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Regulatory variation in D1/D2 co-expressing medium spiny neurons is suggested to predispose addiction-related traits

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Medium spiny neurons of the striatum are known to play major roles in reward circuitry and addiction. Single cell transcriptional and epigenomic profiles of the striatum reveal a diversity of medium spiny neuron (MSN) subtypes in the striatum that are suggested to have distinct functions in addiction pathophysiology. We leverage epigenomic annotations of MSN subtypes as well as statistical genetics and machine learning techniques to study the function of MSN subtypes in addiction-related traits.

First, we profiled the epigenome of the rhesus macaque striatum via single nucleus ATAC-seq. Next, we clustered the nuclei into distinct MSN subtypes organized by neurochemical signaling, compartment, and striatal region. In order to identify MSN subtypes that predispose addiction-related traits, we applied LD score regression to intersect addiction-related genetic variants with human orthologs of MSN subtype-specific *cis*-regulatory elements (CREs). Interestingly, we found CREs of D1/D2 co-expressing MSNs (D1H), a rare neuronal subtype of the striatum, were conditionally enriched with genetic variants associated with addiction-related traits, including smoking initiation and risk tolerance.

Finally, we trained a set of convolutional neural network classifier and regression models to predict the cell type-specificity of MSN subtype CREs. We then applied these models to 1) predict the impact of genetic variants on D1H CRE function and 2) design probes to label D1H in model organisms. Our findings of D1H-specific CREs impacted by addiction-associated genetic variation and MSN subtype targeting will provide a foundation for better understanding the cell type-specific gene-regulatory mechanisms underlying addiction.