Name: Falk W. Lohoff Email: falk.lohoff@nih.gov

Multi-omics analyses of cortical proteome and single cell-type transcriptome identifies novel drug targets for problematic drinking behavior and alcohol use disorder

Daniel B. Rosoff[1,2], AB, ScB; Josephin Wagner[1], MD, MS; Andrew S. Bell[1], BS; Lucas A. Mavromatis[1], ScB; Jeesun Jung[1], PhD; Falk W. Lohoff[1#], MD

[1]Section on Clinical Genomics and Experimental Therapeutics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA
[2]NIH-Oxford-Cambridge Scholars Program; University of Oxford, UK

Integrating proteomic and transcriptomic data in brain tissue with the genetic architectures of problematic alcohol consumption and alcohol use disorder (AUD) has the potential to facilitate identification of much-needed novel therapeutic targets. However, systematic screens of different alcohol use behaviors in the cortical proteome or transcriptome at single cell resolution have not been performed.

Using genome-wide association summary statistics (GWAS) from 5 alcohol consumption behaviors, i.e., alcohol intake frequency (AIF) (N=462,346), binge drinking (N=143,658), total drinks per week (DPW) (N=537,349), problem items from the Alcohol Use Disorders Identification Test (AUDIT-P) (N=121,604), and AUD (45,554 cases; 190,056 controls), we performed systematic drug-target Mendelian randomization (MR) and colocalization screens of ~1,700 dorsolateral prefrontal cortex (dlPFC) proteins (N=722) and ~6,100 unique genes in 8 canonical brain cell types (N=192).

We identified 104 dlPFC proteins and 170 genes in brain cell types that colocalized with the alcohol outcomes. Comparison of the proteins and genes with chromatin-based gene mapping found that 50 of the proteins and 67 of the genes were novel; Replication with independent GWAS data set and comparison across neuropsychiatric disorders prioritized 46 proteins (including SARM1, GFRA1, and CYPB7B1) and 55 cell-type genes (such as PPP4R2, GXYLT2, and UNC79) as targets.

Our data underscored distinct proteomic and transcriptomic signatures of alcohol consumption compared to problematic drinking and AUD. Replication with the physical consequences of problematic drinking and side-effect profiling prioritized potential drug targets to inform future investigation to curb alcohol-related mortality and morbidity.