First Genomic Study of Schizophrenia in African People Reveals Potential Genetic Causes

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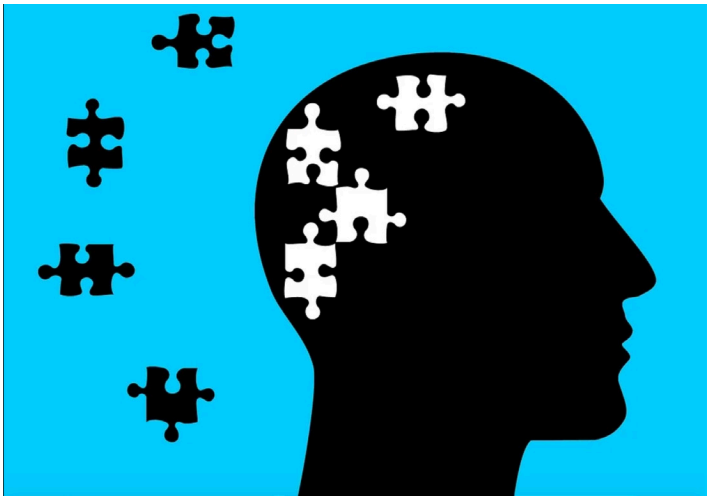
Affecting roughly one percent of the population worldwide, schizophrenia first manifests in the mid-teens to late 30s, and distorts an individual's interpretation of reality. Schizophrenia is diagnosed through the presence of "positive symptoms" which are feelings or behaviors that are usually not present such as hallucinations, delusions, and disordered thinking. In addition, it is diagnosed through presence of "negative symptoms" which are feelings or behaviors that are lost, such as emotional flattening. These positive symptoms and negative symptoms behavior have the effect of impairing daily functioning. Medications that control symptoms are currently the cornerstone of Schizophrenia treatment.

Studies indicate genetics as a factor for the development of Schizophrenia, as first-degree biological relatives of individuals with schizophrenia are approximately 10 times more likely than the general population to develop it. While these studies suggest the heredity plays an important role, a single genetic cause of schizophrenia has not been elucidated. Moreover, triggering factors and environmental influences such as birth complications, drug abuse, childhood background or even time of birth have also been suggested to play a role in its development. This has led to the assumption that schizophrenia is not only a genetically-defined disorder but a dynamic process leading to dysregulation of multiple pathways.

Multiple large-scale population genetic projects have found African populations to be the most genetically diverse. However, European population have been predominately the focus of genetic studies. The relative lack of genetics studies in African and other populations leaves a major gap in understanding human genetics. Almost 99 percent of human evolution took place in Africa after the first modern humans originated and before humans migrated from Africa to Europe and Asia 50,000 to 100,000 years ago. Because of the lack of studies in Africa, many generations of human genetic history are missing from our understanding of human adaptation and of human disease (Gulsuner et al., 2020).

To address this dearth of diverse Schizophrenia-focused genetic studies, an international group of scientists — including investigators from Columbia University Mailman School of Public Health and New York State Psychiatric Institute, as well as the University of Cape Town and the University of Washington — conducted the first genetic analysis of schizophrenia in an ancestral African population, publishing their results in *Science*.



Studies of ancestral African populations like the Xhosa have more diverse background DNA, which facilitates the identification of truly rare mutations.

The researchers analyzed blood samples collected from roughly 900 individuals diagnosed with schizophrenia and 900 controls for the Xhosa population. Their study revealed that participants with schizophrenia are significantly more likely to carry rare, damaging genetic mutations compared to participants without schizophrenia.

These rare mutations, such as *GABRB1*, were also more likely to affect brain and synaptic function. Synapses coordinate the communication between brain nerve cells called neurons; the organization and firing of neuronal synapses are ultimately responsible for learning, memory, and brain function.

In addition, the genes and pathways identified by this research inform the understanding of schizophrenia for all human populations. For example, the researchers found that some of the results could also be generalized to non-African population. By comparing to another study on a Swedish population, the researchers found that as with the Xhosa, Swedish cases were significantly more likely than controls to harbor damaging mutations in genes important to brain and synaptic function and neurotransmitter release.

Further studies in African populations might also suggest potential mechanisms for the design of more effective treatments.

Advances in treatments for schizophrenia depend on characterizing shared mechanisms underlying the illness.

Results from African and European cohorts converge, both implicating disruptions in synaptic architecture. Current antipsychotic medications generally act broadly on synaptic proteins, and they affect firing in neuronal circuits throughout the central nervous system. Although helpful for reducing psychotic symptoms, these agents are not curative and generally do not address the neurocognitive and social difficulties inherent to the disorder (Yang and Tsai, 2017).

However, through studying diverse populations, the characterization of specific components can allow for the development of therapeutics that target specific molecular pathways. Interventions designed to remediate disruptions in synaptic structural organization and signaling pathways potentially offer more specific therapeutic benefits that can address the psychotic symptoms without the disruptions of normal brain function.

One of the most important takeaways from the study is the enormous promise studying diverse populations has for the understanding of the genetic basis of complex human phenotypes. Human biology is universal, and the study of human genomics in Africa provides an invaluable scientific opportunity to better detect and define genes that are critical for health worldwide. The exact causes of schizophrenia, and other complex diseases, will be only be found with a world-wide approach to genetic studies and collaboration.

SOURCES

Donegan, J. J., and Lodge, D. J. (2017). Cell-based therapies for the treatment of schizophrenia. *Brain research*, 1655, 262–269. Available at: doi.org/10.1016/j.brainres.2016.08.010.

Gulsuner, S., Stein, D. J., Susser, E. S., Sibeko, G., Pretorius, A., Walsh, T., Majara, L., Mndini, M. M., Mqulwana, S. G., Ntola, O. A., Casadei, S., Ngqengelele, L. L., Korchina, V., van der Merwe, C., Malan, M., Fader, K. M., Feng, M., Willoughby, E., Muzny, D., Baldinger, A., Andrews, H. F., Gur, R. C., Gibbs, R. A., Zingela, Z., Nagdee, M., Ramesar, R. S., King, M.-C.., and McClellan, J. M (2020). Genetics of schizophrenia in the South African Xhosa. *Science*, 367, 367(6477):569-573. Available at: doi: 10.1126/science.aay8833.

Yang, A. C., and Tsai, S. J. (2017). New Targets for Schizophrenia Treatment beyond the Dopamine Hypothesis. *International journal of molecular sciences*, 18(8), 1689. Available at: doi.org/10.3390/ijms18081689.