

Submitter Name: Brenna Williams  
Submitted email: Brenna.Williams@nyspi.columbia.edu  
PI Name: Jonathan Javitch  
PI email: Jonathan.Javitch@nyspi.columbia.edu

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

Brenna Williams<sup>1</sup>, Caline S. Karam<sup>1,2</sup>, Jonathan A. Javitch<sup>1,2</sup>

<sup>1</sup>Division of Molecular Therapeutics, Research Foundation for Mental Hygiene, <sup>2</sup>Department of Psychiatry, College of Physicians and Surgeons, Columbia University

Genetic factors contribute substantially to an individual's addiction susceptibility; however, the search for risk alleles has yielded limited success. The initial sensitivity to psychostimulants varies significantly, and has been associated with continued use and abuse. This trait can be studied in animal models, which have emerged as powerful tools to investigate the behavioral response to drugs in a controlled and systematic manner. 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 genome-wide association studies to identify novel genes that influence the locomotor response to amphetamine. Our data revealed significant phenotypic variability across genetic backgrounds, confirming that the sensitivity to amphetamine is heritable. Furthermore, they show significant association of a SNP on chromosome 3L with a dramatically heightened response to amphetamine. Gene expression analyses show that multiple closely linked SNPs in this region are cis-eQTLs for the gene encoding Ctr9, a protein previously shown to interact with the dopamine transporter in vitro, and to regulate its localization to the cell membrane in heterologous cells. Using immuno-fluorescence analysis, we have confirmed that Ctr9 is localized to the cytoplasm and cell membrane of dopamine neurons in vivo. Using targeted gene manipulation, we further show that RNAi knockdown of Ctr9 specifically in dopamine neurons leads to increased sensitivity to amphetamine, whereas its overexpression blunts the response. Together, these data point to a novel role for Ctr9 in modulating the behavioral response to psychostimulants.