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Advancing Gene Discovery for Substance Use Disorders Using Additional Traits Related to Behavioral Disinhibition

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Background: Substance use disorders (SUDs) frequently co-occur with each other and with other traits related to behavioral disinhibition, a spectrum of outcomes referred to as externalizing. Nevertheless, genome-wide association studies (GWAS) typically study individual SUDs separately.

Rationale: This single-disorder approach ignores genetic covariance between SUDs and other traits and may contribute to the relatively limited genetic discoveries to date. We used Genomic SEM to estimate SNP effects on a broad factor representing liability to externalizing and SUDs, on factors representing liability to behavioral disinhibition and SUDs separately, and on residualized SUDs. Subsequent gene-based, tissue expression, and polygenic score (PGS) analyses were used to compare the ability of these alternative approaches to identify genetic influences on SUDs.

Hypotheses: We expected to find that 1) analyzing behavioral disinhibition and SUD phenotypes together would improve gene identification and polygenic prediction of SUDs and 2) PGS for residual SUDs to best predict their respective SUD in target samples.

Results: We identified genomic risk loci and genes uniquely associated with Externalizing that are relevant to the neurobiology of substance use. Genes identified for residual SUDs were involved in substance-specific processes (e.g., metabolism). The Externalizing PGS accounted for the most variance in substance outcomes relative to the PGS for the other factors and residual PGS appeared to capture substance specific signals.

Discussion: Our findings suggest that modeling both a broad genetic liability to externalizing behaviors and substance-specific liabilities enhances the detection of genetic effects related to SUDs and explains more variance in substance use outcomes.