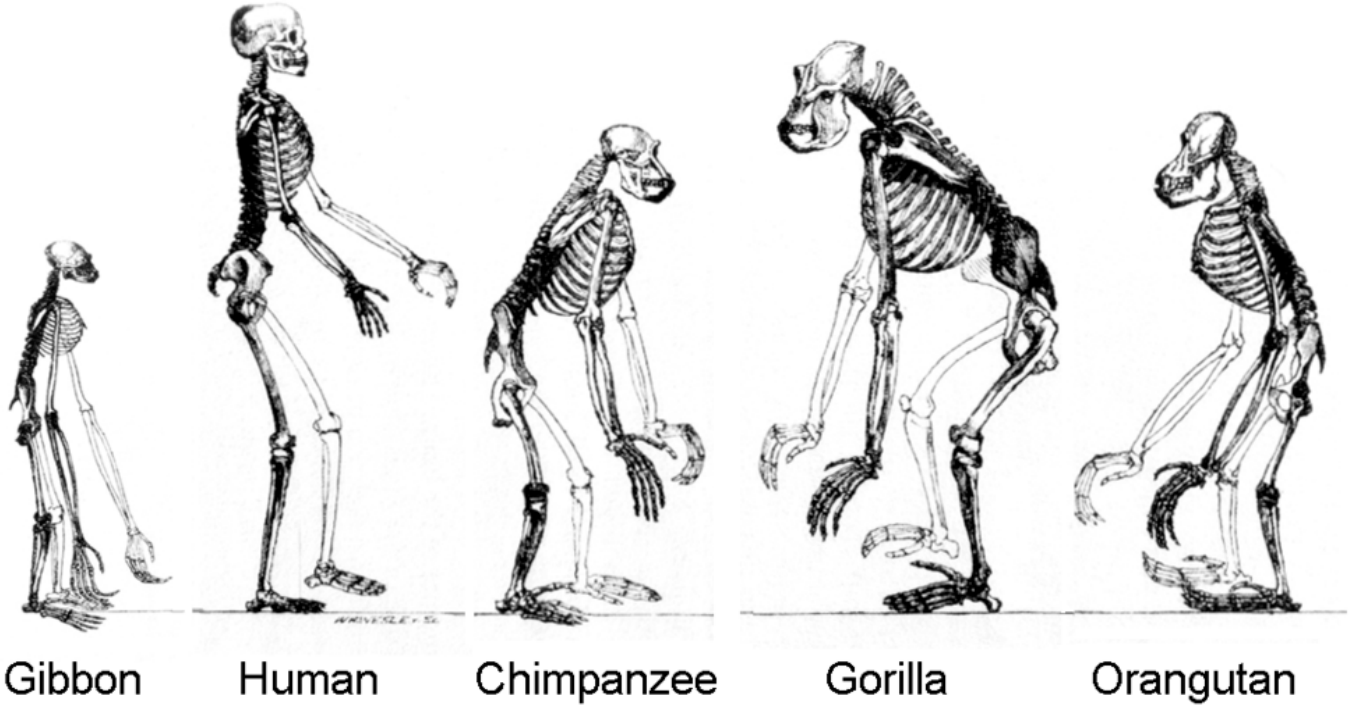
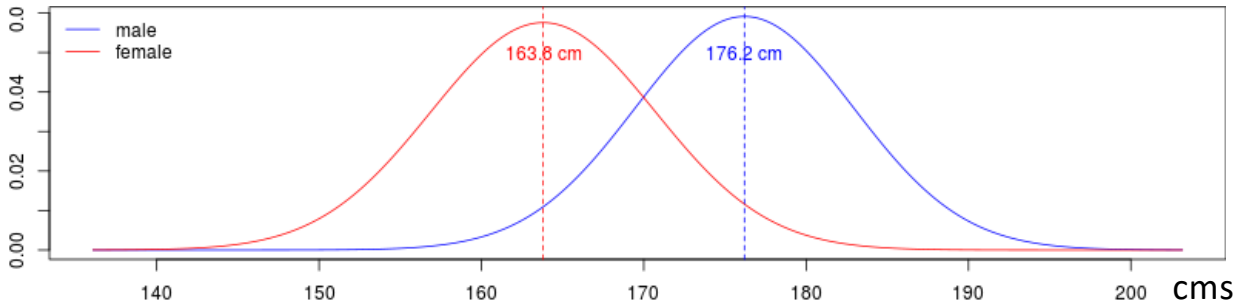
Empreintes de l'adaptation dans le génome humain

Molly Przeworski

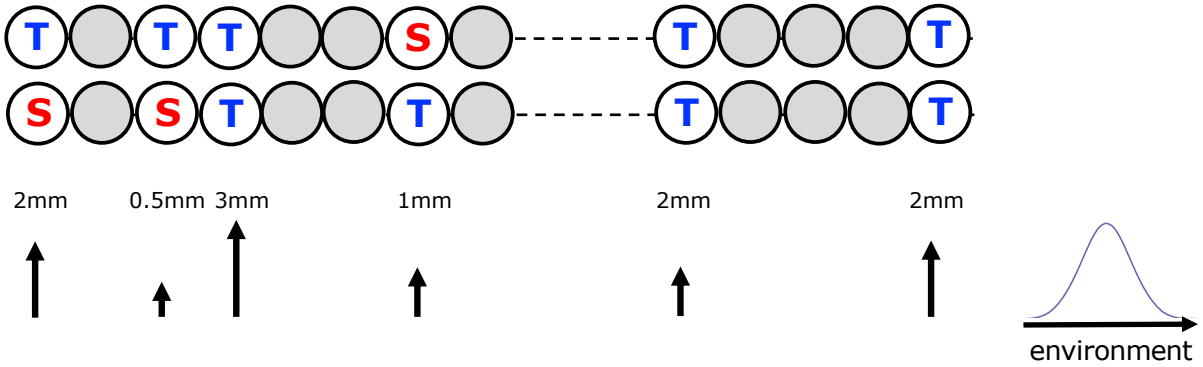
Cours #7



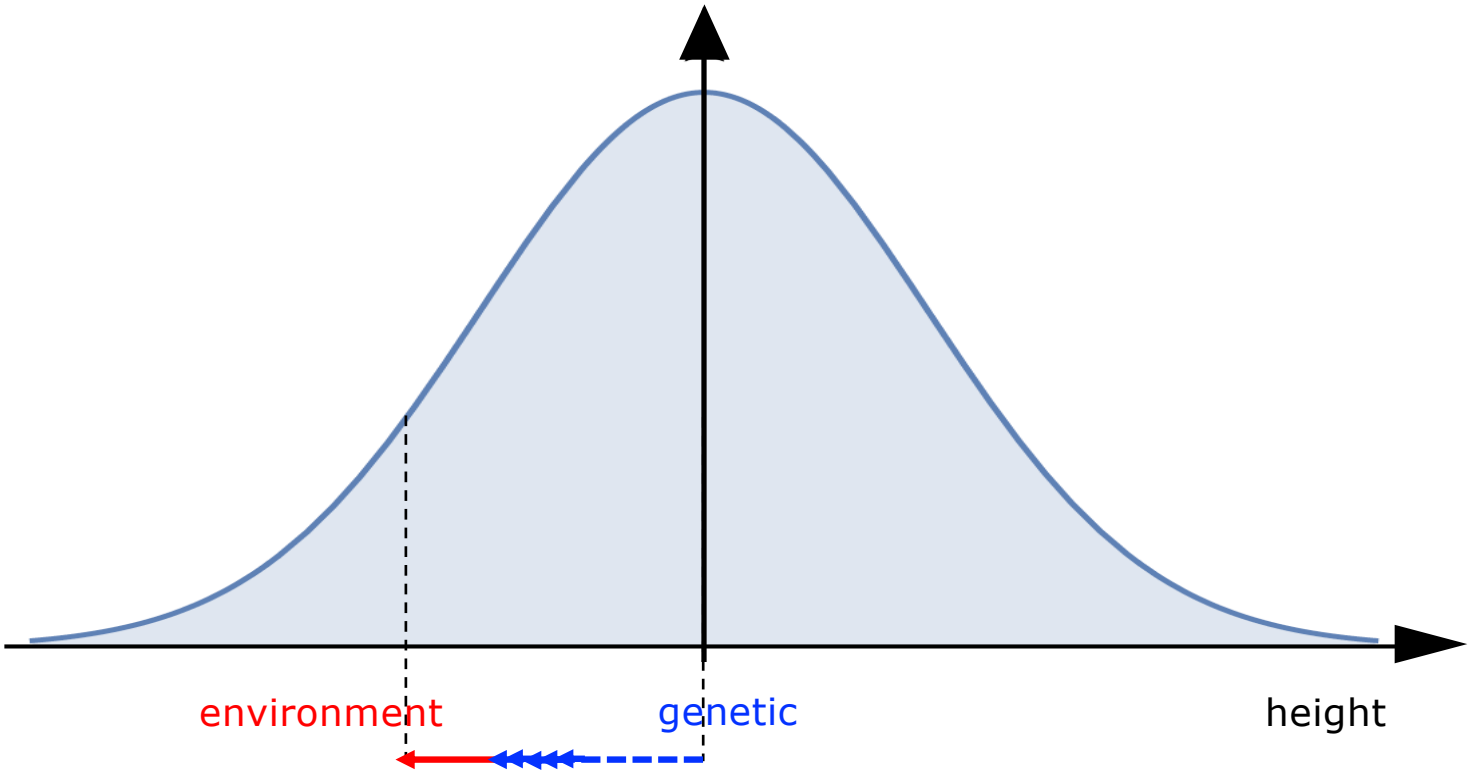
https://en.wikipedia.org/wiki/Ape



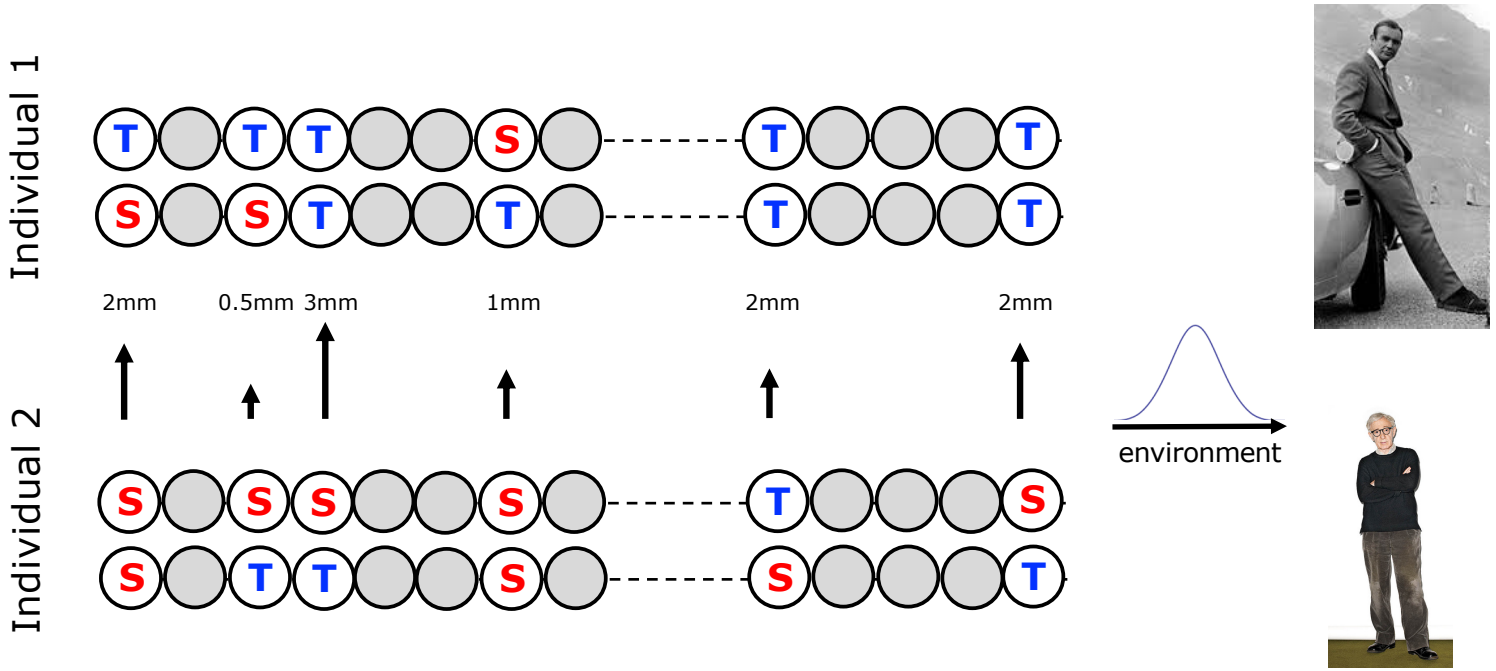
http://talklab.psy.gla.ac.uk/L1_labs/lab_5/index.html



Slide courtesy of Guy Sella



Slide courtesy of Guy Sella

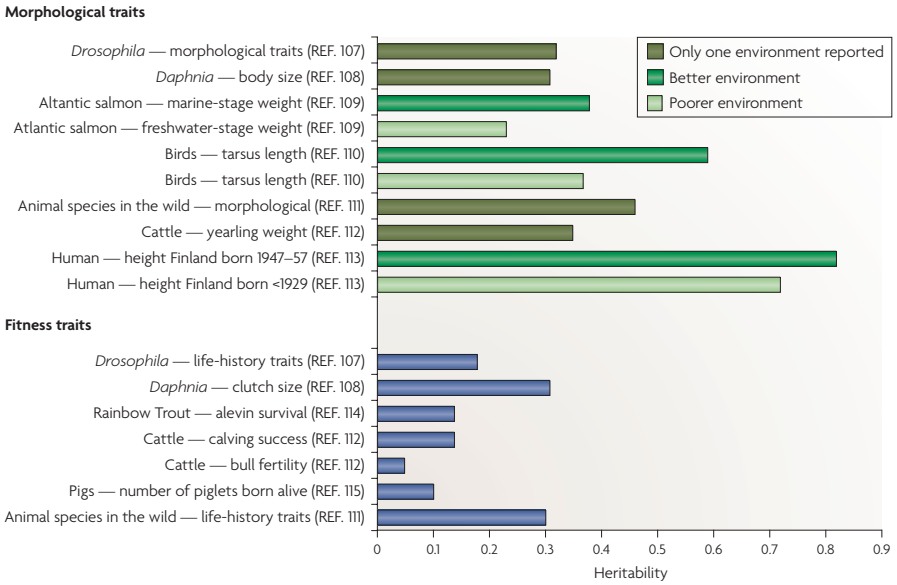


Slide courtesy of Guy Sella

Héritabilité h^2

Taille: $h^2 = 0.84$
Poids: $h^2 = 0.52$
Cholestérol total: $h^2 = 0.61$
Age à la ménopause: $h^2 = 0.47$
Age à la ménarche: $h^2 = 0.62$

Byars et al. PNAS 2009



https://www.nature.com/articles/nrg2322

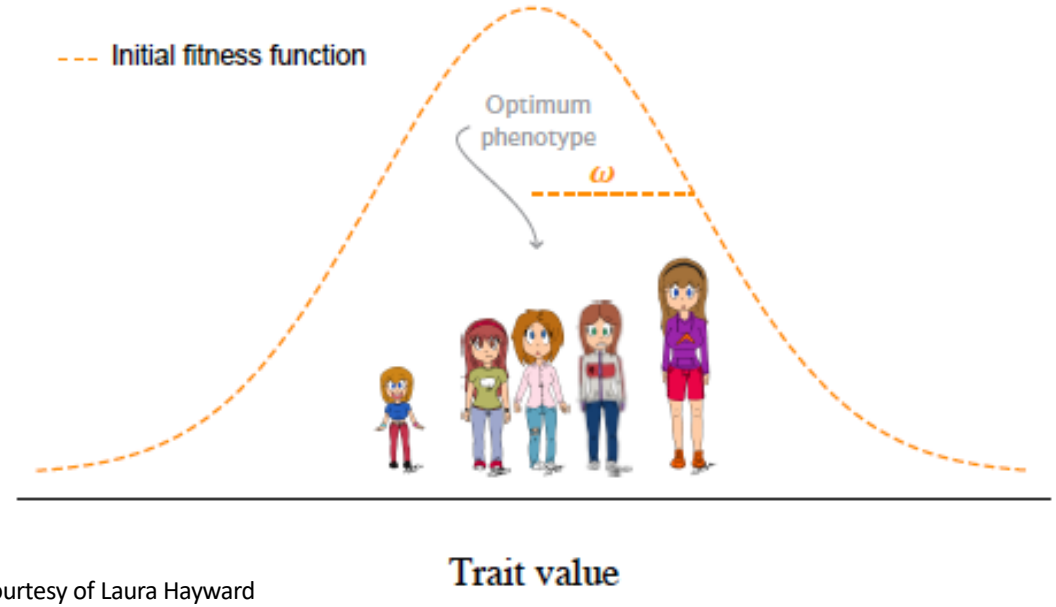
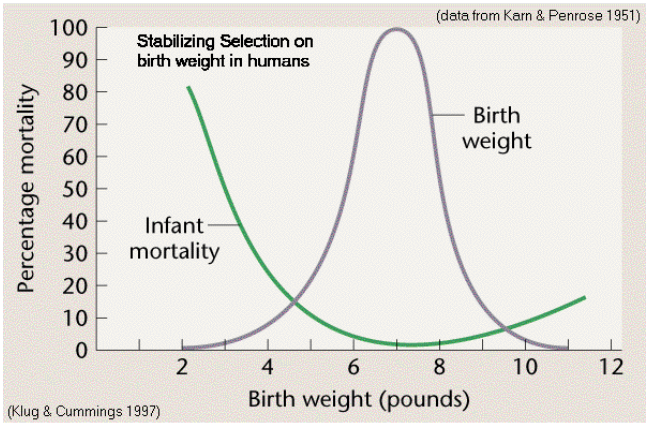


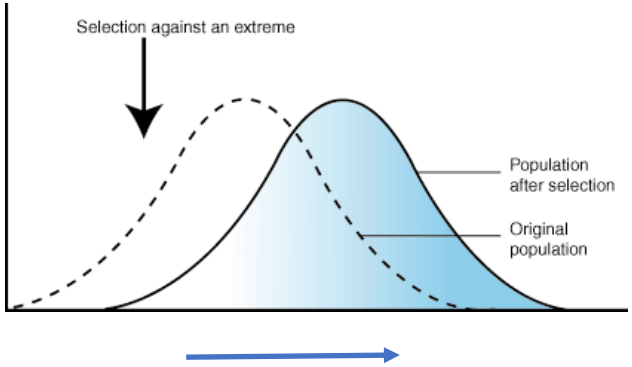
Figure courtesy of Laura Hayward



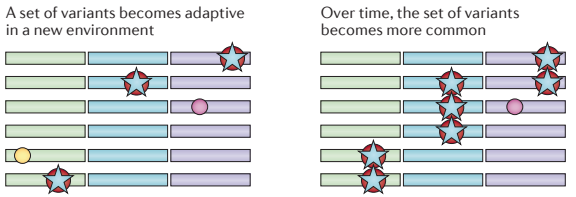
https://www.mun.ca/biology/scarr/2900_Natural_Selection_in_the_Wild.html

For more details about stabilizing selection on complex traits, see Sella & Barton 2019 Annual Reviews of Human Genetics & Genomics, forthcoming

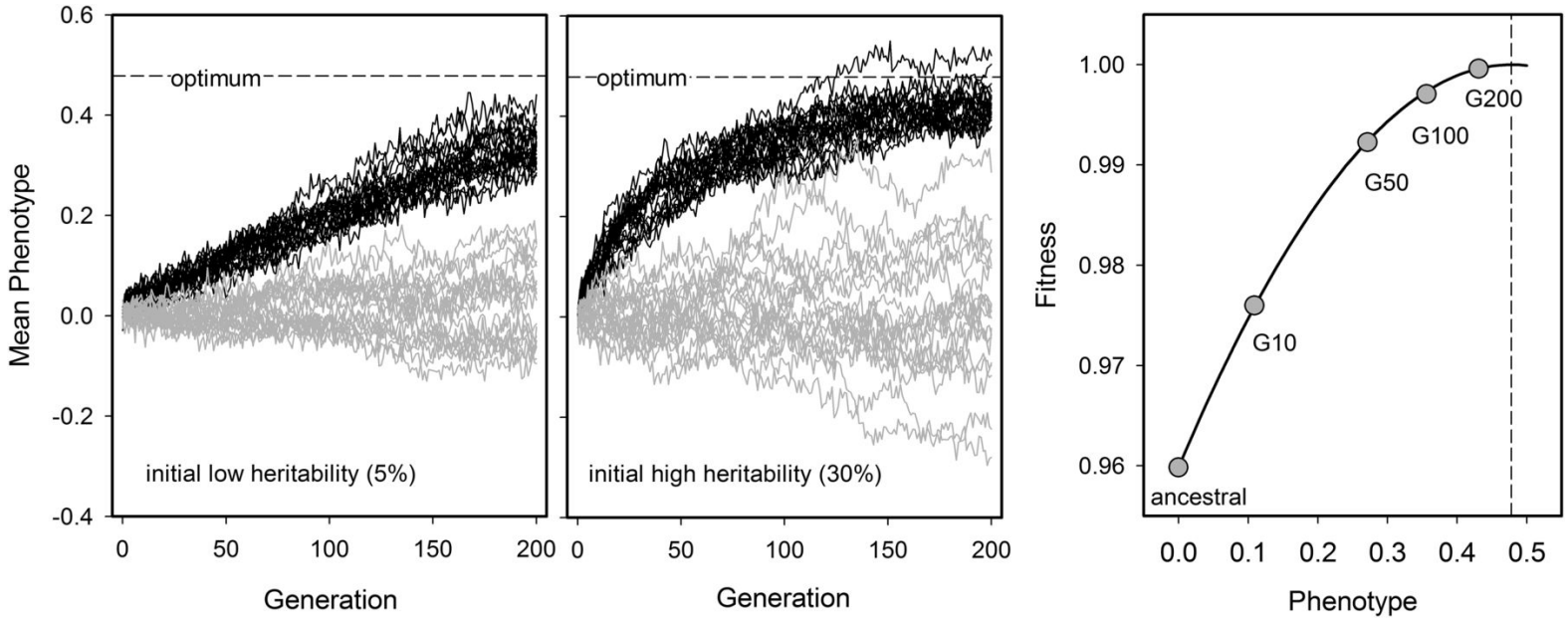
Polygenic selection



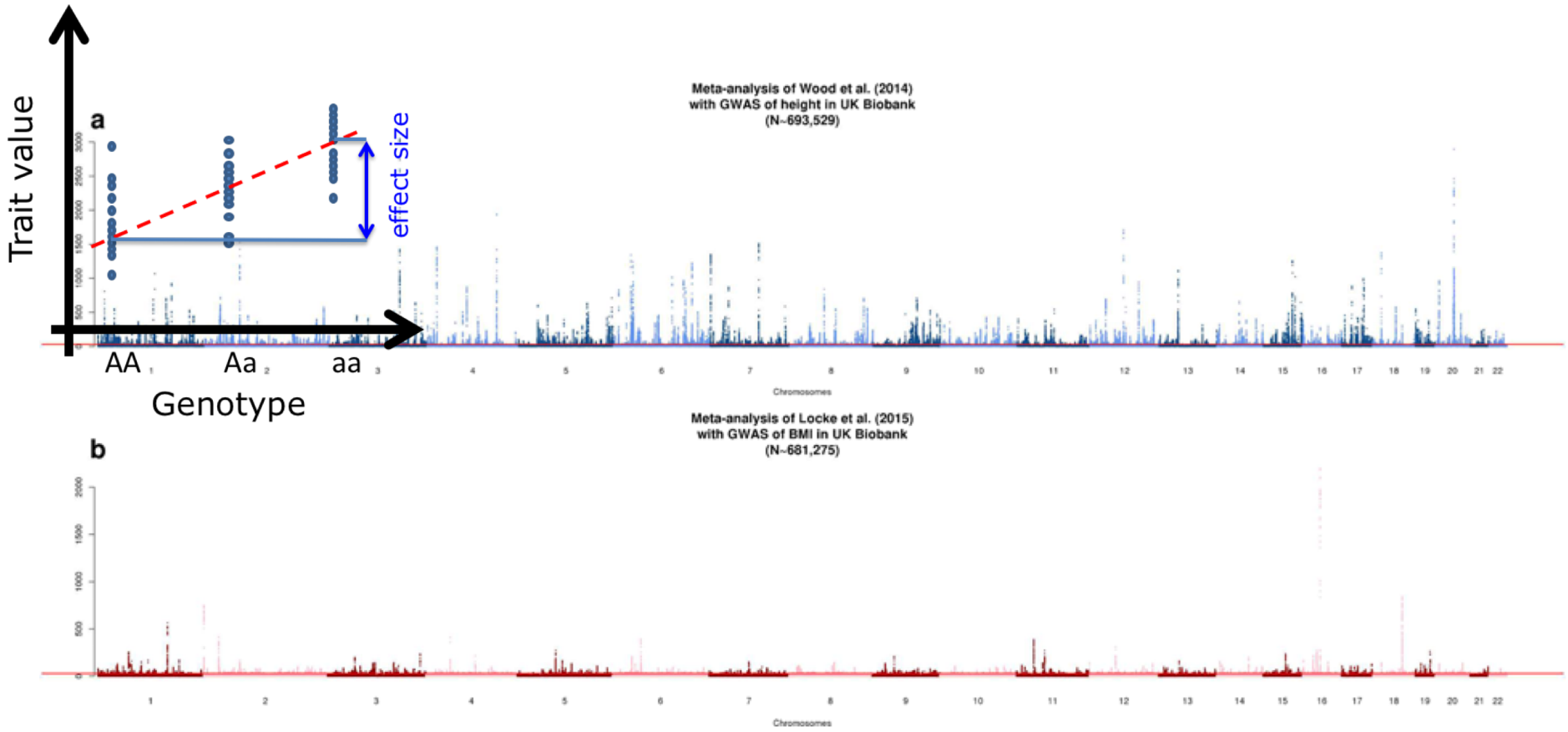
A new optimum is very rapidly attained



Borrowed from Scheinfeldt & Tishkoff 2013

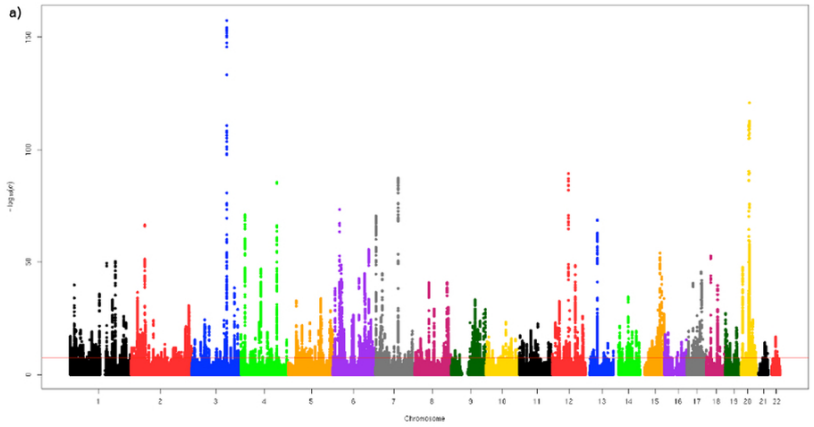


http://www.genetics.org/content/206/2/691

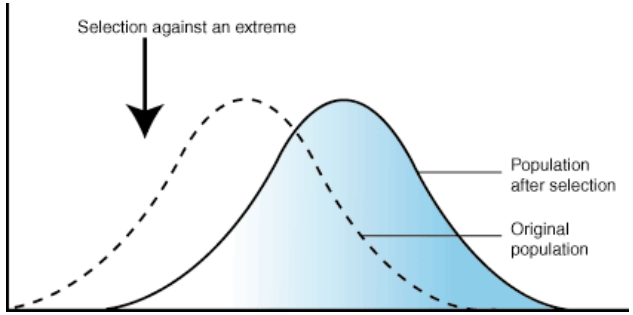


https://academic.oup.com/hmg/article-abstract/27/20/3641/5067845?redirectedFrom=fulltext

Polygenic selection

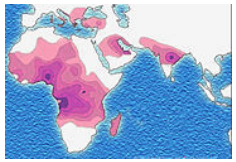


Set of variants
identified in GWAS
in a given population



Does this set show evidence
for directional selection, when
considered jointly?

Selection at present

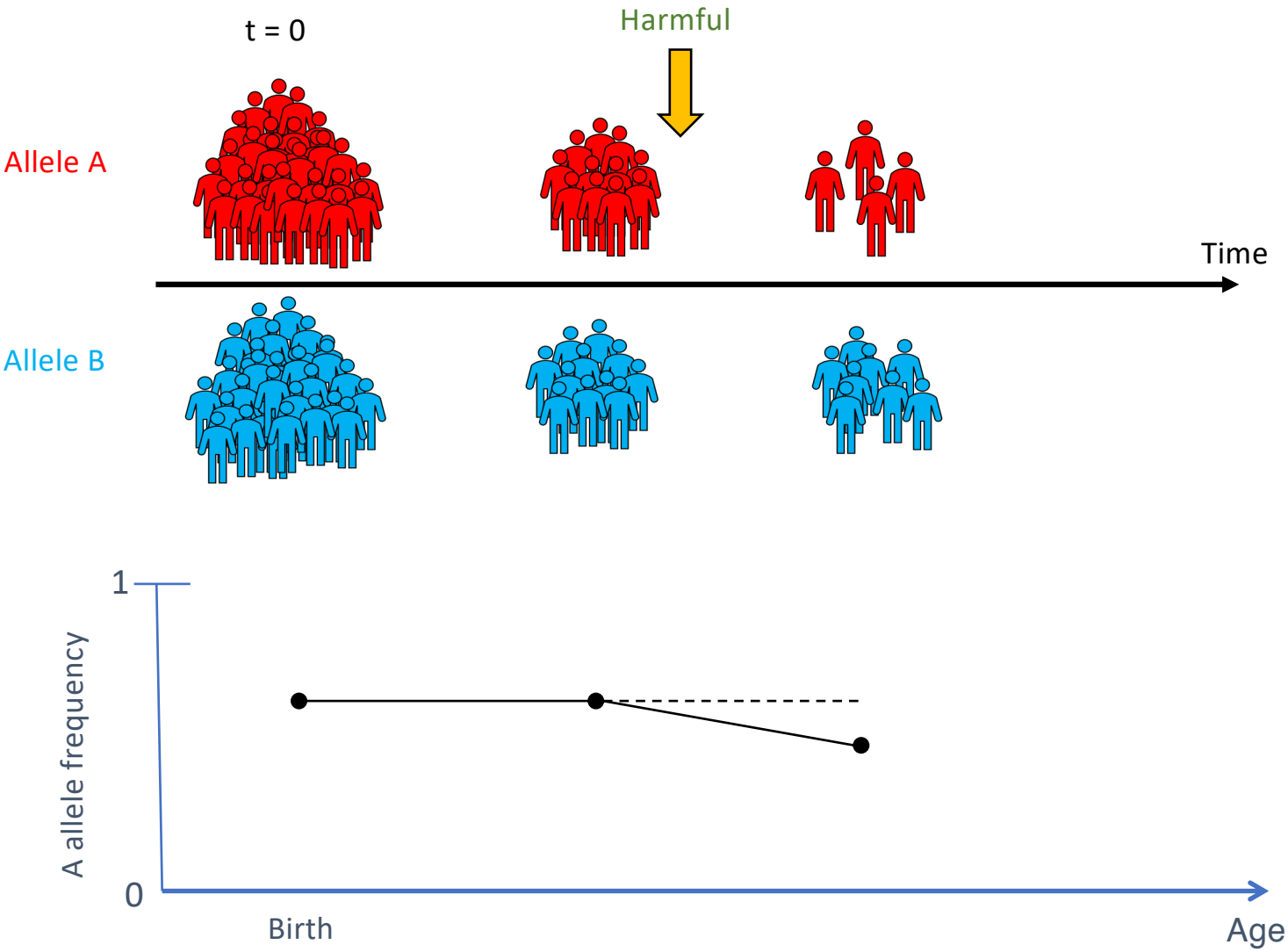


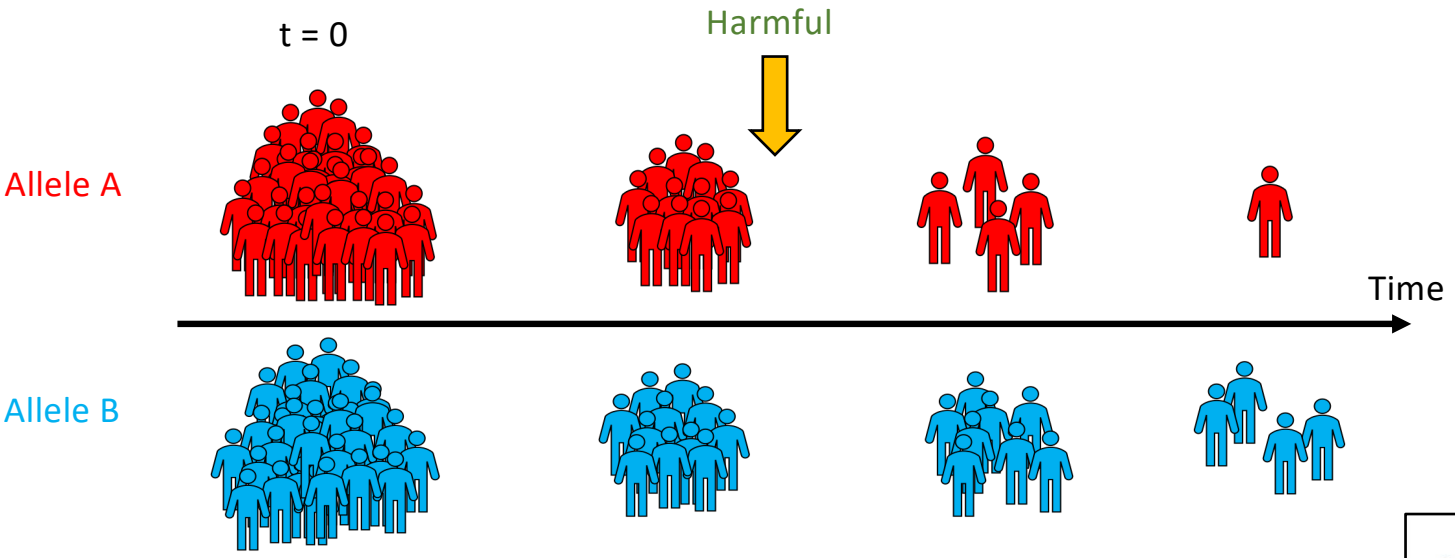
Sickle cell allele frequency

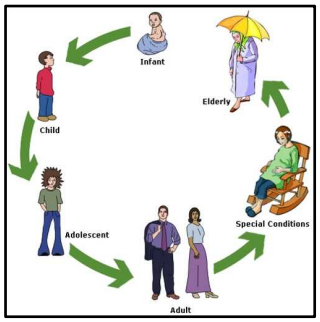
Malaria density

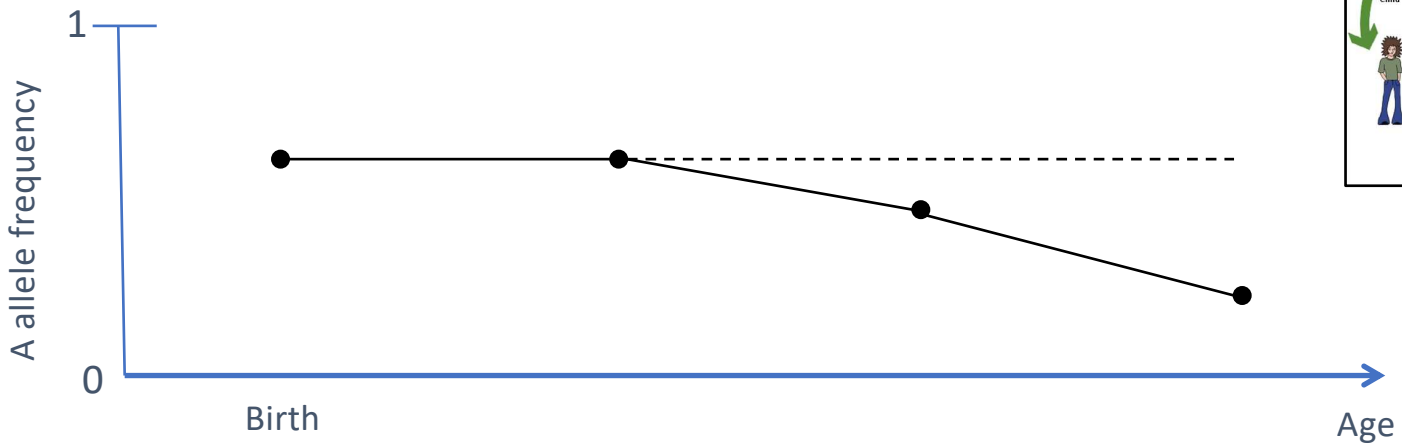
S = sickle cell allele N = non sickle cell allele

	NN	NS	SS
# newborn	160	160	40
# adults	144	160	20

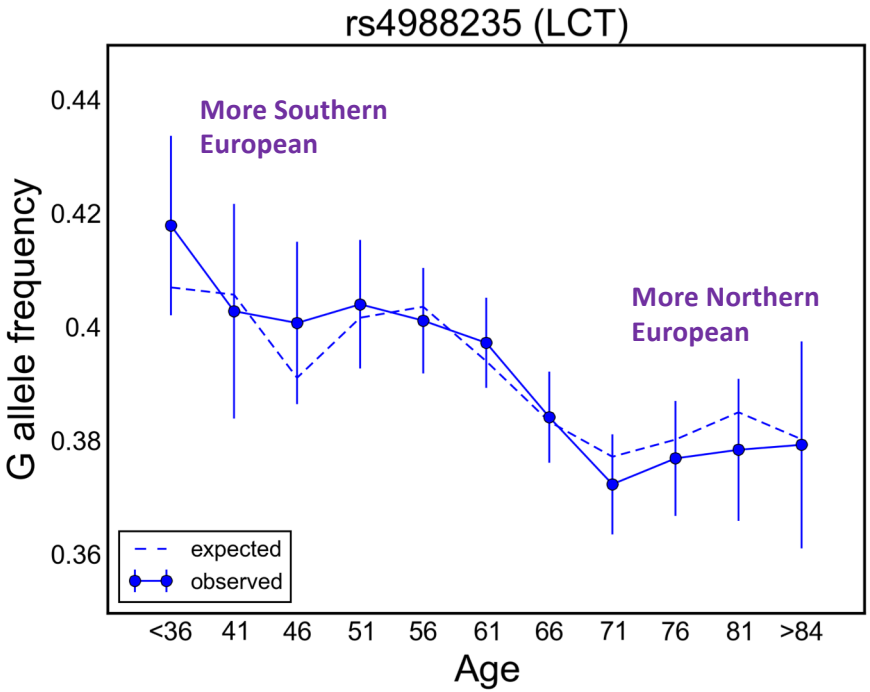

t = 0
Harmful
Allele A
Time
Allele B
1
A allele frequency
0
Birth
Age


t = 0
Harmful
Allele A
Time
Allele B


Infant
Elderly
Child
Special Conditions
Adolescent
Adult


1
A allele frequency
0
Birth
Age

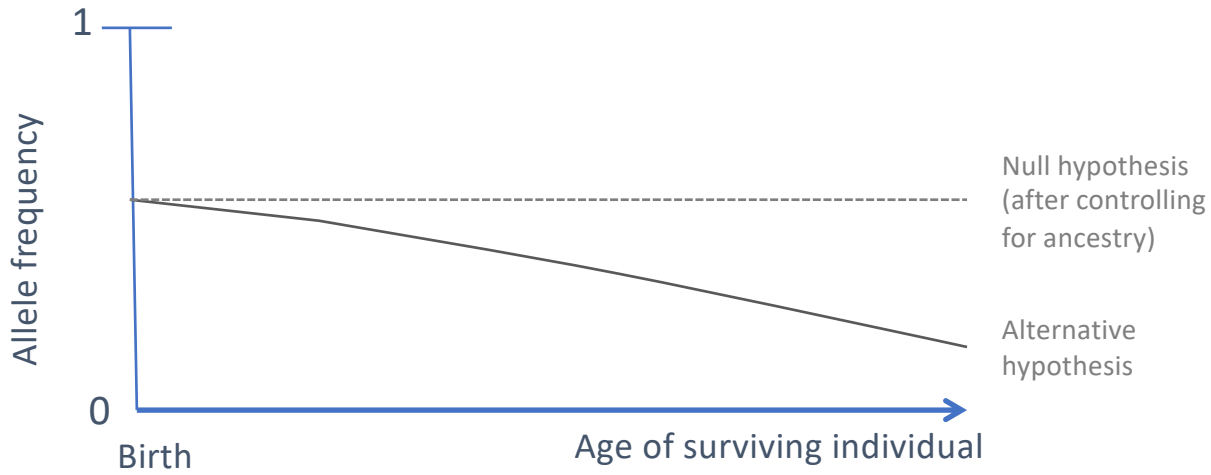
Complication



Viability selection today

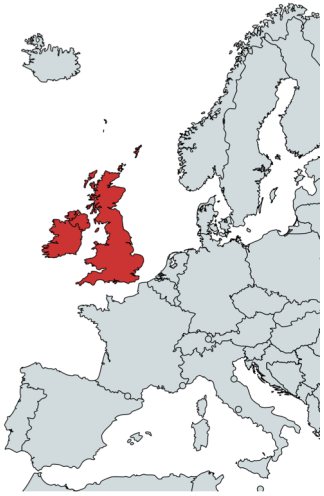
Hakhamanesh Mostafavi

Joe Pickrell



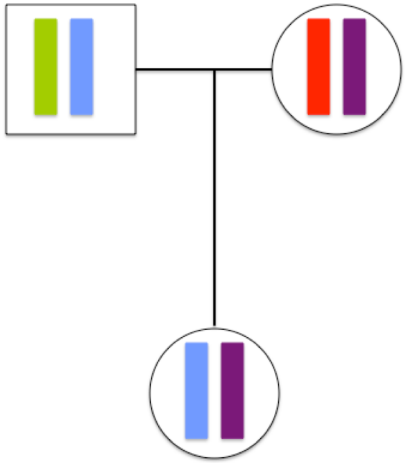
Mostafavi et al. 2017 PLoS Biology

Genotype of individuals predicted by:
Ancestry, Age



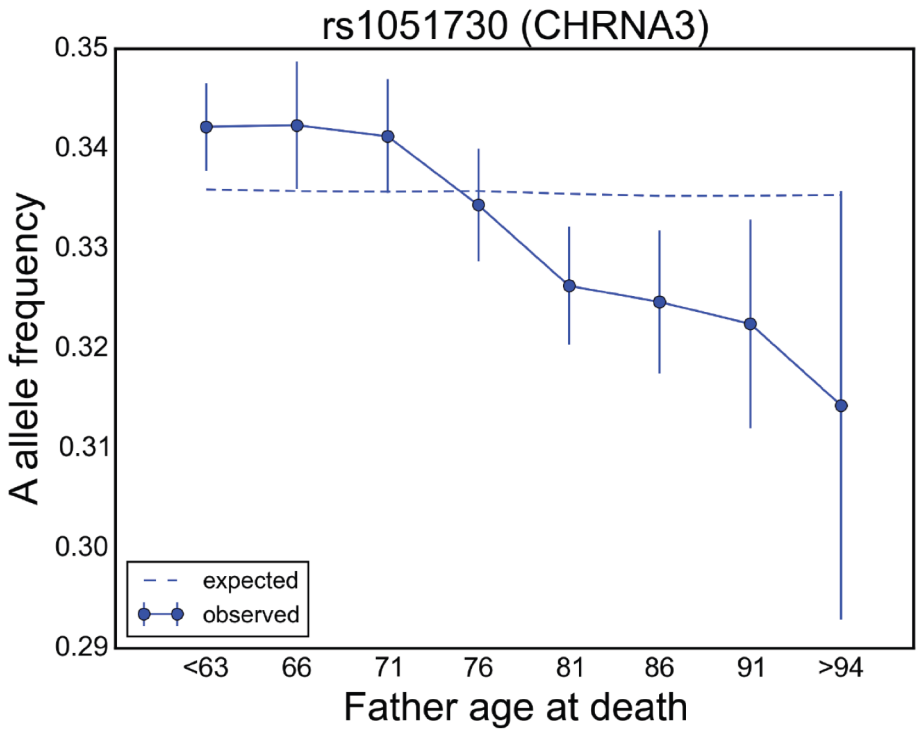
Paternal survival

Maternal survival



Genome-wide
genotype data

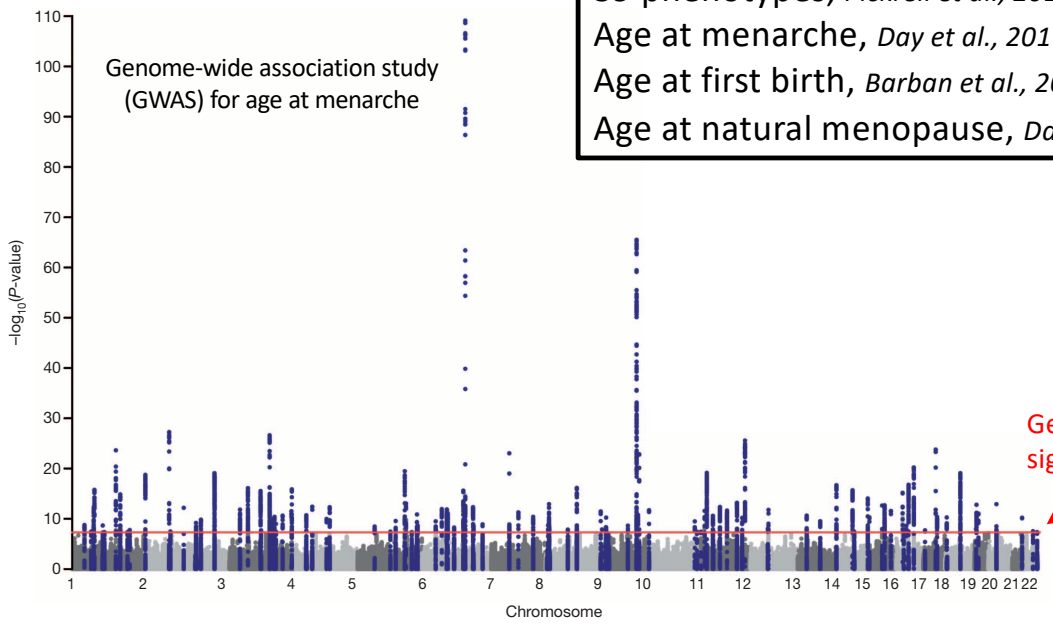
(see Pilling et al. 2016, Joshi et al. 2016, Liu et al. 2016)



Mostafavi et al. 2017

Sets of genetic variants

39 phenotypes, *Pickrell et al., 2016*
Age at menarche, *Day et al., 2017*
Age at first birth, *Barban et al., 2016*
Age at natural menopause, *Day et al., 2015*



Perry et al., 2014

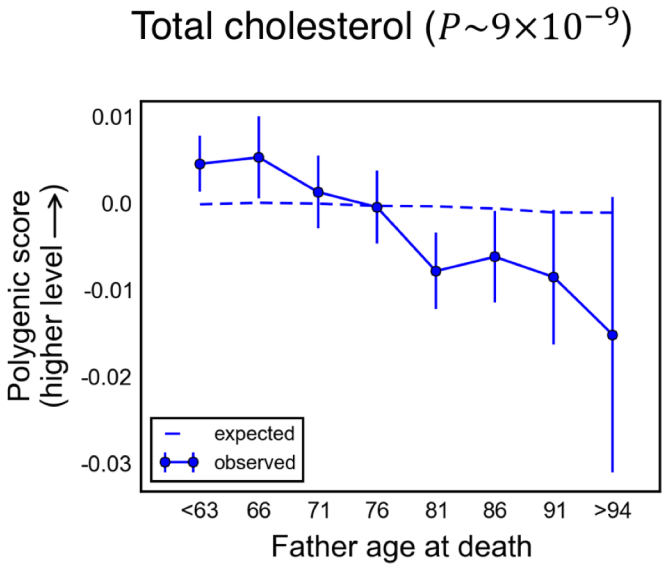
$$S_i = \sum \hat{\beta}_j g_{ij}$$

Polygenic score of individual *i*

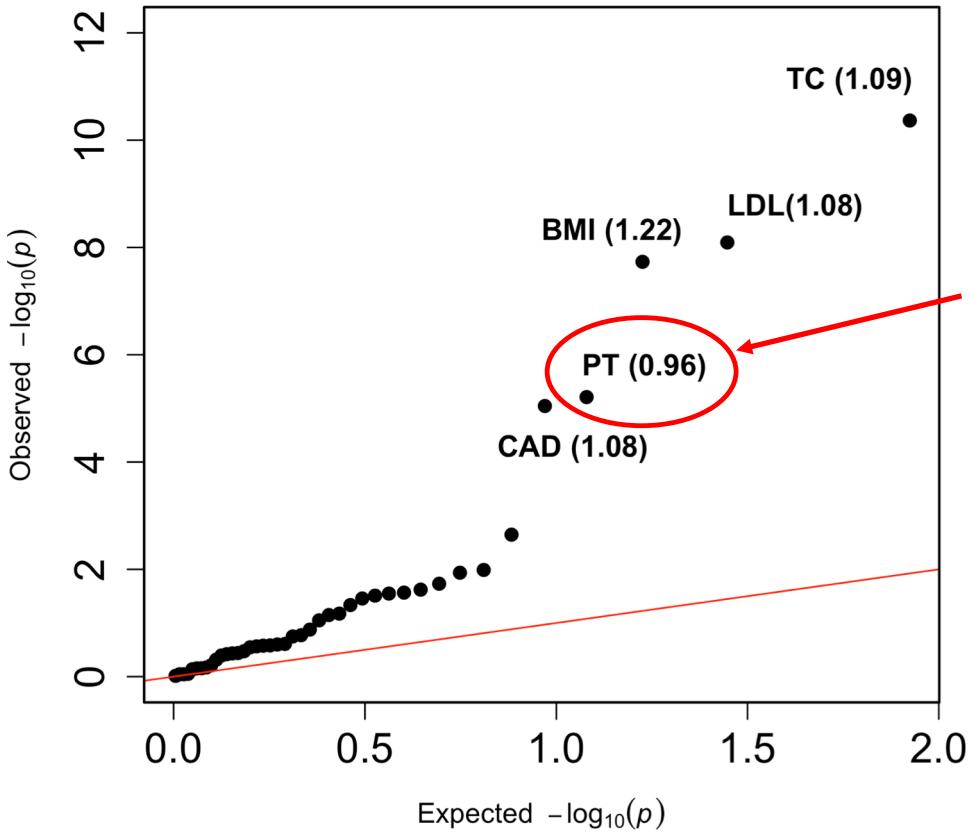
Genotype of individual *i* at locus *j*

Effect size of genetic variant *j* on the phenotype

Traits associated with paternal age at death

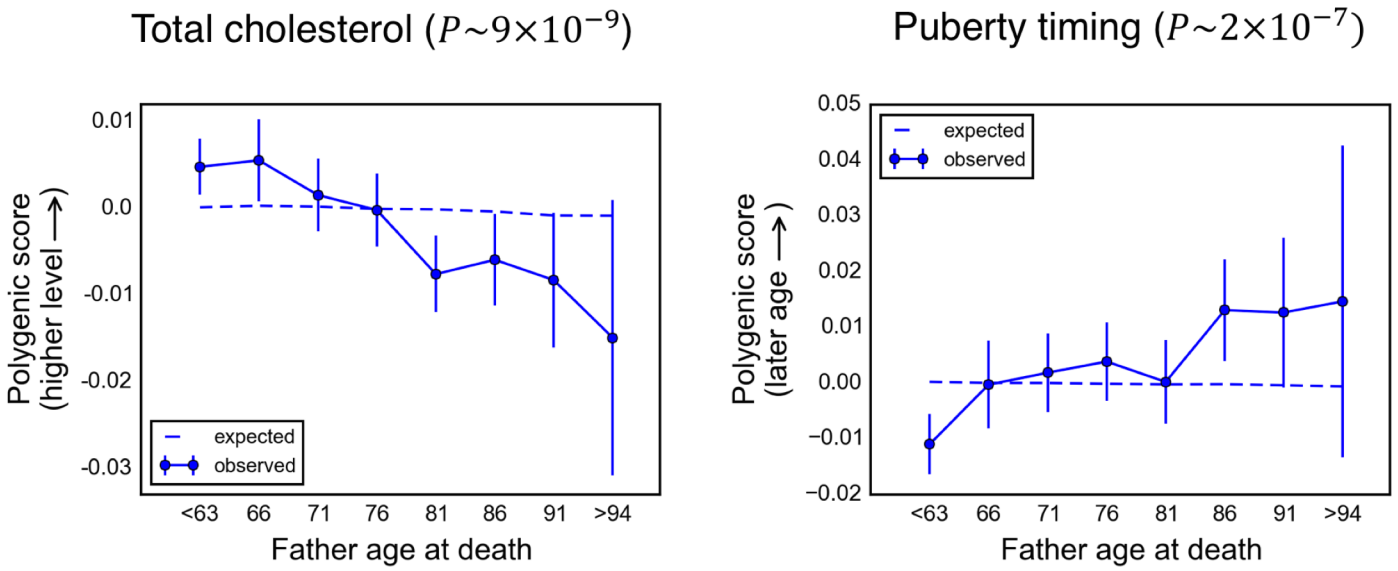


Paternal survival

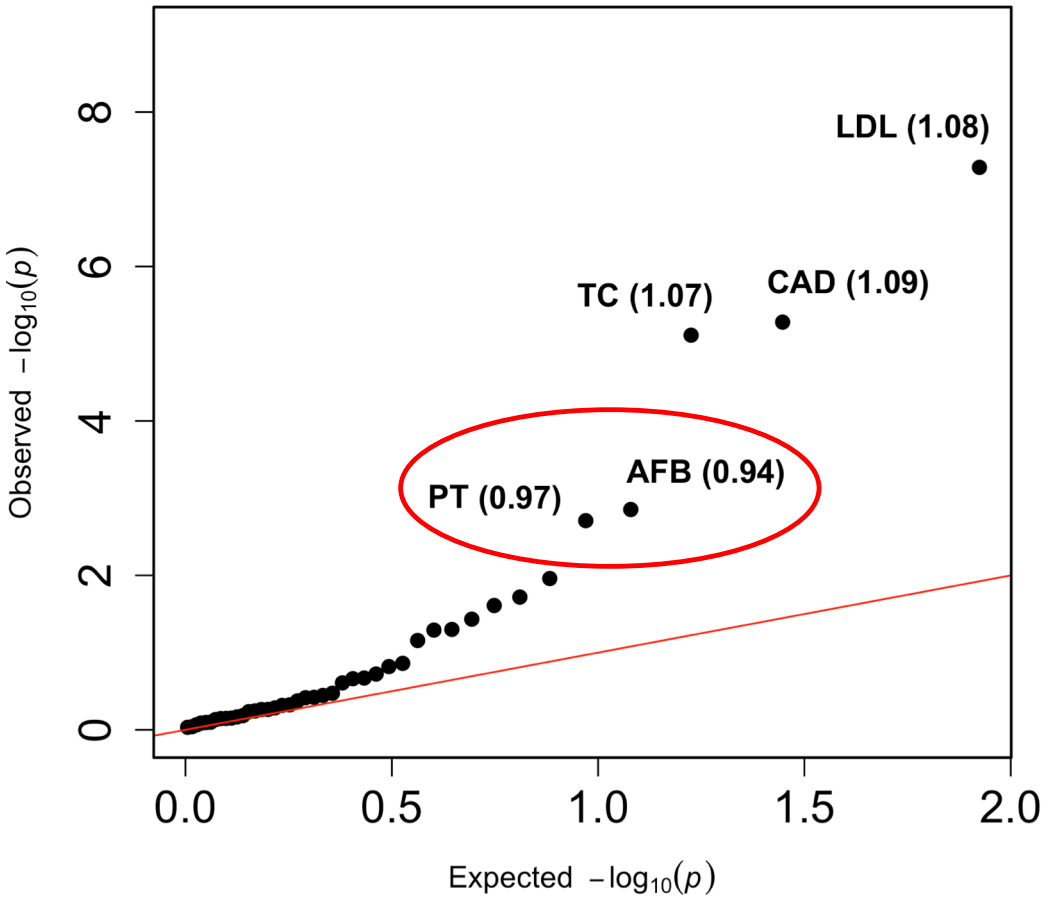


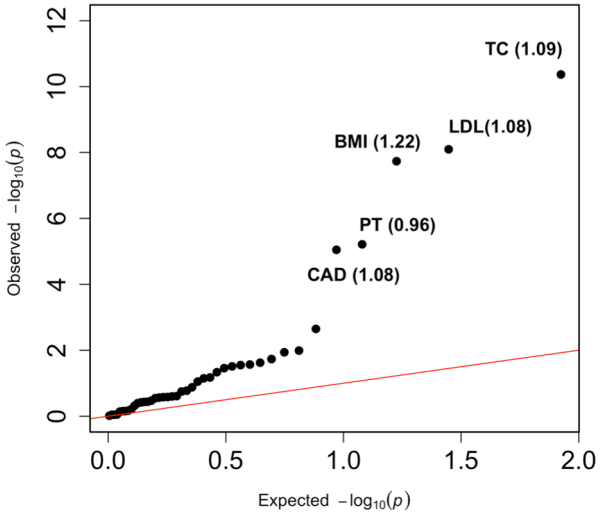
Protective effect of later predicted **age of puberty**

Traits associated with paternal age at death



Maternal survival

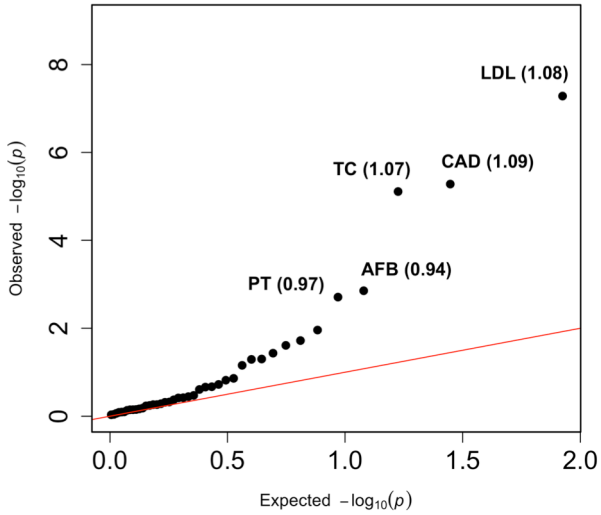




Evidence of directional and stabilizing selection in contemporary humans

Jaleal S. Sanjak[a,b], Julia Sidorenko[c,d], Matthew R. Robinson[c,d,e], Kevin R. Thornton[a,b], and Peter M. Visscher[c,d,1]

[a]Department of Ecology and Evolutionary Biology, University of California, Irvine, CA 92697; [b]Center for Complex Biological Systems, University of California, Irvine, CA 92697; [c]Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia; [d]Institute for Molecular Biosciences, The University of Queensland, Brisbane, QLD 4072, Australia; and [e]Department of Computational Biology, University of Lausanne, Lausanne 1010, Switzerland



Reproductive fitness and genetic risk of psychiatric disorders in the general population

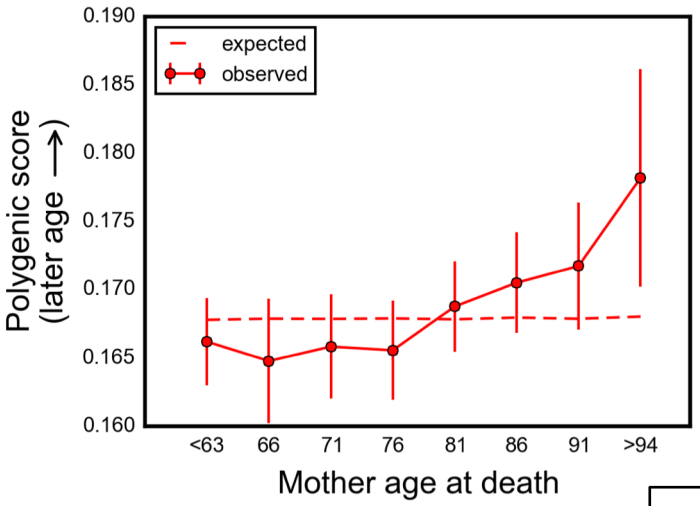
Niamh Mullins[1,2], Andrés Ingason[1], Heather Porter[1,2], Jack Euesden[1,2,3], Alexandra Gillett[1,2], Sigurgeir Ólafsson[1,4], Daniel F. Gudbjartsson[1], Cathryn M. Lewis[1,2,5], Engilbert Sigurdsson[4,6], Evald Saemundsen[7], Ólafur Ó. Gudmundsson[1], Michael L. Frigge[1], Augustine Kong[1], Agnar Helgason[1,8], G. Bragi Walters[1,4], Omar Gustafsson[1], Hreinn Stefansson[1] & Kari Stefansson[1,4]

Selection against variants in the genome associated with educational attainment

Augustine Kong[a,b,1], Michael L. Frigge[a], Gudmar Thorleifsson[a], Hreinn Stefansson[a], Alexander I. Young[c], Florian Zink[a], Gudrun A. Jonsdottir[a], Aysu Okbay[d,e], Patrick Sulem[a], Gisli Masson[a], Daniel F. Gudbjartsson[a,b], Agnar Helgason[a,f], Gyda Bjornsdottir[a], Unnur Thorsteinsdottir[a,g], and Kari Stefansson[a,g,1]

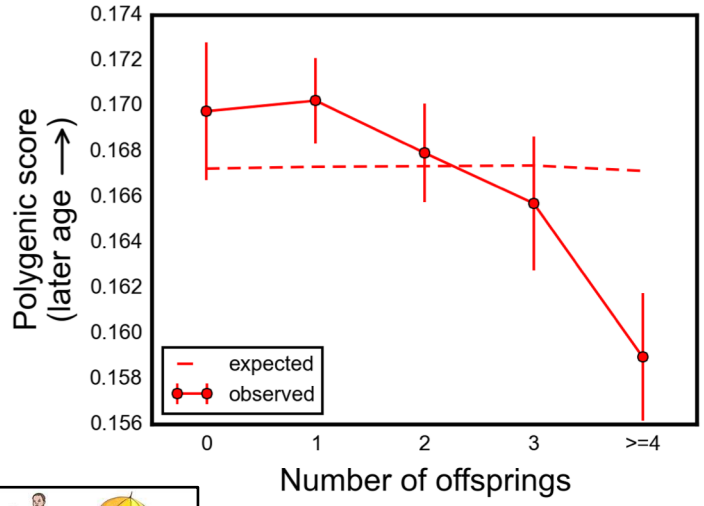
[a]deCODE genetics/Amgen Inc., Reykjavik 101, Iceland; [b]School of Engineering and Natural Sciences, University of Iceland, Reykjavik 101, Iceland; [c]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, United Kingdom; [d]Department of Applied Economics, Erasmus School of Applied Economics, Erasmus University Rotterdam, 3062 PA Rotterdam, The Netherlands; [e]Institute for Behavior and Biology, Erasmus University Rotterdam, 3062 PA Rotterdam, The Netherlands; [f]Department of Anthropology, University of Iceland, Reykjavik 101, Iceland; and [g]Faculty of Medicine, University of Iceland, Reykjavik 101, Iceland

Age of first birth ($p \sim 6 \times 10^{-4}$)

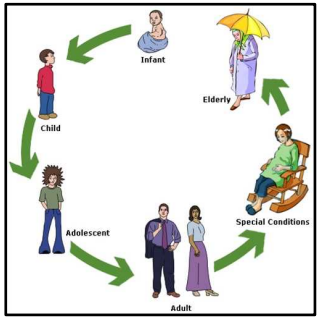


Longevity

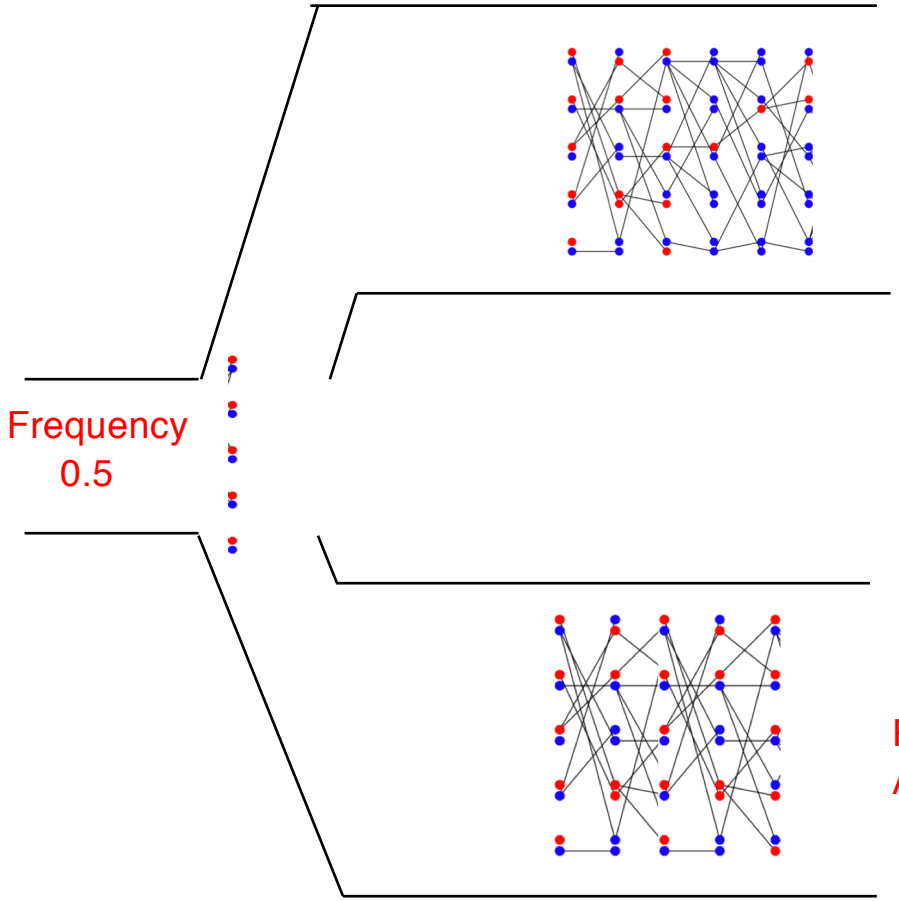
Age of first birth ($p \sim 10^{-10}$)



Fertility



Separation of population leads to divergence in allele frequencies



Population 1
Allele frequency 0.2

Population 2
Allele frequency 0.5

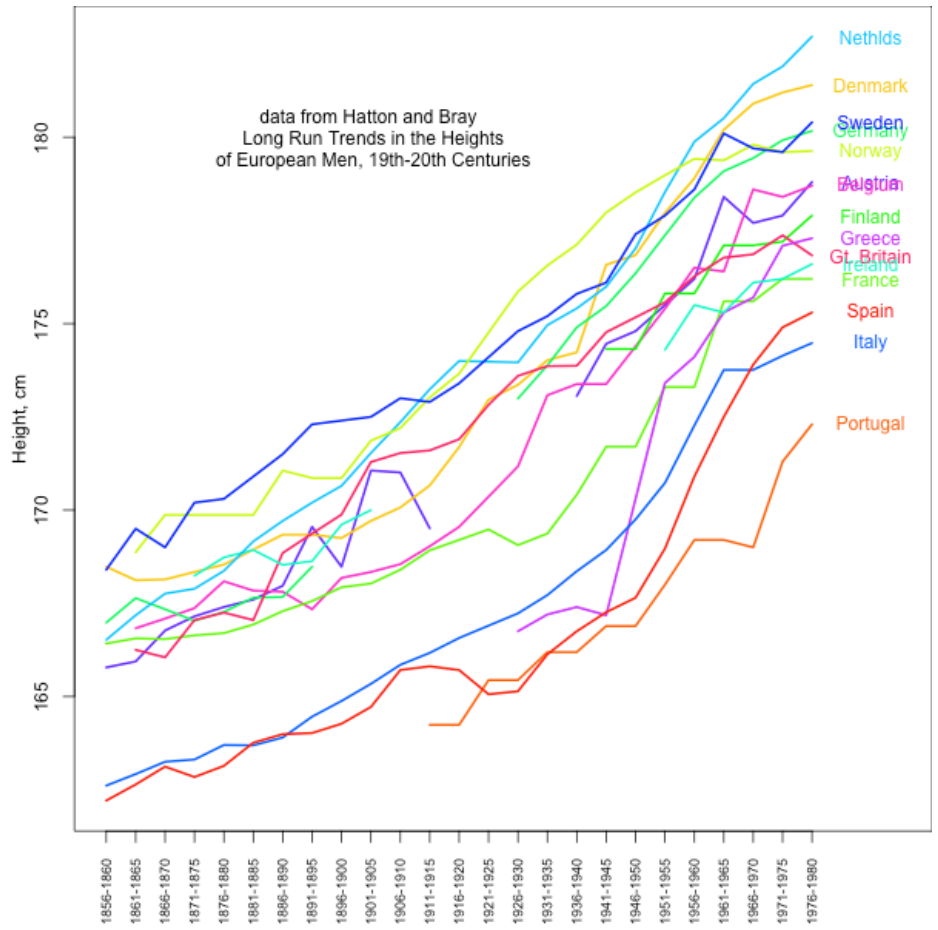
$$S_i = \sum \hat{\beta}_j g_{ij}$$

Polygenic score of individual *i*

Genotype of individual *i* at locus *j*

Effect size of genetic variant *j* on the phenotype

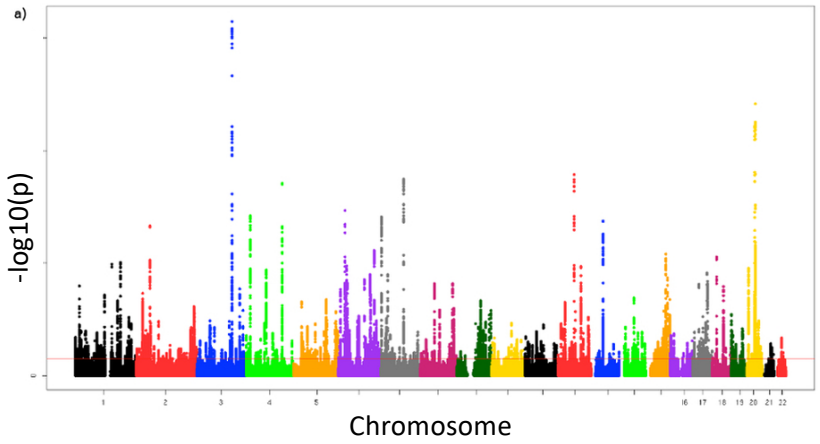
=> Polygenic scores will diverge by genetic drift alone

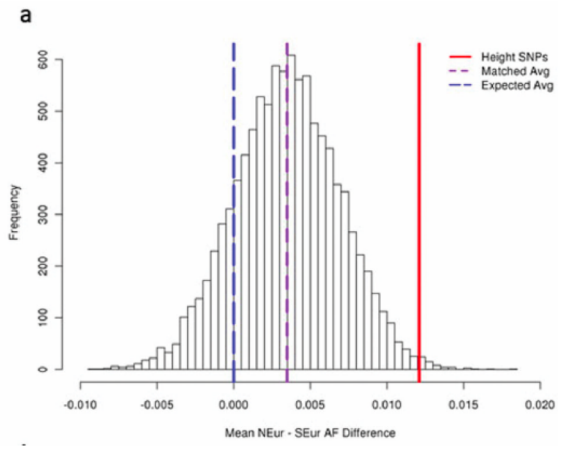


https://gcbias.org/2014/08/07/some-thoughts-on-our-polygenic-selection-paper/

Polygenic selection on variants that influence height in Europe

Genome-wide association study (GWAS) for height





Borrowed from Turchin et al. 2012

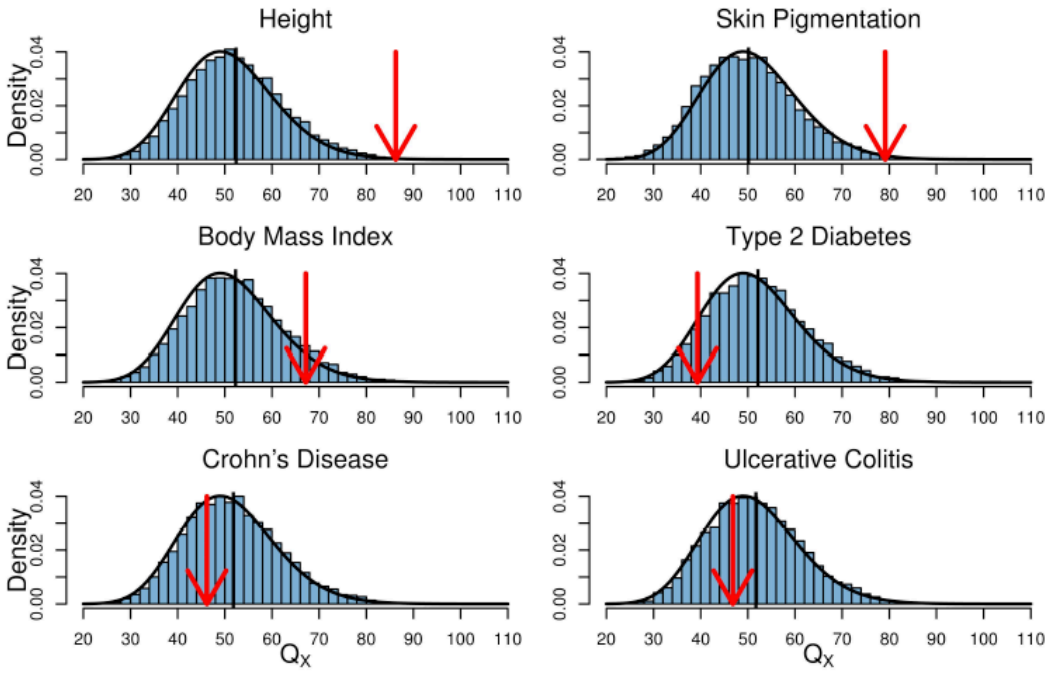


Figure 3. Histogram of the empirical null distribution of Q_X for each trait, obtained from genome-wide resampling of well matched SNPs. The mean of each distribution is marked with a vertical black bar and the observed value is marked by a red arrow. The expected χ^2_{M-1} density is shown as a black curve.

Coop & Berg 2014 Plos Genetics; see also Coop & Berg 2017 BioRxiv

Field et al. 2016 Science; Edge and Coop 2018; Spiedel et al. 2019 BioRxiv

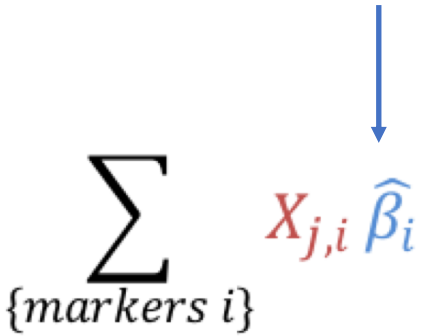
Among many strong assumptions:

❖ Assume Betas estimated without bias
BUT residual environmental confounding in GWAS

❖ Assume Betas fixed in space and time
BUT GxG, GxE

❖ Only genetic effects taken into account
BUT environmental pressure could mitigate or oppose genetic effects

estimated in
GWASed population



https://gcbias.org/2018/03/14/polygenic-scores-and-tea-drinking/
Novembre and Barton 2018 Genetics
Barton, Hermisson and Nordborg 2019 eLife

- What were the typical fitness effects of beneficial changes? Typically small
- How many changes were involved? Probably many, scattered throughout the genome

⇒ Is it meaningful to catalogue them?
⇒ How to test their effects?
⇒ A new view of human adaptations