Modeling Relatedness in Genetic Association Studies

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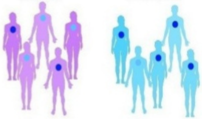

Genetic Association Studies confounded by relatedness

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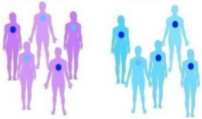

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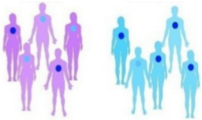

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Selection scans

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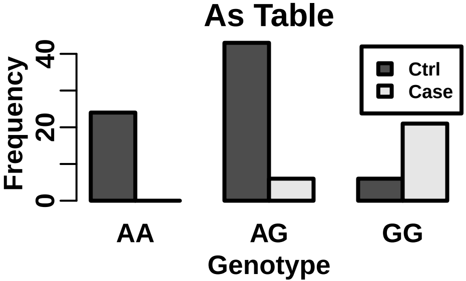

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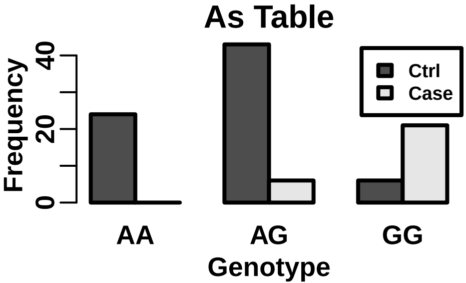

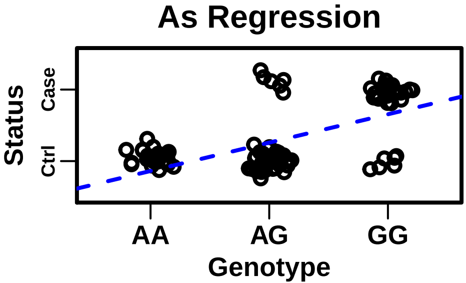

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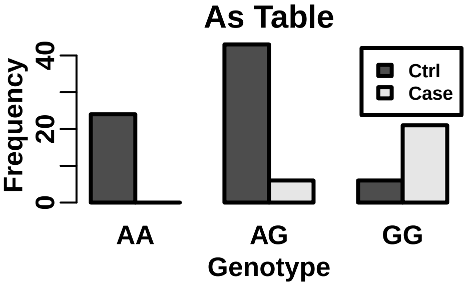

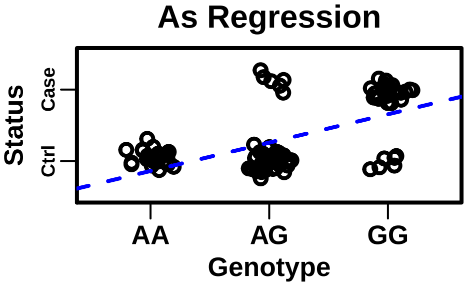

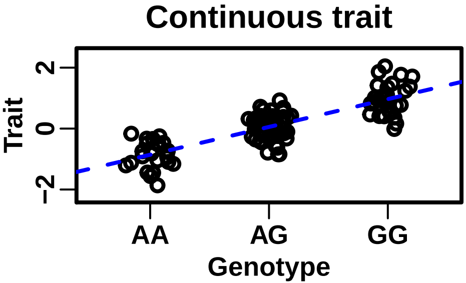

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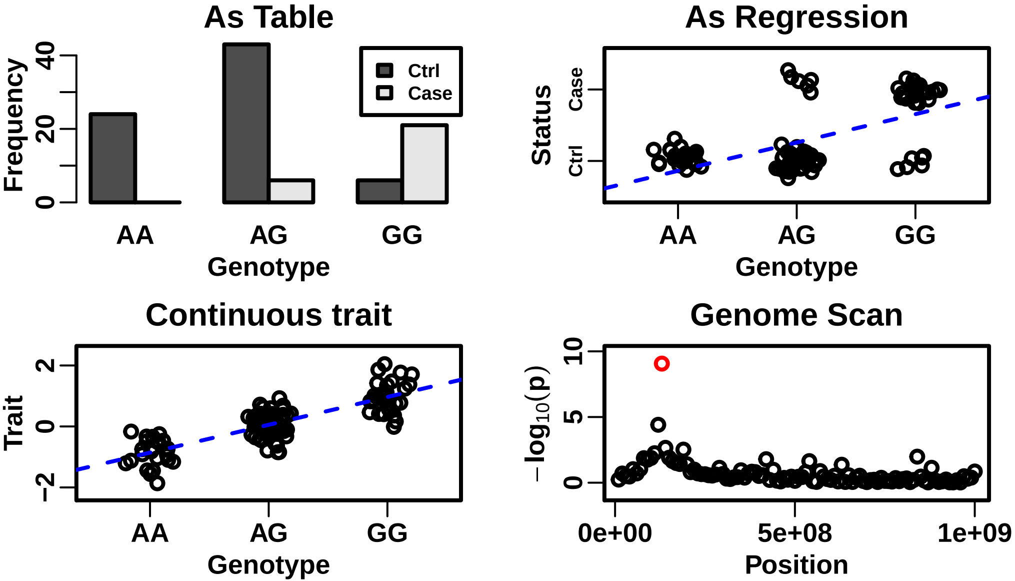

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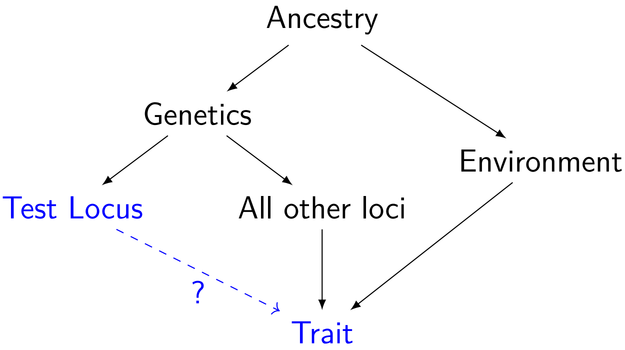
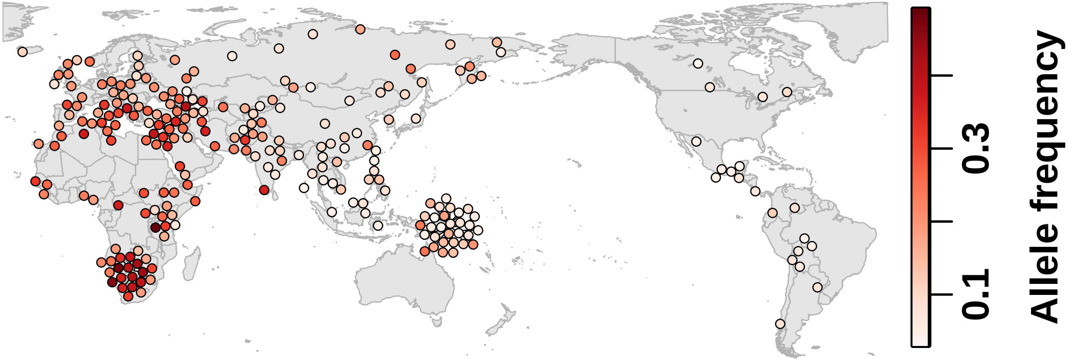


Median-differentiation human locus



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

rs17110306; among loci with minor allele frequency $\geq$ 10%

Basic association tests assume equal allele frequency within cases and controls!

Overview of results

Part I:

- Estimating relatedness under both ancestry and family structure

Part II:

- New approach to genetic association: fast and accurate

New kinship estimator for general relatedness

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

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

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Standard estimator is **biased**:

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

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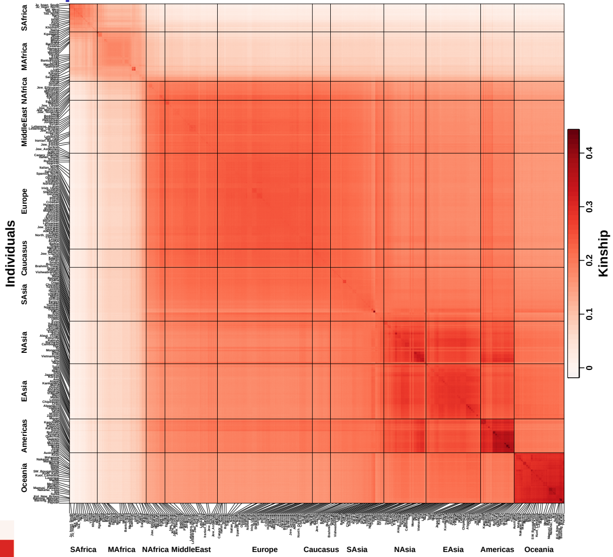
`popkin`: first unbiased kinship estimator! — R package on CRAN

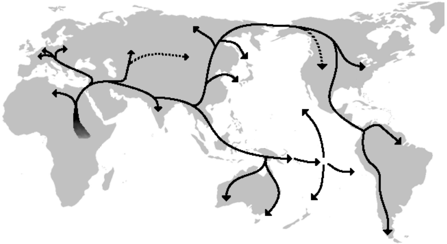
$$A_{jk} = \frac{1}{m}\sum_{i=1}^{m}(x_{ij} - 1)(x_{ik} - 1) - 1, \qquad \hat{A}_{\text{min}} = \min_{u \neq v}\frac{1}{|S_u||S_v|}\sum_{j \in S_u}\sum_{k \in S_v} A_{jk},$$

$$\hat{\varphi}^{\text{new}}_{jk} = 1 - \frac{A_{jk}}{\hat{A}_{\text{min}}} \xrightarrow[m \to \infty]{\text{a.s.}} \varphi_{jk}.$$

https://github.com/StoreyLab/popkin

Kinship matrix of world-wide human population





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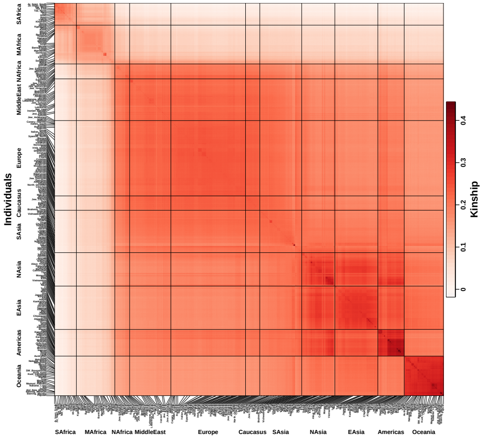
Standard kinship estimator is severely biased

New



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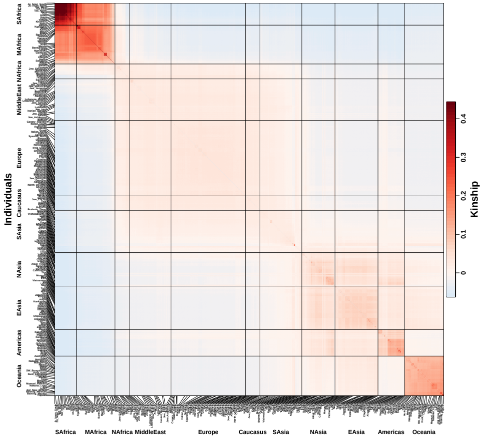

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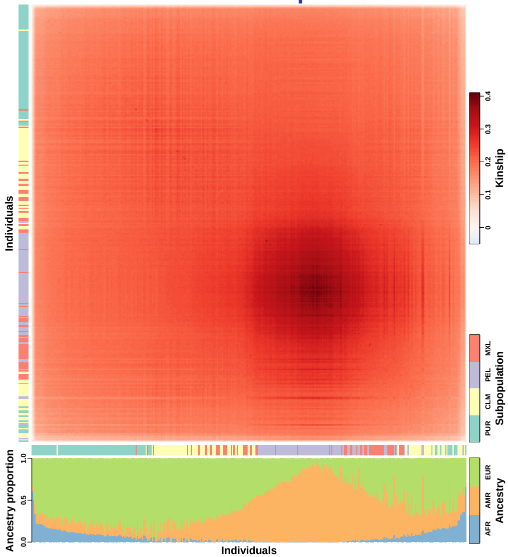
Kinship driven by admixture in Hispanics



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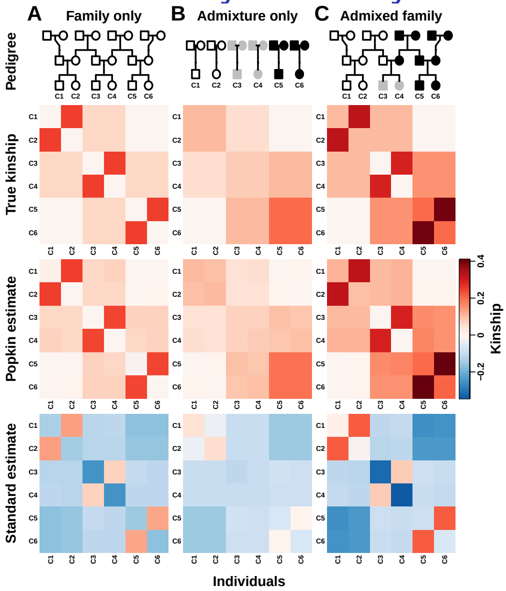
Unified kinship model: ancestry + family structure!



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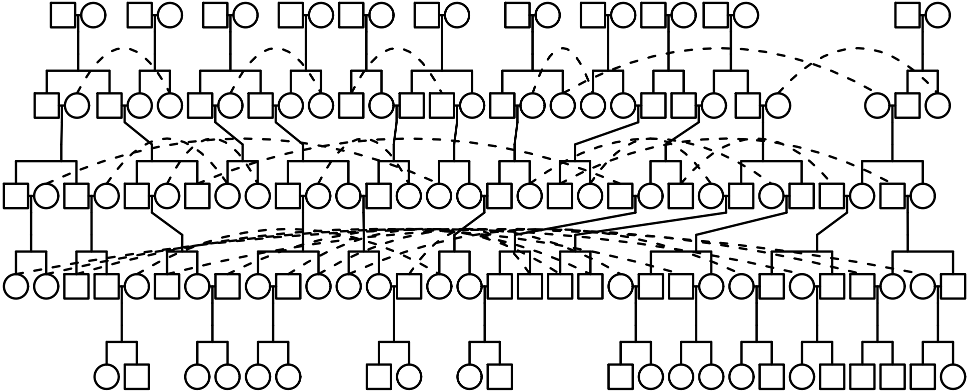

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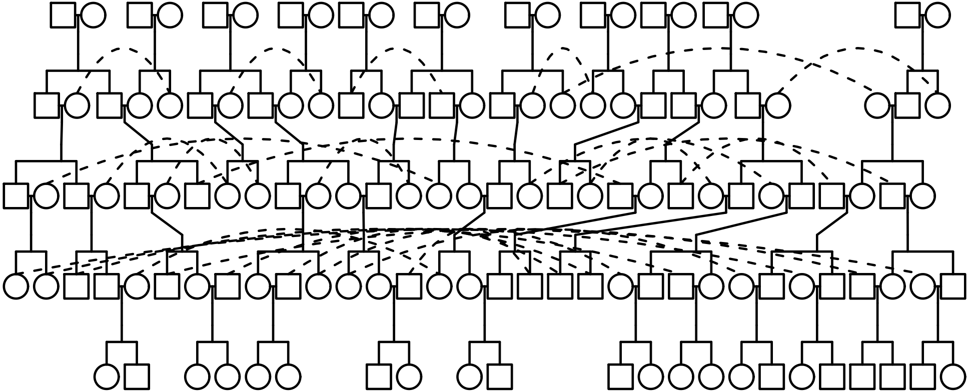

Actual simulation: 1000 individuals, 20 generations!

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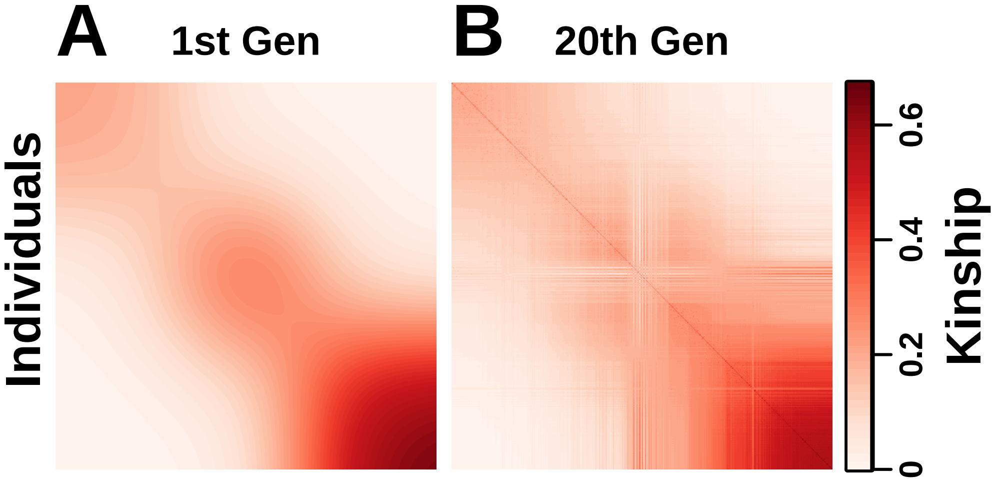

BNPSD https://github.com/StoreyLab/bnpsd

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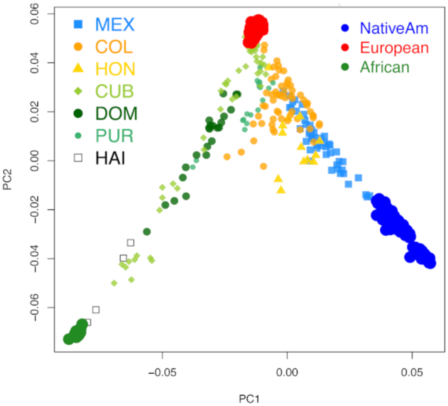

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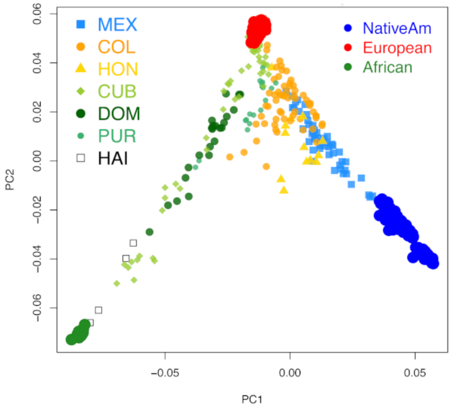

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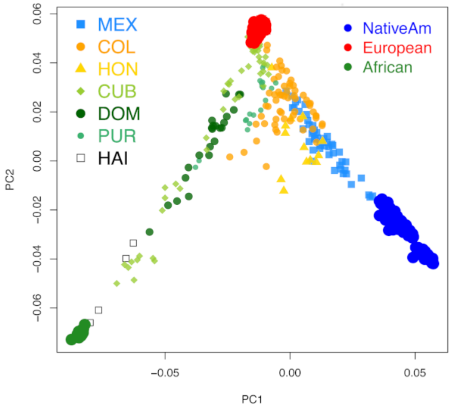

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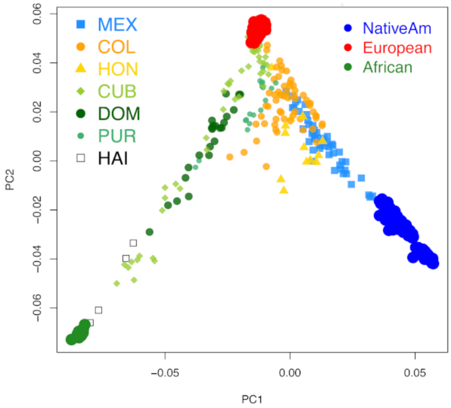

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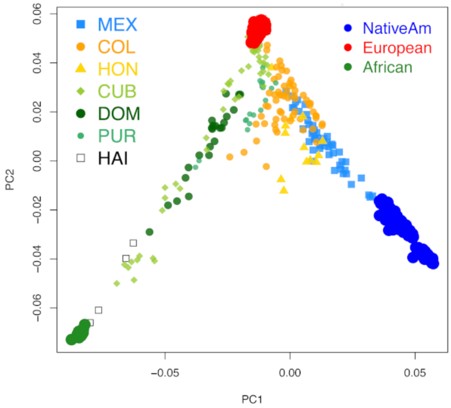

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- Cons:
  - Most computationally intensive
  - Environment is unmodeled

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Objective function handles kinship structure (no covariates):

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Effect size estimator (minimizes O) is linear in genotype! (FAST!)

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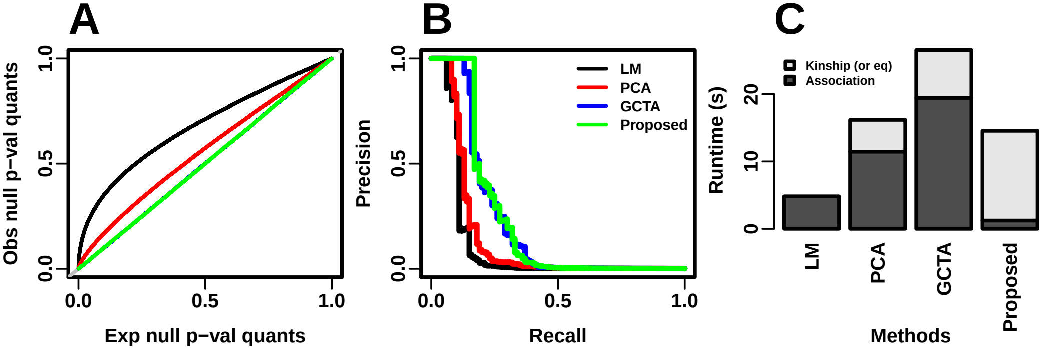
Variance has closed form, yields accurate p-values!

Genetic association on simulated admixture + 20G family



https://github.com/OchoaLab/simtrait

https://github.com/OchoaLab/genio

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Next: real data analysis

- Duke CARRIAGE family data
- dbGaP datasets

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Admixture

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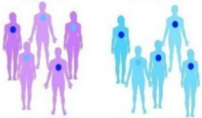

Genetic Association Studies

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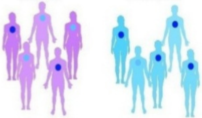

Genetic Association Studies

Heritability

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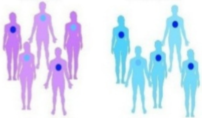

Genetic Association Studies

Heritability

Selection

Acknowledgments

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GCB
Duke Center for Genomic and Computational Biology

Department of Biostatistics & Bioinformatics
Duke University School of Medicine

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