Testing Association of Previously Implicated Gene-Sets in Nicotine Exposed Mouse Models with Human Smoking Phenotypes

Travis J. Mize1,2, Scott A. Funkhouser1, Jordan M. Buck1,3, Jerry A. Stitzel1,3, Marissa A. Ehringer1,3, & Luke M. Evans1,2

1Institute for Behavioral Genetics, University of Colorado, Boulder, CO, USA; 2Department of Ecology and Evolutionary Biology, University of Colorado, Boulder, CO, USA; 3Department of Integrative Physiology, University of Colorado, Boulder, CO, USA

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ABSTRACT:

Tobacco use leads to more than eight million deaths per year worldwide, with cigarette smoking being the single largest contributor. Smoking-related behaviors are partly heritable, yet the genetic contribution to human smoking phenotypes is still not fully understood; however, nicotine exposure mouse models have implicated numerous genes that may be involved in risk for certain behaviors among offspring. Here, we sought to examine whether previously identified genes that are differentially expressed in D1-type striatal medium spiny neurons in developmental nicotine exposure (DNE) mice are associated with human smoking behaviors. Summary statistics from a large GWAS (GSCAN) of four phenotypes (age of smoking initiation, cigarettes per day, smoking cessation, and smoking initiation) were analyzed in conjunction with multi-marker analysis of genomic annotation, or MAGMA. Of the genes contained within each gene-set, TMEM18 and TOX were found to be statistically significant (p<5e-8) at the gene-level in the smoking initiation GWAS. However, this set of differentially expressed genes in DNE mice were no more strongly associated with human smoking behaviors than the rest of the genome. This might not be surprising, given that these were identified as differentially expressed genes in a single cell type due to an environmental exposure and therefore may not represent innate genetic differences. Ongoing analyses include applying stratified LD Score Regression to estimate the heritable contribution of this set of genes and assessing whether the association signal of SNPs within these genes is stronger when only examining those variants that also contribute to expression variation in humans.