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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. Exposure to these psychostimulants 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 significant 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 genome-wide among high consumers and the control flies and identified 3,033 variants associated with increased consumption that reside in 1,963 genes, enriched for genes associated with nervous system and mesoderm development. We assessed the effects of ubiquitous RNA interference (RNAi) on consumption for 22 candidate genes, of which 14 showed a significant increase or decrease in consumption. Extensive recombination in the AIP generates increased statistical power compared to genome-wide association analysis of the DGRP and illustrates the polygenic genetic architecture that underlies variation in cocaine and methamphetamine consumption. Supported by NIH grant U01DA041613.