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African schizophrenia genetic variants

The genetics of schizophrenia have predominately been studied in populations of European and Asian descent. However, studies in Africans, who host the greatest degree of human genetic diversity, have lagged. Examining the exomes of more than 1800 Xhosa individuals from South Africa, about half of which have been diagnosed with schizophrenia, Gulsuner *et al.* identified both rare and common genetic variants associated with the disease. They found that the genetic architecture of schizophrenia in Africans generally reflects that of Europeans but that the greater genetic variation in Africa provides more power to detect relationships of genes to phenotypes.

Science, this issue p. **569**

Abstract

Africa, the ancestral home of all modern humans, is the most informative continent for understanding the human genome and its contribution to complex disease. To better understand the genetics of schizophrenia, we studied the illness in the Xhosa population of South Africa, recruiting 909 cases and 917 age-, gender-, and residence-matched controls. Individuals with schizophrenia were significantly more likely than controls to harbor private, severely damaging mutations in genes that are critical to synaptic function, including neural circuitry mediated by the neurotransmitters glutamine, γ-aminobutyric acid, and dopamine. Schizophrenia is genetically highly heterogeneous, involving severe ultrarare mutations in genes that are critical to synaptic plasticity. The depth of genetic variation in Africa revealed this relationship with a moderate sample size and informed our understanding of the genetics of schizophrenia worldwide.

Schizophrenia is a disabling neurodevelopmental disorder characterized by aberrant perceptions, thought, and social connectivity. An evolutionary perspective is particularly valuable for understanding the genetic origins of the disorder (*1*). Because fewer children are born to persons with schizophrenia, mutations underlying the illness are under negative selection. Therefore, the genetic architecture of schizophrenia is characterized by damaging mutations that are very recent or de novo and thus individually extremely rare (*2*–*5*). Common variants with individually small effects on schizophrenia have also been reported (*6*). Genes implicated by both common and rare alleles operate in pathways that are essential to brain development, including histone modification, neuronal migration, transcriptional regulation, immune function, and synaptic integrity (*3*–*6*).

Until now, nearly all genetic studies of schizophrenia have been based in populations of European or Asian ancestries. The goal of the present study was to identify and characterize genetic influences on schizophrenia in the Xhosa population of South Africa. The study was undertaken not because the Xhosa have an unusual prevalence of schizophrenia, but because African populations harbor the greatest wealth of human genetic diversity (*7*). Nearly 99% of human evolution after the chimpanzee-human divergence 5 to 6 million years ago took place before human migrations from Africa to Eurasia 50,000 to 100,000 years ago. Because relatively small numbers of individuals migrated (*8*), a very large number of alleles remained on the African continent, creating an African-specific tranche of human genetic variation. Alleles of the African tranche are more rare than the common single-nucleotide polymorphisms (SNPs) shared by all populations and more common than recent mutations that appeared subsequently in all populations. In the absence of studies of ancestral African populations, alleles of the African tranche are missing from our understanding of human disease.

The Xhosa trace their history to the migration of Bantu people from the Great Lakes region of eastern Africa to southern Africa centuries ago. Until the arrival of these migrants, southern Africa was occupied exclusively by San peoples, who diverged from other modern humans at least 100,000 years ago (*9*). Archaeological, linguistic, and DNA evidence indicate that the Xhosa people are descended from the admixture of these Bantu and San populations (*10*–*12*). The Xhosa now live throughout South Africa and are the largest population of the Eastern Cape region.

For this project, participants with schizophrenia (cases) were recruited from psychiatric inpatient units and outpatient health clinics in the Eastern Cape Province and Western Cape Province (**Fig. 1A**). Controls were recruited from the same locales, including patients presenting with conditions not related to mental health. Cases and controls were matched for age, gender, education, and region of recruitment (*13*).

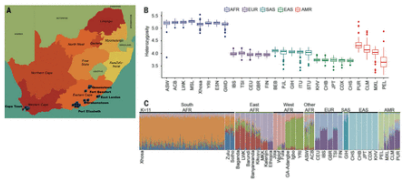

Fig. 1 The Xhosa of South Africa.

(**A**) Sites of the Western Cape and Eastern Cape provinces of South Africa, where cases and controls were recruited. (**B**) Heterozygosity at coding sequence 31.7 Mb of the human genome, calculated in 10-kb intervals, in the Xhosa and other populations from all continents. (**C**) Population structure of the Xhosa with respect to other world populations, evaluated by using ADMIXTURE version 1.3.0 with $K = 6$. Genotypes from populations other than the Xhosa

Vol 367, Issue 6477

Table of Contents

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