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Kockout Mouse Project (KOMP2) has a discovery engine for novel addiction genes

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The Knockout Mouse Project (KOMP) attempts to elucidate the functions of 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 such as open field, light-dark, holeboard, and sleep that are predictive of addiction liability in animal models and humans. We have 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, imaging, genomics, and electrophysiology phenotyping in three lines from this cluster. Our analysis indicates high pleiotropy across behavior and physiology in these knockouts – if a gene deletion leads to a phenotype, in 80% of cases, there are both behavior and physiology effects. Thus, a broad-based analysis of behavior and physiology phenotypes is important to understand the consequences of single gene deletions. Of the three genes that we characterized for addiction phenotypes, two showed altered cocaine responses (sensitized and IVSA traits). In addition, all three showed changes in gene co-expression networks and brain structure, as revealed through RNA-seq and MRI. Electrophysiological characterization revealed cellular changes in key reward-circuit modules that explain altered drug response. Combined, we describe novel mechanisms of neuroadaptations, including synaptic plasticity, that are critical for transition to addiction. We conclude that the KOMP resource is a powerful resource for discovery of novel genes that regulate addiction traits.