# Delineating the genetic basis of amphetamine sensitivity using a Drosophila behavioral model

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Abuse of psychostimulants is a major public health problem with profound psychiatric, medical and psychosocial complications. Genetic factors contribute substantially to an individual's susceptibility to developing addiction; 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. Towards this purpose, we have developed high-throughput assay for the locomotor response to psychostimulants in Drosophila. Genetic mutations that disrupt dopamine (DA) synthesis or dopamine transporter gene (DAT) function inhibit this response, demonstrating that we have a robust behavioral tool to associate genetic variations with phenotypic changes. Our studies have further revealed significant phenotypic variability between substrains of wildtype, non-isogenic Canton S (CS) flies that have been maintained separately in different laboratories. Specifically, we identified one substrain that exhibits profoundly heightened sensitivity (HS) to amphetamine (AMPH). CSHS flies respond uniformly to a low concentration of AMPH that does not elicit a response in other strains, and exhibit a stronger maximal response, suggesting they have acquired a fixed genetic variation with large effect on AMPH sensitivity. Using a combination of genetic approaches and comparative next-generation (Next-Gen) sequencing, we have determined that this HS trait is autosomal recessive and maps it to a defined region on chromosome 3R, and we are currently working towards identifying the specific variant responsible for this trait. A second substrain shows great internal variation in sensitivity to AMPH (CSVS), at both acute and chronic exposures; some flies exhibit an increased maximal response while others exhibit a blunted response. Taken together, our data are evidence of segregated genetic variation, at more than one locus, influencing both acute and delayed responses to AMPH in Drosophila, opening up opportunities to use selective breeding approaches and population studies, in combination with Next-Gen sequencing approaches, to investigate the genetic architecture of amphetamine sensitivity.