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Morphine and Naloxone Responses are controlled by *Oprm1* and *Fgf12* loci in the murine BXD family: Epistasis and time-dependent locomotor interaction effects

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The use of animal models offers key benefits including the ability to dissect molecular mechanisms, identify effective pharmacologic and environmental treatments, replicate, and extend FAIR data. However, it has been challenging to map variants influencing addiction in either rodents or humans, suggesting combined approaches would be advantageous. In this study, we have remapped behavioral responses to opiates and naloxone using a large family of replicable lines of mice. Specifically, we exploited FAIR data from Philip et al (2010) embedded in GeneNetwork.org, including locomotor time-series data following acute morphine and naloxone injections. Using linear mixed model mapping (GEMMA) and dense new BXD genotypes (Ashbrook et al., 2021), we confirm a sex-independent effect for initial locomotor responses to acute morphine (50 mg/kg ip) in both males and females that maps precisely to *Oprm1* (–logP of 10). We also discovered a strong locus on Chr 16 linked only to late phase locomotor response at 150+ min in both sexes. *Fgf12* is a strong candidate in this latter region and has intriguing support in human studies. We discovered a unique time-dependent epistatic interaction between these two loci at 165-180min. Finally, we mapped at least three other significant loci for naloxone responses (30 mg/kg)—one of which also maps to *Oprm1*. We built a network of mRNAs that covary jointly with *Fgf12* and *Oprm1* in three or more brain regions of humans (GTExv8). This set of covariates was highly enriched in gene regions highlighted in a human SUD genetic study of ~1,000,000 individuals. This strengthens the likelihood that the *Oprm1-Fgf12* axis defined in mouse is likely to overlap with SUD mechanisms in human populations. This study demonstrates how FAIR+ data reanalysis can yield striking new results, and how human and animal genetic data can be merged at gene and network levels for bidirectional translational validation.