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## **Variation in Gene Regulation Across Neurons from Seven Different Brain Regions**

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Substance use disorders (SUDs) are multi-stage traits for which several different brain regions have been implicated. Here, we interrogate gene regulatory networks across neurons from seven different brain regions, linked with SUDs: Nucleus Accumbens (NAc), Hypothalamus, Hippocampus, Dorsolateral Prefrontal Cortex, Orbitofrontal Cortex, Anterior Cingulate Gyrus, and Amygdala. We aim to identify regulatory elements and genes with brain region specific activity in order to assess the contribution of distinct brain regions to the genetics of SUDs.

We performed ChIP-seq for H3K27ac, a marker of active regulatory elements, on neurons isolated from each of the seven brain regions in triplicate control samples. We applied Analysis of Variance (ANOVA) to identify regulatory elements with activity patterns that varied across brain regions. While the vast majority of ChIP peaks displayed similar activity across brain regions, we identified 22,714 putative regulatory elements with brain region specific activity. This included 3,256 regulatory elements that were specifically active in the NAc. Using Hi-C data we identified 1533 putative target genes for NAc specific regulatory elements. We found that these genes were enriched amongst genes specifically expressed in the NAc in publicly available datasets, thus supporting the brain region specificity of the regulatory elements we identified. Using heritability analysis we found NAc specific peaks to be significantly enriched for the heritability of alcohol use disorder. Further studies of the dynamics of gene regulatory elements across the brain may serve to aid genomic studies of SUDs and further reveal brain region specific pathology.