

Statistical Genetics Research: Kinship, Bias, Admixture

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How did I get here? A zigzaggy line

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 - ▶ Joined a Comp Bio lab: protein domain prediction + malaria 
 - ▶ Late started doing real statistics: q-values, IFDRs

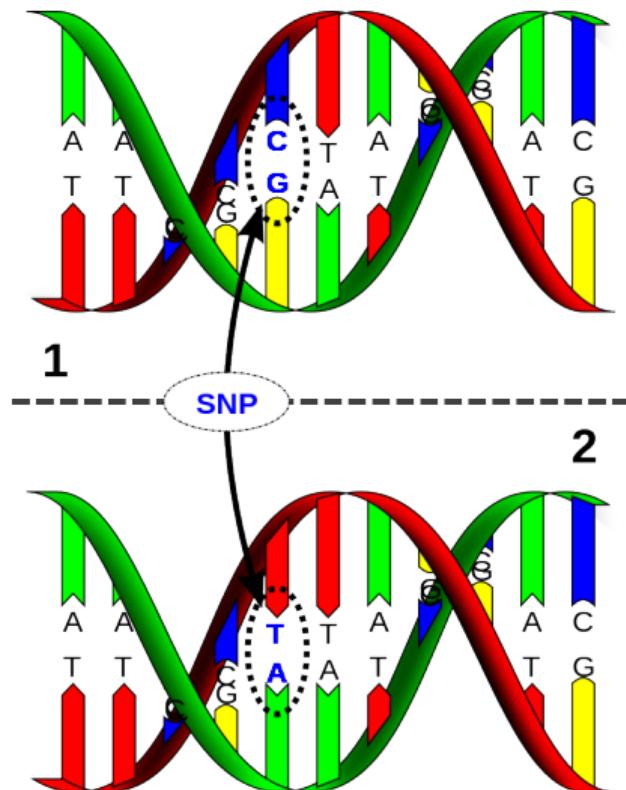
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- ▶ Assistant Professor: Duke, Biostats!

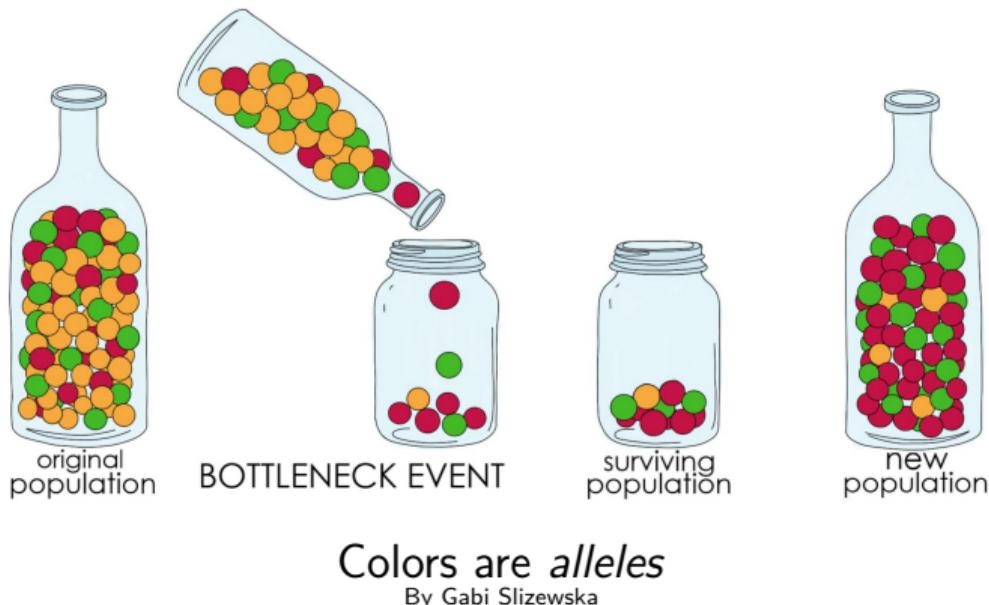
Genetic variation: we're all mutants!



Each newborn has ≈ 70 new mutations!

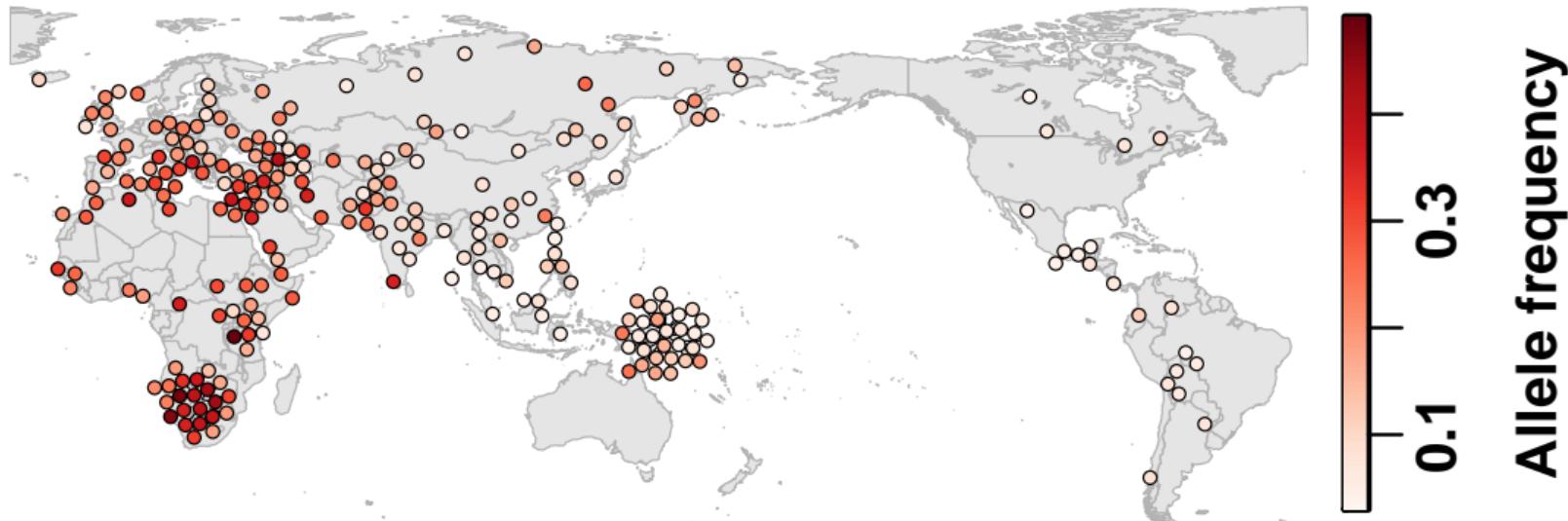
- ▶ Average mutation rate
 $\approx 1.1 \times 10^{-8}$ /base/generation
 - ▶ Higher in male lineage, with age
- ▶ Number of bases in genome
 $\approx 3.2 \times 10^9$, $\times 2$ for both copies

Dynamics of genetic variation



- ▶ Most new mutations are lost
- ▶ Some become common in population
 - ▶ Outcomes are random
 - ▶ Variation greatest in small populations
 - ▶ Even disease alleles can become common

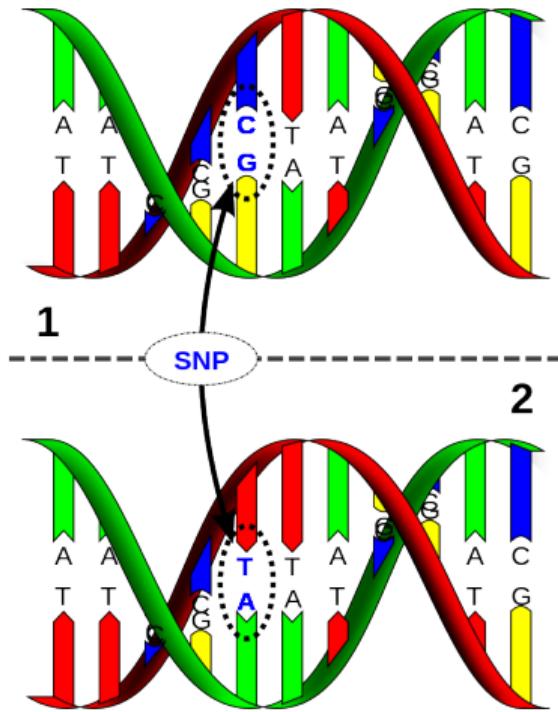
Human genetic structure: a typical allele



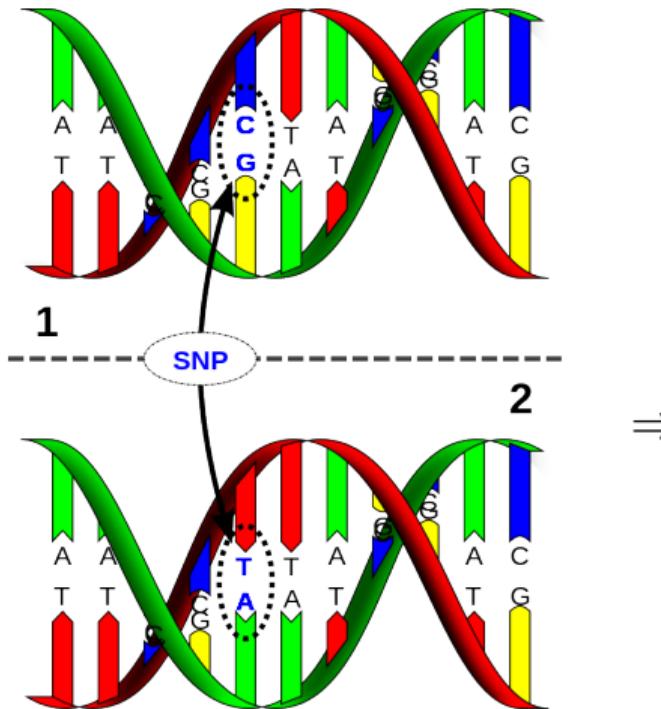
Ochoa and Storey (2019a) doi:10.1101/653279

rs17110306; median differentiation given MAF $\geq 10\%$

Single Nucleotide Polymorphism (SNP) data



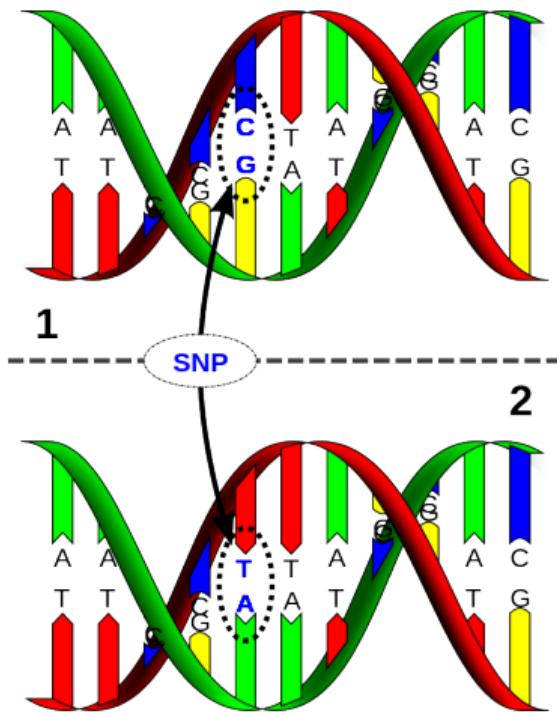
Single Nucleotide Polymorphism (SNP) data



⇒

Genotype	x_{ij}
CC	0
CT	1
TT	2

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Genotype	x_{ij}
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Loci	Individuals
	0 2 2 1 1 0 1
	0 2 1 0 1
	2 ...

X

Dependence structure of genotype matrix

	Individuals						
Loci	0	2	2	1	1	0	1
	0	2	1	0	1		
	2	...					

X

High-dimensional binomial data

- ▶ No general likelihood function
 - ▶ My work: method of moments

Dependence structure of genotype matrix

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Relatedness / Population structure

- ### ► Dependence between individuals (columns)

Dependence structure of genotype matrix

Individuals	
Loci	X
0	2 2 1 1 0 1
0	2 1 0 1
2	...

High-dimensional binomial data

- ▶ No general likelihood function
- ▶ My work: method of moments

Relatedness / Population structure

- ▶ Dependence between individuals (columns)

Linkage disequilibrium

- ▶ Dependence between loci (rows)

New kinship/GRM estimator

Kinship model for neutral genotypes $x_{ij} \in \{0, 1, 2\}$:

$$\text{E}[x_{ij}] = 2p_i, \quad \text{Cov}(x_{ij}, x_{ik}) = 4p_i(1 - p_i)\varphi_{jk}.$$

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Standard estimator is **biased**:

$$\hat{p}_i = \frac{1}{2n} \sum_{j=1}^n x_{ij}, \quad \hat{\varphi}_{jk}^{\text{std}} = \frac{1}{m} \sum_{i=1}^m \frac{(x_{ij} - 2\hat{p}_i)(x_{ik} - 2\hat{p}_i)}{4\hat{p}_i(1-\hat{p}_i)} \approx \frac{\varphi_{jk} - \bar{\varphi}_j - \bar{\varphi}_k + \bar{\varphi}}{1 - \bar{\varphi}}.$$

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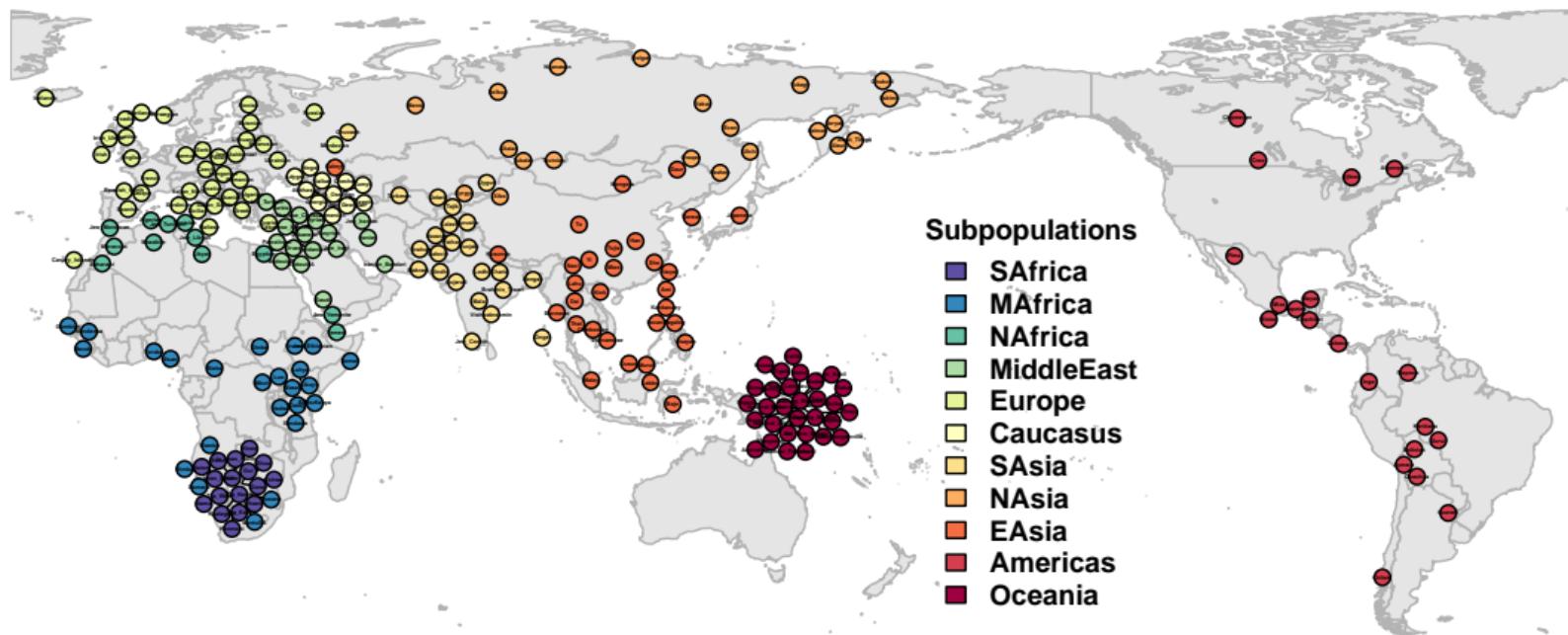
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`popkin`: first unbiased kinship estimator! R package (Ochoa and Storey, 2021)

$$A_{jk} = \frac{1}{m} \sum_{i=1}^m (x_{ij} - 1)(x_{ik} - 1) - 1, \quad \hat{\varphi}_{jk}^{\text{new}} = 1 - \frac{A_{jk}}{\hat{A}_{\min}} \xrightarrow[m \rightarrow \infty]{\text{a.s.}} \varphi_{jk}.$$



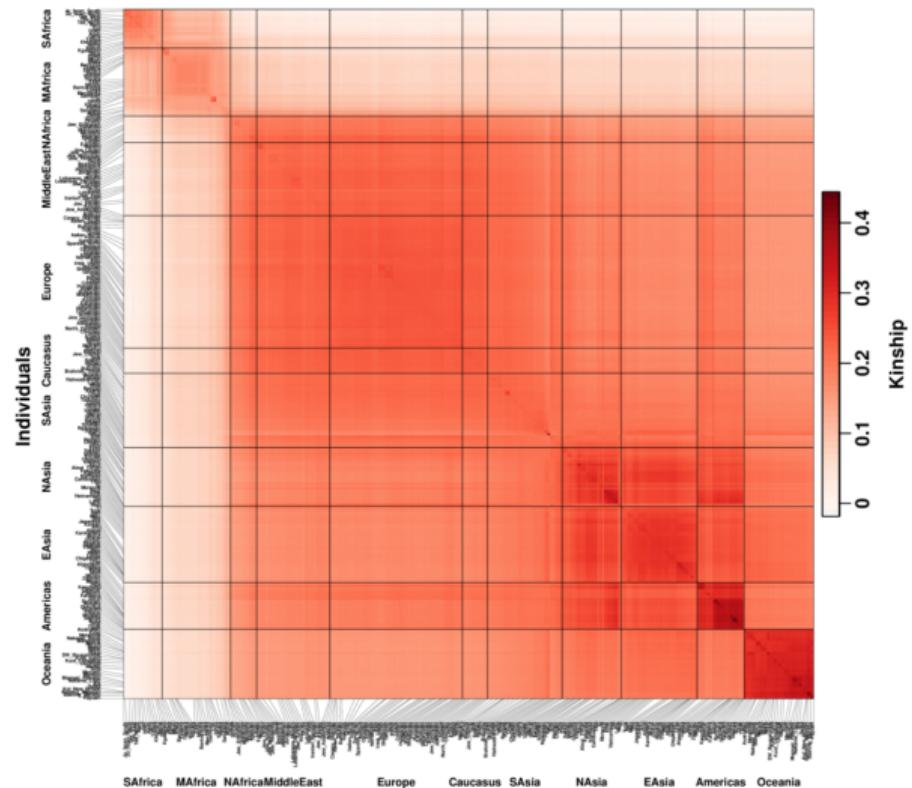
Dataset: Human Origins



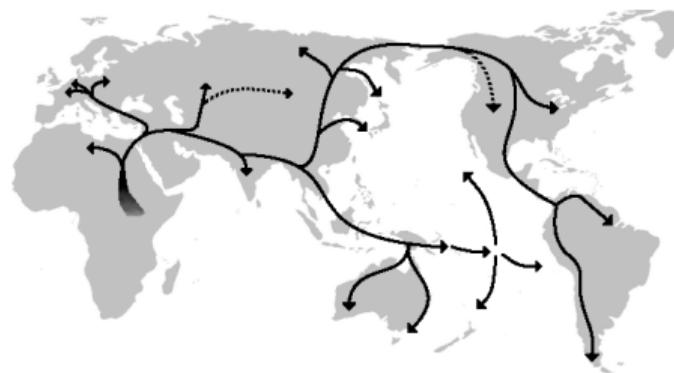
Lazaridis *et al.* (2014), (2016); Skoglund *et al.* (2016)

2,922 indivs. from 243 locs. — 588,091 loci — Array

Kinship matrix of world-wide human population

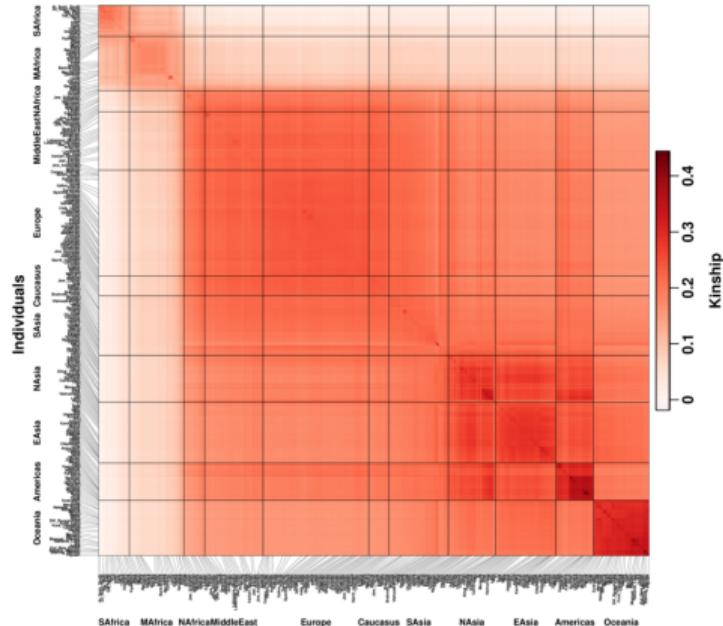


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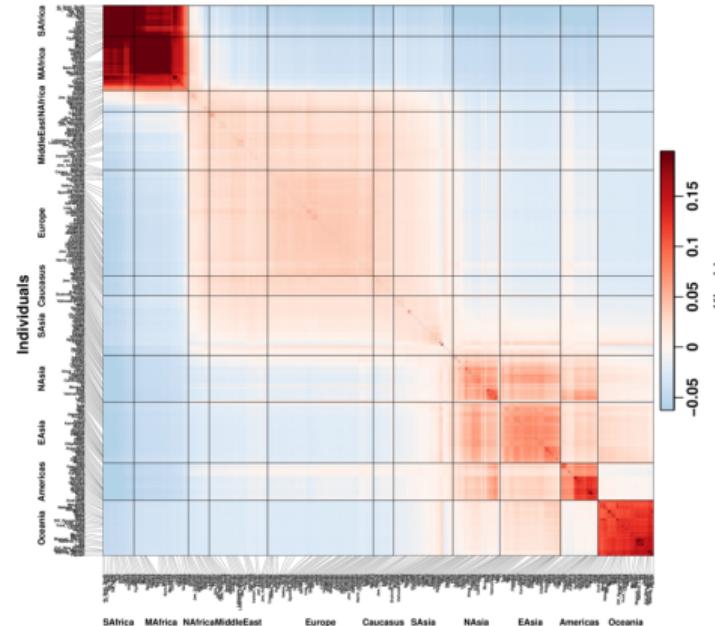


Standard kinship estimator is severely biased

New



Standard



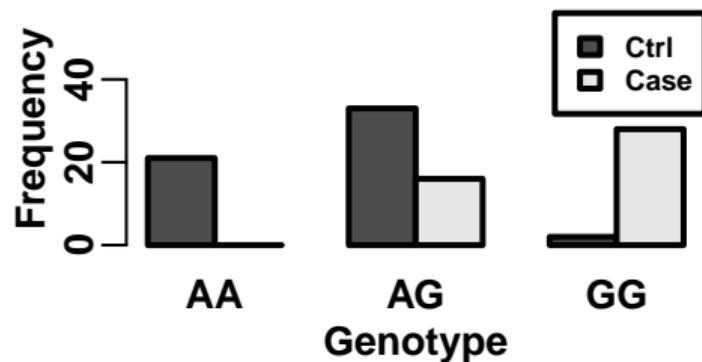
Kinship bias: Consequences? Applications?

- ▶ Genetic association studies
- ▶ Heritability estimation
- ▶ Admixture inference

Genetic association study: genotype-phenotype correlation

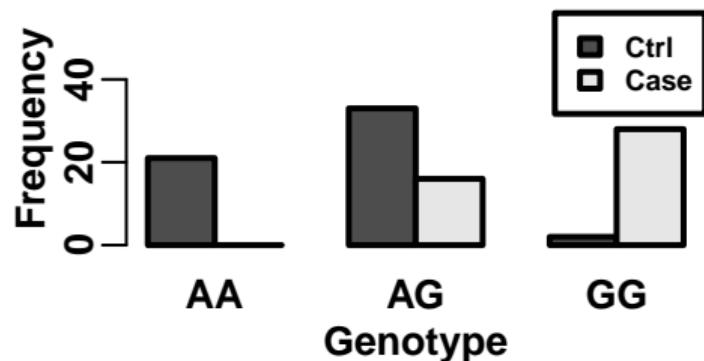
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As Table

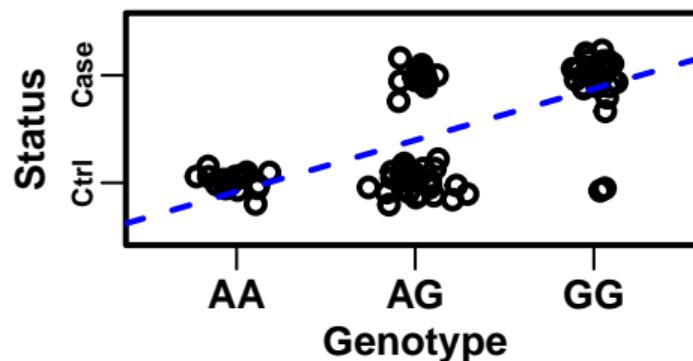


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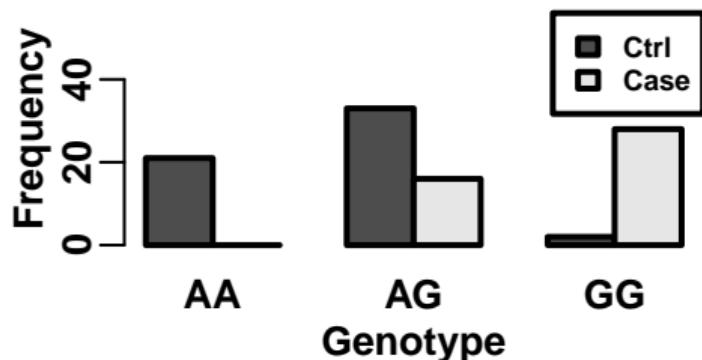


As Regression

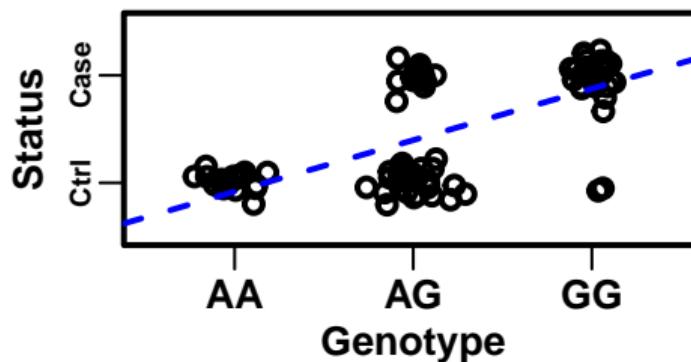


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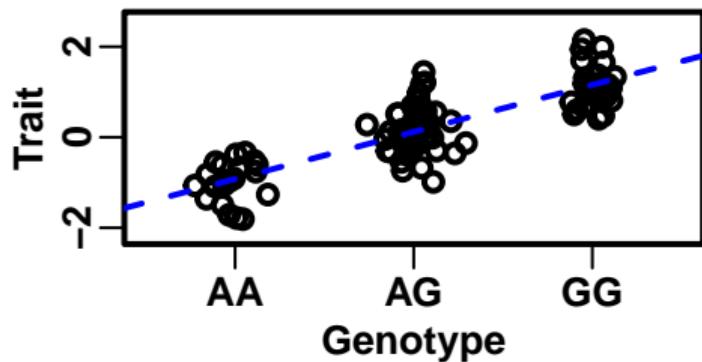
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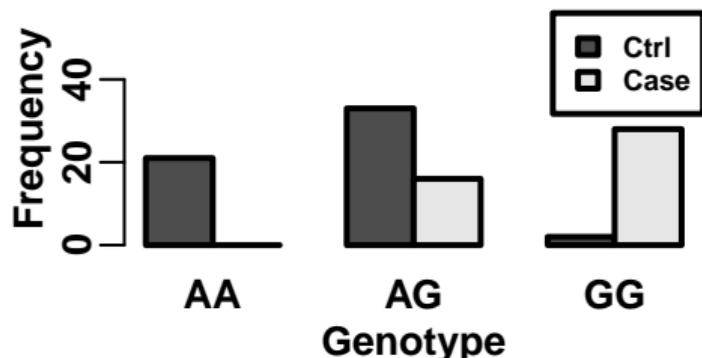


Continuous trait

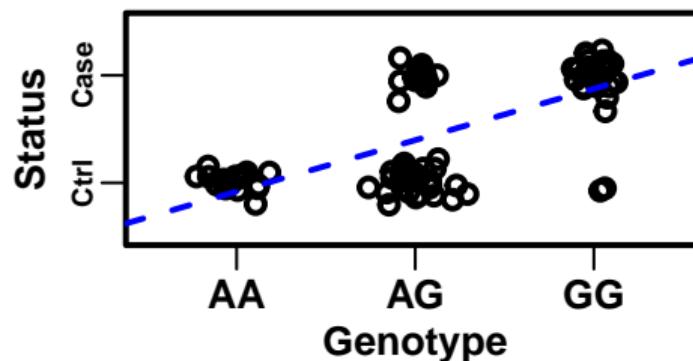


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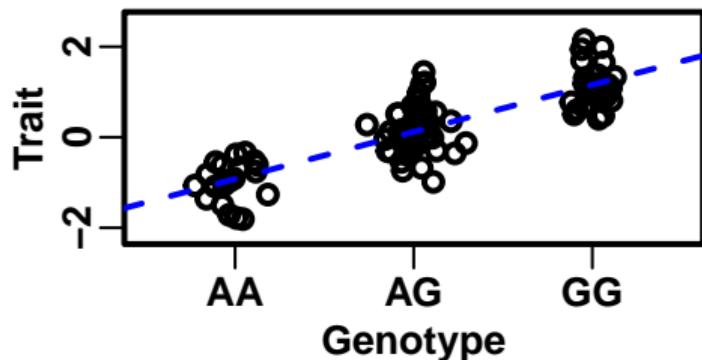
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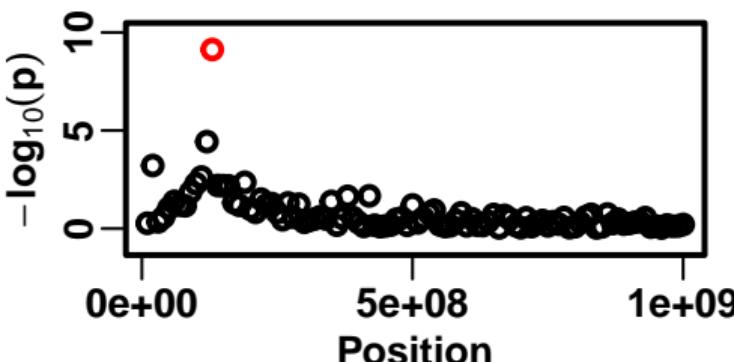
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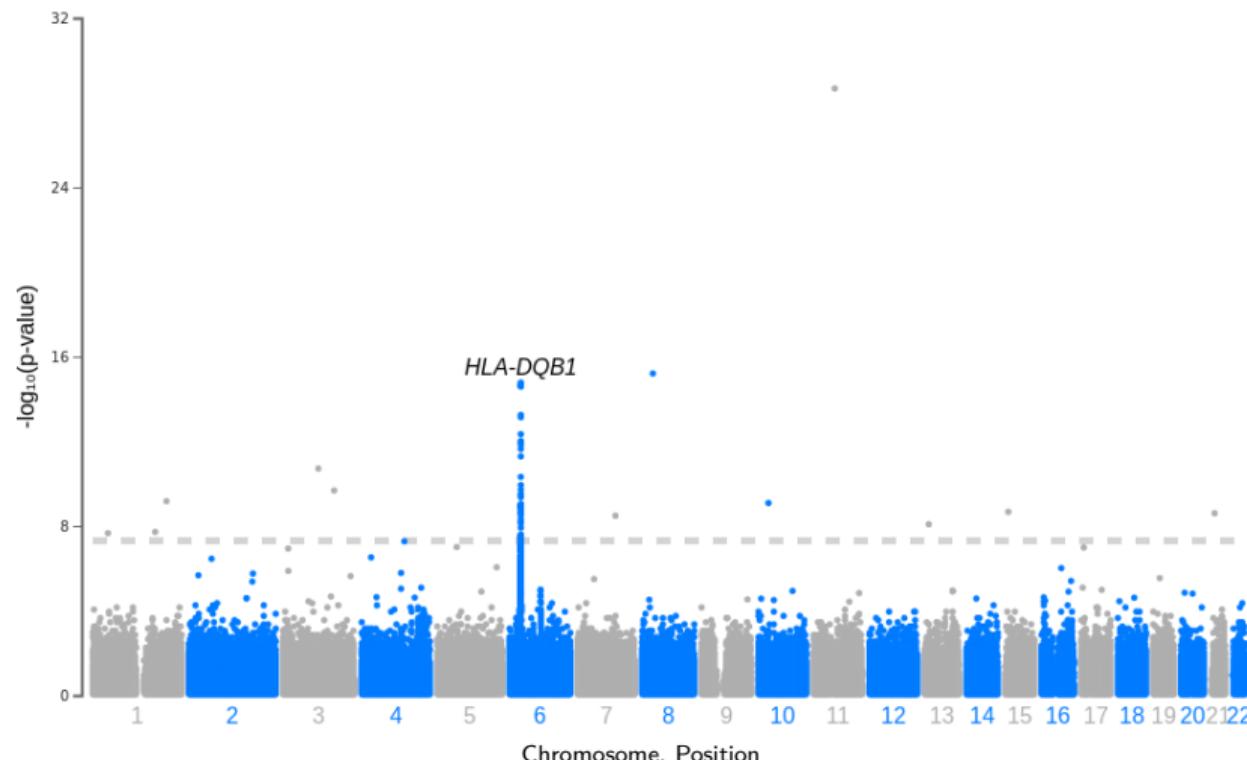


Genome Scan



Nephrotic Syndrome association study

Severe pediatric kidney disease. 1000 cases/1000 controls; multiethnic

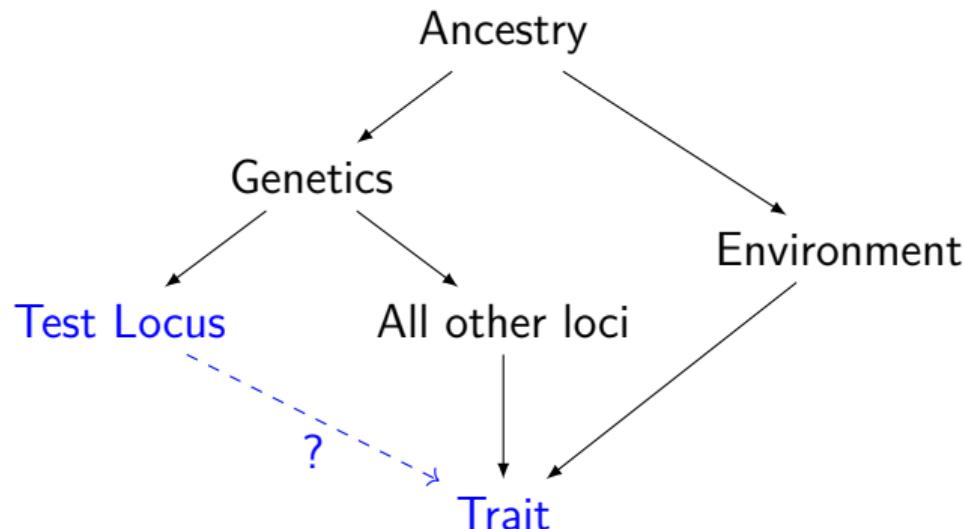


Why is this problem so hard?

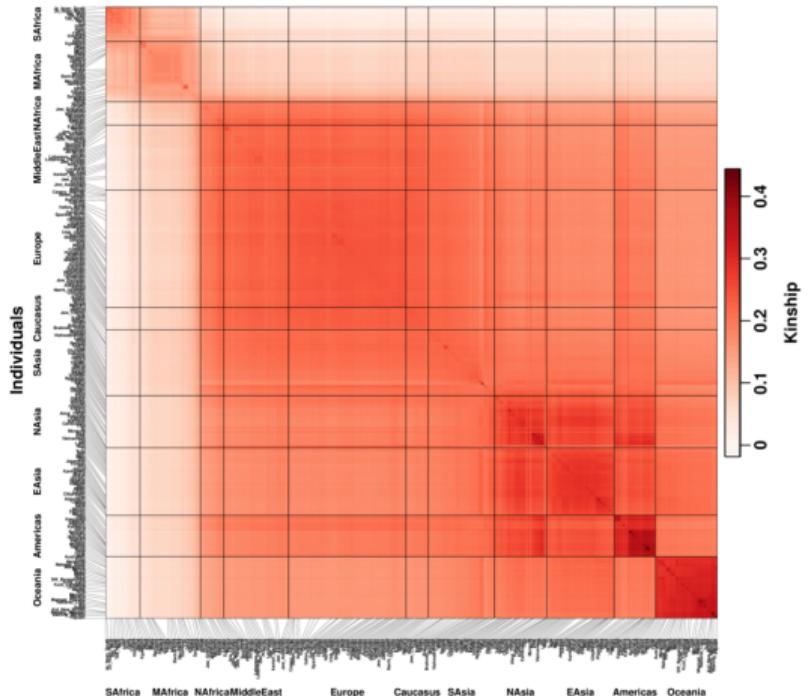
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- ▶ Polygenicity (many causal variants)
- ▶ Confounders
- ▶ Incorrect assumptions: independence / additivity

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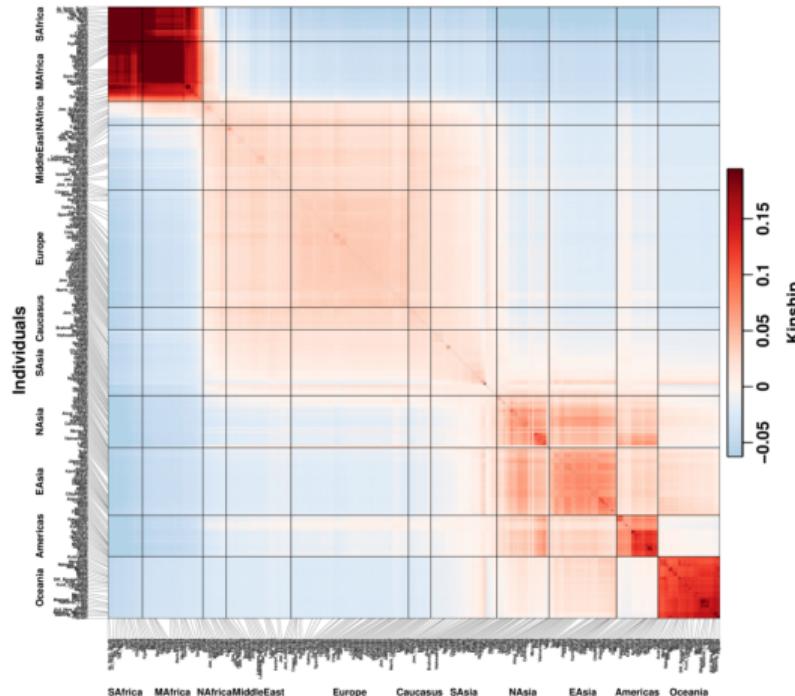
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Kinship bias does not affect genetic associations

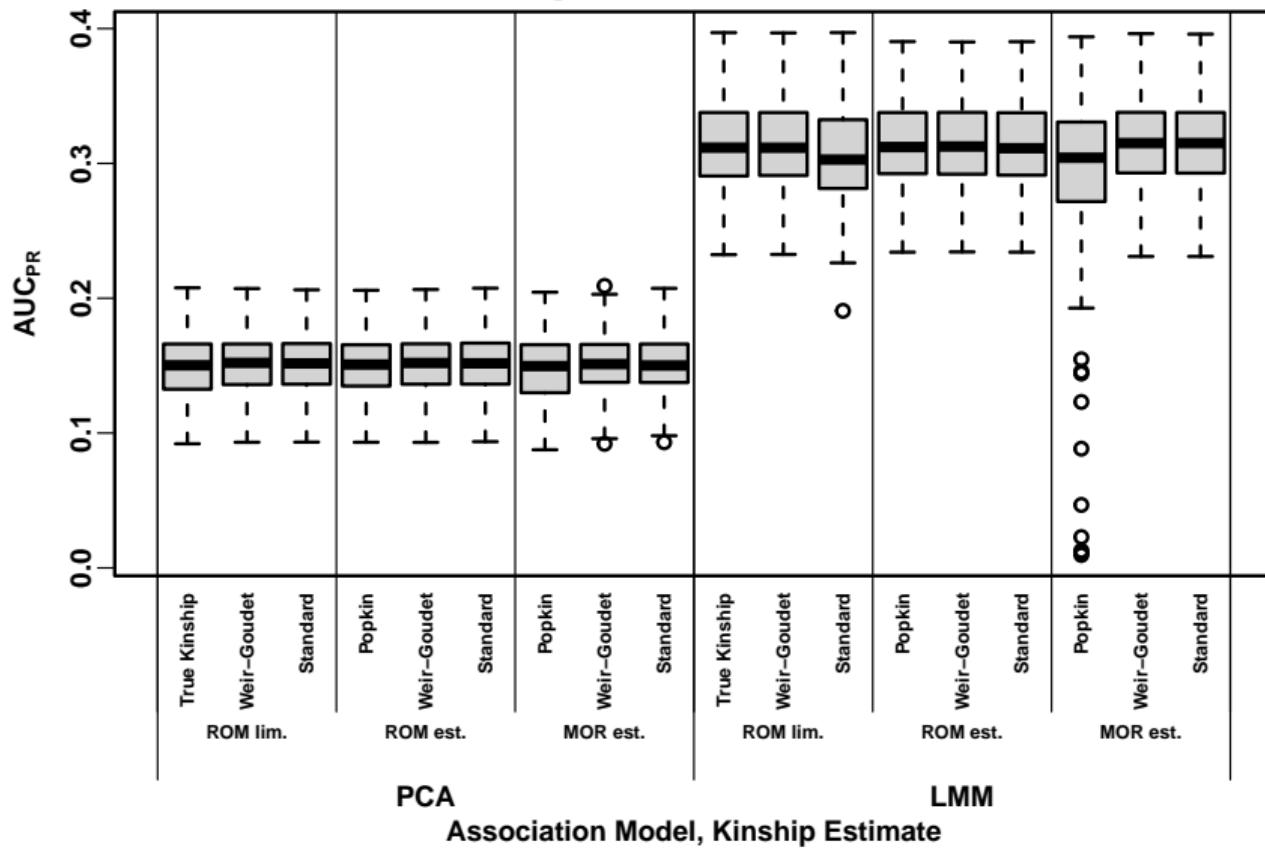


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Kinship bias does not affect genetic associations

Linear algebra proof!

Transforming true to biased kinship
matrices:

Φ : True kinship matrix,

Φ' : Limit of biased estimator,

$$\Phi' = \frac{1}{1 - \bar{\varphi}} \mathbf{C} \Phi \mathbf{C},$$

$$\mathbf{C} = \mathbf{I} - \frac{1}{n} \mathbf{1} \mathbf{1}^\top : \text{Centering matrix.}$$

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Association test is a regression with correlated residuals:

$$\mathbf{y} = \mathbf{1}\alpha + \mathbf{x}_i\beta_i + \mathbf{s} + \epsilon,$$

$$\mathbf{s} \sim \text{Normal}(\mathbf{0}, 2\sigma_G^2 \Phi),$$

$$\epsilon \sim \text{Normal}(\mathbf{0}, \sigma_E^2 \mathbf{I}).$$

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Kinship bias compensated by intercept!

$$\mathbf{s}' = \mathbf{C}\mathbf{s} \sim \text{Normal}(\mathbf{0}, 2\sigma_G^{2'} \Phi'),$$

$$\sigma_G^{2'} = (1 - \bar{\varphi})\sigma_G^2,$$

$$\mathbf{s}' = \mathbf{s} - \mathbf{1}\bar{s},$$

$$\alpha' = \alpha + \bar{s}$$

Kinship bias affects heritability estimation

Model:

$$\mathbf{y} = \mathbf{1}\alpha + \mathbf{s} + \epsilon,$$

$$\mathbf{s} + \epsilon \sim \text{Normal}(\mathbf{0}, 2\sigma_G^2 \Phi + \sigma_E^2 \mathbf{I}).$$

Heritability definition:

$$h^2 = \frac{\sigma_G^2}{\sigma_G^2 + \sigma_E^2}.$$

Variance is estimated with bias:

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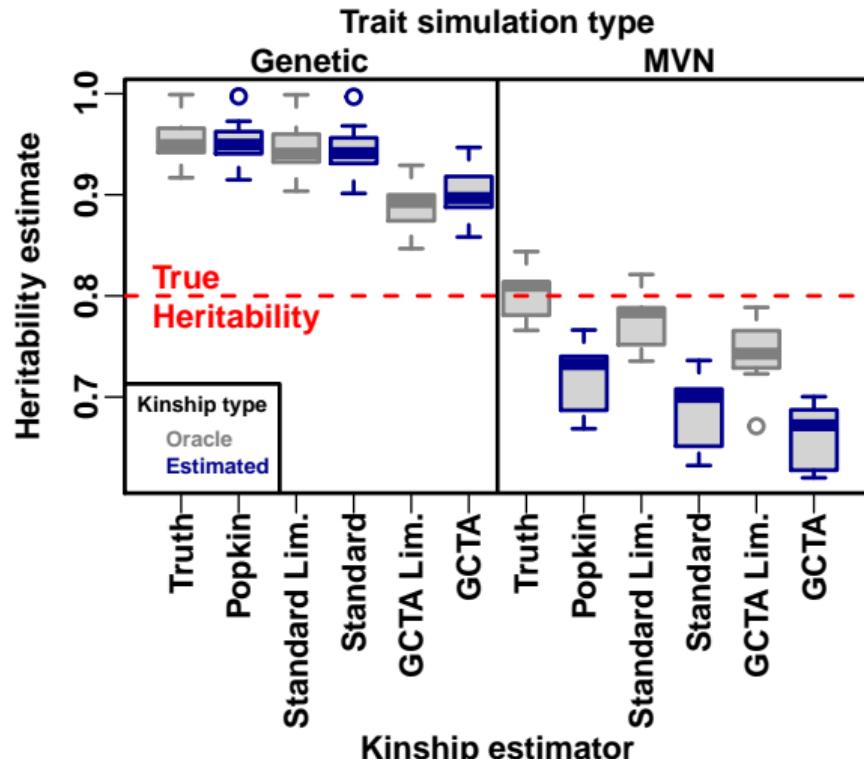
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There are more sources of bias!!!



LIGERA (Llight GEnetic Robust Association): a reversed LMM

Linear mixed-effects model (LMM):

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{s} + \epsilon, \quad \mathbf{s} + \epsilon \sim \text{Normal}(\mathbf{0}, 2\sigma_G^2 \Phi + \sigma_E^2 I).$$

LIGERA:

$$\mathbf{x}_i = \mathbf{Y}\beta + \mathbf{s}, \quad \mathbf{s} \sim \text{Normal}(\mathbf{0}, \sigma^2 \Phi),$$

where here \mathbf{X} , \mathbf{Y} include covariates and intercept.

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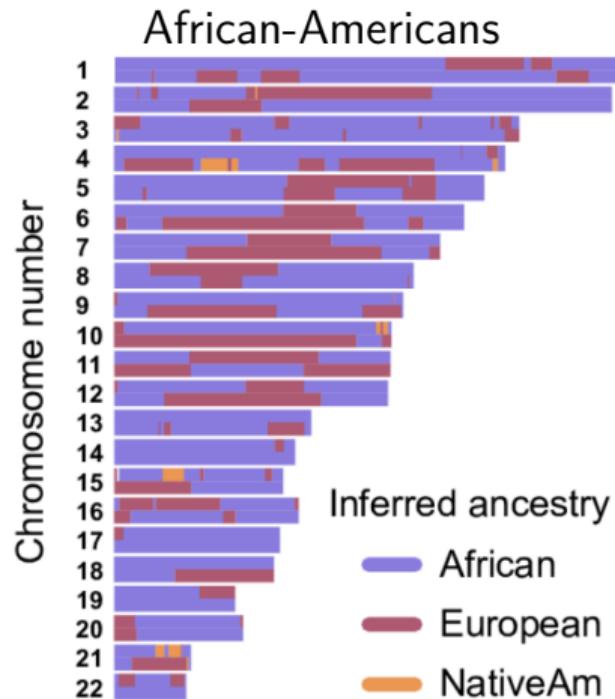
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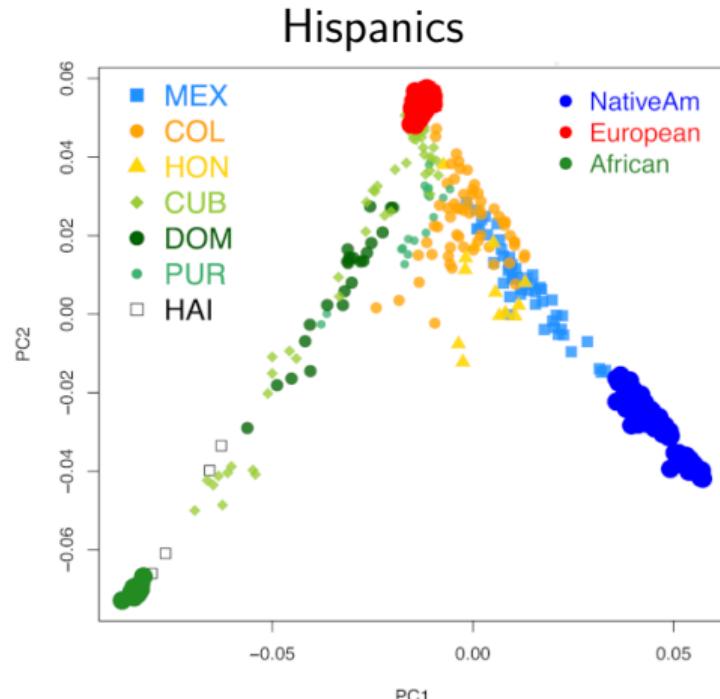
where here \mathbf{X} , \mathbf{Y} include covariates and intercept.

- ▶ LIGERA is faster: no need to fit σ_G^2, σ_E^2 , a slow LMM step!
- ▶ But Standard Estimator is singular, LIGERA requires non-singular Φ

Recently-admixed populations

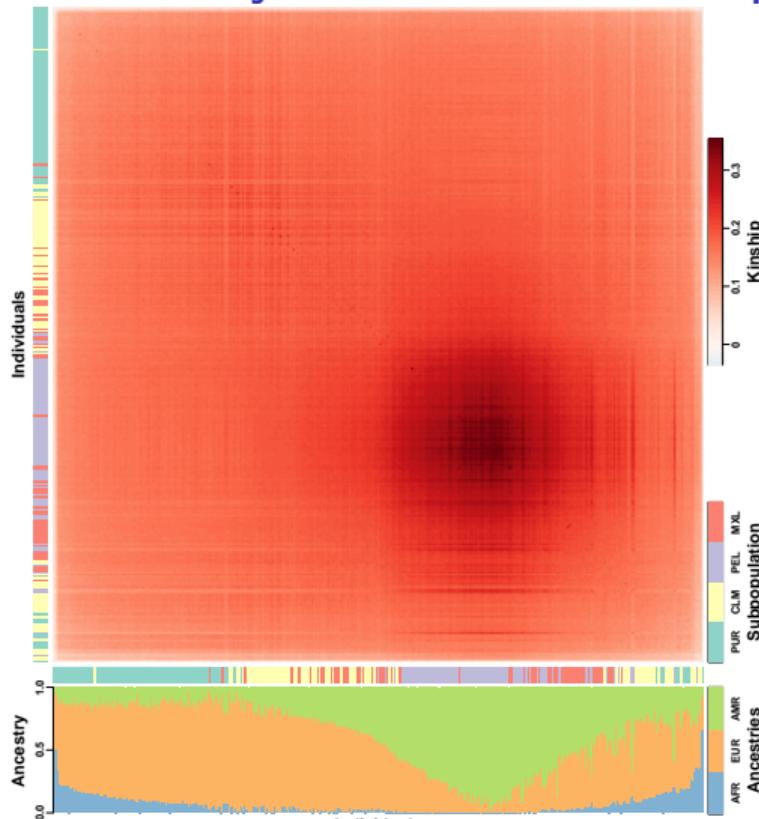


Baharian *et al.* (2016)



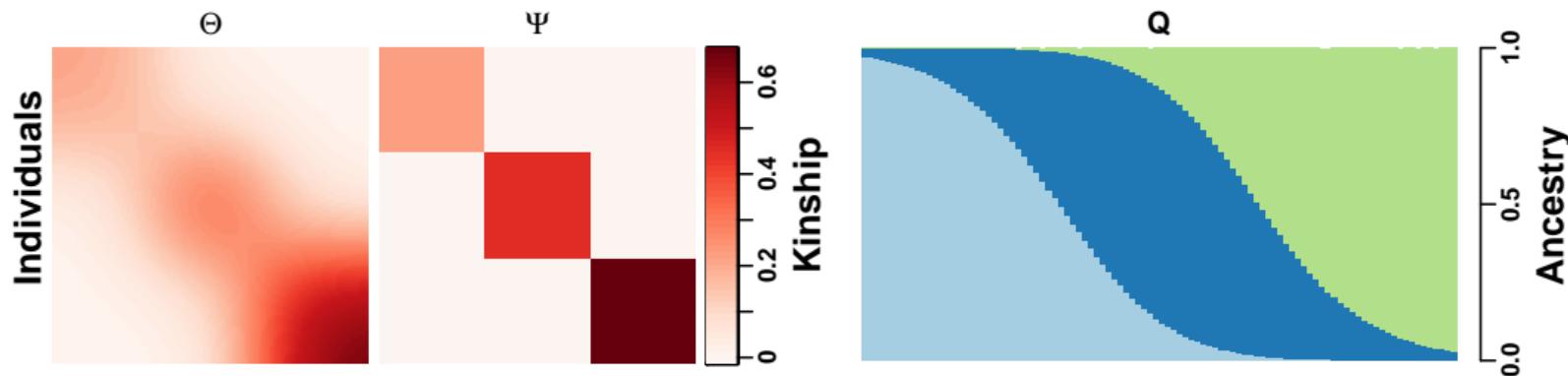
Moreno-Estrada *et al.* (2013)

Population kinship driven by admixture in Hispanics



Ochoa and Storey (2019b) doi:10.1101/653279

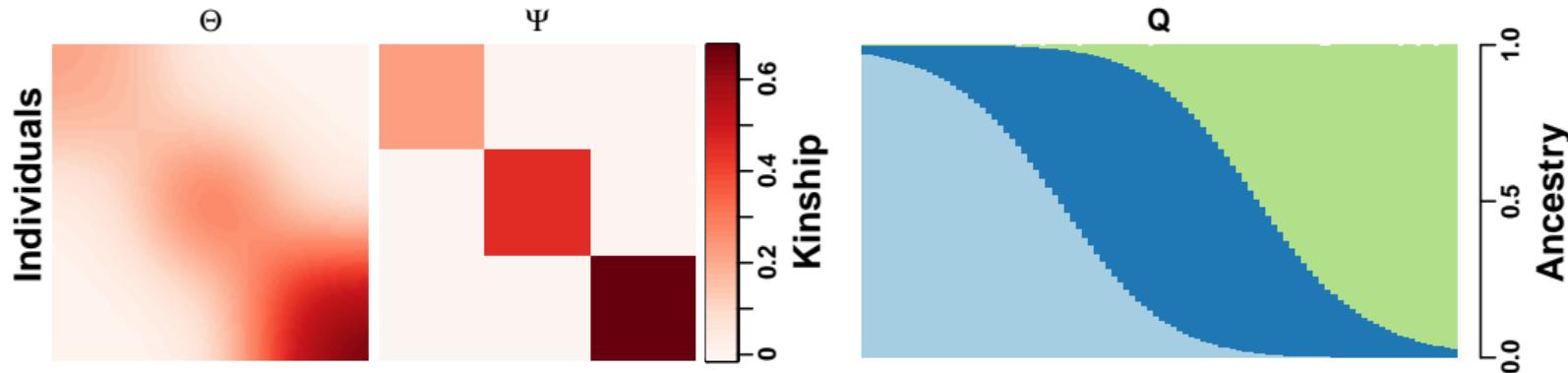
Kinship under the admixture model



$$\Theta = Q\Psi Q^\top$$

(Only for unbiased kinship)

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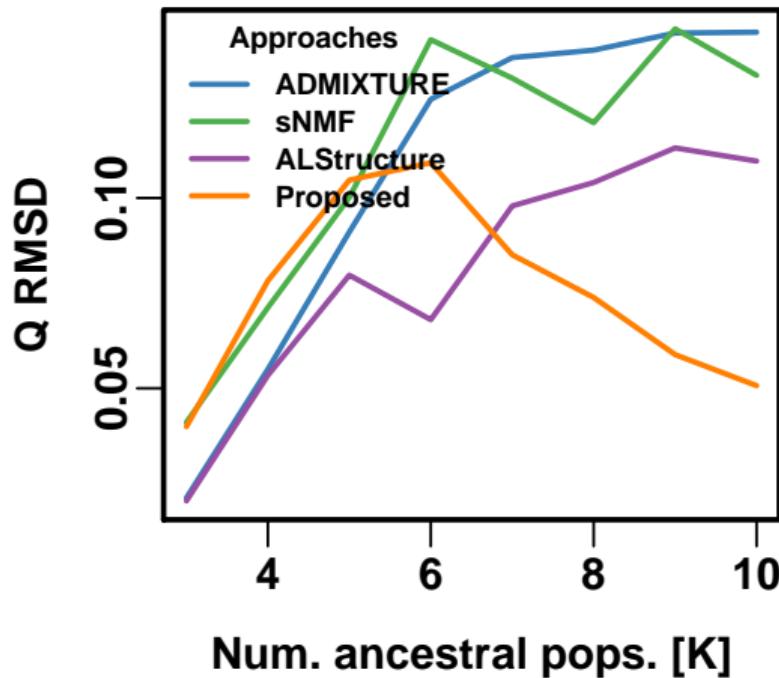
Can we reverse this formula?

Constrained optimization, regularized objective:

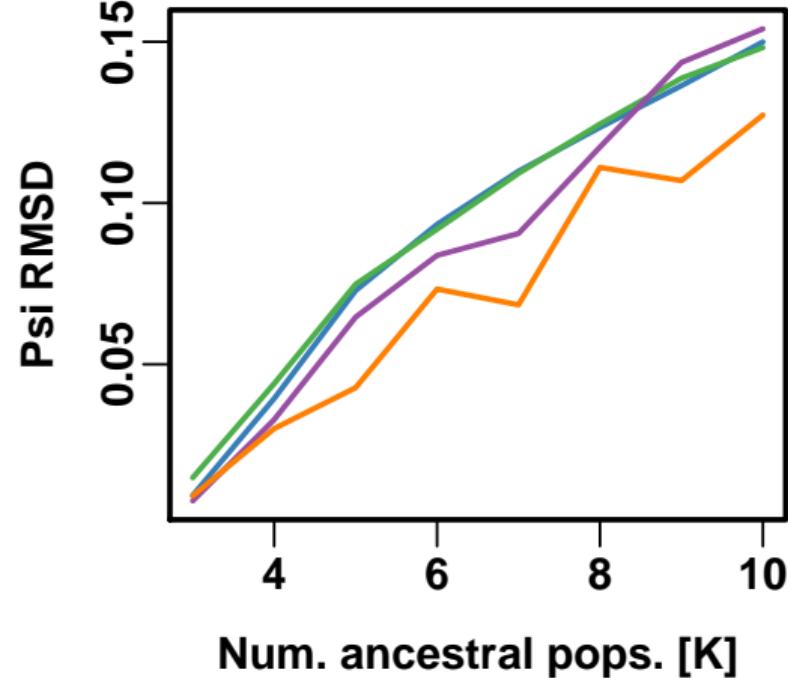
$$F = \|\hat{\Theta} - Q\Psi Q^\top\|^2 + \gamma \text{tr}(\Psi).$$

AdmixCor: accuracy

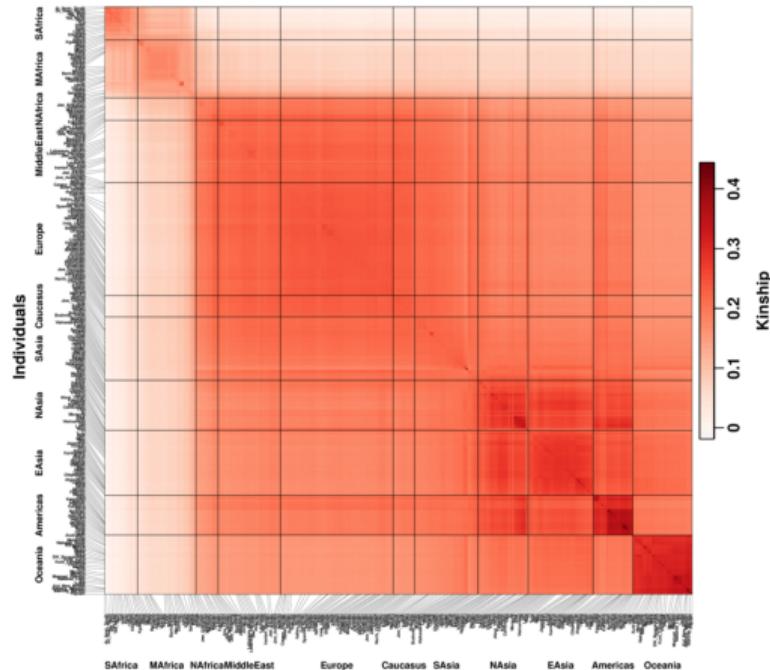
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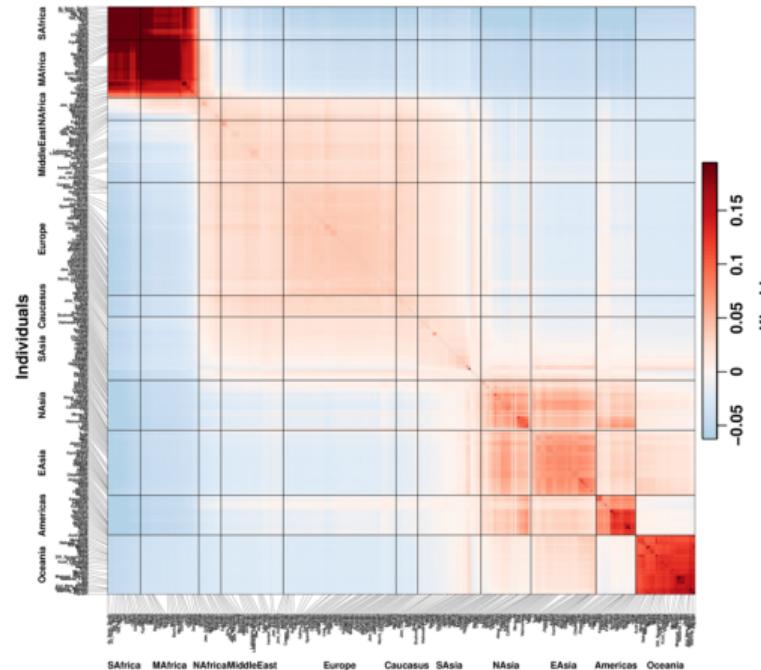
B



Unbiased kinship estimates: new models, opportunities



New "popkin"
kinship estimator



Biased "standard"
kinship estimator

Acknowledgments

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Amika Sood

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Kouros Owzar

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