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## Genetic ancestry and its association with asthma exacerbations among African American patients with asthma

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### Abstract

**Background**—There are large and persisting disparities in severe asthma exacerbations by race-ethnicity, and African American individuals are among those at greatest risk. It is unclear whether this increased risk solely represents differences in environmental exposures and health care, or whether there is a predisposing genetic component.

**Objective**—To assess the relationship between genetic ancestry and severe exacerbations among African American individuals with asthma.

**Methods**—Participants were part of the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE). These individuals were 12–56 years of age; received care from a single, large health system; and had a physician diagnosis of asthma. Genetic ancestry was estimated using a set of validated ancestry informative markers. Severe exacerbations (i.e., asthma-related emergency department visits, hospitalizations, and burst oral steroid use) were prospectively identified from health care claims.

**Results**—We assessed genetic ancestry in 392 African American individuals with asthma. The average proportion of African ancestry was 76.1%. A significant interaction was identified between ancestry and sex on severe exacerbations, such that the risk was significantly higher with increasing African ancestry among males but not among females. The association among males

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persisted after adjusting for potential confounders (relative risk of 4.30 for every 20% increase in African ancestry; P-value 0.029).

**Conclusions**—African ancestry was a significantly and positively associated with severe exacerbations among African American males. These findings suggest that a portion of the risk of asthma exacerbations in this high risk group is attributable to a genetic risk factor which partitions with ancestry.

### Key words(MeSH terms)

asthma; continental population groups; African continental ancestry group; genetic association study; health status disparities; minority health

## INTRODUCTION

Asthma accounts for approximately 14 million days of missed school and 100 million days of restricted activity yearly,<sup>(1)</sup> and direct medical expenditures for asthma exceed \$37 billion annually.<sup>(2)</sup> As much as 43% of these costs may be attributable to asthma exacerbations.<sup>(3)</sup> Moreover, the burden of asthma is not shared equally among groups. For example, in 1999 the prevalence of self-reported asthma among African American individuals was 42.7 per 1000 as compared with a prevalence of 37.6 per 1000 among white individuals.<sup>(4)</sup> But even more dramatic were the differences in asthma-related ED visits, hospitalizations, and death, which showed rates up to 3–5 times higher in African American patients when compared with white patients.<sup>(4–6)</sup>

We have previously showed that response to inhaled corticosteroids does not appear to differ by race-ethnicity or by genetic ancestry,<sup>(7)</sup> and we have shown that race-ethnicity appears to still be a risk factor for asthma exacerbations even accounting for asthma controller medication use and the level of adherence.<sup>(8)</sup> In addition, recent genome wide association studies have demonstrated differences in the genetic predictors of asthma by race-ethnicity.<sup>(9;10)</sup> Therefore, it is reasonable to speculate that differences in asthma exacerbation rates may also have a genetic underpinning.

To assess for the possibility of genetic determinants of asthma exacerbations which differ by race-ethnicity, we examine whether genetic African ancestry is an independent predictor of asthma exacerbations among African American participants in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE). This cohort represents one of the largest and best characterized groups of patients with asthma in the U.S. with detailed longitudinal clinical information.

## METHODS

### Study Population

This study was approved by the institutional review board of Henry Ford Health System. The SAPPHIRE is an ongoing longitudinal cohort study of patients with asthma which has been described in detail elsewhere.<sup>(7;10)</sup> Patients were eligible for inclusion if they fulfill the following requirement: age between 12–56 years; a physician 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 which included the completion of a staff-administered questionnaire, pulmonary function testing, assessment of bronchodilator response, and the collection of blood samples. Spirometry was performed according to current 2005 ATS/ERS recommendations.<sup>(11;12)</sup> Predictive equations from Hankinson et al.

were used to estimate expected lung function values according to each participant's age, sex, and race.<sup>(13)</sup> We assessed bronchodilator response after administering 360 $\mu$ g of albuterol sulfate hydrofluoroalkane from a standard metered dose inhaler (MDI) using an AeroChamber Plus® Z STAT spacer (Monahan Medical Corp., Plattsburgh, NY). Bronchodilator reversibility was measured as the percent change in forced expiratory volume at one second (FEV<sub>1</sub>) pre- and post- albuterol administration.<sup>(11)</sup> We defined reversibility as an improvement in FEV<sub>1</sub> of 12% or greater following the albuterol treatment. Patient smoking status was assessed on the staff-administered questionnaire using questions from the National Health and Nutrition Examination Survey ([www.cdc.gov/nchs/data/nhanes/nhanes\\_05\\_06/fi\\_smq\\_d.pdf](http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/fi_smq_d.pdf)).

Longitudinal information on asthma medication use (i.e., inhaled corticosteroids [ICS] and oral corticosteroids) and clinical events (i.e., asthma-related emergency department (ED) visit and asthma-related hospitalizations) was available on all SAPPHERE patients included in analysis through electronic prescription, pharmacy claims, and encounter data routinely maintained by the health system. We have previously validated the clinical algorithms for detecting these events.<sup>(14)</sup>

### Assessment of Genetic Ancestry

We isolated genomic DNA from whole blood samples. Genotyping was performed on a Sequenom iPLEX® platform (Sequenom, Inc., San Diego, CA) for a set of previously validated ancestry informative markers (AIMs).<sup>(15)</sup> For the purposes of this study we used a subset of 59 markers which were informative for estimating West African (henceforth referred to as African) and European ancestry. The contribution of each marker for determining an individual's ancestry is based primarily on differences in allele frequency for that polymorphism between ancestral populations. As described in detail elsewhere,<sup>(16)</sup> we estimated a single, overall proportion of African ancestry for each study participant 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 which was used in the regression models described below. Of note, since we assumed admixture from two ancestral populations (i.e., African and European), the estimated proportion of European ancestry was 100% minus the percent African ancestry. Earlier studies have shown that 40 biallelic AIMs are sufficient to estimate individual ancestry with a standard error  $\leq 0.1$  when the study population consists of two admixed ancestral populations.<sup>(17)</sup>

### Statistical analysis

We first calculated descriptive statistics for the 392 participants. These measures included mean and standard deviation for continuously distributed variables (e.g., proportion of African ancestry, age, and duration of asthma) and number and percentage for categorical variables (e.g., 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.<sup>(18;19)</sup> As our primary exploratory variable was African ancestry, we restricted our analysis to individuals 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 as this method allows for additional variance within defined groups (rather than assuming a fixed rate,  $\lambda$ ); therefore, it is robust to the presence of additional unmeasured explanatory variables.<sup>(20)</sup>

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 patient age, sex, percent of predicted for measured FEV<sub>1</sub>, percent of bronchodilator reversibility, smoking status (i.e., indicator variables for current and past smoking as compared with never), inhaled corticosteroid use at the time of initial evaluation, and the 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 (i.e., so as 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) >1 from the stratified analyses can be interpreted as the increased likelihood of a severe exacerbation for the factor assessed (conversely, a RR <1 can be interpreted as a lower likelihood for 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 in order 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 RR presented are adjusted for these other variables.

Power estimations were based on the total available sample. We estimated the power for our negative binomial analysis using calculations for a case-control study estimating RR. Accordingly, we assumed admixture was a binary variable split at 80% ancestry; this resulted in 79 males and 127 females with <80% African ancestry and 66 males and 120 females with 80% African ancestry. We also assumed that the prevalence of the primary outcome was 12% in the lower African ancestry group. This gave us 80% power to detect a RR of 2.8 for males and a RR of 2.3 for females with a two-sided alpha level of 0.05.

We used the deviance statistic to measure fit of the negative binomial model.<sup>(20)</sup> The approximate distribution of this statistic is chi-squared, and it was 62.3 with 136 degrees of freedom for males and 204.8 with 238 degrees of freedom for females. The associated p-value for both males and females was >0.90, suggesting that model fit was adequate.

All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).<sup>(21)</sup> We accepted a type-1 error rate of 5%; therefore, a P-value <0.05 was considered statistically significant.

## RESULTS

Table 1 shows the characteristics of 392 self-identified African American individuals with asthma from the SAPPHERE cohort. The average age of the study population 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 ICS medication at the time of their initial visits. The estimated mean proportion of African ancestry among the African American participants was 76.1% (standard deviation, 9.6%; range, 29.4% – 96.5%). This estimate of genetic African ancestry is consistent with other studies of African Americans in the U.S.<sup>(22–25)</sup>

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 2), we did not see a relationship between ancestry and asthma exacerbations (P-value = 0.568 and P-value = 0.257, respectively). However, we did observe a significant sex by ancestry interaction (P-value = 0.010), and after accounting for this interaction the relationship between ancestry and asthma exacerbations was also statistically significant (P=0.009). Not surprisingly, we

observed a significant inverse association between measured percent of predicted FEV<sub>1</sub> and exacerbations in both multivariable models. We also found a positive association between baseline ICS use and asthma exacerbations, as would be expected if individuals 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. Among male participants, the relative rate of a severe exacerbation was increased over four-fold for every 20% increase in the proportion of African ancestry (RR 4.30; P-value 0.029). Among female participants, there was not a significant relationship between ancestry and asthma exacerbations (RR 0.92, P-value 0.678). There was also a significant protective association between increasing FEV<sub>1</sub> and risk of exacerbation among women (RR 0.82 per 10% increase in the measured FEV<sub>1</sub> expressed as percent of predicted, P-value = 0.004).

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

We note for the first time a significant relationship between genetic ancestry and asthma exacerbations among African American men, such that the risk of a severe exacerbation appeared to be four times greater for every 20% increase in African ancestry. In African American females, 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 U.S., African American individuals have rates of asthma-related emergency room visits, hospitalizations, and death that are 2–3 times higher when compared with white individuals.<sup>(26)</sup> Second, the prevalence of asthma and wheezing changes 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.<sup>(27;28)</sup> This pattern may be attributable to differences in lung growth and forced expiratory volume by age and sex,<sup>(29)</sup> or possibly the influence of estrogen (endogenous or exogenous) on asthma risk.<sup>(30)</sup> These epidemiologic observations suggest that differences in asthma presentation by race- ethnicity and sex may be due to genetics or epistasis (i.e., gene-gene interactions).

There are well described differences in lung function<sup>(13;31)</sup> and inhaled corticosteroid (ICS) use<sup>(32–34)</sup> by race-ethnicity, and both of these factors are strongly associated with asthma exacerbations.<sup>(35;36)</sup> Recently we have shown African ancestry to be inversely associated with lung function in both men and women,<sup>(37)</sup> but not associated with response to ICS medication.<sup>(7)</sup> However, in the current study, the relationship between genetic ancestry and asthma exacerbations was still present after accounting for differences in lung function and ICS use, suggesting that ancestry is an independent predictor of exacerbations. Flores and colleagues examined the relationship between ancestry and asthma diagnosis and found that African ancestry was significantly higher in African American individuals with asthma when compared to unaffected individuals.<sup>(38)</sup> These investigators also examined the relationship between African ancestry and exacerbations but did not observe a significant association; however, exacerbations were ascertained by patient self-report and the study did not examine for differences in risk by sex.

Women and men may differ in their immune responses. For example, one group demonstrated that peripheral blood mononuclear cells isolated from women had greater

interleukin-13 and interferon- $\gamma$  production when exposed to rhinovirus when compared with cells from age-matched men.<sup>(39)</sup> This may have implications for asthma exacerbations, since many of these events are triggered by rhinovirus upper respiratory tract infections.<sup>(40)</sup> In addition, a number of other immunologic conditions, such as multiple sclerosis<sup>(41)</sup> and systemic lupus erythematosus,<sup>(42)</sup> differ by both sex and race-ethnicity. Research has demonstrated that these conditions also vary by genetic ancestry,<sup>(43)</sup> and investigators have begun to use this relationship to map for disease-related genes.<sup>(44)</sup>

Our study had important limitations. First, our study was carried out at one site, and as a result our finding we may not be able to generalize our findings to other groups of African American individuals. Nevertheless, our study population had a similar admixture as has been described for other African American groups throughout the U.S.<sup>(22)</sup> In addition, by studying one geographic area, our study may have been less susceptible to confounding by differences in ambient exposures. This is not to say individuals in our study couldn't have experienced different environmental exposures as a result of differences in ancestry. For example, African ancestry is associated with darker skin color,<sup>(45;46)</sup> which may have resulted in discrimination and other untoward events which varied proportionally to the latter.<sup>(47)</sup> However, if our findings were confounded by a relationship between these external exposures (e.g., 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. While earlier studies have indicated that as few as 40 AIMs are sufficient for estimating ancestry in groups with primarily two admixed ancestral populations,<sup>(17)</sup> greater numbers of AIMs may improve the precision of the estimate and current methods can use data derived from genome wide arrays.<sup>(48)</sup> 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 individuals. 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 >99% of prescriptions filled by our covered patient population.<sup>(49)</sup>

In summary, we found a significant and independent association between genetic ancestry and severe exacerbations among African American males with asthma. To our knowledge this 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 may help uncover and localize these genetic determinants.<sup>(50)</sup> 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.

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## Abbreviations

<b>AIM</b>	ancestry informative marker
<b>FEV<sub>1</sub></b>	forced expiratory volume at one second
<b>ICS</b>	inhaled corticosteroid
<b>RR</b>	relative risk
<b>SAPPHIRE</b>	Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity

## References

1. Self-reported asthma prevalence and control among adults--United States, 2001. *MMWR Morb Mortal Wkly Rep.* 2003; 52(17):381–4. [PubMed: 12765201]
2. Kamble S, Bharmal M. Incremental direct expenditure of treating asthma in the United States. *J Asthma.* 2009; 46(1):73–80. [PubMed: 19191142]
3. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. *N Engl J Med.* 1992; 326(13):862–6. [PubMed: 1542323]
4. Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma--United States, 1980–1999. *MMWR Surveill Summ.* 2002; 51(1):1–13.
5. Miller JE. The effects of race/ethnicity and income on early childhood asthma prevalence and health care use. *Am J Public Health.* 2000; 90(3):428–30. [PubMed: 10705865]
6. Asthma mortality and hospitalization among children and young adults--United States, 1980–1993. *MMWR Morb Mortal Wkly Rep.* 1996; 45(17):350–3. [PubMed: 8604212]
7. Gould W, Peterson EL, Karungi G, Zoratti A, Gaggin J, Toma G, et al. Factors predicting inhaled corticosteroid responsiveness in African American patients with asthma. *J Allergy Clin Immunol.* 2010; 126(6):1131–8. [PubMed: 20864153]
8. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol.* 2011; 128(6):1185–91. [PubMed: 22019090]
9. Sleiman PM, Flory J, Imielinski M, Bradfield JP, Annaiah K, Willis-Owen SA, et al. Variants of DENND1B Associated with Asthma in Children. *N Engl J Med.* 2009
10. Torgerson DG, Ampleford EJ, Chiu GY, Gauderman WJ, Gignoux CR, Graves PE, et al. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nat Genet.* 2011; 43(9):887–92. [PubMed: 21804549]
11. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J.* 2005; 26(2):319–38. [PubMed: 16055882]
12. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. *Eur Respir J.* 2005; 26(1):153–61. [PubMed: 15994402]
13. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999; 159(1):179–87. [PubMed: 9872837]
14. Williams LK, Peterson EL, Wells K, Campbell J, Wang M, Chowdhry VK, et al. A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. *J Allergy Clin Immunol.* 2010; 126(2):225–31. 231. [PubMed: 20569973]
15. Yaeger R, vila-Bront A, Abdul K, Nolan PC, Grann VR, Birchette MG, et al. Comparing genetic ancestry and self-described race in african americans born in the United States and in Africa. *Cancer Epidemiol Biomarkers Prev.* 2008; 17(6):1329–38. [PubMed: 18559547]
16. Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. *Genetics.* 2000; 155(2):945–59. [PubMed: 10835412]
17. Hoggart CJ, Parra EJ, Shriver MD, Bonilla C, Kittles RA, Clayton DG, et al. Control of confounding of genetic associations in stratified populations. *Am J Hum Genet.* 2003; 72(6):1492–504. [PubMed: 12817591]



18. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med.* 2009; 180(1):59–99. [PubMed: 19535666]
19. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA, Gern J, et al. Asthma Outcomes: Exacerbations. *J Allergy Clin Immunol.* 2012; 129(3):S34–S48.
20. Simonoff, JS. *Analyzing categorical data.* New York: Springer; 2003.
21. SAS Institute Inc. *SAS/STAT Users Guide.* Cary, NC: SAS Institute Inc; 2008. Version 9.2 ed
22. Parra EJ, Marcini A, Akey J, Martinson J, Batzer MA, Cooper R, et al. Estimating African American admixture proportions by use of population-specific alleles. *Am J Hum Genet.* 1998; 63(6):1839–51. [PubMed: 9837836]
23. Tsai HJ, Kho JY, Shaikh N, Choudhry S, Naqvi M, Navarro D, et al. Admixture-matched case-control study: a practical approach for genetic association studies in admixed populations. *Hum Genet.* 2006; 118(5):626–39. [PubMed: 16273390]
24. Tishkoff SA, Reed FA, Friedlaender FR, Ehret C, Ranciaro A, Froment A, et al. The genetic structure and history of Africans and African Americans. *Science.* 2009; 324(5930):1035–44. [PubMed: 19407144]
25. Bryc K, Auton A, Nelson MR, Oksenberg JR, Hauser SL, Williams S, et al. Genome-wide patterns of population structure and admixture in West Africans and African Americans. *Proc Natl Acad Sci U S A.* 2010; 107(2):786–91. [PubMed: 20080753]
26. Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, et al. National surveillance for asthma—United States, 1980–2004. *MMWR Surveill Summ.* 2007; 56(8):1–54. [PubMed: 17947969]
27. Venn A, Lewis S, Cooper M, Hill J, Britton J. Questionnaire study of effect of sex and age on the prevalence of wheeze and asthma in adolescence. *BMJ.* 1998; 316(7149):1945–6. [PubMed: 9641931]
28. Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. *Thorax.* 1992; 47(7):537–42. [PubMed: 1412098]
29. Hibbert M, Lannigan A, Raven J, Landau L, Phelan P. Gender differences in lung growth. *Pediatr Pulmonol.* 1995; 19(2):129–34. [PubMed: 7659468]
30. Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. *Am J Respir Crit Care Med.* 1995; 152(4 Pt 1):1183–8. [PubMed: 7551368]
31. Zhang Y, McConnell R, Gilliland F, Berhane K. Ethnic differences in the effect of asthma on pulmonary function in children. *Am J Respir Crit Care Med.* 2011; 183(5):596–603. [PubMed: 20889910]
32. Apter AJ, Boston RC, George M, Norfleet AL, Tenhave T, Coyne JC, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. *J Allergy Clin Immunol.* 2003; 111(6):1219–26. [PubMed: 12789220]
33. Williams LK, Joseph CL, Peterson EL, Moon C, Xi H, Krajenta R, et al. Race-ethnicity, crime, and other factors associated with adherence to inhaled corticosteroids. *J Allergy Clin Immunol.* 2007; 119(1):168–75. [PubMed: 17208598]
34. Wells K, Pladevall M, Peterson EL, Campbell J, Wang M, Lanfear DE, et al. Race-ethnic differences in factors associated with inhaled steroid adherence among adults with asthma. *Am J Respir Crit Care Med.* 2008; 178(12):1194–201. [PubMed: 18849496]
35. Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, et al. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol.* 2001; 107(1):61–7. [PubMed: 11149992]
36. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *The Journal of Allergy and Clinical Immunology.* 2004; 114(6):1288–93. [PubMed: 15577825]
37. Kumar R, Seibold MA, Aldrich MC, Williams LK, Reiner AP, Colangelo L, et al. Genetic ancestry in lung-function predictions. *N Engl J Med.* 2010; 363(4):321–30. [PubMed: 20647190]

38. Flores C, Ma SF, Pino-Yanes M, Wade MS, Perez-Mendez L, Kittles RA, et al. African ancestry is associated with asthma risk in African Americans. *PLoS One*. 2012; 7(1):e26807. [PubMed: 22235241]
39. Carroll ML, Yerkovich ST, Pritchard AL, Davies JM, Upham JW. Adaptive immunity to rhinoviruses: sex and age matter. *Respir Res*. 2010; 11:184. [PubMed: 21194432]
40. Johnston SL, Pattemore PK, Sanderson G, Smith S, Campbell MJ, Josephs LK, et al. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *Am J Respir Crit Care Med*. 1996; 154(3 Pt 1):654–60. [PubMed: 8810601]
41. Wallin MT, Page WF, Kurtzke JF. Multiple sclerosis in US veterans of the Vietnam era and later military service: race, sex, and geography. *Ann Neurol*. 2004; 55(1):65–71. [PubMed: 14705113]
42. Bae SC, Fraser P, Liang MH. The epidemiology of systemic lupus erythematosus in populations of African ancestry: a critical review of the “prevalence gradient hypothesis”. *Arthritis Rheum*. 1998; 41(12):2091–9. [PubMed: 9870865]
43. Molokhia M, Hoggart C, Patrick AL, Shriver M, Parra E, Ye J, et al. Relation of risk of systemic lupus erythematosus to west African admixture in a Caribbean population. *Hum Genet*. 2003; 112(3):310–8. [PubMed: 12545274]
44. Reich D, Patterson N, De Jager PL, McDonald GJ, Waliszewska A, Tandon A, et al. A whole-genome admixture scan finds a candidate locus for multiple sclerosis susceptibility. *Nat Genet*. 2005; 37(10):1113–8. [PubMed: 16186815]
45. Parra EJ, Kittles RA, Shriver MD. Implications of correlations between skin color and genetic ancestry for biomedical research. *Nat Genet*. 2004; 36(11 Suppl):S54–S60. [PubMed: 15508005]
46. Shriver MD, Parra EJ, Dios S, Bonilla C, Norton H, Jovel C, et al. Skin pigmentation, biogeographical ancestry and admixture mapping. *Hum Genet*. 2003; 112(4):387–99. [PubMed: 12579416]
47. Krieger N, Sidney S, Coakley E. Racial discrimination and skin color in the CARDIA study: implications for public health research. *Coronary Artery Risk Development in Young Adults*. *Am J Public Health*. 1998; 88(9):1308–13. [PubMed: 9736868]
48. Price AL, Tandon A, Patterson N, Barnes KC, Rafaels N, Ruczinski I, et al. Sensitive detection of chromosomal segments of distinct ancestry in admixed populations. *PLoS Genet*. 2009; 5(6):e1000519. [PubMed: 19543370]
49. Williams LK, Joseph CL, Peterson EL, Wells K, Wang M, Chowdhry VK, et al. Patients with asthma who do not fill their inhaled corticosteroids: a study of primary nonadherence. *J Allergy Clin Immunol*. 2007; 120(5):1153–9. [PubMed: 17936894]
50. McKeigue PM. Prospects for admixture mapping of complex traits. *Am J Hum Genet*. 2005; 76(1): 1–7. [PubMed: 15540159]

### **Clinical implications**

This study suggests that there is a genetic contribution to asthma exacerbations which may be identifiable using approaches that measure and account for individual admixture.

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**Table 1**

Characteristics of African American patients from the SAPPHIRE cohort with longitudinal clinical information (n = 392)\*

Characteristic	
Proportion of African ancestry – mean ± SD (range)*	76.1 ± 9.6 (29.4 – 96.5)
Age in years – mean ± SD	31.2 ± 15.2
Female sex – no. (%)	247 (63.0)
Duration of asthma in years – mean ± SD	17.5 ± 12.5
Age of asthma onset – no. (%)	
Childhood onset (<18 years of age)	271 (69.1)
Adult onset (≥ 18 years of age)	121 (30.9)
Smoking status – no. (%)	
Never	313 (79.8)
Past	40 (10.2)
Current	39 (9.9)
Percent of predicted FEV <sub>1</sub> – mean ± SD	89.6 ± 17.8
Bronchodilator reversibility (percent change) – mean ± SD	0.10 ± 0.12
Bronchodilator reversibility (>12%) – no. (%)	127 (32.4)
Inhaled corticosteroid use – no. (%)	71 (18.1)

SAPPHIRE denotes the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity; standard deviation, SD; and forced expiratory volume in one second, FEV<sub>1</sub>.

\* Each study individual had a single estimate for proportion of African ancestry. This individual measure of global ancestry was determined using 59 ancestry informative markers as described in the methods. Shown is the average proportion of African ancestry across all study individuals (n = 392). Individual African ancestry ranged from 29.4% to 96.5%.

Table 2

Unadjusted and adjusted relationship between African ancestry and asthma exacerbations among African American participants in the SAPPHERE cohort.

Variable	Model 1 <sup>†</sup>		Model 2 <sup>‡</sup>		Model 3 <sup>§</sup>	
	Parameter estimate (β) <sup>*</sup>	P-value	Parameter estimate (β) <sup>*</sup>	P-value	Parameter estimate (β) <sup>*</sup>	P-value
African ancestry	0.12	0.568	0.24	0.257	1.08	0.009
Age			0.10	0.312	0.08	0.399
Female sex			0.29	0.239	4.94	0.010
Ancestry by sex interaction term					-5.94	0.014
Childhood asthma onset			0.30	0.290	0.29	0.306
Current smoker			0.32	0.327	0.43	0.182
Past smoker			-0.11	0.763	-0.04	0.899
Percent of predicted FEV <sub>1</sub>			-0.14	0.041	-0.13	0.052
Bronchodilator reversibility			0.16	0.520	0.16	0.528
Inhaled corticosteroid use			0.55	0.032	0.57	0.024

SAPPHERE denotes the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity and forced expiratory volume in one second, FEV<sub>1</sub>.

<sup>\*</sup> Parameter estimates are of the form  $y = \beta_1x_1 + \beta_2x_2 + \dots + \beta_jx_j + \beta_{int}x_1x_2$ , where  $y$  represents the number of exacerbations;  $x_j$  the independent variable of interest,  $\beta_j$  the effect estimate for that independent variable, and  $\beta_{int}$  the effect estimate for the interaction of two of the covariates. Parameter estimates >0 indicate a positive association between the factor and the likelihood of an asthma exacerbation, and parameter estimates <0 indicate an inverse association between the factor and the likelihood of an exacerbation.

<sup>†</sup> 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.

<sup>‡</sup> 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 of predicted FEV<sub>1</sub> (per 10% increase); bronchodilator reversibility (>12% improvement in FEV<sub>1</sub> = 1, 12% = 0); and inhaled corticosteroid use at the time of study enrollment – assessed by pharmacy fill data (yes = 1, no = 0).

<sup>§</sup> 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).

**Table 3**

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

Variable	Males (n = 145)		Females (n = 247)	
	aRR (95% CI)*	P-value	aRR (95% CI)*	P-value
African ancestry	4.30 (1.16, 15.88)	0.029	0.92 (0.61, 1.39)	0.678
Age	1.42 (0.87, 2.33)	0.166	1.02 (0.83, 1.25)	0.841
Asthma duration	1.02 (0.19, 5.51)	0.984	1.39 (0.80, 2.40)	0.239
Current smoker	2.40 (0.42, 13.75)	0.325	1.41 (0.74, 2.68)	0.297
Past smoker	0.33 (0.04, 3.04)	0.331	1.16 (0.60, 2.27)	0.658
Percent of predicted FEV <sub>1</sub>	1.09 (0.74, 1.62)	0.660	0.82 (0.71, 0.94)	0.004
Bronchodilator reversibility	2.08 (0.61, 7.06)	0.239	1.02 (0.62, 1.71)	0.925
Inhaled corticosteroid use	1.92 (0.60, 6.18)	0.275	1.61 (0.93, 2.78)	0.087

SAPPHIRE denotes the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity; aRR, adjusted relative rate; and forced expiratory volume in one second, FEV<sub>1</sub>.

\* 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 = 1, 18 years = 0); smoking status (separate indicator variables for current smoking and past smoking = 1, never smoker = 0); percent of predicted FEV<sub>1</sub> (per 10% increase); bronchodilator reversibility (>12% improvement in FEV<sub>1</sub> = 1, 12% = 0); and inhaled corticosteroid use at the time of study enrollment – assessed by pharmacy fill data (yes = 1, no = 0).