Shared genetics among major psychiatric disorders

Since 2005, the National Human Genome Research Institute’s database of published genome-wide association studies (GWAS) has accumulated more than 5110 entries for over 500 traits. The rapid growth of data repositories has enabled researchers to undertake large studies and meta-analyses, and has increased the power for detection of trait-associated variants. In The Lancet, the Psychiatric Genomics Consortium (PGC) describes its analysis of genome-wide single nucleotide polymorphism (SNP) data for 33332 cases and 27888 controls distributed among the five major psychiatric disorders in the PGC (major depressive disorder, bipolar disorder, schizophrenia, autism spectrum disorders, and attention deficit hyperactivity disorder). The study has combined some of the leading methodological approaches in genetics to examine the possibility of shared genetic make-up for these diseases. The main innovative contribution of the present study is the combination of qualitative and quantitative analyses of the shared genetic features associated with vulnerability to these five disorders.

Reliability of the results was strengthened by an accurate methodological design. The investigators addressed some typical limitations of GWAS (cryptic population stratification and unknown biological relevance of the detected variants) by inclusion of several case-control samples, all of European ancestry, and by corroboration of results by pathway and expression quantitative trait loci (eQTL) analysis. Pathway analysis might balance genetic heterogeneity bias (i.e., the analysis of a whole molecular pathway avoids spurious associations due to simple interpopulation and intrapopulation individual allele stratification) and eQTL corroborated genetic findings at the functional level; both techniques are crucial to confirmation of the hypothesis-free results of GWAS. Because the unit of analysis is set to functionally interacting molecules, pathway analysis also reduces the risk of type 2 error. Indeed, although individual SNP markers did not reach significance in many GWAS, ranking of SNPs associated previously with different psychiatric disorders identified convergence of pathways in synaptogenesis, axonal guidance, and synaptic plasticity, and now calcium signalling, which is pivotal in the mechanisms of all these biological processes. Nevertheless, genetic effects with odds ratios around 1 are difficult to disentangle from cryptic population stratification, thus deep sequencing of the top regions in homogeneous populations would be appropriate for confirmation of these findings. The design of the present study ensures the collection of a large sample with some degree of diagnostic reliability, but data for patients were obtained only with use of general disease categories; substantial clinical heterogeneity is expected, which could lead to a high risk of missing markers showing genuine associations.

In addition to methodological issues which are pertinent to researchers, genetic studies should provide translational value for clinicians. With this perspective, the present study might contribute to future nosographic systems, which could be based not only on statistically determined clinical categories, but also on biological pathogenic factors that are pivotal to the identification of suitable treatments. Consistent with the present results, voltage-dependent calcium channel antagonists produce antidepressant-like effects.
in mice, and the inositol-1,4,5-triphosphate receptor is a fundamental regulator of calcium release from intracellular stores and a target of lithium.

The overlap of genetic factors in major psychiatric disorders confirms previously reported evidence of abundant pleiotropy in human complex disorders (pleiotropy might involve roughly 17% of genes that are associated with diseases or disease traits). Thus, the same variant might contribute to the risk of different diseases, possibly through specific endophenotypes (heritable traits that segregate with one or more diseases), modulated in both prenatal and postnatal environments through epigenetic changes that associate with chromatin-modifying complexes and involve neuroplastic adaptations (figure). With a simplified perspective, the high frequency of pleiotropic effects suggests that a perturbation (the introduction of a genetic variant in this case) in a biological system determines alterations in a number of downstream molecular processes, which is due to the redundancy of biological systems. Calcium signalling is a crucial regulator of neuronal growth and development, thus abundant pleiotropy in variants affecting this pathway was expected and has now been confirmed. However, family studies suggest some degree of genetic overlap, but also consistent diversity among disorders. This finding is exemplified by the increased risk of major depressive disorder in relatives of patients affected by bipolar disorder, but not the converse. Therefore we agree about the presence of some transdiagnostic risk factors, but many genes and polymorphisms are expected to confer a liability to individual psychiatric diseases.

Although some methodological limitations remain, much progress has been made. New generation exome and full genome sequencing and genome-wide pathway analysis are among the most appealing methodologies. We therefore believe that genetics, possibly thanks to more comprehensive phenotype and endophenotype assessments, can contribute to prediction and prevention of psychiatric diseases, along with the identification of molecular targets for new generations of psychotropic drugs.

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We declare that we have no conflicts of interest.