Integration of Gene Expression in animal studies with GWAS in human datasets to Identify Risk Genes for Nicotine Dependence

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Cigarette smoking is addictive and persistent smoking leads to nicotine dependence. Both family and twin studies have indicated that it is influenced by genetic factors. In recent years, several risk genes for nicotine dependence have been identified. However, these genes account for only a small proportion of observed heritability. It remains a challenge to discover those remaining genetic factors. FTND score is a common measure for nicotine dependence, and the time to smoke the first cigarette in the morning (TFC) can be considered as a measure of nicotine withdrawal since the plasma half-life of nicotine in humans is about 2 hours. To identify genes involved in these phenotypes, we performed a gene-based genome-wide meta-analysis of FTND score and TFC using several African American samples from dbGaP. We also conducted transcriptome sequencing for samples isolated from nucleus accumbens, an important brain region for drug dependence, of chronic nicotine treated and withdrawal mice. Analyses of the RNA sequencing data revealed 28 genes differentially expressed in chronic nicotine treated mice and 290 genes in withdrawal mice. Pathway analyses of these differentially expressed genes indicated that chemokine signaling, adhesion molecules, circadian rhythm pathways were involved in chronical nicotine exposure, and TGF-beta signaling, hedgehog signaling, dopaminergic synapse, serotonergic synapse, calcium signaling, cAMP signaling tryptophan metabolism pathways were involved in nicotine withdrawal. We are currently conducting analyses to integrate differentially expressed genes in nicotine treated and withdrawal mice with GWAS meta-analyses, and we expect to discover some novel genes associated with nicotine dependence and withdrawal. Our study combines human and mouse model studies, and it has great potential in translating and interpreting risk genes discovered in human GWAS.

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