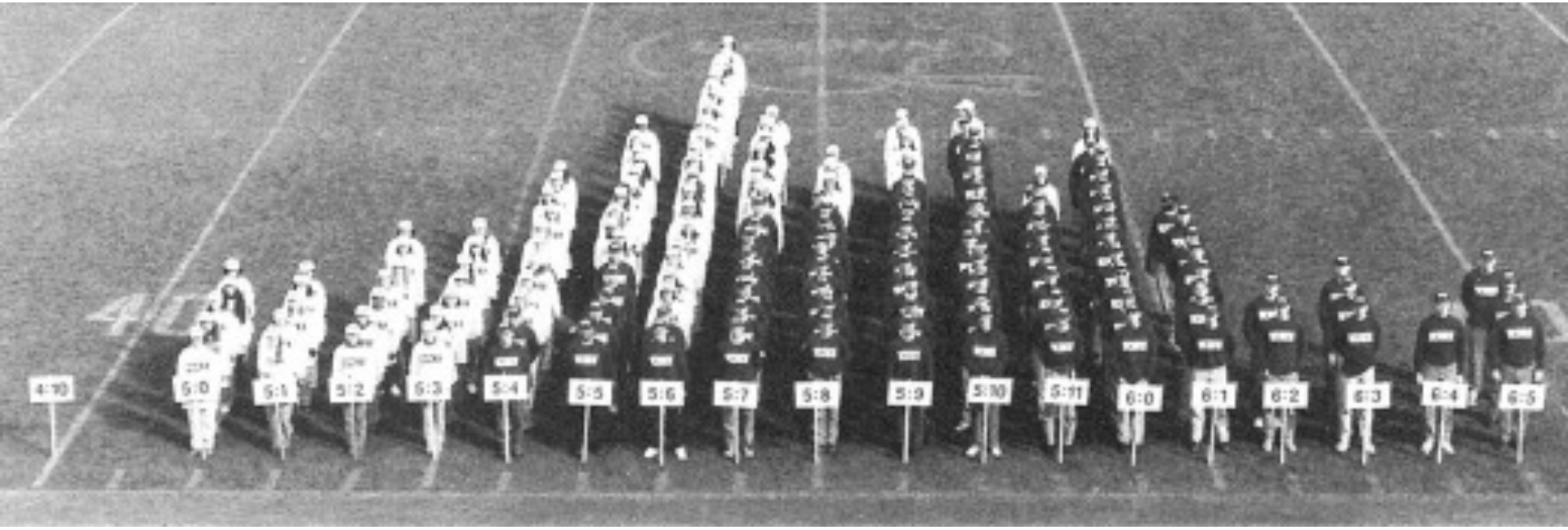
The population genetic underpinnings of missing heritability

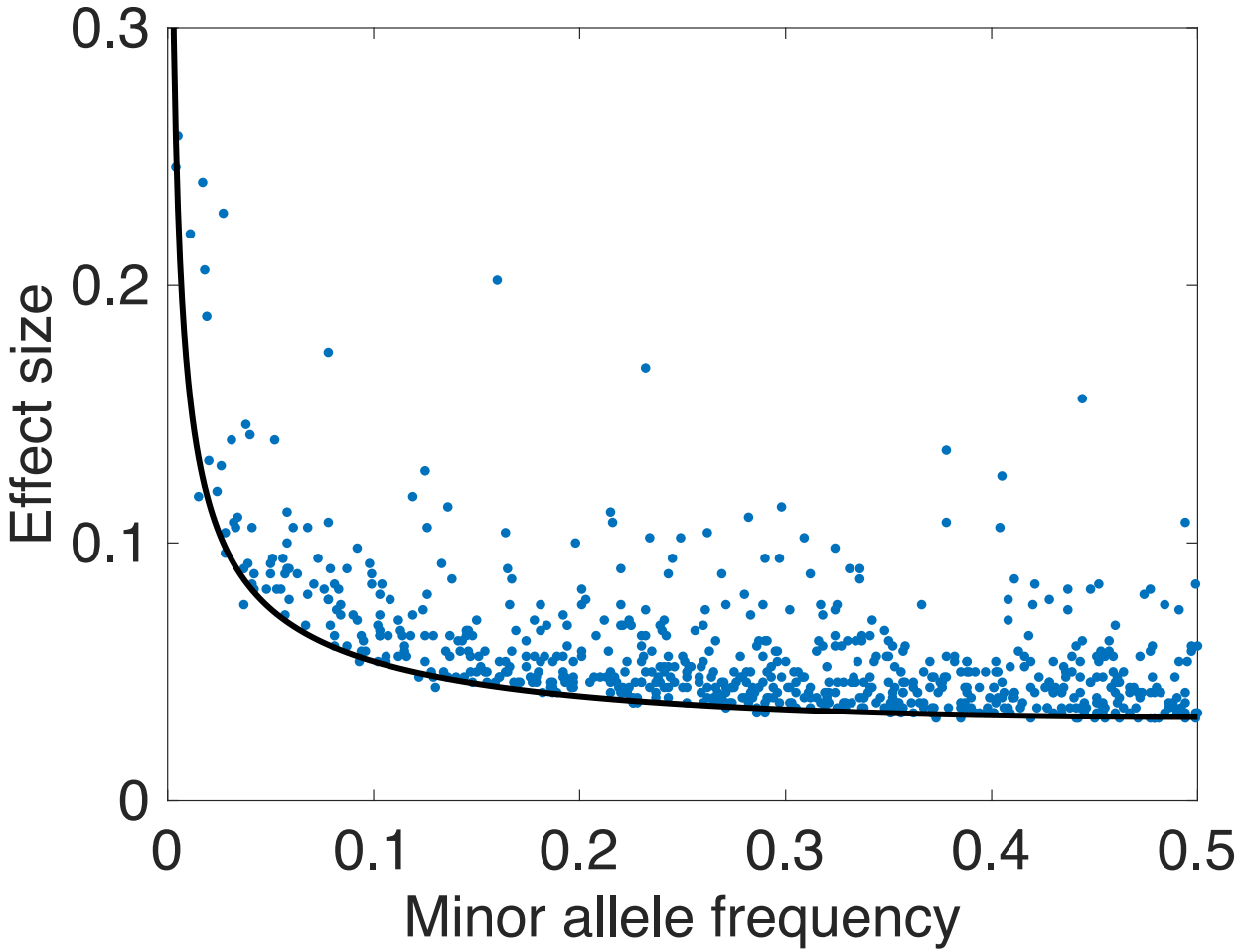


Yuval Simons

Guy Sella
Columbia University

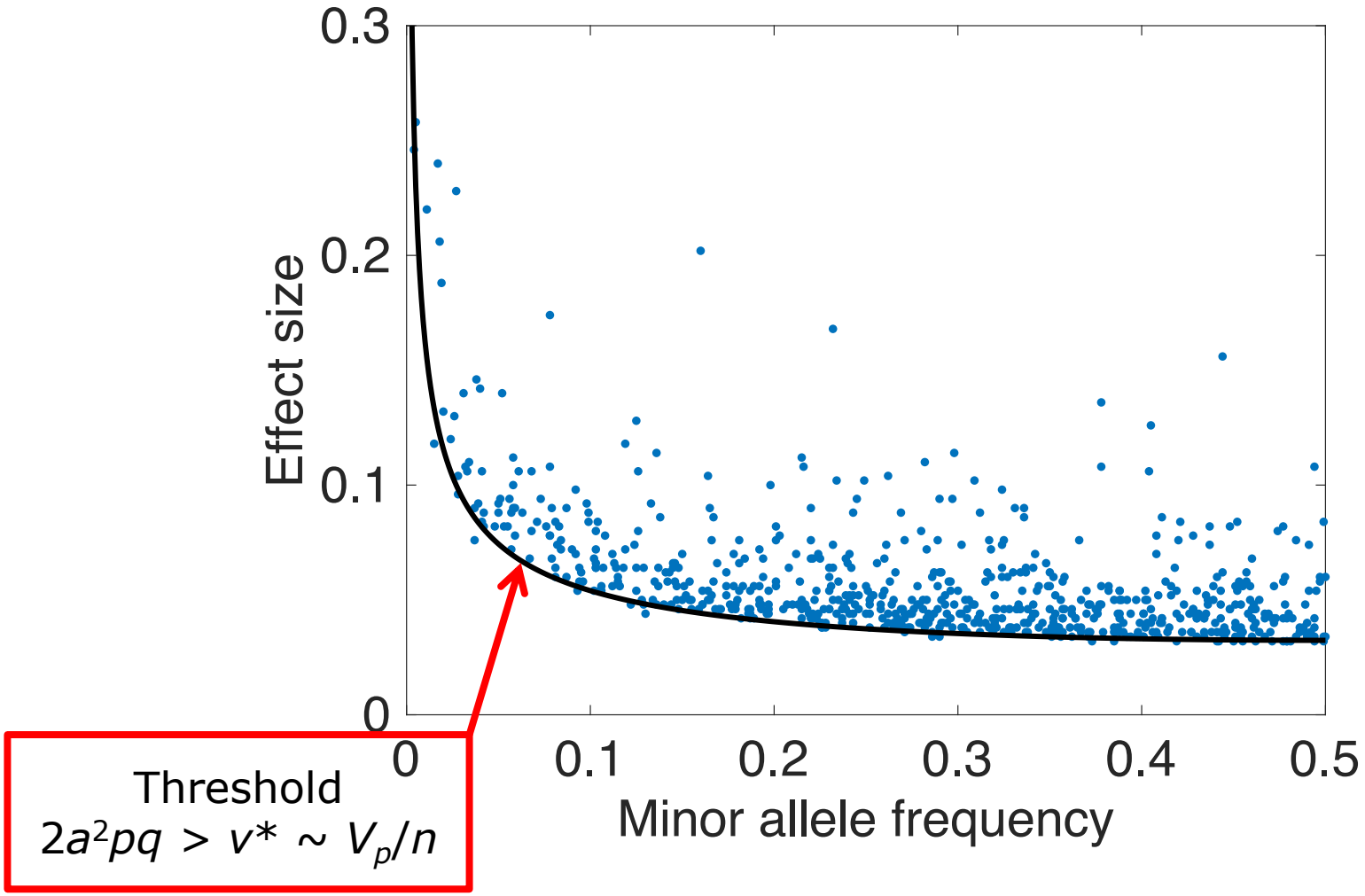
Jeremy Berg

Missing heritability is largely about genetic architecture



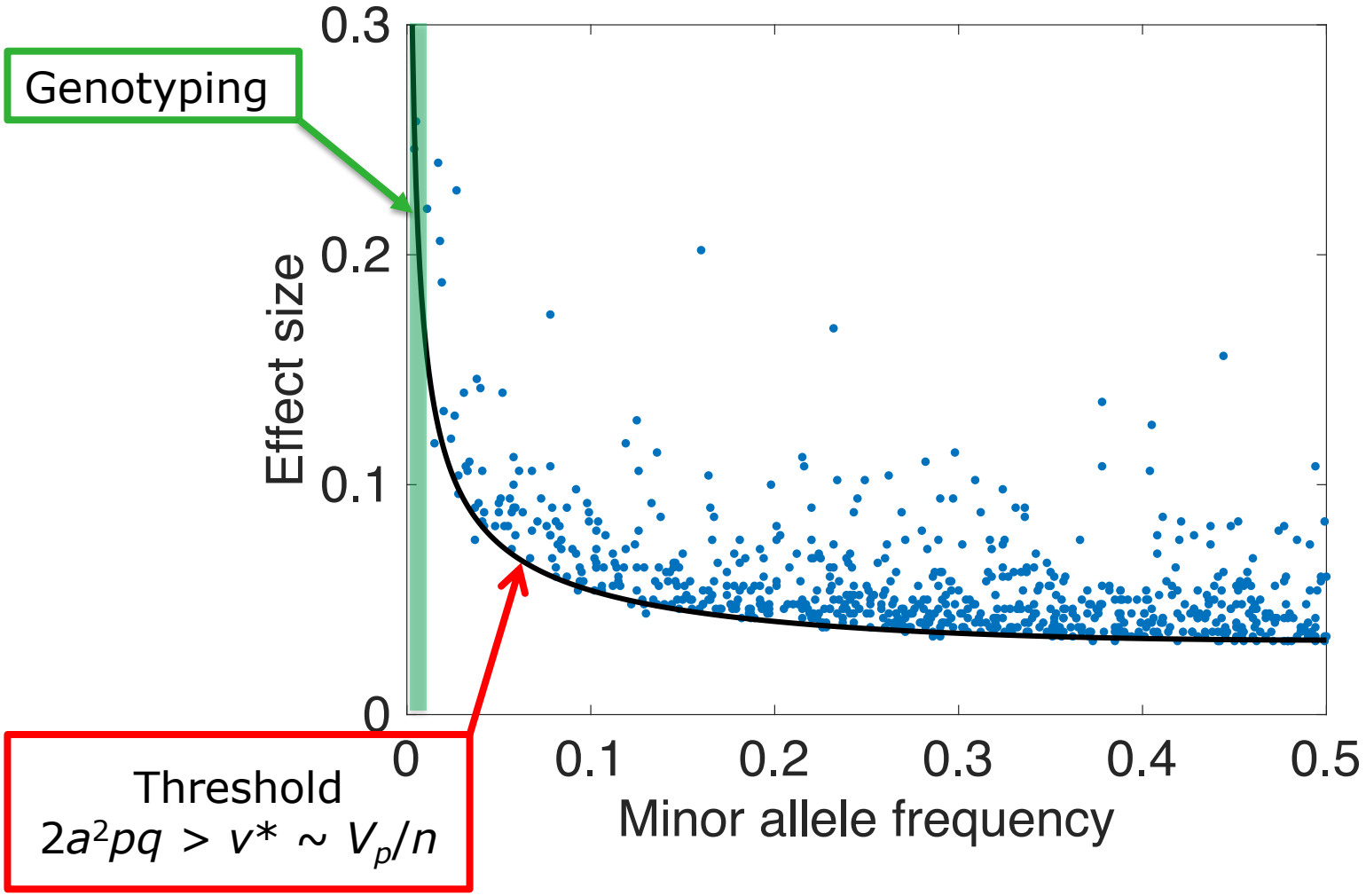
Data from Wood et al. 2014 Nat. Genetics

Missing heritability is largely about genetic architecture



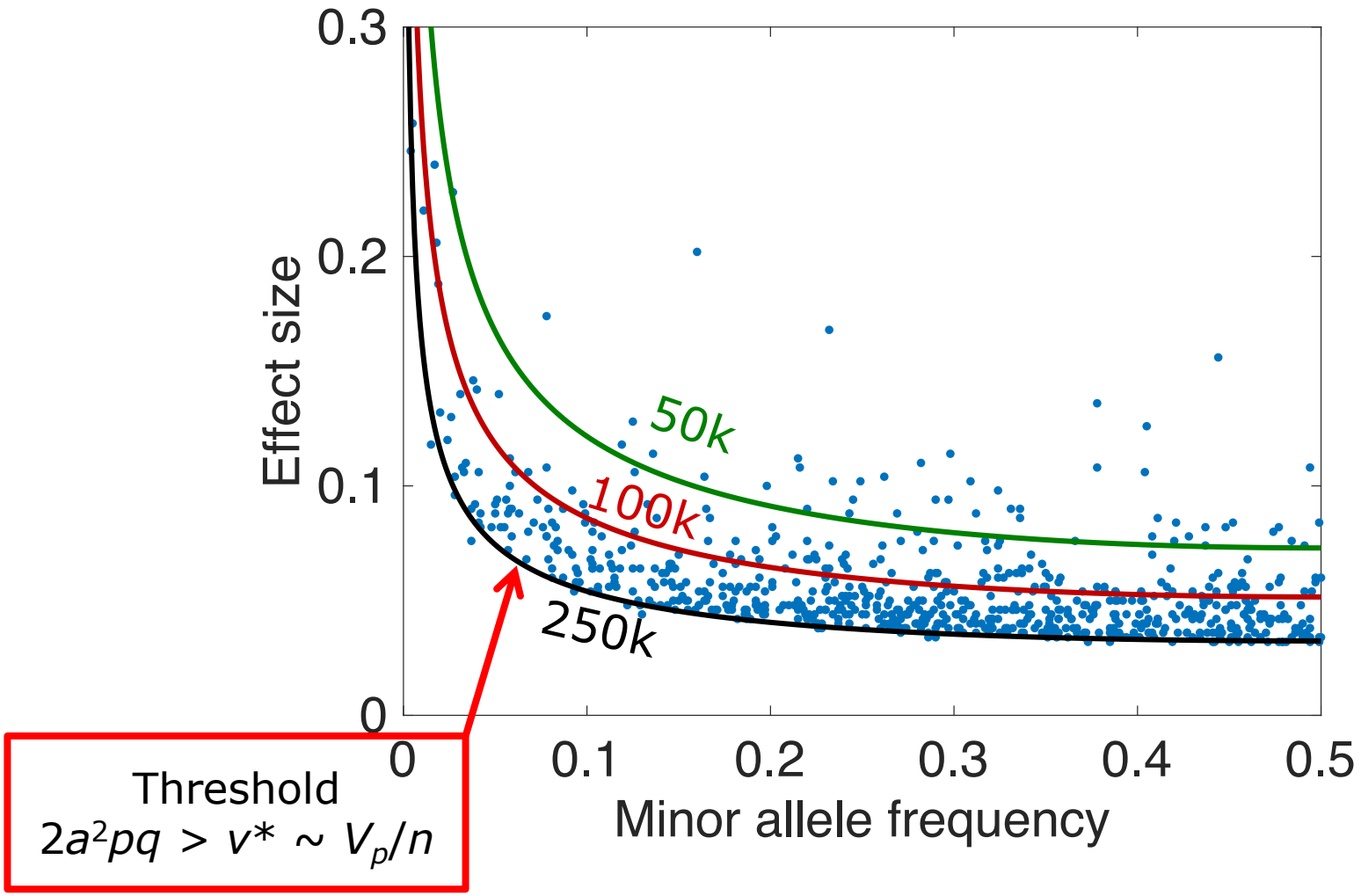
Data from Wood et al. 2014 Nat. Genetics

Missing heritability is largely about genetic architecture



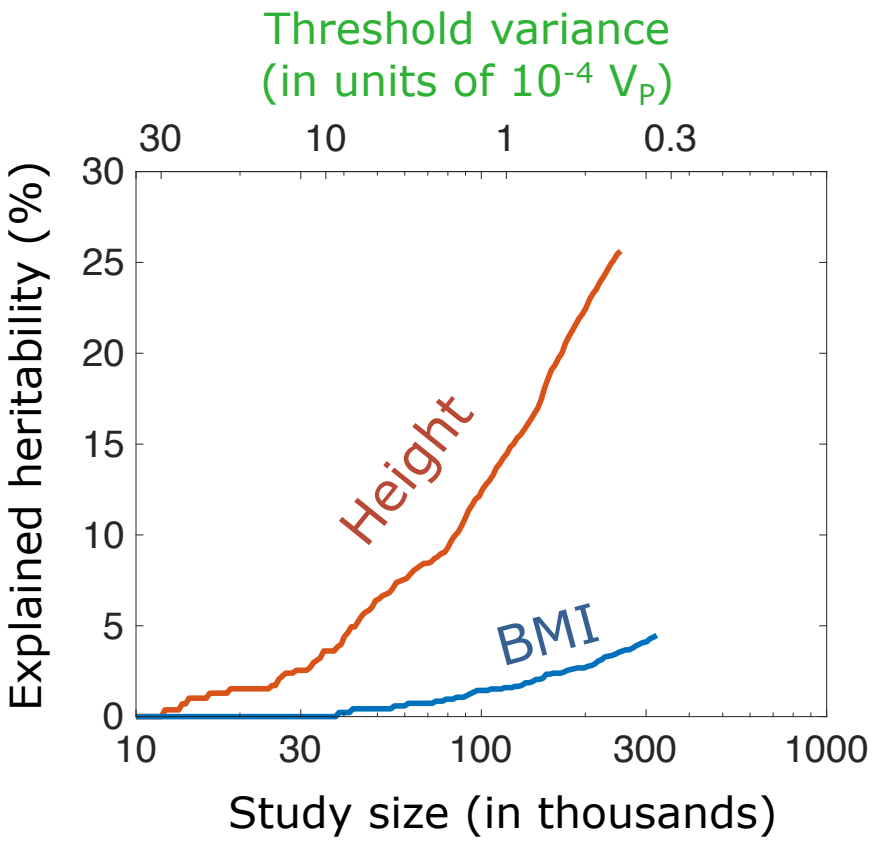
Data from Wood et al. 2014 Nat. Genetics

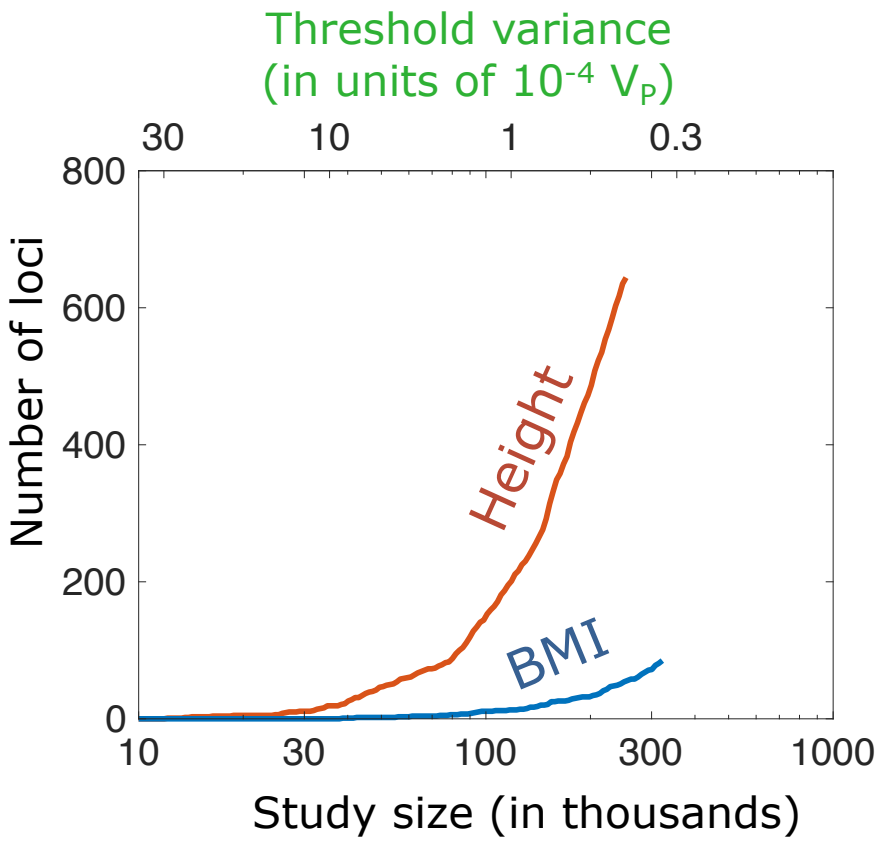
Missing heritability is largely about genetic architecture



Data from Wood et al. 2014 Nat. Genetics

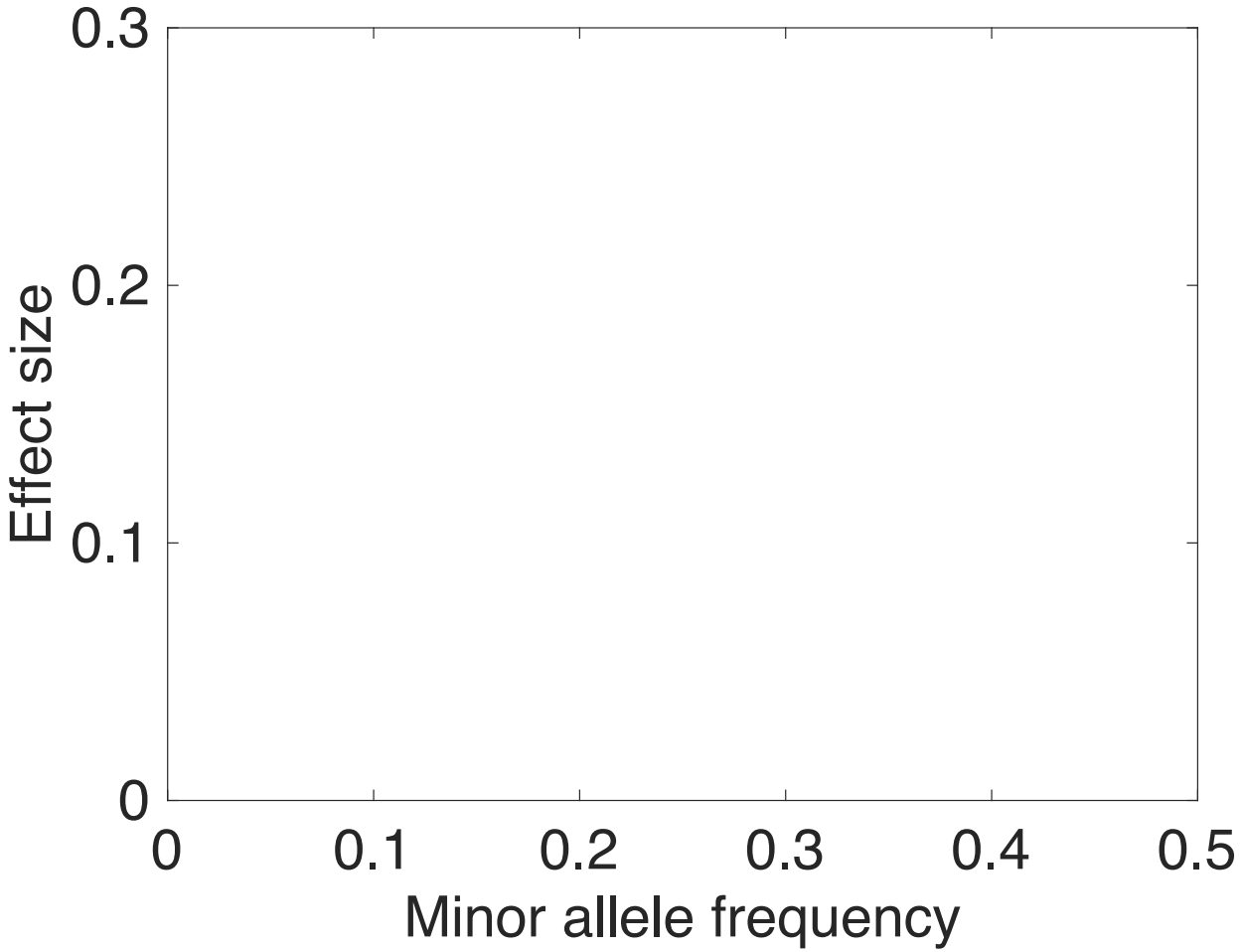
The distribution of variance among loci largely explains what we see in GWAS

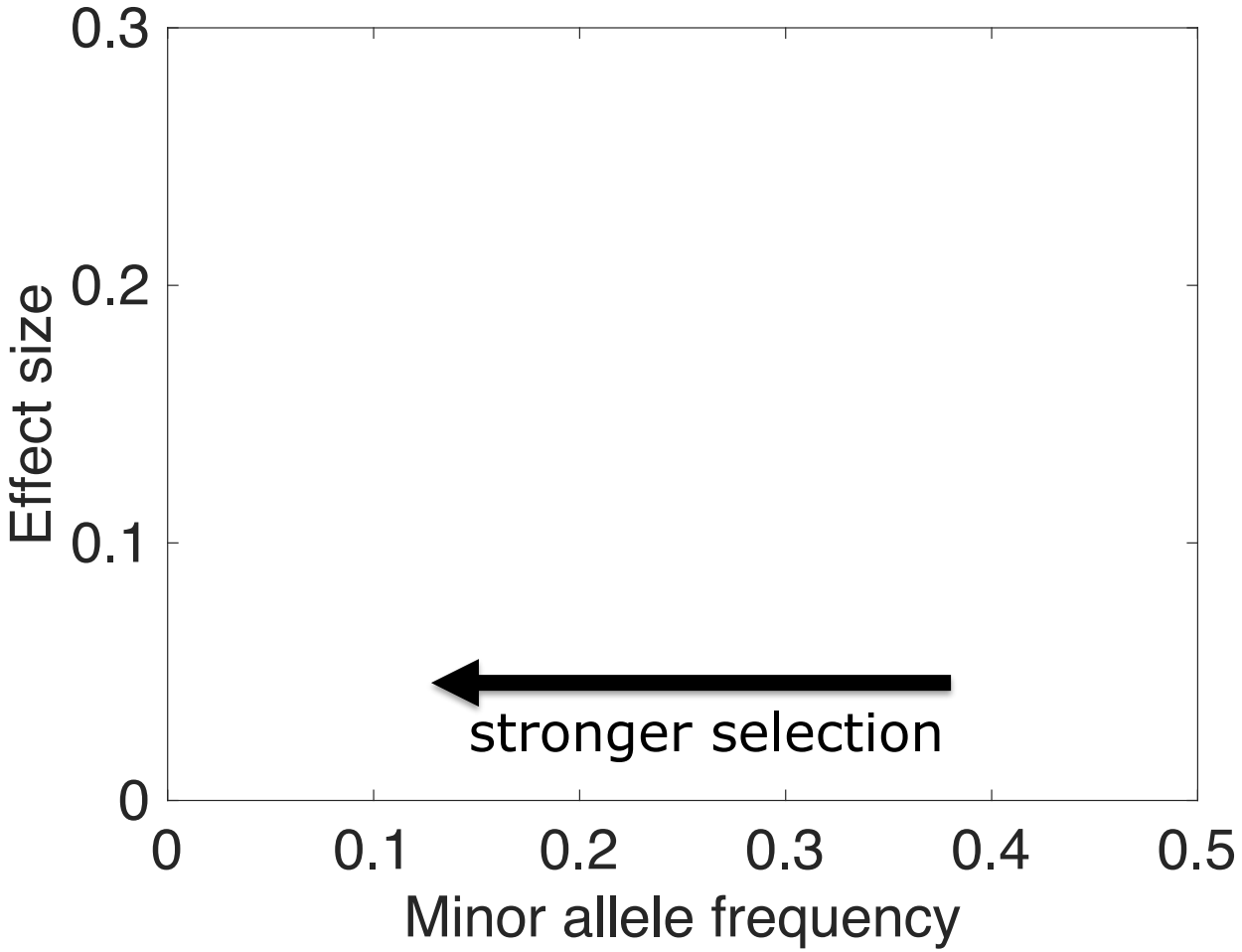




To understand missing heritability and why it differs among traits, we need to understand how architectures are shaped.

Data from Wood et al. 2014 Nat. Genetics & Locke et al. Nature 2014


0.3
0.2
0.1
0
Effect size
0
0.1
0.2
0.3
0.4
0.5
Minor allele frequency


0.3
0.2
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Effect size
stronger selection
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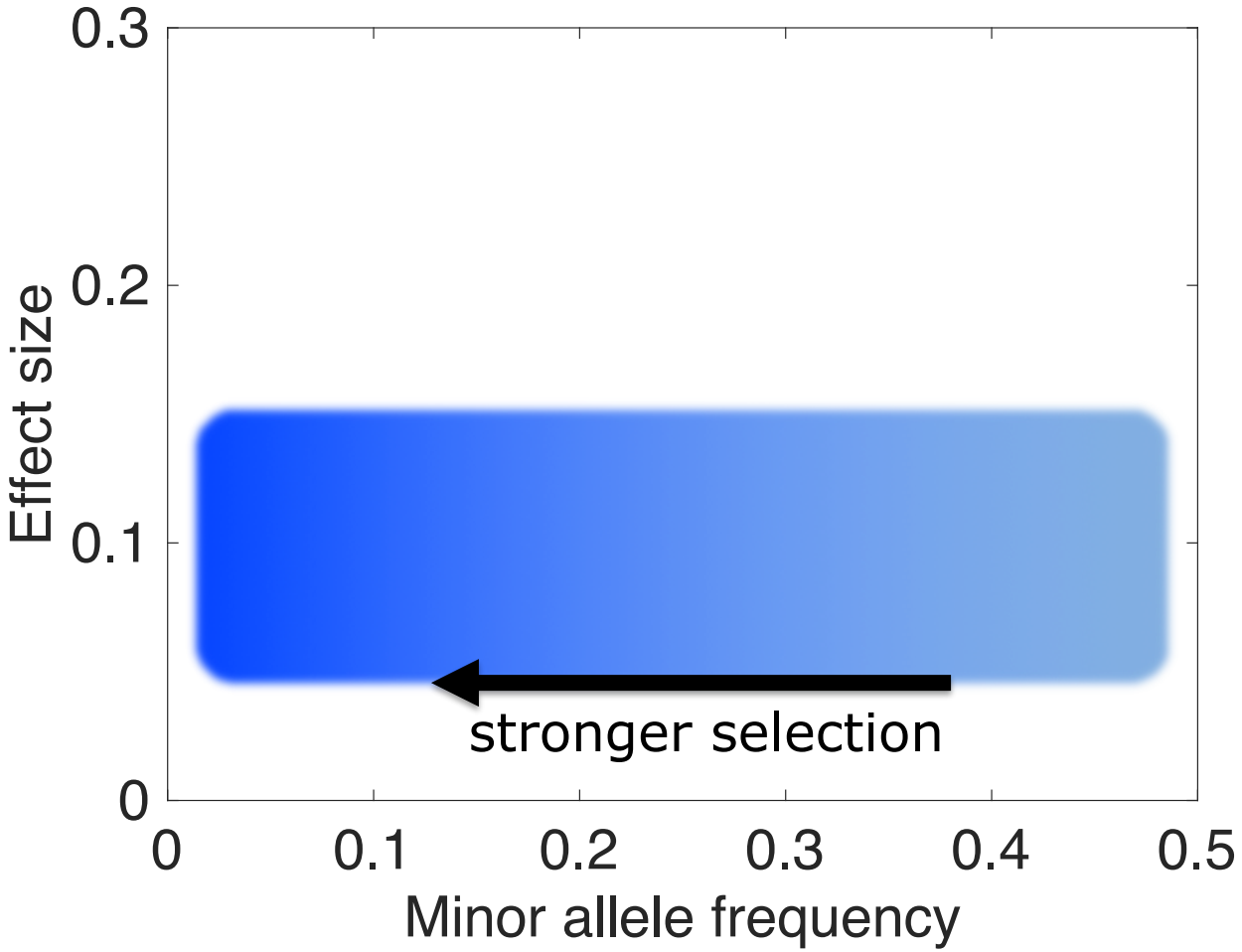
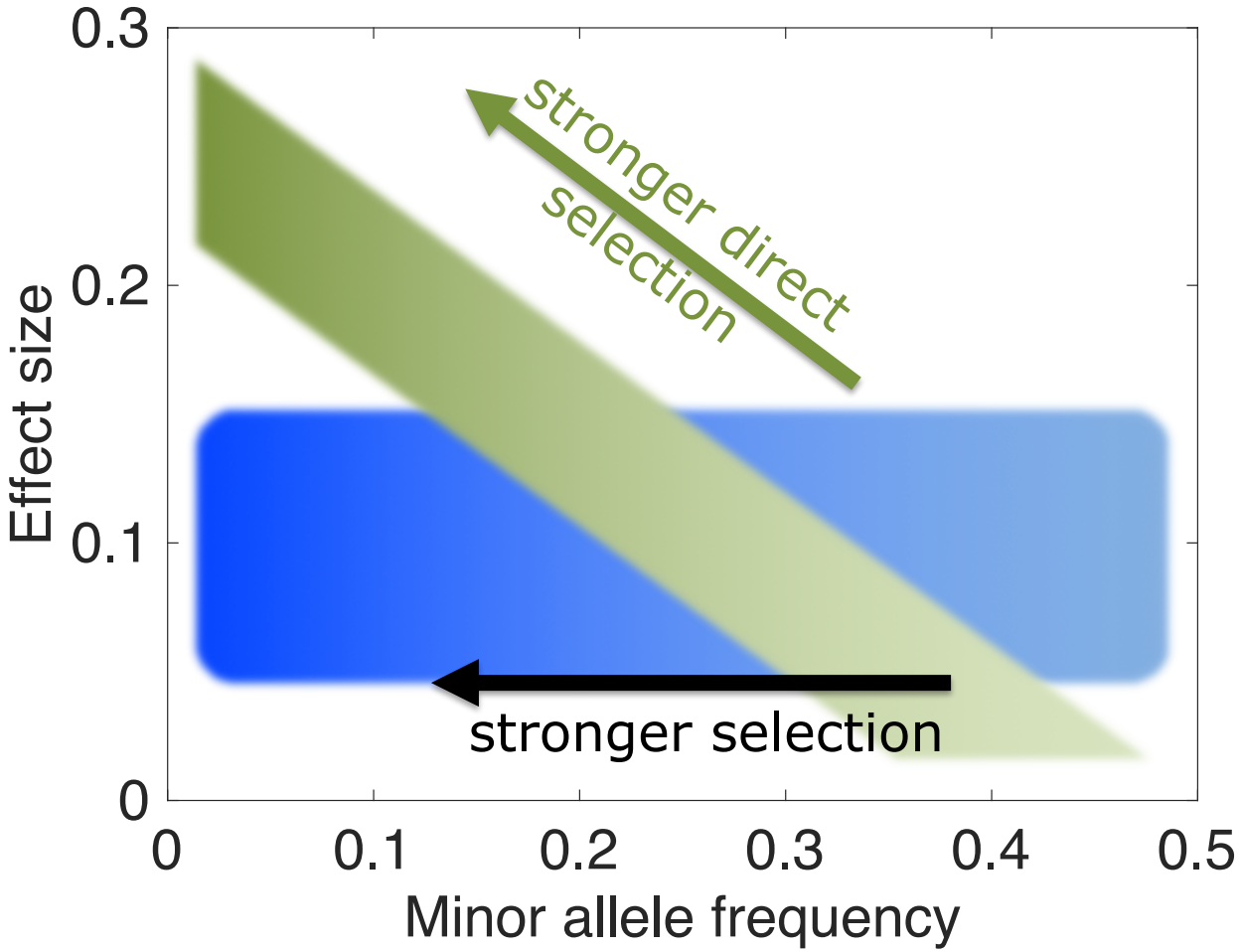
Minor allele frequency

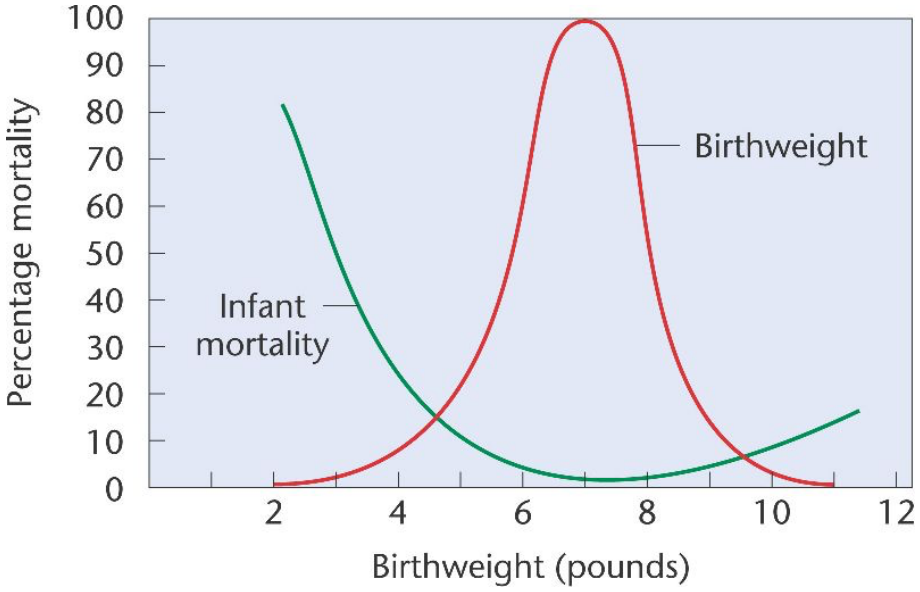

0.3
0.2
0.1
0
Effect size
stronger selection
0
0.1
0.2
0.3
0.4
0.5
Minor allele frequency

Direct and pleiotropic selection are key determinants of architecture



Some observations to guide modeling genetic architecture:

- Often under stabilizing selection.

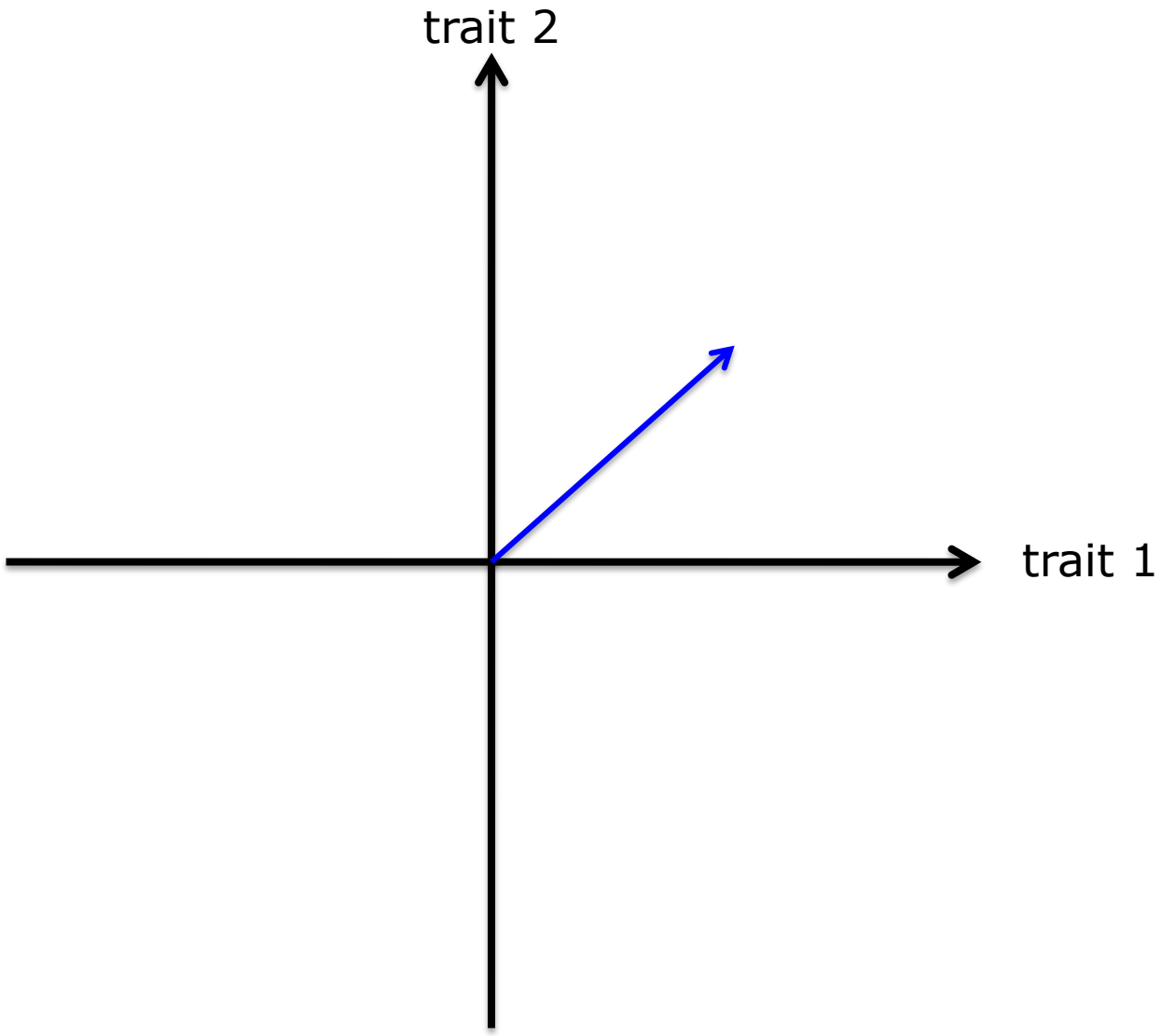


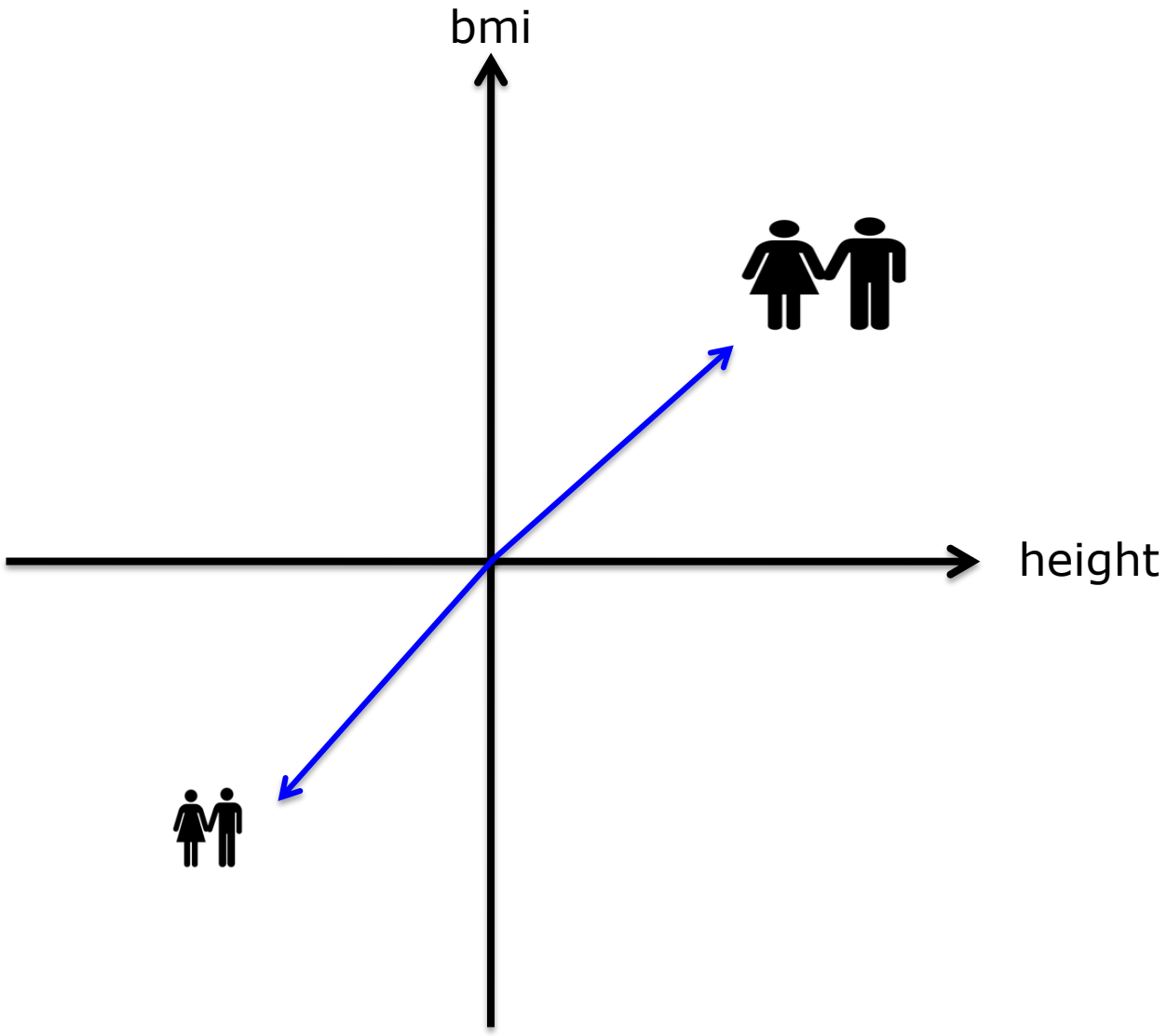
Some observations to guide modeling genetic architecture:

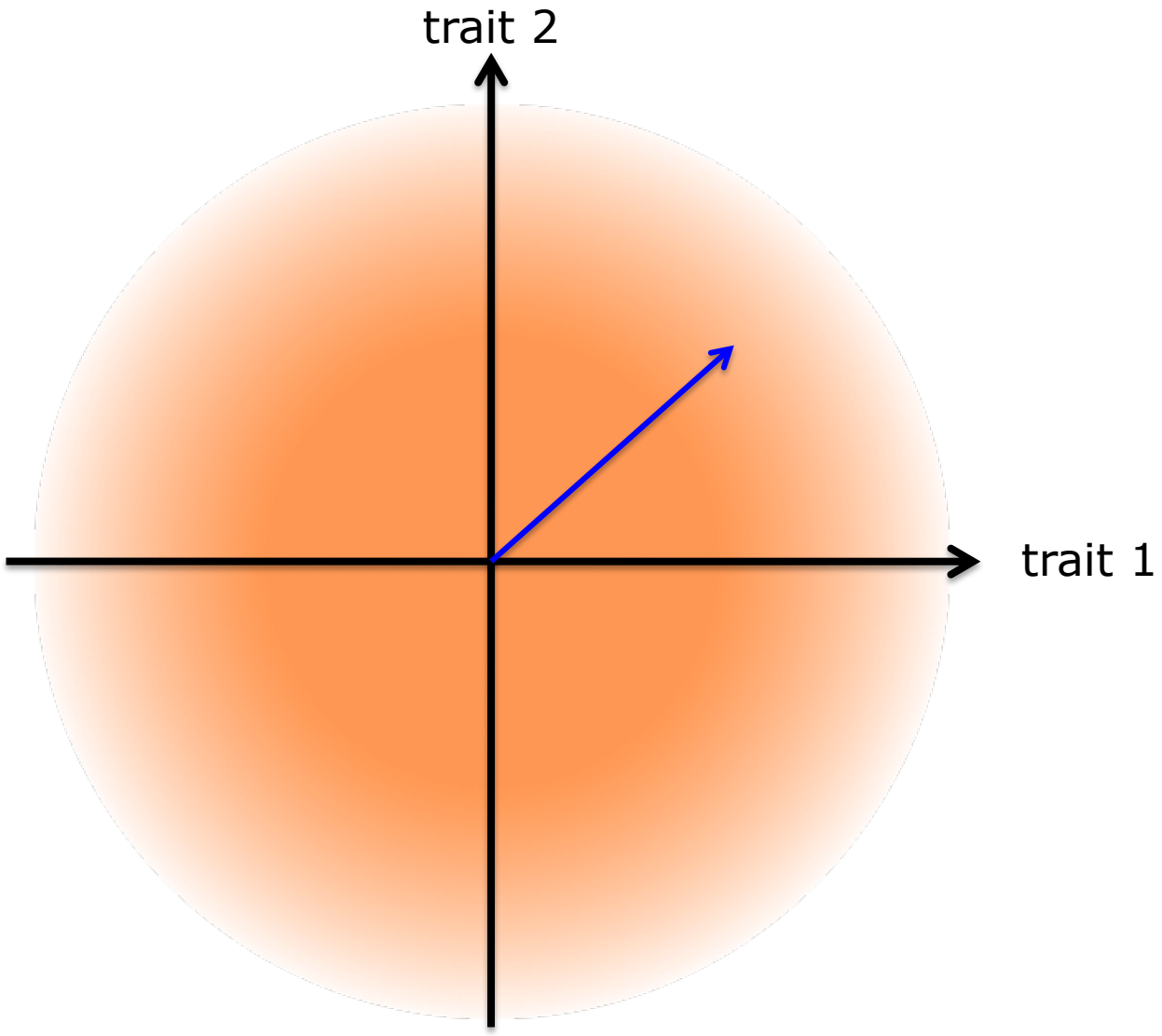
- Often under stabilizing selection.
- Often highly pleiotropic.

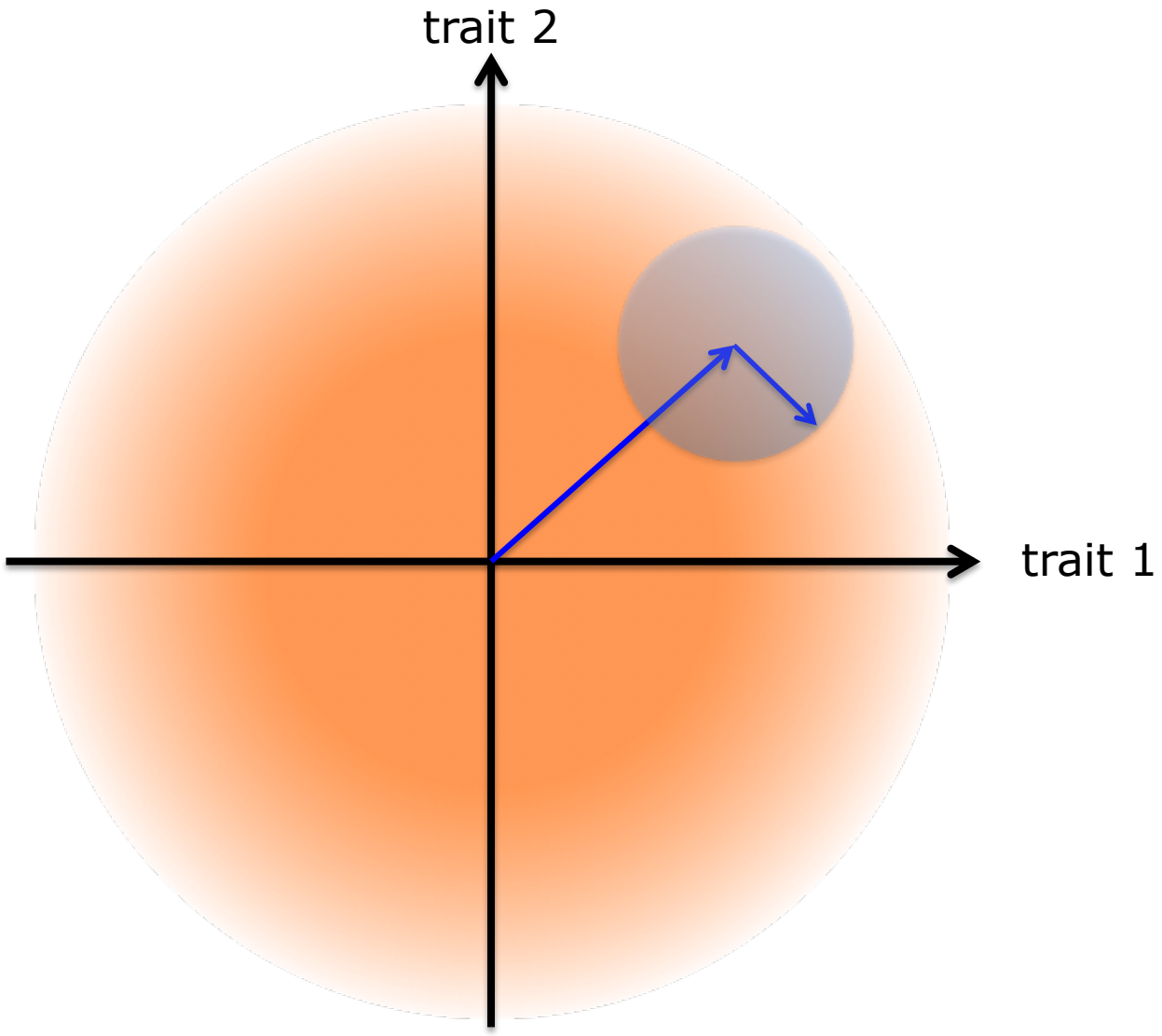
Some observations to guide modeling genetic architecture:

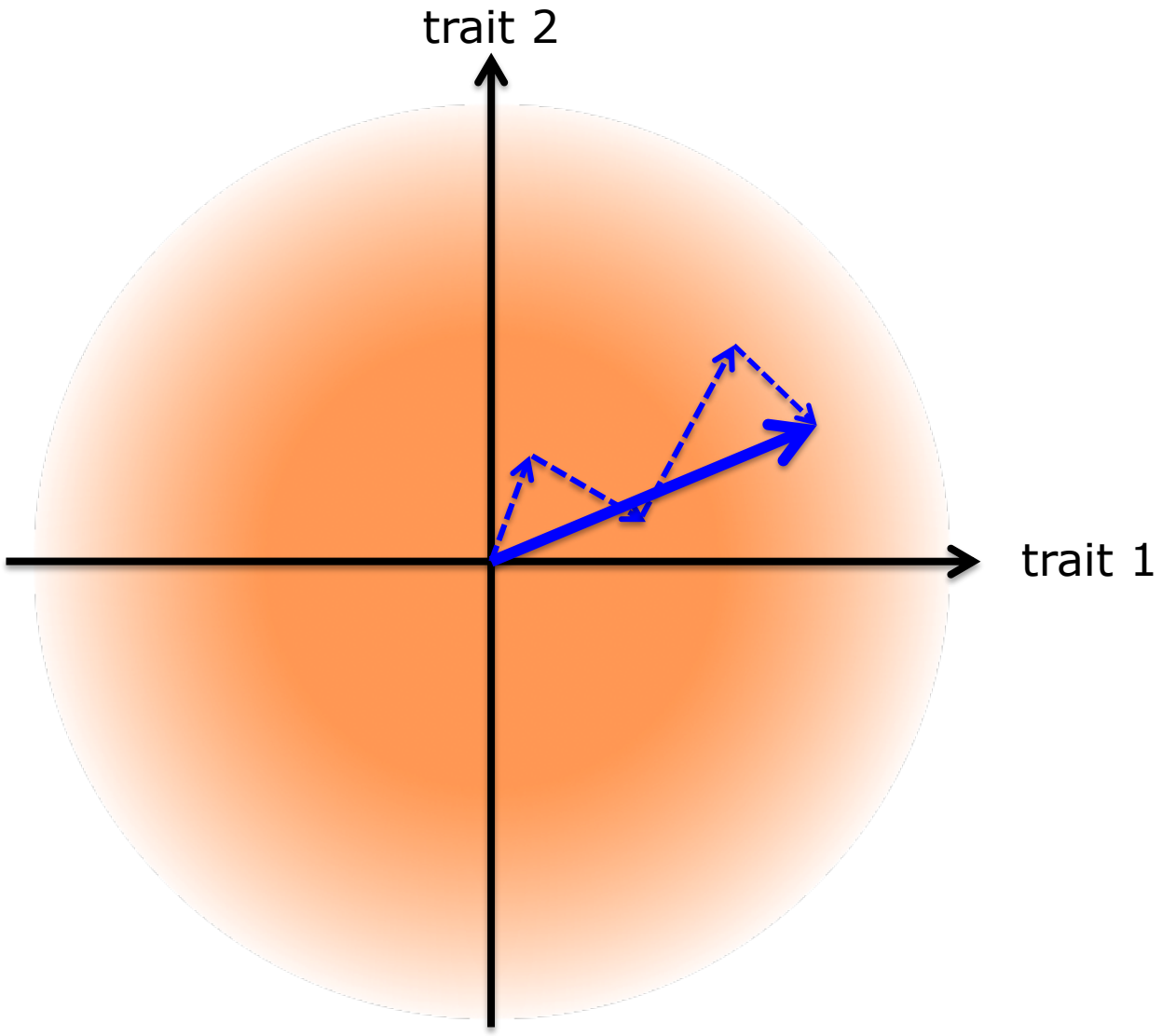
- Often under stabilizing selection.
- Often highly pleiotropic.
- Dominated by many loci of small additive effects.


trait 2
trait 1

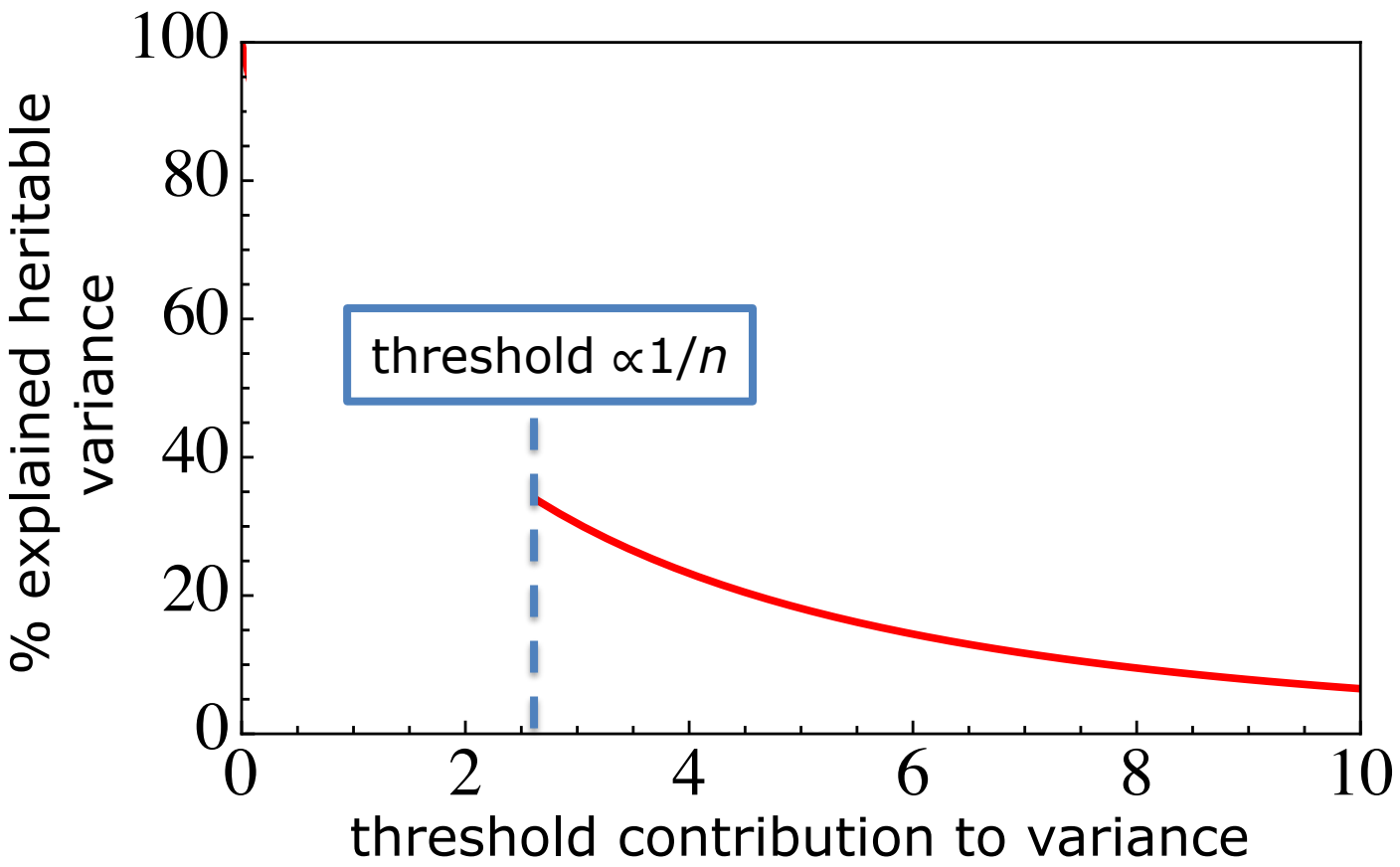

bmi
height


trait 2
trait 1

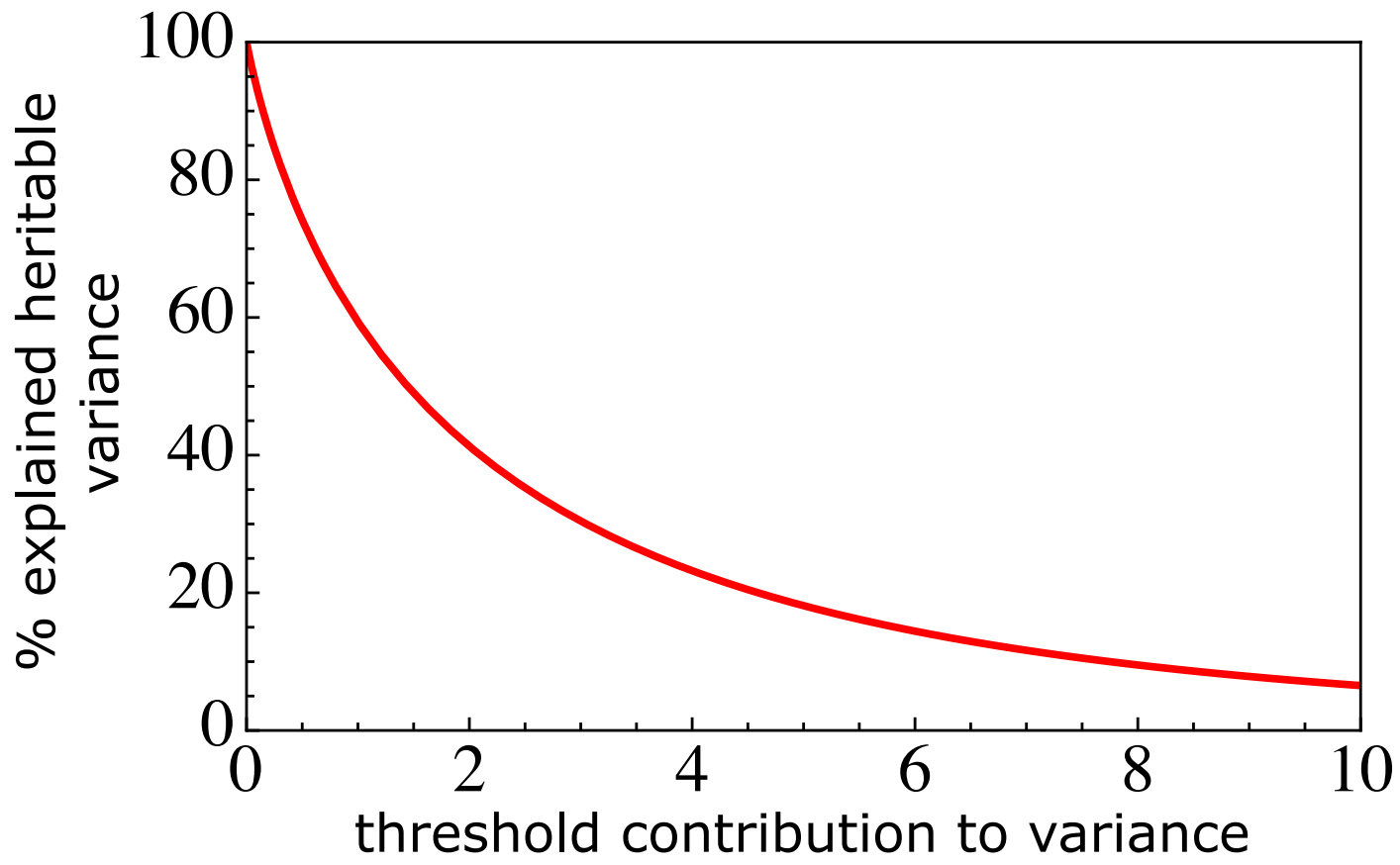

trait 2
trait 1


trait 2
trait 1

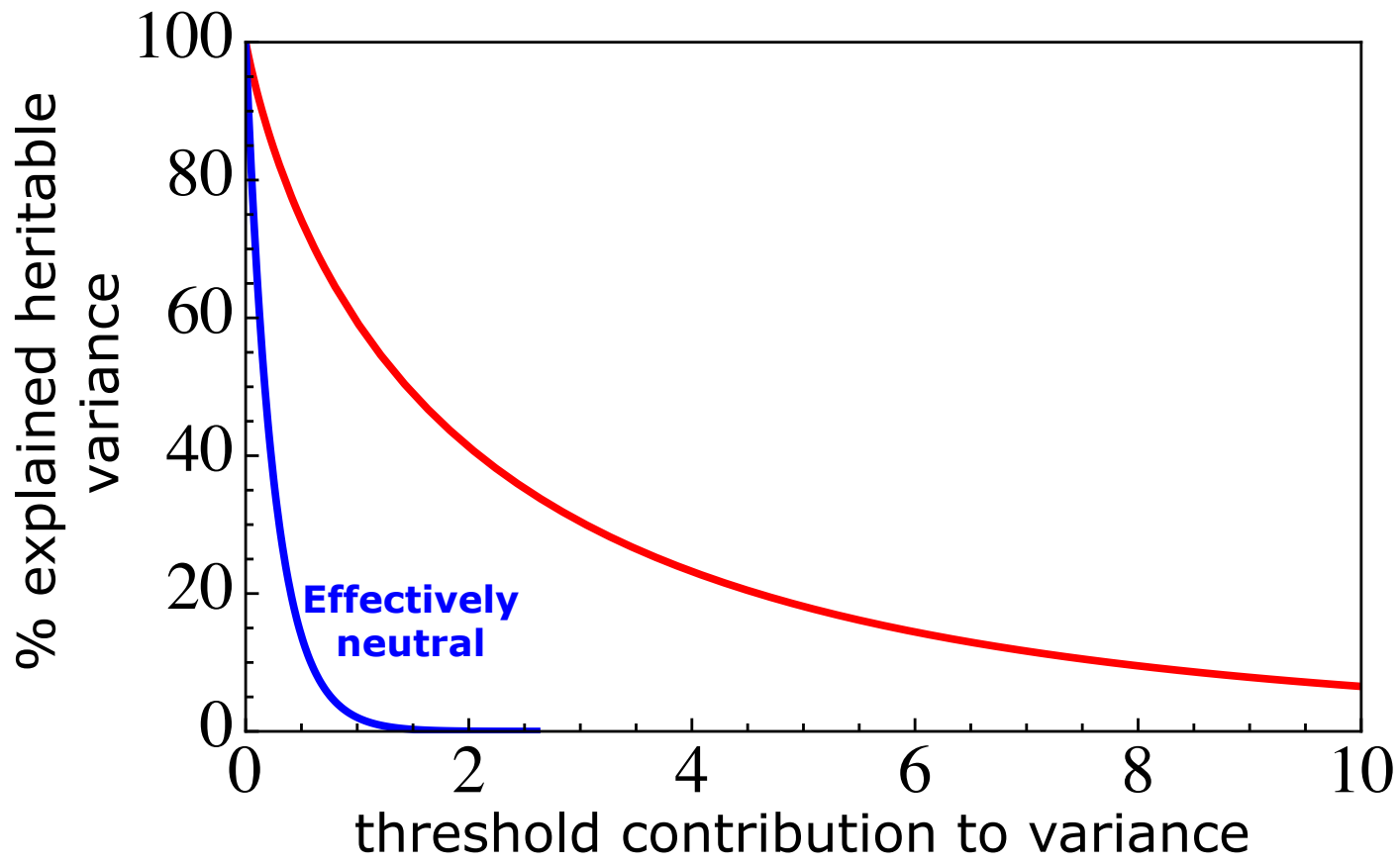
Connecting the model with GWAS



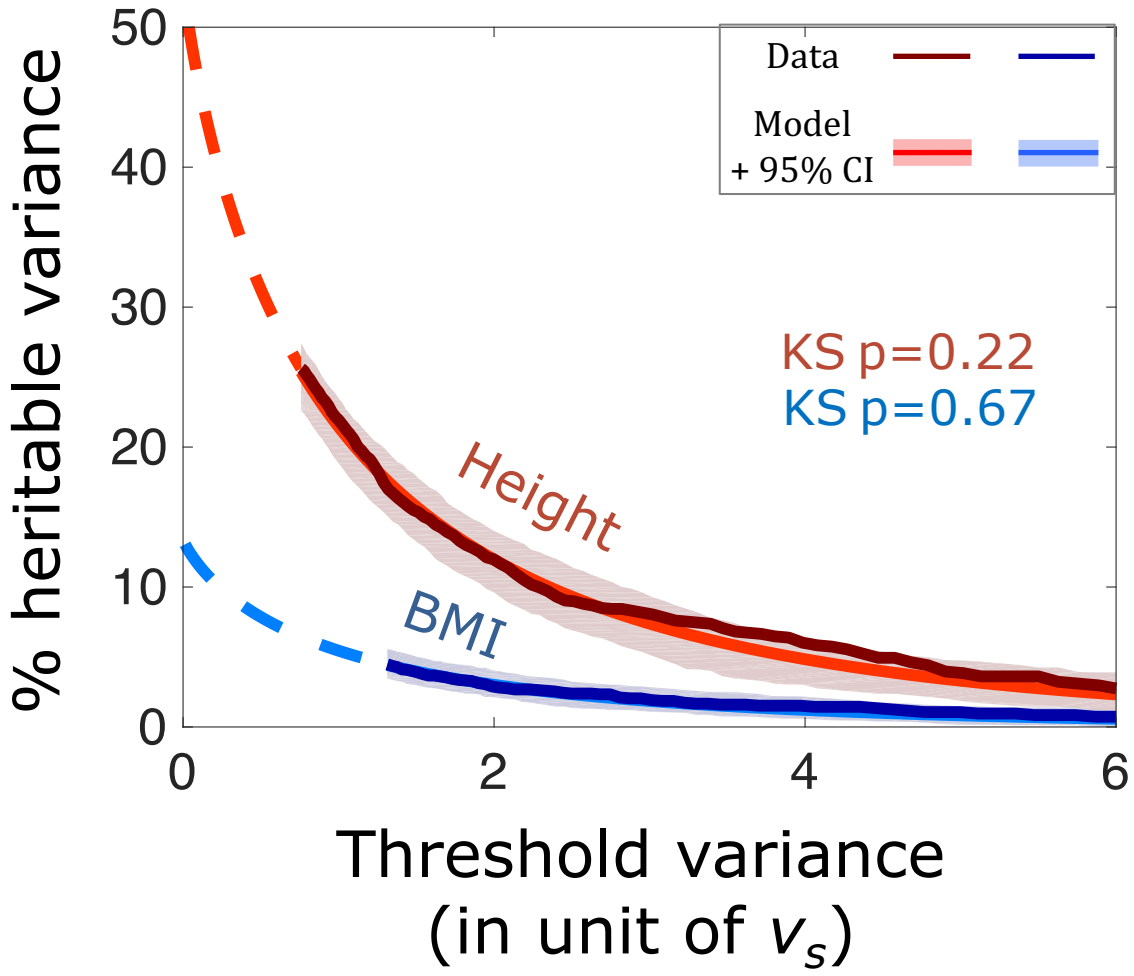
A simple distribution of genetic variances among loci



A simple distribution of genetic variances among loci

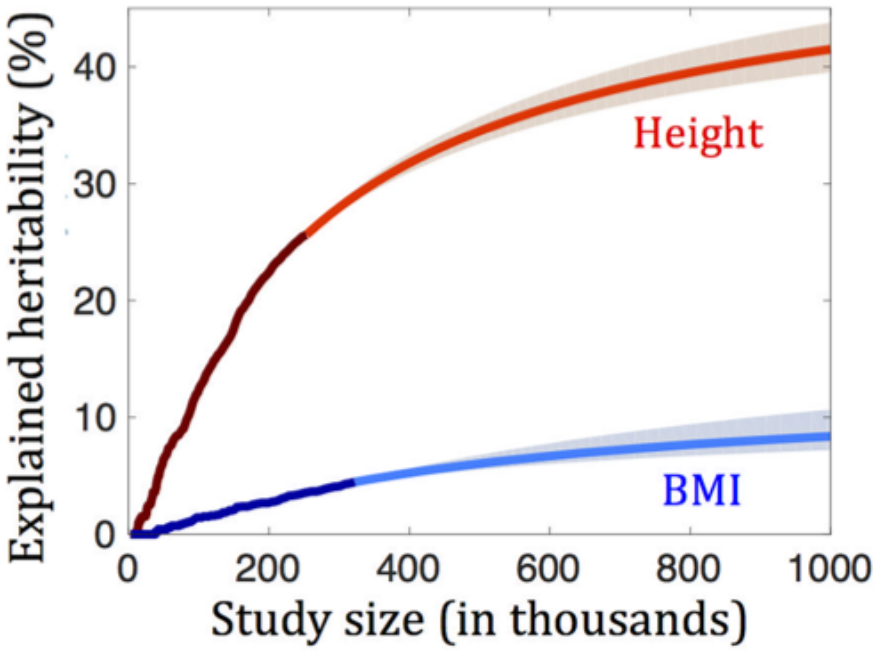


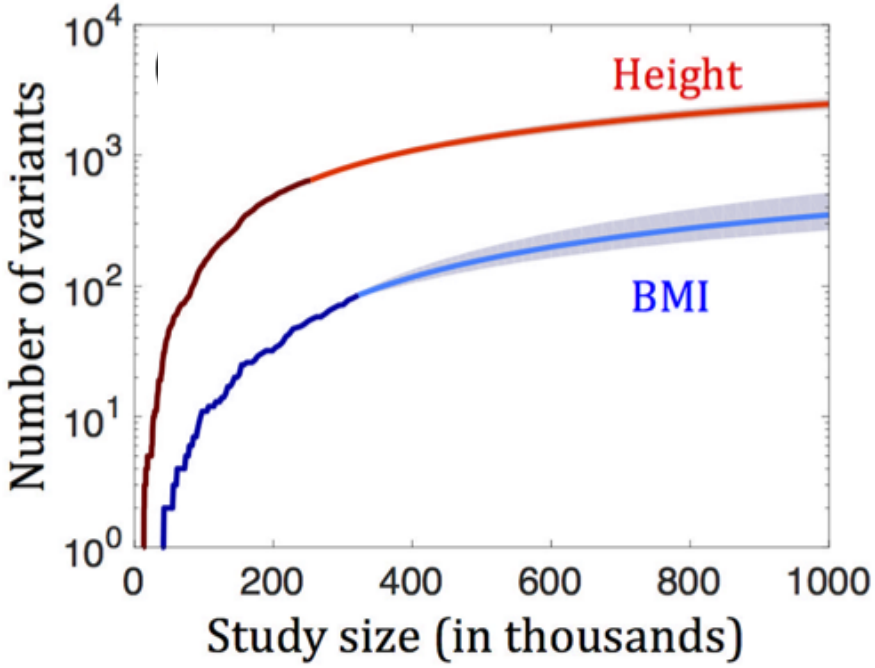
The theory fits the data

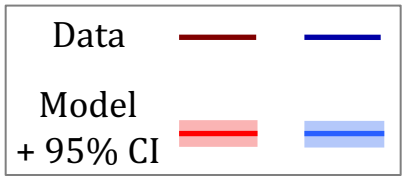


Data from Wood et al. 2014 Nat. Genetics & Locke et al. Nature 2014

Predictions for future GWAS

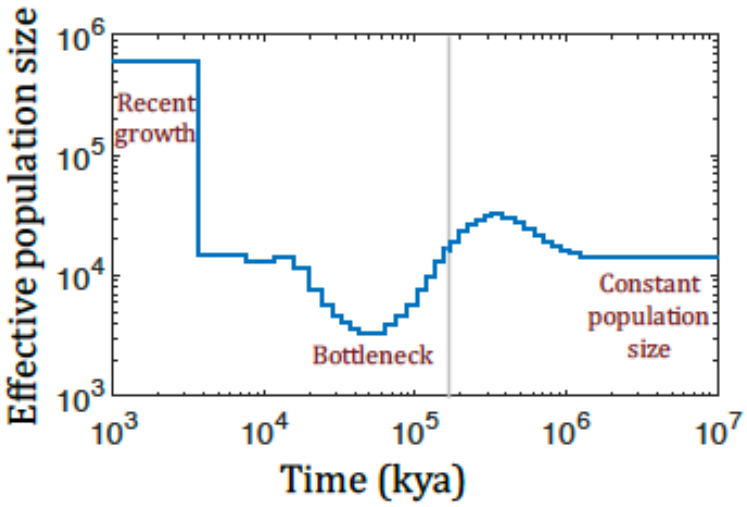




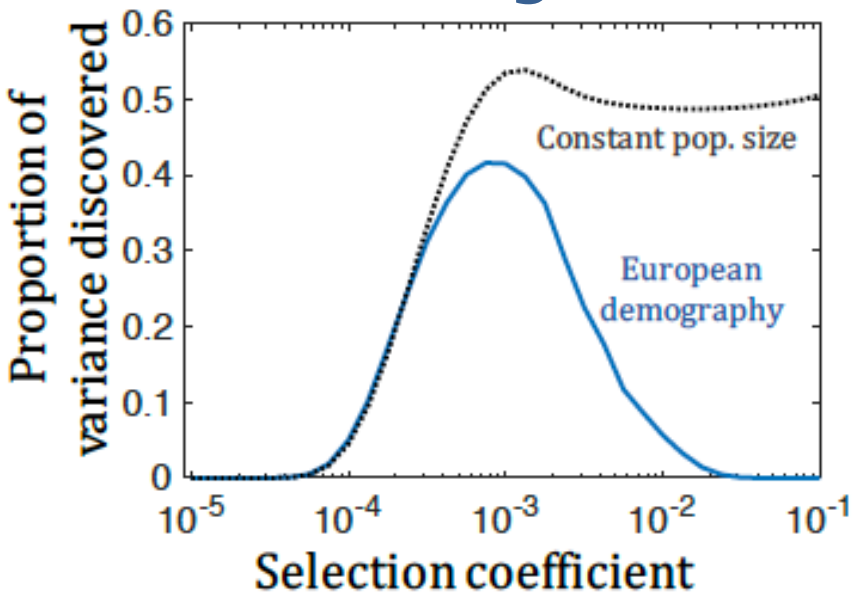


Simons et al. PLoS Biology 2018

Demographic history affects the range of selection effects seen in GWAS



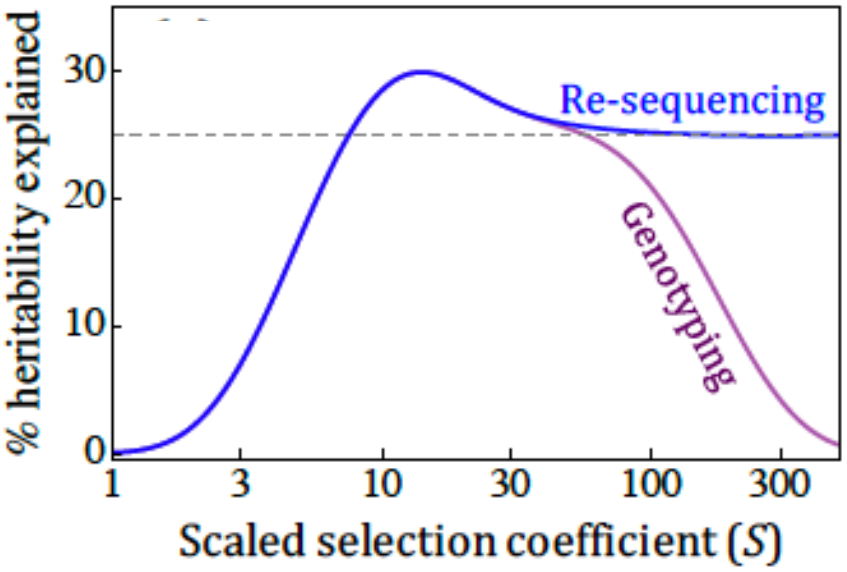
height



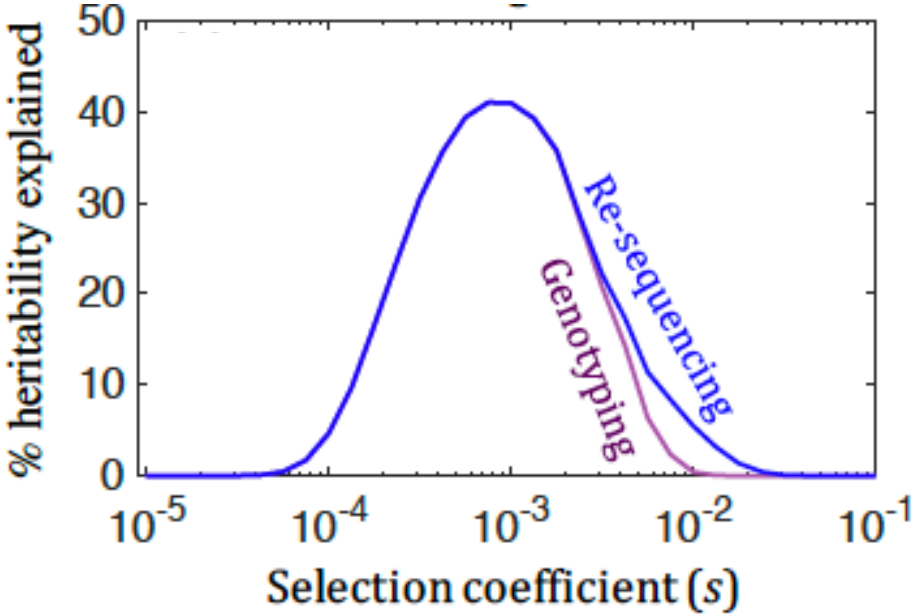
from Schiffles & Durbin Nat Genet 2014

Genotyping effects on missing heritability

Constant population size

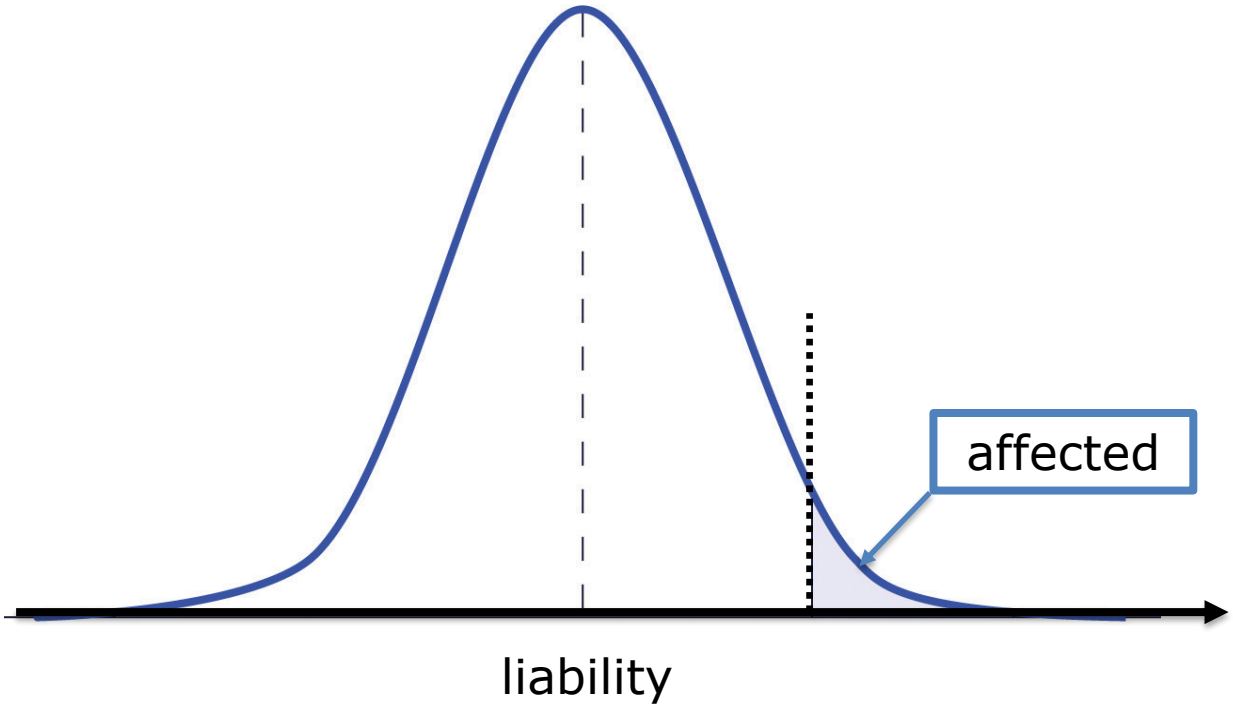


European demography



Parameters adjusted for the GWAS of height

Some complex diseases may be subject to directional (purifying) selection



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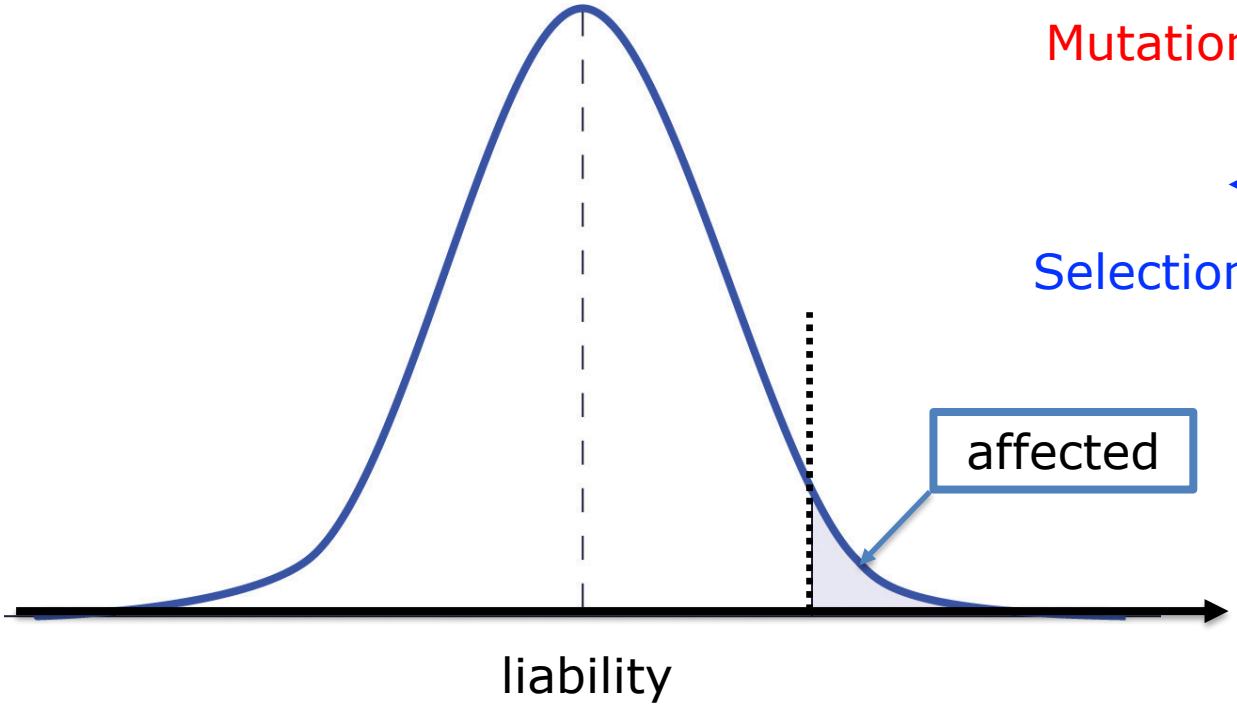
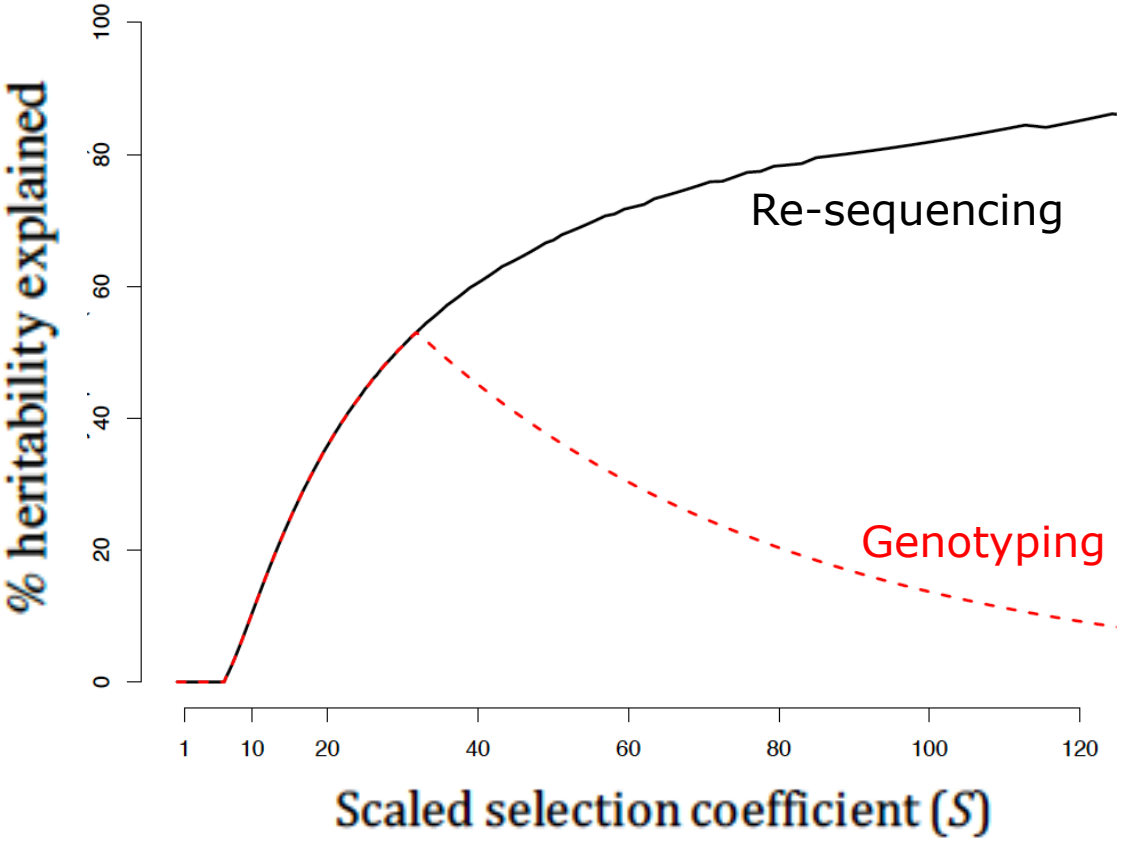


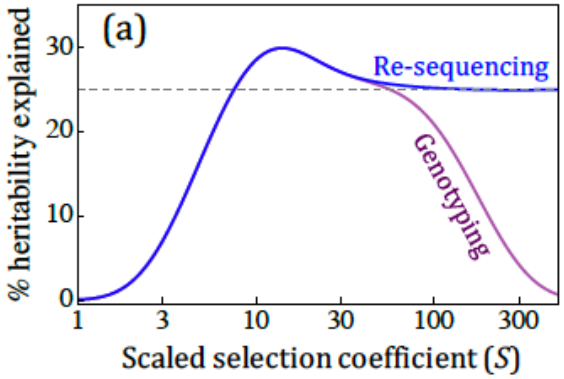
Mutation increases liability (ΔU)

Selection (on disease) decreases liability (ΔS)

Polygenic mutation-selection-drift balance (MSDB)

Missing heritability differs markedly under MSDB and stabilizing selection





Parameters adjusted (roughly) for Schizophrenia

Moving forward

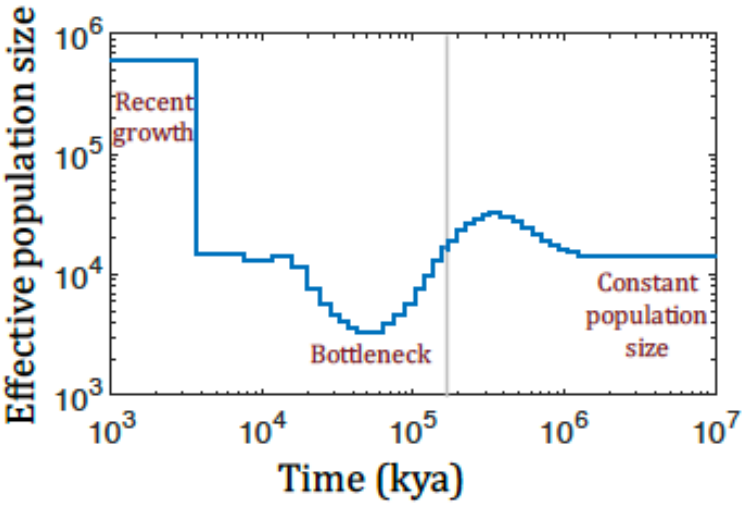
- Understanding how evolution shapes architecture helps explain missing heritability.
- Improving inferences about traits specific evolutionary forces and parameters should allow better predictions and inform study design.

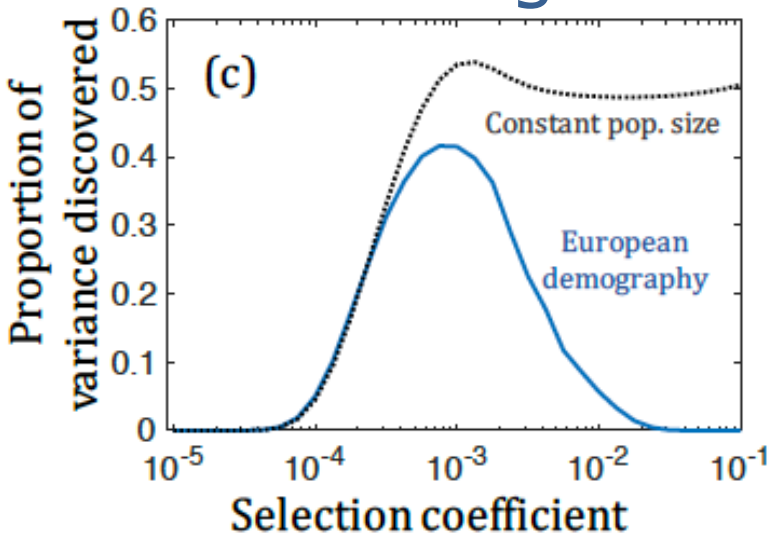
Yuval Simons

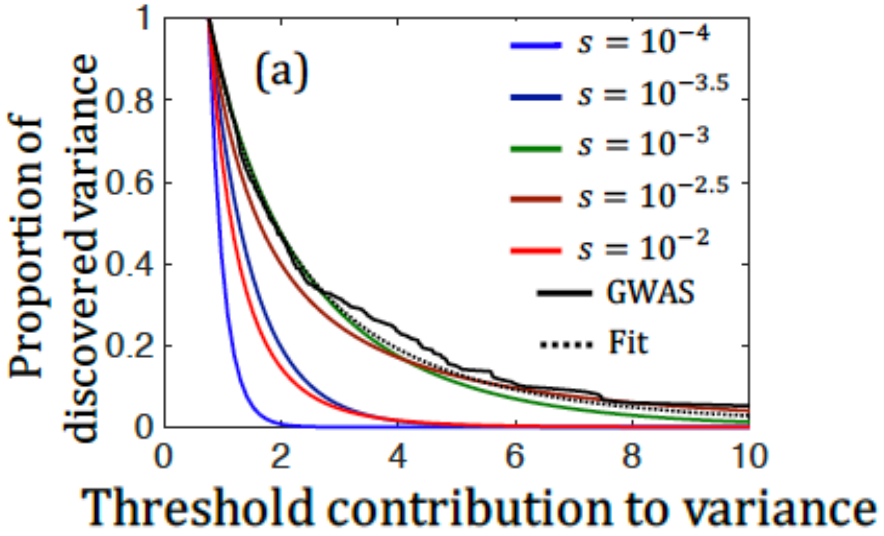
Jeremy Berg

Demographic history affects the range of selection effects seen in GWAS

height

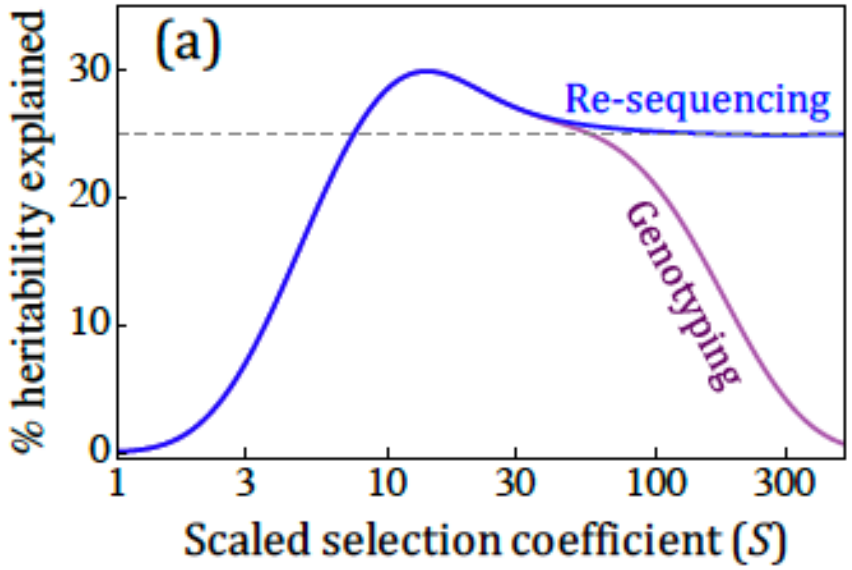






Schiffles & Durbin Nat Genet 2014

Missing heritability differs markedly under MSB and stabilizing selection



Intuition:

When selection is strong: $v \propto a^2 q$ and $q \propto 1/s$

Under MSB: $s \propto a$ and therefore $v \propto a$

Under St.S: $s \propto a^2$ and therefore $v \approx const$

v – genetic variance
s – selection coefficient
a – effect size
q - MAF