Identification of a major QTL influencing oxycodone behavioral sensitivity and dependence in C57BL/6 substrains

Lisa R. Goldberg[1], Stacey L. Kirkpatrick[1], Neema Yazdani[1], David Jenkins[2], Alex Luong[1], Kimberly P. Luttik[1], W. Evan Johnson[2], Megan K. Mulligan[3], and Camron D. Bryant[1]

Opioid addiction is heritable, yet its genetic basis remains poorly understood. Mice are valuable for identifying novel genes that contribute to variation in addiction-associated phenotypes, including acute psychomotor stimulation and conditioned reward. The closely related C57BL/6J and C57BL/6NJ substrains exhibit limited genetic diversity, yet frequently show significant strain differences in addiction-associated traits, including oxycodone-induced (OXY) locomotor activity and naloxone conditioned place aversion. Quantitative Trait Locus (QTL) mapping in closely related substrains drastically reduces the number of segregating genetic variants from millions to thousands, accelerating the identification of the causal genetic factors. We conducted QTL mapping for oxycodone (OXY)-induced conditioned place preference (CPP, N=212), and naloxone (NAL)-induced conditioned place aversion (CPA, N=209), and concomitant behaviors along with saline-treated mice as controls (SAL, N=213). We utilized a 9 day (D) CPP/CPA protocol. Mice received drug (1.25 mg/kg OXY, 4 mg/kg NAL, or SAL, i.p.,) on D2 and D4, and SAL on D3 and D5. Mice were assessed for drug-free CPP/CPA (D8) and drug state-dependent CPP/CPA (D9). Mice were genotyped at 96 informative markers and QTL mapping was performed in R/qtl (scanone, 1000 permutations). We identified a major genome-wide significant QTL for locomotor activity on D2 and D4 in response to OXY (Chr. 1 72.43 cM, LOD= 9.79) that co-mapped to the same region as a QTL for anxiety-like OXY withdrawal behavior in the elevated plus maze (chr. 1 77.33 cM; LOD=5.33). We are currently conducting fine mapping with interval-specific congenics and striatal transcriptome analysis via RNA-seq tofacilitate gene identification and neurobiological mechanisms.

1. Laboratory of Addiction Genetics, Department of Pharmacology and Experimental Therapeutics and Psychiatry, Boston University School of Medicine
2. Department of Medicine, Department of Biostatistics, Boston University School of Medicine
3. Department of Anatomy and Neurobiology, University of Tennessee Health Science Center

FUNDING: R00DA029635 (NIDA; C.D.B.), R03DA038287 (NIDA; C.D.B), R21DA038738-01A1 (NIDA; C.D.B.), Transformative Training Program in Addiction Science (Burroughs Wellcome 9550300872), T32GM00854118 (NIH)