Dissecting the genetic underpinnings of cocaine and methamphetamine consumption in *Drosophila melanogaster*

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Abuse and addiction to psychostimulants like cocaine and methamphetamine present a worldwide health issue. The *Drosophila melanogaster* model system can be used to identify genetic and transcriptional networks that underlie variation in effects of drug exposure that can serve as a blueprint for subsequent studies on humans. *Drosophila* also exhibit many of the effects that are observed in humans when cocaine and methamphetamine are consumed. We have derived an outbred advanced intercross population (AIP) from 37 of the sequenced inbred wild-derived lines of the *Drosophila melanogaster* Genetic Reference Panel (DGRP). The 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 4% sucrose, 4% sucrose + 1.0 μg/μL methamphetamine and 4% sucrose + 1.0 μg/μL cocaine of two replicates of 1,500 flies for each sex and condition. We found significant phenotypic variation in the AIP, in both sexes, for consumption of both drugs; and distinct behavioral effects in some of the tested flies. We collected and froze pools of 150 randomly collected flies and the top 150 consumers for each replicate, sex and condition, and performed whole genome sequencing on each of these pools. We evaluated changes in allele frequencies genome-wide among high consumers and the control flies and identified hundreds of variants associated with drug consumption. These variants are in many novel candidate genes with human orthologues that we will use to further understand the genetic mechanisms underpinning increased drug consumption.