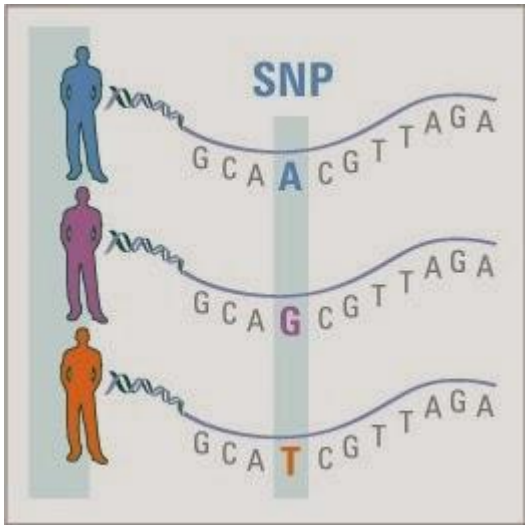

GENOMIC HERITABILITY AND LIKELIHOOD ESTIMABILITY USING THE G-BLUP

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Missing heritability

- Genome Wide Association Studies (GWAS) have reported **large numbers of variants** associated with important complex human traits and diseases (NHGRI, www.genome.gov/GWAStudies).
- A sizable proportion of **inter-individual differences** attributable to genetic factors remains largely **unaccounted for** (Manolio et al., 2009).
- GWAS **lack power** to detect associations of **small-effects variants**.
- With the **G-BLUP** we can estimate the proportion of variance that can be explained by **all-available markers** (Yang et al., 2010).

$$y_i = g_i + \varepsilon_i$$

Error

Genetic Value

Phenotype

$$var(\mathrm{y}_i) = var(\mathrm{g}_i) + var(\varepsilon_i) + 2cov(\mathrm{g}_i, \varepsilon_i)$$

$$\sigma_y^2 = \sigma_g^2 + \sigma_\varepsilon^2$$

$$h^2 = \frac{\sigma_g^2}{\sigma_g^2 + \sigma_\varepsilon^2}$$

Heritability: The proportion inter-individual differences of a trait (or in disease risk) that can be attributed to genetic factors.

Infinitesimal model

$$y_i = \mu + g_i + \varepsilon_i$$

$$\boldsymbol{g} \sim N(0, \mathbf{A}\sigma_a^2), \quad \boldsymbol{\varepsilon} \sim N(0, \mathbf{I}\sigma_\varepsilon^2)$$

Henderson, 1950

Subject	Y	SNP1	SNP2	SNP3	SNPj	SNPp
1	123	AA	gg	AA	…	GG
2	130	Ac	AA	AA	…	GG
3	146	AA	AA	AA	…	GG
i	…	…	…	…	…	…
N	101	Ac	Ag	AA	…	GG

X

G-BLUP

$$y_i = \mu + g_i + \varepsilon_i \text{ where } g_i = \sum x_{ij} u_j$$

$$\boldsymbol{u} \sim N(0, \sigma_u^2), \quad \boldsymbol{\varepsilon} \sim N(0, \mathbf{I}\sigma_\varepsilon^2),$$

$$\boldsymbol{g} \sim N\left(0, \sigma_g^2 = \mathbf{p}\sigma_u^2\right)$$

$$\boldsymbol{Var(y)} = G\sigma_g^2 + I\sigma_\epsilon^2$$

Computing genomic similarities

	I-1	I-2	II-1	II-2	II-3	II-4	III-1	III-2
I-1	1	0	0.5	0.5	0.5	0	0.25	0.25
I-2	0	1	0.5	0.5	0.5	0	0.25	0.25
II-1	0.5	0.5	1	0.5	0.5	0	0.25	0.25
II-2	0.5	0.5	0.5	1	0.5	0	0.25	0.25
II-3	0.5	0.5	0.5	0.5	1	0	0.5	0.5
II-4	0	0	0	0	0	1	0.5	0.5
III-1	0.25	0.25	0.25	0.25	0.5	0.5	1	0.5
III-2	0.25	0.25	0.25	0.25	0.5	0.5	0.5	1

$$\mathbf{G} = \frac{\frac{1}{p}\mathbf{X}\mathbf{X}'}{2\sum \theta_i(1-\theta_i)},$$

$$\mathbf{X} = \{x_i = 0,1,2\}$$

θ_i allele frequency

A: expected proportion of allele sharing.

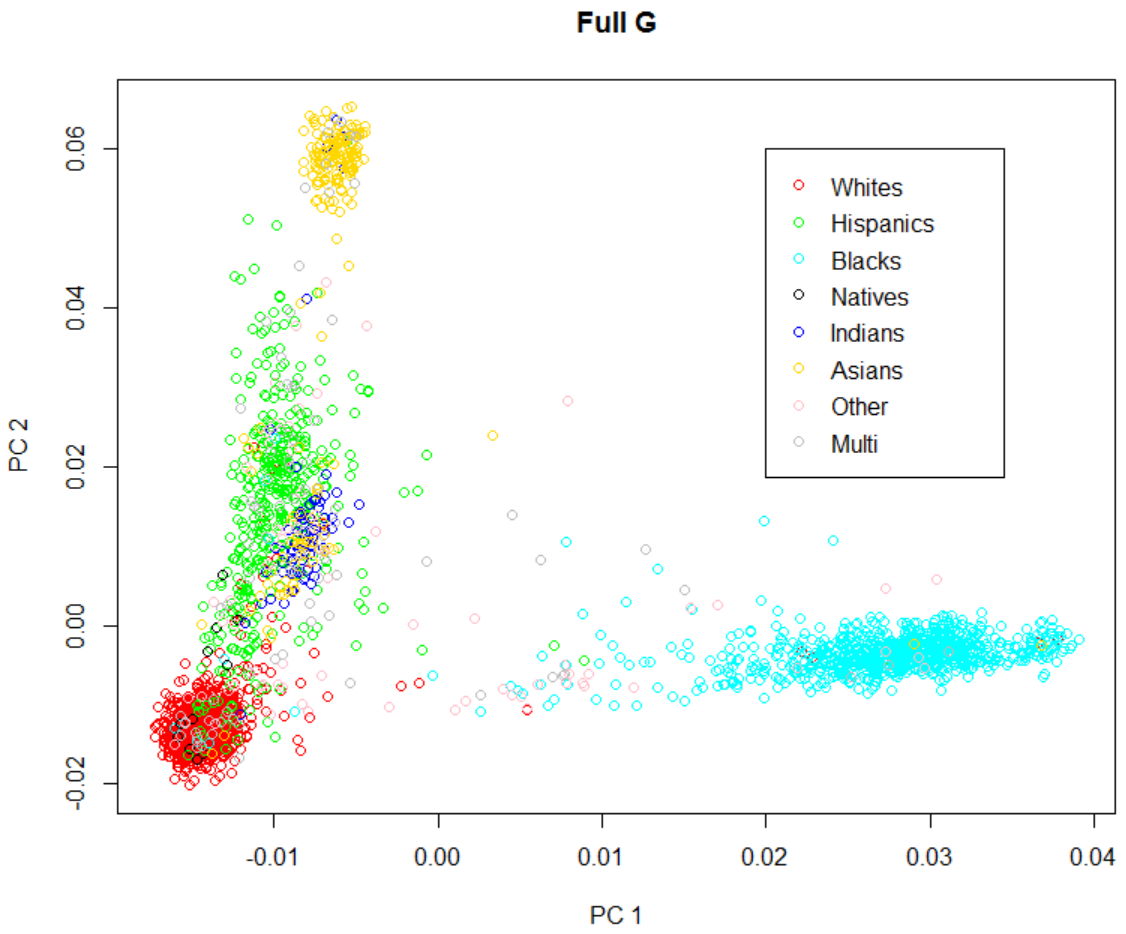
G: realized proportion of allele sharing at markers.

Materials and Methods

Training Interventions & Genetics of Exercise Response

Hypothesis: G-BLUP can explain a sizeable proportion of h^2_G for anthropomorphic traits in the TIGER study (Illumina metabochip)

RACE	SAMPLE SIZE	No. SNPs
Whites	1052	39438
Blacks	721	49679
Hispanics	321	75113
Asians	130	72057



Estimation of h^2_G using:

- **ML**
- **Bayesian methods**
- **Simulations**

ML/Bayesian Inference

$$p(\sigma_\varepsilon^2, \sigma_g^2 | \mathbf{y}, \boldsymbol{\theta}) \propto p(\mathbf{y} | \sigma_\varepsilon^2, \sigma_g^2)\, p(\sigma_\varepsilon^2, \sigma_g^2 | \boldsymbol{\theta})$$

$$\propto N(\mathbf{y} | \mathbf{0}, \mathbf{G}\sigma_g^2 + \mathbf{I}\sigma_\varepsilon^2) \times \chi^{-2}(\sigma_g^2 | df_1, S_1) \times \chi^{-2}(\sigma_\varepsilon^2 | df_2, S_2)$$

Prior distribution

Likelihood function (used in ML)

Distribution of the unknowns given the data and hyper-parameters

---

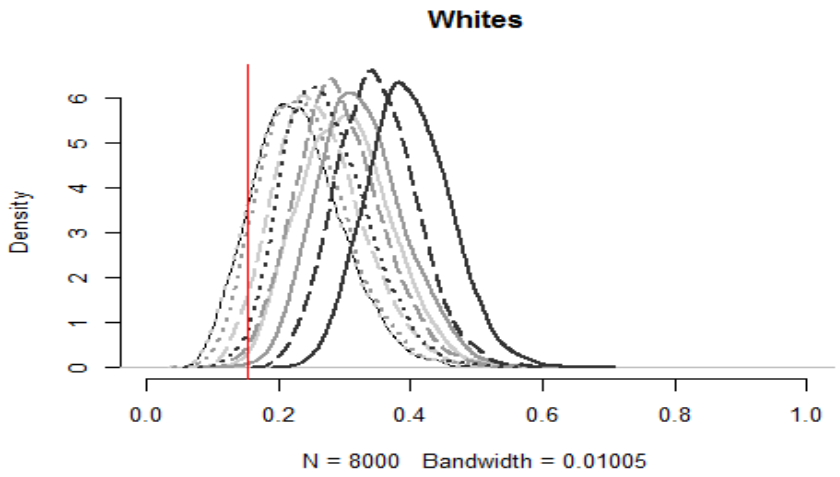
The Scale-Inverse Chi-Sq. Density

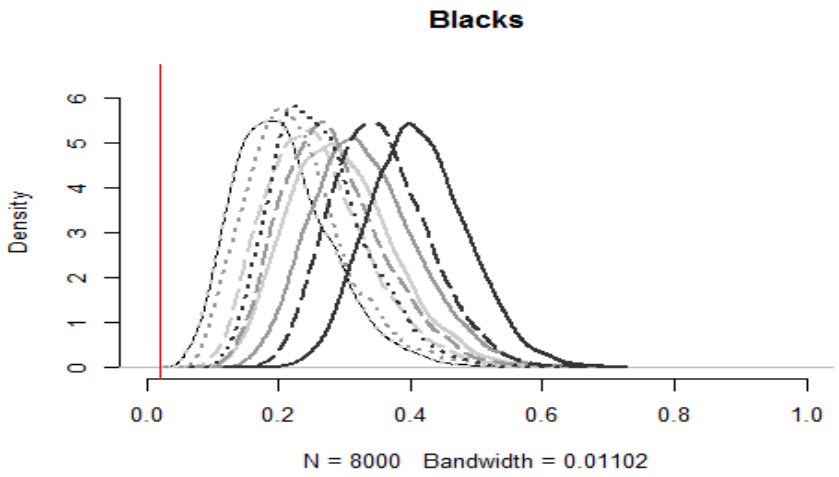
$$\frac{df_0\sigma_0^2 + \sum_{i=1}^{n}(y_i - \mu)^2}{df_0 + n} \longrightarrow \text{Posterior density}$$

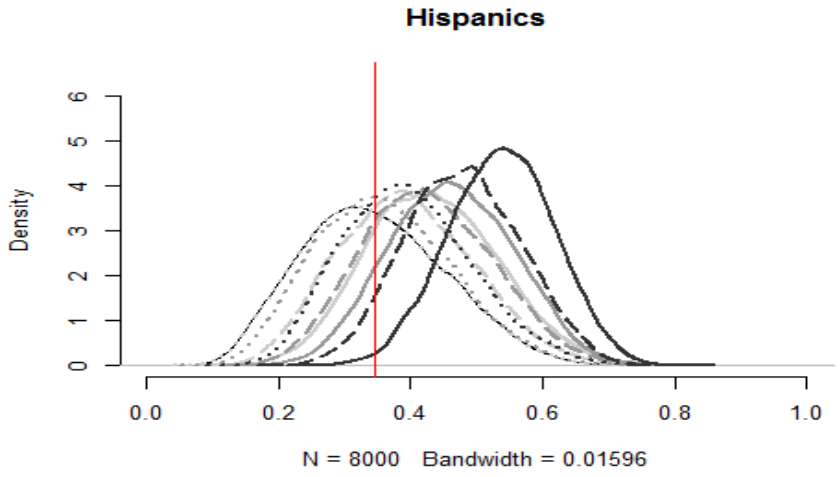
BGLR (R)

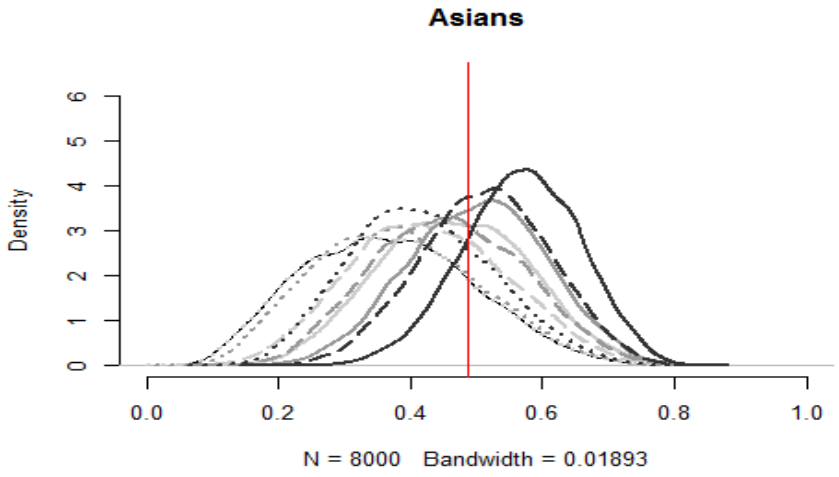
$df_0 = 1, 3, 5;\ \sigma_0^2 = 0.25, 0.5, 0.75$ → Hyperparameters

Distribution of h_G^2 for height using MCMC. Red line = ML estimate

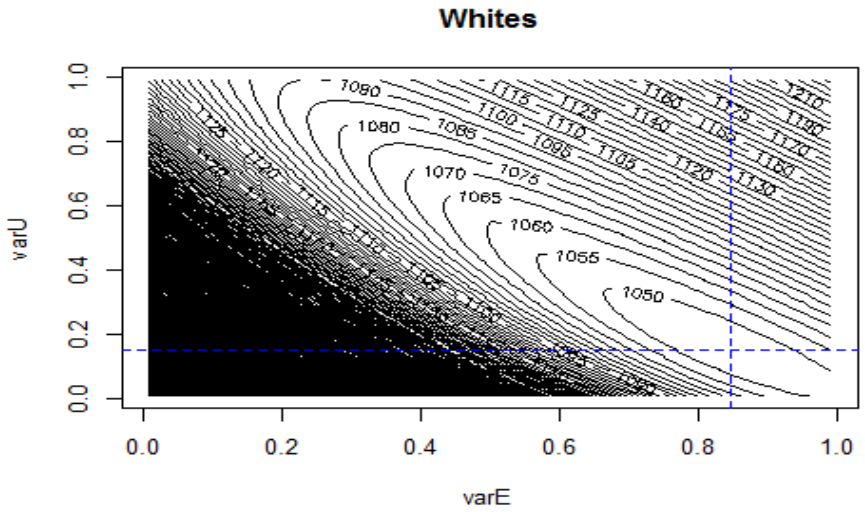


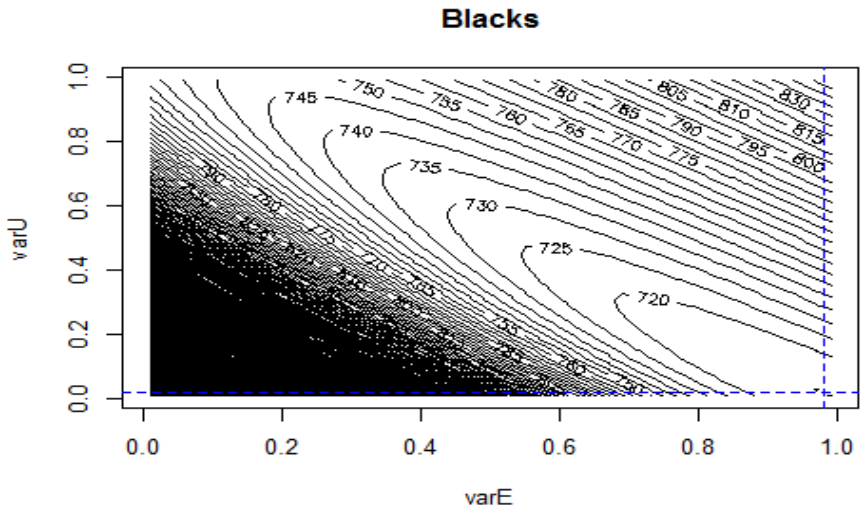


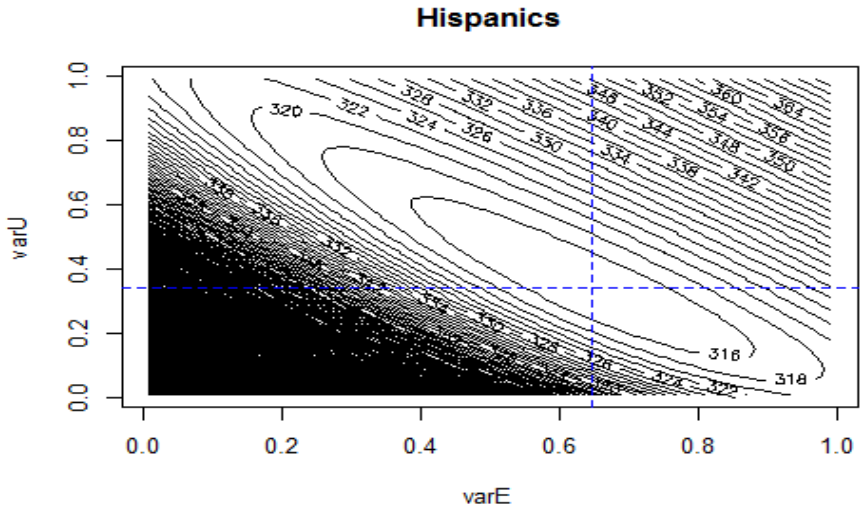


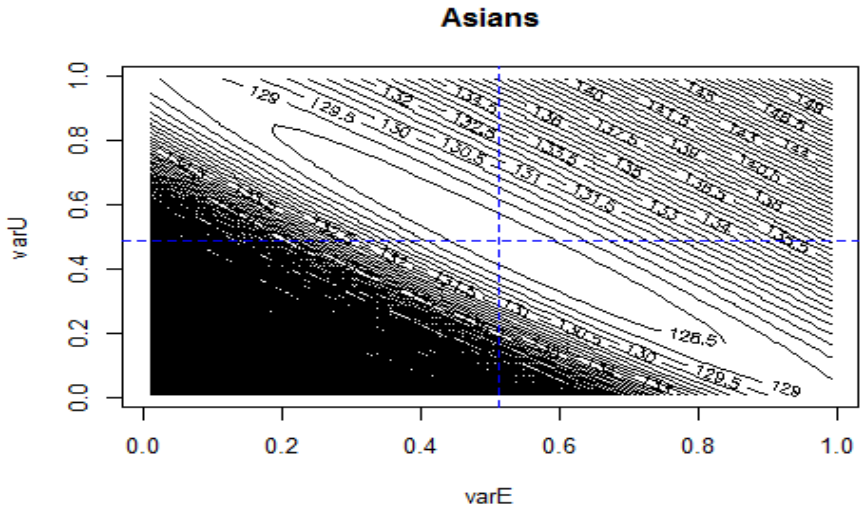


The Neg. Log-Likelihood Surface

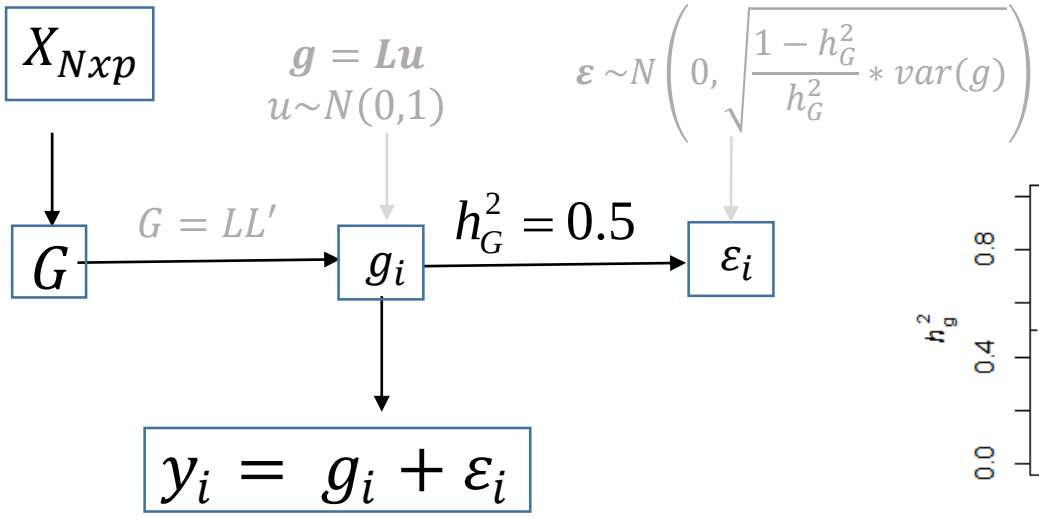




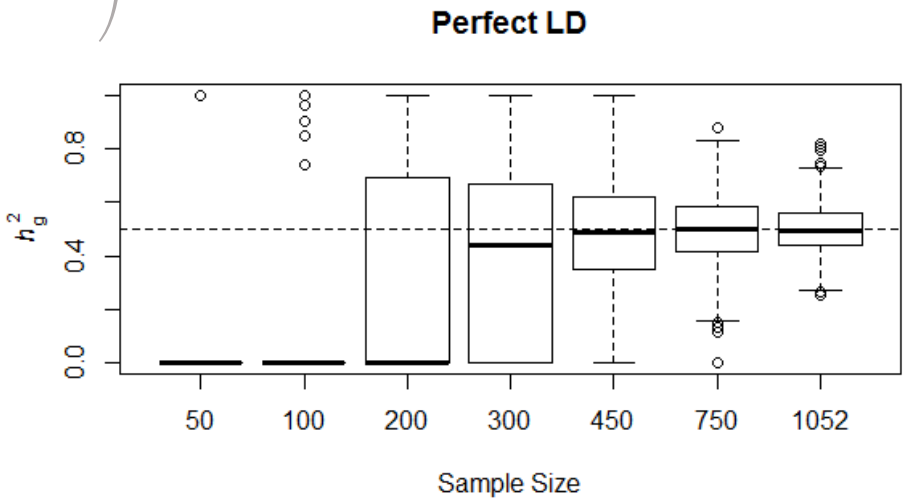


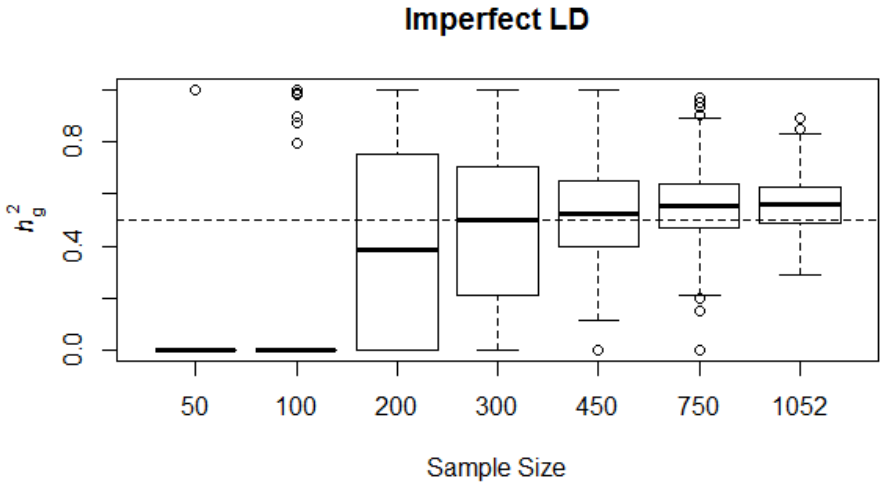


Simulations (ML estimates from 1000 reps)

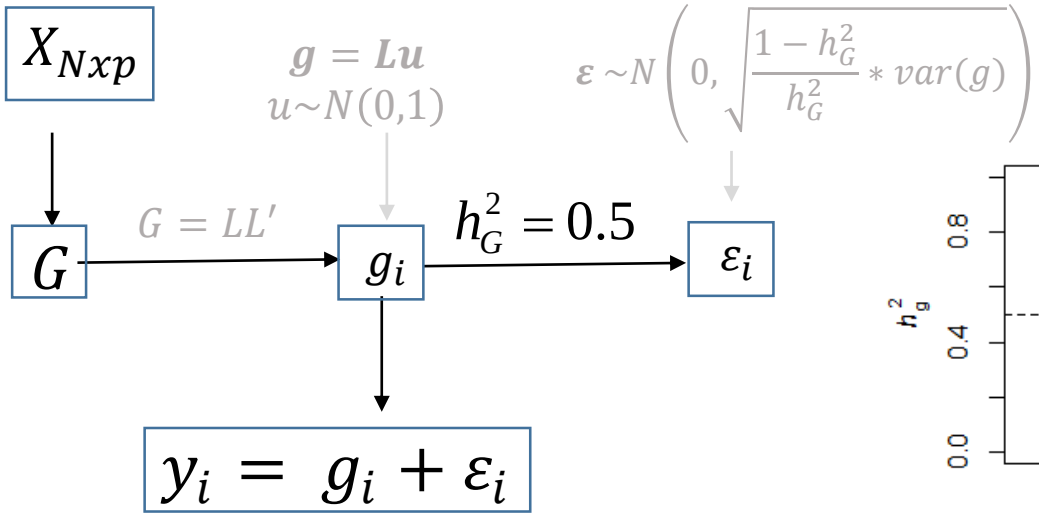


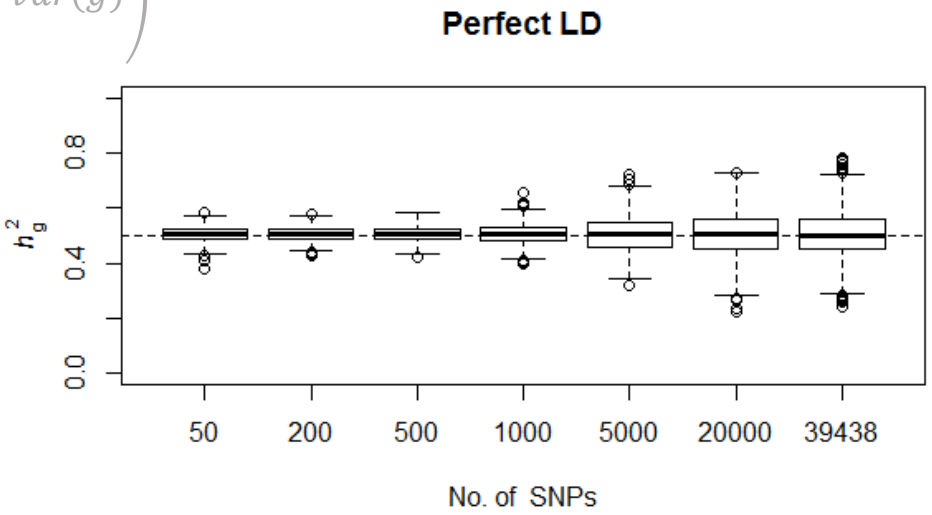
Z_{Nxp} Simulated dataset	W_{Nxp} Predictor dataset
$p = 39438$ $N = 50, 100 \ldots 1052$	$p = 39438$ $N = 50, 100 \ldots 1052$
$p = 250$ $N = 50, 100 \ldots 1052$	$p = 39188$ $N = 50, 100 \ldots 1052$



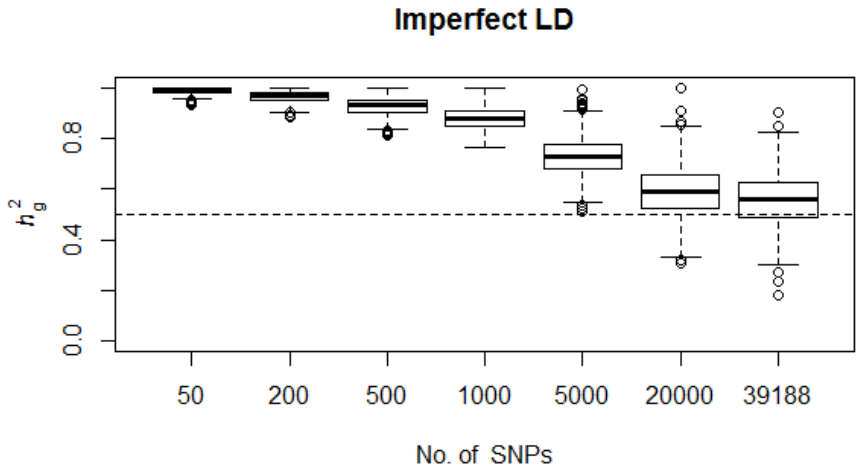


Simulations (ML estimates from 1000 reps)





Z_{Nxp} Simulated dataset	W_{Nxp} Predictor dataset
$p = 50,200, \ldots 39438$ $N = 1052$	$p = 50,200, \ldots 39438$ $N = 1052$
$p = 250$ $N = 1052$	$p = 50,200, \ldots 391888$ $N = 1052$



Conclusions

- Variance component and heritability estimation using ML resulted in some corner solutions.
- Bayesian estimates were very sensitive to choice of prior.
- This was the result of an estimability problem caused by a flat likelihood function; there was a large area corresponding to the same likelihood.
- Thus, variance component estimates should be reported after a careful study of likelihood profiles.
- Simulation studies suggest that the probability of corner solutions reduce by increasing sample size and decreasing SNP density, however lower SNP density might result in increased bias.

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Training Interventions & Genetics of Exercise Response

NIDDK National Institute of Diabetes and Digestive and Kidney Diseases

UAB

Nutrition Obesity Research Center

SSG