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Decoding the Biological Basis of Opioid Addiction using Single Nuclei RNA-seq and Chromatin Accessibility from the Nucleus Accumbens of Outbred Rats

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The nucleus accumbens (NAc) is a key subcortical brain structure that regulates reward behavior and is involved in addiction. However, the specific NAc cell types, their gene regulatory networks, and the influence of genetic variants that contribute to NAc-related addiction phenotypes are unknown. To address this, we leveraged an outbred population of heterogeneous stock (HS) rats that were genotyped and characterized for their drug intake behavior using a model of oxycodone intravenous self-administration (IVSA). We measured gene expression and chromatin accessibility from ~450,000 single-nuclei from NAc tissues collected from 85 rats after 5 weeks of oxycodone abstinence. We identified 15 major cell types within the NAc, including rare D3 medium spiny neurons (MSNs) that express the dopamine receptor Drd3 and constitute ~2% of NAc cells. Differential abundance analysis revealed that an increased D3 MSN abundance was associated with increased drug intake. Furthermore, we performed a latent factor analysis to identify cell type-specific gene expression and chromatin accessibility patterns across individuals. This analysis showed that D3 MSN-specific gene expression patterns were associated with increased oxycodone drug intake. Lastly, we used the rat genotypes to find associations between genetic variation and the D3 MSN gene expression pattern associated with oxycodone intake. This revealed significant hits suggesting a genetic basis for the variability in D3 MSN gene expression patterns and oxycodone drug intake within our HS rat cohort. Overall, our single cell multiomic analysis in the NAc indicates that D3 MSNs exhibit genetically-encoded variability in gene expression, which is statistically associated with oxycodone addiction behaviour in rats.