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Discovery of novel, addiction-relevant genes through endophenotype modelling of Knockout Mouse Project (KOMP) data

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Addiction is a complex, genetic brain disorder with only limited number of candidate genes that has shown consistent replication and deep characterization in preclinical animal models. The Knockout Mouse Project (KOMP) attempts to address this knowledge gap by prioritizing understudied genes in the mammalian genome by creating an encyclopedia of knockout mice harboring individual gene deletions, and phenotyping these lines through a broad-based high throughput phenotyping platform. At JAX, this phenotyping platform includes behavioral assays that assess hyperactivity, anxiety traits and sleep deficits that are predictive of addiction liability in animal models and humans. We performed an integrated analysis of the KOMP behavior and physiology data from JAX and found a cluster of 89 genes that have emotionality and sleep deficits. We carried out in-depth addiction behavior, brain imaging, transcriptomics, and reward- circuit neurophysiology phenotyping in three lines from this cluster. Our analysis discovered high pleiotropy across behavior and physiology in these knockouts. Of the three genes that we characterized for addiction phenotypes, two showed altered cocaine responses (sensitized and IVSA traits) and one exhibited a limited acute-response phenotype. Brain volumetric and transcriptomics analysis detected perturbation in total brain volume and expression differences. Intrinsic and synaptic properties of prefrontal and accumbens shell neurons revealed that these genes are critical regulators of individual neurons and reward-circuit functions that control behavioral outcome in both naive and drug-exposed state. We conclude that the KOMP resource is a powerful resource for discovery of novel genes that regulate addiction traits.