Name: Olivia Corradin Email: corradin@wi.mit.edu

Case-specific epigenetic alterations converge on key genes linked to opioid overdose

Richard Sallari[2], Katreya Lovrenert4, Cynthia Bartels[4], Fatir Qureshi[1], An Hoang[1], Bryan Quach[3], Caryn Willis[3], Dana Hancock[3], Peter Scacheri[4,5], Schahram Akbarian[6], Eric Johnson[3,7], and Olivia Corradin[1,8]

[1]Whitehead Institute Biomedical Research, Cambridge, USA. [2]Axiotl Inc, Cleveland, OH, USA. [3]GenOmics, Bioinformatics, and Translational Research Center, Biostatistics and Epidemiology Division, RTI International, Research Triangle Park, NC, 27709, USA. [4]Department of Genetics and Genome Sciences, Case Western Reserve University, Cleveland, USA. [5]Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, USA. [6]Department of Psychiatry and Department of Neuroscience, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, USA. [7]Fellow Program, RTI International, Research Triangle Park, NC, 27709, USA. [8]Department of Biology, Massachusetts Institute of Technology, Cambridge, USA.

Opioid overdose is a critical public health epidemic. Opioid use disorder is estimated to be about 60% heritable but the factors that contribute to this heritability remain elusive. Epigenetic studies have the potential to identify insights into pathogenic gene dysregulation by revealing a combined snapshot of both genetic and environmental effects on gene regulation. We interrogated the effects of opioid use on the brain using ChIP-seq to quantify patterns of H3K27 acetylation in the dorsolateral prefrontal cortex and nucleus accumbens from 51 opioid-overdose cases and 51 accidental death controls. Here we will present results from both brain regions that have revealed distinctions in gene regulatory activity in opioid overdose cases. We utilized two diverse strategies to interrogate epigenetic differences. First, we utilized linear regression to identify regulatory element changes consistent across opioid cases. This revealed several gene targets involved in MAPK pathway. Next, we reasoned that heterogeneity among the opioid overdose cases may obfuscate epigenetic changes critical to the phenotype of opioid addiction. We devised an information theory-based strategy to identify individual case-specific regulatory alterations termed Variant Enhancer Loci (VELs). While the specific VEL varied greatly among cases, VELs often converged around specific genes across opioid cases, including ASTN2 which has been associated with pain tolerance. We additionally observed these loci to be significantly enriched for generalized anxiety, educational attainment and metrics of high-risk behavior. This study revealed known and novel genes associated with opioid overdose and demonstrated a framework for evaluating epigenetic variation in highly heterogenous diseases.