Improved outlook for people of African descent with treatment-resistant schizophrenia

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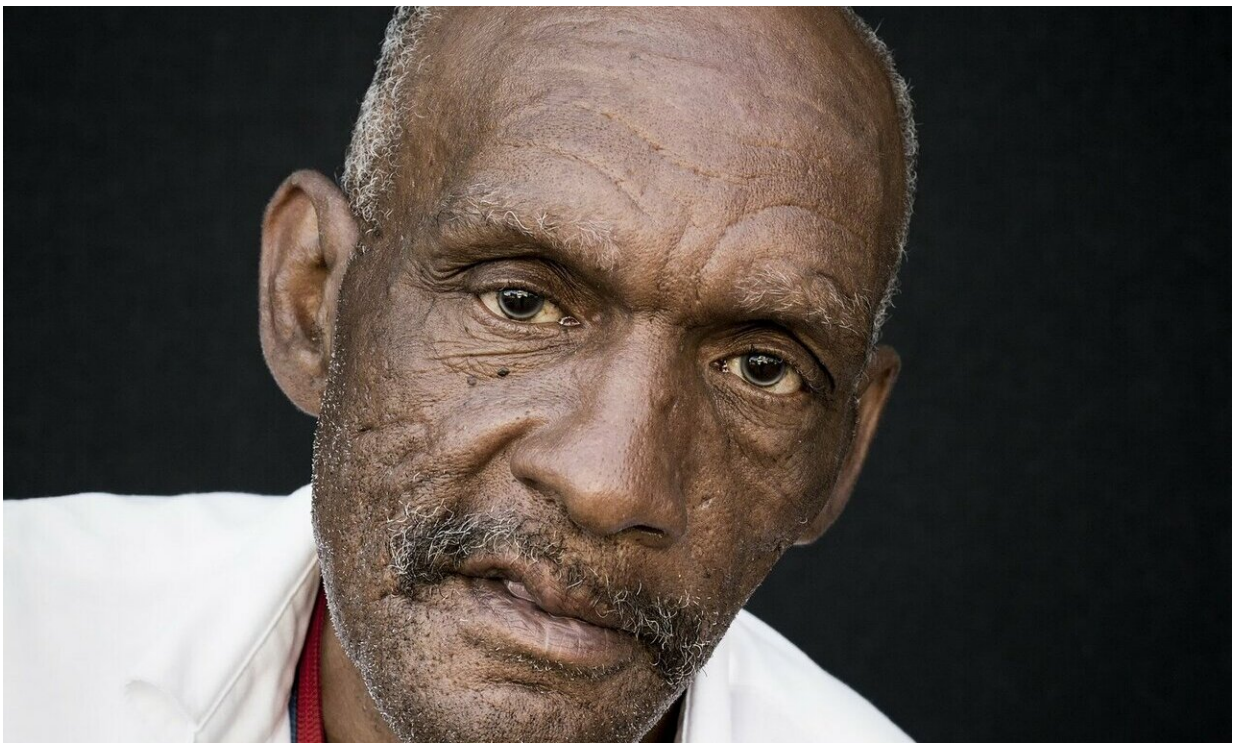

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A study led by researchers at Cardiff University means that more people of African descent who have treatment-resistant schizophrenia could be safely given the drug best proven to manage their symptoms.

The team identified a genetic and benign cause in people of African descent for lower neutrophil levels: a condition that can also be a rare and potentially life-threatening side-effect of the only licensed medication for treatment-resistant schizophrenia.

Professor James Walters, a principal investigator at Cardiff University's MRC Centre for Neuropsychiatric Genetics and Genomics, said: "Clozapine is currently the most effective therapy for people with treatment-resistant schizophrenia. However, it can cause a rare adverse side-effect called neutropenia, which is a reduction of neutrophils, a type of white blood cell used to fight infection."

Neutropenia is thought to affect around 3 in every 100 people prescribed clozapine. In rare cases it can develop into agranulocytosis, a serious and potentially life-threatening condition. As a result, people being treated with clozapine undergo regular blood tests, and if neutropenia is detected treatment is stopped immediately.

"This appears to be more common in people from African or African-Caribbean backgrounds and can mean these groups are more likely to stop being treated with clozapine. Our findings suggest, that in many cases, this increased rate of neutropenia is a result of a benign ethnic neutropenia rather than a reaction to clozapine," added Professor Walters.

The team conducted a genome-wide association study using samples from 552 people of African ancestry taking clozapine.

Dr. Sophie Legge, joint-first author of the study, explained: "We identified a genetic variant in the ACKR1 gene that was strongly associated with lower neutrophil counts, and participants in our sample with this variant were 20 times more likely to develop neutropenia during clozapine treatment than clozapine users without this genetic

variant."

The same genetic variant is responsible for the "Duffy-null' blood group, which is very common in areas of the world in which malaria has been endemic, including many parts of Africa, Asia and Latin America.

People with the Duffy-null blood group are at decreased risk of being infected with malaria, but their neutrophil levels are also lower, on average, than the rest of the population. It is thought to be the source of benign ethnic neutropenia, a hereditary condition affecting at least 25-50% of people with African or Middle Eastern ancestry.

Dr. Legge continued: "There is good evidence that benign ethnic neutropenia does not lead to increased rates of infection or agranulocytosis, so in practice it is likely that many people with treatment-resistant schizophrenia are unnecessarily excluded from taking medication that could help reduce their symptoms."

In light of these findings the team suggest offering a genetic test as a simple and sensitive strategy to diagnose benign ethnic neutropenia before prescribing clozapine.

Dr. Antonio Pardiñas, who co-led the project, said: "Individuals with the condition who show no signs of compromised immune function could have revised neutrophil thresholds in line with current benign ethnic neutropenia monitoring procedures. This would allow more people who would benefit from clozapine to start taking the medication while avoiding the need to stop treatment for many more.

"Crucially, this is dependent on the outcome of additional safety studies, but this pharmacogenetic test has the potential to assist the management of clozapine treatment."

The paper "A genome-wide association study in individuals of African ancestry reveals the importance of the Duffy-null genotype in the assessment of clozapine-related neutropenia' is published in the journal *Molecular Psychiatry*.

More information: Sophie E. Legge et al. A genome-wide association study in individuals of African ancestry reveals the importance of the Duffy-null genotype in the assessment of clozapine-related neutropenia, *Molecular Psychiatry* (2019). DOI: 10.1038/s41380-018-0335-7