

Nucleus accumbens *Drd3* medium spiny neuron abundance is associated with oxycodone intake in outbred rats

The nucleus accumbens (NAc) is a central node in reward circuitry and addiction vulnerability, yet the molecular basis of individual differences in opioid addiction remains poorly defined. To dissect mechanisms underlying oxycodone addiction-like behaviors, we used intravenous self-administration (IVSA) in outbred Heterogeneous Stock (HS) rats and collected NAc tissue from 85 animals following five weeks of abstinence. We generated whole-genome sequencing data and 10x Genomics single-nucleus multi-omic profiles (~500,000 nuclei) to jointly interrogate genetic variation, gene expression, and chromatin accessibility. Latent factor analysis across 14 NAc cell types identified a coordinated molecular signature significantly associated with oxycodone intake, which we term the Factor of Oxycodone (FOXY). FOXY was strongly driven by increased abundance of *Drd3*-expressing medium spiny neurons (MSNs), with higher abundance associated with greater oxycodone intake. Additional contributions arose from transcriptional and chromatin changes in *Grm8*-expressing MSNs and *Chat*-expressing interneurons, cell populations that express the opioid receptor *Oprm1* within the NAc. To evaluate genetic contributions to FOXY, we mapped cis-eQTLs and cis-caQTLs across cell types and trained PrediXcan models to predict genetically regulated gene expression and chromatin accessibility. Genetically predicted molecular profiles explained approximately 18% of the variance in FOXY, suggesting a measurable heritable component to this addiction-associated molecular program. This genetically driven component showed modest correlation with oxycodone intake ($R = 0.18$, $p = 0.14$), indicating that inter-individual genetic differences partially shape the molecular architecture underlying addiction vulnerability. Together, these findings identify a cell type-resolved molecular signature of oxycodone intake in the NAc, prominently driven by *Drd3*-expressing neurons, and demonstrate that a significant fraction of this program is genetically encoded.

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