

Identifying genes that mediate the effect of genetic variation on behavioral variation related to substance use disorders

Substance use disorders (SUDs) and SUD-associated behaviors are known to have an underlying genetic component, with associated genomic loci identified through genome-wide association studies (GWAS) in both humans and model systems. However, identifying the causal genes mediating these genetic effects on SUD-associated behaviors (like anxiety-related behaviors) has remained difficult, while mechanistic understanding has proven even more elusive. Recent work from our lab has applied the quantitative complementation (QC) test, which tests whether a genetic effect is mediated by a given gene (a quantitative trait gene, QTG), in a high throughput manner to dissect multiple genomic loci underlying fear behaviors in mice. Here, we extend QC testing to establish a mechanistic framework for interpreting how genetic effects act on the neural substrate to influence SUD-related anxiety behaviors. We accomplish this by identifying QTGs on a circuit's behavioral function, rather than organismal behavior. Because circuit activity directly gives rise to behavioral output, and circuits are localized in time and space, identifying QTGs at a circuit level will provide immediate clues into biological mechanism. We identified a circuit (the ventral hippocampal to lateral hypothalamus projection) where optogenetic activation in different inbred strains results in differential effects on performance on shuttle box avoidance, a fear-related assay. We optimized our experimental parameters (including surgical targeting, stimulation intensity, and behavioral parameters) on the diversity outbred (DO) population. Our next goal is to map optogenetically evoked behavioral performance, to establish mechanism through which genes mediate genetic effects on behavior.

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