

Ancestry, ancestry-informative markers, asthma, and the quest for personalized medicine

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Conventional wisdom regarding the ultimate utility of human genome discoveries in common complex diseases such as asthma is that with the discovery of genetic polymorphisms that track with specific clinical traits, genetic profiling for personalized medicine will eventually be realized and lead to improvements in the prognosis and prediction of disease in the clinical setting.¹ Acknowledging that few such discoveries have resulted in reliably predictive tests thus far, beyond some of the Mendelian disorders (ie, Huntington disease and phenylketonuria) and perhaps a handful of common diseases (ie, hypertriglyceridemia and age-related macular degeneration), genome-based prediction of common diseases like asthma is nevertheless anticipated in the long-term.² The tremendous investment committed to the field of asthma genetics over the past 2 decades, spanning from the early linkage and candidate gene studies in the early 1990s and into the 21st century to the dozen or so asthma genome-wide association studies performed in just the past few years, is testimony to our confidence in the “gene hunters.”

It is well established and has been demonstrated year after year in survey after survey that asthmatic subjects of African descent have greater asthma morbidity and mortality than white subjects,³ but the extent to which genetic variation contributes to these profound racial and ethnic disparities has not been so clear. Reports of increases in the prevalence and severity of asthma according to African ancestry outside of the United States^{4,5} further support a role for a genetic contribution that is dictated, at least in part, by one's biogeography. Although race and ethnicity are undeniably social constructs reflective of an individual's self-ascribed socio-cultural, psychological, behavioral, and biological identity, the striking racial and ethnic disparities in disease prevalence and severity for common complex disorders, such as asthma, cannot be explained entirely by “nongenetic” factors.⁶ Indeed, however one chooses (or chooses not) to define the biological construct of race,⁷ in the case of asthma, substantial variation in frequencies of high-risk genetic variants according to ancestry has been well established.⁶ This has been of special interest in the field of pharmacogenetics, in which genetic variation in response to treatment according to self-reported race/ethnicity is suspected.

The basis for this suspicion is sound: in addition to differences in frequencies of genetic variants associated with response to asthma medications (eg, response to long-acting β -agonists and Arg16Gly in *ADRB2*), a number of clinical trials have also shown differences according to race and ethnicity in asthma medication responsiveness, such as the Salmeterol Multicenter Asthma Research Trial.⁸ Others have attempted to draw a direct line between race and ethnicity in genetic associations in candidate genes and response to therapy, with mixed results.⁹

An efficient approach to testing the potential role of genetics in disease causation in situations in which there are differences in prevalence, severity, or response to therapy according to continental ancestry is to determine the association between estimated genetic admixture and the phenotype of interest. Genetic ancestry is a “global” concept that refers to the biological architecture of genome variation between populations and can be estimated by using ancestry-informative markers (AIMs). AIMs are unlinked, usually biallelic (single nucleotide polymorphism) markers with high allele frequency differences between ancestral populations (ie, continental Africans and European whites) and are commonly used to estimate the average ancestral proportions for major source populations in admixed groups (ie, African Americans) so that adjustments can be made for confounding caused by population stratification or admixture.² AIMs can also be used to estimate individual- and population-level ancestry to assess the role of ancestry in disease. This approach has already been used successfully in traits for which racial and ethnic disparities are known to exist, including risk of asthma^{10,11} and, most recently, lung function predictions.¹² To date, however, the effect of genetic ancestry in response to asthma medications has not been reported.

Anti-inflammatory medications, especially inhaled corticosteroids (ICSs), are considered the cornerstone to long-term disease management and control of asthma. Unfortunately, there is a long-standing observation that African Americans are less sensitive to ICSs compared with other groups of patients. The study by Gould et al¹³ in this issue of the *Journal* is the first to test for the relationship between African ancestry and response to ICS use. In one of the largest and most exquisitely characterized cohorts of asthmatic patients enrolled in a 6-week ICS treatment trial, 147 self-reporting African Americans living in Detroit, Michigan, and participating in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity (SAPPHIRE) were evaluated for steroid responsiveness measured as a change in FEV₁ over the 6-week period. Gould et al genotyped 107 carefully selected AIMs representing 3 racial groups (West African, European, and Native American), determined individual ancestry using conventional statistical approaches, and tested whether ICS response is related to genetic ancestry at the global level, adjusting for various confounders, such as age, sex, body mass index, income, education, smoke exposure, and other asthma-associated outcomes. The group failed, however, to observe a

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relationship between African ancestry and response to ICSs, although they did observe an association between the degree of baseline bronchodilator reversibility and ICS response.

Gould et al¹³ reasonably concluded that global genetic ancestry might not be responsible for the differences observed in the way African Americans respond to ICS therapy, but rather than dismiss the effect of genetic variation on ICS responsiveness altogether, they aptly note that this study does not rule out the potential for local genetic effects of ancestry. These findings are yet to be determined in SAPHIRE and will likely be forthcoming. That said, there are potential shortcomings of this study, including, as the authors note, the possibility that the effect of genetic ancestry on response to asthma therapy might be medication class specific (ie, might be more relevant for long-acting β -agonists, for example, than for ICSs), inadequate power, and reliability of the AIM panel selected for the SAPHIRE cohort. Power is especially challenging in pharmacogenetic studies, as recently reviewed by Meyers,² and the SEs in the FEV₁ and Asthma Control Test scores in the current study were considerable. However, this study represents one of the largest of its kind, and options for addressing this shortcoming are limited.

On the other hand, the ability to detect global genetic ancestry is highly dependent on not only the representativeness of the AIM panel to the population under examination (ie, the extent to which the AIMs selected from West Africans living in London and South Carolina are representative of the SAPHIRE-enrolled African Americans living in Detroit), as Gould et al¹³ point out, but also the number of AIMs necessary to precisely discriminate the role of ancestry in the outcome of interest. In the current study the investigators relied on only 107 AIMs and limited their estimates of ancestry to African and European ancestry rather than including other reference populations. Importantly, the number of AIMs necessary to accurately assign ancestry is partly a function of the depth of generations because of admixture of the study population¹⁴ and is partly a function of how many other potential ancestral (in this case non-African) components, such as Amerindian and East Asian, have contributed to the mix.¹⁵ It might well be that the 107 markers are not optimal for assigning ancestry to the SAPHIRE-enrolled African Americans from Detroit, and it is possible that many more AIMs will be necessary to detect an association between genetic ancestry and a trait as complicated as response to therapy.

Thus although findings from this study do not support the hypothesis that the degree of how "African" an individual is can

predict how well (or not) that person responds to ICS medication, it does not refute this notion. Importantly, Gould et al¹³ have broken new ground in applying a novel tool in the complicated process of dissecting a particularly complicated phenotype, response to drug therapy, and this might ultimately shed new light on the underlying genetic mechanisms involved.

The quest continues.

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