

Largest study of its kind implicates gene abnormalities in bipolar disorder

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A large genetic study of bipolar disorder has implicated machinery that balances levels of sodium and calcium in neurons. The disorder was associated with variation in two genes that make components of such ion channels. Although it's not yet known if or how the suspect genetic variation might affect the balance machinery, the results point to the possibility that bipolar disorder might stem, at least in part, from malfunction of ion channels.

The largest genetic analysis of its kind to date for bipolar disorder has implicated machinery involved in the balance of sodium and calcium in brain cells. Researchers supported in part by the National Institute of Mental Health, part of the National Institutes of Health, found an association between the disorder and variation in two genes that make components of channels that manage the flow of the elements into and out of cells, including neurons.

"A neuron's excitability – whether it will fire – hinges on this delicate equilibrium," explained Pamela Sklar, M.D., Ph.D., of Massachusetts General Hospital (MGH) and the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, who led the research. "Finding statistically robust associations linked to two proteins that may be involved in regulating such ion channels – and that are also thought to be targets of drugs used to clinically to treat bipolar disorder – is astonishing."

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affect the balance machinery, the results point to the possibility that bipolar disorder might stem, at least in part, from malfunction of ion channels.

Sklar, Shaun Purcell, Ph.D., also of MGH and the Stanley Center, and Nick Craddock, M.D., Ph.D., of Cardiff University and the Wellcome Trust Case Control Consortium in the United Kingdom and a large group of international collaborators report on their findings online Aug. 17, 2008 in *Nature Genetics*.

"Faced with little agreement among previous studies searching for the genomic hot spots in bipolar disorder, these researchers pooled their data for maximal statistical power and unearthed surprising results," said NIMH Director Thomas R. Insel, M.D. "Improved understanding of these abnormalities could lead to new hope for the millions of Americans affected by bipolar disorder."

In the first such genome-wide association study for bipolar disorder, NIMH researchers last fall reported the strongest signal associated with the illness in a gene that makes an enzyme involved the action of the anti-manic medication lithium. However, other chromosomal locations were most strongly associated with the disorder in two subsequent studies.

Since bipolar disorder is thought to involve many different gene variants, each exerting relatively small effects, researchers need large samples to detect relatively weak signals of illness association.

To boost their odds, Sklar and colleagues pooled data from the latter two previously published and one new study of their own. They also added additional samples from the STEP-BD study and Scottish and Irish families, and controls from the NIMH Genetics Repository. After examining about 1.8 million sites of genetic variation in 10,596 people – including 4,387 with bipolar disorder – the researchers found the two

genes showing the strongest association among 14 disorder-associated chromosomal regions.

Variation in a gene called Ankyrin 3 (ANK3) showed the strongest association with bipolar disorder. The ANK3 protein is strategically located in the first part of neuronal extensions called axons and is part of the cellular machinery that decides whether a neuron will fire. Co-authors of the paper had shown last year in mouse brain that lithium, the most common medication for preventing bipolar disorder episodes, reduces expression of ANK3.

Variation in a calcium channel gene found in the brain showed the second strongest association with bipolar disorder. This CACNA1C protein similarly regulates the influx and outflow of calcium and is the site of interaction for a hypertension medication that has also been used in the treatment of bipolar disorder.

Source: National Institute of Mental Health

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