

Genetically driven gene expression associated with nicotine dependence across ten brain regions reveals novel genes and brain regions

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Nicotine dependence (ND) is a highly heritable trait that reduces the likelihood of quitting smoking. However, genetically driven gene regulation across adult human brain regions, as related to ND biology, is poorly understood, with no large-scale genome-wide expression studies. It is now possible to validly impute genetically driven gene expression using recently developed methods and GTEx RNA-Seq as reference data. To identify novel genes and expression patterns associated with ND, we performed a genome-wide study using GTEx RNA-Seq data across 10 brain regions, the S-PrediXcan method, and results from our previous ND GWAS meta-analysis (N=28,677 European/European American [EA]). For replication, we applied S-PrediXcan to a GWAS of heavy vs never smokers from the UK Biobank (N=48,931 EA). We used FDR<0.10 for discovery and a Bonferroni-corrected threshold for replication, by tissue. We identified replicable differential expression of five genes in six brain regions, including a novel ND-associated gene, *SPDYE3* (7q22.1), although little is known about its function. We also identified genes on 15q25.1, including nicotinic receptor genes previously established for ND (*CHRNA5*; *CHRNA3*), and two genes showing limited (*ADAMTS7*) or no prior associations (*TMED3*) with ND. *Preliminary* follow-up of regulatory and ND signals within 15q25.1 using Hi-C data (a molecular technique used to detect genomic interactions), GTEx RNA-Seq brain data, and outside variant analysis, suggests that additional ND risk (compared to risk due to established ND variants in nearby *CHRNA5/A3/B4*) is explained by *ADAMTS7* cerebellar regulatory variants and may be due to a regulatory effect on *CHRNA5*. Additional analyses are needed to confirm these findings and update our results using the latest version of GTEx. Overall, our results indicate the potential importance of brain regions typically overlooked in addiction studies (e.g., cerebellum), highlight additional genes of interest in the established 15q25.1 region, and identify a novel ND-associated gene.