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Mouse inbred strain survey of oxycodone addiction traits in an opioid multi-stage addiction assessment protocol

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In 2016, 42,000 Americans died of opioid related overdoses, with almost half (19,000) involving prescription opioid pain relievers. In humans, polymorphisms are associated with opioid use disorder (**OD**), but a majority of the genetic basis of OD is unexplained. We use murine forward genetic techniques, leveraging the genetic diversity within a panel of 30 classical inbred laboratory mice, to identify novel genetic loci and neurobiological underpinnings of opioid related traits. By associating behavior with the fine mosaic of ancestral haplotypes that have been differently inherited and fixed in classic inbred strains we can identify genetic loci influencing opioid related traits with high resolution. Using a 7-week multi-stage addiction assessment protocol (**MSAAP**) we determined behavioral differences in acute sensitivity, reward, extinction, tolerance, acute withdrawal, and protracted withdrawal responses to oxycodone (**OXY**) administration. Thus far, we have tested 12 inbred strains: BALB/cJ, BALB/cByJ, C3H/HeJ, FVB/NJ, DBA/2J, NOD/ShiLtJ, CBA/J, A/J, NZL/LtJ, MRL/MpJ, BTBR *T⁺ tf/J*, AKR/J. These strains show robust differences at each stage of the MSAAP, as well as sex-specific differences within strains. Heritability estimates indicate that many behaviors observed in OXY-treated mice are highly heritable. Notably, we have observed behavioral differences in the closely related BALB/cJ and BALB/cByJ substrains, which are excellent candidates for forward mapping using an F2 cross. These findings support our hypothesis that genetic differences affect complex behavioral traits associated with different stages of opioid addiction. Complete testing of 30 classical inbred strains will provide finely resolved loci associated with opioid behaviors that will inform candidate gene analysis.