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Epigenetic Variation Linked to Opioid Overdose Converge on Splicing Regulators in the Nucleus Accumbens

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Chromatin studies of substance use disorders have the potential to identify both the genetic and environmental impacts to gene regulation that occur throughout the course of disease. We performed ChIP-seq for H3K27ac, a marker of active promoters and enhancers, in a cohort of tissue samples from the nucleus accumbens of individuals who died from opioid overdose (n= 47) as well as accidental death controls (n=44) (age and ancestry matched). We applied a novel analytical framework to identify epigenetic changes that distinguish individual opioid cases from controls. This approach identified 37,652 Variant Enhancer Loci (VELs), genomic regions where individual cases varied significantly from the expected acetylation patterns observed in controls (P<1E-5). Using caudate nucleus HiChIP data, we found 18 genomic regions with significant convergence of VELs (P<1E-5). This convergence recapitulated observations from a prior study of the prefrontal cortex (n=101), with 22% of VELs identified in both cohorts. Splicing regulation was the top enriched gene ontology amongst NAc convergent loci. Using induced pluripotent stem cell derived medium spiny neurons (iMSNs) we demonstrate that CRISPR inhibition of VEL regions leads to downregulation of CELF5, a splicing regulator. Ongoing studies are investigating the impact of CELF5 dysregulation on splicing in iMSNs. We will demonstrate that large language models like DNABert2 show improved accuracy in predicting convergent VEL loci suggesting an underlying sequence feature or shared trans regulator. These results highlight the value of epigenetic studies for elucidating the etiology of complex traits like opioid addiction.