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Using the genetic architecture of substance use disorders to aid in gene identification: Findings from the Externalizing Consortium

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Human gene identification efforts for substance use disorders (SUDs) continue to lag behind other areas of psychiatry, in part due to constrained sample sizes of available SUD cases. Recent meta-analyses of substance-related phenotypes such as age of initiation, consumption and problems, reveal significant genetic correlations across substance use outcomes. These findings map onto twin data demonstrating significant genetic correlations across substance use disorders and other disorders and traits characterized by behavioral disinhibition. The underlying latent factor has been called Externalizing, and is highly heritable (~80%). Based on a set of well-powered GWAS summary statistics of phenotypes across the externalizing spectrum, we used Genomic SEM to model the latent factors driving the genetic correlations across the externalizing spectrum, and to boost statistical power in GWAS for individual traits. Our initial analyses include GWAS summary statistics for alcohol problems (*n* = 150,640), lifetime cannabis use (*n* = 186,875), ever smoker (n=1,251,809), general risk tolerance (*n* =390,934), ADHD (*n* = 53,293), automobile speeding (*n*=367,151), and number of sexual partners (n=336,121). Across the phenotypes, our effective sample size is ~1.5 million independent observations. Genomic SEM analyses reveal a single latent factor underlying externalizing psychopathology. GWAS of the latent externalizing factor yields 628 independent genome-wide significant loci at a stringent threshold of $r^2 < 0.01$ with a 10,000,000kb window, and measurably increases the statistical power to detect genetic signals across externalizing phenotypes. Our analyses indicate that multivariate analyses provide a useful strategy for enhancing the power to identify variants involved in substance use disorders.