Making sense out of the biological matrix of bipolar disorder

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The more that we understand the brain, the more complex it becomes. The same can be said about the genetics and neurobiology of psychiatric disorders. For "Mendelian" disorders, like Huntington disease, mutation of a single gene predictably produces a single clinical disorder, following relatively simple genetic principals. Compared to Mendelian disorders, understanding bipolar disorder has been extremely challenging. Its biology is not well understood and its genetics are complex.

In a new paper, Dr. Inti Pedroso and colleagues utilize an integrative approach to probe the biology of bipolar disorder. They combined the results of three genome-wide association studies, which examined the association of common gene variants with bipolar disorder throughout the genome, and a study of gene expression patterns in post-mortem brain tissue from people who had been diagnosed with bipolar disorder. The findings were analyzed within the context of how brain proteins relate to each other based on the Human Protein Reference Database protein-protein interaction network.

"None of our research approaches provides us with sufficient information, by itself, to understand the neurobiology of psychiatric disorders. This innovative paper wrestles with this challenge in a creative way that helps us to move forward in thinking about the neurobiology of bipolar disorder," commented Dr. John Krystal, Editor of Biological Psychiatry.

Dr. Pedroso explained, "We combined information about genetic

variation from thousands of cases and controls with brain gene expression data and information from protein databases to identify networks of genes and proteins in the brain that are key in the development of bipolar disorder."

The analysis resulted in the ability to define risk gene variants that were deemed functional, by virtue of the association with changes in gene expression levels, and to group these functional gene variants in biologically meaningful pathways.

The results implicated genes involved in several neural signaling pathways, including the Notch and Wnt signaling pathways. These pathways are key processes in neurotransmission and brain development and these findings indicate they are also likely to be involved in causing this severe disorder. The authors noted that three features stand out among these genes: i) they localized to the human postsynaptic density, which is crucial for neuronal function; ii) their mouse knockouts present altered behavioral phenotypes; and iii) some are known targets of the pharmacological treatments for bipolar disorder.

Dr. Gerome Breen, senior author on the study and Senior Lecturer at King's College London Institute of Psychiatry, said, "Our study provides some of the first evidence to show the biochemical and developmental processes involved in causing risk for developing this life-long and costly illness. We have highlighted potential new avenues for new drug treatments and intervention."

More information: The article is "Common Genetic Variants and Gene-Expression Changes Associated with Bipolar Disorder Are Over-Represented in Brain Signaling Pathway Genes" by Inti Pedroso, Anbarasu Lourdusamy, Marcella Rietschel, Markus M. Nöthen, Sven Cichon, Peter McGuffin, Ammar Al-Chalabi, Michael R. Barnes, and Gerome Breen (doi: 10.1016/j.biopsych.2011.12.031). The article

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