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Meta-analysis of transcriptome-wide association studies across 13 brain tissues identified novel clusters of genes associated with nicotine addiction

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Background and significance: The rise of genome-wide association study (GWAS) has revealed valuable information about genetic variants associated with complex biological traits. However, interpreting the GWAS results is challenging. Transcriptome-wide association studies (TWAS) incorporated expression quantitative trait loci (eQTL) cohorts as a reference panel to detect associations with the phenotype at the gene level and were gaining popularity in recent years. For nicotine addiction, several important susceptible genetic variants were identified by GWAS, but TWAS that detected genes associated with nicotine addiction and unveiled the underlying molecular mechanism in the brain were still lacking.

Hypothesis and Methods: We hypothesized that genes regulated the nicotine addiction in a tissue-specific manner in the brain but had shared regulatory mechanism across multiple tissues. In our study, we first performed tissue-specific TWAS on cigarettes per day (CPD) in 13 brain tissues and then meta-analyzed the results while considering the heterogeneity across the tissues, and identified clusters of genes associated with nicotine addiction with unique cross-study patterns. This study was conducted in two large epidemiological cohorts: UK Biobank and the GWAS & Sequencing Consortium of Alcohol and Nicotine use.

Results and Discussion: We identified three gene clusters with unique biological pathways associated with CPD across brain tissues in both cohorts, including 20 homogenous genes in all tissues, 8 partially homogeneous genes in the cortex, cerebellum, and hippocampus tissues, and 10 tissue-specific genes in only a few specific brain tissues. The findings will provide important biological insights into the regulatory mechanism of nicotine dependence in the brain.