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SYSTEMS GENETIC ANALYSIS OF NICOTINE WITHDRAWAL DEFICITS IN LEARNING USING THE BXD GENETIC REFERENCE PANEL

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Cognitive deficits, such as disrupted learning, are a major symptom of nicotine withdrawal. These deficits are heritable, yet the genetic basis is unknown. Our lab has developed a mouse model of nicotine withdrawal deficits in learning, using chronic nicotine exposure via osmotic minipumps and fear conditioning. Here, we aimed to utilize the BXD genetic reference panel to identify genetic variants underlying nicotine withdrawal deficits in learning. Male and female mice (n=6-11 per sex per strain, 31 strains) received either chronic saline or nicotine (NIC, 6.3 mg/kg per day for 12 days), and then were tested for hippocampus-dependent learning deficits using contextual fear conditioning. Quantitative trait locus (QTL) mapping analyses using GeneNetwork (1000 permutations) identified a significant QTL on chromosome 4 (82.4 Mb, LRS =23.74, $p<0.05$). Using publicly available hippocampal gene expression data from naive animals, we identified 7 positional candidates (*Ptprd*, *Slc24a2, Lurap1, Snpac3, Plaa, Rps6, Mysm1*) that overlapped with our behavioral QTL and correlated with our behavioral data. Additionally, to investigate the phenotype of the high and low responders, we assessed four strains that exhibited extreme phenotypic variation (BXD64/98/56/124) in NIC-induced locomotor activity, NIC-induced hypothermia, and NIC metabolism. These NIC-induced phenotypes did not segregate into the same high and low responder groupings as the learning phenotype, providing further evidence that the cognitive deficits during NIC-withdrawal are genetically independent from other NIC-induced phenotypes. To expand upon these results and identify transcriptome changes associated with NIC withdrawal, we will soon complete mRNA-sequencing in the BXD lines exhibiting extreme phenotypic variation.