Pop Gen meets Quant Gen and other open questions

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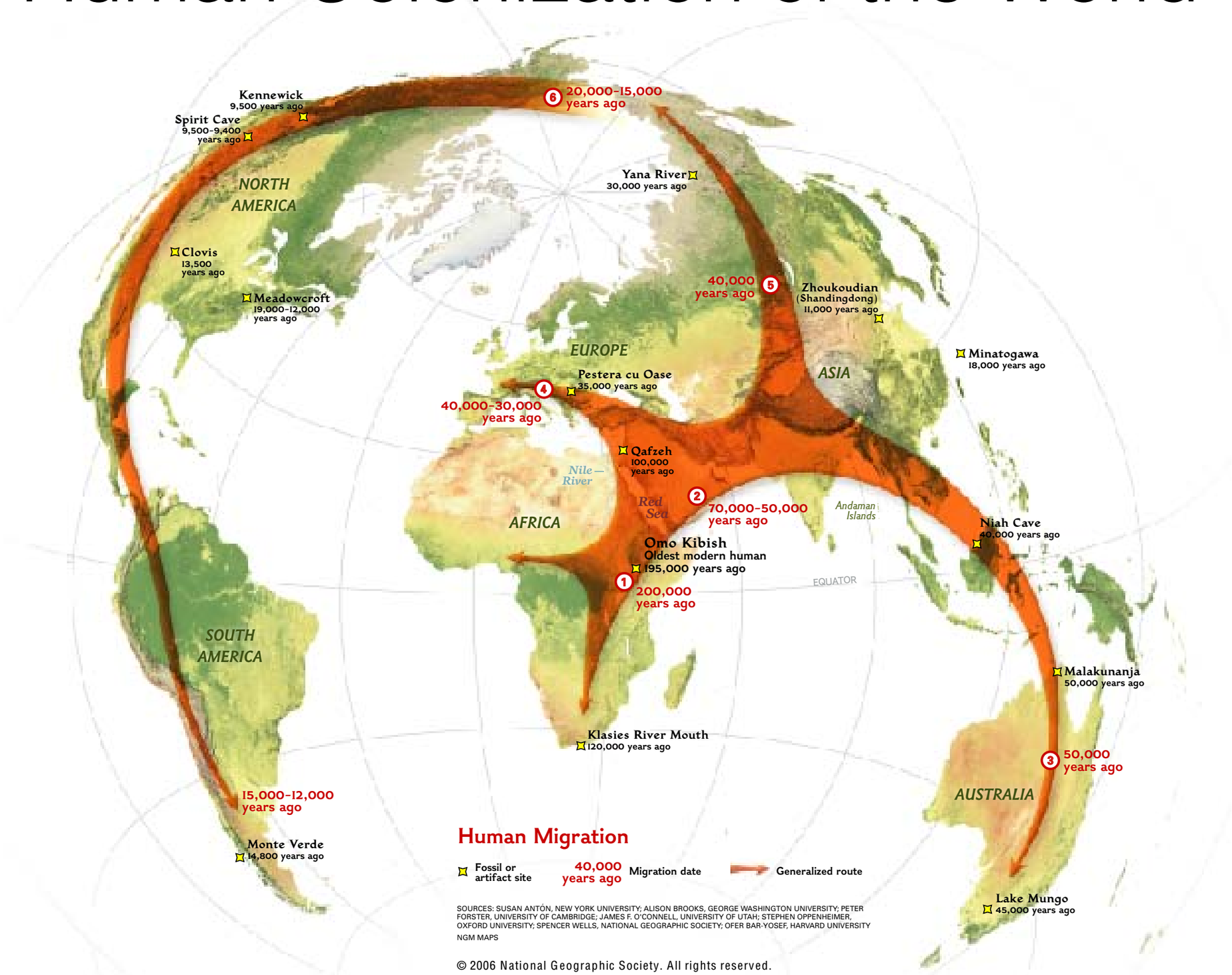
Modern Human Genomics

http://www.finca.org

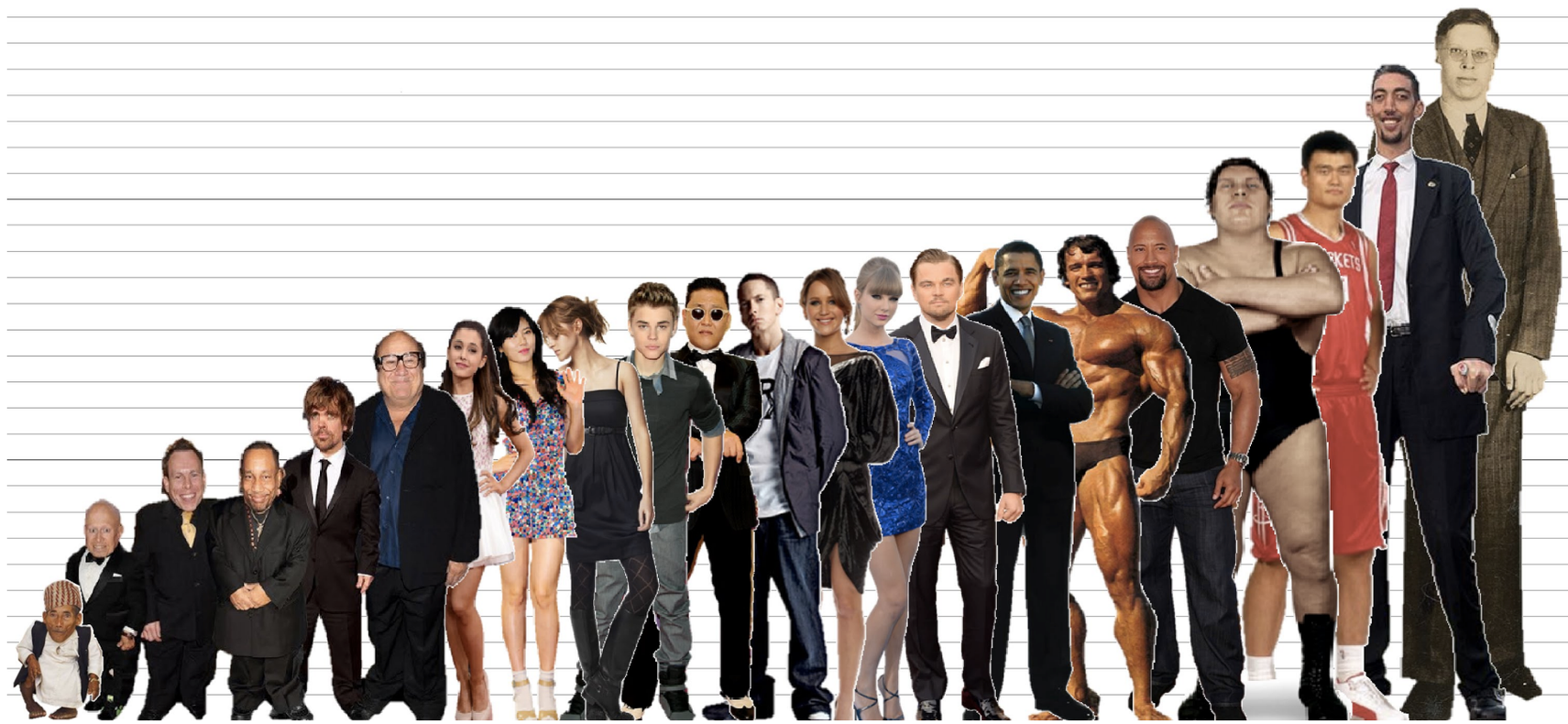
Human Colonization of the World



http://ngm.nationalgeographic.com

Heritability and Human Height

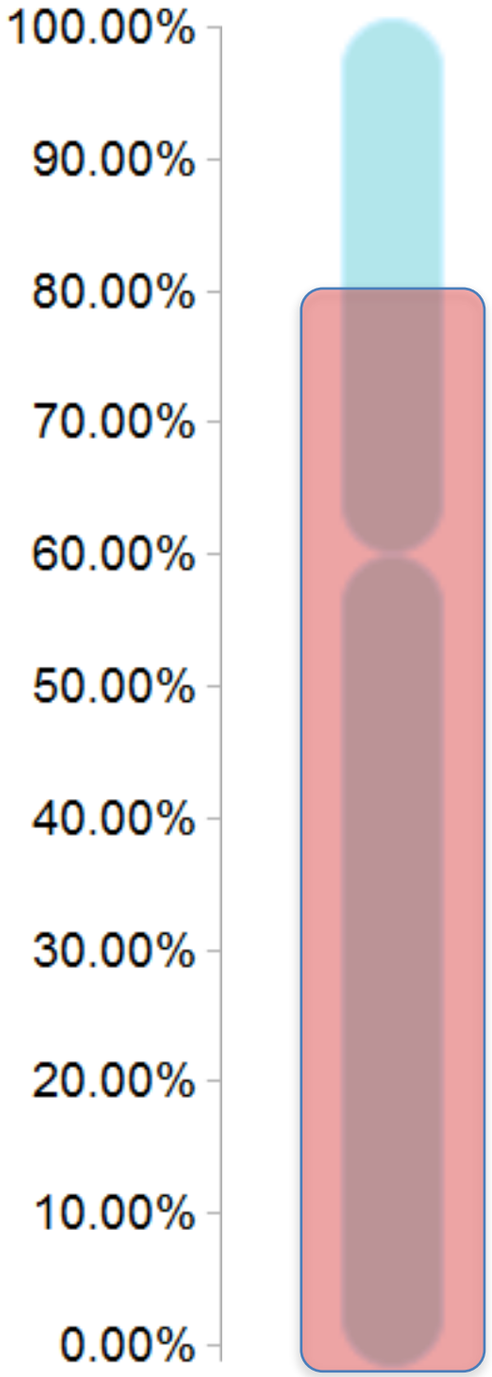
Studies of heritability ask questions such as how much genetic factors play a role in **differences in height between people**. This is not the same as asking **how much genetic factors influence height in any one person**.

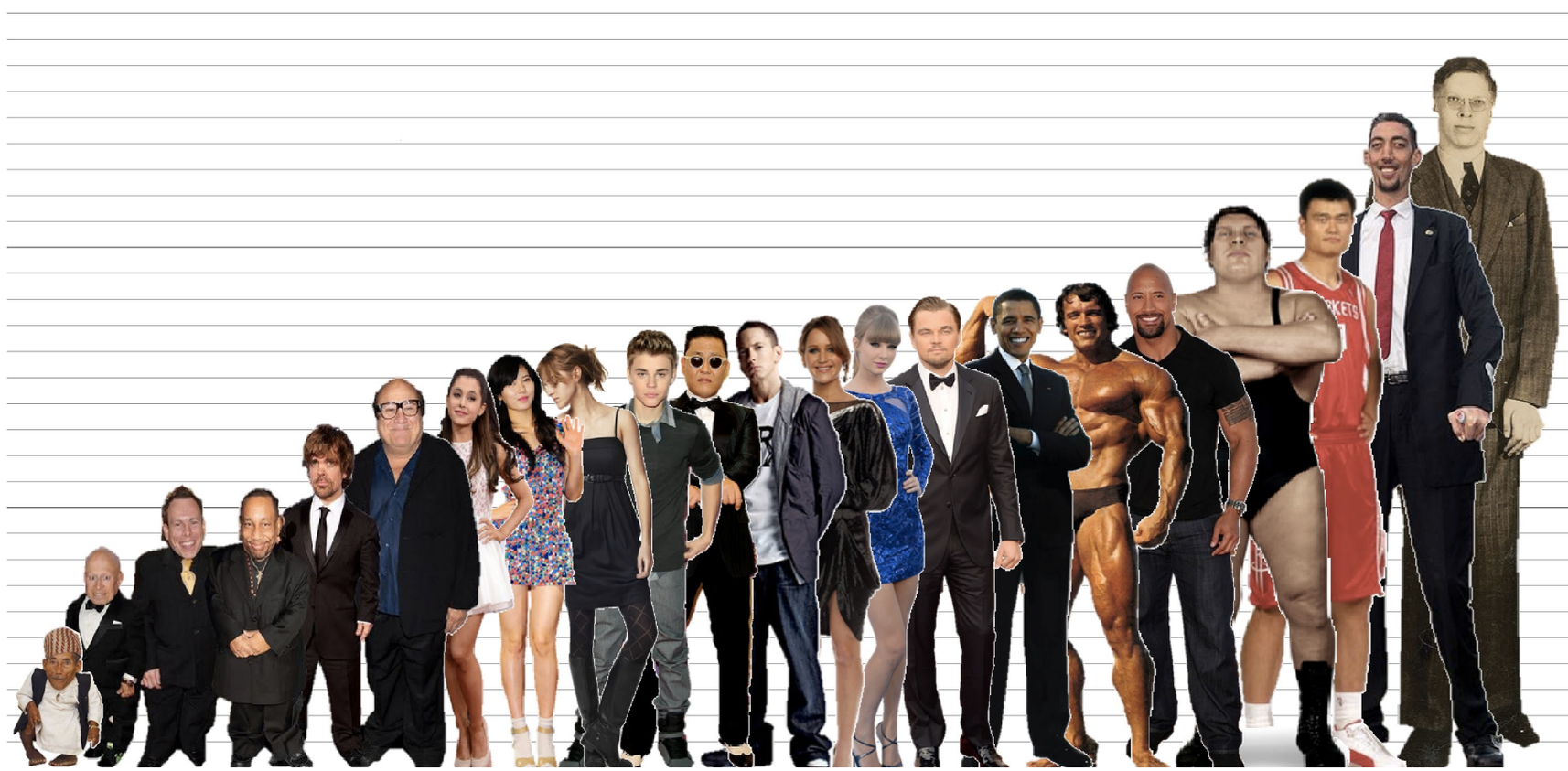


https://en.wikipedia.org/wiki/Heritability

http://i.ytimg.com/vi/E0Aeks_id6c/maxresdefault.jpg

An estimated 80% of variation in height driven is driven by genetics



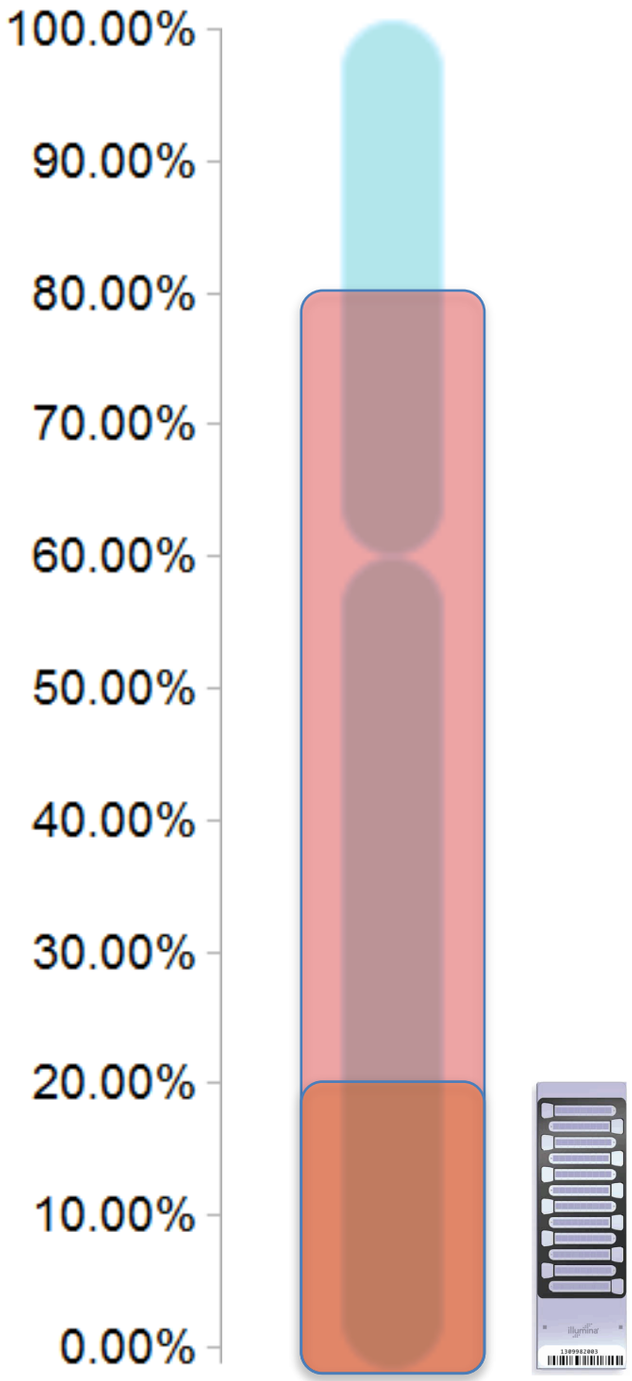


Large twin study

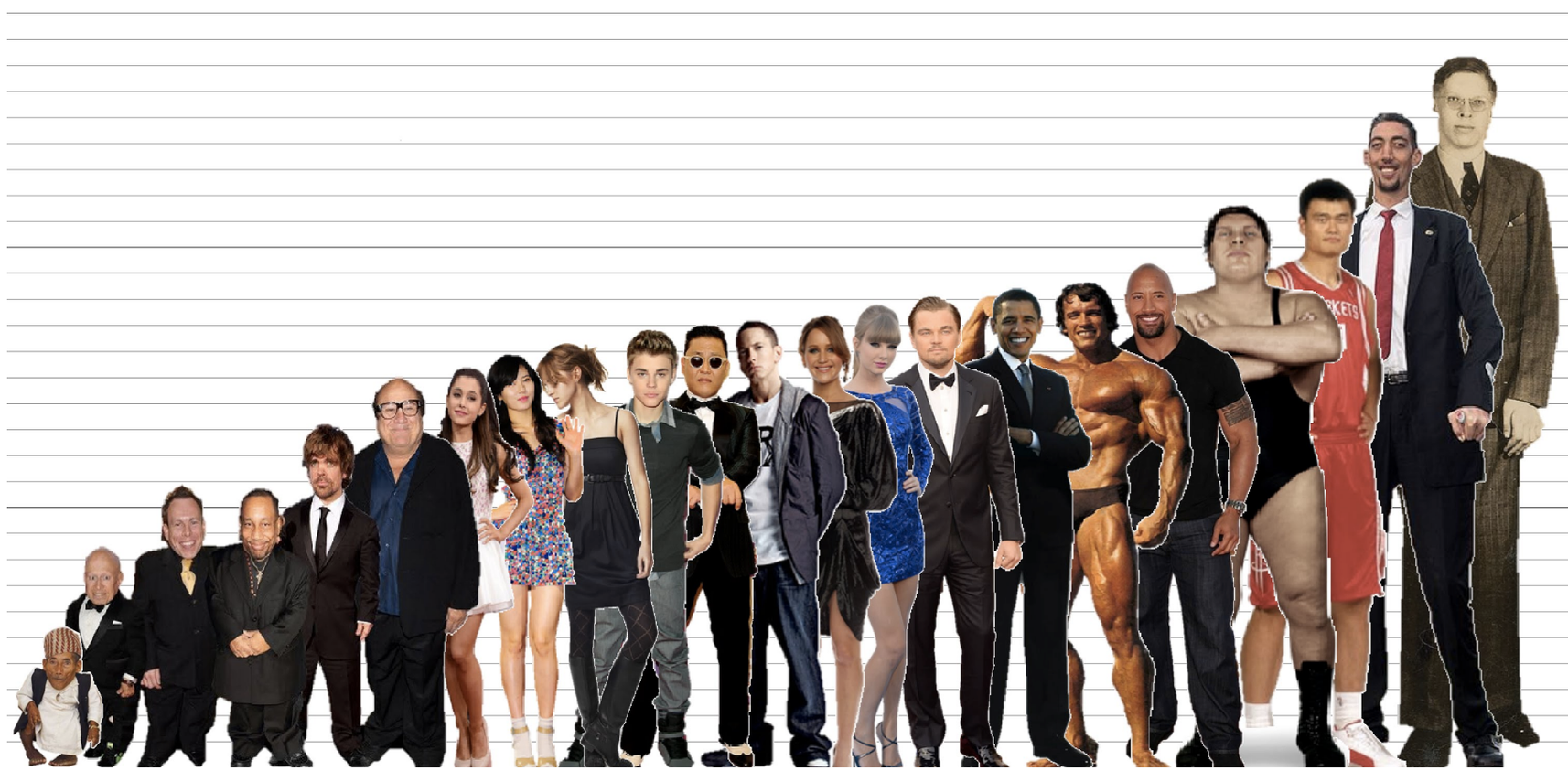
Silventoinen et al, 2003 Twin Research

http://i.ytimg.com/vi/E0Aeks_id6c/maxresdefault.jpg

But GWAS explain only 20% of the variation in height



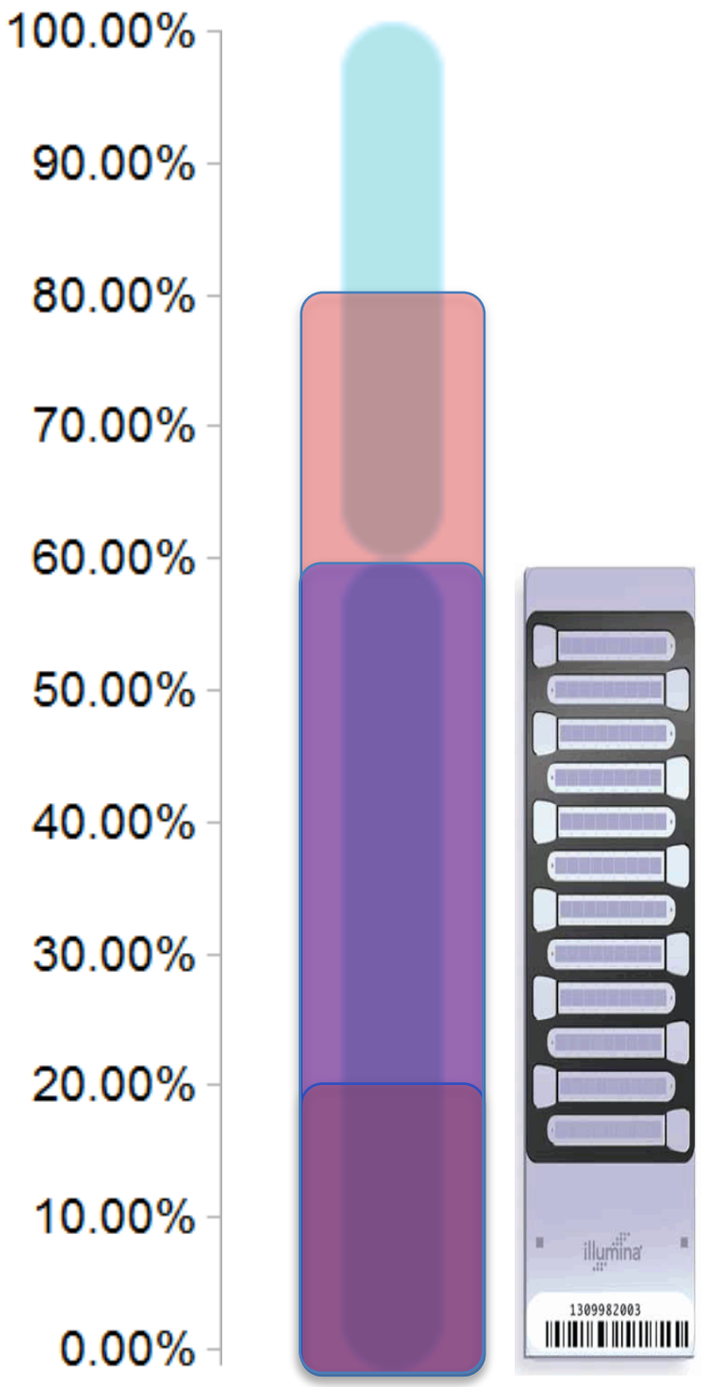
h^2_{GWAS} : The narrow-sense heritability explained by summing the effects of GWAS identified SNPs.



250,000 subjects

Wood et al, 2014 Nat. Genet.
i.ytimg.com/vi/E0Aeks_id6c/maxresdefault.jpg

GWAS have the potential to explain 60% of the variation in height



h_g^2 : The narrow-sense heritability explained by all genotyped SNPs.

250,000 subjects

Wood et al, 2014 Nat. Genet.
i.ytimg.com/vi/E0Aeks_id6c/maxresdefault.jpg

Challenges For Studying Complex

The case of the missing heritability Maher, *Nature* (2008).

Major Problem

- There are no complex traits in which we know:
    - The number of causal variants
    - The frequencies of all the causal variants
    - The effect sizes of all the causal variants
    - The fitness effect of all the causal variants
- We need a thorough simulation study where we can vary all of these parameters and see how they effect our answer!

Possible Origins Of Missing Heritability

Candidates
Common variants of weak effect
Incomplete linkage to causal alleles/multiple causal alleles in locus
GxG / GxE Interactions
Rare variants
Structural variation

From GWAS To Deep Sequencing

- Genome-wide association studies (GWAS) seek to identify common variants that contribute to common disease

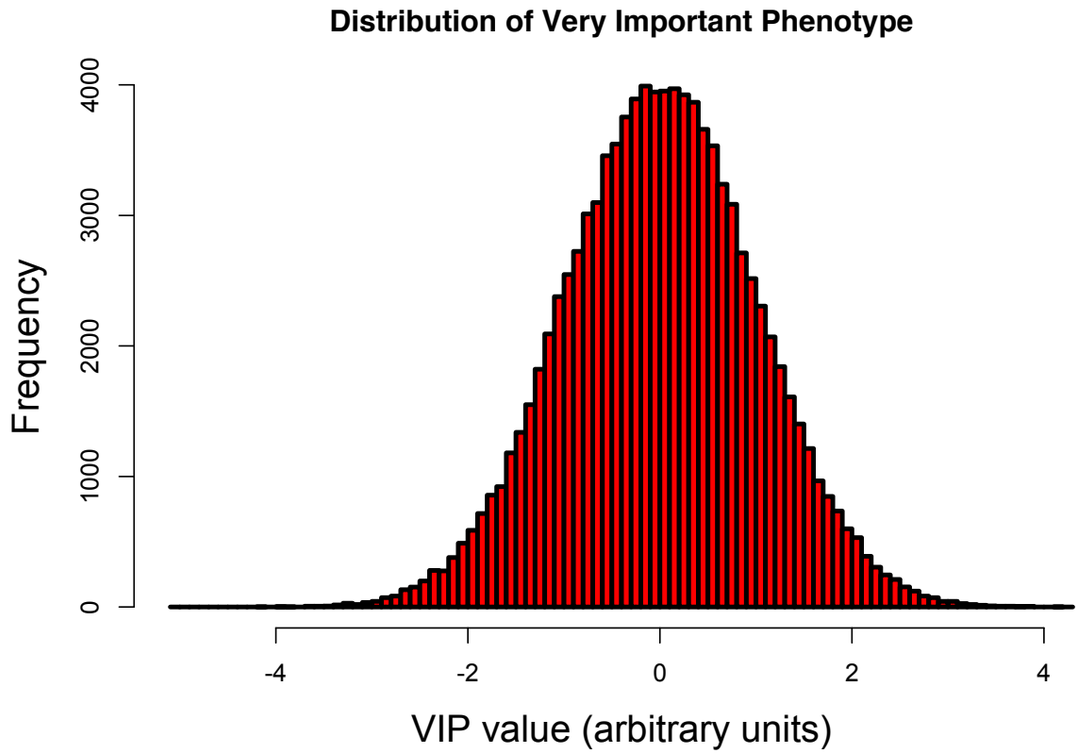
- Successfully identified many candidate disease-associated genes

- Challenges:
  - Generally have low relative risk
  - Explain only a small proportion of the phenotypic variance

  - Provides candidate loci, but causal variant is rarely typed

- Implication:
  - Predictive power of GWAS is minimal…

“Missing” heritability - calculating variance accounted for by GWAS



Suppose *k* variants are found to be associated with VIP…

Contribution from each SNP

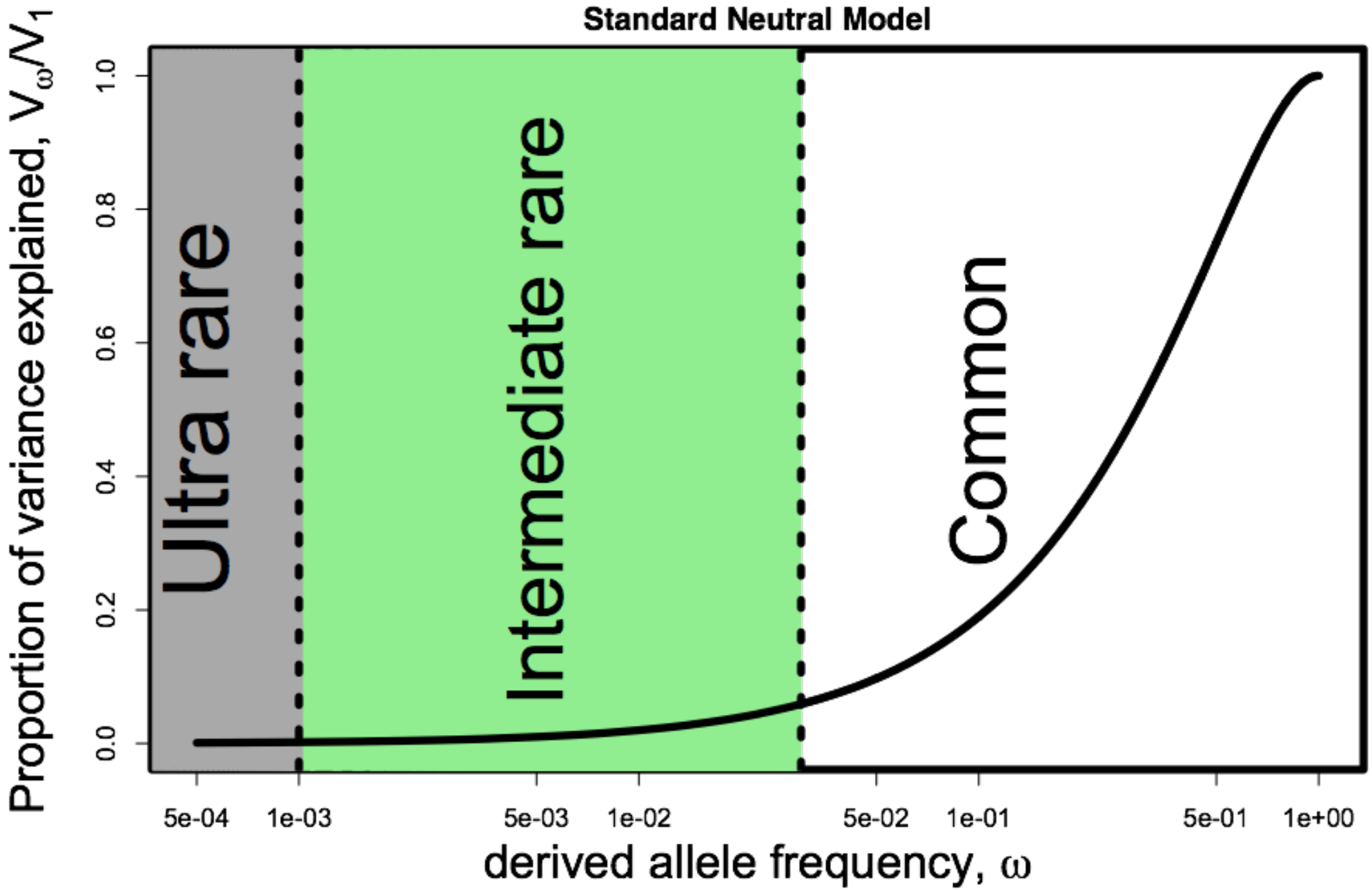
$$v = \frac{1}{2} z^2 x(1-x)$$

Total variance from GWAS

$$V_{\text{GWAS}}(P) = \sum_k v_k$$

Compare to GWAS $V_{\text{GWAS}}(P) < h^2 \times V(P)$

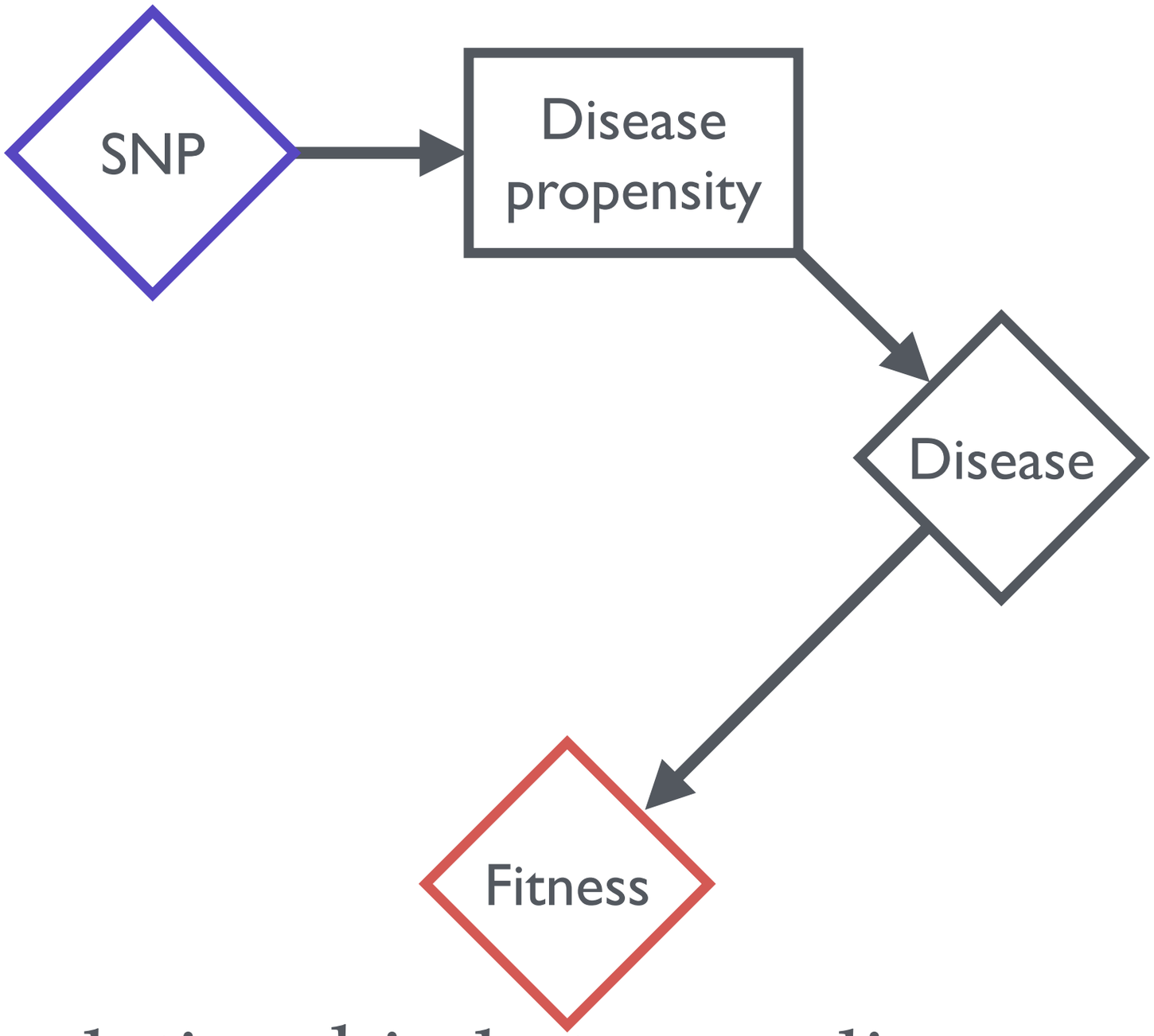
Where is the “missing” heritability?



Population Genetics

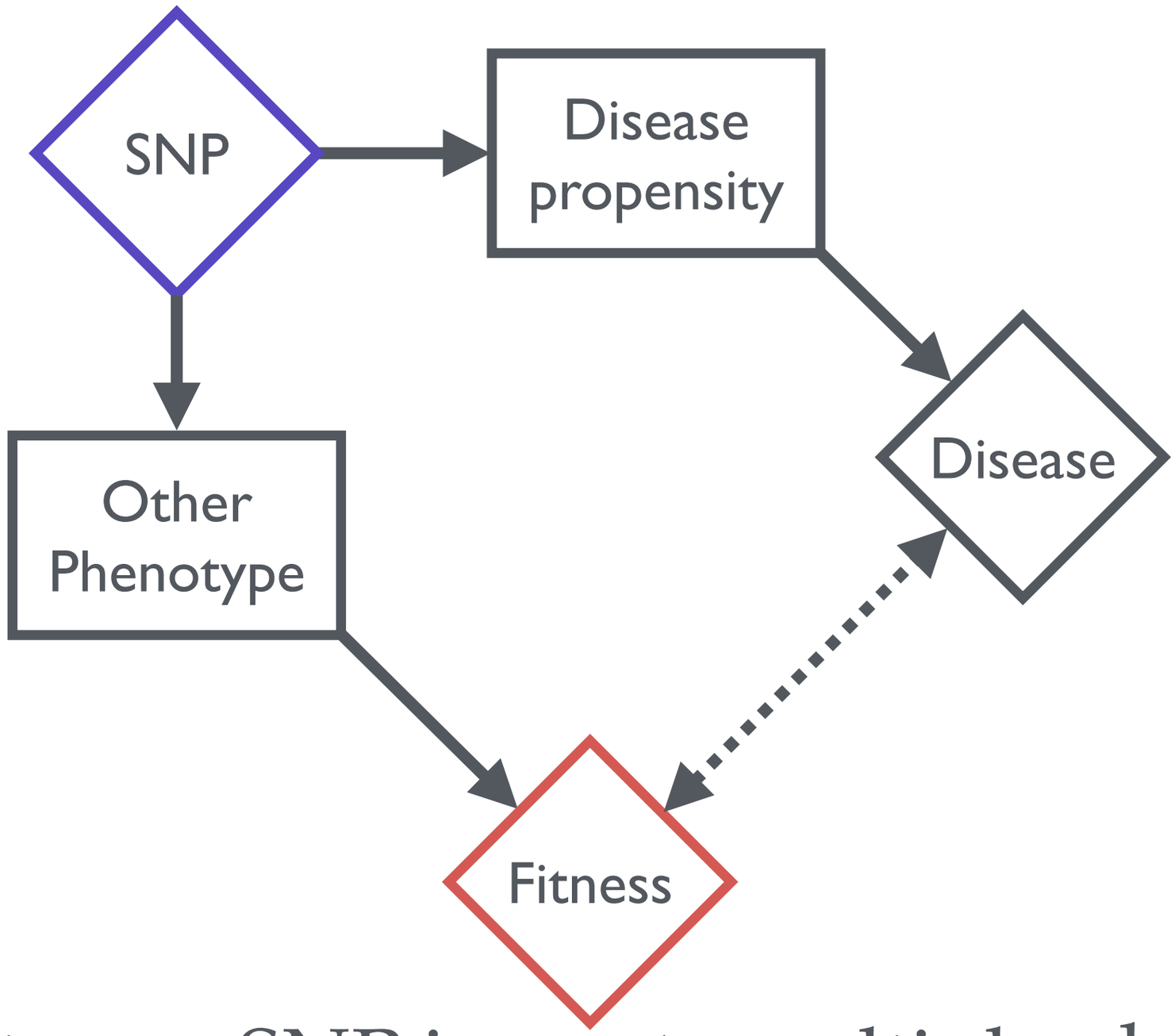
- Why would cases have an excess of **rare** non-synonymous variants in disease-associated genes?
    - Recent neutral mutations that have not had time to spread
    - Deleterious mutations restricted to low frequency
- Population genetic analyses are ideally suited to distinguish these cases.

Evolutionary Models Of Complex Disease



Direct relationship between disease and fitness

Evolutionary Models Of Complex Disease



Pleiotropy: SNP impacts multiple phenotypes

Uricchio et al., Genome Research (2016)

The Model Of Eyre-Walker (2010)

- The phenotypic effect size has a direct relationship to selection coefficient of causal mutations:

$$z = \delta S^{\tau}(1 + \epsilon)$$

- Where:
  - $\varepsilon \sim N(0, \sigma^2)$
  - δ = random sign (trait increasing / decreasing)
  - S = selection coefficient
  - τ = measures how the mean absolute effect of a mutation on the trait increases with the strength of selection

Eyre-Walker, PNAS (2010)

The Model Of Simons Et Al (2014)

- The phenotypic effect size **may** have a direct relationship to selection coefficient of causal mutations:

$$z_s \propto \begin{cases} s & \text{with probability } \rho \\ s_r & \text{with probability } (1-\rho) \end{cases}$$

- Where:
  - ρ = Probability that the trait effect is proportional to the selection coefficient: **Pleiotropy**!!
  - s = selection coefficient
  - s_r = random selection coefficient

Simons et al, Nat Genet (2014)

The Model Of Uricchio Et Al (2016)

- A hybrid of the two: $z_s \propto \begin{cases} \delta|s|^{\tau} & \text{with probability } \rho \\ \delta|s_r|^{\tau} & \text{with probability } (1-\rho) \end{cases}$
- Where:
  - δ = random sign (trait increasing / decreasing)
  - τ = measures how the mean absolute effect of a mutation on the trait increases with the strength of selection
  - ρ = Probability that the trait effect is proportional to the selection coefficient: **Pleiotropy**!!
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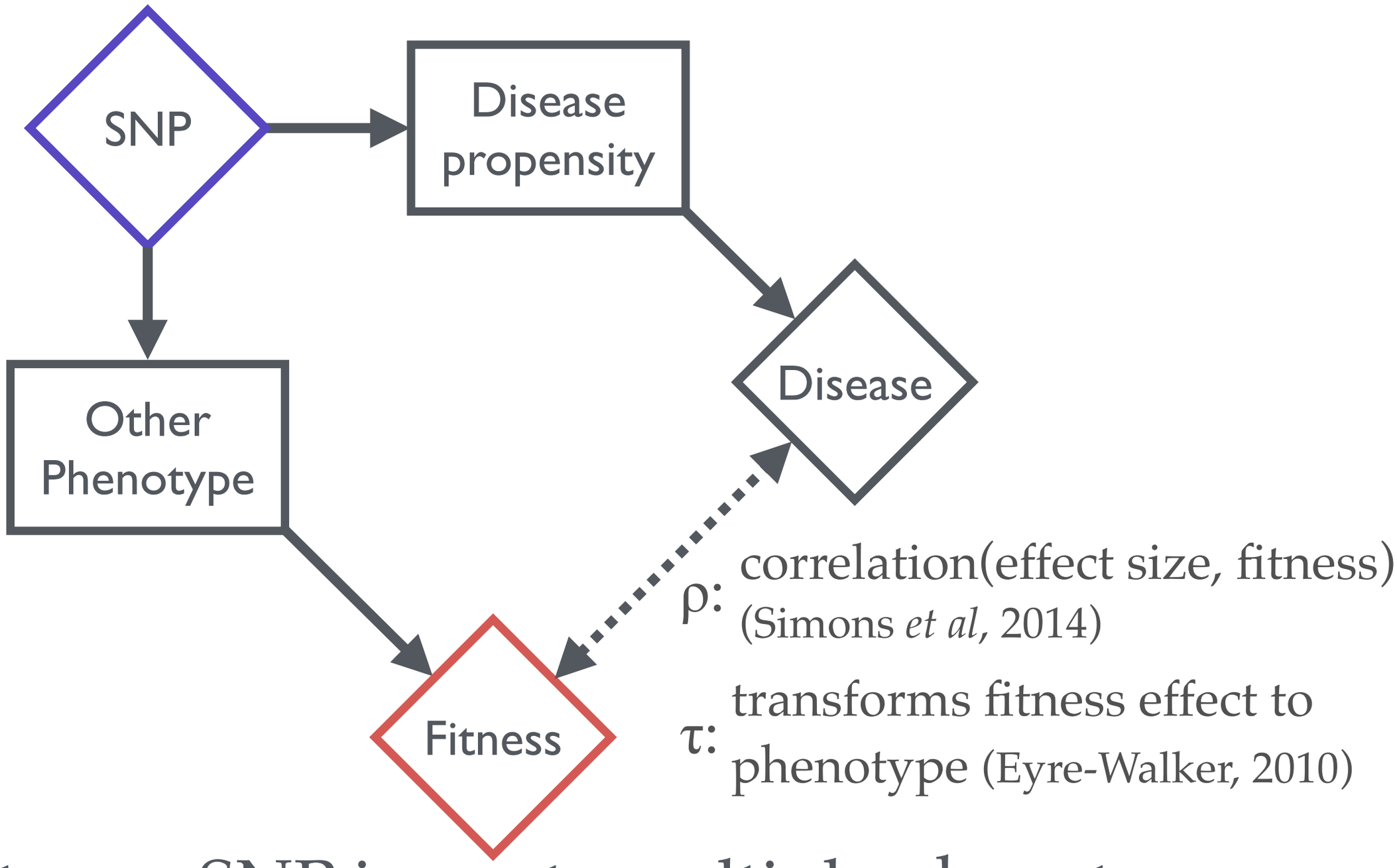
Uricchio et al, Genome Research (2016)

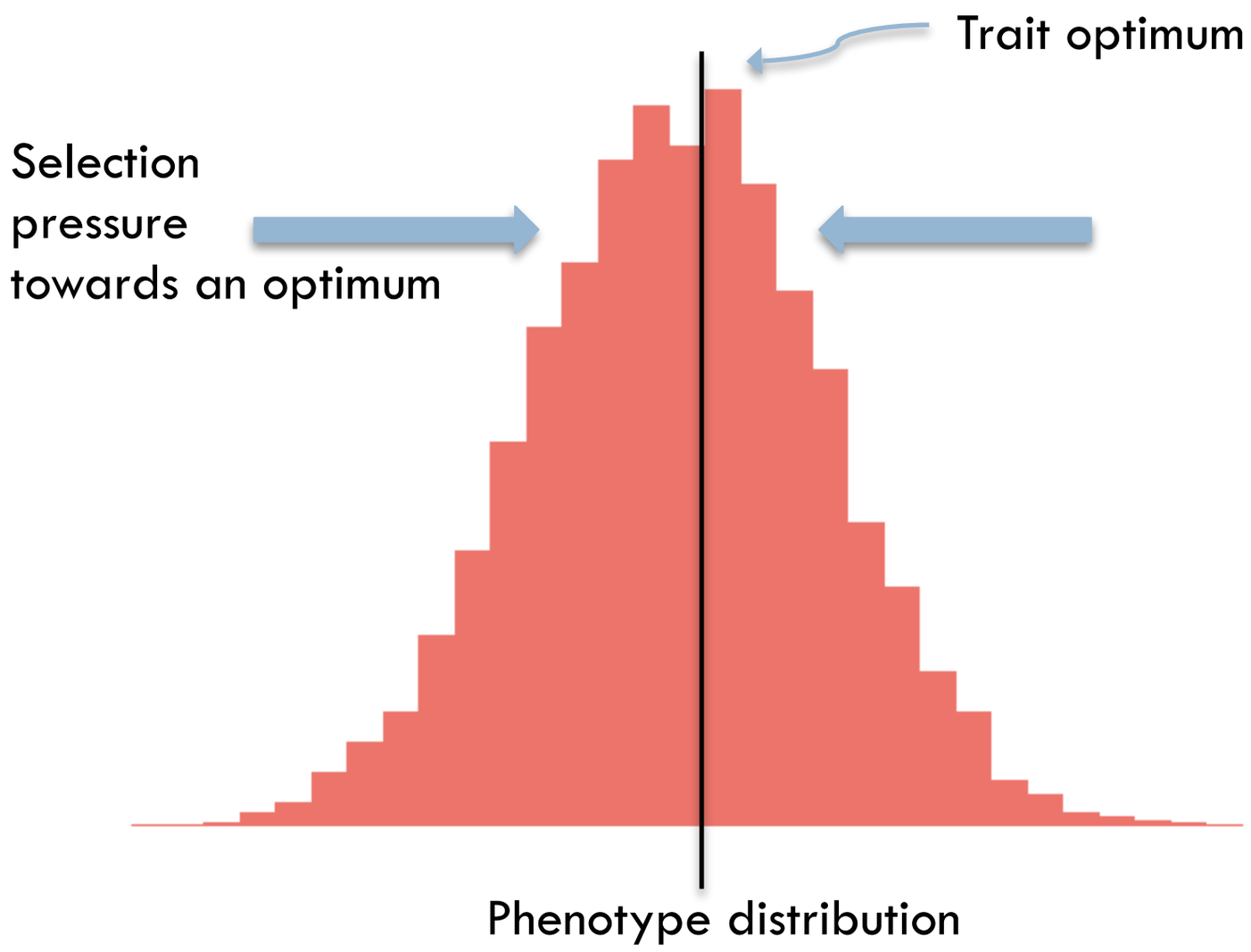
Evolutionary Models Of Complex Disease



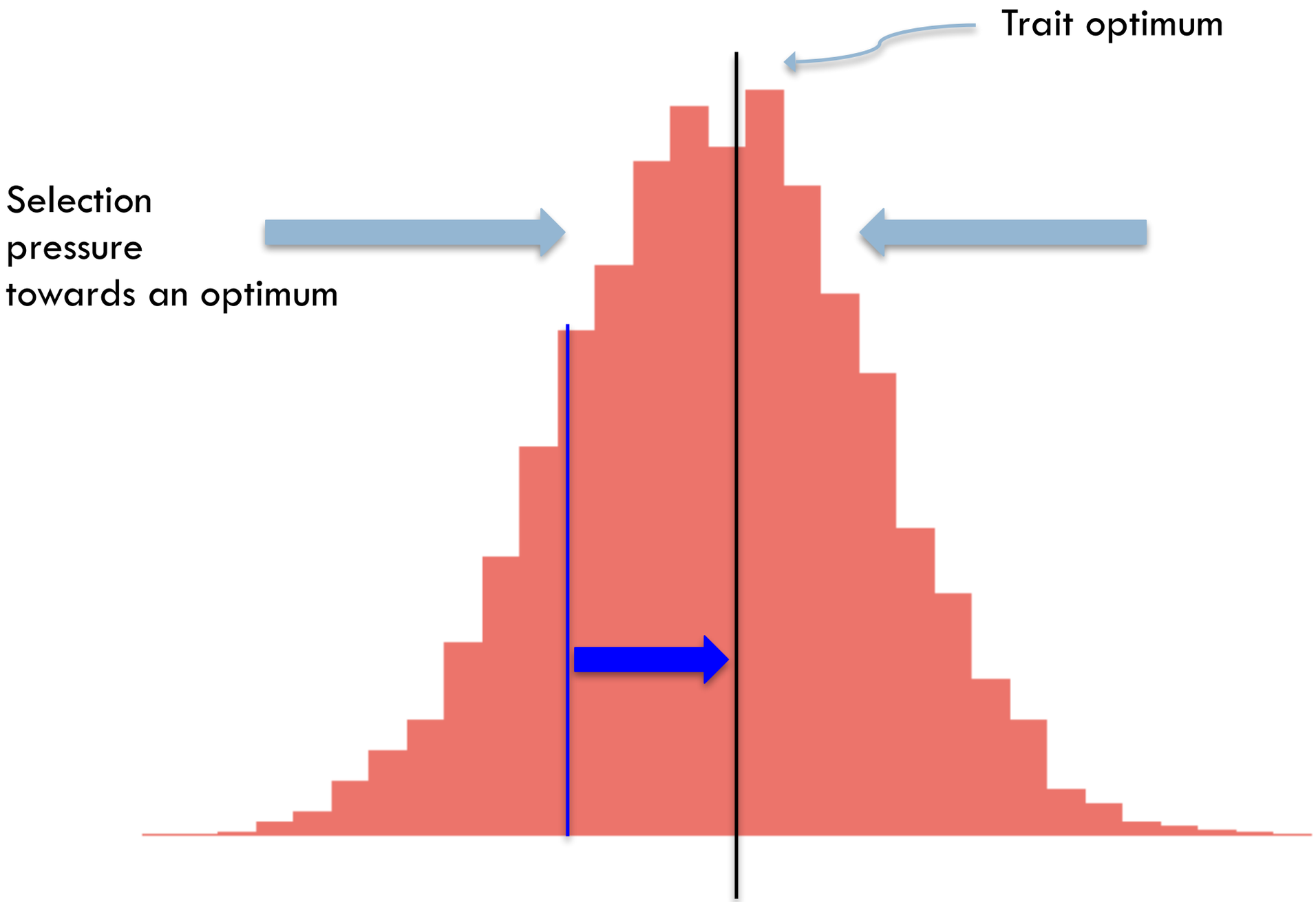
Pleiotropy: SNP impacts multiple phenotypes

Uricchio et al., Genome Research (2016)

Why should we think about evolution?



Stabilizing selection



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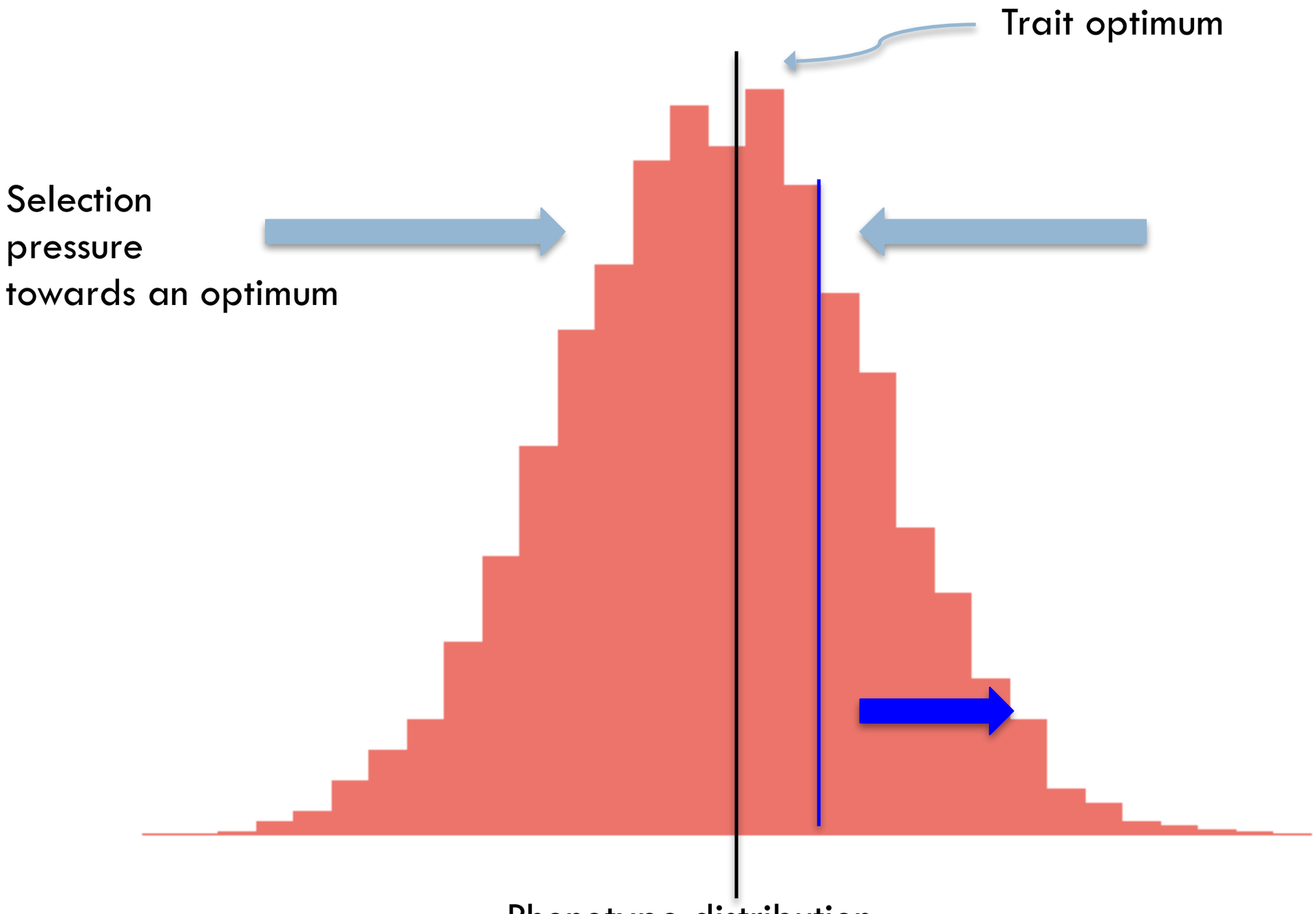

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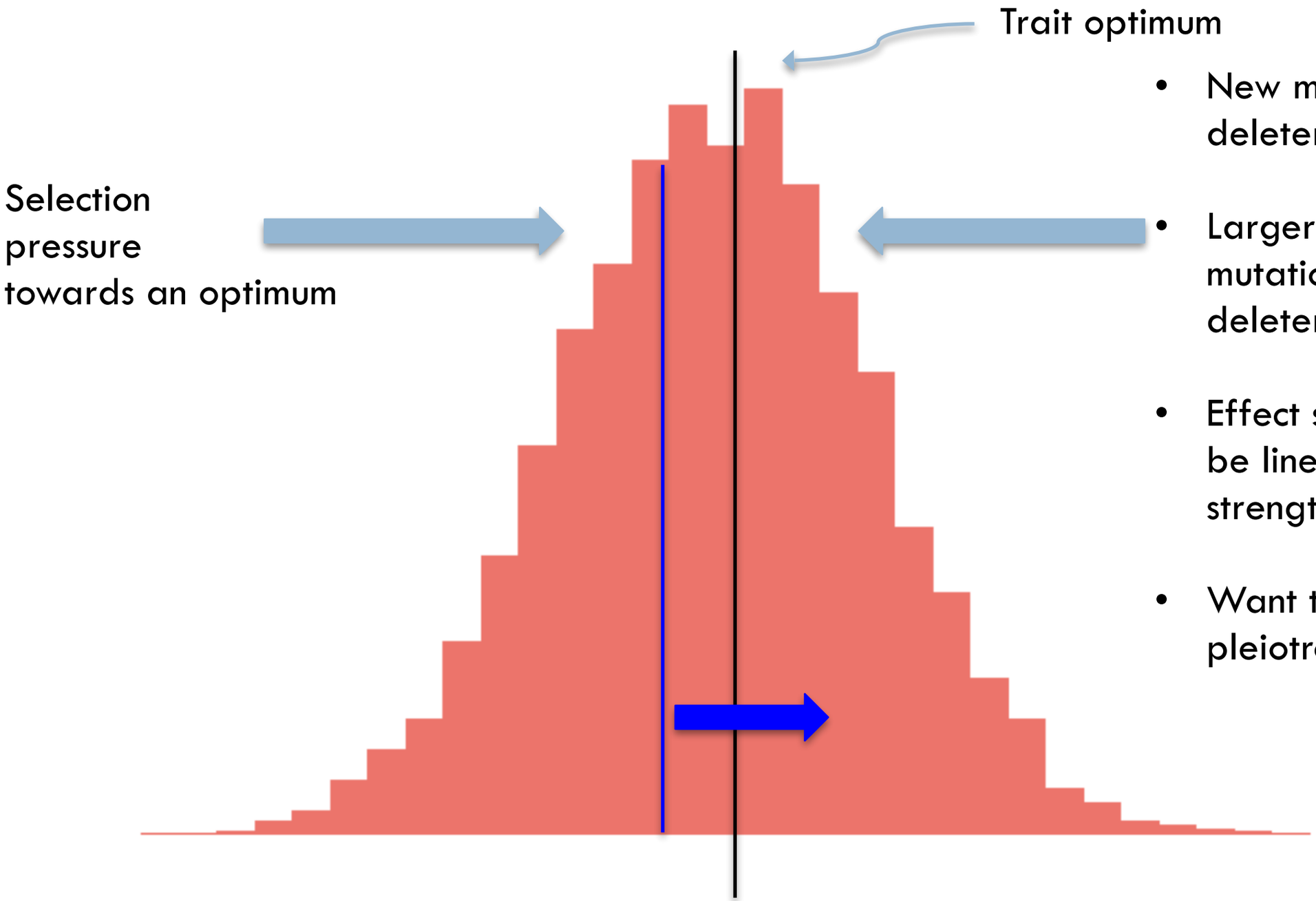
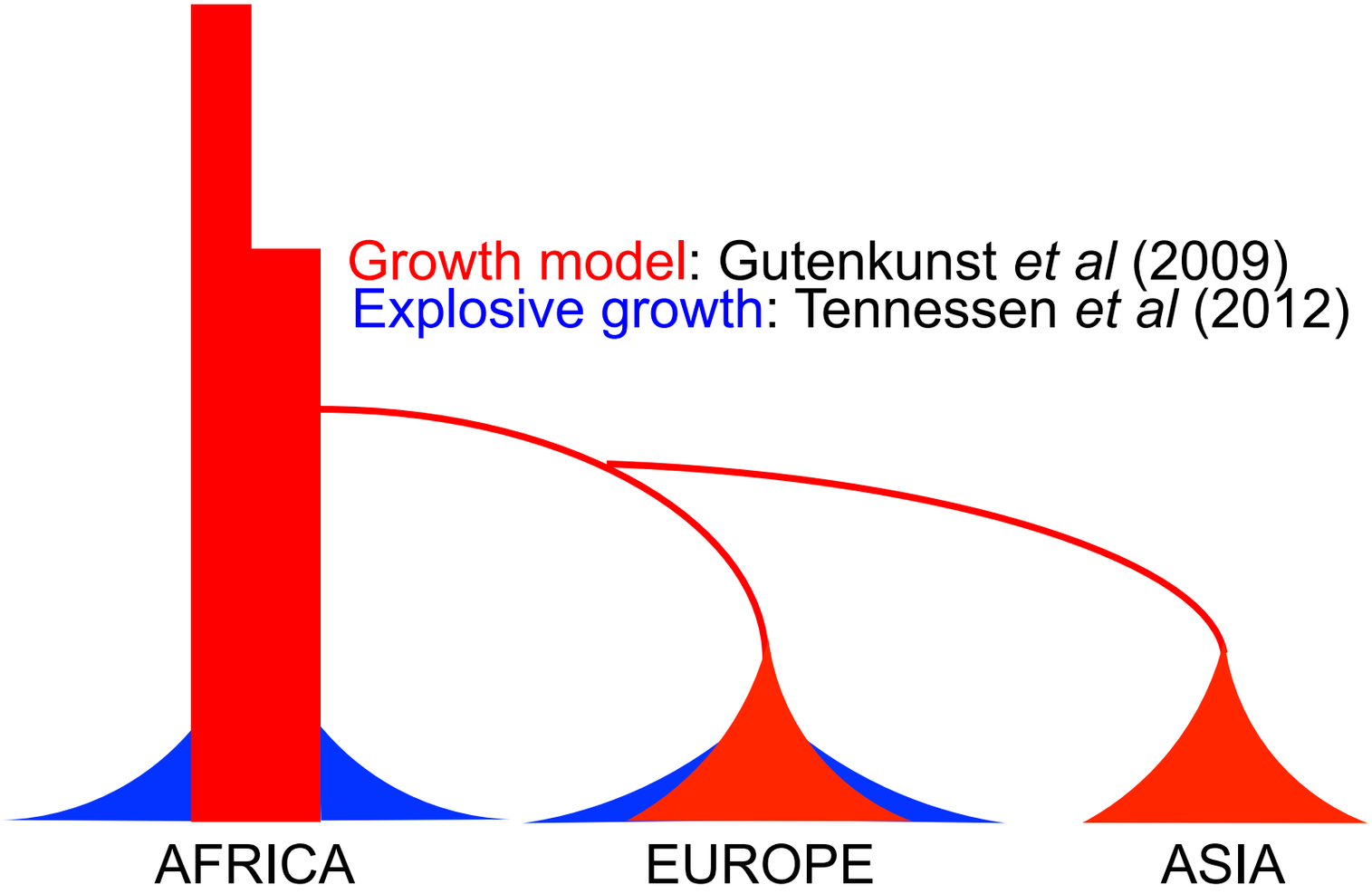
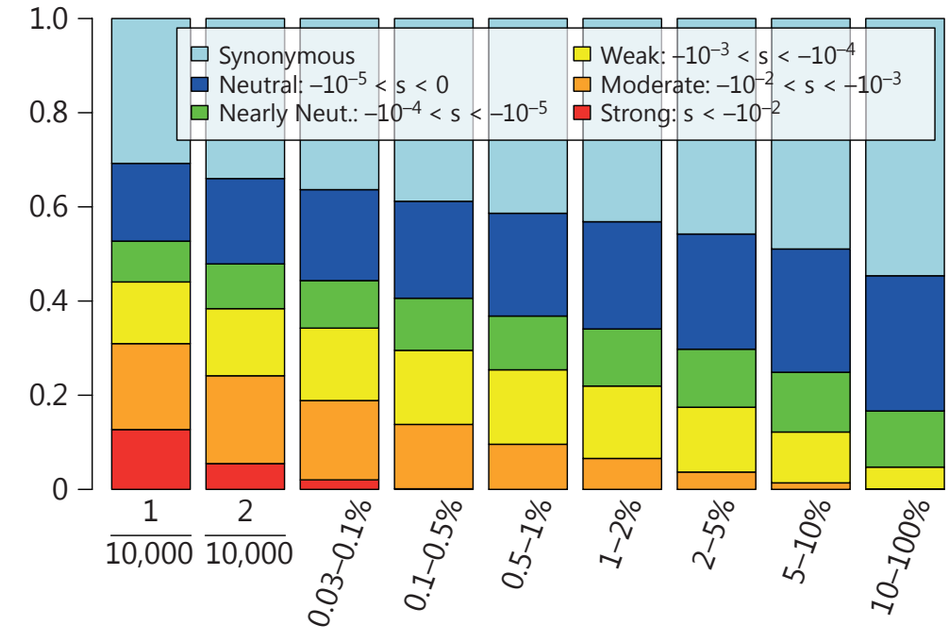


- New mutations deleterious
- Larger effect mutations are more deleterious
- Effect sizes may not be linear in selection strength
- Want to allow for pleiotropy

Human-specific demography and Selection



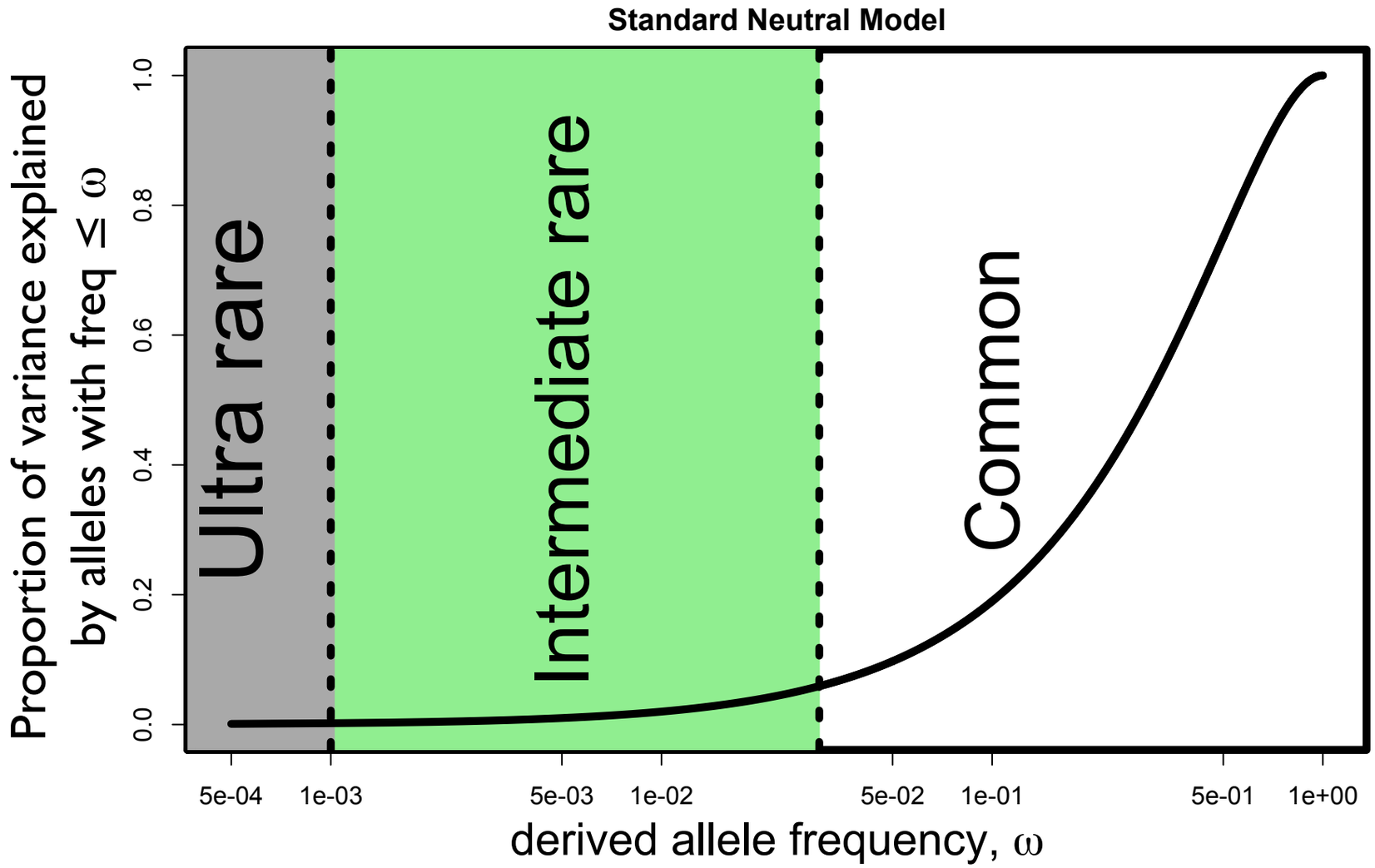
Fitness effects in non-coding DNA:
Torgerson *et al* (2009)



effect size = f(demography, natural selection)

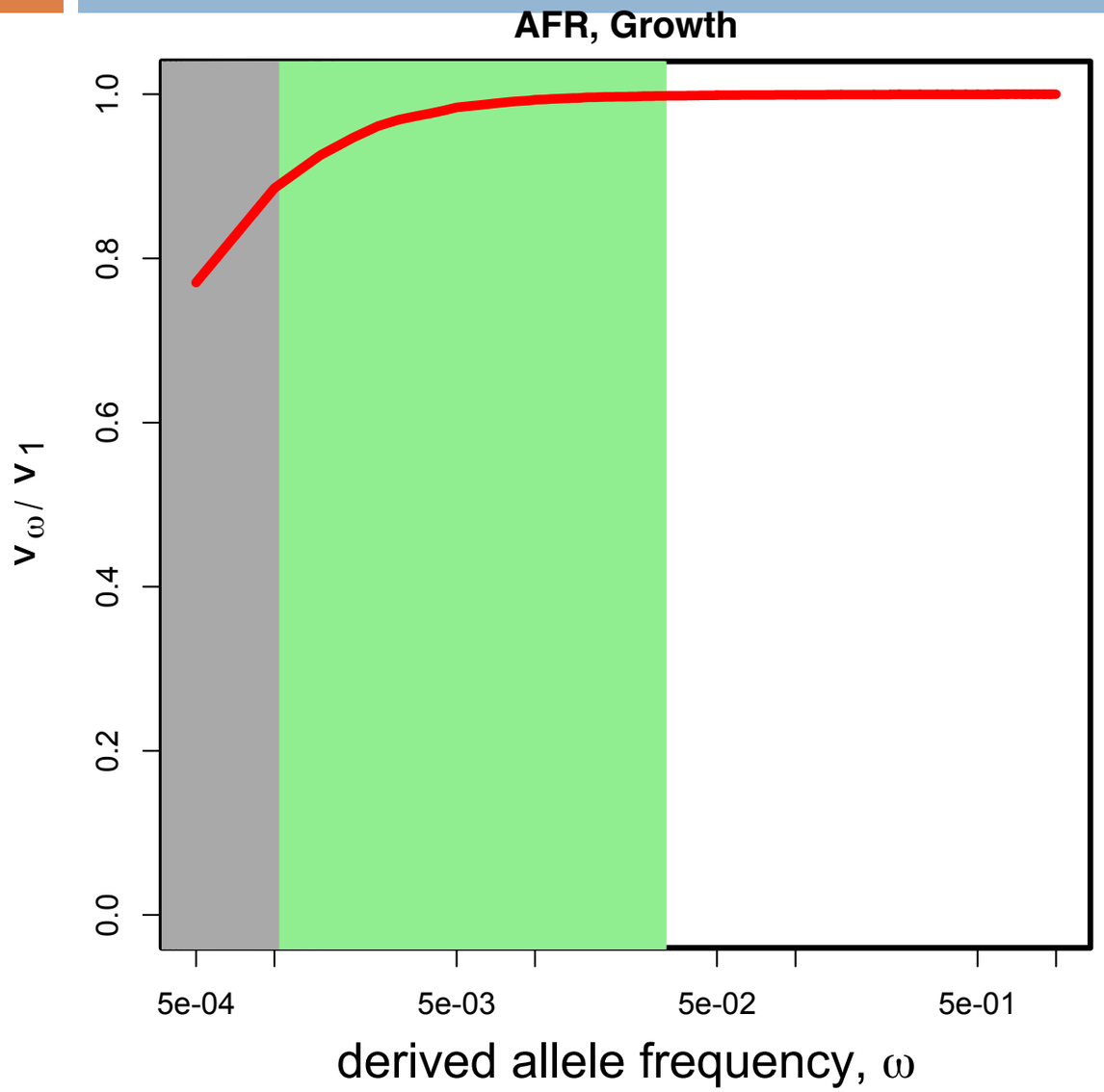
Uricchio, et al. *Genome Res* **26**, 863-873 (2016).

Neutral model: most variance explained by common alleles



Uricchio, et al. *Genome Res* **26**, 863-873 (2016).

Genetic architecture is altered by selection and demography



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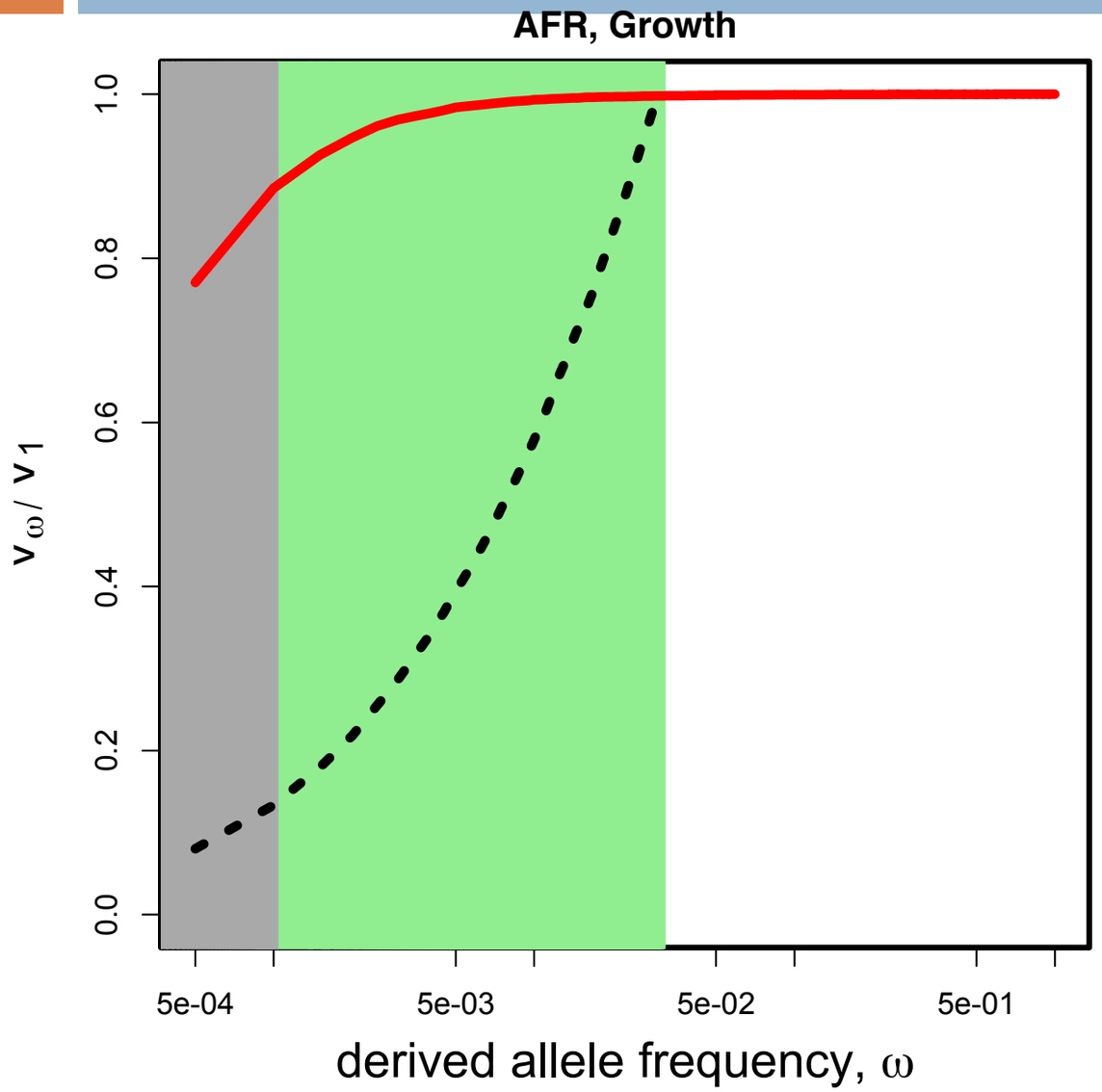

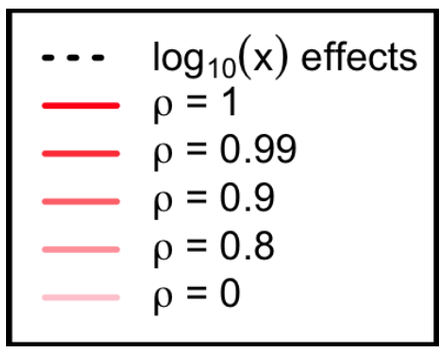

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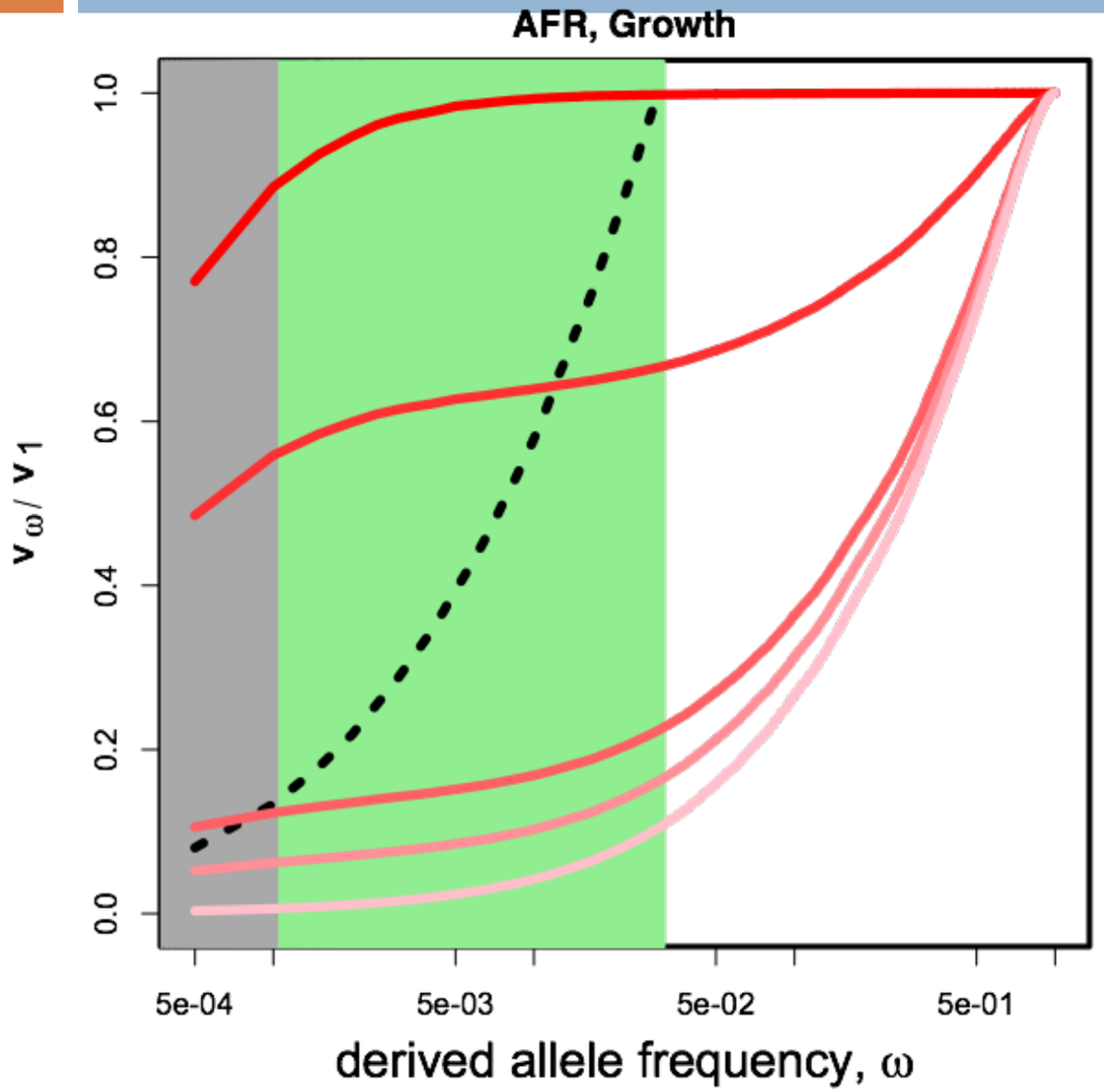

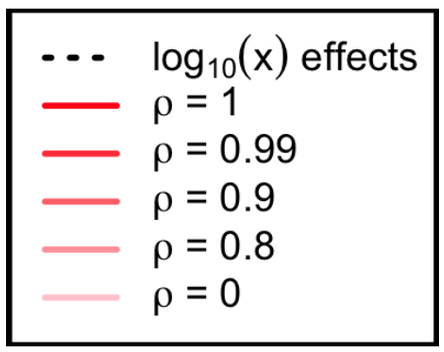

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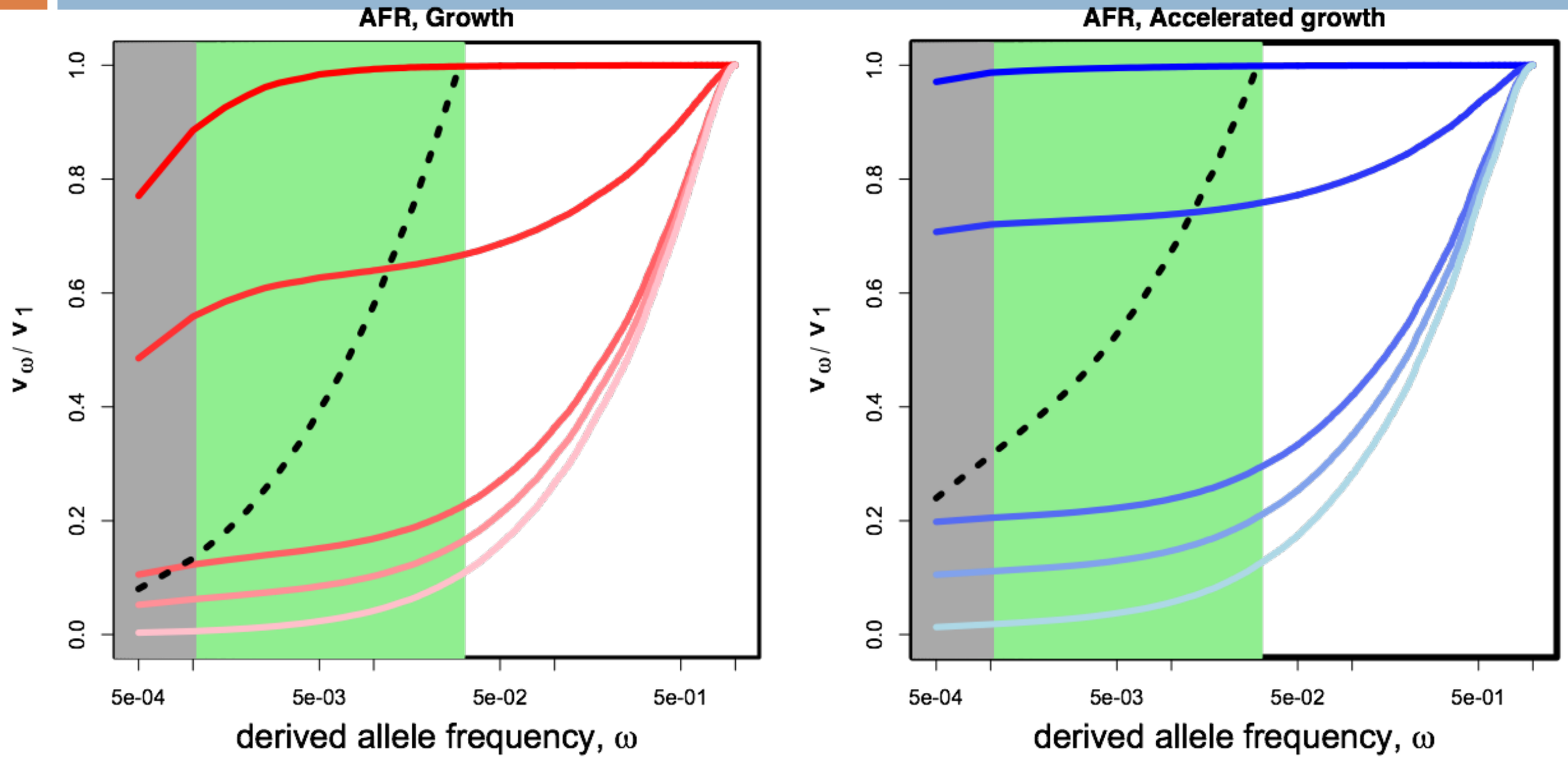
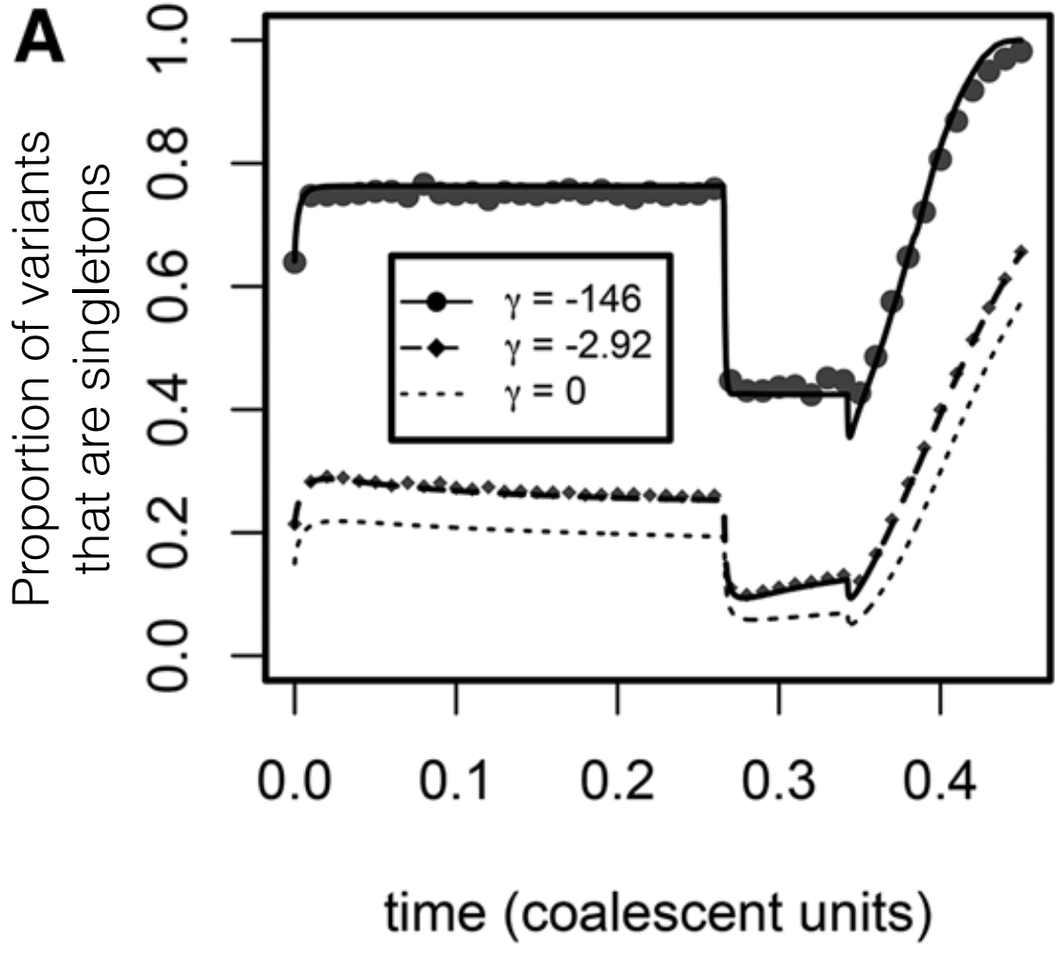


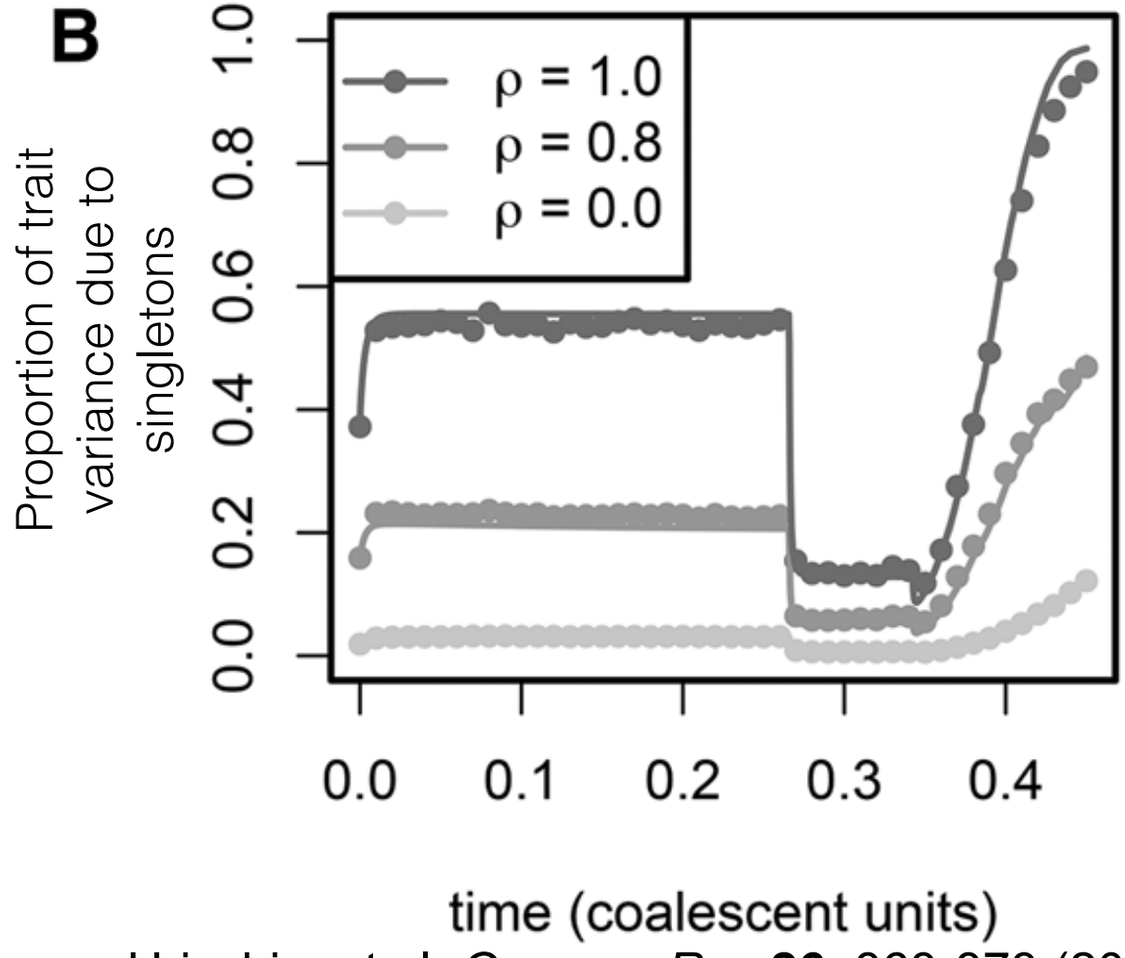
Implication: in some cases, largest effect alleles are very rare, so we may not detect them with GWAS!

Uricchio, et al. *Genome Res* **26**, 863-873 (2016).

Demography and selection matter!

- As populations expand and contract, or strength of selection changes, the frequency spectrum responds.
- This can **and should** impact the genetic architecture of traits!

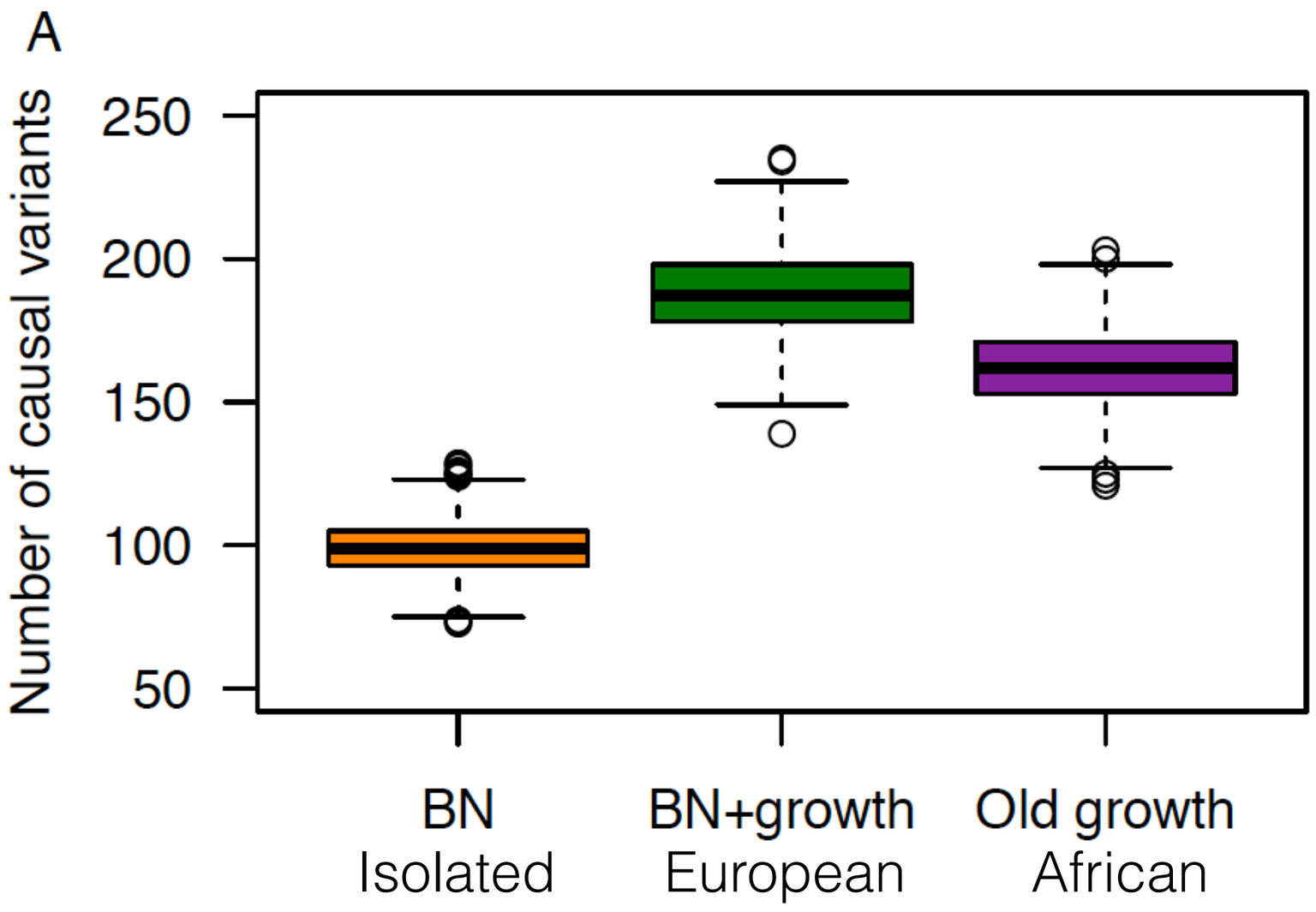




Uricchio, et al. *Genome Res* **26**, 863-873 (2016).

Demography and selection matter!

- Demography and selection also impacts the number of causal variants!



Lohmueller, *PLoS Genet* (2014).

Open Questions

- What does does the genetic architecture of a complex trait really look like?
- How many causal variants are there?
- Proportion of effects from rare/common alleles?
- Additive vs epistatic interactions?
- Pleiotropy?

- Large-scale RNA sequencing + WGS
  - 4 European populations
  - 360 individuals
    - low coverage WGS + high coverage exome: Phase 3.
    - RNA-seq: median depth 58.3M reads
      - Gene expression:
        log2 transformed, median centered, and quantile normalized.
      - 10,077 unique genes.

Hernandez, et al. (bioRxiv, 2019)

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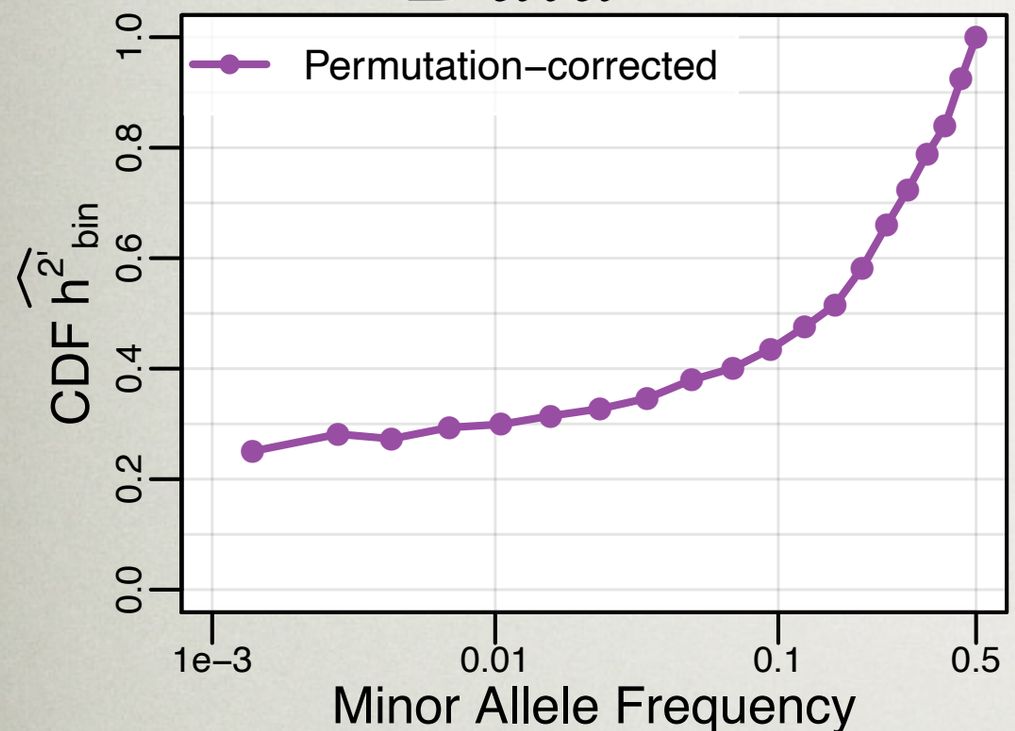
    - 10,077 unique genes.

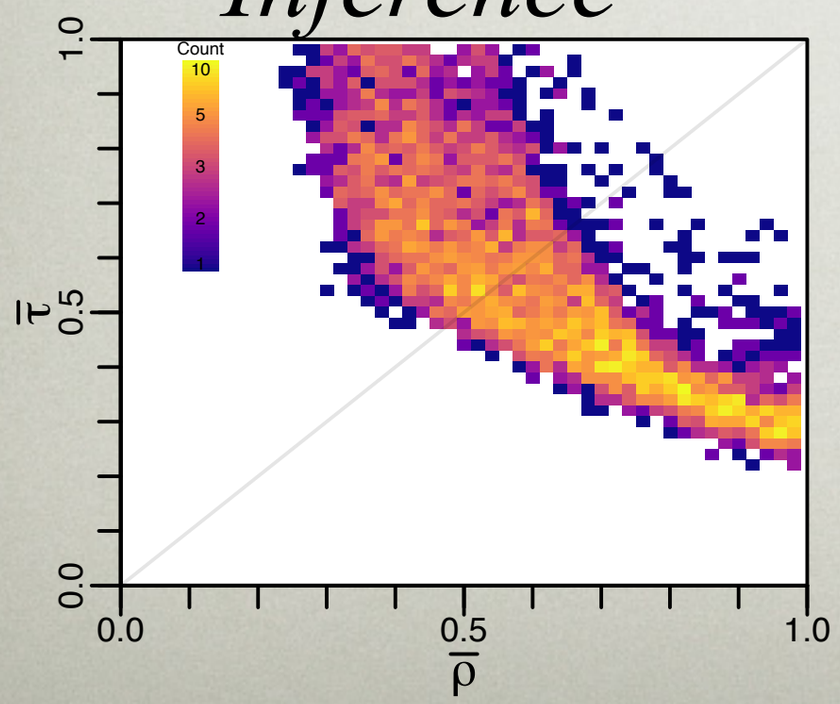
- Our sample size is **small**, but can we learn anything about the **genetic basis of complex traits from these 10k genes**?
- Let's analyze heritability of gene expression due to *cis* variation (within 1Mb of gene)

Estimating parameters

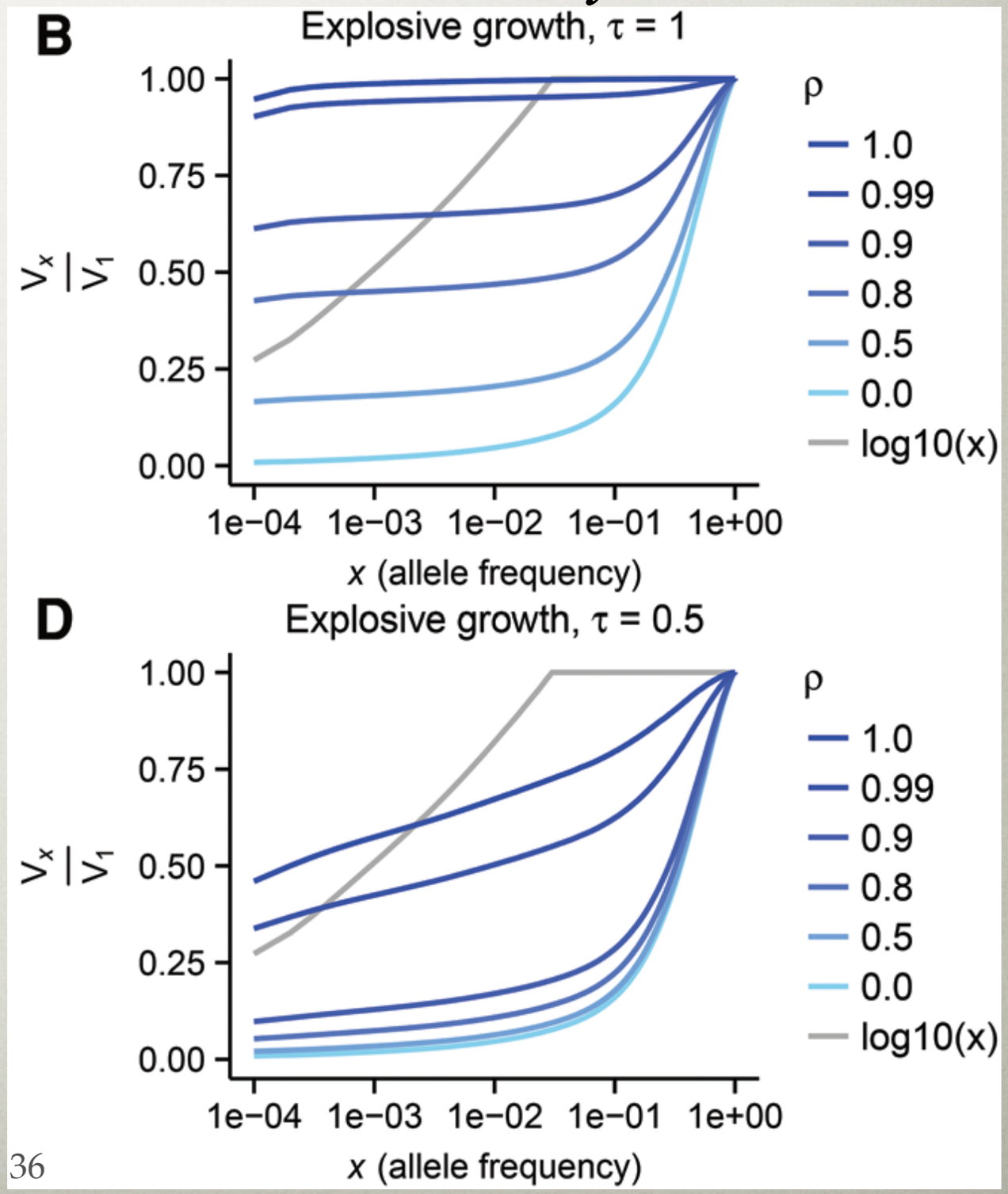
Data



Inference



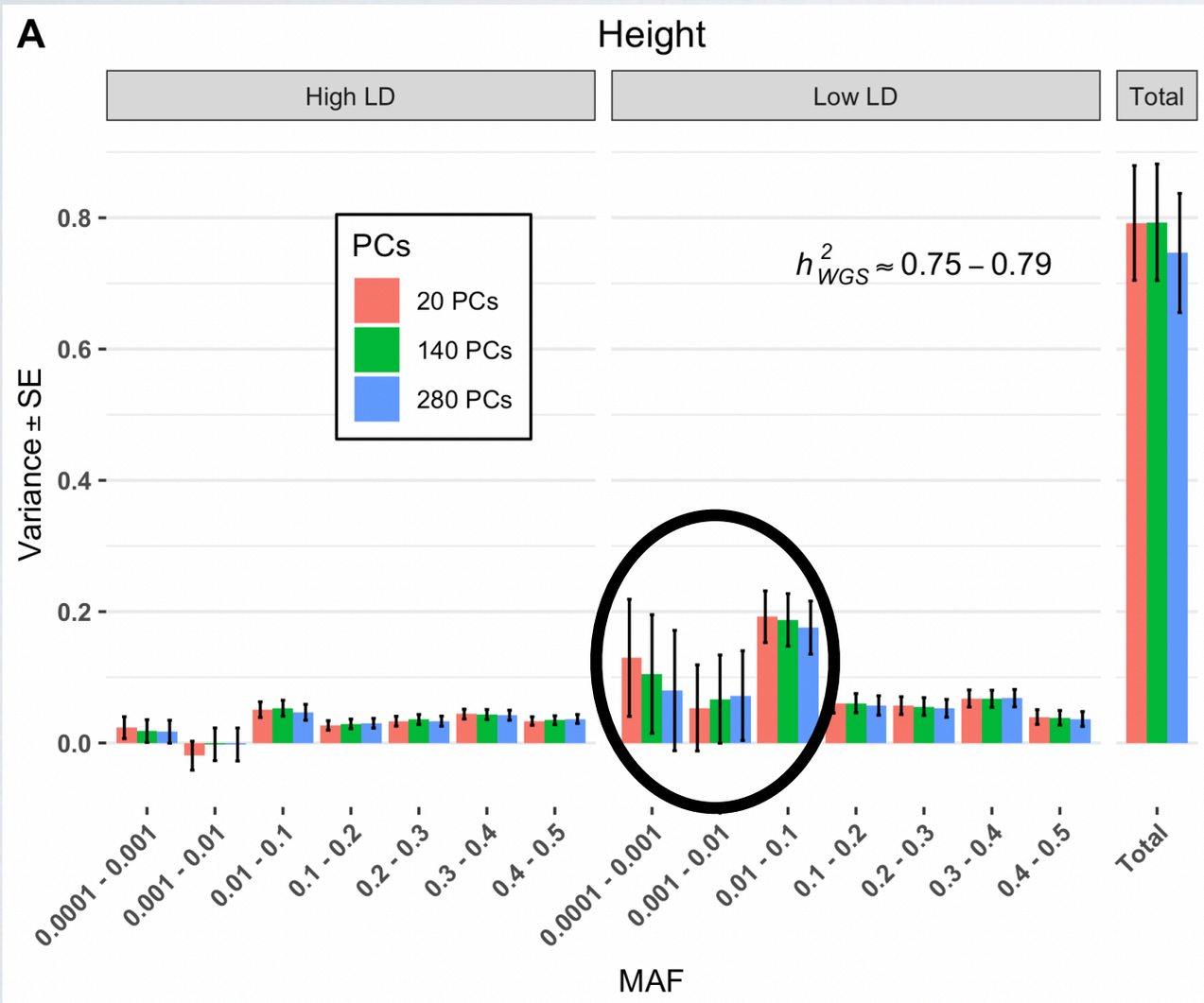
Theory

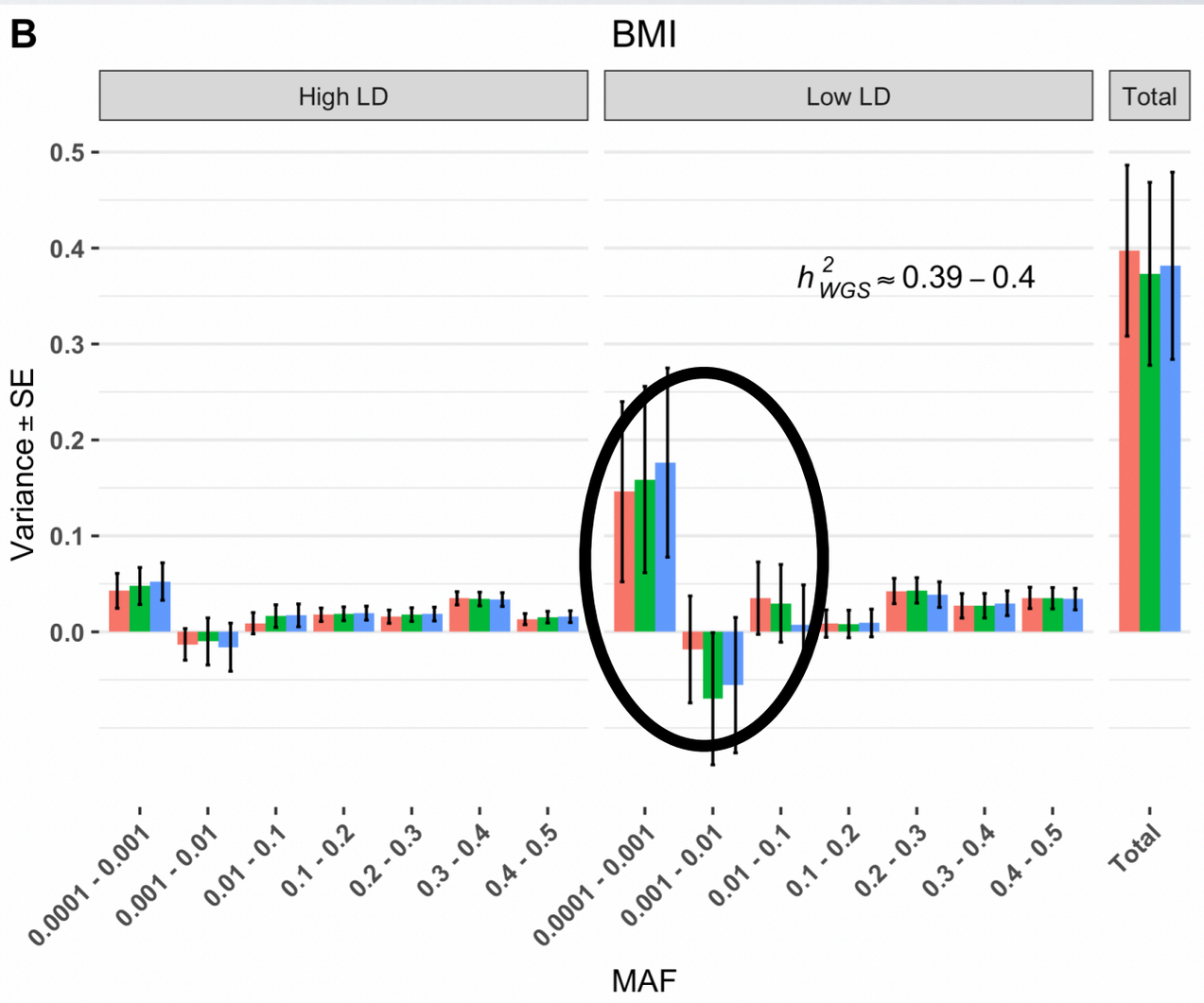


HUMAN HEIGHT AND BMI

n = 21,620 Individuals

Low MAF explains >50% of heritability





Wainschtein, et al. Recovery of trait heritability from whole genome sequence data. **bioRxiv**.

CONCLUSIONS

- Patterns of genetic variation within and between populations are shaped by their evolutionary history.
    - Demography: Growth/decline, migration/admixture
    - Natural selection
- These same evolutionary forces shape the genetic architecture of complex traits!
- Evolutionary forces that increase the incidence of rare variants, also increase the role of rare variants in complex traits!