Name: Kyle Sullivan
Email: sullivanka@ornl.gov
PI Name: Daniel Jacobson
PI email: jacobsonda@ornl.gov
Presentation preference: Oral Presentation

Multi-omic network analysis identifies key neurobiological pathways in opioid addiction

Kyle A. Sullivan[1], David Kainer[1], Matthew Lane[2], Michael R. Garvin[1], Alice Townsend[2], Bryan C. Quach[3], Caryn Willis[3], Nathan C. Gaddis[3], Ravi Mathur[3], Olivia Corradin[4], Brion S. Maher[5], Peter C. Scacheri[6], Sandra Sanchez-Roige[7,8], Abraham A. Palmer[9,10], Vanessa Troiani[11], Elissa Chesler[12], Dana B. Hancock[3], Eric O. Johnson[3,13], and Daniel A. Jacobson[1]

[1]Computational and Predictive Biology Group, Oak Ridge National Laboratory, Oak Ridge, TN; [2]Bredesen Center for Interdisciplinary Research and Graduate Education, University of Tennessee-Knoxville, Knoxville, TN; [3]GenOmics, Bioinformatics, and Translational Research Center, Biostatistics and Epidemiology Division, RTI International, Research Triangle Park, NC; [4]Whitehead Institute for Biomedical Research, Cambridge, MA; [5]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [6]Department of Genetics and Genome Sciences, Case Western Reserve University, Cleveland, OH; [7]Department of Psychiatry, University of California San Diego, La Jolla, CA; [8]Division of Genetic Medicine, Vanderbilt University Medical Center, Nashville, TN; [9]Department of Psychiatry, University of California San Diego, La Jolla, CA; [10]Institute for Genomic Medicine, University of California San Diego, La Jolla, CA; [11]Geisinger Health System, Danville, PA; [12]The Jackson Laboratory, Bar Harbor, ME; [13]Fellow Program, RTI International, Research Triangle Park, NC

Recent genome-wide association studies and omic-wide gene dysregulation studies in postmortem human brains have begun to robustly identify variants and genes associated with opioid addiction (OA). Empirically linking these genes to neurobiological pathways will help to elucidate the biological drivers underlying the observed associations and provide hypotheses for experimental studies. Here we applied a systems biology approach to connect OA-associated genes using a multiplex network with 15 network layers from distinct types of biological experimental evidence, including four brain region-specific gene expression networks constructed using explainable-AI with GTEx RNA-seq expression data. Our analysis focused on 15 OA-associated genes: five GWAS-derived genes (*OPRM1*, *FURIN*, *KDM4A*, *PPP6C*, and *PTPRF*), five differentially expressed genes (*DUSP4*, *DUSP6*, *EGR4*, *ETV5*, and *NPAS4*) from postmortem dorsolateral prefrontal cortex (dlPFC), and five genes from opioid-related epigenetic alterations to the dlPFC, including H3K27 hypoacetylation by ChIP-seq (*ASTN2*, *DUSP4*, *ENOX1*, *GABBR2*, *KCNMA1*) and DNA hypermethylation (*NTN1*). Using network mining algorithms, we identified a strong level of functional connection among these genes, with a high level of gene recovery (AUC=0.93) and a tight network of only 96 additional genes needed to connect all 15 OA-associated genes. Novel connections between genes were observed, including a scaffolding protein (*FLNA*) binding to both *OPRM1* and *FURIN*. Results also included multiple functional links between genes that modulate MAPK signaling (*DUSP4*, *DUSP6*, and *PPP6C*), a signaling pathway previously shown to respond to morphine exposure. Together, we identify key pathways that underlie OA-associated genes by integrating multi-omic datasets with a systems-level approach.