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Genetic variation in opioid-induced respiratory depression

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The US is in the midst of an opioid overdose epidemic during a global pandemic. Opioid-induced respiratory depression is the leading cause of death in overdose victims. We have demonstrated the genetic heritability of respiratory response to morphine in our advanced mouse populations, the Diversity Outbred and Collaborative Cross populations, which are well suited for a systems genetic approach to discover biological mechanisms of complex traits. Previously we reported a morphine respiratory depression QTL on chromosome 5 (n=312). We have now identified two additional QTL (n=336), one for survival time in response to morphine on chromosome 6 (LOD=8.42, $p<0.05$) and using a GWAS approach for mapping the binary trait of survival in response to a dose of morphine, rs26883853 on chromosome 11 (LOD=4.5, $p<0.1$). Candidate genes for both human and mouse loci are being tested using mouse models. We have performed heritability studies of fentanyl responses using the eight founder strains of the collaborative cross and have estimated the LD_{50} for each of the strains. The strain differences in sensitivity to fentanyl vary in directions and magnitudes and are uncorrelated to differences observed for morphine across the eight strains and two sexes. Based on the strain LD50s, a probe dose has been determined for use in mapping fentanyl-induced respiratory depression phenotypes in a cohort of 600 DO mice. These data, in combination with the morphine study, will enable comparison of OIRD risk loci across drugs and species for identification of conserved and broadly effective risk loci and intervention targets.

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