Genetic Variation in nicotine withdrawal in Mice

M. Imad Damaj¹, Asaf Peer², Alyssa White¹, Yasmin ElKhaleif¹, Vivek Philip², and Vivek Kumar²

¹Department of Pharmacology and Toxicology, Medical College of Virginia Campus, Virginia Commonwealth University, 1217 E Marshall St, Richmond, VA 23298, USA; ²Jackson Laboratory, Bar Harbor, ME 04609, USA

Significance: Mouse substrains can be a powerful source for discovery of genes regulating complex behavior. In this study, we report that C57BL/6J (B6J) and C57BL/6NCrl (B6N) substrains differ significantly in nicotine withdrawal after chronic administration. In addition, we report the results of our initial genetic mapping of nicotine withdrawal using the reduced complexity crosses.

Methods: We characterized several nicotine withdrawal signs (physical and affective) in adult B6J and B6N mice. To map the genetic basis of these traits, we conducted nicotine spontaneous withdrawal testing on 200 B6J x B6NJ-F2 mice alongside 200 saline control F2 mice.

Results: Both B6N and B6J expressed physical and affective withdrawal signs in nicotine-dependent mice. However, withdrawal signs were more intense in B6N mice. Nicotine plasma levels did not differ between the two substrains. Furthermore, the Cyfip2 (S968F) mutation did not contribute to the differences seen in nicotine withdrawal signs. Significant variability in withdrawal traits in the F2 mice was observed. QTL mapping of nicotine withdrawal traits revealed that there are distinct and overlapping QTLs for nicotine and saline treated groups. This is a first step in identifying the genetic architecture that regulates differential withdrawal responses to nicotine in the B6J and B6N substrains.

Conclusions: These results provide an evaluation of the behavioral differences to nicotine withdrawal behaviors that contribute to smoking behavior. The QTLs identified thus far, allow us to dissect the genetic architecture of nicotine withdrawal using reduced a complexity cross. We plan to pursue these QTLs to identify specific underlying genes.