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Elucidating genetic risk factors for externalizing and internalizing alcohol use disorder behaviors through large-scale cross-disorder GWAS

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The genetic risk component for alcohol use disorder (AUD) includes variants involved in externalizing and internalizing risk behaviors. Evidence suggest that attention deficit hyperactivity disorder (ADHD) and major depressive disorder (MDD) represent the ends of continuous distributions in the population of inattentive/impulsive and depressive/internalizing behaviors respectively. Cross-disorder GWAS of AUD and ADHD and MDD could therefore highlight genetic risk factors involved in externalizing and internalizing AUD risk behaviors.

We performed cross-disorder GWAS of AUD(N=313,959), ADHD(N=225,534) and MDD (N=1,349,887) and identified nine genome-wide significant loci for AUDxADHD and 70 for ADHDxMDD. Genetic correlation (r_g) analyses identified notable differences including a stronger positive r_g of AUDxADHD with risky behavior ($r_g = 0.50$) compared to AUDxMDD ($r_g = 0.22$), whereas AUDxMDD demonstrated higher r_g with loneliness ($r_g = 0.67$) compared to AUDxADHD ($r_g = 0.21$), supporting that AUDxADHD and AUDxMDD variants overlap variants related to externalizing and internalizing behaviors respectively.

Both AUDxADHD and AUDxMDD risk genes demonstrated significant increased expression across all brain developmental stages in RNA-seq data from BrainSpan. GWAS results were linked to single-cell sequencing data from prenatal and adult brain, by calculating the single-cell disease relevance score (scDRS). We identified significantly increased scDRS for AUDxADHD and AUDxMDD in several neuronal cell-types with a stronger signal for AUDxADHD in dopaminergic and glutamatergic neurons while AUDxMDD showed a stronger signal for GABAergic neurons.

Our results suggest that cross-disorder GWAS of AUD with ADHD and MDD identifies genetic variants associated with different behavioral domains and that these variants might affect behavior partly through different biological mechanism involving different neuronal cell types.