Asthma susceptibility

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Editorial

Asthma susceptibility: Learning from genetic diversity

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Asthma is a common chronic respiratory disease across all countries and ethnicities. The Global Burden of Disease Initiative reported that in 2017 asthma affected 272.7 million people globally and caused 500,000 deaths.[1] Asthma prevalence and its disease burden is high in non-White minorities. In the United States, higher rates of asthma-related emergency department visits, hospitalizations, and deaths have been reported in Black children than in White children.[2] This may be due to poor socioeconomic status, housing conditions, adverse exposures to things such as smoking and air pollution, and suboptimal access to health care. In addition, genetic ancestry may influence ethnic disparities in asthma.

Asthma is a complex disease that is associated with many genetic and environmental factors. According to twin studies, the heritability of asthma is estimated to be between 60% and 80%.[3] Over the past 15 years, the genetic basis of asthma has been revealed by genome-wide association studies (GWASs). These studies systematically compared the prevalence of millions of genetic variants across the genome in large groups of case patients and controls. A 2019 review reported that 128 asthma-associated single-nucleotide polymorphisms (SNPs), single–base pair variations in the genome, have been described as being of genome-wide significance.[3] However, these discoveries have been made almost completely in populations of European ancestry. This marks a paradox in asthma research: populations with high disease burden, such as those of African ancestry, are strongly underrepresented in genetic studies. This evoked a call for change, with an increasing number of genetic studies performed in populations of non-European ancestry.[4-6]

In this issue of the *Journal of Allergy and Clinical Immunology,* this change is illustrated by Chang et al, who present the largest meta-analysis of genetic variation and susceptibility to asthma in African American individuals to date.[7] First, they conducted GWASs on asthma in 3 cohorts collected at the Children's Hospital of Philadelphia (CHOP), which were stratified according to 3 different types of SNP-arrays used in GWASs.[7] Children aged 4 years and older (N = 6975 cases) with asthma were identified from clinical records as having a history of asthma and using relevant asthma medication. The genetic makeup of these children was compared with that of 4429 controls without asthma or asthma medication.[7] Although the individual GWASs yielded no significant result in each separate CHOP cohort, combining the 3 cohorts revealed a novel locus at genome-wide significance in an intergenic region on chromosome 6 between *RFX6* (a transcription factor in β-cells of the pancreas) and *VGLL2* (a protein with a transcriptional enhancer factor 1 [TEF-1] interaction domain); the functional effect of this locus is currently unknown.[7] Next, they performed a meta-analysis of 19,628 subjects (10,761 case patients and 8,867 controls) combining GWAS summary statistics of CHOP's 3 data sets with the results of 10 studies in African American subjects of the Consortium on Asthma among African Ancestry Populations in the Americas.[5,7] Meta-analysis of these 13 data sets yielded 12 loci that met the classical criterion for genome-wide significance (5×10^{-8}).[7]

Independent replication is needed before definitive conclusions regarding the relevance of these loci can be made. However, because no other large-scale asthma genetics studies in African American individuals are available, Chang et al compared their results with those of studies in subjects of mostly European descent.[7] Among the 12 associated loci, 1 at chromosome 9p24.1 (including *IL33*) in individuals of European descent was previously reported. Conversely, loci found in populations of European descent were investigated for their association in African American individuals.[7] Change et al investigated not only the lead SNPs found in European individuals but also highly correlated SNPs in the chromosomal region.[7] A total of 43 of 202 SNPs associated with asthma in populations of European descent also showed evidence for association in African American individuals,[7] indicating overlap of genetic susceptibility to asthma across populations.

To interpret these findings, characteristics of the genome of individuals of African ancestry and those of European ancestry need to be considered. Although the genome worldwide is 99.9% similar between all members of the human family, genetic variation remains. This variation is driven by spontaneous mutations and crossing-over events during gametogenesis, genetic drift, and selection. Genetic variations at neighboring loci are often correlated: alleles are observed together in blocks in the population that are called haplotypes. This phenomenon is called linkage disequilibrium (LD), which is defined as the nonrandom association of alleles in the population. The extent of LD is much smaller in populations of African descent than in populations of European descent because of the higher number of generations (Fig 1). Thus, because of their longer population history, people of

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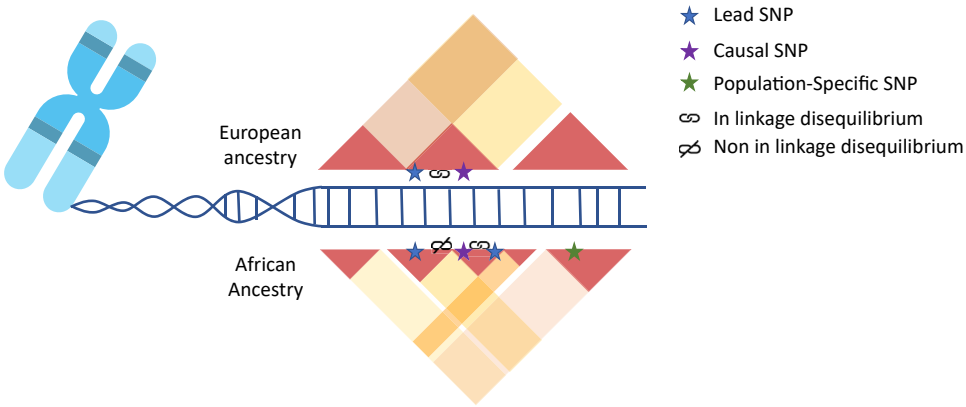

FIG 1. Genetic variation differs between populations. Some genetic variants are common in populations of African ancestry but may be rare or not polymorphic (*green star*) in a population of European ancestry. LD refers to genetic correlation of SNPs that are inherited closely together within a population; these SNPs are observed within an LD block. The red triangle shows that SNPs in this block have high LD, which is stronger in populations of European ancestry (*upper panel*) than in populations of African ancestry (*lower panel*). The lead SNPs (*blue stars*) are independent SNPs having the most significant association during GWASs. Causal SNPs are SNPs that have a function in asthma (*purple star*). Because of the difference in LD between populations of European ancestry and populations of African ancestry, the lead SNP (*blue stars*) that is in LD with the causal SNP (*purple stars*) in European individuals might not be in LD with the causal SNP in Africans. As a result, even though causal SNPs are the same, the associated SNPs can be different among different populations.

African descent are characterized by significantly higher genetic diversity than people of European descent are. Allele frequencies are often different between different populations, and population-specific variants exist.

This has consequences for genetic studies. First, risk variants prevalent in Africans may be hard to bring to light in European populations because some risk SNPs are population-specific variants or common only in specific populations. Second, the genome of African Americans is often a combination of different ancestries, called an admixed population. This results in a mosaic of haplotypes of different ancestral origins.[8] Conducting GWASs on admixed groups may be challenging because heterogeneity can pose statistical challenges and may reduce their power.[8] In the CHOP study, the population structure was compared with that of the reference population from the 1000 Genomes Project; to detect risk variants in African Africans, the principal components that reflect genetic ancestry were adjusted for.[7] Alternatively, admixture may be used to accelerate gene discovery when the disease under study is associated with genetic ancestry at a certain locus. This strategy, called admixture mapping, is especially effective when risk allele frequencies are markedly different between the different ancestral populations.[4]

Third, the extent of LD has consequences for the design and interpretation of GWASs. LD is conveniently used in GWASs by testing a limited number of SNPs (that tag a region of the genome) rather than sequencing the whole genome. Often, the associated SNP reported in genetic studies is not the functional causal variant, yet it is located in an LD block in which it tags the causal variant. Fig 1 shows that the LD block around a causal asthma SNP covers a larger range in European populations than in populations of African descent. Thus, asthma risk SNPs in population of European descent are not necessarily in LD with the causal SNP in populations of African descent. Fourth, because LD blocks are much smaller in African populations than in European populations, a higher number of SNPs need to be tested to cover the genome, which will necessitate more tests[9] and affect the genome-wide significance cutoff. In the CHOP study, 8 loci surpassed a more stringent threshold of 3×10^{-8}, even though this stringent threshold is based on analysis of European ancestry genomes.[7] Thus, an even more stringent threshold may be needed in genetic studies of populations of African ancestry. In the CHOP study, SNPs were replicated across diverse populations by considering LD.[7] This is a meaningful attempt; however, the appropriate significance thresholds of these cross-population comparisons may need further work. It should be noted only a quarter of SNPs found in populations of European ancestry were replicated in meta-analysis of populations of African ancestry—a finding that is possibly related to incomplete coverage of the genome by older versions of SNP arrays.[7] SNP arrays specifically for populations of African ancestry in combination with population-specific imputation panels may help. In future studies, whole genome sequencing technology may be helpful to capture more variants and enable a full cross-ancestry genomic comparison.

Finally, functional genetic studies on subjects of African ancestry will accelerate our understanding of asthma. Because smaller LD blocks may cover fewer genes, disease SNPs may be more directly linked to related genes that could constitute novel drug targets for asthma.[3] This was illustrated by Ober et al, who showed that the asthma risk allele on chromosome 17q regulated gene expression of gasdermin B (GSDMB) in nasal epithelial cells in African American study subjects.[10] Thus, next to a call for genetic studies, more functional genetic studies in populations of African ancestry are recommended: this may accelerate gene discovery.

In conclusion, the study by Chang et al[7] illustrates how we can learn from genetic studies in populations of non-European descent. It shows evidence of shared and unique genetic causes of asthma across populations. Moreover, it illustrates which methodologic challenges need to be addressed. Future functional genetic studies in populations of African descent will accelerate gene discovery in asthma. As genetically supported drug targets

have a more than 2-fold higher success in leading to drugs that reach the market than drug targets without genetic support do,[3] the benefits of these studies may be universal.

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