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Identifying Integrated Pathways Among Multi-Omics of Nicotine Addiction Using Network Embedding Approaches

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While many genetic loci have been associated with cigarette smoking, understanding the combination of biological pathways across brain regions that contribute to nicotine addiction circuitry and are associated with genetic risk is important in order to enhance treatment efficacy. Here, we have utilized MENTOR (Multiplex Embedding of Networks for Team-Based Omics Research) as an integration tool to identify common biological pathways from multi-omic data sets related to nicotine addiction. We first identified 310 unique genes related to cigarette smoking heritability from a genome-wide association study (GWAS) of smoking cessation from the GWAS & Sequencing Consortium of Alcohol and Nicotine Use (GSCAN) from European-ancestry individuals. Next, we identified DNA methylation (DNAm) CpG sites associated with cigarette smoking from postmortem brain tissue from the nucleus accumbens (NAc) and dorsolateral prefrontal cortex (dlPFC) of subjects with or without a lifetime history of cigarette smoking. We then used a combination of epigenome-wide association study results and wavelet transform-based methods to identify discrete loci and broader chromosomal patterns of smoking-induced DNAm alterations to these brain regions. Finally, we combined GWAS- and DNAm-identified genes with differentially expressed genes from the NAc and dlPFC to cluster these genes using MENTOR in combination with gene-gene networks from the NAc and dlPFC. Using the network embeddings developed from MENTOR, we identified biological pathways common among these omics types and brain regions, as well as the extent to which these pathways were implicated by GWAS and omics from the dlPFC and NAc.

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