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Establishment and Characterization of Novel Mutant Mouse Models for the Addiction Research Community

Understanding the genetic basis of addiction vulnerability requires validated animal models that capture the complexity of the disease. The Knockout Mouse Project (KOMP) has generated thousands of mouse lines with single-gene deletions, creating a vast but underutilized resource for addiction genetics. In this study, we summarize the completion of a multi-year project (NIDA U01 DA051235) designed to systematically screen and characterize novel mutant mouse models for addiction-related traits. Leveraging the JAX KOMP2 high-throughput phenotyping pipeline, we identified over 80 knockout lines that have phenotypes predictive of addiction liability, including anxiety, high-novelty reactivity, and altered sleep/circadian rhythms. We prioritized ~60 lines for deep addiction phenotyping. These lines underwent a rigorous battery of tests, including cocaine locomotor sensitization, oral methamphetamine and sucrose preference, high-resolution open field phenotyping, circadian assessment, omics (RNAseq), and whole brain MRI imaging. We find a high percent (over 25%) of these mouse lines show dysfunction in addiction-relevant behaviors. Once completed, this project has established a new catalog of validated mouse models for reward behaviors, accompanied by a rich, multi-modal dataset linking gene function to brain structure, gene expression, and behavior. These resources will be made available to the scientific community to accelerate the discovery of novel therapeutic targets.

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