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One of these things is not like the others: Genetic Variation in Morphine and Fentanyl Response in Mice

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The US is amid an opioid overdose epidemic. There is extensive inter-individual variation in responses to opioids in humans, which manifests as substantial variability in lethal dosage, contributing to the dangers of experimentation with these drugs. We have taken a systems genetic approach using the complementary advanced mouse resources of the Collaborative Cross (CC) and Diversity Outbred (DO) mice utilizing genetic variation to understand the mechanism of overdose in response to opioid exposure. Using the founder strains, we determined the heritability of various respiratory and opioid overdose traits and then, using DO mice, identified QTL. Trait correlation analysis was performed using the CC panel, relating baseline respiratory metrics and opioid response. Finally, we have performed bulk RNA-Seq on two respiratory control regions, the pre-Bötzinger complex and the Nucleus Tractus Solitarius. Weighted correlation network analysis of gene expression and phenotypic data has identified networks and hub genes correlated with various phenotypes. Sample results from the pre-Bötzinger show that Module 40 (F=2.256, p=9.5E-05 and padj=0.0001) contained 61 genes with a hub gene of *Cdc42.* When correlated with morphine response phenotypes of the CC mice, this module positively correlates with the duration of steady-state respiratory depression in response to 436 mg/kg morphine across the CC panel (Pearson r=0.554, p=0.020). Within this module, the most significant pathway enrichment was 14.5 fold (p <0.0001, padj= 0.027) for the KEGG Spliceosome pathway containing genes *Hnrnpa1*, *Hnrnpk*, *Srsf3*, *Srsf7*, *Smndc1* and *Tra2b.* We expect this approach will allow us to identify novel overdose reversal agents. R01DA048890