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Flying high: Delineating the genetic basis of amphetamine sensitivity using a *Drosophila* behavioral model

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Psychostimulant abuse is a major public health problem with profound 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. 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 a behavioral model using *D. melanogaster* for high-throughput genetic screening of amphetamine-induced behaviors. We screened the *Drosophila* Genetic Reference Panel (DGRP), a collection of inbred lines with fully sequenced genomes, and performed genome wide association studies (GWAS) to identify novel gene variants that influence the response to amphetamine. Our data reveal significant phenotypic variability across genetic backgrounds. They implicate over 200 candidate genes and highlight several functional gene pathways associated with amphetamine sensitivity. In parallel, we used an advanced intercross population (AIP) derived from 40 of the DGRP lines, and tested over 4,000 flies for amphetamine-induced hyperactivity. We are currently performing deep DNA sequencing on pools of flies at the extremes of the distribution of the locomotor response. This approach enables us to query the effect of rare alleles in the DGRP, given that the AIP has intermediate allele frequencies at all segregating loci. It also allows us to detect SNPs that may be hidden by epistatic interactions in the DGRP lines. These data will complement our findings from the GWAS and allow us to generate and refine comprehensive gene networks associated with amphetamine sensitivity.