Submitter Name: Yunlong Liu
Submitted email: yunliu@iupui.edu

Alcohol Abuse Associated Allele Specific Expression and Regulation in Human Brain Tissue

Xi Rao[1], Kriti Thapa[2], Hai Lin[1], Hongyu Gao[1], Katherine A. Hargreaves[3], Joseph Ipe[3], Hongmei Gu[2], Manav Kapoor[4], Sean P. Farris5, Tatiana Foroud[1], Alison M. Goate[4], R. Dayne Mayfield[5], Todd C Skaar[3], Howard J. Edenberg[1, 2], Yunlong Liu[1]

[1]Department of Medical & Molecular Genetics, Indiana University School of Medicine; [2]Department of Biochemistry & Molecular Biology, Indiana University School of Medicine; [3]Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine; [4]Ronald M. Loeb Center for Alzheimer's Disease, Department of Neuroscience, Icahn School of Medicine at Mount Sinai; [5]Waggoner Center for Alcohol and Addiction Research, University of Texas at Austin.

Alcohol abuse and alcoholism are significant public health problems. Understanding the molecular mechanism of how alcohol affects the brain will be crucial to prevent alcohol abuse and to reverse the impact of heavy drinking on brain. Animal models have been widely used to identify candidate mechanisms. However, due to ethical considerations, there were very limited molecular evidence from human brain. Through collaboration between the Collaborative Studies on Genetics of Alcoholism (COGA) and Integrative Neuroscience Initiative on Alcoholism (INIA) Consortia, we obtained four regions of brain tissues of 60 human samples from NSW Brain Bank (Australia), of which 30 were heavy drinker and 30 were social/non-drinkers. By integrating deep RNA-seq data with GWAS array results, we identified 90 genes with alcohol abuse associated differential allele-specific expression (ASE) in either of four brain regions, many of which have previously been implicated in neurological diseases. Single nucleotide variants (SNVs) in potential regulatory regions of these genes from GWAS array were further examined for cis-regulatory activity. Hundreds of SNVs were identified as highly potential cis-regulators based on their open chromatin environment, identification as expression quantitative trait loci (eQTLs) in GTEx, and prediction of altering transcription factor binding and miRNA binding sites. Using massively parallel reporter assay, we validated several functional SNVs in 3'UTR and will further identify functional SNVs in enhancer and promoter regions. Our findings will advance the understanding of alcohol abuse associated gene regulation in human brain and serve as a research framework for further study with expanded human brain tissues.