

# Genetic roots of bipolar disorder revealed by first genome-wide study of illness

**The likelihood of developing bipolar disorder depends in part on the combined, small effects of variations in many different genes in the brain, none of which is powerful enough to cause the disease by itself, a new study shows. However, targeting the enzyme produced by one of these genes could lead to development of new, more effective medications.**

The research was conducted by scientists at the National Institutes of Health's National Institute of Mental Health (NIMH), with others from the Universities of Heidelberg and Bonn and a number of U.S. facilities collaborating in a major project called the NIMH Genetics Initiative.

The study is the first to scan virtually all of the variations in human genes to find those associated with bipolar disorder. Results were published online May 8 in *Molecular Psychiatry* by Amber E. Baum, PhD, lead researcher Francis J. McMahon, MD, and colleagues.

"This is an example of how advances in genetics research feed into practical applications. This research would not have been possible a very few years ago. We now have a new molecular target scientists can investigate in their search for better medications for bipolar disorder," said NIH Director Elias A. Zerhouni, MD.

About 5.7 million American adults have bipolar disorder, which also is called manic-depressive illness. Symptoms include extremes in mood, from pronounced over-excitement and elation, often coupled with severe irritability, to depression. Children also may have the condition, usually in a more severe form than adults.

"We're beginning to get a foothold on the genetics of this complex brain disorder," said NIMH Director Thomas R. Insel, MD.

Most people occasionally have mood swings, but the shifts that occur in bipolar disorder, and the changes in behavior and energy level that accompany them, are sometimes disabling. Lithium and the other mood-stabilizing medications used to treat the condition help many patients.

But some people do not respond to these medications, and clinicians need more options so that they can tailor treatments to each patient. People inherit different gene variations, which may influence whether or not they respond to a given medication. Identifying and targeting these variations could help scientists develop additional medication options that take these differences into account.

One of the genes the researchers correlated with the disorder, DGKH, is active in a biochemical pathway through which lithium is thought to exert its therapeutic effects. The gene produces an enzyme (diacylglycerol kinase eta) that functions at a point closer to the root of the lithium-sensitive pathway than does the protein that lithium is thought to target. Scientists can now try to develop more effective medications by focusing on new compounds that act on the DGKH enzyme or regulate how much of the enzyme is produced. The DGKH gene is on chromosome 13.

Several other genes detected in the study produce proteins involved in this and other biochemical pathways thought to play a role in bipolar disorder. Understanding the effects that variations of these genes have on brain-cell function could lead to explanations of how they contribute to the condition and how it might be better prevented or treated.

"Treatments that target just a few of these genes or the proteins they make could yield substantial benefits for patients. Lithium is still the primary treatment for bipolar disorder, but DGKH is a promising target for new treatments that might be more effective and better tolerated," McMahon said.

The finding was enabled by recent genetics technology that allows researchers to scan, in a single experiment, thousands of genes for variations. Everyone has the same genes, but variations in them influence whether or not a person gets a specific disease. In this study, researchers compared variations found in the scans of 413 adults who had bipolar disorder with variations found in the scans of 563 healthy adults.

By pooling the genetic material of the adults with bipolar disorder, the U.S. researchers were able to scan the entire group at a small fraction of the cost of scanning each person's material individually. The genetic material of the healthy group was pooled and scanned separately, again at a fraction of the cost of individual scans. The researchers then zeroed in on the gene variations that occurred more often in the people with bipolar disorder and examined them individually.

An important issue in genetics research is that findings correlating specific genes with specific diseases in one population may not apply to other populations. This study addressed that issue by focusing on US participants of European ancestry, then repeating the study in a large group of patients in Germany. Similar outcomes were found in both populations, strengthening the validity of the results. A subsequent study is examining whether the results apply to other populations, and will look for common variations among them.

The researchers will soon make the results of their scans available, on a website, to other scientists who are pursuing this line of research.

Source: National Institute of Mental Health

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