Submitter's Name: Manav Kapoor
Submitter's email: manav.kapoor@mssm.edu

Integrative analysis of omics summary statistics to identify genes associated with substance use disorders

Manav Kapoor[1], Michael Chao[1], Dayne Mayfield[2], Yunlong Liu[3], Arpana Agrawal[4], Howard Edenberg[3], COGA collaborators and Alison Goate[1]

[1]Dept. of Neuroscience, Icahn School of Medicine at Mount Sinai; [2]Waggoner Center for Alcohol and Addiction Research, The University of Texas at Austin; [3]Biochemistry/ Molecular biology, Indiana University School of Medicine; [4]Dept. of Psychiatry, Washington University in St. Louis

Significance: Identification of causal variants and genes underlying the GWAS loci is essential to understanding the biology of substance use disorders (SUDs).
Hypothesis: Integration of "omics" data is a key step toward prioritization of genes and regulatory elements to be followed up by functional studies. We performed a Mendelian randomization analysis to integrate SUD GWAS datasets with gene expression and methylation quantitative trait loci (eQTLs and mQTLs) in large brain (N=1200), blood (N=35K) and myeloid (N=1500) datasets.
Results: Integrated analyses prioritized unique as well as shared cell types, regulatory elements, genes and pathways among alcohol dependence (AD), alcohol consumption (AC), and smoking (initiation, cessation, and heaviness). We also performed weighted gene co-expression analysis using mRNA expression data in brain (frontal-cortex) and prioritized networks and modules enriched for the variants associated with AD, AC and smoking. The AD variants were enriched in networks related to immune system regulation (e.g. *FKBP5, IL4R, IFITM3*) while smoking and AC GWAS variants were enriched for genes related to calcium signaling pathway (e.g. *CHRNA2, CHRNA6, CNR1*). Follow-up analysis using single nuclei RNA-Seq data from brains of alcoholics (N=25) validated above observation and showed enrichment of AD GWAS variants in astrocyte-expressed genes, while AC variants were primarily expressed in endothelial cells. We have created an online public resource to visualize the results of integrative analysis (https://lcad.shinyapps.io/alcoholGWAS/) to plan functional studies.
In conclusion, integrative analysis has identified several shared and specific genes/ pathways associated with SUDs. These common and specific pathways could provide insights for identifying therapeutic targets.