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Advancing Genomic Understanding of Externalizing Psychopathology via a Multi-Ancestry GWAS of 3 Million Individuals

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Background, rationale/significance, hypothesis: Psychiatric disorders characterized by behavioral disinhibition, including ADHD and substance use disorders, often co-occur and lead to significant difficulties for individuals and their communities. These 'externalizing' disorders are influenced by a complex interplay of biological and environmental factors – many of which are shared across disorders. Motivated by substantial heritability and genetic correlations among relevant phenotypes, the Externalizing Consortium previously conducted a GWAS of externalizing in ~1.5 million individuals, identifying 579 loci. Here, we present updated analyses in over 3 million individuals, further advancing genomic discovery and polygenic prediction.

Results: We used Genomic SEM to analyze the genetic factor structure of externalizing, estimate genetic correlations with other traits, and conduct a multivariate GWAS of the transdiagnostic factor. Critically, these analyses incorporated new data from ancestrally diverse samples and additional clinical phenotypes (e.g., cannabis, tobacco, and opioid use disorders). Bio-annotation and bioinformatic approaches were used to characterize the biological correlates of externalizing, followed by polygenic prediction in independent cohorts. A common externalizing factor explained the majority of genetic variance among phenotypes, and our multivariate GWAS identified over 1,400 associated loci, many harboring genes involved in neurodevelopment. The polygenic index (PGI) explained 12% of the variance in externalizing – a 30% improvement over the original PGI.

Discussion: Our findings underscore the importance of cutting across diagnostic boundaries to better understand the complex etiologies of externalizing disorders. By integrating multi-ancestry data and novel statistical approaches, we advance genomic discovery and illuminate key neurodevelopmental pathways across the lifespan, identifying potential avenues for targeted interventions and therapeutic development.