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New study sheds light on genetics of schizophrenia in South Africa

A recent international study including several University of Cape Town (UCT) researchers emphasises that rare genetic mutations may play an important role in the cause of the illness.

The study, "Genetics of Schizophrenia in the South African Xhosa," published in the journal Science, is the first genetic analysis of schizophrenia in an ancestral African population, the South African amaXhosa.

Co-author Professor Dan Stein, head of the Department of Psychiatry at UCT, said: "The World Mental Health Survey consortium and the Global Burden of Disease studies have emphasised how prevalent and burdensome mental disorders are. Schizophrenia is an important component of that."

Schizophrenia affects approximately 1% of people in all parts of the world and is one of the leading causes of disability worldwide. This study revealed that amaXhosa individuals with schizophrenia are significantly more likely to carry rare damaging genetic mutations compared to amaXhosa individuals without severe mental illness.

Furthermore, the genes disrupted by the rare damaging mutations of these patients are likely to be involved in the organisation and function of brain synapses. Synapses coordinate the communication between neuronal cells, and the firing and organisation of neuronal synapses are ultimately responsible for learning, memory and brain function.

The study was undertaken not because the amaXhosa have an unusual prevalence of schizophrenia, but because there is need for genetics work in African populations, and because these populations have the greatest wealth of human genetic diversity. Importantly, the depth of genetic variation in Africa allowed findings on schizophrenia to emerge using a moderate sample size, and this helps inform our understanding of the genetics of schizophrenia worldwide.

Co-author Professor Raj Ramesar, head of the Department of Pathology and Division of Human Genetics at UCT, continues on this point: "We all share the vast majority of our

genome. As a tool when looking at the relationship between populations we look at the tiny bits that we know we vary by, and these can provide insights. We're keen on findings that will lead to better management of the illness locally. To some extent it's still very early. Schizophrenia is a combination of mutations and various other factors."

Human biology is universal. The genes and pathways identified by this research inform the understanding of schizophrenia for all human populations and provide potential mechanisms to design new more effective treatments.

In clinical studies it is important that the highest ethical standards are adhered to. For the current study the researchers took measures to ensure this.

One challenge for genetics research on serious mental disorders is ensuring that participants provide fully informed consent. Stein notes that the team used stringent measures to assess whether participants fully understood the study. One of the first publications from the study detailed how a structured instrument was used to make sure that participants understood the aim of the research.

Ramesar notes that the study also set up a Community Advisory Board (CAB) in order to ensure appropriate engagement with the community. "We made sure that our researchers were members of the community who could speak the home language of participants. We also carefully translated questionnaires, with the assistance of Prof Zingela." Carefully designed tool

Ensuring that both community and patient voices were represented in the research was important. Co-author Dr Goodman Sibeko, Head of the Division of Addictions Psychiatry at UCT, notes that the CAB provided valuable insights into the conduct of the current study. This resulted in another early publication from that study that focused on community engagement.

Regarding consent Stein says, "It is true that people with a mental disorder may be vulnerable in key ways. However, mental health advocates, including people with these conditions, have been vocal in their calls for more research on mental disorders. So we need to be careful of stereotyping people with mental disorders. They can understand the need for research, and we should not withhold from them the right to participate in such work."

The Human Heredity and Health in Africa (H3Africa) Consortium is focused on facilitating research into diseases in Africa. The consortium is concerned with building infrastructure, resources, training, and ethical guidelines to assist in the development of a sustainable African research enterprise – "led by African scientists, for the African people". The late Professor Bongani Mayosi, Dean of the UCT Faculty of Health Sciences, was an advocate for the importance of genetics in Africa and played a key role in H3Africa. The current study was part of the H3Africa consortium, and was funded by National Institutes of Mental Health (NIMH).

ENDS

Note to editors

The project was lead by Jon McClellan and Mary Claire King at the University of Washington, Seattle; Dan Stein at the University of Cape Town, South Africa; and Ezra Susser at Columbia University, New York. The Xhosa community participated in the development and conduct of the research. The project was supported by the National Institute of Mental Health of the U.S. National Institutes of Health.

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