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Genetic Variation in Opioid Induced Respiratory Depression in Mice

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Opioid prescription for treatment of pain has nearly quadrupled from 1999 to 2014. This has led to an epidemic in addiction and overdose deaths in the United States. Morphine binds to opioid receptors in the peripheral and central nervous system, producing sedation and euphoria in addition to analgesia. There are substantial inter-individual differences in response to opioids, resulting in variation in sensitivity to opioid overdose and treatment responses. However, the factors and underlying mechanisms that influence responses to opioids remain unknown. Previous studies in mice have revealed strain differences in opiate lethality and respiratory sensitivity. However, these studies were conducted in the context of limited genetic variation consisting of a few mouse strains, and with survival as the only endpoint. Our hypothesis is that genetic variants in inbred strains of mice influence the innate variability in opioid-induced responses in respiratory rate, respiratory depression and associated lethality of natural and synthetic opioids. To test this hypothesis we have used the founders of the advanced, high-diversity mouse populations, the Collaborative Cross (CC) and Diversity Outbred (DO) to identify distinct genetic differences in opiate lethality and respiratory sensitivity. We have mapped and identified five quantitative trait loci (QTL) for survival time, recovery time and depth or respiratory depression due to morphine administration in 300 DO mice. We have begun to prioritize and test candidate genes within the intervals. This unbiased genetic approach is expected to identify novel targets for new and innovative approaches to predict, prevent and treat opioid overdose.