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Important gene variants found in certain African populations

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In the nearly 20 years since the Human Genome Project was completed, experts in genetic variants increasingly have raised concerns about the overemphasis on studying people of European descent when performing large population studies. A study appearing October 31 in the journal *Cell* aims to address some of this disparity by focusing on populations living in rural Uganda, thus revealing several new genetic variants related to human health.

"This study highlights the high level of diversity in African populations that remains undiscovered despite large numbers of gene sequences that have been generated from Europeans," says co-senior author Manjinder Sandhu, who studies genomic diversity at the University of Cambridge in the UK. "We found that more than a quarter of the genetic variation we observed in the Ugandan population had not been discovered."

The participants in the study came from 25 villages in a rural part of southwestern Uganda. Using blood samples, the investigators generated genotypes from about 5,000 individuals and conducted whole-genome sequencing on about 2,000 individuals. The researchers collected information through electronic questionnaires; carried out physical measurements such as blood pressure, height, and weight; and tested the blood samples for medically important markers such as cholesterol and glucose.

The investigators made several findings related to genetic variants and health. "We found many new associations with blood traits, liver function tests, and glucose-related traits," Sandhu says. "Most of these relate to genetic variants that are either unique to Africans or rare in non-Africans. They may not have been readily discovered even in very large studies of non-African populations."

Specifically, they found that height is less genetically determined among rural Ugandans relative to what's been seen in European studies. In contrast, LDL cholesterol levels appear to be more genetically determined relative to Europeans.

"We think this might relate to differences in the impact of diet and nutrition relative to genetic influences between African and European populations," says co-first author Deepti Gurdasani, a career development fellow at Queen Mary's University of London. "For example, the genetic influences on height might be more limited by malnutrition in early childhood in these populations. On the other hand, so-called Western dietary patterns possibly have a lower influence on cholesterol levels, making these more genetically determined."

The researchers also found an association between a genetic variant that causes alpha-thalassemia among Africans and levels of glycated hemoglobin. This genetic variant, found in 22% of Africans, protects against severe malaria. It is rare in populations where malaria isn't endemic. "Because glycated hemoglobin is

commonly used to diagnose diabetes, this finding suggests that it needs careful evaluation as a test for diabetes in relevant populations," says co-senior author Ayesha Motala, of KwaZulu Natal University in South Africa.

The study also revealed important findings about human history and migration. "Uganda is a melting pot of different cultures and languages, and we wanted to understand the genetic structure and history of populations within the country," says Pontiano Kaleebu, the Director of Uganda Virus Research Institute and Director of the MRC/UVRI & London School of Hygiene and Tropical Medicine Uganda Research Unit, who co-led the project. "These studies highlight the extensive movement and population expansions that have occurred within and into Africa over the past few thousand years."

Analysis revealed that the genomes of Ugandans are a mosaic of many ancestries, likely reflecting the extensive migration from surrounding regions spanning hundreds to thousands of years. It also showed that significant Eurasian ancestry has entered the region at multiple time points, ranging from a few hundred years ago to about 4,000 years ago.

Although the researchers identified new genetic variants associated with disease, they say much more research is needed to understand how these genetic variants affect disease traits. This will require not just looking at genomes but also at functional effects of genomes on gene expression and protein levels.

In the future, they also plan to look at individuals from other parts of Africa, especially indigenous hunter-gatherer populations such as the Khoe-San populations in Namibia and South Africa and the rainforest hunter-gatherer populations in central Africa.

"This study confirms that genetic causes of disease may be different in Africans and provides opportunities to identify new genes associated with disease that would not be identified in European studies," Gurdasani concludes. "This kind of research will allow us to identify new targets for therapies that could potentially be useful for all populations."

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Cell, Gurdasani et al. "Uganda Genome Resource enables insights into population history and genomic discovery in Africa" https://www.cell.com/cell/fulltext/S0092-8674(19)31120-1