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Dissecting the Genetic Basis of Variation in Cocaine and Methamphetamine Consumption in *Drosophila melanogaster*

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Studies on *Drosophila melanogaster* can identify genetic and transcriptional networks that underlie variation in voluntary consumption of cocaine and methamphetamine to serve as a blueprint for subsequent studies on humans. Psychostimulant exposure in flies results in behavioral and physiological effects that resemble those observed in humans. We derived an outbred advanced intercross population (AIP) from 37 of the sequenced inbred wild-derived lines of the *Drosophila melanogaster* Genetic Reference Panel (DGRP). These lines are maximally genetically divergent, have minimal residual heterozygosity, are not segregating for common inversions, and are not infected with *Wolbachia pipientis*. We assessed voluntary consumption of sucrose, methamphetamine-supplemented sucrose and cocaine-supplemented sucrose and found phenotypic variation in the AIP, in both sexes, for consumption of both drugs. We performed whole genome sequencing and extreme QTL mapping on the top 10% of consumers for each replicate, sex and condition, and an equal number of randomly selected flies. We evaluated changes in allele frequencies among high consumers and controls. We identified 3,033 variants associated with increased consumption in 1,963 genes, enriched for genes associated with nervous system development. We assessed effects of ubiquitous RNA interference (RNAi) on consumption for 22 candidate genes, of which 14 showed an increase or decrease in consumption. To functionally validate SNPs associated with drug consumption, we constructed 20 new AIPs which were homozygous for 10 alternative alleles in an otherwise randomized background. We tested differences in average consumption for each population pair and observed sexually dimorphic differences in genotype- and condition-specific effects. Supported by 1U01-DA041613.