Name: Caryn Willis Email: cdwillis@rti.org
PI Name: Bradley T. Webb PI email: bwebb@rti.org

Gene Correlation Networks Replication Analysis Across Studies to Identify Top Candidate Gene Targets in Opioid Use Disorder

Caryn Willis[1], Melyssa S. Minto[1], Bryan C. Quach[1], Jeran K. Stratford[2], Megan Carnes[1], Matthew Schu[1], Ravi Mathur[1], Eric Otto Johnson[3], Javan Carter[1], Tracy L. Nolen[4], Nathan Vandergrift[1], Thomas Kosten[5], Bradley T Webb[1]

[1]Omics, Epidemiology, and Analytics Program, RTI International, Research Triangle Park, North Carolina, USA; [2]Bioinformatics and Computational Biology Program, RTI International, Research Triangle Park, North Carolina, USA; [3]Fellow Program, RTI International, Research Triangle Park, North Carolina, USA; [4]Clinic Research Network Center, RTI International, Research Triangle Park, North Carolina, USA; [5]Baylor College of Medicine, Houston, Texas, USA

Opioid use disorder (OUD) is a significant public health problem and is associated with alterations in reward circuitry which is reflected in changes in neuronal gene expression. Understanding OUD's neurobiological mechanisms is critical to identifying new targets for treatment and prevention. Network analyses can offer additional insights beyond single gene differential expression analyses. However, interpretation and replication of network analyses can be challenging. Here we develop a framework to address this challenge and attempt to identify expression networks robustly altered across datasets with the goal of finding treatments that target networks as opposed to individual genes.

Using four independent postmortem brain gene expression studies of OUD, we performed Weighted Gene Correlation Network Analysis (WGCNA). Each network of correlated genes was reduced to a representative eigengene and tested for association with OUD status. 64 primary networks were identified across independent studies and 15 showing robust association (FDR<.01) with OUD. Cross-study network gene assignments and sizes were inconsistent, making direct replication of OUD associated networks challenging. To perform replication, a primary study's network structure was imposed onto a replication dataset via single vector decomposition to produce an equivalent replication network. Examining all possible replication networks (n=192) showed a wide range of cross-dataset network correlations determined by gene loading values (-0.21 to 0.95) with 58 being modest (r>0.60). Of the replication networks, 11 showed consistent associations with OUD. Networks with high cross-dataset correlations and consistent associations with OUD contain neuronal expressed genes that are strong candidates targets for OUD pharmacotherapy.