

Behavioral individuality reveals genetic control of phenotypic variability

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Julien F Ayroles, Sean M Buchanan, Chelsea Jenney, Kyobi Skutt-Kakaria, Jennifer Grenier, Andrew G Clark, Daniel L Hartl, Benjamin L de Bivort
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Variability is ubiquitous in nature and a fundamental feature of complex systems. Few studies, however, have investigated variance itself as a trait under genetic control. By focusing primarily on trait means and ignoring the effect of alternative alleles on trait variability, we may be missing an important axis of genetic variation contributing to phenotypic differences among individuals. To study genetic effects on individual-to-individual phenotypic variability (or intragenotypic variability), we used a panel of *Drosophila* inbred lines and focused on locomotor handedness, in an assay optimized to measure variability. We discovered that some lines had consistently high levels of intragenotypic variability among individuals while others had low levels. We demonstrate that the degree of variability is itself heritable. Using a genome-wide association study (GWAS) for the degree of intragenotypic variability as the phenotype across lines, we identified several genes expressed in the brain that affect variability in handedness without affecting the mean. One of these genes, *Ten-a* implicated a neuropil in the central complex of the fly brain as influencing the magnitude of behavioral variability, a brain region involved in sensory integration and locomotor coordination⁶. We have validated these results using genetic deficiencies, null alleles, and inducible RNAi transgenes. This study reveals the constellation of phenotypes that can arise from a single genotype and it shows that different genetic backgrounds differ dramatically in their propensity for phenotypic variability. Because traditional mean-focused GWASs ignore the contribution of variability to overall phenotypic variation, current methods may miss important links between genotype and phenotype.

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I fully expect researchers to demonstrate that this study and its companion study "Neuronal control of locomotor handedness in Drosophila" have general applicability for humans, especially during womb-life.

Stress studies in the human fetus' environment should show changes at least as significant as temperature had in this study on the developing fruit fly pupae.

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