Study uncovers cell type-specific genetic insights underlying schizophrenia

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Schizophrenia is a complex disease with variable presentations, and the diverse nature of this mental health disorder has made understanding the mechanisms that cause the disease, and subsequently developing effective treatments, especially challenging.

In a new study, published May 23 is *Science*, a team led by McLean Hospital researchers used comprehensive genetic and cellular analyses to shed new light on the intricate molecular mechanisms underlying schizophrenia. Their new work provides a map for how the genes known to increase risk of schizophrenia affect specific cells within the brain.

"We discovered which cell types express genes associated with schizophrenia risk differently, which biological functions are impacted within those cells, and which transcription factors are important for these changes," explained lead and co-corresponding author, W. Brad Ruzicka MD, Ph.D., director of the Laboratory for Epigenomics in Human Psychopathology at McLean Hospital. "This understanding will allow future treatments to be tailored to specific genes and cell types, as well as individuals with schizophrenia."

Schizophrenia affects approximately 24 million people, or 1 in 300 people, worldwide, according to the World Health Organization.

For the new study, a multi-center team of researchers conducted a comprehensive single-cell analysis of transcriptomic changes in human prefrontal cortex, examining postmortem brain tissue from 140

individuals across two independent cohorts. Their analyses included more than 468,000 cells.

They uncovered unprecedented insights into the cellular basis of schizophrenia, linking genetic risk factors to specific neuronal populations.

Specifically, the researchers found that excitatory neurons emerged as the most affected cell group, with transcriptional changes implicating neurodevelopment and synapse-related pathways. Additionally, they found that known genetic risk factors for schizophrenia converge on alterations in specific neuronal populations, highlighting the interplay between rare and common genomic variants.

Through transcriptomic analysis, two distinct subpopulations of individuals with schizophrenia were identified, marked by the expression of specific excitatory and inhibitory neuronal cell states.

The new study suggests potential links between schizophrenia pathology and processes such as neurodevelopment, synaptic signaling, and transcriptional regulation, implicating key transcriptional regulators associated with both schizophrenia and neurodevelopmental disorders.

The study's authors anticipate that insights gleaned from this research could pave the way for targeted interventions and personalized treatments for schizophrenia, potentially improving clinical outcomes for individuals affected by this debilitating and often disabling disorder.

The research team is now working to expand on these findings by investigating other regions of the brain and the molecular impact of other psychiatric diseases such as bipolar disorder. They are also pursuing another dimension of complexity in this system by investigating isoform expression of implicated genes and how these cell type-specific

gene expression changes lead to functional and potentially druggable changes in the protein space.

"This work advances understanding of schizophrenia pathophysiology at greater detail across both the complex landscape of cells within the brain, and the diverse experiences of people with this disease," said Ruzicka, who is also associate medical director of Harvard Brain Tissue Resource Center at McLean, and an assistant professor of Psychiatry at Harvard Medical School.

"Our increased mechanistic understanding of schizophrenia provides avenues for future research to unravel the genetic and environmental underpinnings of this complex disease so we can provide our patients better care."

In addition to Ruzicka, co-authors from McLean include Sivan Subbaraju; Daniel Reed Tso; and Makayla Hourihan.

More information: W. Brad Ruzicka et al, Single-cell multi-cohort dissection of the schizophrenia transcriptome, *Science* (2024). DOI: 10.1126/science.adg5136.
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