Fine mapping of a distal chromosome 1 region influencing opioid addiction traits in a reduced complexity cross

Camron D. Bryant[1*], Lisa R. Goldberg[1,2], Julia C. Kelliher[1], Stacey L. Kirkpatrick[1], Alex Luong[1], Kimberly P. Luttik[1], Jiayi Wu[1,3], Eric R. Reed[4], David F. Jenkins[4,5], Jacob A. Beierle[2], Julia L. Scotellaro[1], Timothy A. Drescher[1], Neema Yazdani[1], Ali Al Abdullatif[6], Benjamin Wolozin[6], William E. Johnson[5], Megan K. Mulligan[7]

[1]Laboratory of Addiction Genetics, Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine (BUSM); [2]T32 Graduate Training Program in Biomolecular Pharmacology, BUSM; [3]Genetics and Genomics, Program in Biomedical Sciences, BUSM; [4]Bioinformatics Program, Boston University; [5]Computational Biomedicine, BUSM, [6]Laboratory of Neurodegeneration, Department of Pharmacology and Experimental Therapeutics, BUSM; [7]Genetics, Genomics, and Informatics, University of Tennessee Health Science Center

Opioid addiction is a nationwide epidemic. Both genetic and environmental factors influence opioid addiction risk, however the genetic basis remains mostly unknown. We developed a multi-stage addiction assessment procedure (MSAAP) for measuring opioid addiction traits in mice to map the genetic basis of behaviors associated with the progressive stages of addiction, including acute sensitivity, reward, tolerance, and emotional-affective withdrawal. We generated a reduced complexity F2 cross between closely related C57BL/6 substrains to map the genetic basis of opioid addiction traits induced by acute and chronic oxycodone (5-20 mg/kg). We identified a single, major quantitative trait locus (QTL) on distal chromosome 1 (LOD=4.7-9.8, 152-180 Mb) for several behavioral traits assessed via MSAAP that accounted for a majority of the parental strain variance in behavior. We then backcrossed selectively chosen recombinant F2 mice within the locus to generate multiple quasi-congenic lines for rapid fine mapping – we effectively reduced the size of the interval to 6 Mb (167.67-173.67 Mb). Striatal, cis-expression QTL (eQTL, eeQTL) mapping of the marker nearest the behavioral QTL interval (181.32 Mb) identified Pou2f1, Pcp4l1, Cadm3, Atp1a2, Ncstn, Ildr2, Kcnj9, Gpr161, Aim2, Igsf9, and Nuf2 as eQTL genes in or within 1 Mb of the behavioral QTL interval (FDR < 5%). Positional cloning is underway and will aid in identifying the quantitative trait gene (QTG). Differential gene expression analysis as a function of inheritance of the chromosome 1 QTL interval corroborated the eQTL findings and identified a gene network predicted to be regulated by hub genes encoding the neurodegenerative proteins amyloid precursor protein (APP) and microtubule-associated protein tau (Mapt). We are currently validating Mapt as a hub gene for MSAAP behaviors in tau -/- mice. To summarize, behavioral and eQTL mapping combined with transcriptome analysis identified candidate QTGs and downstream network hub genes involved in opioid addiction traits.