Submitter Name: Hyejung Won
Submitter Email: hyejung_won@med.unc.edu

Elucidating the neurobiological bases of cigarette smoking and nicotine dependence

Hyejung Won[1,2]; Nancy Y.A Sey[1]; Bryan C. Quach;[3] Eric O. Johnson[3]; Dana B. Hancock[3] and the Nicotine Dependence GenOmics (iNDiGO) Consortium

[1]UNC Neuroscience Center, University of North Carolina; [2]Department of Genetics, University of North Carolina; [3]Research Triangle Institute International

Nicotine use remains a public health crisis resulting in adverse health outcomes. Genome-wide association studies (GWAS) have identified more than 300 genetic regions associated with nicotine dependence and smoking phenotypes. However, a majority of these variants reside in non-coding regions of the genome, making it a challenge to characterize their biological impact. Gene mapping tools including MAGMA have been developed to predict the putative target genes by converting SNP-level P-values to gene-level P-values. While MAGMA is a powerful tool, it annotates SNPs based on linear proximity, largely ignoring long-range regulatory interactions that have been shown to be critical for gene regulation and highly tissue-specific. We therefore developed Hi-C coupled MAGMA (H-MAGMA), which harvests the capacity of MAGMA while leveraging chromatin interaction profiles in the human brain in assigning non-coding SNPs to their target genes. Here, we apply H-MAGMA to GWAS of cigarettes per day (CPD) from the GSCAN consortium and nicotine dependence (ND) from the iNDiGO consortium, from which we identified 944 and 41 genes associated with CPD and ND, respectively (FDR<0.05). CPD- and ND- associated genes were enriched for acetylcholinergic signaling and synaptic transmission, recapitulating the known etiology of nicotine dependence. By characterizing the developmental expression trajectories of these genes, we identified early brain development (1st trimester) as a critical developmental stage for both ND and CPD. ND- and CPD-associated genes were highly expressed in neurons and astrocytes, highlighting central cell types for developing ND.