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A Tale of Two Opioids: The Genetics of Opioid-Induced Respiratory Depression in Response to Fentanyl and Morphine in Mice

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A major challenge in addressing opioid overdose is that opioids act at multiple levels in the peripheral and central nervous systems, resulting in diverse phenomena, including Opioid-Induced Respiratory Depression (OIRD). Our work in the Collaborative Cross (CC) founder strains have shown that opioid sensitivity is a heritable trait. In a survey of both sexes of the founder strains, the LD50 of morphine differed by 4-fold, and the LD50 of fentanyl differed by 150-fold. Using the Diversity Outbred Mouse population, we identified survival QTL unique to morphine and fentanyl. To determine if the baseline respiratory parameters of naïve-CC mice predict opioid sensitivity, we phenotyped drug-naive CC mice by plethysmography. We determined their OIRD response to morphine using the PiezoSleep system. Performing high-throughput phenotyping utilizing this system allowed us to determine the recovery time for CC mice in response to a non-lethal dose of morphine and the survival time for CC mice in response to a lethal dose of morphine. We calculated the degree of respiratory depression and the morphine LD50 for each CC strain. These morphine response traits were correlated with plethysmography-derived parameters such as respiratory rate, tidal volume and minute ventilation. We have identified phenotypically sensitive and resistant CC strains by multivariate outlier analysis. These CC phenotypes will be analyzed with RNA-Seq data from respiratory control regions of the brain. The expression profiles will be integrated with human -omics data from overdose samples to identify mouse strains best associated with overdose risk or resilience in humans at the transcript level.