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The genetic basis of natural variation in amphetamine sensitivity in Drosophila

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Using a combination of genomic and computational approaches, we aim to harness the power of Drosophila genetics to identify novel genes that influence the sensitivity to psychostimulants. We have conducted a genome-wide association study (GWAS) by screening inbred lines of the Drosophila Genetic Reference Panel (DGRP) and identified several functional gene networks associated with altered sensitivity to amphetamine. We are currently in the process of validating candidate genes by targeted gene knockdown. We have also screened an advanced intercross population (AIP) derived from a subset of DGRP lines for amphetamine-induced hyperactivity, and completed deep DNA sequencing on pools of flies at the extremes of the phenotypic distribution. Using extreme QTL analysis of these data we can probe the effects of rare alleles in the DGRP, as well as detect SNPs that may be hidden by epistatic interactions in the DGRP lines. We have also performed RNA-seq on the extreme pools of the AIP, to identify groups of co-regulated genes that associate with the high and low responses to amphetamine. These transcriptional data will inform our genetic findings, and allow us to generate and refine comprehensive gene networks associated with amphetamine sensitivity. Towards this goal, we are employing computational techniques such as consensus clustering and iterative Random Forests to predict locomotor and circadian behaviors in Drosophila, at baseline and in response to amphetamine over time. Using these approaches, we aim to query our datasets individually and in combination, to uncover the regulatory mechanisms modulating the cellular and behavioral responses to psychostimulants.