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**COMMENTARY/PERSPECTIVE**

# Asthma Research for All of the United States

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Asthma disproportionally affects different ethnic/racial groups, with Puerto Ricans and African Americans suffering the highest asthma prevalence and morbidity, Mexicans the lowest, and non-Hispanic whites in between. Genome-wide association studies of asthma have found both shared and race/ethnic-specific genetic risks factors for asthma. However, the majority of genetic asthma research is performed in populations of European descent, which limits the benefits of genetic research to European populations. It is important to biomedical and clinical research to include more diverse and underrepresented populations. The rich genetic diversity of all populations can be leveraged to scientific advantage. For example, admixture mapping provides a more powerful approach than traditional genome-wide allelic association studies in discovering genetic associations for complex diseases. By being more inclusive we can achieve a better understanding of the genetics of asthma, address health disparities, and ensure that scientific advances will benefit populations worldwide.

## Introduction

Asthma is a complex, multifactorial disorder that is characterized by chronic inflammation of the airways of the lungs that leads to recurrent wheezing, shortness of breath, chest tightness, or coughing. Among children and adults in the United States, Puerto Ricans and African Americans are disproportionately affected, suffering the highest asthma prevalence rates at 14.2% and 9.5%, respectively, while non-Hispanic whites have a prevalence of 7.8% and Mexicans 3.9%.[1,2] These disparities extend to asthma mortality, as Puerto Ricans and African Americans are 4 times more likely than Mexicans to be hospitalized or to die from asthma.[3] Socioeconomic and environmental factors explain some of these differences, but no study to date has been able to measure effect sizes to account fully for these large discrepancies among different racial/ethnic populations.[4,5]

Genetic variation is estimated to account for 35%–75% of the differences in the risk of developing asthma.[6,7] Two large asthma consortia meta-analyzed independent genome-wide association studies (GWASs) of asthma and found asthma risk alleles with moderate effect sizes that replicated across multiple study populations.[8,9] The GABRIEL consortium, consisting of populations throughout Europe, reported genome-wide significant asthma susceptibility alleles at 7 loci, including the *SMAD3* locus.[8] The EVE Asthma Genetics Consortium, comprised of U.S. investigators with GWASes of European, African American and Latino ethnicities, was also able to replicate susceptibility loci reported by GABRIEL in a more diverse population consisting of participants with European, African American or African Caribbean, and Latino ancestry from the United States and Mexico.[9] Two additional loci only replicated in populations of European descent and a novel susceptibility allele that was only significant in populations with African descent was found. These studies demonstrated that there are shared as well as race/ethnic-specific genetic risk factors in the development of asthma.

Recently, the EVE consortium completed replication of 3,186 candidate risk alleles for asthma that were identified in their primary meta-analysis.[10] Two novel associations were replicated in European populations; however, no associations were replicated in African American and Latino populations. The lack of replication emphasizes the ancestry-specific associations of asthma, as well as the difficulty of studying genetic differences in admixed populations. GWASs identify genetic markers, common single-nucleotide polymorphisms (SNPs), that were selected to tag large linkage disequilibrium (LD) blocks, associated with a particular phenotype. LD occurs when alleles are nonrandomly associated with each other, making it difficult to distinguish a single causal mutation from positive associations. LD blocks also usually contain multiple genes or regions with unknown function that obfuscates the biological implications of GWAS signals. Because African American and Latino populations have mixed ancestries and greater genetic variability than European populations, associations between a genetic marker and the causal allele are expected to be much weaker and thus, more challenging for researchers to discover replicable associations among admixed populations.

## Studying Admixed Populations

Genome-wide ancestry association testing (or admixture mapping) is an alternative to the traditional genome-wide

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(allelic or SNP) association model that is theoretically more suitable for studying asthma in Latino and African American populations. The method can be applied to any disease where risk alleles are at varying frequencies in the ancestral populations of admixed individuals. Asthma is especially appropriate for this kind of analysis due to its high heritability and >2-fold differences in prevalence between ethnic groups in the United States. Admixture mapping differs from a typical GWAS in that the variable compared between cases and controls is genetic ancestry at a given location in the genome (ie, local ancestry) rather than genotypes at SNPs. Local ancestry is estimated using information spanning multiple SNPs, and can therefore capture more of the underlying genetic variation at a locus than compared with analyzing SNPs independently. Past GWAS results have found allelic associations moderate in effect size that only explained a small proportion of the genetic variation.[8,9,11–17] Since GWASs are designed to detect common variants, this suggests that rare variants or structural variants that cannot be detected by GWAS may play a larger role in the risk of developing asthma. Local ancestry associations are more likely to identify candidate regions containing population-specific rare variants that contribute to disease, as rare variants are more likely to differ in composition and frequency between populations with varying demographic histories.[18] Admixture mapping of populations with diverse ancestral backgrounds offers an alternative to the GWAS model for gene discovery and will potentially allow for the discovery of novel variations to account for the "missing heritability" of asthma.[19]

The EVE consortium expanded upon their primary meta-analysis by performing an admixture mapping meta-analysis to test for additional loci associated with asthma in Latino populations.[20] Latinos area diverse population with a mixture of African, European, and Native American ancestral backgrounds. Combined with the variation in asthma prevalence between subgroups, the heterogeneity of Latinos makes them the ideal focus for admixture mapping of asthma. Gignoux et al. identified a genome-wide significant admixture mapping peak centered on the *SMAD2* locus in 3,902 individuals from 4 different Latino populations recruited across Mexico, Puerto Rico, and the United States. The peak also replicated in the same direction in an independent sample of 3,774 Latinos from the Gene-Environments and Admixture in Latino Asthmatics (GALAII) study, a multicenter nationwide case/control study of asthma. *SMAD2* expression in the blood was measured in a subset of GALAII individuals and was found to be significantly reduced in Latino children with asthma compared with healthy controls. Follow-up fine-mapping of *SMAD2* to determine the causal variants driving the admixture signal identified several polymorphisms in the promoter region that were significantly associated with asthma, but none of these findings would have been discovered in the primary GWAS meta-analysis.[9] This study demonstrated the hidden potential of available genome-wide data for additional disease mapping strategies as well as the importance of including diverse ethnicities for complex disease studies.

The power of admixture mapping over GWAS based on allelic association testing was demonstrated by Torgerson et al. in a study of asthma susceptibility differences among different Latino subgroups.[21] The study included 253 Puerto Rican and 276 Mexican subjects with asthma and their parents who were recruited from hospitals in the San Francisco Bay Area, New York City, Puerto Rico, and Mexico for the Genetics of Asthma in Latino Americans (GALA) study. Although this population size is considered underpowered for a traditional GWAS, Torgerson et al. found that ancestry at the *8q12* locus was significantly associated with asthma in both Puerto Rican and Mexicans, but with Native American and African ancestry, respectively. This suggests that a particular loci may have shared genetic risk factors, but with different alleles in their respective populations. African ancestry at the *6p15* loci was also significantly associated with asthma in Mexican subjects, but not in Puerto Rican subjects, demonstrating that admixture mapping is also capable of discovering ethnic-specific associations. Admixture peaks were enriched for previously identified asthma susceptibility genes, thus validating this approach as a method to discover associations. The increased statistical power of admixture mapping over traditional GWAS came from increased coverage of the genome through using local ancestry as a marker instead of an SNP and the reduced number of statistical comparisons. This study took advantage of the diverse ancestral background among Latinos to maximize discoveries in asthma and health disparities.

## Biases in Genetic Research

Much of the knowledge to be gained through studying admixed and diverse populations has been ignored by the genetics community.[22] Currently, there is a large bias in genetic research in that 96% of participants in published GWASs were of European descent.[22,23] As of May 2012, only one published GWAS of asthma has focused on African Americans[11] and 2 on Latinos.[13,14] One reason for the European focus of GWAS is the ease of discovery within this population due to their low level of variation and high level of LD compared with other populations. GWASs are also designed to test common variants, those found in ≥5% of the population, but most commercial arrays were designed to cover genetic variations found in European populations. A common variant for European populations may be rare in populations of non-European descent,[18] thus reducing the power of GWAS to detect associations in different populations with typical commercial arrays. Researchers also prefer to study a single population in order to reduce issues of population stratification. It is difficult to disentangle how much an association between disease and genetic variance is due to socioeconomic or environmental differences that come with race rather than from the status of the disease itself, thus forcing researchers to include more confounders and require larger sample sizes to deal with multiple populations. However, this should not limit researchers from including underrepresented populations, especially since this would also limit the translatability of their studies to those of European descent.

## One Size Does Not Fit All

The lack of diversity in genetic research creates skewed knowledge of the genetic etiology of asthma. Genomic studies often do not translate well from one population to another due to the way genotyping arrays were designed and how genomic studies are interpreted. Different populations have different LD structures,[24,25] meaning that the link between SNPs and causal mutations will vary and

associations may be population specific. In a GWAS of asthma susceptibility, Sleiman et al. replicated an SNP association in the *DENNDIB* gene in 2 independent samples of European Americans.[15] However, when they attempted to replicate the same association in an African American population, the association was in the opposite direction. This "flip-flop" effect is possible when the association found is not the causal mutation itself, but rather, a genetic marker for an LD block.[26] In other instances, if the causal mutation is rare or absent in a certain population, the association may even be nonexistent. For example, in the Solomon Islands, the isolated aboriginal population has the highest prevalence of blonde hair outside of Europe. Kenny et al. found a single mutation in the *TYRP1* gene, which explained 47% of the hair variation. This mutation was unique to the Solomon Island population and was not found in populations of European descent.[27] These differences in genetic structure between populations make it less likely that discoveries in one population will be generalizable to other populations without first attempting to replicate these findings.

Not only do genes differ between populations, but environmental factors and gene–environment interactions may also vary, further complicating the generalizability of genetic studies. Environmental smoke exposure has been associated with early asthma development, lower lung function, and increased asthma exacerbations,[28–31] but cigarette smoking and environmental tobacco smoke exposure differs by race/ethnicity[32,33] and socioeconomic status.[34,35] In addition, the nicotine metabolism rate has been shown to vary by race/ethnicity,[32,33,36] influencing the potential to which races are affected for a given level of exposure. *In utero* tobacco smoke exposure has been associated with worse asthma control, suggesting genetic imprinting via methylation that needs to be further explored.[37] The ethnic-specific environments and gene–environment interactions complicate our understanding of the genetic etiology of asthma, but also emphasize the importance of studying diverse populations.

## Conclusions

To date, most genomic studies are still limited to populations of European descent, even within the United States.[22,23] Underrepresented ethnic groups such as African Americans and Puerto Ricans suffer the highest asthma prevalence and morbidity rates, yet are unable to benefit from genetic research. With the dropping costs of genetic sequencing, as well as the introduction of new commercial microarrays designed for non-European populations,[38] there is no reason not to include underrepresented populations. Much of the disappointment and recent backlash against GWASs has been due to the European-centric focus of past studies that has limited discoveries and benefits to those of European descent. Admixture mapping provides an alternative approach to the typical GWAS model, allowing for greater power and discovery in admixed populations.[19,21] Health disparities in asthma are currently being ignored by the genetic community, but by expanding our research to include more diverse communities, we will be able to obtain a better understanding of the complexities of asthma for all of the United States and address the health disparities.

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## Author Disclosure Statement

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