Across 14 Psychiatric Disorders Mapping the Genetic Landscape

Scientists at the Psychiatric Genomics Consortium Cross Disorder Working Group (CDG3) analyzed genetic data from 14 psychiatric disorders to assess how much genetic risk is shared across disorders versus how much is disorder-specific.

They identified five major underlying factors explaining, on average, around two-thirds of each disorder's genetic variance, though some conditions, such as Tourette's syndrome, retain substantial disorder-specific variance, and found 238 loci associated with at least one of the cross-disorder factors, including 27 loci shared across two or more factors.

The analysis also identified hundreds of loci that differentiate pairs of disorders, particularly those from different genomic factors, with disorders within the same factor showing very few differentiating loci, consistent with strong within factor similarity.

Their findings offer insights into more biologically grounded psychiatric classification and treatment.

Study

Compared with earlier cross-disorder efforts, this analysis benefited from much larger sample sizes and the inclusion of substance use disorders. Because ancestral diversity varied widely across datasets, the primary analyses were restricted to participants of European-like genetic ancestry, with supplementary cross-ancestry checks that were often underpowered and therefore interpreted cautiously.

The researchers compiled genome-wide association study (GWAS) summary statistics for 14 psychiatric disorders, drawn from diagnostic manual-based criteria and from GWAS datasets powered by these criteria.

These included updated results for eight disorders from earlier Cross Disorder Group analyses, namely anorexia nervosa, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder, bipolar disorder, major depression, obsessive compulsive disorder (OCD), schizophrenia, and Tourette's syndrome, and six newly added disorders (alcohol, cannabis, and opioid use disorders, anxiety disorders, post traumatic stress disorder (PTSD), and nicotine dependence).

Sample sizes varied, and most analyses were restricted to people of European-like genetic ancestry to ensure statistical comparability. CDG3 represents a substantial improvement in statistical power and disorder coverage compared with earlier CDG1 and CDG2 analyses.

Several analytic frameworks were used. Linkage disequilibrium score regression (LDSC) was used to estimate genome-wide genetic associations between disorders. Popcorn assessed cross-ancestry genetic correlations to evaluate generalizability. MiXeR, a bivariate causal mixture model, quantified the aggregate number of shared causal variants, regardless of effect direction.

Genomic structural equation modelling (genomic SEM) identified latent genetic factors underlying shared risk across disorders. This approach evaluated multiple model structures, including a five-factor correlated model and a hierarchical p-factor model representing general psychopathology. Local analysis of co-variant association (LAVA) examined regional genetic correlations across 1,093 linkage disequilibrium (LD)- independent genomic regions, identifying hotspots in which multiple disorders shared local genetic architecture.

The study also used case-case GWAS (CC GWAS) to identify loci that distinguish disorders, with nearly all disorder-distinguishing loci occurring between disorders assigned to different genomic factors, and almost none occurring between disorders within the same factor, supporting the factor structure.

Together, these methods triangulated genetic overlap from global, regional, functional, and loci-specific perspectives.

Findings

Genome-wide LDSC analyses showed widespread genetic overlap across the 14 disorders, forming clusters of particularly strong correlation, such as major depression with anxiety and PTSD, and schizophrenia with bipolar disorder.

Cross-ancestry analyses indicated that some findings, such as schizophrenia, appeared more consistent across European-like and East-Asian-like datasets. In contrast, others, such as PTSD and major depression, showed weaker cross-population consistency and remain limited by insufficient statistical power.

MiXeR analyses revealed that disorders shared more causal variants than implied by LDSC correlations, suggesting that most shared variants influence disorders in the same direction.

Genomic SEM identified five latent genetic factors, compulsive (anorexia nervosa, OCD, Tourette's), schizophrenia, bipolar, neurodevelopmental (autism, ADHD, Tourette's), internalizing (major depression, PTSD, anxiety), and substance use disorders (SUD) (alcohol, cannabis, opioid use, nicotine dependence, and a smaller cross loading from ADHD).

These factors accounted for most of each disorder's heritability attributable to single-nucleotide polymorphisms (SNPs), though Tourette's syndrome showed substantial disorder-specific genetic variance.

A higher-order p factor explained shared variance across all five factors, loading most strongly on internalizing disorders but with significant heterogeneity across SNPs, indicating that factor-

specific signals remain essential to capture divergent genetic effects and that the p factor alone is insufficient to represent the genetic architecture of psychopathology.

Correlations between factors and external traits showed meaningful patterns, including strong links with neuroticism, stress sensitivity, and suicidality, as well as distinct associations with cognitive performance and socioeconomic characteristics for some factors.

LAVA analyses identified 101 genomic hotspots where multiple disorders shared significant local correlations, with especially dense overlap between major depression, anxiety, major depression, PTSD, and bipolar, schizophrenia.

Conclusion

This large-scale analysis shows that psychiatric disorders share substantial genetic foundations, with five broad genomic factors explaining much of their heritable risk. The strongest shared architecture was seen for schizophrenia, bipolar disorder, and internalizing disorders, all of which had very few disorder-specific loci in CC GWAS analyses, reinforcing their high degree of genetic similarity.

Biological analyses pointed to distinct cellular pathways underpinning different factors, such as excitatory neuron involvement in schizophrenia and bipolar disorder, and oligodendrocyte-related processes in internalizing disorders, with many pleiotropic genes showing elevated expression in fetal and early-life brain tissue, pointing to important developmental mechanisms.

These findings support moving toward a more biologically informed psychiatric classification system that complements rather than replaces existing symptom-based diagnostics.

Strengths include an unprecedented sample size, diverse analytic methods, and the integration of genome-wide, regional, and functional insights.

Limitations include uneven ancestral representation, which required restricting most analyses to European-like datasets; considerable variation in GWAS sample sizes; the possibility of cross-trait assortative mating inflating correlations; diagnostic misclassification; and varying diagnostic precision across studies.

Despite these limitations, the work provides a comprehensive map of shared genetic architecture and identifies promising targets for future mechanistic research and therapeutic development.

Source:

https://www.news-medical.net/news/20251212/Massive-genetics-study-shows-what-truly-separates-and-unites-14-psychiatric-disorders.aspx