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Smoking-informed methylation QTLs in human nucleus accumbens

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The GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) identified hundreds of genome-wide significant variants associated with smoking behaviors (age of initiation, initiation, cigarettes per day, and cessation). Most are noncoding variants with unknown neurobiological effects. To evaluate their regulatory potential, we used genome-wide genotypes and DNA methylation (DNAm) data in postmortem human nucleus accumbens (NAc) from the LIBD Human Brain Repository to identify *cis*-methylation quantitative trait loci (mQTL) and investigate epistatic interactions by cigarette smoking. Active smokers (N=52) and nonsmokers (N=168) were defined based on cotinine and next-of-kin reporting. We used the joint 2df method to simultaneously test variant and smoking-by-variant interaction effects on DNAm, adjusting for biological and technical covariates. Multiple testing correction was applied using a two-stage approach based on eigenMT and Bonferroni methodologies. We found >2 million significant mQTLs ($p_{\text{adj}} < 0.05$) representing 51,315 unique CpGs. We assessed mQTLs among 371 overlapping GSCAN-identified variants. Of these, 229 (62%) were significant mQTLs, all driven by main effects of the variant on DNAm with no evidence of interaction with smoking. The top mQTLs of the 229 that overlapped with GSCAN were annotated to *HLA-G*, *BRWD1*, *ZNF207*, and *SLC25A20* (all $p < 1e-50$). The most significant of which, rs3115418-cg04567952 ($p_{\text{unadj}} = 1.9e-101$), was identified by GTEx as a NAc eQTL for the *TYW5* gene. We present the first genome-wide mQTL map in the human NAc and report enriched overlap with genetic variants of smoking behaviors, suggesting that regulation of DNAm levels in the brain may help explain the neurobiology underlying smoking GWAS loci.