Submitter name: Dana Hancock
Submitted email: dhancock@rti.org

Genome-wide DNA methylation differences in nucleus accumbens of smokers vs. nonsmokers

Christina A. Markunas[1], Bryan Quach[1], Stephen A. Semick[2], Ran Tao[2], Laura J. Bierut[3], Thomas M. Hyde[2], Joel E. Kleinman[2], Eric O. Johnson[1], Andrew E. Jaffe[2], and Dana B. Hancock[1]

[1]Center for Omics Discovery and Epidemiology, Behavioral Health Research Division, RTI International, Research Triangle Park; [2]Lieber Institute for Brain Development (LIBD); [3]Department of Psychiatry, Washington University School of Medicine

Background: Peripheral blood studies have identified numerous DNA methylation (DNAm) biomarkers of cigarette smoking, but their relevance as neurobiological indicators is unknown due to DNAm tissue-specificity. In contrast, blood-based studies may not detect smoking-related DNAm differences in brain.

Rationale/significance: We report the first genome-wide DNAm study of smoking in human brain, focusing on nucleus accumbens (NAc) as an addiction-relevant tissue.

Hypothesis: Comparing DNAm in NAc of smokers vs. nonsmokers will reveal novel DNAm changes that underlie neurobiological processes of smoking and will extend a subset of previously identified smoking-associated CpGs from blood to brain.

Methods: Illumina HumanMethylation EPIC data were generated for 239 decedents: 58 cases (cotinine>12 ng/mL and next-of-kin report of current smoking) vs. 181 controls (cotinine=0 ng/mL and next-of-kin report of no current smoking). Following quality control, 221 decedents (120 Caucasian [23% cases], 101 African American [26% cases]) and 789,678 CpGs remained. Separately by ancestry, DNAm by smoking was tested using linear regression models adjusted for age, sex, cell-type proportions, DNAm-derived negative control principal components (PCs), and genotype-derived PCs. Ancestry-specific results were combined via meta-analysis.

Results: Cross-ancestry meta-analysis identified 7 CpGs that exceeded false discovery rate <0.05. Of these, 4 CpGs are upstream or within genes that were previously indicated as blood-based smoking biomarkers (Joehanes *et al.* 2016): *ZIC1, ZCCHC24, KIAA0146*, and *APCDD1L*. The remaining CpGs are novel for smoking.

Discussion: Our findings provide the first evidence for smoking-related DNAm changes in human NAc, highlighting CpGs that were previously undetected as peripheral biomarkers and may reflect brain-specific processes.