to determine the degree to which African American patients respond to ICS medication and whether the level of response is influenced by other factors, including genetic ancestry.

Methods: Patients aged 12 to 56 years who received care from a large health system in southeast Michigan and who resided in Detroit were recruited to participate if they had a diagnosis of asthma. Patients were treated with 6 weeks of inhaled beclomethasone dipropionate, and pulmonary function was remeasured after treatment. Ancestry was determined by genotyping ancestry-informative markers. The main outcome measure was ICS responsiveness defined as the change in prebronchodilator FEV₁ over the 6-week course of treatment.

Results: Among 147 participating African American patients with asthma, average improvement in FEV₁ after 6 weeks of ICS treatment was 11.6%. The mean proportion of African ancestry in this group was 78.4%. The degree of baseline bronchodilator reversibility was the only factor consistently associated with ICS responsiveness, as measured by both an improvement in FEV₁ and patient-reported asthma control ($P = .001$ and $P = .021$, respectively). The proportion of African ancestry was not significantly associated with ICS responsiveness.

Conclusions: Although baseline pulmonary function parameters appear to be associated with the likelihood to respond to ICS treatment, the proportion of genetic African ancestry does not. This study suggests that genetic ancestry might not contribute to differences in ICS controller response among African American patients with asthma. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: Inhaled corticosteroids, asthma, race-ethnicity, continental population groups, ancestry, urban health

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More than 20 million persons are estimated to have asthma currently in the United States.¹ African American patients appear to be particularly susceptible to asthma-related complications, with rates of asthma-related emergency department visits, hospitalizations, and death approximately 2 to 3 times the rates found in white subjects.¹ There might be many reasons for these apparent disparities,² including differences in the following factors: allergic sensitization and environmental exposures,³⁻⁶ access to care,⁷ adherence to and use of asthma controller therapy,^{8,9} and treatment response.^{10,11}

Inhaled corticosteroids (ICSs) are considered first-line therapy for the treatment of persistent asthma¹² because their use has been consistently shown to reduce airway responsiveness, diminish symptoms, and prevent exacerbations.¹³⁻¹⁵ However, at least 1 *in vitro* study has suggested that steroid responsiveness might differ between African American and white patients, as evidenced by between-group differences in the ability of dexamethasone to suppress T-cell proliferative responses.¹⁶ Given the existing disparities in asthma morbidity by race-ethnicity and the importance of ICS therapy in asthma control, it is important to clarify the factors associated with ICS responsiveness among African American patients with asthma because this knowledge might improve the tailoring of asthma controller therapy.

Abbreviation used

ACT: Asthma Control Test

ICS: Inhaled corticosteroid

SAPPHIRE: Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity

As we and others have previously shown, there tends to be considerable variation in the proportion of African and European ancestry among African American subjects.^{3,17} Because genetic substructure tends to follow historic geographic boundaries between ancestral groups,¹⁸ we reasoned that treatment response might also differ according to biogeographic ancestry among African American patients with asthma. In other words, were between-population genetic differences the explanation for disparities in treatment response among patients with asthma, we would also expect this to be reflected in a significant relationship between ancestral proportion and ICS response within African American subjects.

Therefore this study sought to identify the degree to which African American patients with asthma respond to ICS therapy and the factors associated with treatment response (eg, age, sex, socioeconomic status, asthma duration, allergic sensitization, passive smoke exposure, and pulmonary function). Many of these factors have been associated with asthma control and severity and thus might also influence treatment response.^{6,19-21} We were also keenly interested in assessing for a potential association between genetic ancestry and ICS treatment response for the reasons mentioned. Treatment response was defined by both the change in pulmonary function (ie, FEV₁) and the change in patient-reported asthma control after 6 weeks of inhaled beclomethasone dipropionate treatment. Study participants were self-identified African American patients with asthma recruited within the city of Detroit as part of the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity (SAPPHIRE).

METHODS**Study population and setting**

The Institutional Review Board of the Henry Ford Health System approved the study as described. All study patients received care through a large health system serving southeast Michigan. Those patients residing within the outer city boundaries of Detroit (including the cities of Hamtramck and Highland Park) were invited for screening if they met the following criteria: age 12 to 56 years, at least 1 coded clinical diagnosis of asthma (ie, from the electronic record), and no recorded diagnosis of chronic obstructive pulmonary disease or congestive heart failure. The age criterion was selected to be consistent with current US asthma guidelines, which recommend similar controller treatment for patients who are 12 years of age and older.¹² Informed written consent was obtained for study participants or their guardians before the first screening examination, and written assent was obtained from all participants who were minors.

Screening assessment

On the initial screening visit, patients answered a staff-administered structured questionnaire, performed spirometry with an assessment of bronchodilator response, and provided a blood sample for DNA analysis and serologic testing. Where available, the survey instrument included validated questions adapted from multiple sources. These questions included asthma onset, disease triggers, asthma control as assessed by the Asthma Control Test (ACT; QualityMetric, Inc, Lincoln, RI),²² detailed household socioeconomic

questions and self-identified race-ethnicity (available at: <http://www.census.gov/dmd/www/2000quest.html>), health-related missed work and school,²³ tobacco exposure,^{24,25} environmental smoke exposure (available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/fi_smq_d.pdf),²⁵ and environmental exposures.²⁶ A venous blood sample was collected for subsequent DNA isolation and serologic testing.

Spirometry was performed in accordance with current 2005 American Thoracic Society/European Respiratory Society recommendations^{27,28} by using a Fleisch-type pneumotachometer (KoKo PFT Spirometer; nSpire Health, Inc, Louisville, Colo). Predicted values for pulmonary function parameters, such as FEV₁, were obtained by using standard equations derived from the US population.²⁹ If possible, patients were asked to withhold their bronchodilator medications 12 hours before lung function tests. We determined bronchodilator response by administering increasing doses of inhaled albuterol sulfate hydrofluoroalkane (GlaxoSmithKline, Research Triangle Park, NC). A 360- μ g dose of albuterol was delivered from a standard metered-dose inhaler by using an AeroChamber Plus Z STAT spacer (Monahan Medical Corp, Plattsburgh, NY). Albuterol was administered a second time (180 μ g for children <16 years and 360 μ g for persons $\geq$ 16 years) if a greater than 12% improvement in FEV₁ was not achieved after the first dose. Baseline bronchodilator reversibility was calculated as the percentage change in FEV₁ before and after albuterol administration on the initial screening visit.^{30,31}

ICS treatment trial

Subjects who confirmed that they had a prior clinical diagnosis of asthma were eligible for the 6-week ICS treatment trial to assess corticosteroid responsiveness if they also met the following criteria (ie, in addition to the criteria for screening): baseline FEV₁ between 40% and 90% of predicted value, greater than 12% baseline bronchodilator reversibility, no smoking in the preceding year or a less than 10 pack-year smoking history total, not pregnant at the time of enrollment and not intending to get pregnant during the 6-week treatment period, and steroid naive (ie, not treated with an oral corticosteroid or ICS in the 4 weeks preceding enrollment). Subjects who met these criteria and agreed to treatment received 160 μ g of beclomethasone dipropionate hydrofluoroalkane (Teva Specialty Pharmaceuticals LLC, Horsham, Pa) twice daily through a metered-dose inhaler for a total of 6 weeks. Participants were instructed in proper inhaler technique, including use of the provided spacer (AeroChamber Plus Z STAT). Medication adherence was assessed electronically with the use of Doser CT (Meditrack products, Hudson, Mass), a monitoring device that attaches to the inhaler.^{32,33} This was done to account for the level of use and its potential effect on treatment response over the study period. To estimate adherence, we divided the number of canister actuations registered by the prescribed number of doses (ie, 168) over the 6-week treatment period. In situations in which the follow-up was not precisely at 6 weeks, we adjusted the denominator accordingly for the number of days between the initial and follow-up visits.

DNA isolation, genotyping, and assessment of ancestry

Genomic DNA was extracted from whole blood by using a Gentra AutoPure LS (Gentra Systems, Inc, Minneapolis, Minn). Genotyping was performed with iPLEX gold (Sequenom, Inc, San Diego, Calif). Each subject was genotyped for 107 single nucleotide polymorphisms, which were informative for determining subjects' ancestry because of their differing allele frequencies in continental population groups. This set of ancestry-informative markers has been described in detail elsewhere³⁴ but in short was developed from the following ancestral populations: West African subjects living in London, United Kingdom and South Carolina; subjects of European ancestry from Coriell's North American Caucasian panel (Coriell Institute for Medical Research, Camden, NJ); and Native American subjects (ie, Mayan and Nahua) from villages in Tlapa in the state of Guerrero, Mexico.

We used the software package PSMIX to determine individual ancestry by using maximum likelihood estimation.^{35,36} The procedure stopped when the change in the parameter estimate between consecutive iterations was less

than 10^{-6} . As an independent check, we estimated ancestral proportions using the program STRUCTURE, which uses a Bayesian approach.³⁷ The correlation between ancestry estimates using both approaches was 0.99, but in the final analysis, we used the estimates derived from PSMIX.

Allergen-specific and total serum IgE levels

Individual IgE levels were measured from stored serum samples. Assays for allergen-specific IgE were performed by using a commercial assay (ImmunoCAP; Phadia AB, Portage, Mich). The samples were analyzed for IgE levels to the following aeroallergens: dog (*Canis domesticus*), cat (*Felis domesticus*), cockroach (*Blattella germanica*), ragweed (short, *Ambrosia artemisiifolia*), grass (timothy, *Phleum pratense*), *Alternaria* species (*Alternaria alternata*), and dust mite (*Dermatophagoides farinae*). Individual allergen-specific IgE levels greater than or equal to 0.35 IU/mL were considered positive. Allergic sensitization was defined as having 1 or more positive allergen-specific IgE measurement to one of the 7 aeroallergens tested. We also measured total serum IgE using a commercial assay from the same manufacturer.

Statistical analysis

Our analysis was restricted to SAPHIRE participants who by self-report were African American. We assessed steroid responsiveness as the change in FEV₁ and ACT score before and after ICS therapy. Linear regression was used to model these continuous outcome variables. We assessed the univariable and multivariable relationship between potential predictors of steroid responsiveness and outcomes. These predictor variables included age, sex, body mass index (in kilograms per meter squared), household income (log transformed to normalize its distribution), educational level (dichotomously defined as high school degree or less vs more than a high school degree), percentage of African ancestry, baseline ACT score (dichotomously defined as ≤ 19 [poor control] and > 19 [good control] and included in only the model with change in FEV₁ as the dependent variable), asthma duration, individual allergen-specific sensitivity (dichotomously defined as positive or negative for each allergen: dog, cat, cockroach, ragweed, timothy grass, *Alternaria* species, and dust mite), total serum IgE level (natural log transformed to normalize the distribution and reduce the influence of outliers), passive smoke exposure (because all participants were reported nonsmokers), baseline percent predicted FEV₁, baseline bronchodilator reversibility, and level of adherence to study medication. Because some study subjects were minors, we used the income and level of educational attainment for the head of the household as proxies for socioeconomic status. Backward stepwise regression was used to identify those factors related to steroid responsiveness. At each step, the variable with the largest *P* value was excluded in the model; the procedure stops when all remaining variables have *P* values of less than .05. As a secondary analysis, we assessed for factors associated with changes in patient-reported asthma control after 6 weeks of ICS therapy (ie, the change in ACT score before and after therapy). Again we assessed the univariable and multivariable relationship between change in asthma control (continuously measured) and the aforementioned potential predictor variables (ie, with the exception of baseline ACT score). Backward stepwise regression was used to identify those factors related to steroid responsiveness as measured by improvement in patient-reported asthma control. All analyses were performed with SAS version 9.1 software (SAS Institute, Inc, Cary, NC).³⁸

RESULTS

Of the 1,985 patients from Detroit screened, 1,777 (89.5%) identified themselves as African American. Of these patients, 214 met the criteria for enrollment in the 6-week ICS treatment trial, and 185 agreed to enroll. Of those enrolled, 147 (79.5%) completed the 6-week assessment. The characteristics of those patients who did and did not complete the 6 weeks of treatment are shown in Table I. None of the characteristics examined

differed between those who finished treatment and those who did not. Among those who completed the study, average age was 32.7 years (SD, 13.6 years), and average duration of asthma was 21.1 years (SD, 12.8 years). The average proportion of African ancestry was 78.4%, and the distribution of African and European ancestry is shown in Fig 1. More than half (87 [59.2%]) had poorly controlled asthma at baseline, as defined by an ACT score of 19 or less, and most (126 [85.7%]) had at least 1 positive allergen-specific IgE result. Adherence to treatment was good on average, with patients taking 79.3% of their prescribed dose during the study period.

The average percentage improvement in prebronchodilator FEV₁ after 6 weeks of ICS treatment was 11.6% (Table I), and the distribution of FEV₁ improvement across all study participants is shown in Fig 2. After accounting for all of the factors assessed, only the degree of baseline bronchodilator reversibility and baseline FEV₁ percent predicted were associated with ICS treatment response (Table II, adjusted model). Every 1% increase in baseline bronchodilator reversibility was associated with an ICS treatment-related improvement in FEV₁ of 0.48% (SE, 0.14%). Conversely, percent predicted FEV₁ at baseline was inversely associated the change in FEV₁ in that subjects with lower percent predicted FEV₁ at baseline were more likely to improve after 6 weeks of treatment (0.41% improvement in FEV₁ per 1% lower baseline percent predicted FEV₁). The backward stepwise regression model also demonstrated that baseline percent predicted FEV₁ and baseline bronchodilator reversibility were associated with ICS treatment response (*P* = .001 for both). In none of these models was the proportion of African ancestry significantly associated with the change in FEV₁ after 6 weeks of ICS treatment.

We also examined the factors associated with ICS treatment response, as assessed by changes in patient-reported asthma control (ie, a change in ACT score over the course of therapy). In the unadjusted analysis the degree of baseline bronchodilator reversibility (a 0.13-point improvement in ACT score per 1% increase in baseline bronchodilator reversibility, *P* = .006) and baseline FEV₁ percent predicted (a 0.12-point improvement in ACT score per 1% lower baseline percent predicted FEV₁, *P* = .013) were associated with subsequent patient-reported treatment response (Table III). Household income was also negatively associated with the change in the ACT score (*P* = .002). In the stepwise regression model household income was again negatively associated with treatment-related improvement in asthma control (*P* = .001), whereas baseline bronchodilator reversibility was positively associated with treatment-related improvement in asthma control (a 0.11-point improvement in ACT score per 1% increase in baseline bronchodilator reversibility, *P* = .021).

Post-hoc analysis using a 15% improvement in FEV₁ as a cut point for defining ICS responsiveness did not substantively change our conclusions, with the exception that baseline ACT score was also significantly associated with this outcome in the stepwise model (data not shown). In addition, when categorizing the results of allergen-specific IgE values to just atopic and non-atopic (ie, patients with ≥ 1 allergen-specific IgE result vs none), atopy was still not associated with ICS treatment response. Finally, adding and removing socioeconomic variables (ie, income and education level) from the regression models did not affect the relationship (ie, the lack of relationship) between ancestry and ICS treatment response.

TABLE I. Characteristics of African American participants with asthma who completed 6 weeks of ICS therapy and those who did not

Characteristic	Subjects who completed the study (n = 147)	Subjects who did not complete the study (n = 38)	P value*
Age (y), mean $\pm$ SD†	32.7 $\pm$ 13.6	31.3 $\pm$ 13.0	.574
Female sex, no. (%)	86 (58.5)	25 (65.8)	.414
Body mass index (kg/m ²), mean $\pm$ SD	33.3 $\pm$ 10.1	32.5 $\pm$ 11.2	.650
Household income, median (range)	\$32,500 (\$1,000-\$225,000)	\$27,500 (\$1,000-\$162,000)	.320
>High school education, no. (%)	89 (60.5)	18 (47.4)	.143
African ancestry, mean proportion $\pm$ SD‡	78.4 $\pm$ 10.6	78.1 $\pm$ 12.4	.888
ACT score at baseline, mean $\pm$ SD†	17.5 $\pm$ 5.2	17.4 $\pm$ 4.9	.935
ACT score $\leq$ 19 (ie, poor control) at baseline, no. (%)	87 (59.2)	26 (68.4)	.298
Duration of asthma (y), mean $\pm$ SD§	21.1 $\pm$ 12.8	22.9 $\pm$ 13.2	.460
Positive allergen-specific IgE result (ie, $\geq$ 0.35 kUA/L), no. (%)			
Cat	72 (52.2)	23 (62.2)	.279
Dog	79 (57.3)	20 (54.1)	.728
Dust mite	69 (50.0)	17 (46.0)	.661
Cockroach	60 (43.5)	16 (43.2)	.980
Timothy grass	67 (48.6)	19 (51.4)	.762
Ragweed	80 (58.0)	17 (46.0)	.191
<i>Alternaria</i> species	75 (54.4)	21 (56.8)	.794
$\geq$ 1 positive allergen-specific IgE measurement	126 (85.7)	32 (84.2)	.815
Total serum IgE level (kU/L), geometric mean $\pm$ geometric SD	170.8 $\pm$ 4.1	185.1 $\pm$ 4.9	.766
Passive smoke exposure, no. (%)¶	68 (46.3)	16 (42.1)	.647
FEV ₁ percent predicted at baseline, mean $\pm$ SD†	74.6 $\pm$ 13.3	72.9 $\pm$ 12.6	.470
FEV ₁ percent reversibility at baseline, mean $\pm$ SD†	22.0 $\pm$ 12.8	23.1 $\pm$ 13.9	.629
ICS adherence during treatment period (%), mean $\pm$ SD#	79.3 $\pm$ 22.1	—	—
Average improvement in FEV ₁ after 6 wk of ICS medication, mean $\pm$ SD†	11.6 $\pm$ 16.5	—	—

*For the comparison of subjects who completed therapy with those who did not.

†Data were available for 147 and 38 patients, respectively.

‡African ancestry was estimated by using the 107 ancestry-informative markers and the software program PSMIX. Data were available for 135 and 35 patients, respectively.

§Data were available for 146 and 36 patients, respectively.

||Data were available for 138 and 37 patients, respectively.

¶Passive smoke exposure was assessed by means of a survey using questions derived elsewhere.²⁵

#Assessed as a ratio of actual canister actuations to prescribed dose over the 6-week treatment period. Data were available for 135 patients.

DISCUSSION

This study is one of the largest to date to assess ICS responsiveness in African American patients with asthma. As a result, we have made a number of observations that might influence future approaches and opinions regarding asthma controller treatment in this population group.

First, we observed that the average improvement in FEV₁ after a 6-week course of ICS therapy was 11.6% in our study population. This is comparable with other studies assessing ICS responsiveness using similar entry criteria but having a much lower proportion of African American patients. For example, in the Predicting Response to Inhaled Corticosteroid Efficacy trial, Martin et al³⁹ treated 72 patients with 6 weeks of inhaled beclomethasone. Subjects were aged 18 to 55 years, had a baseline percent predicted FEV₁ of between 55% and 85% with documented methacholine responsiveness, denied corticosteroid exposure for the 4 weeks preceding enrollment, and had less than 10 pack-years of smoke exposure with no smoking in the preceding year. Most of these subjects (55.6%) were considered non-Hispanic white. The mean improvement in FEV₁ was 8.3% after 6 weeks of therapy.

Similarly, Tantisira et al⁴⁰ examined ICS responsiveness after 6 to 8 weeks of ICS therapy in 3 clinical trials involving both children and adults. The mean percentage change in FEV₁ was 7.0%, 8.3%, and 6.7% among studies comprised of 7.0%, 14.1%, and

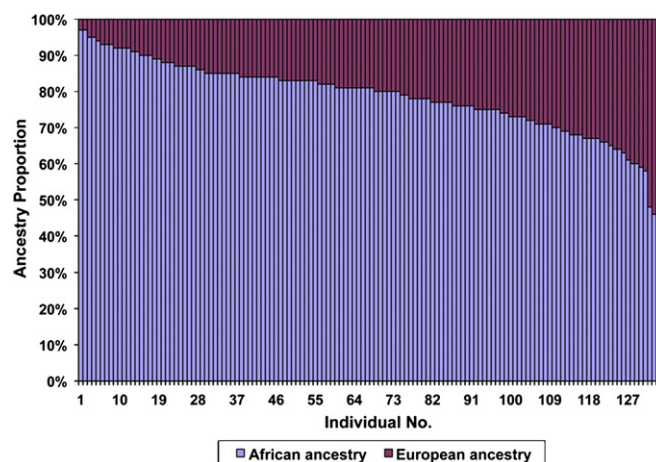


FIG 1. Distribution of African (blue) and European (purple) ancestry for African American patients with asthma who completed 6 weeks of ICS therapy. Genetic ancestry was estimated in 135 of the 147 participants who completed therapy.

18.8% African American patients, respectively. In short, improvement in FEV₁ after 6 weeks of ICS therapy was not lower in our SAPPHIRE study population, despite including only self-reported African American patients with asthma.

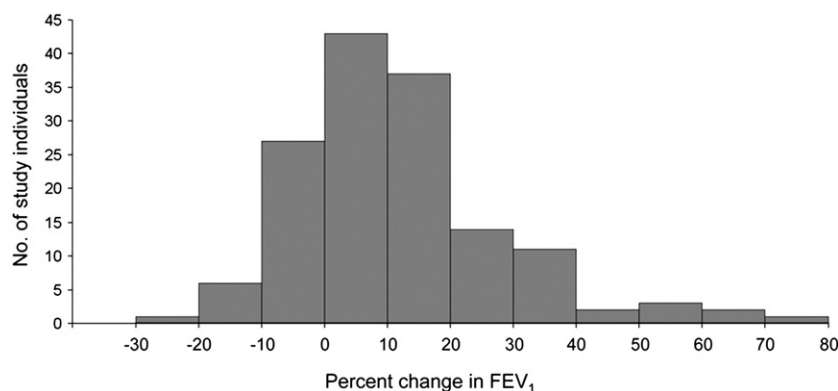


FIG 2. Distribution of the change in FEV₁ between baseline and after 6 weeks of ICS treatment among study participants (n = 147).

TABLE II. Characteristics related to the change in FEV₁ after 6 weeks of ICS treatment among African American patients with asthma*

Characteristic	Unadjusted models		Adjusted model†		Backward stepwise model‡	
	Change in FEV ₁ ± SE (%)	P value	Change in FEV ₁ ± SE (%)	P value	Change in FEV ₁ ± SE (%)	P value
Age (per 10-y interval)	1.52 ± 1.00	.132	0.35 ± 1.37	.800		
Female sex	−1.75 ± 2.77	.528	−2.59 ± 2.78	.354		
Body mass index (per 1-unit increase in kg/m ²)	0.19 ± 0.13	.162	0.06 ± 0.14	.698		
Household income	−0.77 ± 1.03	.456	1.13 ± 1.09	.303		
>High school education	−2.80 ± 2.78	.316	0.19 ± 2.93	.949		
African ancestry (per 10% increase in African ancestry)§	0.64 ± 1.36	.637	−3.01 ± 13.30	.821		
ACT, poor control	6.44 ± 2.73	.020	2.57 ± 2.79	.359		
Duration of asthma (per 5-y interval)	0.74 ± 0.53	.167	−0.10 ± 0.64	.879		
Positive allergen-specific IgE result¶						
Cat	5.57 ± 2.77	.047	2.90 ± 3.95	.465		
Dog	2.11 ± 2.84	.459	−2.61 ± 4.03	.519		
Dust mite	0.24 ± 2.81	.933	−1.94 ± 3.65	.596		
Cockroach	−1.89 ± 2.83	.506	−2.37 ± 3.17	.455		
Timothy grass	4.07 ± 2.79	.147	3.58 ± 3.25	.272		
Ragweed	3.95 ± 2.83	.165	3.65 ± 3.44	.291		
Alternaria species	0.59 ± 2.82	.834	−2.62 ± 3.15	.408		
Total serum IgE level#	0.96 ± 0.99	.336	0.51 ± 1.35	.707		
Passive smoke exposure**	−4.56 ± 2.71	.095	−3.10 ± 2.61	.237		
FEV ₁ percent predicted at baseline (per 1% decrease)††	0.68 ± 0.09	.001	0.41 ± 0.14	.005	0.42 ± 0.12	.001
FEV ₁ percent bronchodilator reversibility at baseline (per 1% increase)‡‡	0.74 ± 0.09	.001	0.48 ± 0.14	.001	0.52 ± 0.13	.001
ICS adherence during treatment period (per 10% increase in adherence)§§	0.04 ± 0.64	.955	0.04 ± 0.58	.949		

*Outcome was a continuous measure of the percentage increase in FEV₁ between the initial FEV₁ measured at the baseline visit and the initial FEV₁ measured at the follow-up visit after 6 weeks of ICS therapy. The relationship between the predictor variables and outcome was assessed by using linear regression.

†Adjusted for all other variables shown.

‡All variables shown are included in the model initially. The variables with the highest *P* values are sequentially dropped, and the model is refit after each exclusion until all the variables left are significant at a *P* value of less than .05. The variables presented are those that remain in the final model.

§African ancestry was estimated by using the 107 ancestry-informative markers and the software program PSMIX.

||The ACT has a score range of 5 to 25, with higher scores signifying better control. The results were dichotomized, with patient scores of 19 or less considered to be poor control.

¶Individual allergen-specific IgE results of 0.35 kUA/L or greater were considered to be positive.

#Total IgE levels were natural log transformed to normalize their distribution.

**All participants were current nonsmokers. Passive smoke exposure was assessed by means of a survey using questions derived elsewhere.²⁵

††Based on the predictive equation of Hankinson et al.²⁹

‡‡The percentage change in measured FEV₁ from baseline after administration of albuterol. All participating patients had at least 12% reversibility at baseline.

§§Assessed as a ratio of actual canister actuations to prescribed dose over the 6-week treatment period.

Differential response to asthma medications by race-ethnicity has been previously reported by us and others.⁴¹⁻⁴³ However, this differential response might be medication class specific, such as to inhaled β -agonists.^{44,45} In a recent study assessing step-up

treatments for children with poorly controlled asthma, Hispanic and non-Hispanic white children were more likely to show improvement with an added long-acting β -agonist medication when compared with an additional leukotriene receptor

TABLE III. Characteristics related to the change in ACT scores after 6 weeks of ICS treatment among African American patients with asthma*

Characteristic	Unadjusted models		Adjusted model†		Backward stepwise model‡	
	Change in ACT score ± SE	P value	Change in ACT score ± SE	P value	Change in ACT score ± SE	P value
Age (per 10-y interval)	−0.31 ± 0.44	.478	−0.81 ± 0.63	.202		
Female sex	0.71 ± 1.21	.559	2.58 ± 1.26	.043		
Body mass index (per 1 unit increase in kg/m ²)	0.04 ± 0.06	.533	−0.03 ± 0.07	.619		
Household income	−1.41 ± 0.44	.002	−1.63 ± 0.48	.001	−1.51 ± 0.42	.001
>High school education	−1.09 ± 1.21	.370	0.36 ± 1.34	.790		
African ancestry (per 10% increase in African ancestry)§	−2.97 ± 5.94	.618	−3.31 ± 6.09	.588		
Duration of asthma (per 5-y interval)	−0.06 ± 0.23	.810	0.16 ± 0.17	.577		
Positive allergen-specific IgE result						
Cat	1.05 ± 1.22	.390	0.55 ± 1.79	.760		
Dog	0.20 ± 1.24	.870	−0.69 ± 1.83	.707		
Dust mite	−0.88 ± 1.22	.471	−1.75 ± 1.66	.294		
Cockroach	−0.44 ± 1.24	.722	−1.04 ± 1.45	.475		
Timothy grass	1.00 ± 1.22	.413	1.94 ± 1.49	.195		
Ragweed	1.30 ± 1.24	.294	2.59 ± 1.55	.097		
Alternaria species	−0.81 ± 1.23	.508	−1.16 ± 1.43	.420		
Total serum IgE level¶	0.09 ± 0.43	.837	−0.32 ± 0.62	.607		
Passive smoke exposure#	−1.50 ± 1.19	.210	−1.89 ± 1.19	.116		
FEV ₁ percent predicted at baseline (per 1% decrease)**	0.12 ± 0.05	.013	0.03 ± 0.06	.618		
FEV ₁ percent bronchodilator reversibility at baseline (per 1% increase)††	0.13 ± 0.05	.006	0.08 ± 0.06	.200	0.11 ± 0.05	.021
ICS adherence during treatment period (per 10% increase in adherence)‡‡	0.34 ± 0.26	.190	0.27 ± 0.27	.309		

*Outcome was a continuous measure of the difference in ACT scores between the baseline assessment and after 6 weeks of ICS therapy. Positive changes reflect an improvement in patient-reported asthma control over the treatment period. The relationship between the predictor variables and outcome was assessed by using linear regression.

†Adjusted for all other variables shown.

‡All variables shown are included in the model initially. The variables with the highest *P* values are sequentially dropped, and the model is refit after each exclusion until all the variables left are significant at a *P* value of less than .05. The variables presented are those that remain in the final model.

§African ancestry was estimated by using the 107 ancestry-informative markers and the software program PSMIX.

||Individual allergen-specific IgE results of 0.35 kUA/L or greater were considered to be positive.

¶Total IgE levels were natural log transformed to normalize their distribution.

#All participants were current nonsmokers. Passive smoke exposure was assessed by means of a survey using questions derived elsewhere.²⁵

**Based on the predictive equation of Hankinson et al.²⁹

††The percentage change in measured FEV₁ from baseline after the administration of albuterol. All participating patients had at least 12% reversibility at baseline.

‡‡Assessed as a ratio of actual canister actuations to prescribed dose over the 6-week treatment period.

antagonist medication or an ICS medication.⁴⁶ In contrast, African American children appear to respond equally well to long-acting β -agonist or ICS step-up therapy.

To our knowledge, this is the first study to evaluate the relationship between genetic ancestry and ICS responsiveness. We and others have previously demonstrated a wide range of African and European admixture among African American patients.^{3,17,47} This is relevant to the current study in that genetic variation tends to follow historic geographic boundaries between populations.²⁴ Therefore, were there a strong genetic underpinning for disparate ICS response between persons of African and European ancestry, we would expect that association would be evident, even when assessing the relationship with ancestry within African American subjects. Given our sample size and the variation in African ancestry within our study population, we estimate that we had 80% power to detect a correlation as small as 0.24 between ancestry and ICS responsiveness (as defined by a change in FEV₁). The proportion of African ancestry was not associated with ICS treatment response in any of our analyses.

This study also confirms the association between baseline bronchodilator responsiveness and steroid-related improvement in pulmonary function seen by other groups.^{39,48} In fact, our data suggest that the degree of baseline bronchodilator responsiveness explains much variation in treatment response, such as 32.9% of

the variation in FEV₁ improvement and 5.2% of the variation in ACT improvement (data not shown). The negative association that we observed between income level and the change in self-reported asthma control over the course of ICS treatment might relate to environmental exposures that mitigate treatment response or perhaps to differences in other stressors that affect asthma management.⁴⁹

It is important to note this study's limitations. First, this study was performed in only one city and therefore might not be representative of African American patients in other US locations. Moreover, it also remains to be seen whether these findings hold for other admixed groups, such as Puerto Rican patients, who have even higher rates of asthma.² Nevertheless, our study does constitute one of the largest evaluations of ICS responsiveness in African American patients to date, and our estimates of admixture are very similar to those reported for African American subjects in other areas of the United States.^{34,50} In estimating African ancestry, we used markers informative for West African ancestry. Although this assumption might have resulted in some incorrect estimates of ancestry, recent studies suggest that West African origin accounts for the majority of genetic variance in African American subjects and that, on average, other African populations account for approximately 8% of individual ancestry.^{51,52}

There are undoubtedly other factors associated with ICS responsiveness that might have been overlooked by us or that await discovery (and therefore are not included in our models). Medication adherence, which we have previously shown to be associated with poor asthma outcomes,⁵³ was not found to be associated with treatment response. However, this is most likely the consequence of the high levels of medication adherence in this study overall (ie, approximately 81% of study subjects had >50% adherence; data not shown), which allowed us to assess other factors associated with drug response.

Although our study population was limited to those patients who met our restrictive entry criteria, this was done so as to be comparable to existing studies of ICS responsiveness.^{39,48} However, these criteria were not perfectly congruent with severity categories used in current US guidelines.¹² Lastly, we assessed the change in FEV₁ as a continuous measure of ICS response. We thought that this was a reasonable approach given the normal distribution of the outcome variable and the greater power inherent in this analytic design. Nevertheless, other studies have used various thresholds for FEV₁ improvement to define a therapeutic response.^{39,48} As a *post-hoc* analysis, we show that our study conclusions are not altered by using a 15% improvement in FEV₁ as a cut point.

In summary, our study found that the proportion of African ancestry was not significantly associated with response to inhaled steroids, the quintessential asthma controller medication. This does not rule out the possibility of genetic determinants specific to African and European ancestry but rather suggests that such local genetic effects might be offsetting when assessed as an overall (or global) ancestral proportion. Moreover, although we observed a consistent relationship between the degree of baseline bronchodilator reversibility and ICS responsiveness, the proportion of variance explained suggests that there are other important determinants. Some genetic determinates of ICS response have already been described⁵⁴⁻⁵⁶; however, there are undoubtedly other important genetic, environmental, and gene-environment interactions that play a role in response to controller therapy. As these determinants become better known, we might be able to better tailor or personalize our selection of medications to those most likely to respond. This has particular relevance to groups disproportionately affected by disease complications,⁵⁷ such as African American patients with asthma. This study importantly suggests that global genetic ancestry might not be such a factor when considering ICS therapy for African American patients with asthma; however, replication in other African American study populations with asthma is needed to confirm these findings.

Clinical implications: Although African American patients disproportionately experience asthma-related complications, response to ICS controller therapy does not appear to be dependent on a subject's proportion of African ancestry.

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