Discovery through Diversity: Insights into the Genetics of Lung Function in Latino Youth

Racial and ethnic minorities in the United States face health disparities in asthma severity and control (1, 2). These health disparities result from a complex interaction of environmental, socioeconomic, and genetic factors (3). As high-throughput technology has evolved, whole-genome sequencing (WGS) has enhanced our ability to identify the genetic determinants of respiratory disease. Although populations of European descent represent roughly 15% of the world population, approximately 80% of the existing genome-wide association studies are conducted in this ancestry population (4). Prior studies have demonstrated that SNPs strongly associated with complex disease in European ancestry populations may fail to replicate the same relationship in other ancestral populations (5). This lack of inclusion prevents racial and ethnic minorities from accessing the full benefits of genomic research and precision medicine (4).

From a scientific perspective, genomic research in ethnic minority groups has been instrumental in illuminating disease pathogenesis (2, 6, 7). In asthma, prior research has demonstrated that differing proportions of genetic ancestry may shape disease susceptibility and severity of disease among African American and Latino American populations (1, 2, 8, 9). These findings are particularly salient because ethnic and racial minorities have high rates of asthma and poor responses to traditional therapies (2). Admixture mapping, a methodology that leverages shared genetic variance and differing allele frequencies among ancestral populations, holds promise for uncovering associations between ancestry at specific genetic loci and disease states (10).

In this issue of the *Journal*, Lee and colleagues (pp. 962–972) investigate the genetic architecture of lung function in Puerto Rican youth and identify an inflammatory pathway that may be leveraged for the development of targeted asthma therapeutics (11). The study used WGS data from the NHLBI-sponsored Trans-Omics for Precision Medicine Program in minority populations by integrating admixture mapping to identify ancestry-specific variants associated with asthma-related phenotypes, including lung function. The authors conducted this investigation in the GALA II (Gene-Environment and Admixture in Latino Americans) case-control study and limited the population to subjects from Puerto Rico. The authors identified genomic regions associated with lung function measurements and used a combination of chromatin immunoprecipitation (ChIP-seq), RNA sequencing, and expression quantitative trait loci analysis to discover the functional implications of their findings. The authors identified potential causal variants within two genomic regions associated with lung function measurements, building on their prior work demonstrating that differences in the proportion of African, European, and Native American ancestry influence asthma susceptibility among Latino American individuals. The authors employed ChIP-seq assays in human bronchial epithelial and smooth muscle cells as well as RNA sequencing and expression quantitative trait loci analysis in publicly available tissue sources to assess the functionality of the identified genetic regions.

Lee and colleagues identified two significant genome-wide peaks on admixture mapping for African and Native American ancestral origin that were associated with lung function measurements (11). One of the peaks, which was found using association testing between local genetic ancestry and FEV_1, was identified on the chromosomal region 1q32 and associated with a 0.12-L decrement in FEV_1 per each additional allele of African origin. Using the same admixture mapping technique for subjects of Native American ancestry, the authors also describe a chromosomal region at 5q35.1 that associated with a 0.15-L increase in lung function for each allele of Native American ancestry. The top Native American ancestry SNP, rs12153426, is intronic to *SLIT3*. *SLIT3* encodes slit guidance ligand, a secreted protein that interacts with roundabout homolog protein to influence cell migration (12), and is a novel target for future research into the mechanism of its influence on lung function.

Conditional analyses on the associations between lung function measurements and locus-specific ancestry failed to demonstrate a single SNP driving the observed admixture mapping peaks (11). Consequently, the authors pursued a multiple SNP joint-effect modeling approach, which unveiled associations between the lead ancestry SNPs and lung function. On fine mapping, there were two windows that were suggestive of an association with lung function measurements on each of the chromosomal regions of interest, primarily driven by rare variants. To investigate the role of these variants, Lee and colleagues conducted ChIP-seq experiments in white blood cell– and lung-related lines. These experiments were complemented by gene expression analyses on the four African ancestry–associated SNPs identified on admixture mapping. Two of these SNPs were associated with decreased expression of *TMEM9* (transmembrane protein 9) observed in nasal epithelial cells and with decreased lung function. The authors noted that the minor alleles of these SNPs showed a higher prevalence in subjects of African ancestry compared with their counterparts of European descent. Using RNA sequencing data, the authors found that increased *TMEM9* expression was inversely correlated with proinflammatory cytokines IL-6 and IL-1β gene expression in nasal epithelial cells. Lee and colleagues indicate that the gene expression profiling implicates *TMEM9* as a potential therapeutic target in pulmonary disease.

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TMEM9 has been linked to enhanced protein expression levels from the canonical Wnt/β-catenin pathway. In TNF-α (tumor necrosis factor α)-induced LX-2 cells, the overexpression of TMEM9 has been associated with increased expression of IL-6 and IL-1β (13). Conversely, cell transfection with TMEM9-siRNA decreased the expression of these cytokines. The findings by Lee and colleagues expand our understanding of the potential role of *TMEM9* in asthma pathogenesis by providing evidence that reduced TMEM9 expression may associate with reduced FEV_1 and the IL-6/IL-1β asthma subtype (14).

This study advances our knowledge of the role of ancestry-specific variants in asthma. There is a paucity of research investigating asthma genetics in underrepresented populations, such as Latino American individuals from Puerto Rico. The work expands the authors' prior research demonstrating that lower expression of SMAD2 (9), which is a transcriptional modulator that mediates the signal of TGF-β (transforming growth factor-β), was associated with a higher frequency of asthma exacerbations in Puerto Rican subjects by identifying novel ancestry-specific pathways that may explain changes in lung function. By providing evidence that *TMEM9* and *SLIT3* may be involved in asthma pathogenesis, the authors underscore the benefits of dedicated and continuous genetic research on at-risk but understudied populations of mixed ancestry.

Although this study highlights the merits of integrating WGS and admixture mapping to identify ancestry-specific variants associated with asthma-related phenotypes, there are important limitations. First, this study included a relatively small sample from a geographically distinct region in which significant founder effects have been observed (15, 16). It is imperative to increase the recruitment of underrepresented ancestral populations in genomics research to obtain the power necessary to improve discovery (4). With the current sample, the results pertaining to the identified SNPs may not demonstrate generalizability beyond this specific population even among other admixed Latino populations, which may limit future therapeutic implications. Further investigation is also necessary to assess potential gene–environment interactions that govern disease susceptibility and treatment response.

In conclusion, this study provides evidence that asthma subtypes may be associated with genetic ancestry in admixed populations and identifies novel candidates that are attractive targets for future research in traditionally underrepresented populations. As health disparities in asthma susceptibility and severity remain pervasive, genomics research including underrepresented populations may provide a critical approach to improve disease outcomes (2). Our field must rise to the challenge of understanding how insights gained from genetic studies in diverse ancestral populations can be aptly applied to reduce health disparities. ■

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