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 Subburaju; Daniel Reed Tso; and Makayla Hourihan.


Provided by McLean Hospital