

A Genome-Wide Association Meta-Analysis of Any Substance Use Disorder

Substance use disorders (SUDs) frequently co-occur, which in part may be explained by shared genetic architecture. Given this comorbidity, conducting a genome-wide association study (GWAS) of a lowpass phenotype, such as having any SUD, may be a more accurate reflection of real-world substance use.

A GWAS of having any substance use disorder was performed in European-like (EUR-like; ncases= 19,491; ncontrols= 190,232) and African-like (AFR-like; ncases=11,429; ncontrols=56,141) genetic ancestry subsamples in All of Us v.8. The EUR-like summary statistics were then meta-analyzed with another GWAS of any SUD in FinnGen (ncases=30,806; ncontrols=362,304). In All of Us, any SUD was derived by two instances of ICD 9/10 codes for either alcohol, cannabis, tobacco, stimulant, or opioid use disorders at least 30 days apart. Analyses were conducted in PLINK 2.0 and included age, sex, genotyping site, and first 10 ancestry-specific genetic principal components as covariates.

In All of Us, tobacco use disorder (77% - 82.8% within cases) was the most common SUD, followed by alcohol use disorder (29.5% - 31.3%). 23 and 1 independent genome-wide significant SNPs were identified in the EUR-like and AFR-like GWASs, respectively. When meta-analyzed with FinnGen, 166 independent significant SNPs were identified, and genes previously identified across several individual SUD GWAS were implicated, including PDE4B, DRD2, and NFKB2. While substance-specific genes were also implicated, including ADH1B (alcohol), and OPRD1 (opioids), they were less significant than the cross-SUD genes noted above. No tobacco use-specific genes were identified despite this being the most common SUD endorsed. Genetic correlations with previous SUD GWAS ranged between 0.71 (cannabis use disorder) and 0.82 (addiction-rf).

These findings suggest that the any SUD phenotype primarily captures general genetic liability towards substance use disorders and highlights the importance of phenotyping in genetic studies. Future GWAS of substance use disorders should compare lowpass and deep phenotyping outcomes.

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