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Researchers find first strong genetic risk factor for bipolar disorder

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Credit: Susanna Hamilton, Broad Communications

The main treatment for bipolar disorder, lithium, was approved a half-century ago but doesn't help all patients and has significant side effects. Little progress has been made in finding better therapies, in part because

scientists don't fully understand how the condition arises or exactly how lithium improves symptoms when it does work.

A genetic study involving thousands of people with bipolar disorder has revealed new insight into the condition's molecular underpinnings. Led by scientists at the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard who collaborated with colleagues around the globe, the effort pinpoints a gene called AKAP11 as a strong risk factor for both bipolar disorder and schizophrenia. The findings may provide clues to how lithium works, as the AKAP-11 protein is known to interact with a molecular pathway modified by the drug. While many common genetic variants of small effects have been discovered, AKAP11 is the first gene found to have a large effect on bipolar disorder risk. This result has already kicked off new research at the Broad to further study the disorder in cells and animals, with a focus on molecular mechanisms that can in turn lead to identification of biomarkers to match patients with treatments and develop novel therapies.

The study appears in *Nature Genetics*.

"This work is exciting because it's the first time we've had a gene with large-effect mutations for bipolar disorder," said Steven Hyman, director of the Stanley Center for Psychiatric Research, a core member of the Broad, and Harvard University Distinguished Service Professor of Stem Cell and Regenerative Biology. "This is an important step toward the kind of research into disease mechanisms that, across the history of medicine, has underwritten successful therapeutics."

Big study, big effect

Bipolar disorder is a severe, heritable mood disorder that affects approximately 1 percent of the population and often begins in early

adulthood. A better understanding of the condition's biological roots could lead to more effective therapies that can improve quality of life.

Scientists in the Stanley Center partnered with colleagues around the world in the Bipolar Exome Consortium to identify rare differences in the DNA sequence that alter proteins with the hope of discovering ones with a large impact on disease risk. Although rare mutations may only occur in a minority of patients, the strong impact on disease risk means that they can illuminate the biological mechanisms involved in the condition. Those insights could one day lead to new ways of treating the disorder that improve symptoms in many people, even those without the rare mutation.

The researchers began by comparing the exomes, or protein-coding portion of the genome, of roughly 14,000 people with bipolar disorder to 14,000 healthy controls. People with the condition were more likely to carry gene variants that result in abnormally truncated, dysfunctional proteins. Some of these variants were in genes already associated with risk for schizophrenia, another severe mental illness that often begins after adolescence.

The team next incorporated results of a large-scale study conducted by the Schizophrenia Exome Sequencing Meta-analysis (SCHEMA) consortium. They combined the exome sequences of 24,000 people with schizophrenia who participated in the SCHEMA study with those of 14,000 people with bipolar disorder, and compared the genome sequence in those with the conditions to that of healthy controls. This analysis revealed rare protein-truncating variants in the AKAP11 gene that raise disease risk several-fold, making it the strongest genetic risk factor found for bipolar disorder to date.

"The AKAP11 variants don't contribute much to risk among the population as a whole, but the real value is what they reveal about the

roots of disease, and that's why we're really focused on them," said senior author Benjamin Neale, director of genetics for the Stanley Center and co-director of the Program in Medical and Population Genetics at the Broad, where he is also an institute member. Neale is also an associate professor in the Analytic and Translational Genetics Unit at Massachusetts General Hospital and an associate professor in medicine at Harvard Medical School, and he co-led the study with first author Duncan Palmer, a postdoctoral fellow in Neale's lab.

The protein product of AKAP11 interacts with another protein called GSK3B, a molecular target of lithium that is a potential mechanism of efficacy. Thus, the discovery offers intriguing clues to lithium's effects in the body that may shed light on the action of lithium and lead to the identification of other therapeutic targets.

New variants, new models

To explore the molecular and behavioral effects of the AKAP11 gene variants uncovered in the study, Stanley Center researchers are now creating cellular and animal models carrying an altered form of the gene. The truncating variants effectively disable one copy of the gene in the genome, potentially cutting the abundance of the AKAP-11 protein in half. Models carrying genetic variants like these—and the protein alterations they produce—are easier to create in the lab than those with more common disease-related variants that occur in non-coding parts of the genome and that have unclear effects on protein function. For the first time, scientists will be able to employ research models harboring the same variants found to clearly increase risk in humans.

The researchers are also exploring whether AKAP-11 or one of its molecular partners could serve as a biomarker for the condition, to aid in diagnosis or help ensure that future clinical trials include patients who are most likely to benefit from a particular therapy.

The researchers and their colleagues aim to keep recruiting more patients with bipolar disorder for large-scale studies that could uncover still more genetic risk factors. "Ideally, we'd like to find risk variants across the whole genome, which will give us the very best chance of coming up with treatments for everyone," said Hyman. "This is a first, and we're hoping we're going to find many more genetic factors. It's going to take a lot of exome sequencing, but it is very exciting."

More information: Duncan S Palmer et al, Exome sequencing in bipolar disorder reveals shared risk gene AKAP11 with schizophrenia, *Nature Genetics* (2021). DOI: 10.1101/2021.03.09.21252930

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