Submitter Name: Paige Lemen
Submitted Email: plemen1@uthsc.edu
PI name: Hao Chen
PI email: hchen@uthsc.edu

Molecular and Phenotypic Causes and Networks Linked to Morphine and Naloxone Responses in the BXD Family: Time-Dependent Locomotor Effects

Paige Lemen[1], Price Dickson[2], Guy Mittleman[3], Alexander Hatoum[4], Arpana Agrawal[4], Benjamin Reiner[5], Wade Berrettini[5], Robert W Williams[1], Hao Chen[1]

[1]The University of Tennessee Health Science Center, Memphis, TN, [2]Marshall University, Huntington, WV
[3]Ball State University, Muncie IN, [4]Washington University, St. Louis, MO, [5]University of Pennsylvania, Philadelphia, PA

The use of animal models offers key benefits including the ability to dissect molecular mechanisms, to identify effective pharmacologic and environmental treatments, and to replicate, extend FAIR data. Animal models that incorporate a high level of genetic diversity can be powerful complements to human GWA studies and tools to rigorously test Bayesian causal models of specific gene action and pleiotropic outcomes with essentially no confounders. However, it has been highly challenging to map variants influencing addiction in either rodents or humans, suggesting combined approaches would be advantageous. In the current 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, PMID:19958391), including locomotor time-series data following acute morphine and naloxone injections. Using linear mixed models and new genotypes (PMID:33472028), we confirm a massive sex-independent effect for initial locomotor responses that maps to Oprm1 (–logP ~10). We discovered a new locus on Chr 16 associated with late locomotor responses (150+ min) in both sexes. Fgf12 and Opa1 are strong candidates in this region with provisional support in human association studies. We have also mapped at least three other significant loci for naloxone responses—one of which aligns with Oprm1. 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 even network levels for bidirectional translational validation.