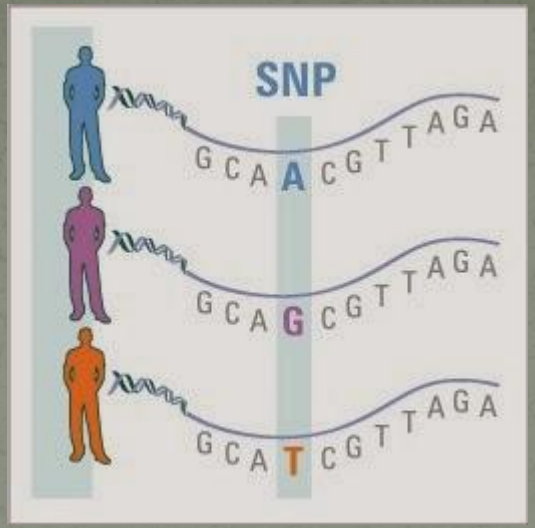

Estimation of genetic relatedness and heritability

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BST 775, Fall 2013
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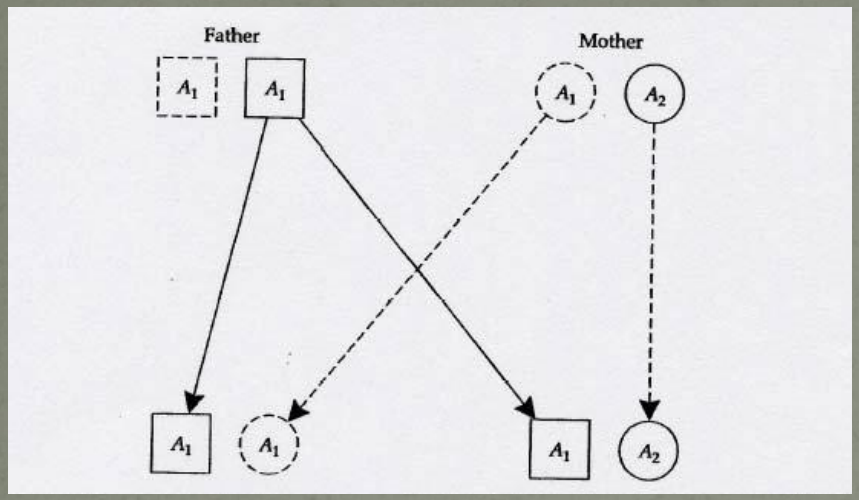
Genetic Relatedness. Why study it?



Lynch M, Walsh B(1998) Genetics and analysis of quantitative traits.

Utility:

- Forensics
- Agriculture and Animal breeding
- Ecology
- Human Genetics

P(IBD): Probabilities that sets of genes have descended from a single ancestral gene

- Mapping human genes
- Predicting genotype frequencies
- Estimating genetic variances

Genetic relatedness over the years..

- Traditionally, estimates of genetic relatedness (probabilities of IBD) were calculated from known pedigrees (Malecot 1969, Wright; 1943)
- Later, there were methods to estimate cryptic relatedness or recent ancestry

- **E.g.: Thompson's MLE:** The joint probability of genotypes G_1 and G_2 of individuals 1 and 2, conditional on their degree of pairwise relatedness parameterized by $\mathbf{k} = (k_0, k_1, k_2)$ and conditional on the allele frequencies in the population is:

$$P(G_1, G_2 | k) = \mathbf{k_0} P(G_1) P(G_2) + \mathbf{k_1} P(G_1) P(G_2|G_1) + \mathbf{k_2} P(G_1) I(G_2=G_1)$$

For L multiple linked loci: $$P(\mathbf{G_1}, \mathbf{G_2} | \mathbf{k}) = \prod_{j=1}^{L} P(G^{(j)}_1, G^{(j)}_2 | \mathbf{k})$$

MLE is the value of $\mathbf{k}$ that maximizes this joint probability; subject to constraints $0 \leq \mathbf{k_0}, \mathbf{k_1}, \mathbf{k_2} \leq 1$ and $\mathbf{k_1}^2 \geq 4\, \mathbf{k_0}\, \mathbf{k_2}$

- Queller and Goodnight (1989), Ritland (1996), Lynch and Ritland (1999), and Wang (2002) are some other non-likelihood based methods for estimating genetic relatedness

Genomic relationship matrix (G)

- Originated in animal breeding
- Used to estimate the proportion of chromosome segments shared by individuals
- Genes that are IBS (identical by state) can be shared through common ancestors not recorded on pedigree
- Greatly useful for genomic prediction in quantitative genetics

Why am I concerned about G?

- *To estimate genetic variances and heritability for human traits!*
- h^2 :Proportion of variation in phenotype that is attributable to the genotype; the additive genetic component is called **narrow-sense** heritability

$$h^2 = \frac{\sigma^2{}_G}{\sigma^2{}_G + \sigma^2{}_E}$$

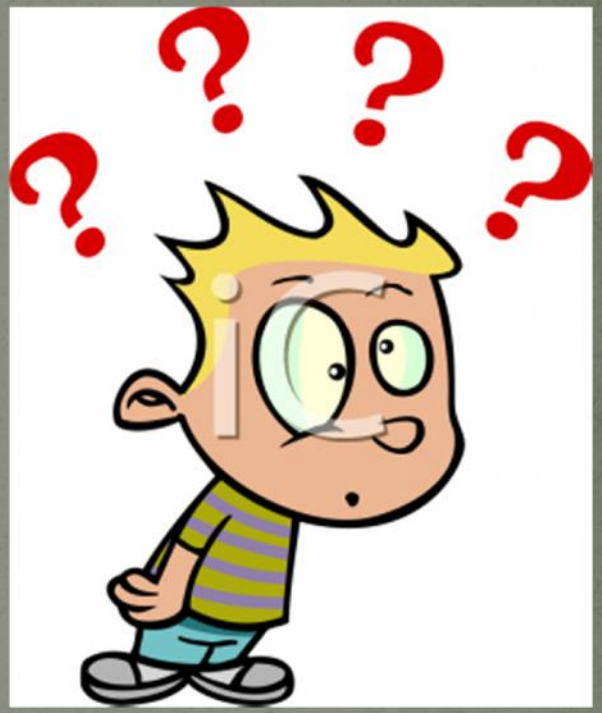
- Dense genotype data can explain large amount of genetic variation when using whole genome statistical models
- LD is generated by the short genomic regions passed by remote common ancestors
- h^2 =causal variant heritability that is tagged by the genotyped SNPs

…however, despite dense genotypic data….

- There is missing heritability!!

Why is heritability missing?

- Rare variants and undetected CNVs
- Insufficient sample sizes
- Causal variants are not in complete LD with the genotyped SNPs
- Mismatch between genetic architecture and statistical modeling



Yang Study (2010)

- Using Whole Genome Prediction (WGP) method on human height:

Common SNP variation explained 45% of the phenotypic variance, accounting for more than 50% of the expected heritability of height (approx. 80%)

- Results suggest infinitesimal model for height

How to make use of G?

Basic Model

- $y_j = \mu + g_j + e_j$ where $g_j = \sum z_{ij} u_i$
- w_{ij} is the genotype of individual *i* at the j^{th} of *m* diallelic loci with additive coding of genotypes, $E(w_{ij}) = 0$ and $Var(w_{ij}) = 1$; $e_i \sim iid\ N(0, \sigma^2_e)$ $u_i \sim iid\ N(0, \sigma^2_g/m)$
- $Var(Y) = \sigma^2_g \frac{WW'}{m} + \sigma^2_e I = \sigma^2_g G + \sigma^2_e I$
- In reality G is unknown so a G matrix is estimated using genome-wide sample of SNPs

Methods for estimating G

- If P is the matrix of allele frequencies, *n* is the number of individuals, *m* is the number of markers and X is the allele sharing matrix (0,1,2) and Z is the allele sharing matrix centered at its mean, i.e. Z =X-P:

- Van Raden et al. 2008 (VAN)
- $G = \frac{ZZ'}{2 \sum p_i(1-p_i)}$

- Leutenegger et al. 2009(DEF)
- G = ZDZ' where D is diagonal with $D_{ii} = \frac{1}{m[2p_i(1-p_i)]}$ (weights markers by reciprocals of expected variance

- Legarra et al. 2009 (LEG)
- $G = \frac{ZZ'}{tr(ZZ')/n}$

Methods for estimating G

- Gianola et al. 2010 (GIA)
- $$G = \frac{ZZ'}{\left((p_0 - q_0)^2 + \left(\frac{2\sum_{i=i}^{m} p_i(1-p_i)}{m}\right)\left(\frac{\alpha+\beta+2}{\alpha+\beta}\right)\right)m}$$

p_0 and q_0 are expectations of allele frequencies from a Beta distribution with hyper-parameters α and β

- Unified Additive Relationship - Yang et al. 2010 (UAR)

$$G = ZDZ'$$

$$\text{diag}(G) = G_{ii} = 1 + \frac{1}{m}\sum_k \frac{x_{ik}^2 - (1+2p_k)x_{ik} + 2p_k^2}{2p_k(1-p_k)}$$

Provides an unbiased estimate of inbreeding coefficient

- Adjusted Unified Additive Relationship - Yang et al. 2010 (aUAR)

$$G^*_{ij} = 1 - \frac{1}{m * Var(G)} * G \quad i \neq j$$

$$= 1 + \left(1 - \frac{1}{m * Var(G)}\right) * (G - 1) \quad i \neq j$$

Corrects for sampling error of UAR

- So.. the diagonal of the G is important..

Simulation – Toy example

- 1500 individuals simulated with 1000 SNPs at 50% heritability
- Allele frequencies drawn from a beta distribution
- Effects assigned to 100 QTL (drawn from a normal distribution)and genetic signal = X*b_0
- Error calculated from a N$\left(0, \sqrt{\frac{1-h^2}{h^2} * var(b_0)}\right)$
- Phenotypes simulated as y = signal + error

Simulation – Toy example

- After model-fitting, almost the entire h^2 was recovered using any of the Gs when all QTL were included (except GIA which over-estimated h^2)

$$h^2 = \frac{\sigma^2{}_G}{\sigma^2{}_G + \sigma^2{}_E}$$

Upon adding a small constant to the diagonal up to 0.5 ↓

$$h^2 = \frac{\sigma^2{}_G}{\sigma^2{}_G + \sigma^2{}_E}$$

Dataset

The TIGER Study

- …"how variation in DNA sequence may influence levels of body fatness and fitness both prior to and following a 30-week exercise program".
- …"how genes may alter response to exercise and diet interventions is not known."
- 3,200 men and women (18-30 yrs) drawn from the student population at UAB
- Genotyped using the Illumina Metabochip; ~200,000 SNPs of interest for metabolic and atherosclerotic / cardiovascular disease traits

Source: www.tigerstudy.org

Hypothesis

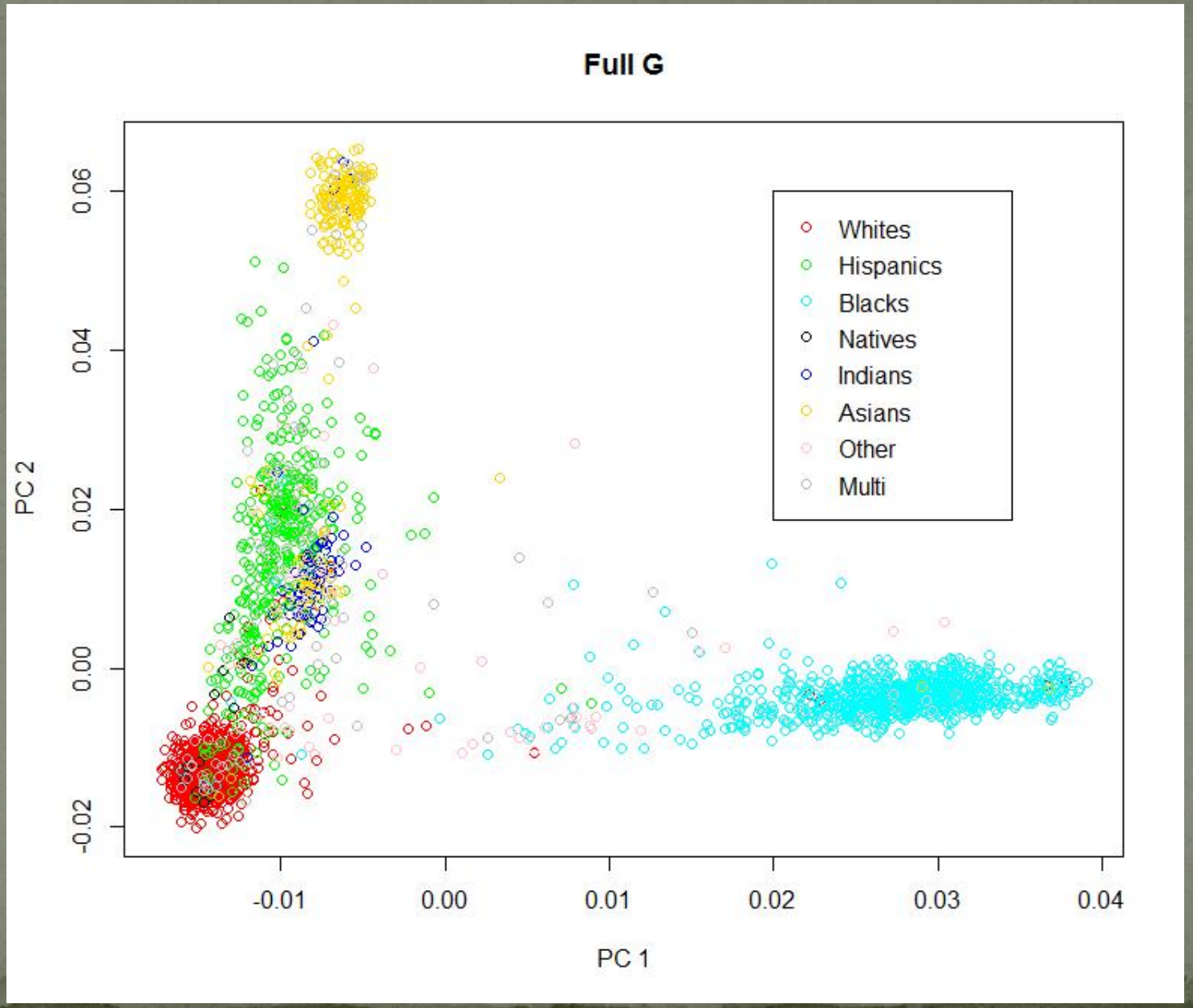
Genetic variance in body composition, obesity and bone composition can be explained using a whole-genome genetic model e.g., (Yang et al., 2010) with the high-density-genotyping from the Illumina MetaboChip platform for each trait.

Quality control:

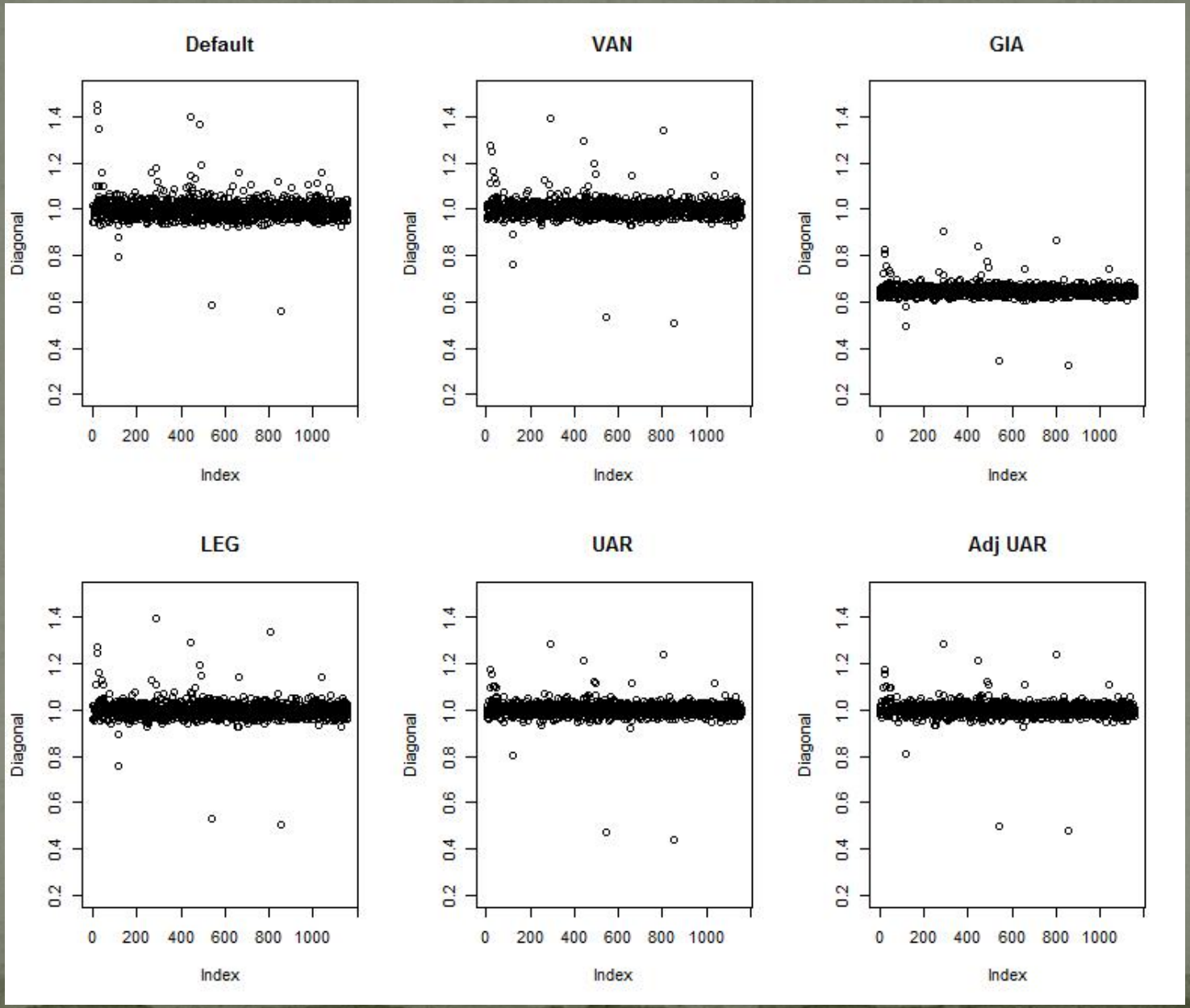
- SNPs with minor allele frequency lesser than 5% were removed
- Individuals with missing values greater than 5% were removed

Results

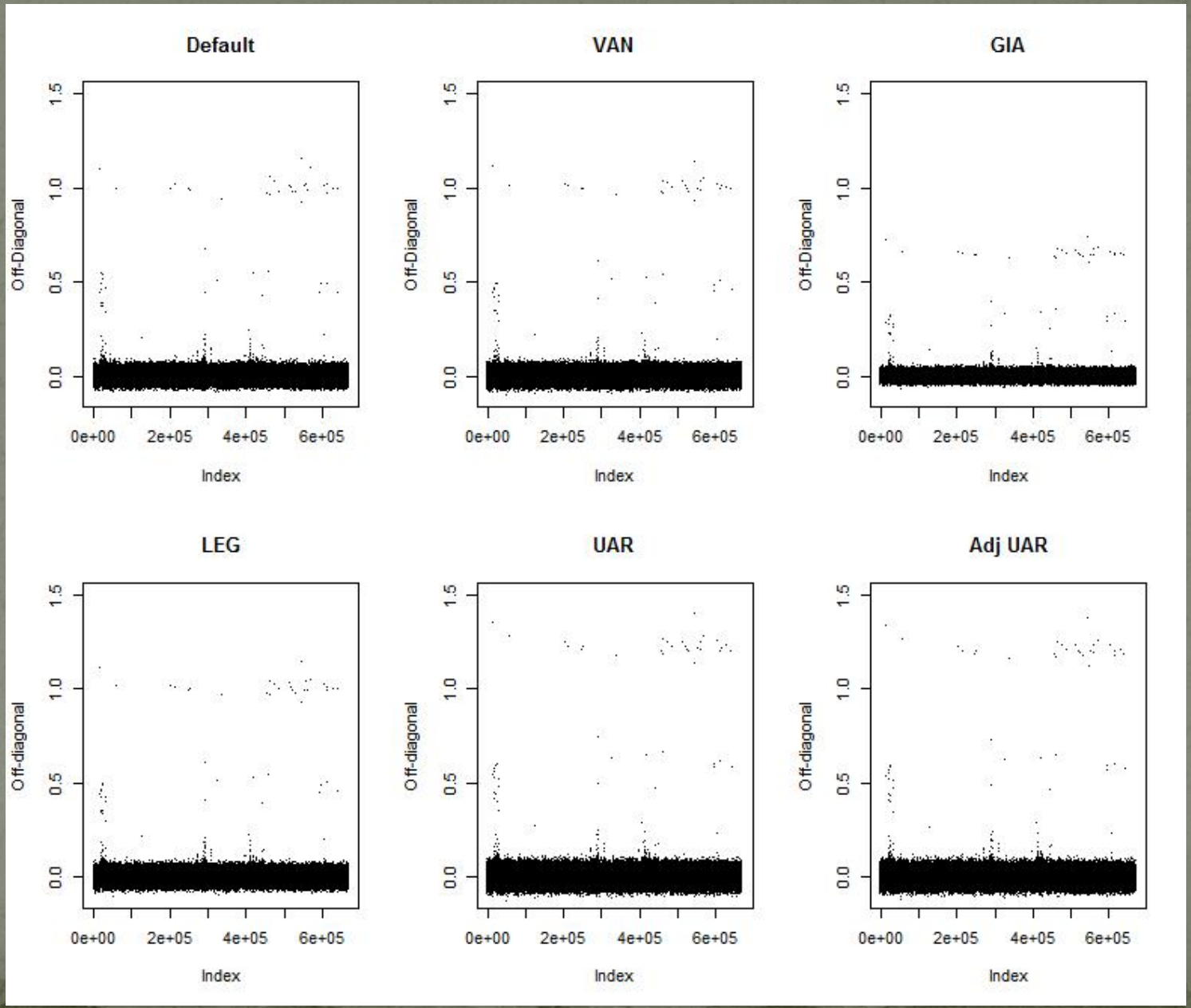
Principal Component Analysis



G matrix analysis (Whites)



G matrix analysis (Whites)

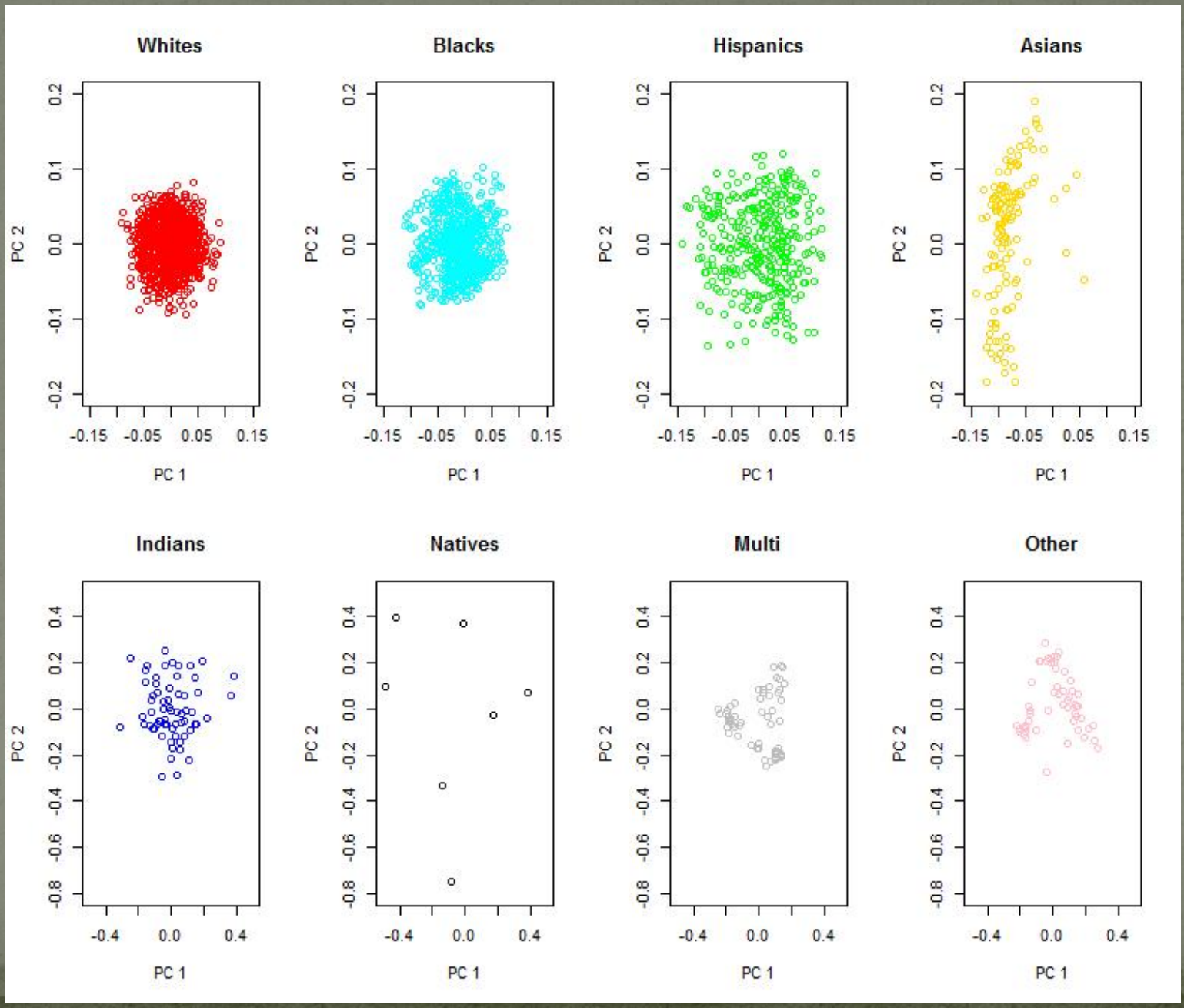


Further QC

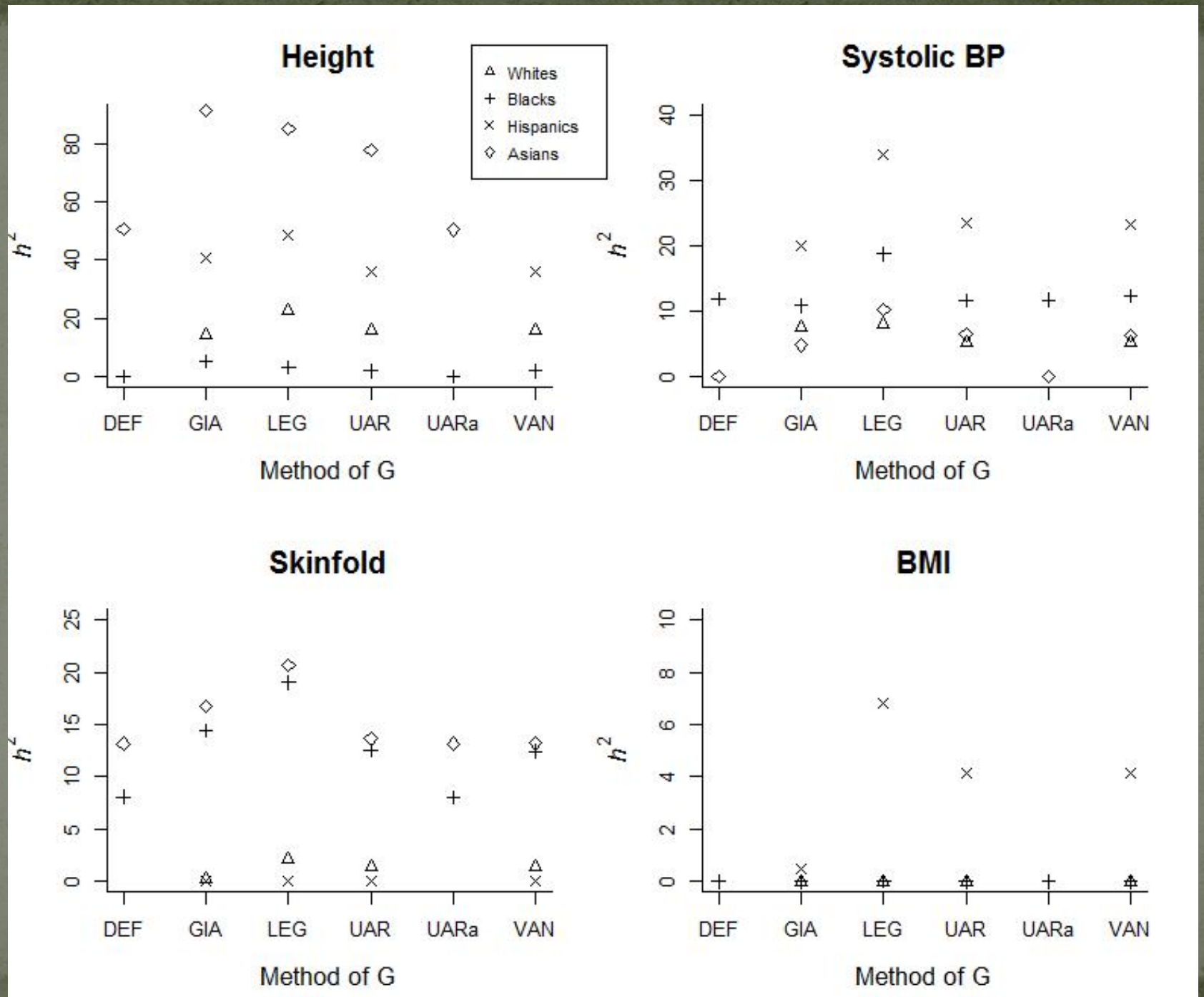
- QC was performed *by race*, as before
- Individuals with relatedness > 10% (per race) were removed

RACE	SAMPLE SIZE	No. SNPs
Whites	1054	39438
Blacks	721	49679
Hispanics	321	75113
Asians	130	72057

Principal Component Analysis – by race



Heritability estimates using REML


Height
Whites
Blacks
Hispanics
Asians
h^2
0
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40
60
80
DEF
GIA
LEG
UAR
UARa
VAN
Method of G
Systolic BP
h^2
0
10
20
30
40
DEF
GIA
LEG
UAR
UARa
VAN
Method of G
Skinfold
h^2
0
5
10
15
20
25
DEF
GIA
LEG
UAR
UARa
VAN
Method of G
BMI
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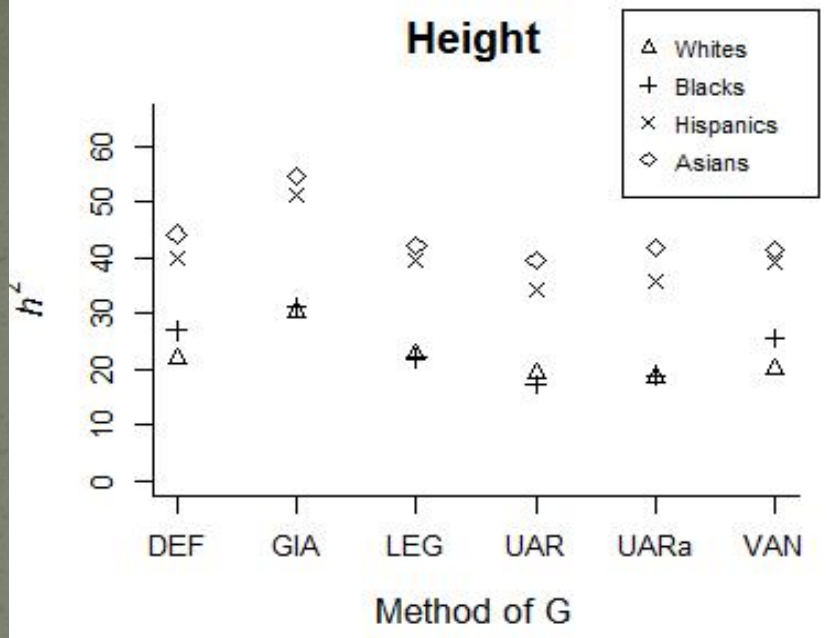
VAN
Method of G

Heritability estimates using MCMC


Height
Whites
Blacks
Hispanics
Asians
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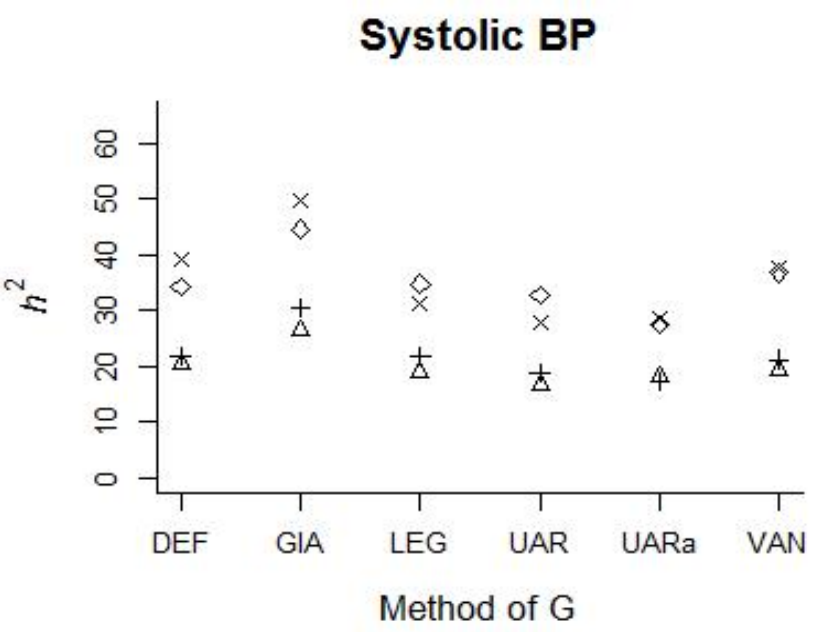
Method of G


Systolic BP
h^2
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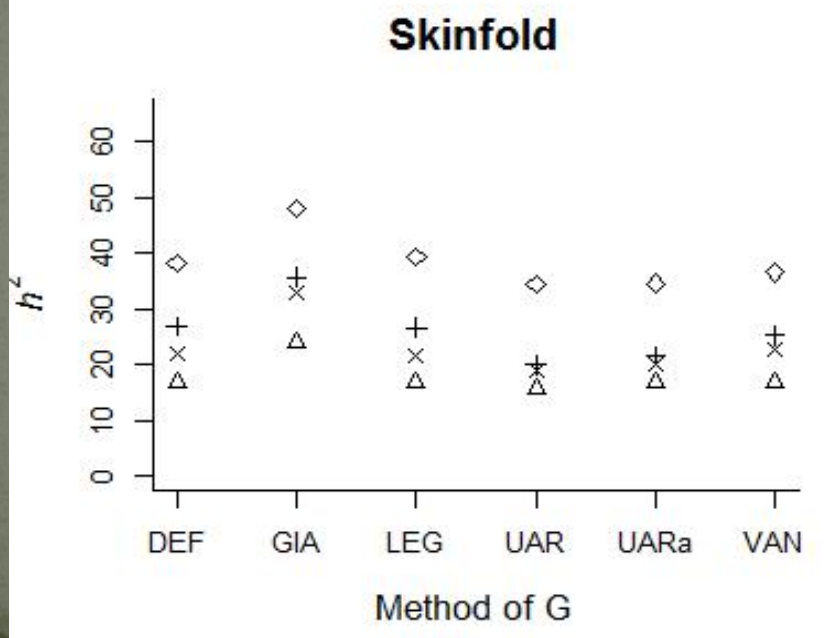
VAN
Method of G


Skinfold
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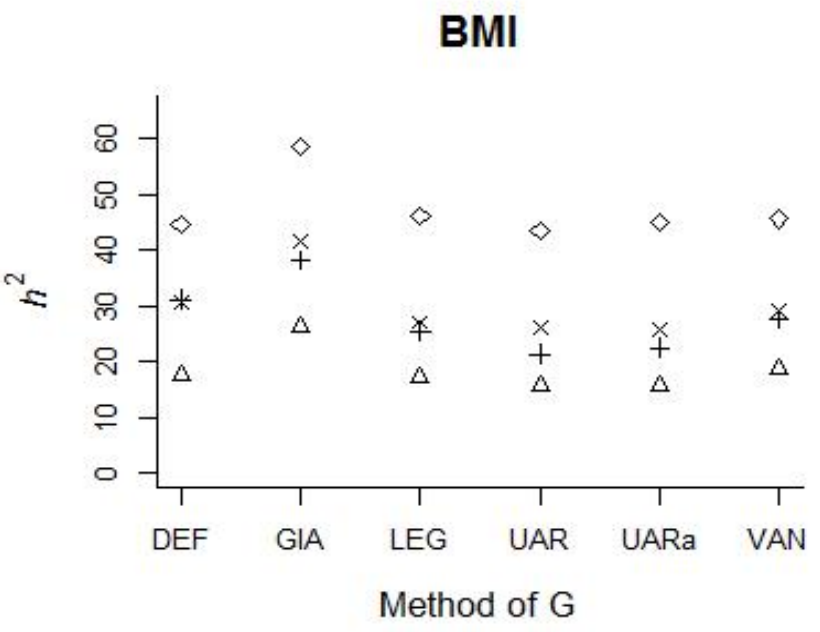
Method of G


BMI
h^2
0
10
20
30
40
50
60
DEF
GIA
LEG
UAR
UARa
VAN
Method of G

Conclusions

- Differences in h^2 ranged from 0% – 5% between the different methods to estimate G (excluding GIA) for MCMC.
- UAR and aUAR were sometimes not positive definite, preventing model fitting using REML.
- Sample size and SNP density could affect h^2 estimates.
- REML could not partition the total variability between genetic and residual for traits like BMI whereas MCMC was able to.

Thanks!