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OMICS Perspectives Unveil Neural Circuitry Adaptations in Chronic Heroin Addiction: A Genome-Wide Analysis of Epigenetic Signatures and Transcriptional Programs

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Chronic heroin use has several consequences including advancing to addiction. Neural cells and non-neural cells like glial cells collectively craft the neural circuitry beginning from experimental substance use to advanced stages of dependency and addiction. To recognize the substance addiction related neural circuit adaptations in the brains of heroin users requires a synthesis of OMICS perspectives. Therefore, we conducted genome-wide analysis of chromatin accessibility in the neurons and non-neurons of striatum from heroin users and compared it to a control group. Downstream analysis encompassed differential peak analysis, chromatin co-accessibility, footprinting, TF cooccurrence and DNA variant identification. We identified loci of neurotensin, ASCL1, BDNF, ATF2, EGR1, GRIN2A/B, GRM3/7 and EDN3 showing higher accessibility in neural cells, whereas loci PENK, CHRNA1, GABRB1, and PRL were found less accessible, while glias showed genes enriched in structural integrity and support. This study also identified differential TF occupancy involving FOS, JUN, ATF2, PHOX2B/2A among others, while PHOX2B and Arid5a/3b were identified in glias, using footprinting. DNA variants within the promotes of PRMT3, CTH, CERS6, and PHOX2A were found to alter the binding sites of TFs that had shown differential occupancy during footprinting. Performing differential TF co-occurrence identified TF-pairs DRGX-PDX1, DRGX-VAX1, EMX1-PAX4, EN1-PAX4, and ESX1-PAX4 to significantly co-occur in heroin users. Lastly, we used the combined pool of differential TF binding sites along with various datapoints resulting from the downstream analyses to propose two distinct neural circuits active in neurons and glias of chronic heroin users.