Where is the Missing Heritability Hiding? Lessons From *Drosophila*

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Heritability – the fraction of phenotypic variation for quantitative traits due to genetic variation – is high for many human diseases and quantitative traits. Many well-powered and replicated genome wide association (GWA) studies in human populations have identified common variants significantly associated with quantitative traits, but the associated variants typically only account for a small fraction of the total heritability, a phenomenon known as 'missing heritability'. There are many plausible reasons why this phenomenon can occur, but little attention has been paid to the hypothesis that missing heritability is due, at least in part, to context-dependent effects of causal variants. We used the powerful *Drosophila* genetic model system to investigate the contribution of gene-environment interactions and epistasis to genetic variation of lifespan, a model fitness trait. We found that the majority of genetic variation for lifespan is due to genotype by sex interaction, genotype by environment interaction, and genetic variation in sex dimorphism that varies with the physical environment. Remarkably, the variants that have significant genotype by sex or environment interaction effects have opposite effects between sexes or environments – *i.e.*, they exhibit antagonistic pleiotropy. Further, we find evidence of extensive epistasis, and the epistatic effects are also sex- and environment-specific. Thus the significant variants have small effects on lifespan averaged over both sexes and all environments and genetic backgrounds, even though their effects are large within each context. Context-dependent effects can therefore account in part for missing heritability and contribute to the maintenance of genetic variation for quantitative traits in natural populations.