New research examines the relationship between complex traits and non-European ancestry

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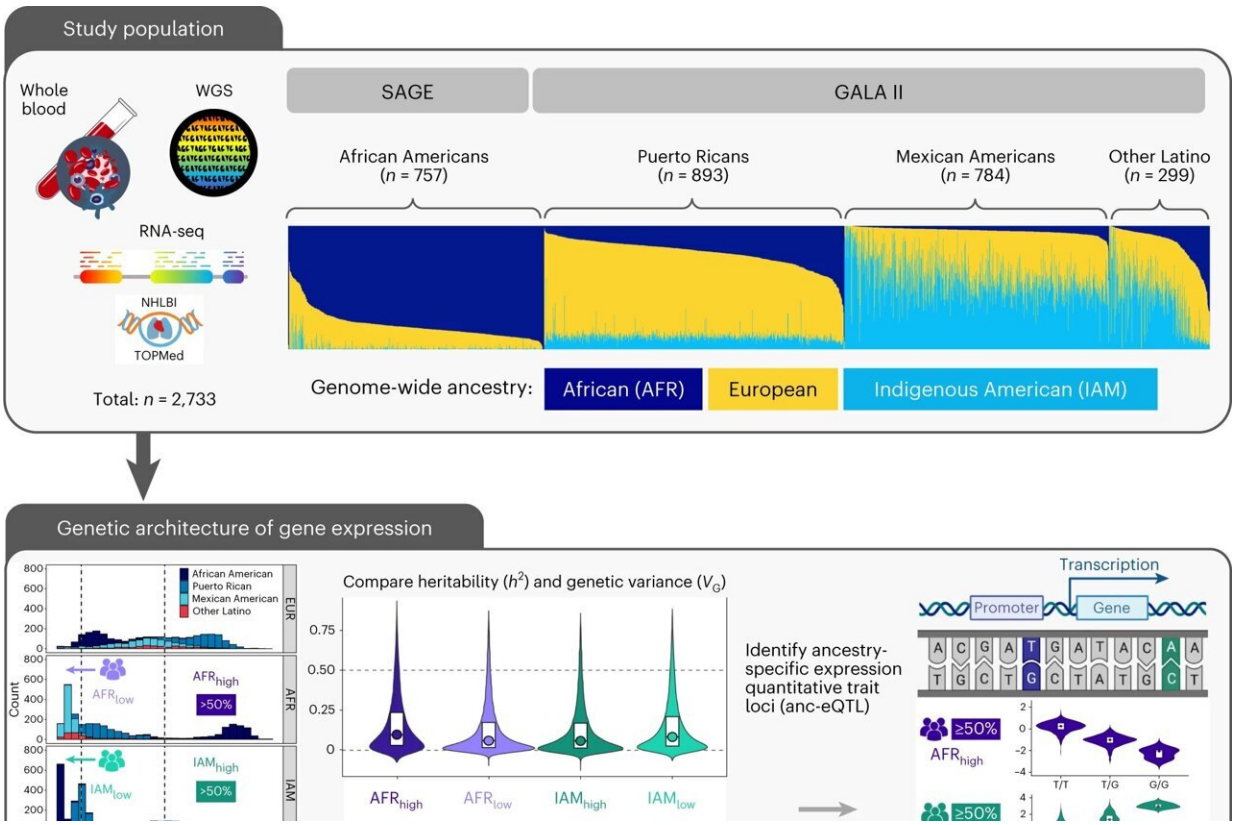

Study overview. This study included TOPMed WGS and whole transcriptome data generated from whole-blood samples of SAGE AA and GALA II Latino individuals (n = 2,733). We compared elements of the genetic architecture gene expression, such as cis-heritability and genetic variance, across participant groups defined based on self-identified race/ethnicity and genetic ancestry. We performed eQTL mapping and identified eQTLs that were specific to AFR or

IAM ancestry. Finally, we developed genetic prediction models of whole-blood transcriptomes and performed comparative TWASs using GWAS summary statistics generated from the PAGE study and the UKB. Credit: *Nature Genetics* (2023). DOI: 10.1038/s41588-023-01377-z

Exploring diverse ancestry is a critical factor in furthering medical research.

A new study published in *Nature Genetics* from researchers in the Department of Biomedical Informatics (DBMI) at the University of Colorado School of Medicine, in partnership with the University of California San Francisco and Stanford University, is the largest of its kind that focuses on ancestry correlations with biomedical traits and the first study to examine the role of genetic variants across diverse ancestries in regulating gene expression.

"We're trying to understand how genetic variability around the world allows us to gain a deeper understanding of the relationship between genetics and RNA levels and then protein levels and physiology," says DBMI associate professor and study co-senior author Chris Gignoux, Ph.D. "The genome and gene expression each on their own only tells us so much. Having these layers coming together helps us a lot more."

Gignoux describes the genetic control of gene expression as a dial that controls the amount of the gene that gets transcribed into RNA and protein levels, ultimately impacting function in various ways.

The study analyzed whole genome and RNA sequencing from African American and Latino children. Researchers say their findings demonstrate the importance of measuring gene expression across multiple populations because those gene expressions can vary greatly

depending on ancestry and enable new discoveries that may also reduce health care disparities for historically underrepresented populations.

Gignoux's lab used data from The National Heart, Lung, and Blood Institute-funded Trans-Omics for Precision Medicine (TOPMed) consortium and the National Human Genome Research Institute-funded Population Architecture using Genomics and Epidemiology (PAGE) Study. They analyzed whole genome and RNA sequencing data from 2,733 African American and Hispanic/Latino children, exploring ancestry and heterozygosity-related differences in the genetic architecture of whole blood gene expression.

"The ultimate goal was that we learn by looking at gene expression patterns in populations that came from the same ethnic group," Gignoux explains. "Individuals from across Latin America do not reflect one homogeneous population, so that was part of the reason why it was important to not just look at Hispanics in one group, but to highlight what we can learn from studying Mexican Americans and Puerto Ricans, specifically. We're able to leverage some of that diversity to understand some of these patterns."

Because ethnicity is a sociopolitical identity, understanding the relationship between genetics and ancestry is quite complex and can vary greatly between individuals. This is true even within certain populations such as individuals of Puerto Rican descent.

Historically, there's been a deficit in genetics research focused on people of non-European descent, but knowing more about the relationship between genetic variability and gene expression can inform deeper research into many different health issues.

That's been proven true in examples such as the medical community's knowledge of heart attacks, which for decades only focused on men.

With more research, it became apparent that risk factors and symptoms look much different in women.

Without studying diverse populations, it's nearly impossible to know a disease might present in another group of people. The work done by Gignoux and his fellow researchers, including researchers from the various communities represented, may help inform more discoveries that are significant to diverse populations, just like identifying different risk factors women face with heart attacks.

"We're not going to know what we don't know unless we look, and that has the potential to impact how we think about individuals' risk factors for a number of different conditions and traits," Gignoux says.

"It's also important to look in the right kind of ways and develop the methodologies so that we can leverage these kinds of diversity-focused efforts. The hope is that as these kinds of initiatives move forward in genetic and non-genetic disciplines there's an opportunity to improve our understanding of biomedical traits for anyone who walks into the clinic."

More information: Christopher Gignoux, Gene expression in African Americans, Puerto Ricans and Mexican Americans reveals ancestry-specific patterns of genetic architecture, *Nature Genetics* (2023). DOI: 10.1038/s41588-023-01377-z.
www.nature.com/articles/s41588-023-01377-z

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