Genome-wide Interaction Analysis with Sex Reveals *PEX11G* as a Novel Gene for Nicotine Dependence

Dana B. Hancock[1], Sean Olson[1], Yuelong Guo[1], Sharon M. Lutz[2], Fangyi Gu[3], Christina A. Markunas[1], Nathan C. Gaddis[1], Kendra A. Young[2], Maria Teresa Landi[3], Daniel W. McNeil[4], Mary L. Marazita[5], Neil E. Caporaso[3], Nancy L. Saccone[6], Timothy B. Baker[7], John E. Hokanson[2], Laura J. Bierut[6], Eric O. Johnson[1]

[1]RTI International, Research Triangle Park, NC; [2]University of Colorado Anschutz Medical Campus , Aurora, CO; [3]National Cancer Institute, Bethesda, MD; [4]West Virginia University, Morgantown, WV; [5]University of Pittsburgh, Pittsburgh, PA; [6]Washington University, St. Louis, MO; [7]University of Wisconsin, Madison, WI

Animal models and human studies have demonstrated profound differences between males and females in their patterns of smoking initiation, dependence, and cessation. Genetic variants may contribute to some of the observed sex differences. None of the prior genome-wide association study (GWAS) analyses of nicotine dependence have considered SNP × sex interaction on a genome-wide scale. To identify SNPs that show differential associations between males and females, we carried out a multi-ancestry genome-wide meta-analysis that tested main SNP associations and SNP × sex interactions for nicotine dependence across 10 study samples: total N=18,302 (11,498 of European and 6,804 of African ancestries). Using 15 million 1000 Genomes-imputed SNPs, we tested associations with Fagerström Test of Nicotine Dependence-defined mild/moderate/severe dependence. Analyses were conducted separately by ancestry and study sample and adjusted for sex, age, eigenvectors for population stratification, and other study-specific covariates. Results were combined via inverse variance-weighted meta-analysis. We observed genome-wide significant association for an intronic SNP in the peroxisomal biogenesis factor 11 gamma (*PEX11G*) gene on chromosome 19 (main SNP association $P=4.1\times10^{-8}$ and SNP × sex interaction $P=1.4\times10^{-7}$) in the African ancestry sample. The minor allele frequency was 7% compared to 0% among European ancestry samples. The minor allele was associated with increased risk in males but decreased risk in females: odds ratio=1.4 and 0.8, respectively, for severe vs. mild dependence. The significantly associated SNP flanks an active enhancer element in several adult brain tissues, and it marks a DNase hypersensitivity site in fetal male, but not female, brain based on data from the Roadmap Epigenomics Consortium. Because of the opposing directions of association by sex, which were consistent across all of our African ancestry samples, the SNP was not detected in standard GWAS meta-analysis (P=0.10) without consideration for SNP × sex interaction. Independent replication testing with interaction is underway. Very little has been reported about the putative function of *PEX11G*, but peroxisomal activity has

been implicated in nicotine metabolism. This newly discovered *PEX11G* SNP association for nicotine dependence highlights the importance of considering sex beyond simple adjustment as a covariate and suggests that modeling genome-wide SNP × sex interaction may similarly reveal novel genetic loci for other addiction phenotypes.