

Abbreviations used

AIM: Ancestry informative marker

ED: Emergency department

ICS: Inhaled corticosteroid

RR: Relative rate

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

asthmatic patients that has been described in detail elsewhere.^{7,10} Patients were eligible for inclusion if they fulfilled the following requirements: age between 12 and 56 years, a physician's diagnosis of asthma, member of the affiliated health plan with both medical and pharmaceutical coverage, and no prior history of congestive heart failure or chronic obstructive pulmonary disease.

Eligible patients were invited for an initial evaluation that included the completion of a staff-administered questionnaire, pulmonary function testing, assessment of bronchodilator response, and collection of blood samples. Spirometry was performed according to current 2005 American Thoracic Society/European Respiratory Society recommendations.^{11,12} Predictive equations from Hankinson et al¹³ were used to estimate expected lung function values according to each participant's age, sex, and race. We assessed bronchodilator response after administering 360 μ g of albuterol sulfate hydrofluoroalkane from a standard metered-dose inhaler using an AeroChamber Plus Z STAT spacer (Monahan Medical, Plattsburgh, NY). Bronchodilator reversibility was measured as the percentage change in FEV₁ before and after albuterol administration.¹¹ We defined reversibility as an improvement in FEV₁ of 12% or greater after albuterol treatment. Each patient's smoking status was assessed on the staff-administered questionnaire by using questions from the National Health and Nutrition Examination Survey (www.cdc.gov/nchs/data/nhanes/nhanes_05_06/ft_smq_d.pdf).

Longitudinal information on asthma medication use (ie, ICSs and oral corticosteroids) and clinical events (ie, asthma-related ED visits and asthma-related hospitalizations) was available on all SAPPHIRE patients included in the analysis through electronic prescriptions, pharmacy claims, and encounter data routinely maintained by the health system. We have previously validated the clinical algorithms for detecting these events.¹⁴

Assessment of genetic ancestry

We isolated genomic DNA from whole-blood samples. Genotyping was performed on a Sequenom iPLEX platform (Sequenom, San Diego, Calif) for a set of previously validated ancestry informative markers (AIMs).¹⁵ For the purposes of this study, we used a subset of 59 markers that were informative for estimating West African (henceforth referred to as African) and European ancestry. The contribution of each marker for determining a subject's ancestry is based primarily on differences in allele frequency for that polymorphism between ancestral populations. As described in detail elsewhere,¹⁶ we estimated a single overall proportion of African ancestry for each study participant by using the program STRUCTURE, which analyzed the genotype calls at the 59 AIMs collectively. It was this single, individual-level estimate of overall African ancestry that was used in the regression models described below. Of note, because we assumed admixture from 2 ancestral populations (ie, African and European), the estimated proportion of European ancestry was 100% minus the percentage of African ancestry. Earlier studies have shown that 40 biallelic AIMs are sufficient to estimate individual ancestry with an SE of 0.1 or less when the study population consists of 2 admixed ancestral populations.¹⁷

Statistical analysis

We first calculated descriptive statistics for the 392 participants. These measures included means and SDs for continuously distributed variables (eg, proportion of African ancestry, age, and duration of asthma) and numbers and percentages for categorical variables (eg, sex and smoking status).

The primary outcome was a severe exacerbation defined as one of the following: burst use of oral corticosteroids, an asthma-related ED visit, or an asthma-related hospitalization. These have been recognized as the core measures for severe asthma exacerbations by the American Thoracic Society, the European Respiratory Society, and the National Institutes of Health.^{18,19} Because our primary exploratory variable was African ancestry, we restricted our analysis to subjects whose self-reported race was African American. We used negative binomial regression to regress the number of severe exacerbations on African ancestry. We selected negative binomial regression because this method allows for additional variance within defined groups (rather than assuming a fixed rate, λ); therefore it is robust to the presence of additional unmeasured explanatory variables.²⁰

Our first regression model (model 1) assessed the univariable relationship between African ancestry and exacerbations. Our next model (model 2) adjusted for potential confounders, including the patient's age, sex, percent predicted FEV₁, percentage of bronchodilator reversibility, smoking status (ie, indicator variables for current and past smoking compared with never smoking), ICS use at the time of initial evaluation, and age of asthma onset. Our third model (model 3) adjusted for all of the potential confounders previously mentioned but also included an interaction term between sex and ancestry (to assess for potential differences in the relationship between ancestry and exacerbations by sex). Given an apparent interaction by sex, we performed stratified analyses for the relationship between African ancestry and exacerbations among men and women separately. A relative rate (RR) of greater than 1 from the stratified analyses can be interpreted as increased likelihood of a severe exacerbation for the factor assessed; conversely, an RR of less than 1 can be interpreted as lower likelihood of a severe exacerbation. Our models estimated the RR for each percentage increase in African ancestry on the likelihood of severe exacerbation; parameter estimates from these models were rescaled to present the relationship for a 20% change in African ancestry in the tables. The stratified analyses also accounted for all of the potential confounders described above (with the exception of sex), and therefore all of the RRs presented are adjusted for these other variables.

Power estimations were based on the total available sample. We estimated the power of our negative binomial analysis using calculations for a case-control study estimating RRs. Accordingly, we assumed admixture was a binary variable split at 80% ancestry; this resulted in 79 male and 127 female subjects with less than 80% African ancestry and 66 male and 120 female subjects with 80% or greater African ancestry. We also assumed that the prevalence of the primary outcome was 12% in the group with lower African ancestry. This gave us 80% power to detect an RR of 2.8 for male subjects and an RR of 2.3 for female subjects with a 2-sided α level of .05.

We used the deviance statistic to measure the fit of the negative binomial model.²⁰ The approximate distribution of this statistic is χ^2 , and it was 62.3 with 136 *df* for male subjects and 204.8 with 238 *df* for female subjects. The associated *P* value for both male and female subjects was greater than .90, suggesting that model fit was adequate.

All analyses were performed with SAS version 9.2 software (SAS Institute, Cary, NC).²¹ We accepted a type 1 error rate of 5%, and therefore a *P* value of less than .05 was considered statistically significant.

RESULTS

Table 1 shows the characteristics of 392 self-identified African American subjects with asthma from the SAPPHIRE cohort. The average age of the study population was 31.2 years, but approximately two thirds (69.1%) had asthma since childhood. Nearly one third (32.4%) of patients demonstrated bronchodilator reversibility, and 18.1% had prescription fills suggesting the use of an ICS at the time of their initial visits. The estimated mean proportion of African ancestry among the African American participants was 76.1% (SD, 9.6%; range, 29.4% to 96.5%). This estimate of genetic African ancestry is consistent with other studies of African Americans in the United States.²²⁻²⁵

TABLE I. Characteristics of African American subjects from the SAPHIRE cohort with longitudinal clinical information (n = 392)*

Characteristic	
Proportion of African ancestry, mean $\pm$ SD (range)*	76.1 $\pm$ 9.6 (29.4-96.5)
Age (y), mean $\pm$ SD	31.2 $\pm$ 15.2
Female sex, no. (%)	247 (63.0)
Duration of asthma (y), mean $\pm$ SD	17.5 $\pm$ 12.5
Age of asthma onset, no. (%)	
Childhood onset (<18 y of age)	271 (69.1)
Adult onset ($\geq$ 18 y of age)	121 (30.9)
Smoking status, no. (%)	
Never	313 (79.8)
Past	40 (10.2)
Current	39 (9.9)
Percent predicted FEV ₁ , mean $\pm$ SD	89.6 $\pm$ 17.8
Bronchodilator reversibility (% change), mean $\pm$ SD	0.10 $\pm$ 0.12
Bronchodilator reversibility (>12%), no. (%)	127 (32.4)
ICS use, no. (%)	71 (18.1)

*Each study subject had a single estimate for proportion of African ancestry. This measure of global ancestry was determined by using 59 AIMs, as described in the Methods section. Shown is the average proportion of African ancestry across all study subjects (n = 392). Individual African ancestry ranged from 29.4% to 96.5%.

We next assessed the relationship between the proportion of African ancestry and the risk of an asthma exacerbation. In the initial unadjusted and adjusted analyses (Table II), we did not see a relationship between ancestry and asthma exacerbations ($P = .568$ and $P = .257$, respectively). However, we did observe a significant sex-ancestry interaction ($P = .010$), and after accounting for this interaction, the relationship between ancestry and asthma exacerbations was also statistically significant ($P = .009$). Not surprisingly, we observed a significant inverse association between measured percent predicted FEV₁ and exacerbations in both multivariable models. We also found a positive association between baseline ICS use and asthma exacerbations, as would be expected if subjects with more serious asthma were prescribed controller therapy.

Given the apparent interaction between ancestry and sex on asthma exacerbations, we repeated the analysis after stratifying by sex (Table III). Among male participants, the relative rate of a severe exacerbation was increased more than 4-fold for every 20% increase in the proportion of African ancestry (RR, 4.30; $P = .029$). Among female participants, there was not a significant relationship between ancestry and asthma exacerbations (RR, 0.92; $P = .678$). There was also a significant protective association between increasing FEV₁ and risk of exacerbation among women (RR, 0.82 per 10% increase in the measured percent predicted FEV₁; $P = .004$).

As an additional *post hoc* analysis, we included patient-reported passive smoke exposure as a separate covariate in our regression models. Inclusion of this variable did not significantly change any of the aforementioned associations (data not shown).

DISCUSSION

For the first time, we note a significant relationship between genetic ancestry and asthma exacerbations among African American men, such that the risk of a severe exacerbation appeared to

be 4 times greater for every 20% increase in African ancestry. In African American female subjects we did not observe a significant relationship between African ancestry and severe asthma exacerbations.

It is important to interpret our findings in the context of the epidemiology of asthma. First, based on national surveillance data from the United States, African American subjects have rates of asthma-related ED visits, hospitalizations, and death that are 2 to 3 times higher when compared with those of white subjects.²⁶ Second, the prevalence of asthma and wheezing differs by age and sex. Specifically, wheezing and asthma are more common in prepubescent boys when compared with girls; however, this pattern reverses by young adulthood.^{27,28} This pattern might be attributable to differences in lung growth and forced expiratory volume by age and sex²⁹ or possibly the influence of estrogen (endogenous or exogenous) on asthma risk.³⁰ These epidemiologic observations suggest that differences in asthma presentation by race-ethnicity and sex might be due to genetics or epistasis (ie, gene-gene interactions).

There are well-described differences in lung function^{13,31} and ICS use³²⁻³⁴ by race-ethnicity, and both of these factors are strongly associated with asthma exacerbations.^{35,36} Recently, we have shown African ancestry to be inversely associated with lung function in both men and women³⁷ but not associated with response to ICS medication.⁷ However, in the current study the relationship between genetic ancestry and asthma exacerbation was still present after accounting for differences in lung function and ICS use, suggesting that ancestry is an independent predictor of exacerbations. Flores et al³⁸ examined the relationship between ancestry and asthma diagnosis and found that African ancestry was significantly higher in African American subjects with asthma when compared with unaffected subjects. These investigators also examined the relationship between African ancestry and exacerbations but did not observe a significant association; however, exacerbations were ascertained based on patient self-report, and the study did not examine for differences in risk by sex.

Women and men might differ in their immune responses. For example, one group demonstrated that PBMCs isolated from women had greater IL-13 and IFN- γ production when exposed to rhinovirus compared with cells from age-matched men.³⁹ This might have implications for asthma exacerbations because many of these events are triggered by rhinovirus upper respiratory tract infections.⁴⁰ In addition, a number of other immunologic conditions, such as multiple sclerosis⁴¹ and systemic lupus erythematosus,⁴² differ by both sex and race-ethnicity. Research has demonstrated that these conditions also vary by genetic ancestry,⁴³ and investigators have begun to use this relationship to map for disease-related genes.⁴⁴

Our study had important limitations. First, the study was carried out at one site, and as a result, we might not be able to generalize our findings to other groups of African American subjects. Nevertheless, our study population had a similar admixture, as has been described for other African American groups throughout the United States.²² In addition, by studying one geographic area, our study might have been less susceptible to confounding by differences in ambient exposures. This is not to say subjects in our study could not have experienced different environmental exposures as a result of differences in ancestry. For example, African ancestry is associated with darker skin color,^{45,46} which might have resulted in discrimination and other untoward events that

TABLE II. Unadjusted and adjusted relationships between African ancestry and asthma exacerbations among African American participants in the SAPHIRE cohort

Variable	Model 1*		Model 2†		Model 3‡	
	Parameter estimate (β)§	P value	Parameter estimate (β)§	P value	Parameter estimate (β)§	P value
African ancestry	0.12	.568	0.24	.257	1.08	.009
Age			0.10	.312	0.08	.399
Female sex			0.29	.239	4.94	.010
Ancestry-sex interaction term					−5.94	.014
Childhood asthma onset			0.30	.290	0.29	.306
Current smoker			0.32	.327	0.43	.182
Past smoker			−0.11	.763	−0.04	.899
Percent predicted FEV ₁			−0.14	.041	−0.13	.052
Bronchodilator reversibility			0.16	.513	0.16	.528
ICS use			0.55	.032	0.57	.024

*Model 1 includes just the variable representing the proportion of African ancestry. The parameter estimate represents the effect of a 20% increase in African ancestry.

†Model 2 includes African ancestry as in model 1 but adjusts for all other variables shown. These variables include age (per 10-year increment), female sex (female = 1, male = 0), childhood asthma onset (<18 years = 1, ≥18 years = 0), smoking status (separate indicator variables for current smoking and past smoking = 1, never smoker = 0), percent predicted FEV₁ (per 10% increase), bronchodilator reversibility (>12% improvement in FEV₁ = 1, ≤12% = 0), and ICS use at the time of study enrollment assessed by pharmacy fill data (yes = 1, no = 0).

‡Model 3 includes all covariates included in models 1 and 2 but also includes an interaction term between African ancestry and sex (coded as described above).

§Parameter estimates are of the form $y = \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_i x_i + \beta_{int} x_1 x_2$, where y represents the number of exacerbations, x_i represents the independent variable of interest, β_i represents the effect estimate for that independent variable, and β_{int} represents the effect estimate for the interaction of 2 of the covariates. Parameter estimates of greater than 0 indicate a positive association between the factor and the likelihood of an asthma exacerbation, and parameter estimates of less than 0 indicate an inverse association between the factor and the likelihood of an exacerbation.

TABLE III. Adjusted relationship between African ancestry and asthma exacerbations among African American participants in the SAPHIRE cohort stratified by sex

Variable	Male subjects (n = 145)		Female subjects (n = 247)	
	Adjusted RR (95% CI)*	P value	Adjusted RR (95% CI)*	P value
African ancestry	4.30 (1.16-15.88)	.029	0.92 (0.61-1.39)	.678
Age	1.42 (0.87-2.33)	.166	1.02 (0.83-1.25)	.841
Asthma duration	1.02 (0.19-5.51)	.984	1.39 (0.80-2.40)	.239
Current smoker	2.40 (0.42-13.75)	.325	1.41 (0.74-2.68)	.297
Past smoker	0.33 (0.04-3.04)	.331	1.16 (0.60-2.27)	.658
Percent predicted FEV ₁	1.09 (0.74-1.62)	.660	0.82 (0.71-0.94)	.004
Bronchodilator reversibility	2.08 (0.61-7.06)	.239	1.02 (0.62-1.71)	.925
ICS use	1.92 (0.60-6.18)	.275	1.61 (0.93-2.78)	.087

*Models are adjusted for all of the following variables: African ancestry (per 20% increase in African ancestry), age (per 10-year increment), childhood asthma onset (<18 years of age = 1, ≥18 years of age = 0), smoking status (separate indicator variables for current smoking and past smoking = 1, never smoker = 0), percent predicted FEV₁ (per 10% increase), bronchodilator reversibility (>12% improvement in FEV₁ = 1, ≤12% = 0), and ICS use at the time of study enrollment assessed by pharmacy fill data (yes = 1, no = 0).

varied proportionally to the latter.⁴⁷ However, if our findings were confounded by a relationship between these external exposures (eg, discrimination) and ancestry, we would have expected to see an association in both men and women.

Second, we used only 59 AIMs to estimate ancestry. Although earlier studies have indicated that as few as 40 AIMs are sufficient for estimating ancestry in groups with primarily 2 admixed ancestral populations,¹⁷ greater numbers of AIMs might improve the precision of the estimate and current methods can use data derived from genome-wide arrays.⁴⁸ Yet this imprecision or misclassification would have likely resulted in our underestimating the true effect of ancestry. Unfortunately, these individual-level estimates of global ancestry do not allow us to localize specific

chromosomal regions where ancestry is associated with exacerbations.

A final limitation is that we did not reassess our findings in a replication population of African American subjects. This was due, in part, to the somewhat unique combination of data available for our study population, a well-characterized, diverse cohort with near-complete capture of longitudinal clinical outcomes. For example, in an earlier study of asthma medication use, we showed that we could capture greater than 99% of prescriptions filled by our covered patient population.⁴⁹

In summary, we found a significant and independent association between genetic ancestry and severe exacerbations among male African American subjects with asthma. To our knowledge, this is the first report of such an association, and it suggests that at least part of the risk of asthma exacerbations is genetic and partitions with ancestry. Our findings also suggest that analytic approaches, such as admixture mapping, might help uncover and localize these genetic determinants.⁵⁰ The importance of identifying and understanding the predictors of these potentially life-threatening complications cannot be understated, especially given their frequency and the large and persisting disparities by race-ethnicity.

Clinical implications: This study suggests that there is a genetic contribution to asthma exacerbations, which might be identifiable by using approaches that measure and account for individual admixture.

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