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World scientists give a nod to UCT-led study to fill the African genome gap

The idea of sequencing the genomes of three million Africans to build a more representative human reference genome is receiving global support, Professor Ambroise Wonkam, director of Genetic Medicine of African Populations (GeneMAP) at the University of Cape Town's (UCT) Division of Human Genetics, has learned after a piece he wrote in the illustrious journal *Nature* recently.

The piece, titled 'Sequence three million genomes across Africa', in which Wonkam introduced and unpacked his vision, was met with an enthusiastic global response, contrary to what he had believed. When he initially formulated the idea, he anticipated a measure of resistance.

"My biggest reservation was that maybe it was too big, too crazy and too expensive. To be honest, I have never even written a science paper with original data that raised that much interest!" he says.

Wonkam's Three Million African Genomes (3MAG) vision can be backtracked about thirty years to the launch of the Human Genome Project (HGP), an international research effort to determine the DNA sequence of the entire human genome. Spanning more than a decade and costing $3 billion, the project resulted in the publication of the first accurate and complete human genome sequence.

As the HGP website explains, "the project gave us the ability, for the first time, to read nature's complete genetic blueprint for building a human being." During the course of the 10-year study, the cost of sequencing decreased significantly, turning it into a much more accessible technology.

It revolutionised medicine and led to thousands of genome-wide association studies (GWAS) that have been conducted to shed light on the role genes play in a host of diseases, conditions and treatments. While the HGP strived to be as demographically representative as possible, subsequent studies have been focused largely on European and Asian populations, despite the fact that Africa contains more genetic diversity than any other continent.

In his paper, Wonkam reveals that so far less than 2% of human genomes analysed have been those of people of African ancestry. "The reference genome sequences built from the HGP are missing many variants from African ancestral genomes. A 2019 study estimated that

a genome representing the DNA of the African population would have about 10% more DNA than the current reference," he writes.

This oversight has had obvious drawbacks for the development of appropriate clinical interventions and health equity for African populations, and has been to the detriment of the global population at large. "The main reason for this is ancestry. Since this is where humans originated, we are all – in fact – African and would benefit from a more representative human reference genome," he says.

Wonkam proffers that African genomes can reveal genes and variants that contribute to health and disease not found in previous Eurocentric studies. Because they collectively have more genetic variations and less intermixing with other, non-African populations, finding variants likely to contribute to specific conditions will also be easier.

The Human Heredity and Health in Africa (H3Africa) consortium – a collaboration between the African Society of Human Genetics (AfSHG), the National Institute of Health (NIH) in the United States (US) and the Wellcome Trust – has boosted the study of genomics and environmental determinants of diseases that are common among African populations by supporting 30 institutes across the continent. Drawing to a close in 2022, H3Africa has laid a firm foundation on which 3MAG can be built.

"H3Africa is probably the strongest base to work from," says Wonkam. "It has strengthened the training of African-based scientists and built a genetic community on the continent. It has also sequenced the genomes of thousands of Africans already, which would be a good place for us to start." Apart from this, Wonkam says that other publicly available datasets include the UK Biobank (which includes 8 000 genomes labelled black or African) and the Trans-Omics for Precision Medicine (TOPMed) programme in the US.

"The proportion of individuals we select from each region will be determined by how homogenous or heterogenous the populations are," explains Wonkam. "A country like Sudan is extremely heterogenous, which means we'd need a large proportion of the population."

Wonkam believes while the best time to have started this project was thirty years ago, the second-best time is now.

While Wonkam may be credited with envisioning 3MAG, he by no means feels possessive over the project. "My hope is that this paper may give voice to what many of us have been thinking. And if it does, then I see many people carrying the project forward," he concludes.

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