Name: Yunlong Liu, Ph.D. Email: yunliu@iu.edu

Closing the Loop on Addiction GWAS: Multi-Omic Resolution, Perturbational Validation, and Therapeutic Prioritization

Genome-wide association studies (GWAS) have identified numerous loci associated with substance use disorders (SUDs), yet these findings largely reflect statistical association and do not directly resolve causal genes or mechanisms. To move beyond association, functional genomic data are required to connect risk variants to gene regulation and cellular context.

We implemented an integrative framework combining population-level GWAS with single-cell multiome data, massively parallel reporter assays (MPRA), and AI-based prioritization across five addiction-related phenotypes: problematic alcohol use (PAU), cannabis use disorder (CUD), opioid use disorder (OUD), tobacco use disorder (TUD), and a cross-phenotype addiction risk factor (addiction-RF). Using single-cell RNA-seq and chromatin accessibility profiles, we performed cell-type-specific eQTL and caQTL analyses to link genetic variation to gene expression and regulatory activity in defined cellular populations. These QTL mappings were integrated with GWAS signals to prioritize genes supported by both association and functional regulatory evidence.

Across phenotypes, we identified 51 genes significant in at least three SUD traits in one or more cell types. Four genes, UQCRC1, DALRD3, AMT, and MST1, were significant across all five phenotypes and localize to the chromosome 3p21.31 region, highlighting a shared locus of addiction liability.

To further probe functional consequences of prioritized genes, we performed CRISPR interference (CRISPRi) perturbations and measured downstream transcriptional effects, enabling assessment of putative regulatory impacts on gene expression. To inform potential mechanisms and therapeutic hypotheses, we integrated perturbational signature data from Connectivity Map (CMap) and examined concordance with real-world evidence from insurance claims for signals consistent with therapeutic modulation or clinical phenotypes.

Taken together, our results show that embedding cell-type-resolved functional genomics and perturbational validation within large-scale GWAS analyses both increases power to discover genes implicated in substance use disorders and yields genetically informed leads for mechanistic follow-up and therapeutic prioritization.

Authors:
Submitter: Yunlong Liu, Professor, Indiana University School of Medicine, Indianapolis, IN

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