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Integrated analysis of JAX-KOMP2 data reveals a cluster of genes predictive of addiction phenotypes.

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The KOMP2 phenotyping pipeline at JAX has characterized over 800 mouse knockout lines in 10 behavioral and 18 physiology assays. We carried out a multidimensional and multivariate network analysis to discover a module of 81 genes with hyperactivity, anxiety, impulsivity, and sleep phenotypes, all predictive of addiction vulnerability. We selected three knockout lines from this module for detailed addiction relevant behavior, imaging, genomic, and electrophysiology characterization. We find that two of the three knockout lines show phenodeviance in cocaine sensitization and IVSA. Here we present detailed addiction relevant characterization of *Tropomodulin 2* (*Tmod2*).

Tmod2 is a neural specific actin-regulating gene that regulates cell structure. *Tmod2* KO have dramatically reduced sensitized response to cocaine and fail to acquire in cocaine IVSA paradigm. In order to elucidate mechanism, we characterized synaptic and intrinsic electrophysiological properties of cortical and nucleus accumbens neurons in adults and P0 mice. We find a comparative decline in cocaine-induced synaptic plasticity in *Tmod2* KO with increased mEPSC amplitude and mIPSC frequency. Intrinsic property characterization revealed hyperexcitability of neurons in cortex and striatum. These neuronal properties provide a mechanistic basis of addiction phenotypes that are regulated by *Tmod2*.

Combined our integrated analysis shows that the JAX-KOMP2 data is a powerful resource to discover novel genes that regulate addiction. Indeed, two of the three genes selected from a module of 81 genes show addiction phenotypes. We propose that characterization of other genes in this module is of high priority for the addiction genetics community.