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Nearly isogenic BALB/cJ and BALB/cByJ substrains differ in opioid state dependent learning, spontaneous withdrawal, and weight loss in response to oxycodone: Planning a reduced complexity cross.

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Opioid dependence is a heritable substance use disorder, however we know little about its genetic etiology. Using forward murine genetic studies we can identify novel genetic and neurobiological pathways relevant to the human condition. To facilitate gene mapping of opioid addiction traits in a Reduced Complexity Cross (**RCC**), we phenotyped two nearly isogenic inbred mouse substrains, BALB/cJ and BALB/cByJ, for behavioral responses to the mu opioid receptor agonist oxycodone (**OXY**). The low genetic diversity and high phenotypic diversity between these substrains facilitates gene mapping. To capture multiple stages of addiction related behaviors we used our multistage addiction assessment protocol (**MSAAP**) to examine OXY-induced locomotion, drug-free and state-dependent conditioned place preference (**CPP**), acute antinociception EC50s and EC50 shifts (tolerance), spontaneous emotional/affective withdrawal, and body weight loss. We found substrain differences in state-dependent CPP, OXY induced analgesia, acute emotional/affective withdrawal, and body weight loss in response to OXY. Interestingly, our data shows BALB/cJ mice show increased state dependent, but not drug free conditioned place preference compared to BALB/cByJ mice, suggesting differences in state dependent learning. BALB/cJ mice also show increased emotional affective withdrawal, and OXY induced weight loss, suggesting they are generally more sensitive to psychological and behavioral effects of OXY. Future studies will employ a systems genetic approach combining behavioral QTL, expression QTL, and single cell RNA-sequencing to identify the genetic basis and molecular mechanisms underlying genetic differences in OXY phenotypes.