Submitter Name: Olivia Corradin
Submitted email: corradin@wi.mit.edu
PI Name (if different): NA
PI email (if different): NA

Hypoacetylated neuronal enhancers in opioid overdoses converge on the regulatory circuit of specific genes

Olivia Corradin[1], Schahram Akbarian[2], Cynthia Bartels[3], Dana Hancock[4], An Hoang[1], Eric Johnson[4], Katreya. Lovrnert[3], Deborah Mash[5], Bryan Quach[4], Richard Sallari[6], Peter Scacheri[3];

[1]Whitehead Institute Biomedical Research; [2] Department of Neuroscience, Icahn School of Medicine at Mount Sinai; [3]Department of Genetics and Genome Sciences, Case Western Reserve University; [4]Center for Omics Discovery and Epidemiology, RTI International; [5]Dr. Kiran C. Patel College of Allopathic Medicine, Nova South Eastern University; [6]Tempus Precision Medicine Company

Opioid overdoses are the leading cause of accidental death, surpassing automobile accidents. Genetics is a major contributor to opioid addiction (OA), yet the key genetic loci remain largely unknown. We interrogated the effects of opioid abuse on the brain using ChIP-seq to quantify patterns of H3K27 acetylation in dorsolateral prefrontal cortical neurons isolated from 51 opioid-overdose cases and 51 accidental death controls. Using linear regression, we identified 388 peaks that were consistently hypoacetylated in OA relative to controls (P<8E-8). These peaks were enriched near genes in the MAPK pathway (q<0.01) and other genes previously implicated in OA. We reasoned that heterogeneity among the OA cases may obfuscate epigenetic changes critical to the phenotype of opioid abuse. We utilized an information theory-based strategy to identify of individual case-specific regulatory alterations which we call Variant Enhancer Loci (VELs). 80,000 VELs with substantially reduced H3K27ac in at least one opioid case were identified (FDR 0.05). We identified putative gene targets of these peaks using promoter-capture Hi-C data. While only 10% of VELs were found in multiple cases, 60% of VEL target genes were common to multiple cases. Thus, while the specific VEL varies among cases, VELs often converge around specific genes across opioid cases. We identified several genes including GABBR2 and KCNMA1 with significantly pronounced VEL convergence (P<1E-5). These VEL target genes were identified in >10 OA cases with multiple hypoacetylated peaks targeting the same gene in most samples. Collectively these results reveal known and novel genes associated with opioid abuse.