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Genome-wide association study of psychostimulant-induced behavior in *Drosophila melanogaster*

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Genetic factors contribute substantially to an individual's addiction susceptibility; however, the search for risk alleles has yielded limited success. We have developed approaches using *Drosophila* as a model for high-throughput screening of amphetamine-induced behaviors. We screened the *Drosophila* Genetic Reference Panel of inbred, fully sequenced lines, and performed GWAS to identify novel genes that influence the locomotor response to amphetamine. Our data reveal significant phenotypic variability across genetic backgrounds, confirming that the sensitivity to amphetamine is heritable and dissociable from basal locomotion. Our data also show significant association of a SNP on chromosome 3L, in the upstream regulatory region of the gene encoding the transcription regulator Ctr9, with a dramatically heightened response to amphetamine. We have now shown that dopamine neuron-specific knockdown of Ctr9 leads to a dramatic increase in the response to amphetamine and methamphetamine, whereas overexpression blunts the response. Ctr9 has been also shown to interact with the dopamine transporter (DAT), the major molecular target of psychostimulants. We characterized the expression and localization of Ctr9 in whole adult fly brain and observed extensive expression of Ctr9 in the brain. Preliminary experiments co-staining with an anti-dDAT antibody revealed colocalization of the two proteins in dopamine neurons. Together, these data point to a novel role for Ctr9 in modulating the behavioral response to psychostimulants. Current experiments are aimed at probing the functional relevance of the interaction of Ctr9 with DAT, as well as the role of Ctr9 in transcription, on the cellular, physiological, and developmental determinants of amphetamine-induced behavior.