Name: Kyle Sullivan
PI Name: Daniel Jacobson
PI Email: jacobsonda@ornl.gov

Identifying Integrated Pathways Among Multi-Omics of Nicotine Addiction Using Network Embedding Approaches

Kyle A. Sullivan¹, Alice Townsend², Matthew Lane², Anna Vlot¹, Peter Kruse², Bryan C. Quach³, Greg Keele³, Caryn Willis³, Melyssa S. Minto³, Julie D. White³, Ke Xu^{4,5}, Bradley E. Aouizerat⁶, Eric O. Johnson^{3,7}, Dana B. Hancock³, and Daniel A. Jacobson¹

¹Computational and Predictive Biology Group, Oak Ridge National Laboratory, Oak Ridge, TN ²Bredesen Center for Interdisciplinary Research and Graduate Education, University of Tennessee-Knoxville, Knoxville, TN

³GenOmics and Translational Research Center, RTI International, Research Triangle Park, NC
 ⁴Department of Psychiatry, Yale School of Medicine, New Haven, CT
 ⁵Veterans Affairs Connecticut Healthcare System, West Haven, CT
 ⁶Translational Research Center, College of Dentistry, New York University, New York, NY
 ⁷Fellow Program, RTI International, Research Triangle Park, NC

While many genetic loci have been associated with cigarette smoking, understanding the combination of biological pathways across brain regions that contribute to nicotine addiction circuitry and are associated with genetic risk is important in order to enhance treatment efficacy. Here, we have utilized MENTOR (Multiplex Embedding of Networks for Team-Based Omics Research) as an integration tool to identify common biological pathways from multi-omic data sets related to nicotine addiction. We first identified 310 unique genes related to cigarette smoking heritability from a genome-wide association study (GWAS) of smoking cessation from the GWAS & Sequencing Consortium of Alcohol and Nicotine Use (GSCAN) from European-ancestry individuals. Next, we identified DNA methylation (DNAm) CpG sites associated with cigarette smoking from postmortem brain tissue from the nucleus accumbens (NAc) and dorsolateral prefrontal cortex (dIPFC) of subjects with or without a lifetime history of cigarette smoking. We then used a combination of epigenome-wide association study results and wavelet transformbased methods to identify discrete loci and broader chromosomal patterns of smoking-induced DNAm alterations to these brain regions. Finally, we combined GWAS- and DNAm-identified genes with differentially expressed genes from the NAc and dIPFC to cluster these genes using MENTOR in combination with gene-gene networks from the NAc and dIPFC. Using the network embeddings developed from MENTOR, we identified biological pathways common among these omics types and brain regions, as well as the extent to which these pathways were implicated by GWAS and omics from the dIPFC and NAc.