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NEUROPSYCHIATRIC DISORDERS

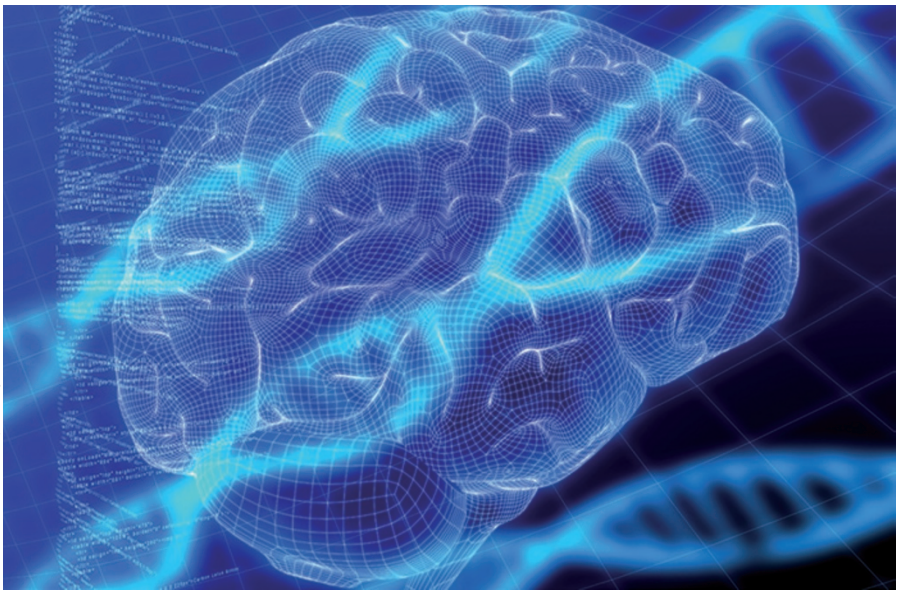
Blurring diagnostic boundaries: common genetic risk variants in major psychiatric disorders

A large study incorporating genome-wide association study (GWAS) data from over 60,000 individuals has uncovered genetic risk variants that are common to a range of major psychiatric disorders, raising important questions about the aetiology and diagnostic classification of these conditions. The research, which was published in *The Lancet*, was conducted by the Psychiatric Genomics Consortium (PGC)—an organization that was founded in 2007 with the specific aim of performing meta-analyses of GWASs relating to psychiatric disease.

"We have long known, from pedigree and twin studies, that genes play an important role in the risk of a broad range of psychiatric disorders," explains Jordan Smoller from Massachusetts General Hospital, Boston, MA, USA, one of the leaders of the study. "In the past 5 years, large-scale GWASs have begun to identify specific genetic variants that underlie this risk, particularly for schizophrenia, bipolar disorder and autism."

The new study brought together single-nucleotide polymorphism (SNP) data on five neuropsychiatric disorders —autism spectrum disorders, attention deficit–hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia—from 33,332 cases and 27,888 controls. As Smoller indicates, this was the first time that all five conditions had been examined simultaneously in a single GWAS.

The researchers identified SNPs that exceeded genome-wide statistical significance at four loci: regions of chromosomes 3p21 and 10q24, and the L-type voltage-gated calcium channel subunit genes *CACNA1C* and *CACNB2*. "It may be that genetic variation in basic systems, like calcium channel signalling, increase the risk of a general susceptibility to neuropsychiatric disorders, and that some combination of other genetic and nongenetic risk factors then channel this risk into the development of specific disorders," says Smoller.



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These findings are especially timely in view of the impending publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the standard reference text for the classification of psychiatric disorders. "The current system for defining psychiatric disorders—and still the basis for the newest version of the DSM—relies on grouping symptoms that have been defined by a consensus of experts," Smoller points out. "Our findings may inform efforts to ultimately move beyond this purely descriptive system of classification to one based on the causes of illness; these results suggest that disorders that we think of as quite different may in fact have some degree of shared biology."

The authors acknowledge that their study has a number of limitations. For instance, misdiagnosis in some cases —schizophrenia and bipolar disorder, in particular, can be difficult to distinguish from one another—could have caused the degree of genetic overlap to be overestimated. Also, the current analysis was restricted to individuals of European ancestry, and whether the genetic associations are generalizable to other populations is currently unknown.

The team now plans to use cellular and animal models, as well as additional studies in humans, to explore the molecular mechanisms through which the shared genetic variants exert their effects. The PGC is also extending its investigations to include other neuropsychiatric disorders, including obsessive–compulsive disorder, Tourette syndrome, post-traumatic stress disorder, and anorexia nervosa.

"The ultimate goal is to get a comprehensive picture of the genetic architecture of neuropsychiatric disorders with the hope that this can lead to new insights into the biology and treatment of these disorders," concludes Smoller.

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Original article Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* doi:10.1016/S0140-6736(12)62129-1