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Uncovering Environmentally Associated Epigenetic Regulatory Mechanisms in Opioid Exposure Using Chromatin QTL Mapping and Foundation Models

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Opioid use disorder (OUD) is a major public health crisis, affecting an estimated 2.1 million individuals in the United States. This condition is associated with epigenetic modifications in the brain that influence gene expression and may contribute to OUD susceptibility and pathogenesis. To investigate the extent to which these alterations are driven by genetic versus environmental factors, postmortem samples from the nucleus accumbens (NAc) and prefrontal cortex (PFC) of a mixed-ancestry cohort, consisting of both opioid overdose cases and accidental death controls, were analyzed. Following quality control, 91 NAc samples (47 cases, 44 controls) and 98 PFC samples (44 cases, 54 controls) were retained. Genotype data were integrated with ChIP-seq data to identify H3K27ac quantitative trait loci (hmQTLs), which are regions where H3K27ac occupancy is associated with genetic variants.

QTL mapping revealed that certain regulatory effects were influenced by genetic variants only in the presence or absence of opioid exposure. Specifically, 1,417 and 874 hmQTLs exhibiting this context-dependent effect were identified in the NAc and PFC, respectively. Environmentally responsive hmQTLs colocalized with 255 expression QTLs, including genes like CELF5, SULT1A1, and SLC2A1. To validate case-specific effects, DNABERT, a transformer-based deep learning model, was adapted to predict H3K27ac occupancy based on sequence data. Trained on control samples, the model showed decreased predictive accuracy (Δ=9.9%, $p < 0.001$) in opioid-exposed cases, suggesting that the observed epigenetic differences likely stemmed from environmental influences beyond DNA sequence alone. These findings support context-specific regulatory regions in OUD and highlight AI's potential to investigate these hypotheses.