

Non-additive genetic effects in academic performance

Ralph Porneso^{1, }

 @RPorneso

 ralphporneso@gmail.com

Espen Moen Eilertsen¹ Perline Demange¹ Ziada Ayorech¹ Nicola Barban² Alexandra Havdahl³ Eivind Ystrøm¹

¹ PROMENTA, Department of Psychology, University of Oslo

² Department of Statistics "P. Fortunati", University of Bologna, Italy

³ Centre for Genetic Epidemiology and Mental Health, Norwegian Institute of Public Health, Oslo, Norway

Introduction

GWAS leveraging measures collected at multiple time points have found novel genetic associations. We hypothesize that a subset of these variants may be involved in **gene-by-gene (GxG)** or **gene-by-environment (GxE)** interaction. We propose an analytic approach that concurrently models SNPs' phenotype level and heteroskedastic effect longitudinally.

Methods

Population and within-family longitudinal (and delta) GWAS in the form of a 3-level hierarchical generalized linear mixed effects model (HGLM) (Cao, Maxwell, and Wei 2015; Rönnegård, Shen, and Alam 2010):

$$Y_{ijk} = \mathbf{X}_{ijk}\beta + G_{1ijk}\gamma_1 + G_{2ijk}\gamma_2 + \mu_{ijk} + \delta_{ij} + \epsilon_i,$$

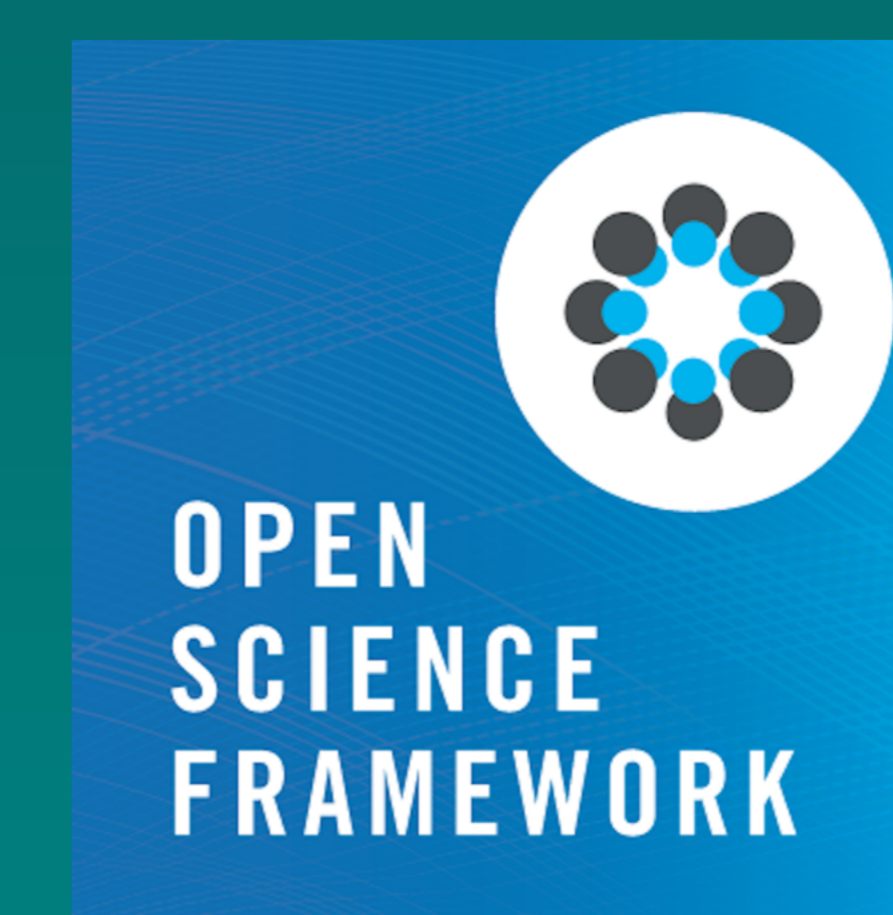
where \mathbf{X} is a matrix of covariates (i.e., time, sex, batch, 10 PCs) including the intercept with β as their respective effect size, G_1/G_2 are the copies of the effect allele (expressed as deviation from the family mean) with γ_1/γ_2 as their effect on phenotype mean, μ_{ijk} is the random intercept of individual, δ_{ij} is the genetic relatedness matrix (GRM) and

$$\epsilon_i \sim N(0, G_{0i}\sigma_0^2 + G_{1i}\sigma_1^2 + G_{2i}\sigma_2^2)$$

We assume uncorrelated variance components: $\mu_{ijk} \sim N(0, \sigma_\mu^2)$, $\delta_{ij} \sim N(0, \sigma_F^2\Phi)$, and $\epsilon_i \sim N(0, \mathbf{V}_E)$ where \mathbf{V}_E is an $n \times n$ matrix with the i^{th} diagonal equal to $G_{0i}\sigma_0^2 + G_{1i}\sigma_1^2 + G_{2i}\sigma_2^2$ and Φ is $2 \times$ the kinship matrix.

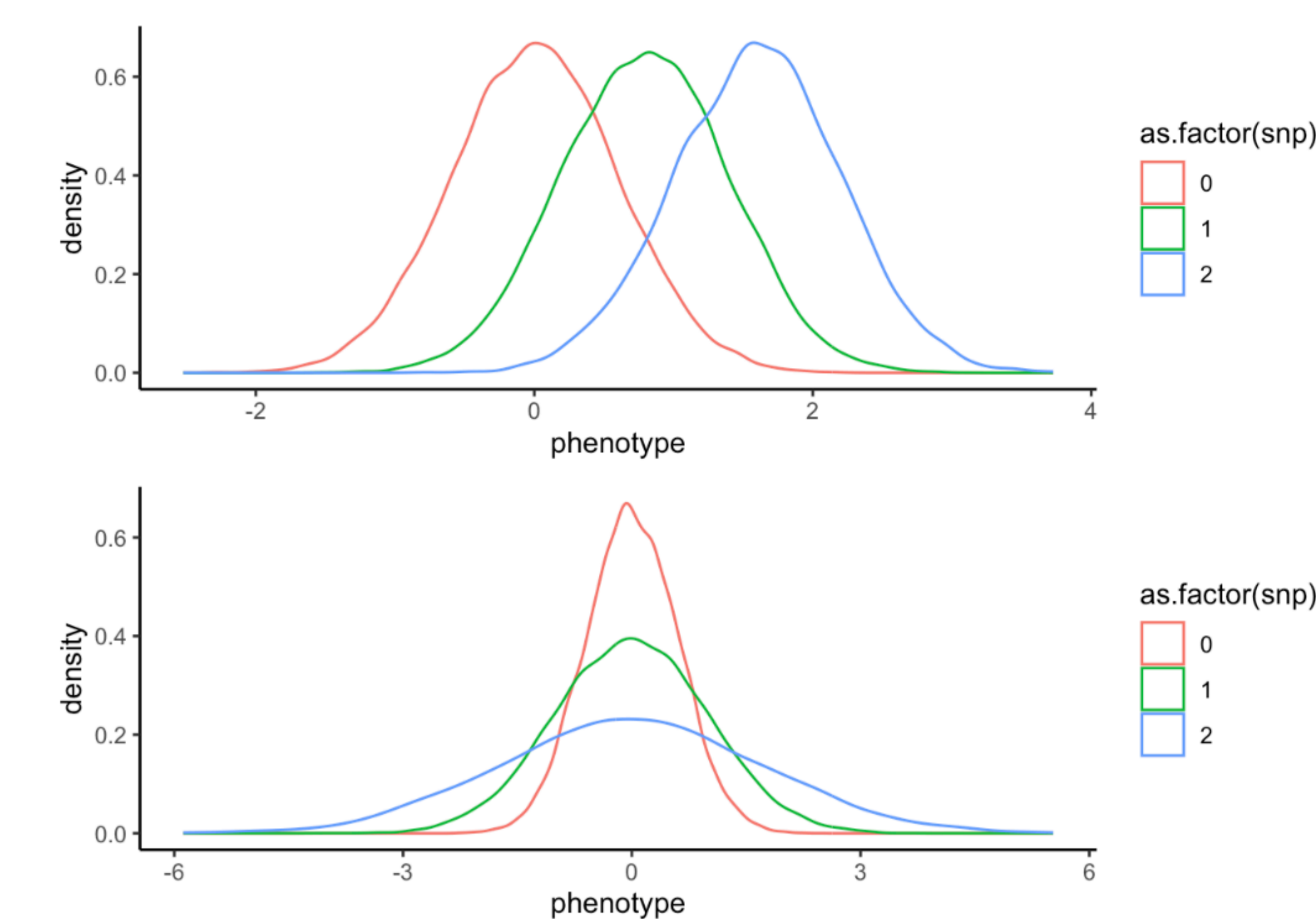
SNPs with heteroskedastic effect are indicative of GxG and GxE.

We employ longitudinal (delta) GWAS and vQTL to detect them.

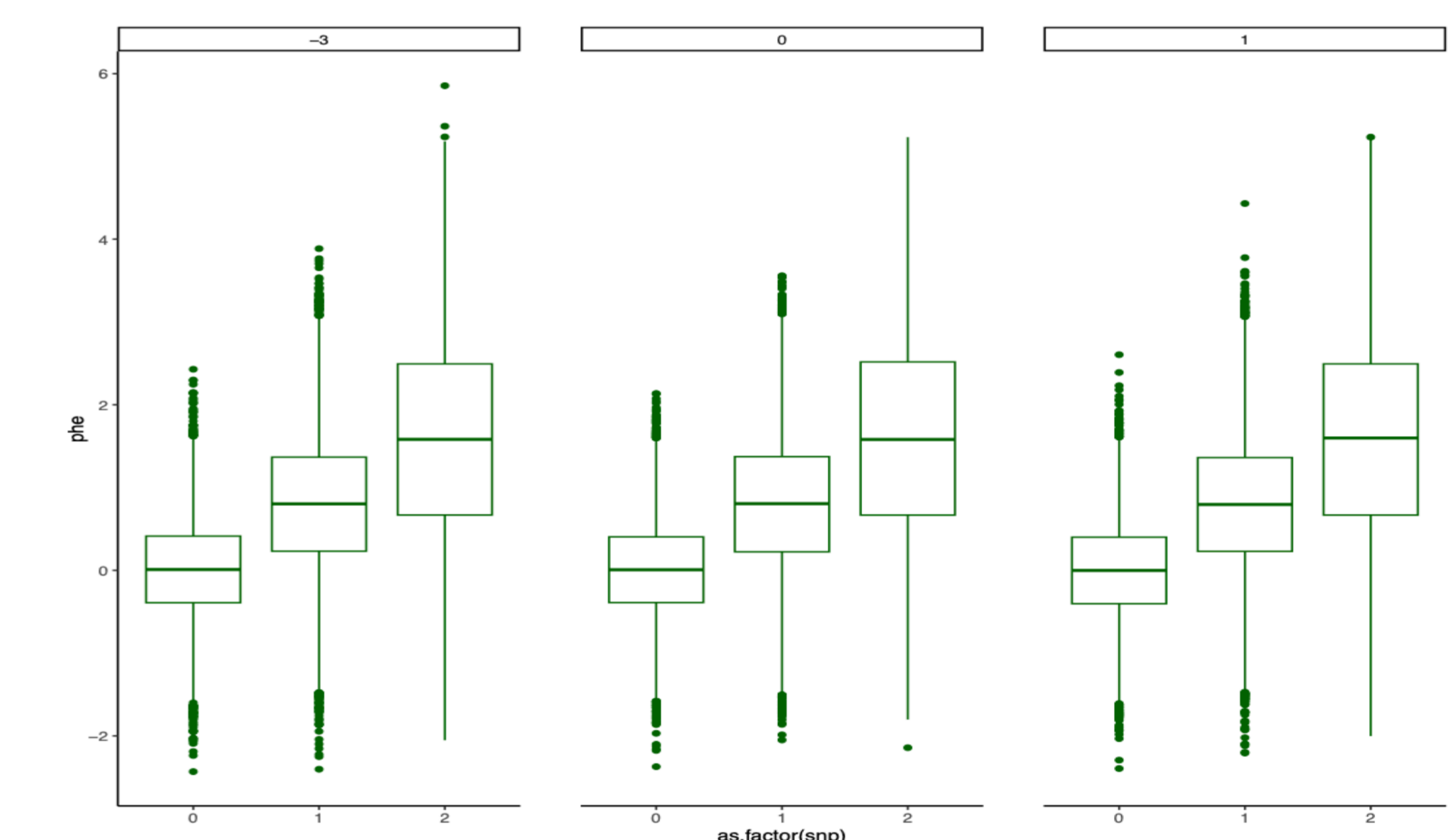


Simulation Results

SNP mean vs. heteroskedastic effect visualized affecting phenotype variance and kurtosis.

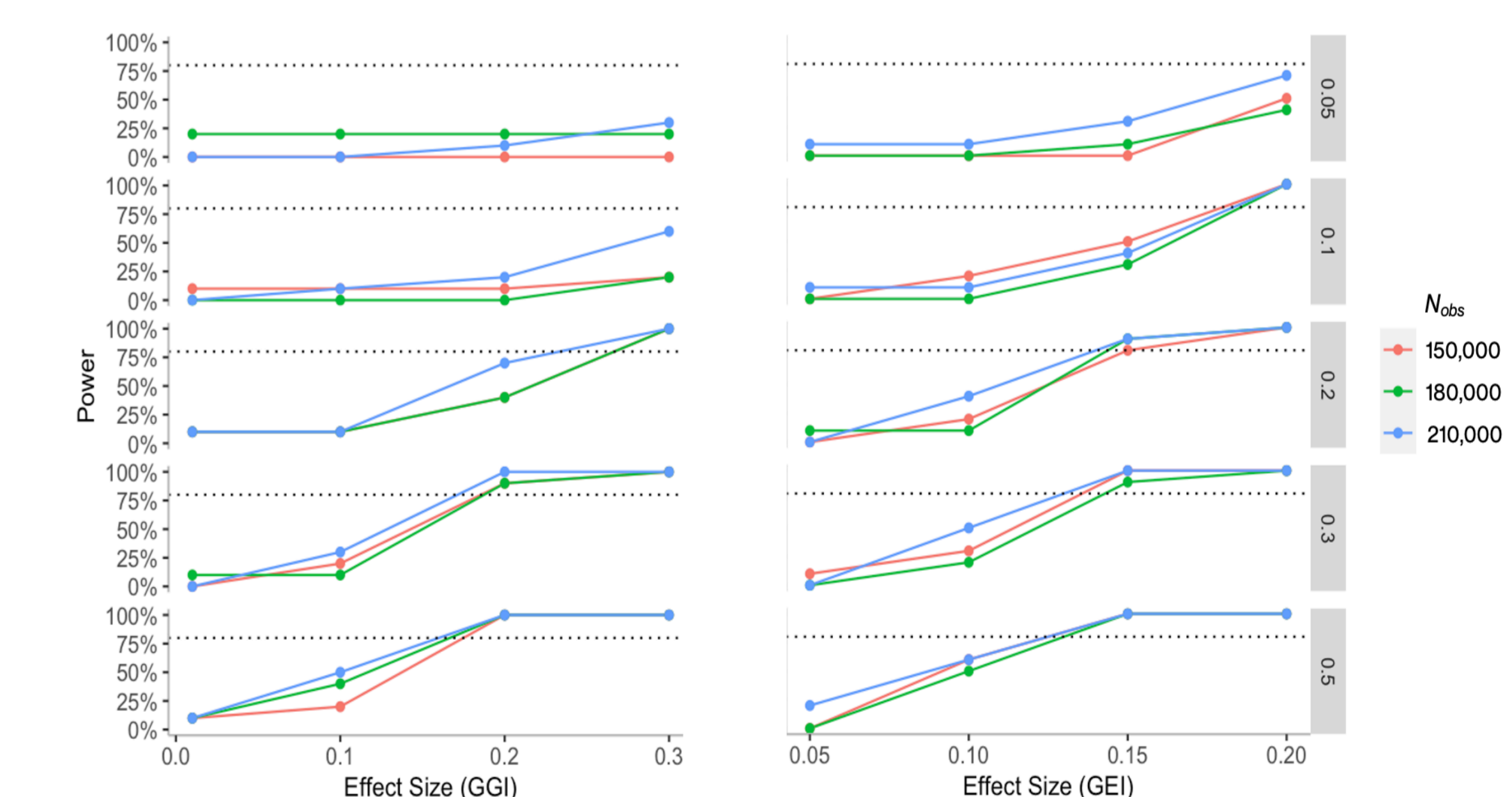


Mean and variance effects are inherently correlated.



This mean-variance relationship must be decorrelated (Young, Wauthier, and Donnelly 2018): $d_l = \alpha_{vl} - r_{av}\alpha_{vl}$.

Non-additive effects are more difficult to detect.



References

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