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Africa's first genetics study sheds light on inherited disorders

New research investigating the genetic modifiers of long-term survival in individuals with sickle cell anaemia (SCA) reveals a range of possible pathways for novel therapeutic interventions. Professor Ambroise Wonkam, principle investigator and director of Genetic Medicine of African Populations (GeneMAP) in the University of Cape Town's (UCT) Division of Human Genetics, says apart from the study's clinical potential, the fact that it is so deeply rooted in Africa also presents the opportunity for a paradigm shift in science policy and diplomacy.

Sickle cell disease (SCD) is the umbrella term for a range of inherited disorders in which the red blood cells have an abnormal crescent or banana shape, which block small blood vessels. As a monogenic disorder, it is caused by a mutation in a single gene, which is responsible for production of the protein, haemoglobin. Making up 70% of the content of red blood cells, haemoglobin is essential for the transportation of oxygen through the body. SCA is the most severe manifestation of SCD.

What makes SCA particularly interesting as a genetic disorder is its prevalence in sub-Saharan Africa. "Among the 300 000 babies that are born with the condition every year, 80% are in sub-Saharan Africa," says Wonkam. "It is, in essence, an African disease."

Counterintuitively, however, over the past 50 years, most of the truly critical research into SCA has been conducted outside of Africa – mostly in Europe and the United States. With its cohort of 192 African SCA patients recruited at African hospitals and conducted at an African university by African researchers, Wonkam's genetic study, using next generation DNA sequencing, is truly a first for the continent.

Despite the prevalence of SCA in Africa, medical care has been less than optimal. This can be ascribed to several factors, including lack of access to resources and non-availability of specific effective interventions, such as the screening of newborn infants and systematic penicillin use for the presentation of infections.

According to Wonkam, it has been shown that, due to this lack of clinical interventions, in most African settings, at least 50% of African children with SCA will die before they turn five years old.

Simultaneously, however, the same regions of sub-Saharan Africa are also home to SCA patients who have turned 50 or 60 years old.

"Why is it that some people - who live in an environment that is not favourable in terms of healthcare access, and stressors including high temperatures, malaria and other infections – manage to survive while others die at a much younger age?" Wonkam asks. "Our hypothesis is that these long survivors living with SCA may be protected by some genetic factors."

Furthermore, he explains, if this is indeed the case, the genetic modifiers present in these individuals may hold the key for exploring new routes of treatment for other SCA patients. "If we know how it works in their body," he says, "we can provide new treatment looking at those pathways."

Wonkam and his research team started by recruiting SCA patients of 40 years or older who had received minimal clinical interventions. They then selected a control group of patients who had suffered from strokes, one of the most severe effects of SCA, as well as an 'intermediate' group who were under 40 and had never experienced a stroke.

The recruitment process took place in Cameroon and produced a study cohort of 25 long-survivors, 25 stroke patients and 50 intermediate patients.

The study revealed that patients in the long-survivor group did indeed present certain genetic modifiers that patients in the stroke group did not.

"We found that people who had survived longer, had recurrent changes in those genes," explains Wonkam.

The most interesting aspects of this finding was the fact that glutamine was recently validated as a treatment for SCA by the Food and Drug Administration (FDA), in the United States of America (USA). "This means that some of the patients actually make glutamine available to themselves naturally," Wonkam says. "In other words, they are naturally able to treat themselves."

Other interesting findings in the long-survivor group included more efficient metabolism of the micronutrient selenium as well as the presence of genes that assist in keeping blood pressure low.

In the stroke cohort, the researchers found that patients tended to have a mutation in the blood coagulation pathway. Wonkam says this implies that thinning the blood of SCA patients may be a clinical intervention worth investigating. "What our study has shown is that there could be a few other routes for therapeutic manipulation that have not yet been explored."

For a disease where the current definitive treatment is a bone marrow transplant, and – in the near future - gene therapy and gene editing, this provides a major breakthrough. "At the moment, we do not yet have widely available treatment that is affordable to the 300 000 babies born with sickle cell disease every single year worldwide," Wonkam says.

Wonkam comments: "I believe this is probably one of the landmark findings that have been performed in Africa where most of these patients live."

"It is our hope that this may shift a bit of paradigm in terms of science policy and diplomacy. We hope that funders will see what can actually be done in Africa and channel more means here. We also hope that this will help amplify the voices of more researchers that are working on SCD in Africa," Wonkam concludes.

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