

## Common Psychiatric Disorders Share Genetic Underpinnings

A massive undertaking by the Brainstorm Consortium to analyze the genomes of nearly 900,000 individuals has revealed strong genetic overlap between common psychiatric disorders.

These include attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, major depressive disorder (MDD), and schizophrenia. Neurologic disorders, such as Parkinson's disease and Alzheimer's disease, appear more distinct from each other.

"Uncovering the genetic influences and patterns of overlap between different genetic risk factors allows us to better understand the root causes of these conditions and potentially identify specific mechanisms appropriate for tailored treatments," first author Verner Anttila, PhD, research fellow at the Broad Institute of the Massachusetts Institute of Technology and Harvard University, in Cambridge, told Medscape Medical News.

"The high degree of genetic correlation among the psychiatric disorders suggests that current clinical categories do not accurately reflect the underlying biology, which may play a role in, for example, the difficulties psychiatry has had in developing new treatments. The results suggest that these new heritability-based approaches may allow us to improve diagnostic criteria, particularly for the psychiatric disorders," said Anttila.

The study was published online June 21 in Science.

### Genetic Overlap

The researchers quantified genetic overlap across 25 psychiatric and neurologic disorders from genome-wide association studies (GWAS) of 265,218 patients and 784,643 control persons and assessed the relationship of those disorders to physical and cognitive phenotypes from nearly 1.2 million individuals.

They found significant genetic overlap across different types of psychiatric disorders, particularly between ADHD, bipolar disorder, MDD, and schizophrenia. They also found overlap between anorexia nervosa and obsessive-compulsive disorder (OCD), as well as between OCD and Tourette syndrome.

The high degree of genetic overlap among the psychiatric disorders suggests a need to refine psychiatric diagnostics, the researchers say. "The tradition of drawing these sharp lines when patients are diagnosed probably doesn't follow the reality, where mechanisms in the brain might cause overlapping symptoms," Benjamin Neale, PhD, co-senior author, from the Broad Institute and the Analytical and Translational Genetics Unit at Massachusetts General Hospital, said in a news release.

In contrast, neurologic disorders, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis, appear more distinct from one another and from the psychiatric disorders, except for migraine, for which there was a significant genetic link to ADHD, MDD, and Tourette syndrome.

"Neurological disorders showed a more limited extent of genetic correlation than that of the psychiatric disorders, suggesting greater diagnostic specificity and/or more distinct etiologies," the authors write.

Both psychiatric and neurologic disorders showed robust correlations with cognitive and personality phenotypes.

For example, with regard to the personality phenotypes, neuroticism, "which has by far the largest sample size," showed significant correlations with MDD, anxiety, and Tourette syndrome.

Within the cognitive phenotypes, genetic factors that predispose individuals to certain psychiatric disorders — namely, anorexia, autism, bipolar disorder, and OCD — correlated significantly with factors associated with higher childhood cognitive measures, including more years of education and attending college. However, neurologic disorders, particularly Alzheimer's disease and stroke, showed a negative correlation with these cognitive measures.

"We were surprised that genetic factors of some neurological diseases normally associated with the elderly were negatively linked to genetic factors affecting early cognitive measures. It was also surprising that the genetic factors related to many psychiatric disorders were positively correlated with educational attainment," Anttila said in a news release. "We'll need more work and even larger sample sizes to understand these connections."

#### From Genetics to Therapeutics

"This study is the first to look at genetic correlations for neurological disorders, and consequently also the first one to compare psychiatric and neurological disorders," Anttila told Medscape Medical News. "The size of the study, both in terms of disorders and individuals studied, represents a considerable expansion on previous work — for many disorders, by at least an order of magnitude."

Reached for comment, Christopher Klein, MD, neurologist at the Mayo Clinic, Rochester, Minnesota, said that understanding the genetic susceptibility in human brain diseases is important, as it can "assist in clinical classifications and ultimately improved pharmacological and behavioral therapeutics.

"The Brainstorm Consortium authors advance this study by looking at diverse brain disorders by meta-analysis of GWAS genetic associations in classically defined ICD coded psychiatric and neurologic disorders. Most importantly, also studied were relationships with behavioral cognitive phenotypes," said Klein.

The finding of shared pathogenesis and heritability among diverse psychiatric disorders "suggest more common molecular associations than previously appreciated in what appear to be clinically distinct disorders," said Klein. "In contrast, and predictably, classic neurologic disorders like Alzheimer's, Parkinson's, multiple sclerosis did not have strong overlap genetic associations.

"Nevertheless, some behavioral cognitive phenotype and genetic overlaps were found between both psychiatric and neurologic disorders. As an example, migraine had behavioral overlap with many psychiatric disorders, suggesting shared pathogenic mechanism."

Klein said this work "provides support of continued study in this area in the hope of better classification and care of this diverse group of patients. Emphasized in future work will be the need to identify the specific molecular mechanisms that underlie the chromosomal association found by GWAS analysis."

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