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Forward genetic screen of the KOMP2/IMPC resource identifies addiction mutants

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Significance: *We seek to establish novel single gene deletion mouse models for the study of addiction phenotypes.* The Knockout Mouse Project (KOMP2) and the International Mouse Phenotyping Consortium (IMPC) have developed a library of single gene deletions of over 5000 mouse genes. We mined the KOMP2 data at The Jackson Laboratory for lines that have behavioral deficits that are predictive of addiction such as anxiety, hyperactivity, and sensory processing deficits. We have tested a subset of these lines in a dedicated addiction phenotyping pipeline. We present the results of the first two years of this screen.

Methods: We rederived 36 KOMP2 lines. KOMP2 uses C57BL/6N mouse strain which harbors a *Cyfip2* mutation that significantly alters reward phenotypes. Therefore, we backcrossed all founders to C57BL/6NJ-Cyfip2$^{J/J}$, a C57BL/6N strain with the corrected *Cyfip2* allele. We have characterized baseline behaviors in the open field to confirm the KOMP2 phenotypes. We have characterized cocaine sensitization, sucrose preference, methamphetamine preference, circadian wheel running behaviors in these strains. We have also collected data for advanced behavioral phenotyping for social interaction, gait/posture and other phenotypes. Brains were collected for MRI, and reward brain regions were used for RNAseq.

Results: We show that approximately 1/4 strains tested so far have reward deficits. Surprisingly, we have not found any deficits in circadian wheel running behavior. Genomics and MRI analysis are pending.

Conclusions: The results so far demonstrate that KOMP2 is a rich resource for novel addiction mutants. Future continuation of these results and integrated analysis of the behavior, structural, and genomics data will yield novel insights into addiction biology. We describe four new models for the addiction research community that can be accessed immediately.

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