Shared genetics may shape treatment options for certain brain disorders

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Bipolar disorder is characterized by transitions between depression and mania. Credit: Wikipedia

Symptoms of schizophrenia and bipolar disorder, including psychosis,

depression and manic behavior, have both shared and distinguishing genetic factors, an international consortium led by researchers from Vanderbilt University and Virginia Commonwealth University is reporting.

The consortium's findings, which were published online June 14 in the journal *Cell*, are raising hopes that genetics could help characterize and eventually inform more effective treatment options for patients with these brain disorders.

"We can show that some of these symptoms which comprise these diagnoses have underlying biology that can be studied separately and characterized," said first author Douglas Ruderfer, Ph.D., assistant professor of Medicine, Psychiatry and Behavioral Sciences, and Biomedical Informatics in the Vanderbilt University School of Medicine.

"Of the many interesting findings reported here, one of the most important has been our ability to classify the risk genes for schizophrenia and bipolar disorder into three broad groups: those that influence risk for both disorders about equally, those that impact only on risk for schizophrenia with no apparent effect on bipolar illness and the smaller group that appear to act only specifically on bipolar illness," said senior author Kenneth Kendler, MD, director of the Virginia Institute for Psychiatric and Behavioral Genetics at VCU.

Schizophrenia and bipolar disorder are among the world's leading causes of disability. Although they are clinically distinct entities, they are often both seen within the same families and share overlapping symptoms.

With the sequencing of the human genome and development of powerful computational tools, it became possible to look for genetic variants that explain the biological basis for the differences between these two brain

disorders—and their common symptoms.

The problem was numbers, said Ruderfer, an investigator in the Vanderbilt Genetics Institute who came to Vanderbilt in 2016 from the Icahn School of Medicine at Mount Sinai in New York City. Researchers needed to study thousands of patients in order to tease out "needles" from their genetic "haystacks."

Toward that end Kendler and another pioneer in psychiatric genetics—the late Pamela Sklar, MD, Ph.D.—along with a number of other investigators including especially Patrick Sullivan helped organize the Psychiatric Genomics Consortium. In 2014, they, Ruderfer and their colleagues, published the first evidence that differences between bipolar disorder and schizophrenia have a genetic basis.

The current study, authored by the consortium's Bipolar Disorder and Schizophrenia Working Group, involved more than 500 investigators at more than 200 institutions in 34 countries.

Pooling their resources, the researchers were able to accumulate more than 53,000 individuals diagnosed with bipolar disorder or schizophrenia and substantial information on 28 symptoms of these disorders.

The researchers compared genotypes, the genetic readout, of individuals with the disorders to those from 54,000 controls who did not have either mental illness. They also compared the genotypes of people who had differing symptoms of bipolar disorder or schizophrenia.

The analysis, called a genome-wide association study, identified dozens of loci, or chromosomal locations, that were shared, and multiple loci that were divergent between bipolar disorder and schizophrenia. The researchers were able to quantify genetic risk of each disorder in each individual and correlate the genetic component with the symptoms.

Some of these genetic components clearly distinguished between the two illnesses, while others, particularly those that were associated with psychosis, were shared. In other words, people who experienced psychotic symptoms had similar genetic traits—whether they had been diagnosed with bipolar disorder or schizophrenia.

More research is needed. But "if we could utilize genetics as a kind of biomarker, (potentially) we could inform treatment and tie that to outcome and course of illness," Ruderfer said.

More information: Douglas M. Ruderfer et al. Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes, *Cell* (2018). DOI: 10.1016/j.cell.2018.05.046

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