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Dissecting the Genetic Basis of Variation in Cocaine and Methamphetamine Consumption in Outbred Populations of *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 as a blueprint for subsequent studies on 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 consumption of sucrose, methamphetamine-supplemented sucrose and cocaine-supplemented sucrose and observed phenotypic variation in the AIP for consumption of both drugs, in both sexes. 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 control flies and identified 3,033 variants significantly associated with increased consumption that reside in 1,962 genes following Bonferroni corrections for multiple tests. Many of these genes are associated with development of the nervous system. We assessed the effects of RNA interference (RNAi) on drug consumption for 22 candidate genes, of which 13 showed a significant change in consumption in at least one sex. To assess causality at the level of individual SNPs, we constructed allele-specific AIPs which were homozygous for alternative target alleles in five intergenic SNPs and five genes and measured average consumption for each population. These experiments revealed extensive sexual dimorphism and genotype- and treatment-specific effects. Supported by U01-DA041613.