Submitter Name: Chad A. Highfill
Submitted email: chighfi@clemson.edu
PI Name: Trudy Mackay
PI email: tmackay@clemson.edu

Genetics of Cocaine and Methamphetamine Consumption and Preference in Drosophila melanogaster

Chad A. Highfill[1], Brandon M. Baker[1], Robert R.H. Anholt[1], Trudy F.C. Mackay[1]

[1]Department of Genetics and Biochemistry, Clemson Center for Human Genetics, Clemson University

Illicit use of psychostimulants, such as cocaine and methamphetamine, constitutes a significant public health problem. Whereas neural mechanisms that mediate the effects of these drugs are well-characterized, genetic factors that account for individual variation in susceptibility to substance abuse and addiction remain largely unknown. Drosophila melanogaster can serve as a translational model for studies on substance abuse, since flies have a dopamine transporter that can bind cocaine and methamphetamine, and exposure to these compounds elicits effects similar to those observed in people, suggesting conserved evolutionary mechanisms underlying drug responses. Here, we used the D. melanogaster Genetic Reference Panel to investigate the genetic basis for variation in psychostimulant drug consumption, to determine whether similar or distinct genetic networks underlie variation in consumption of cocaine and methamphetamine, and to assess the extent of sexual dimorphism and effect of genetic context on variation in voluntary drug consumption. Quantification of natural genetic variation in voluntary consumption, preference, and change in consumption and preference over time for cocaine and methamphetamine uncovered significant genetic variation for all traits, including sex-, exposure- and drug-specific genetic variation. Genome wide association analyses identified both shared and drug specific candidate genes, which could be integrated in genetic interaction networks. We assessed the effects of ubiquitous RNA interference (RNAi) on consumption behaviors for 34 candidate genes: all affected at least one behavior. Finally, we utilized RNAi knockdown in the nervous system to implicate dopaminergic neurons and the mushroom bodies as part of the neural circuitry underlying experience-dependent development of drug preference.