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TITLE: Heteroscedastic regression modeling elucidates gene-by-environment interaction

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ABSTRACT:

Gene-by-environment interaction (GxE) is inferred when a genetic measure accounts for differing amounts of variance in a phenotype across levels of the environment. However, total variance in the phenotype may shift as a function of the environment irrespective of its genetic etiology such that the *proportional* effect of the genetic measure is constant. We expand the traditional GxE regression model to directly model heteroscedasticity, and we derive a test statistic, ξ , for inferring whether GxE can be plausibly attributed to a more general effect of the environment on the dispersion of the phenotype. In simulation studies, we demonstrate that the test statistic can be utilized, along with evaluations of other model parameters, to adjudicate between multiple hypotheses regarding GxE. We then apply this method to test whether previous reports of increasing penetrance of polygenic scores for BMI in more recent birth cohorts may be due to more general secular increases in the variance of BMI. We provide an R function for estimating heteroscedastic GxE regression models and calculating ξ .

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