Name: Rudong Li, Ph.D. Email: rudoli@iupui.edu
PI Name: Yunlong Liu, Ph.D. PI email: yunliu@iupui.edu
Presentation preference: poster or podium

Investigating genetic inheritability of RNA alternative splicing in alcohol use disorders

Rudong Li[1,2], Andy B. Chen[1,2], Steven X. Chen[1,2], Dongbing Lai[2], Jill L. Reiter[1,2], Tatiana Foroud[2], Howard J. Edenberg[2,3], Yunlong Liu[1,2]

[1]Center for Computational Biology and Bioinformatics, Indiana University School of Medicine
[2]Department of Medical and Molecular Genetics, Indiana University School of Medicine
[3]Departments of Biochemistry and Molecular Biology, Indiana University School of Medicine

Alcohol use disorder (AUD) is a genetically heritable psychiatric disorder characterized by the problems caused by excessive alcohol consumption. Although significant efforts have been focusing on identifying risk loci through the genome-wide association studies, less is known about the roles of pre-mRNA splicing in AUD. We designed a Mendelian Randomization (MR)-based approach for identifying the transcripts whose splicing variants may contribute to the traits related to alcohol consumption. For each alternative splicing event, we first developed an Elastic Net-based predictive model for inferring the splicing outcomes based on the genotypes of the common SNPs within the gene region, using the RNA-seq data from the CommonMind Consortium. We applied these splicing models to the genotypes of the subjects in the Collaborative Studies on Genetics of Alcoholism study, and examined the association between the inferred splicing outcome with traits related to AUD using GEE (Generalized Estimation Equations) method. This analysis identified 27 events whose inclusion status may contribute to AUD. We further conducted the same analysis in the Australian Twin-family Study of Alcohol Use Disorder dataset. Six of the 27 splicing events were replicated (FDR<0.05). Further analysis suggests that pathways related to immune response and neurodegeneration are enriched for the downstream genes of these splicing events. In conclusion, this work investigated how genetically predicted RNA splicing might impact the risk for AUD, which highlighted neuro-immunological functions. This work also establishes a framework for studying the impact of RNA splicing in the genetics of other complex diseases.