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Shared and Unique 3D Genomic Features of Substance Use Disorders Across Multiple Cell Types

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Recent genome-wide association studies (GWAS) have revealed shared genetic components among alcohol, opioid, tobacco and cannabis use disorders. However, the extent of the underlying shared causal variants and effector genes, along with their cellular context, remain unclear. We leveraged our existing 3D genomic datasets comprising high-resolution promoter-focused Capture-C/Hi-C, ATAC-seq and RNA-seq across >50 diverse human cell types to focus on genomic regions that coincide with GWAS loci. Using stratified LD regression, we determined the proportion of genome-wide SNP heritability attributable to the features assayed across our cell types by integrating recent GWAS summary statistics for the relevant traits: alcohol use disorder (AUD), tobacco use disorder (TUD), opioid use disorder (OUD) and cannabis use disorder (CanUD). Statistically significant enrichments ($P<0.05$) were observed in 14 specific cell types, with heritability reaching 9.2-fold for iPSC-derived cortical neurons and neural progenitors, confirming that they are crucial cell types for further functional exploration. Additionally, several pancreatic cell types, notably pancreatic beta cells, showed enrichment for TUD, with heritability enrichments up to 4.8-fold, suggesting genomic overlap with metabolic processes. Further investigation revealed significant positive genetic correlations between T2D with both TUD and CanUD ($FDR<0.05$) and a significant negative genetic correlation with AUD. Interestingly, after partitioning the heritability for each cell type's cis-regulatory elements, the correlation between T2D and TUD for pancreatic beta cells was greater ($r=0.2$) than the global genetic correlation value. Our new genomic insights into substance use disorders implicate cell types where functional follow-up studies could reveal causal variant-gene mechanisms underpinning these traits.

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