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Chromatin QTL analysis identifies genetic variants that influence H3K27ac in opioid overdose cases

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Despite significant public health measures, drug overdose is the leading cause of accidental death in the United States, with incidents involving opioids accounting for the majority of cases (77%). Opioid use has been associated with epigenetic changes that alter gene expression in the brain. The cause of these epigenetic changes however remains unclear. Chromatin quantitative trait loci mapping (QTL) enables identification of the impact of genetic variants on chromatin state. Investigating the genetic contributions to changes in regulatory elements will further understanding of the epigenetic changes observed in patient tissue samples.

Towards this goal, postmortem brain samples were collected from the nucleus accumbens (NAc, n=91) region of a mixed ancestry cohort. The cohort includes n=47 individuals who died from opioid overdose and n=44 accidental death controls. ChIP-seq analysis of H3K27 acetylation, a marker of active regulatory elements, was performed. Both ChIP assays and genotype information were analyzed using an allele-specific statistical framework (RASQUAL), to identify H3K27ac QTLs (hmQTLs), i.e. genetic variants associated with changes in H3K27ac occupancy.

In total, hmQTLs were identified for 2,006 unique chromatin regions. Performing RASQUAL analysis on the case and control groups separately revealed a subset of hmQTL (n=521) that were significant in the opioid overdose cases, but not in the controls. The most significant of these sites were proximal to the genes CHID1, CCNY, KCNJ4 and MED12L. Identifying genetic variants that influence chromatin state only in the context of opioid overdose provides new opportunities to investigate the interplay between genetic variants, epigenetics and opioid use.