Submitter Name: Meghan Chenoweth Submitter Email: meghan.chenoweth@utoronto.ca

Sex-Dependent Genetic Architecture of Tobacco-Related Biomarkers

Meghan Chenoweth[1,2,3], Caryn Lerman[4], Jo Knight[2,5], Rachel Tyndale[1,2,3]

[1]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health; [2]Department of Psychiatry, University of Toronto; [3]Department of Pharmacology and Toxicology, University of Toronto; [4]USC Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California; [5]Data Science Institute, Lancaster University

Tobacco use is highly heritable, differs by sex, and dose-dependently increases disease risk. Nicotine is metabolized to cotinine (COT) which is further metabolized to 3'hydroxycotinine (3HC). COT and COT+3HC are biomarkers which capture tobacco intake more accurately than self-reported measures (e.g. cigarettes/day). We conducted a genome-wide genotype-by-sex (GxS) interaction analysis of COT and COT+3HC in treatment-seeking Europeans (n=541 males, n=389 females) (NCT01314001). COT and COT+3HC were measured from blood samples collected at baseline. Linear regression models in PLINK2 included genotypes (coded additively), sex, GxS interaction terms, and covariates. For COT, five suggestive ($P<5x10^{-6}$) loci on chr 13, 4, 10, 6, and 12 were identified; the top variant was rs1813692 (3' of *TCB1D4*; beta=-0.24, se=0.05, GxS $P=1.29x10^{-6}$). Mean COT (in ng/ml) was 208, 230, and 253 in rs1813692 AA, AT, and TT females, compared to 276, 253, and 228 in males, respectively. For COT+3HC, three suggestive loci on chr 18, 17, and 5 were identified; the top variant was rs4427876 (3' of *MIR924HG*; beta=0.30, se=0.06, GxS $P=7.39x10^{-7}$). Mean COT+3HC (in ng/ml) was 506, 378, and 318 in rs4427876 CC, CT, and TT females, compared to 262, 326, and 345 in males, respectively. Six of these eight suggestive loci were associated with tobacco-related (e.g. smoking initiation) and/or psychiatric (e.g. schizophrenia, depression, alcohol dependence) traits in the GWAS Catalog. A more granular understanding of the factors that differentially influence tobacco intake in women and men may identify risk factors for heavier use and sex-specific opportunities to promote cessation and mitigate disease risk.