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Detection of H3K4me3 identifies neuroHIV signatures and detects genomic effects of Methamphetamine in addiction pathways in post-mortem HIV+ brain specimens that are not eligible to transcriptome analysis

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Human post-mortem specimens are extremely valuable resources for investigating translational hypotheses. Tissue repositories collect clinically assessed HIV-positive and negative specimens (including age, viral load, treatments, substance use patterns and cognitive functions). One challenge is the limited number of specimens qualified for transcriptional studies, mainly due to RNA quality resulting from long post-mortem intervals (PMI). We hypothesized that epigenomic signatures are more stable than RNA for assessing global changes associated with outcomes of interest. H3K27Ac or RNA Polymerase (Pol) are not consistently detected by Chromatin Immunoprecipitation (ChIP), the enhancer H3K4me3 histone modification was abundant and stable up to the 72hr PMI. We tested our ability to use HeK4me3 in human frontal cortex from HIV+ individuals with or without Methamphetamine (Meth +/-) use disorder criteria, which exhibited poor RNA quality and were not eligible for transcriptional profiling. Systems strategies that are typically used in transcriptional metadata were applied to H3K4me3 peaks revealing consistent genomic activity differences in regions where addiction and neuronal synapses pathway genes are represented, including genes of the dopaminergic system, as well as inflammatory pathways. The resulting comparisons have mirrored previously observed effects of Meth on suppressing gene expression, suggesting that H3K4me3 detection in chromatin may reflect transcriptional patterns, thus providing opportunities for analysis of larger numbers of specimens from cases with substance use and neurological deficits. In conclusion, the detection of H3K4me3 in isolated chromatin can be an alternative to transcriptome strategies to increase the power of association using specimens with large PMI and low RNA quality.