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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 and pathways regulating complex behavior. In this study, we report that C57BL/6J (B6J) (Jackson Lab) and C57BL/6NCrI (B6N) (Charles River) substrains, differ significantly in several nicotine withdrawal signs 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 (somatic, hyperalgesia, anxiety-like behaviors and sucrose preference) in male adult B6J and B6N mice. In addition, we measured nicotine and cotinine plasma levels in these two substrains after nicotine dosage. To map the genetic basis of these traits, we conducted an initial testing on 100 B6J x B6NJ-F2 mice alongside 100 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. In addition, nicotine metabolism and levels did not differ between the two substrains after chronic administration. In addition, the *Cyfp2* (S968F) mutation that is known to regulate psychostimulant response, did not contribute to the differences seen in nicotine withdrawal signs. Significant variability in the various nicotinic withdrawal traits in the F2 mice was observed.

Conclusions: These results provide an evaluation of the behavioral differences to experimenter-administered nicotine as measured in several withdrawal behaviors that contribute to smoking behavior. These results suggest that these substrains are useful for genetic studies on nicotine dependence.