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What we've learnt from building Africa's biggest genome library

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The human genome was first sequenced in 2003 by multiple research centres across the world. The breakthrough was hailed as the dawn of a new era. Genetics would swiftly transform our response to disease and lead to personalised medicine.

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In the past decade there has been substantial progress in terms of studying genetic factors giving rise to disease. But much of this has been focused on European populations. Little progress has been made in examining the factors associated with disease among Africans.

Until very recently, only a few hundred whole genome sequences of individuals within Africa had been completed. Researchers largely relied on genetic data from African-Americans. These have provided many new insights. But they don't reflect the continent's full genetic diversity.

Africa is known to be where humans originated. From Africa, they migrated to other parts of the world. This makes it the most genetically diverse region in the world. Diversity among other populations represents a subset of the diversity within Africa.

This genetic diversity provides unique opportunities to examine genetic factors associated with disease that can't be examined in Europeans where diversity is much lower. This highlights the need for much larger studies of genetic causes of disease within Africa.

We conducted a study to build one of the largest genome resources from within Africa. We developed a rich, diverse resource using genome wide data from 6,400 Ugandans – the Uganda Genome Resource. It included whole genome sequencing of nearly 2,000 people.

The study built on the long standing research programme of the Medical Research Council Uganda and Uganda Virus Research Institute. Its aim has been to establish a clinical and genomic data resource to understand population health and disease in the region.

The team also incorporated data on 14,000 individuals from different parts of the continent. It did this in collaboration with the University of KwaZulu-Natal and the Centre of Genomics and Global Health, National Institutes of Health. This allowed us to examine genetic determinants of traits within the population.

Around a quarter of the genetic variation identified had not been discovered before. We found a higher level of genetic diversity in the Ugandan population than seen in similar studies of European populations.

Modern Uganda appears to be a complex mosaic of genetic flow from many different communities that have migrated from surrounding regions within Africa – and from Europe or the Middle East. This gene flow appears to have occurred repeatedly, dating back from around 100 years ago to as long as 4,500 years ago.

Our work is an important step forward in African medical genetics research. But much more research is needed to understand how these genetic variants affect disease traits. That means looking at the functional effects of genomes on gene expression and protein levels.

What we found

In our study, we discovered ten new associations with blood traits, liver function tests and indicators of diabetes. Most of these new associations relate to genetic variants that are unique to the Ugandan population or very rare in non-Africans. These would not have been discovered even in very large studies of Europeans.

For example, we identified an association between a genetic variant that causes alpha-thalassemia, a blood disorder that leads to anaemia, and glycated haemoglobin levels, which are commonly used for diagnosis of diabetes. This genetic variant is found in 22% of Africans. It has become very common in some regions within Africa because it also protects against severe malaria. It remains very rare in other populations where malaria isn't endemic. Our findings suggest that the utility of glycated haemoglobin as a diagnostic tool for diabetes may require re-evaluation in regions where alpha-thalassemia – a blood disorder that reduces the production of haemoglobin – is common.

The richness of the Uganda resource also offered us other opportunities. For example, we were able to study the extent to which genetic differences influence differences in traits among Ugandans relative to previous studies in European populations. We found that heritability – the extent to which genetic differences encode differences in traits or diseases – may differ between Ugandans and Europeans.

We also found that height is less genetically determined in rural Ugandans relative to previous European studies. We think that this might relate to differences in the impact of environmental factors between rural Ugandan and European populations. For example, the genetic influences on height might be more limited by nutritional influences in early childhood.

Our findings highlight the usefulness of examining genetically diverse populations within Africa. They underscore how this can lead to new discoveries and help us understand the genetic encoding of traits that may be different within Africa

relative to other populations.

Next steps

Africa is central to our understanding of human origins, genetic diversity and disease susceptibility. There is a clear scientific and public health need to develop large-scale projects that examine disease susceptibility across diverse populations across the continent. That work should be integrated with initiatives to improve research capacity in Africa.

We now need larger and more diverse studies of genetic causes of disease across the region. These will foster the development of new treatments that will benefit people living in Africa as well as people of African descent around the world.

Future work will look at individuals from other parts of Africa. The aim will be to get a deeper understanding of genetic diversity among indigenous hunter-gatherer populations. These include the Khoe-San populations in Namibia and South Africa and the rain forest populations in central Africa. In addition, we will be expanding current studies of genetic causes of disease to 100,000 individuals across the region.

The data was collected by researchers from universities and research institutes from Africa and the UK, including Queen Mary University of London, the University of KwaZulu-Natal, MRC/UVRI & London School of Hygiene & Tropical Medicine Uganda Research Unit, the US National Institute of Health and the University of Cambridge.

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