Name: Lu Wang
Email: lu.wang.lw763@yale.edu
PI Name: Hang Zhou
PI email: hang.zhou@yale.edu

Whole-exome Sequencing Study of Alcohol Use Disorder in 1,668 European Americans and 1,547 African Americans

Lu Wang[1,2], Henry R. Kranzler[3,4], Joel Gelernter[1,2], Hang Zhou[1,2]

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, CT; [2]VA Connecticut Healthcare System, West Haven, CT; [3]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA; [4]Veterans Integrated Service Network 4, Crescenz Veterans Affairs Medical Center, Philadelphia, PA

Background/hypothesis
Alcohol use disorder (AUD) is a leading cause of death and disability worldwide. There has been substantial progress made in genetic studies of AUD and problematic drinking. However, the SNP-based heritability attributable to common variants is low, reflecting a large amount of missing heritability. Whole-exome sequencing (WES) has been shown to be a powerful tool to identify variants associated with disease risks. Although rare variants can augment common variants, which have small effect sizes, there is a lack of WES studies for AUD.

Methods
We used WES to study 4,530 samples from the Yale-Penn sample. DSM-IV alcohol dependence (AD) was diagnosed using the Semi-structured Assessment for Drug Dependence and Alcoholism. After quality control procedures, 1,668 European American (EA, 1,409 cases and 259 controls) and 1,547 African American (AA, 1,156 cases and 391 controls) participants were retained for subsequent analysis. We carried out single-variant association analysis in EAs and AAs, separately, followed by a cross-ancestry meta-analysis. We also performed gene-based association analysis and other downstream analyses.

Results
In within-ancestry analyses, no variants reached genome-wide significance in EAs or AAs. RAB6A*rs61758773, RGMA*rs201874145 and DNAH17*rs185973414 are among the top variants nominally associated with AD. In the cross-ancestry meta-analysis, we identified the well-known functional variant rs1229984 in ADH1B associated with AD (p=5.98e-08).

Conclusions
Our study confirmed the association between rs1229984 and AD. However, the sample lacked power to identify novel rare variants contributing to AD risk. Recruitment of additional samples or incorporating WES data from biobanks (e.g., UK Biobank) is warranted to identify rare coding variants to help account for the missing heritability in the analysis of common variation.