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Whole-animal massively parallel reporter assay dissects the region-specific transcriptional impact of human addiction genetic variants

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Genetic variants for substance use and substance use disorders largely coincide in brain open chromatin. Most risk variants for complex human traits that lie in the non-coding genome at candidate enhancer regions are thought to alter mRNA transcription of nearby genes. While computational methods exist to nominate candidate variants for causal impact on genome function, few are experimentally validated *in vivo*. To overcome the bottleneck in identifying which risk variants have causal mechanisms to predispose complex behaviors, we test hundreds of risk variants from genome wide association studies in a massively parallel reporter assay library. We package this library with an engineered adeno-associated virus that efficiently crosses the blood-brain barrier to transduce neurons across the central nervous system. Our whole-animal massively parallel reporter assay (WhAMPRA) empowers discovery of altered transcription in candidate enhancers due to small nucleotide differences. We collect WhAMPRA samples from the medial prefrontal cortex, dorsal striatum, and nucleus accumbens and identified enhancers that are tissue specific. We find a handful of candidate enhancers where single nucleotide polymorphisms sufficiently altered transcription rates of the reporter gene. With WhAMPRA, we bridge the gap between risk variant discovery through genome wide association studies and the molecular mechanisms that predisposes individuals to complex diseases and disorders.