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Genetic Variation in nicotine withdrawal in Mice

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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.