

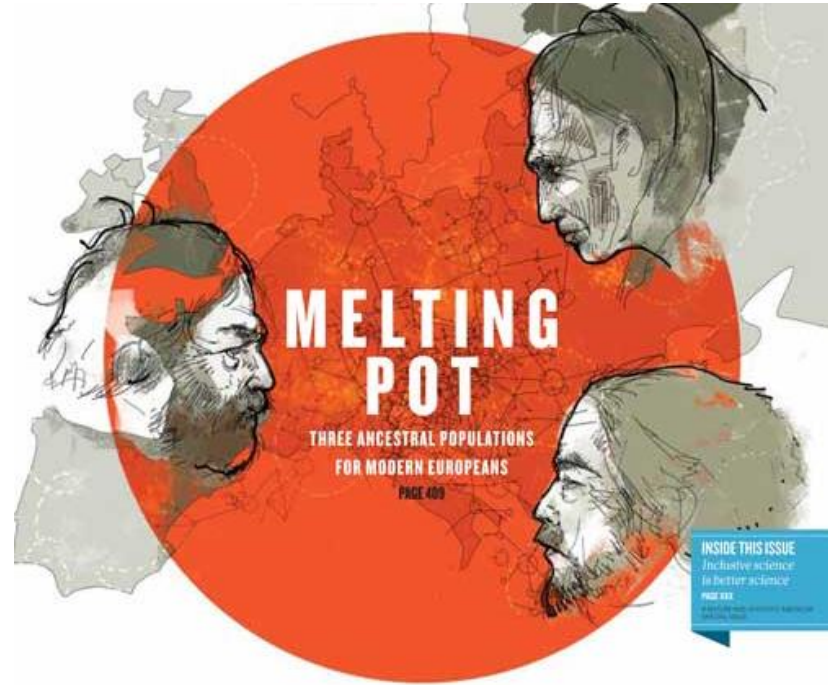
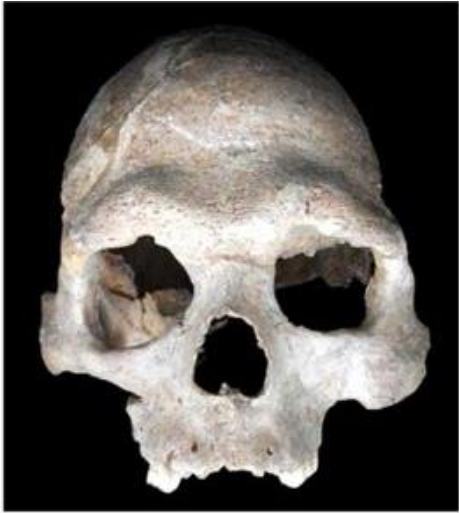
Learning about human demography and natural selection with ancient DNA

Iain Mathieson

Department of Genetics

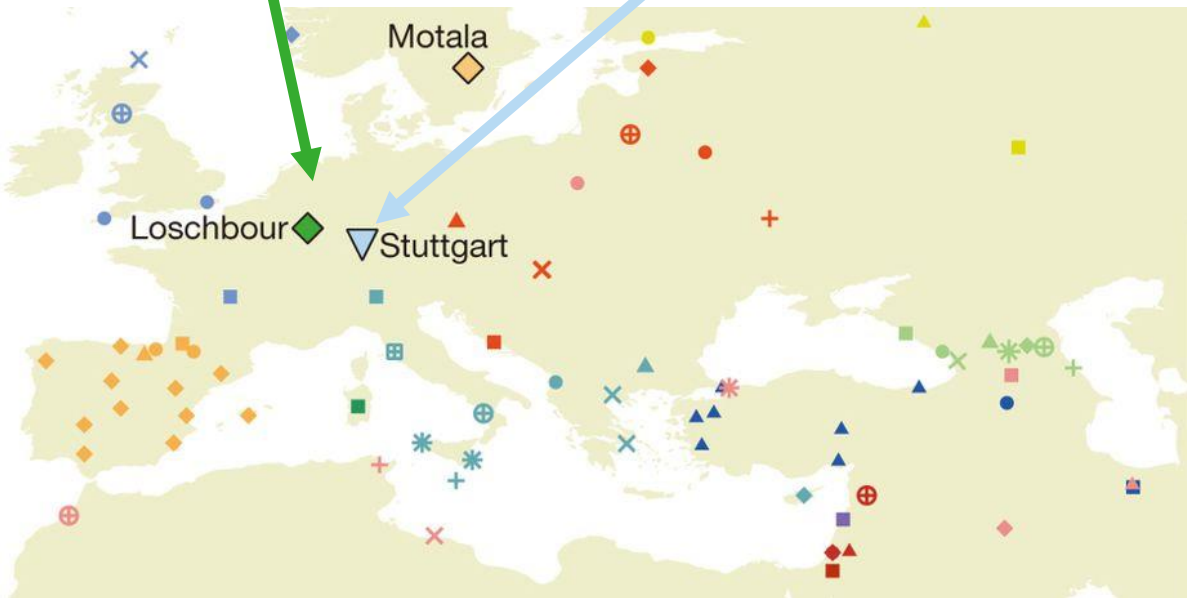
Perelman School of Medicine

University of Pennsylvania

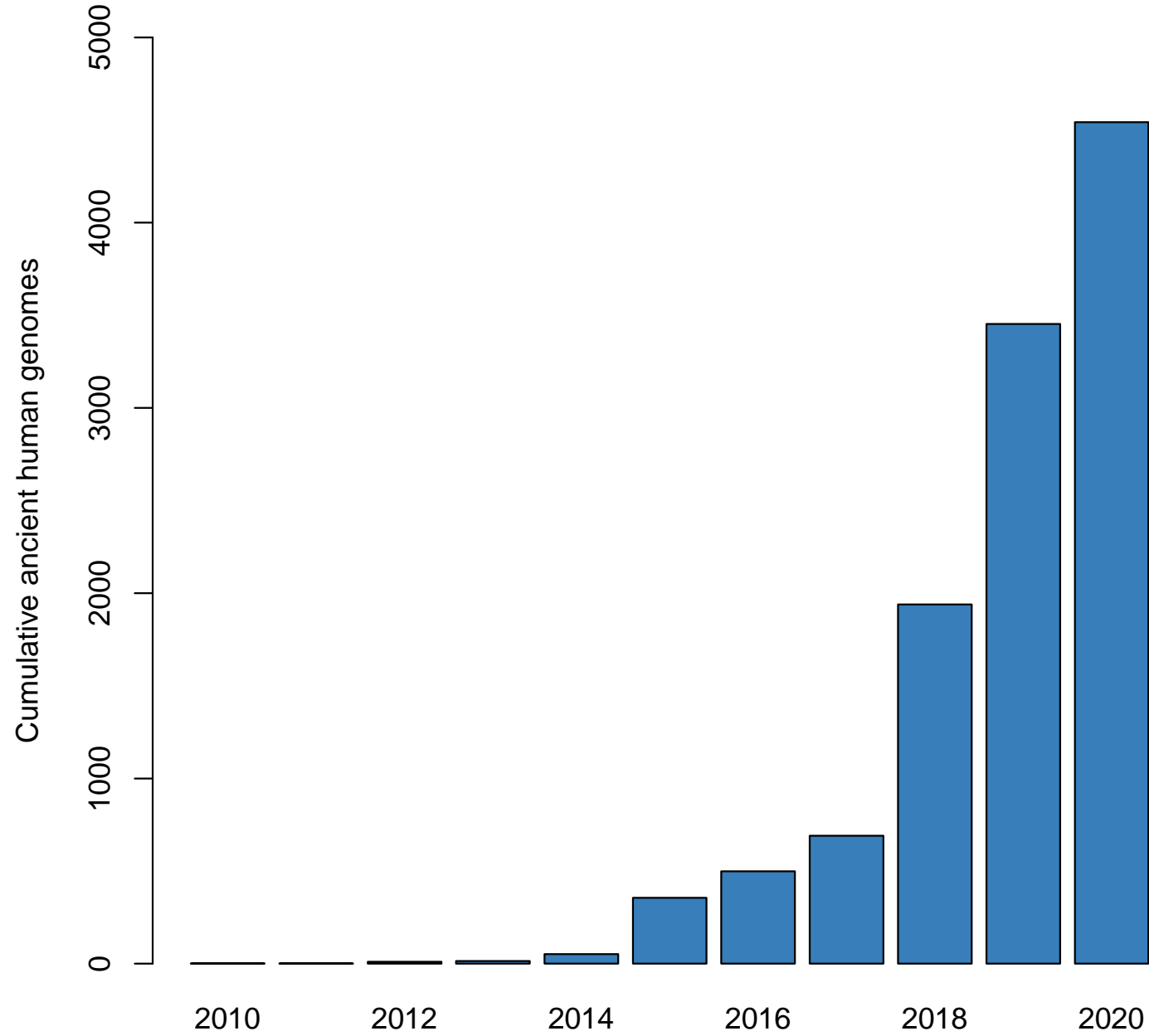


Lazaridis et al. 2014

“Ancient human genomes suggest three ancestral populations for present-day Europeans”

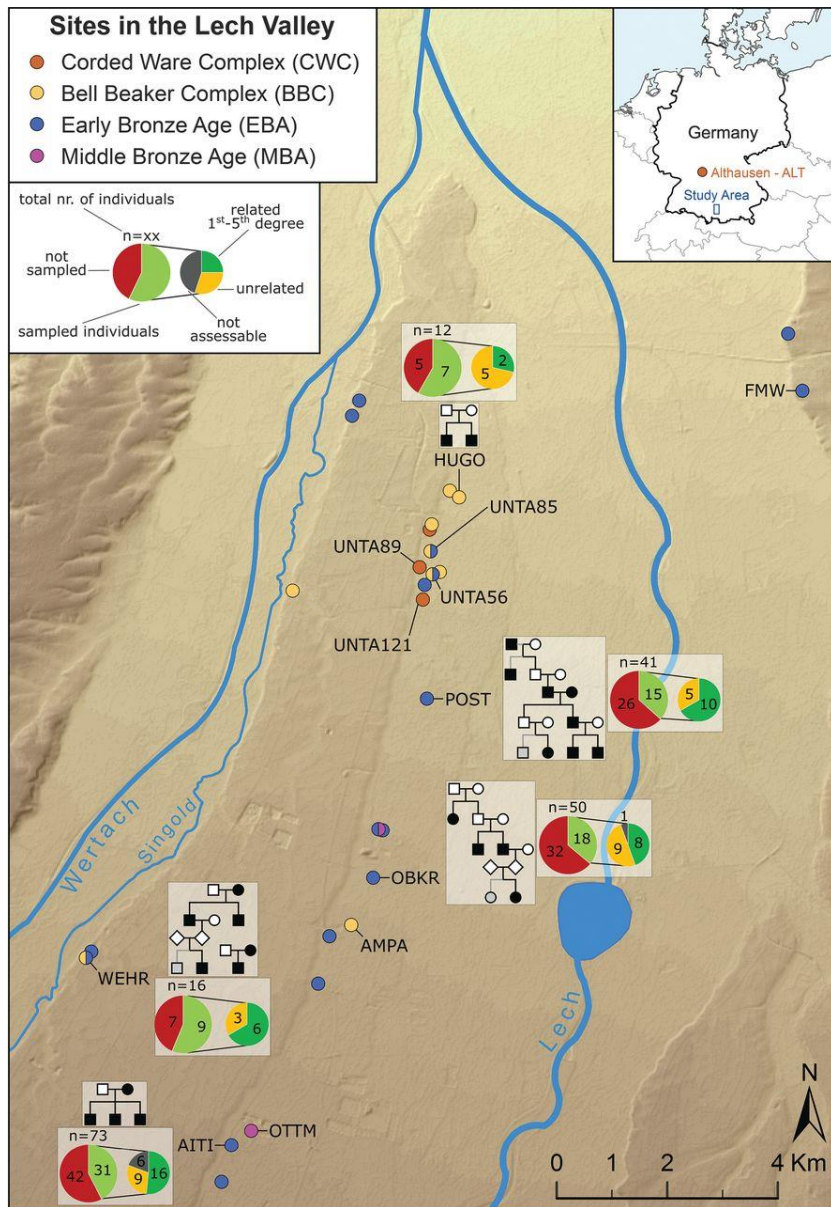


Cumulative published ancient human genome-wide data

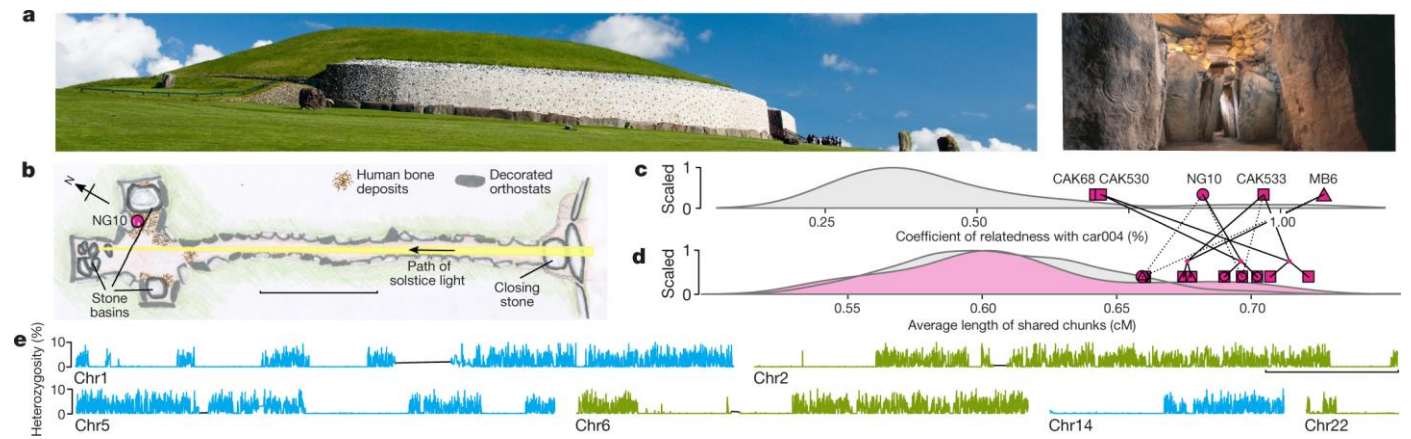




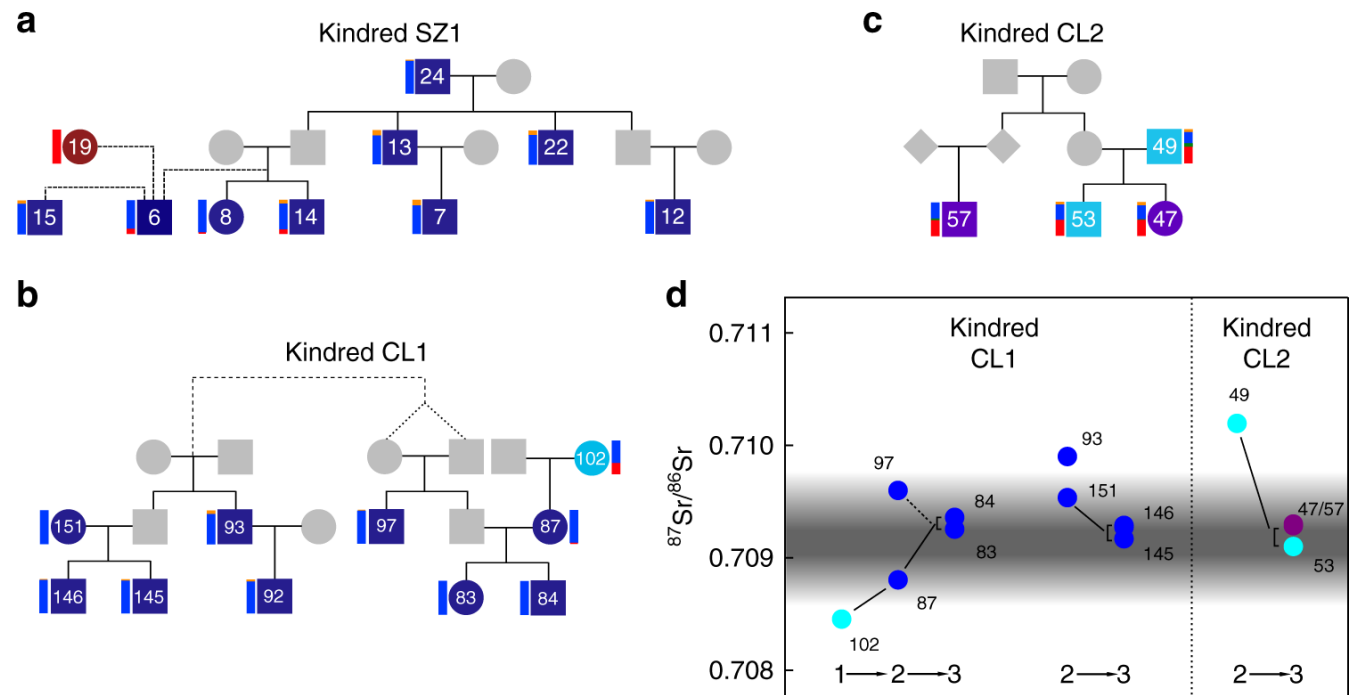
Haak, Lazaridis et al. 2015 *Massive migration from the steppe was a source for Indo-European languages in Europe*⁴



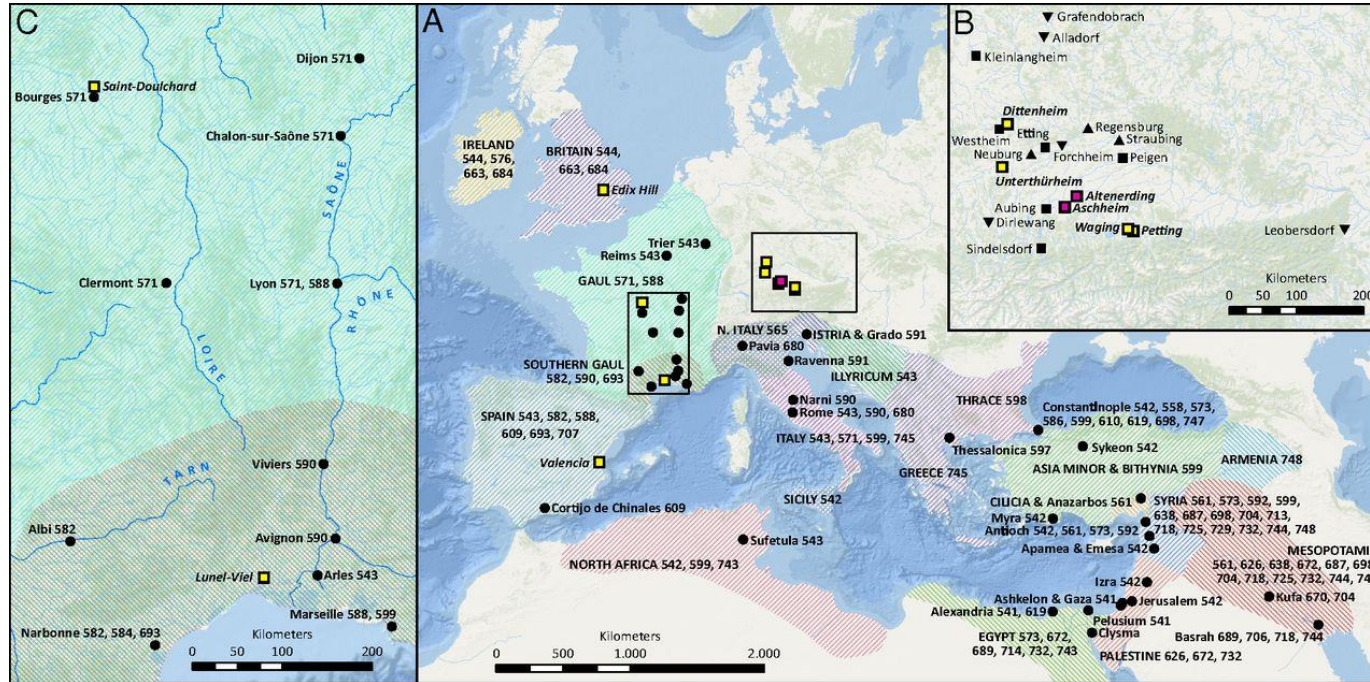
Mitnik et al. 2019 *Kinship-based social inequality in Bronze Age Europe*



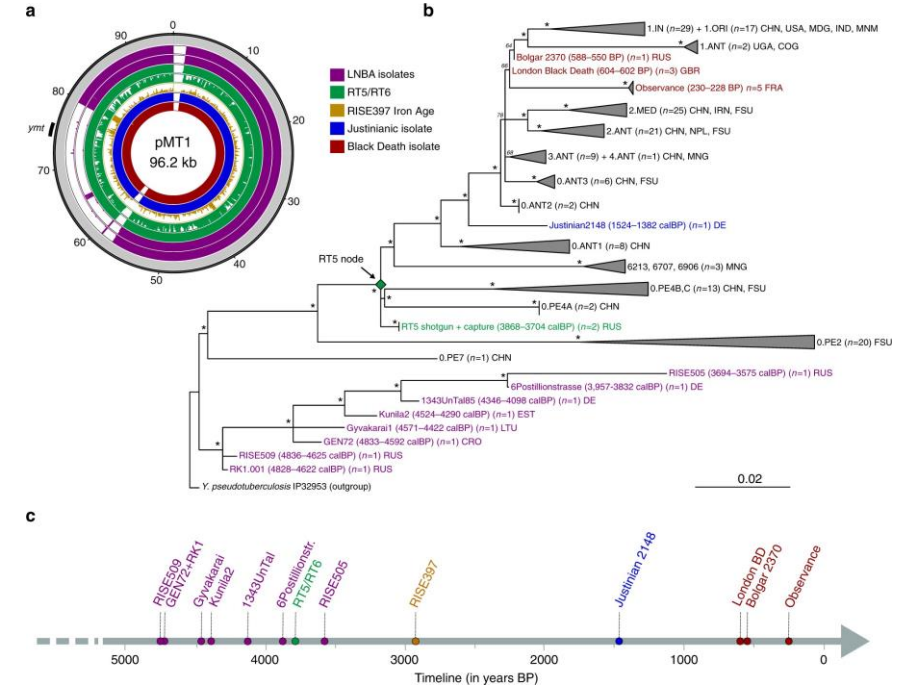
Cassidy et al. 2020 *A dynastic elite in monumental Neolithic society*



Amorim et al. 2018 *Understanding 6th-century barbarian social organization and migration through paleogenomics*



Keller et al. 2018 Ancient *Yersinia pestis* genomes from across Western Europe reveal early diversification during the First Pandemic (541–750)



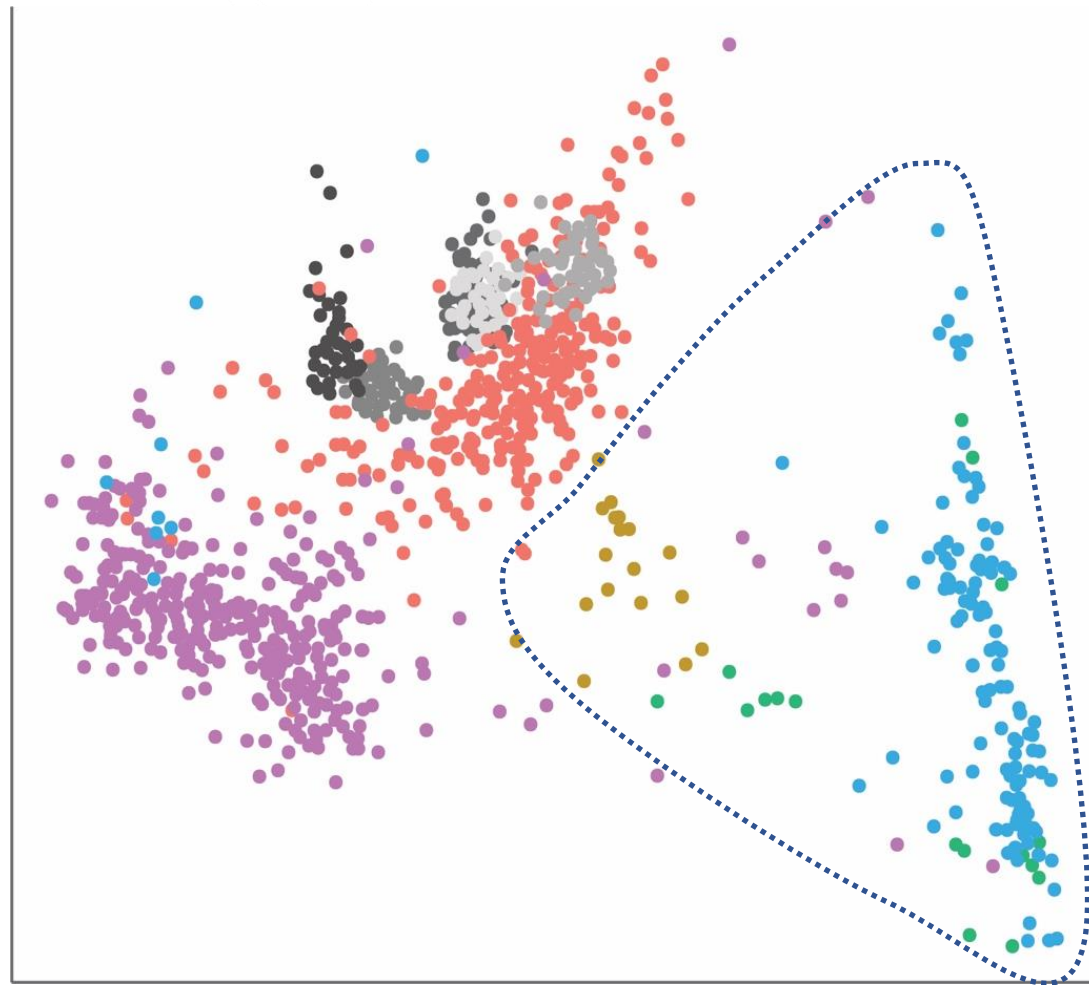
Spyrou et al. 2018 Analysis of 3800-year-old *Yersinia pestis* genomes suggests Bronze Age origin for bubonic plague

How do humans adapt to environmental, cultural and social change?

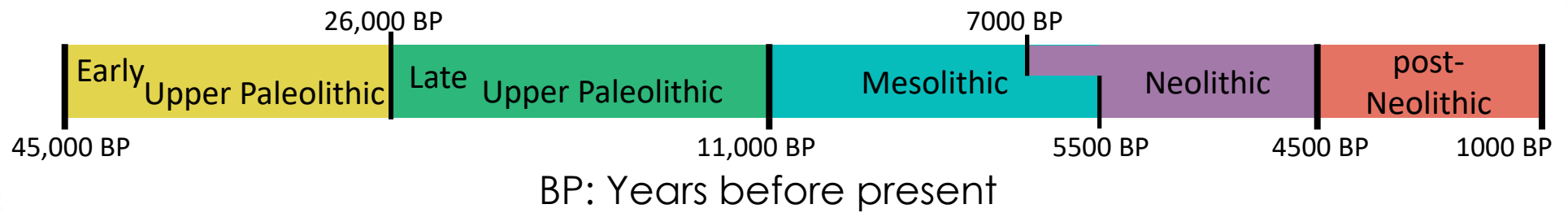


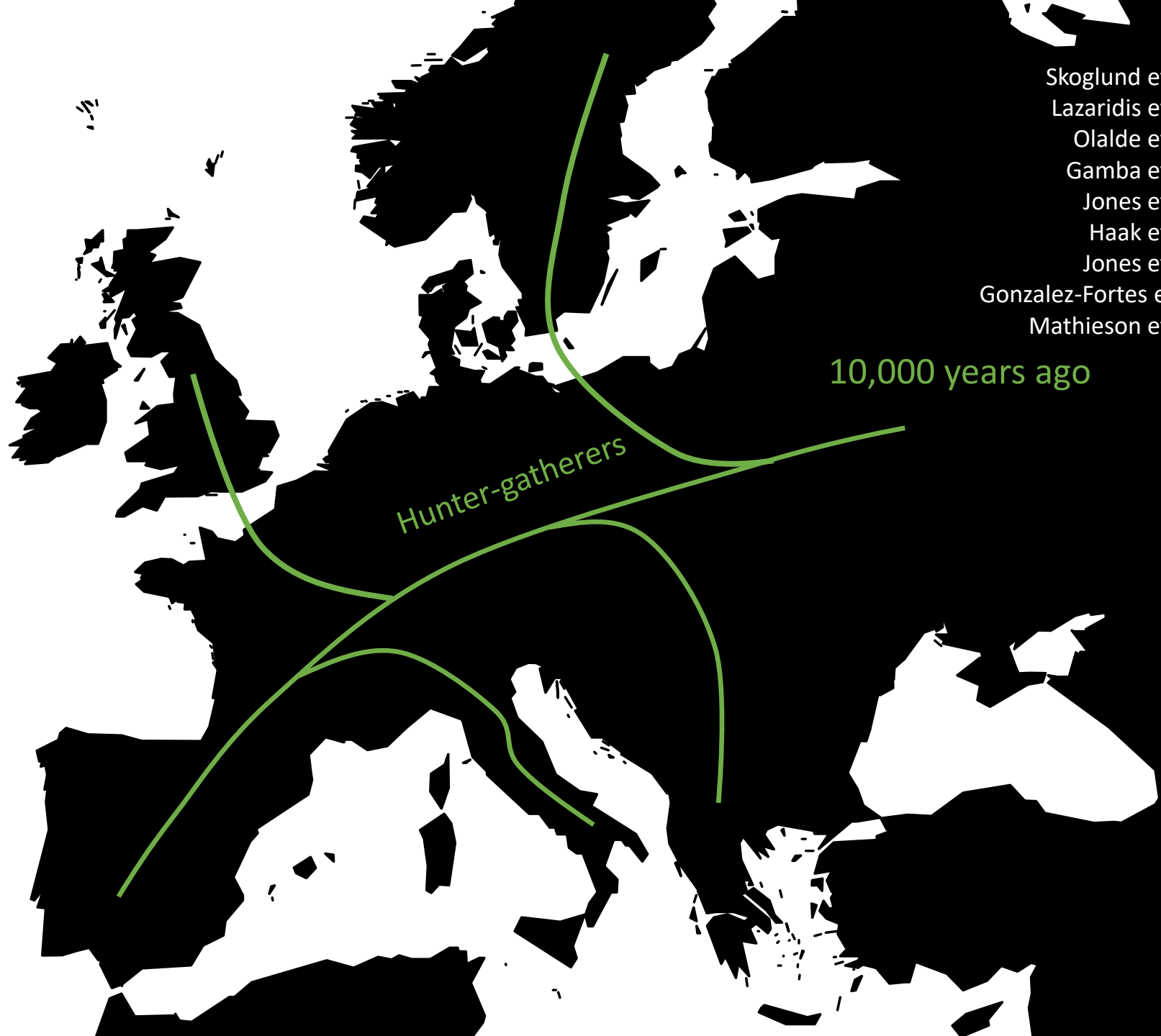


The genetic history of Europe

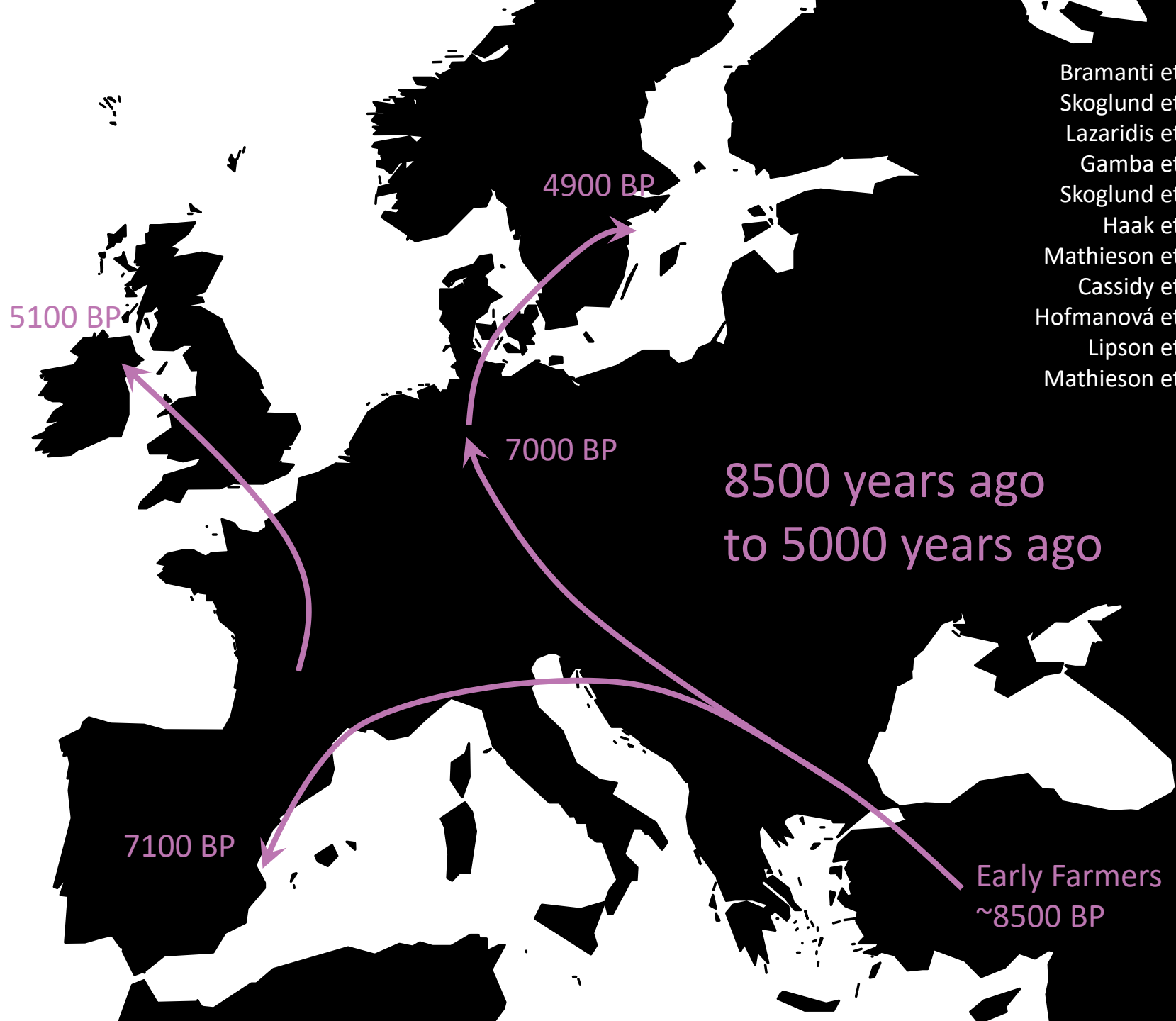


- Early Upper Paleolithic
- Late Upper Paleolithic
- Mesolithic
- Neolithic
- post-Neolithic
- Great Britain (GBR)
- Finland (FIN)
- Iberian (IBS)
- Northern European (CEU)
- Italian (TSI)

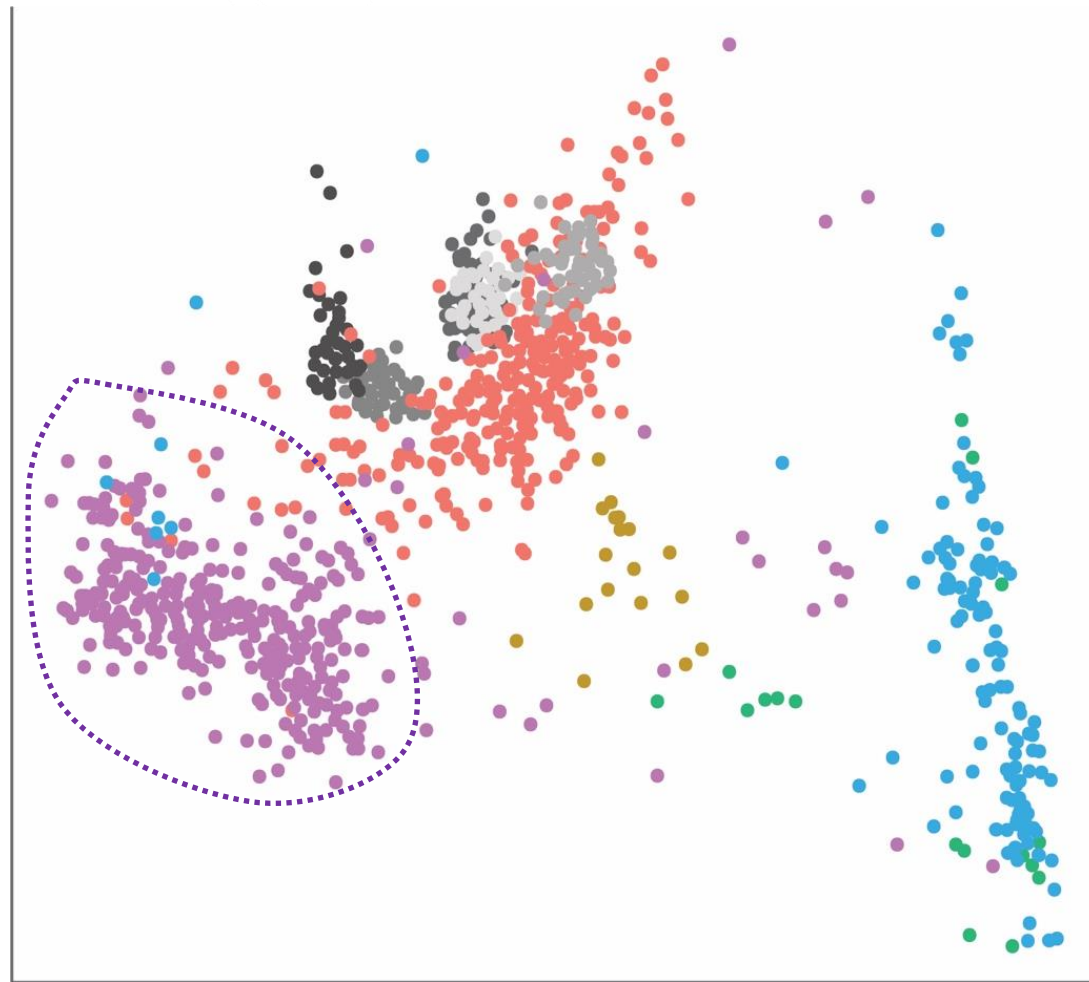




Skoglund et al. 2012
Lazaridis et al. 2014
Olalde et al. 2014
Gamba et al. 2014
Jones et al. 2015
Haak et al. 2015
Jones et al. 2017
Gonzalez-Fortes et al 2018
Mathieson et al. 2018



Bramanti et al. 2009
Skoglund et al. 2012
Lazaridis et al. 2014
Gamba et al. 2014
Skoglund et al. 2014
Haak et al. 2015
Mathieson et al. 2015
Cassidy et al. 2016
Hofmanová et al. 2016
Lipson et al. 2017
Mathieson et al. 2018

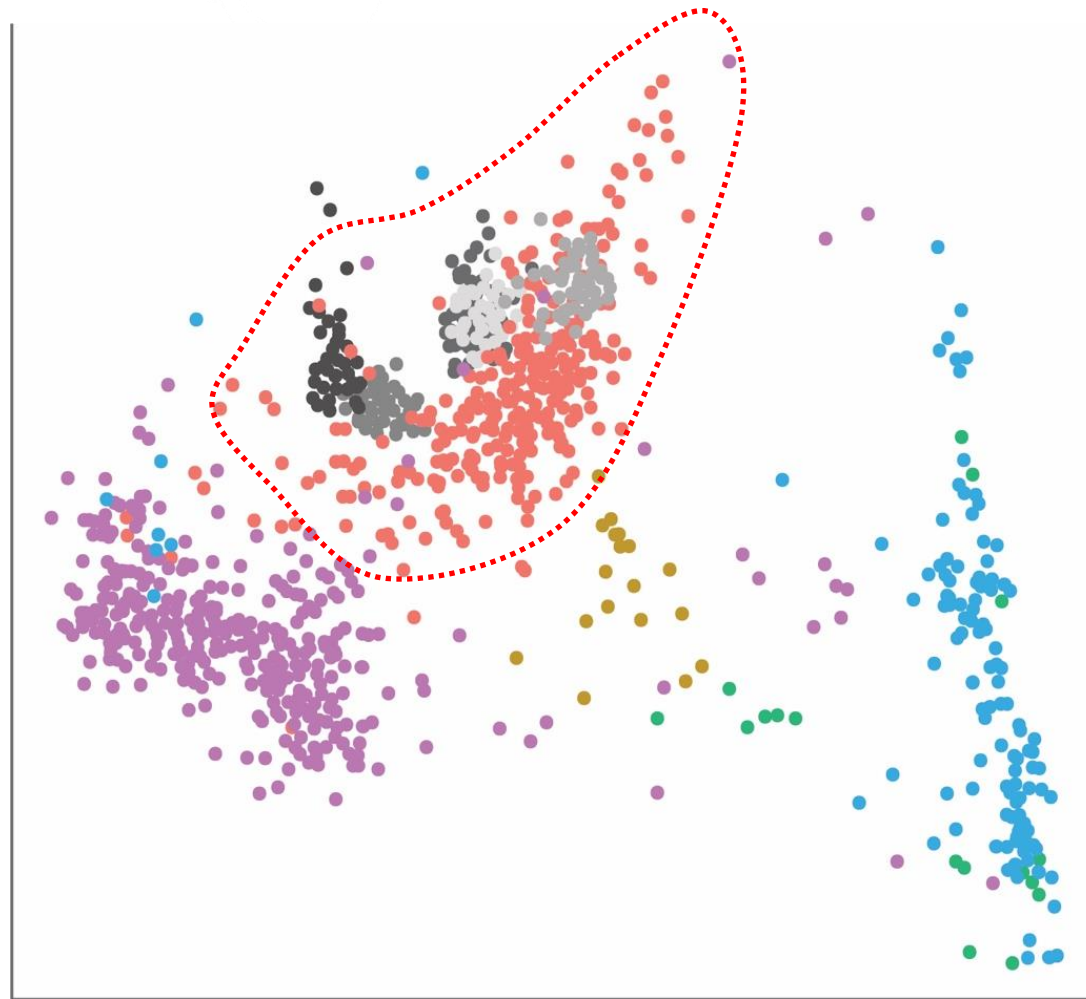


- Early Upper Paleolithic
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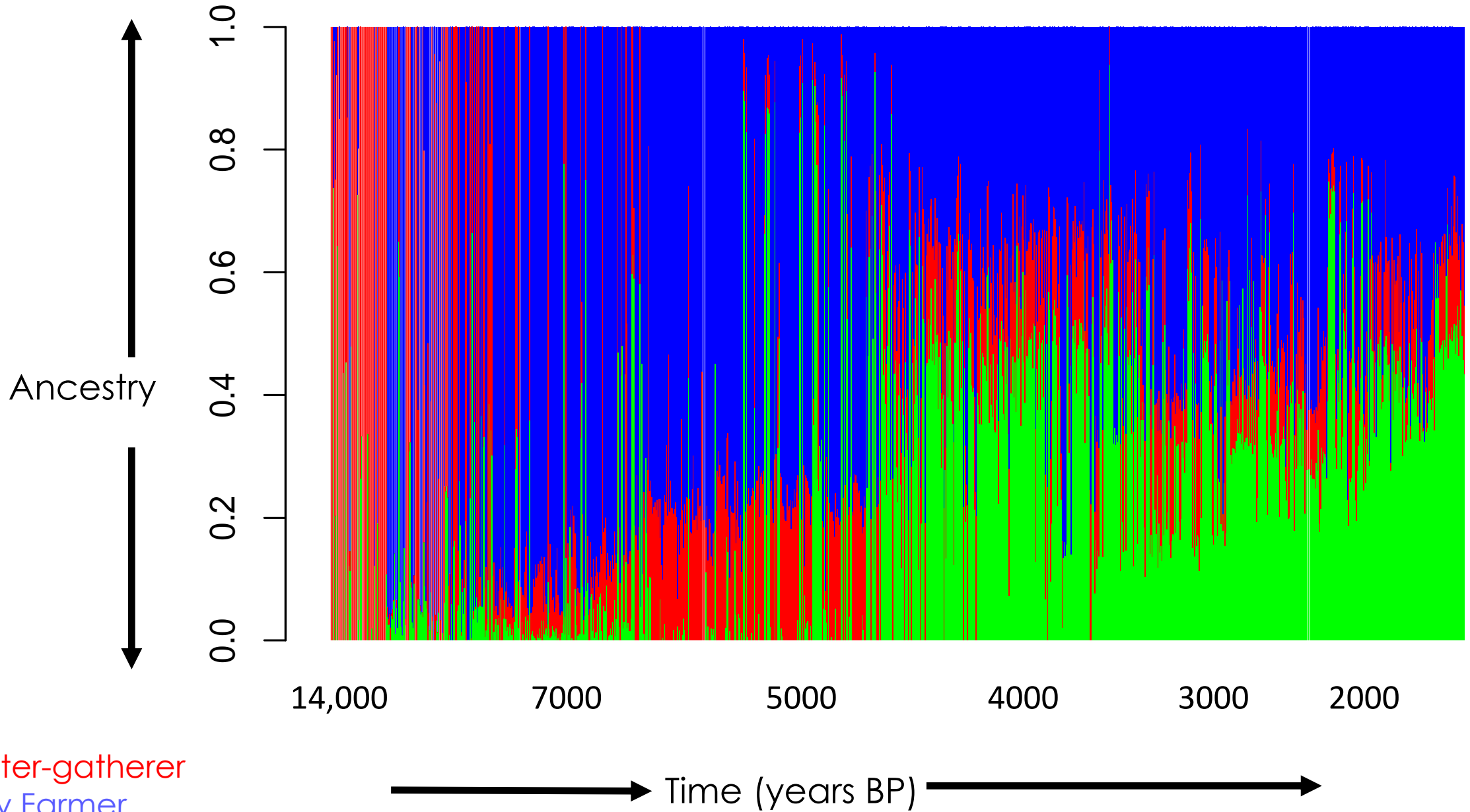
Allentoft et al. 2015
Haak et al. 2015
Olalde et al. 2018
Gamba et al. 2014
Cassidy et al. 2016





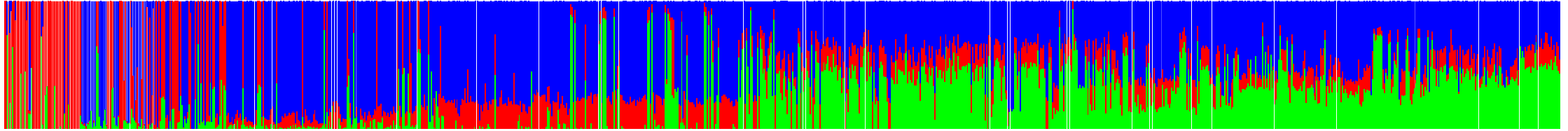
- Early Upper Paleolithic
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- Great Britain (GBR)
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- Northern European (CEU)
- Italian (TSI)





Hunter-gatherer
Early Farmer
Steppe

How do humans adapt to environmental, cultural and social change?



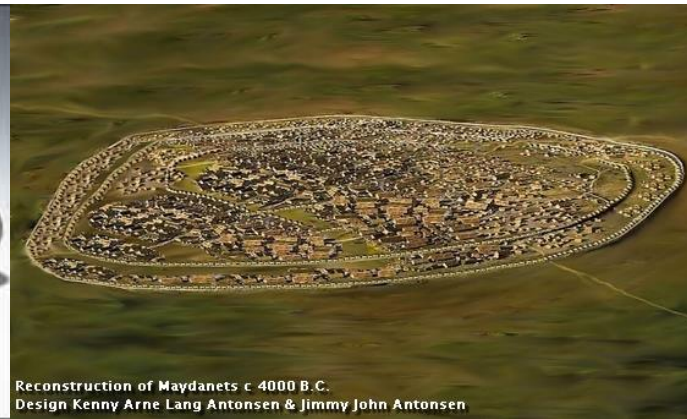
Changes in genetic ancestry



Agriculture



Metallurgy



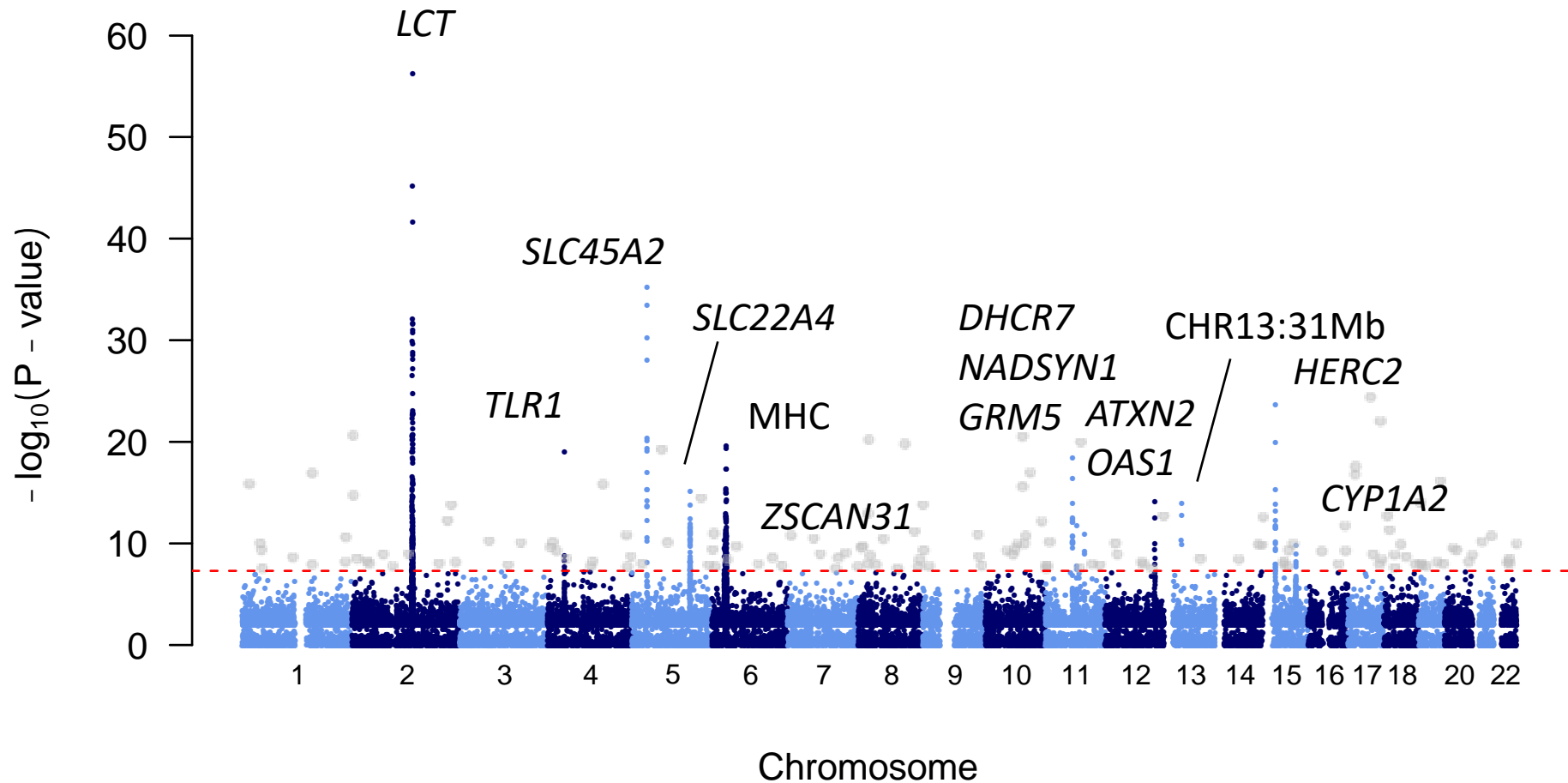
Urbanization



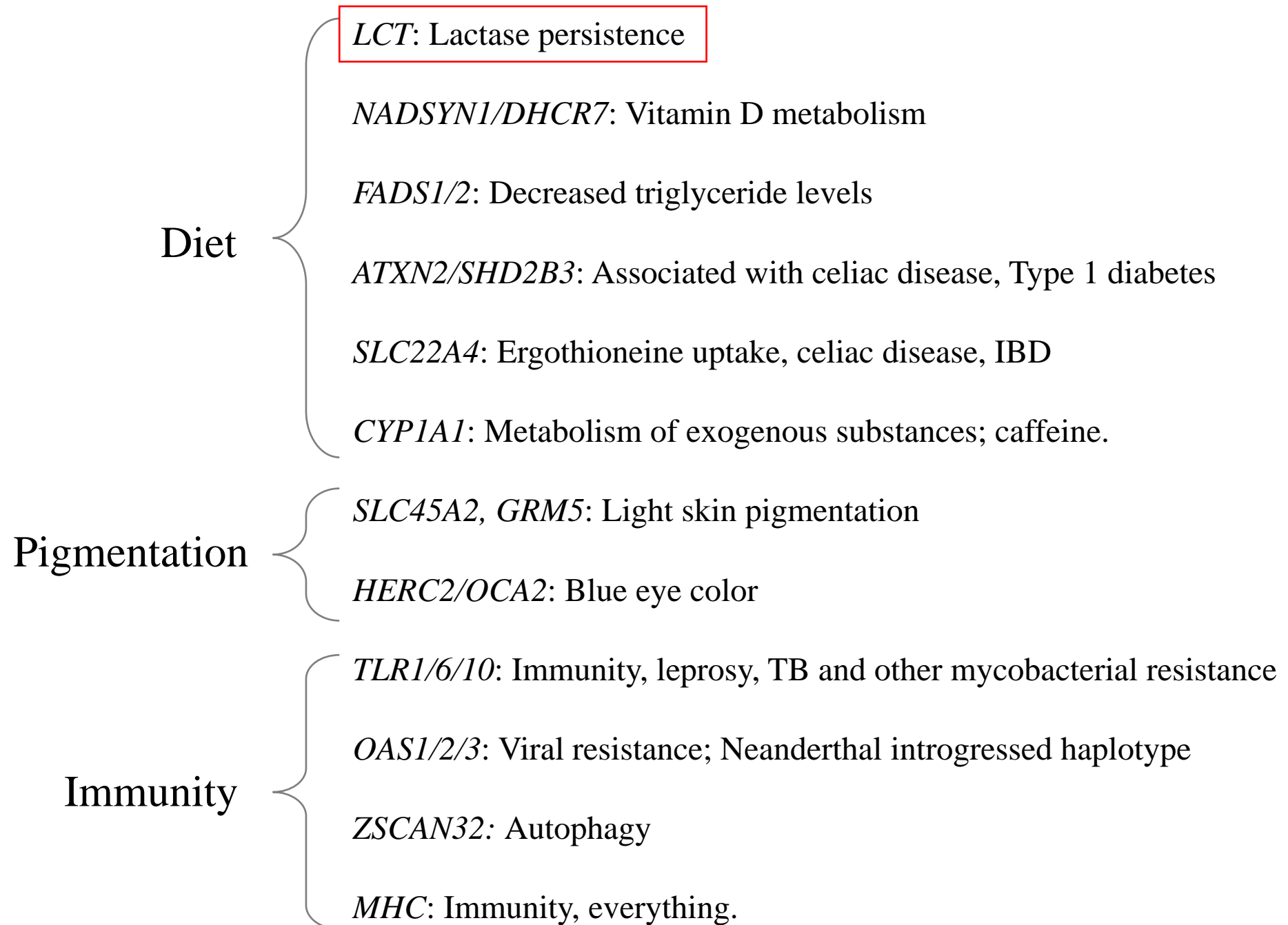
Social hierarchy

Detecting selection with ancient DNA

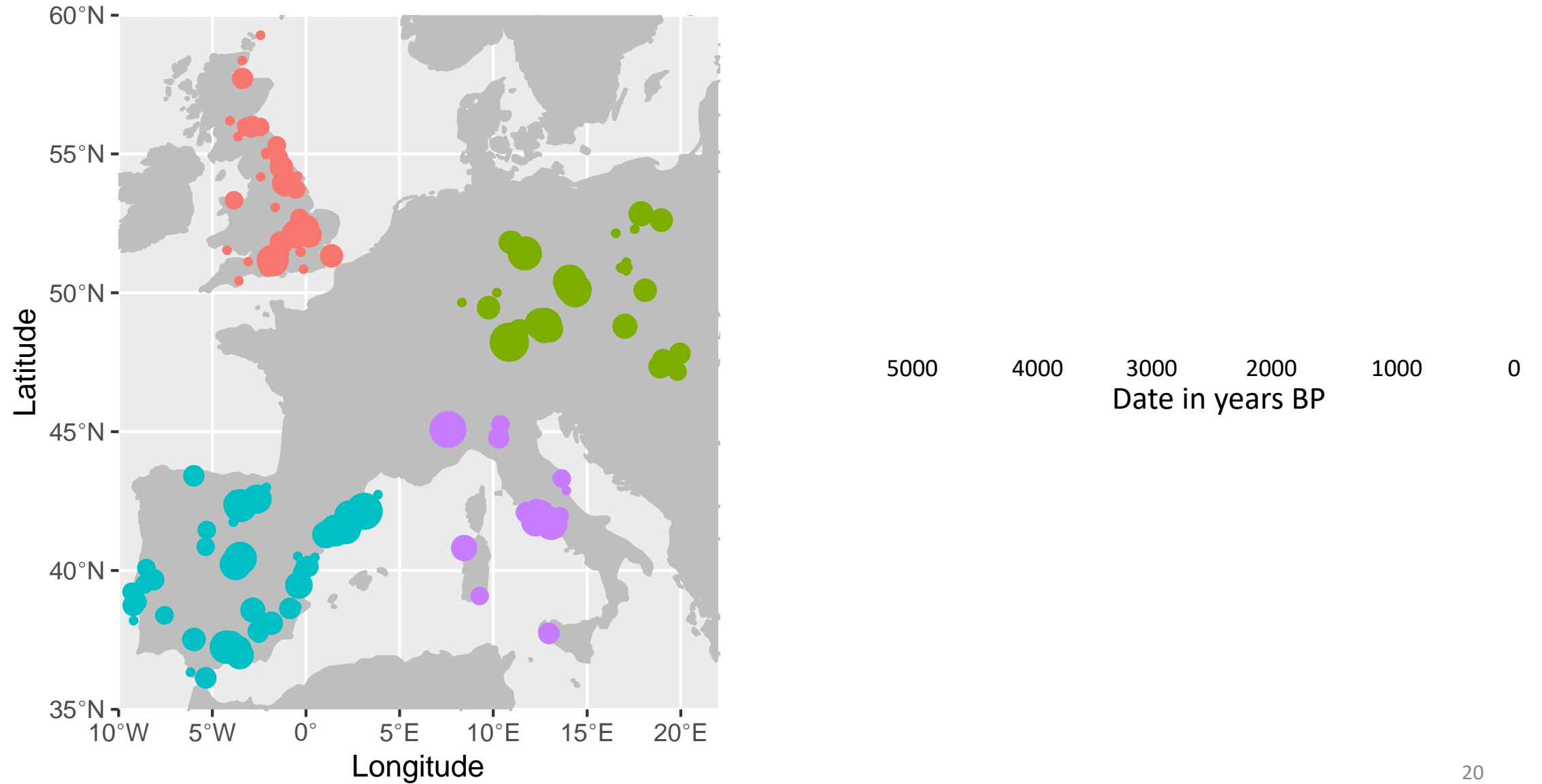
14 genome-wide significant signals of selection



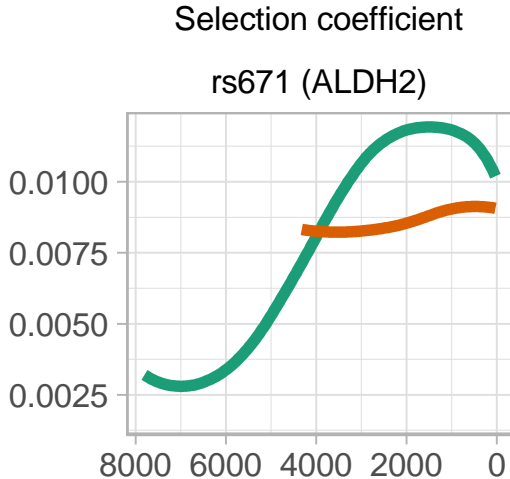
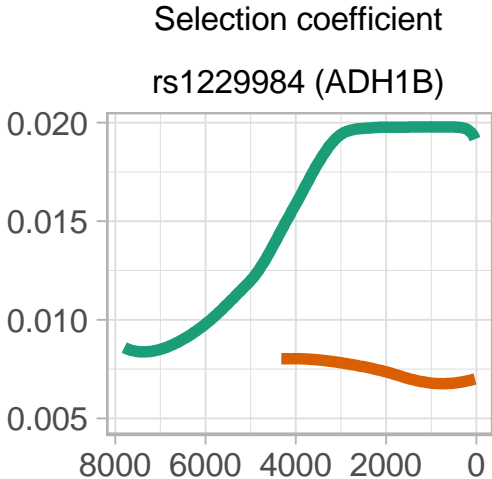
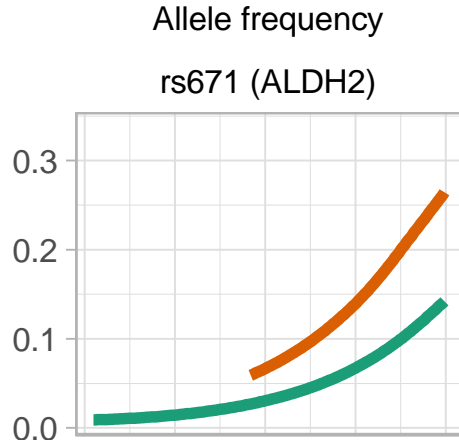
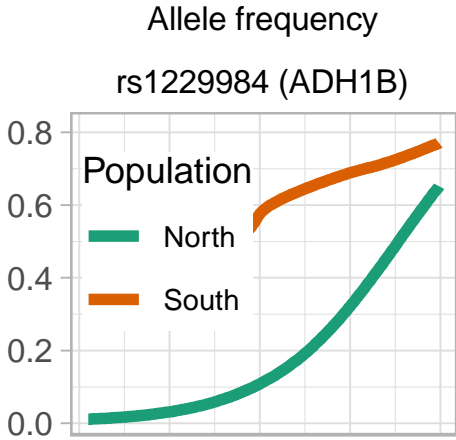
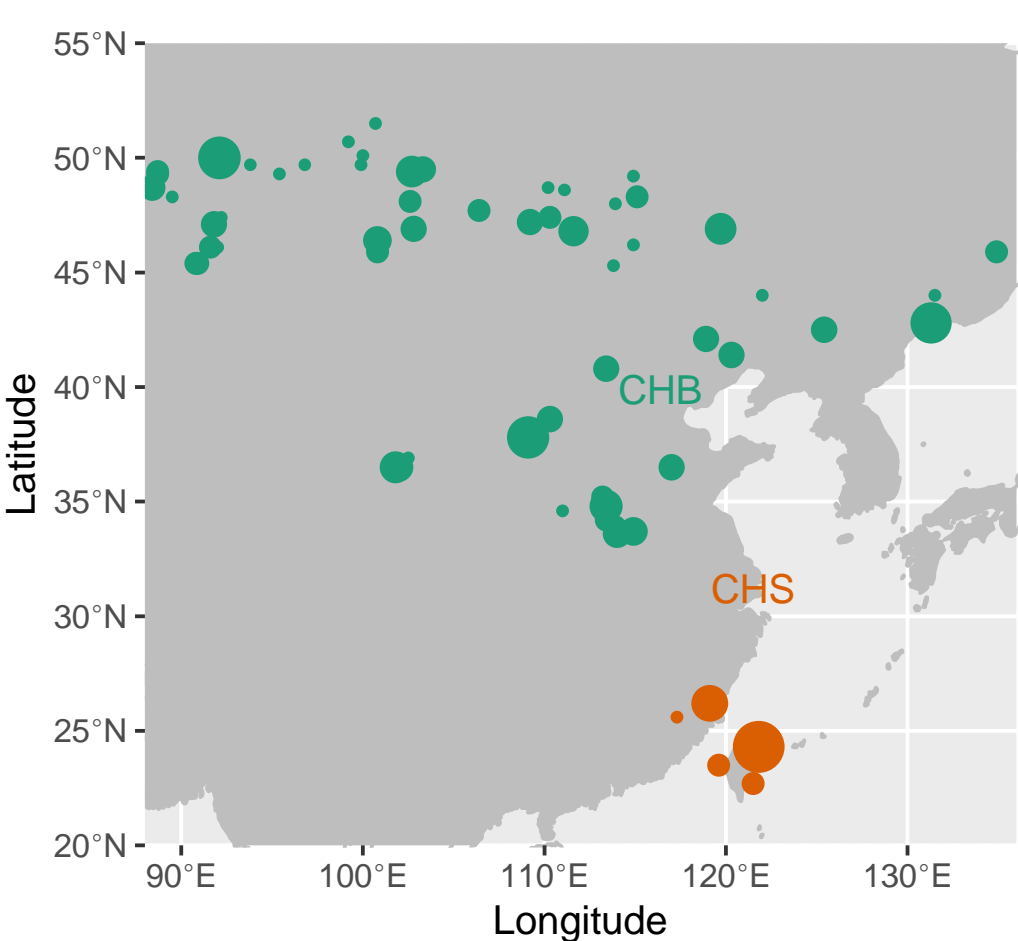
Mathieson I et al.
Genome-wide signals of selection in 230 ancient Eurasians
December 2015



Lactase persistence appears very recently



Selection on the alcohol dehydrogenase pathway in East Asia



Diet

LCT: Lactase persistence

NADSYN1/DHCR7: Vitamin D metabolism

FADS1/2: Decreased triglyceride levels

ATXN2/SHD2B3: Associated with celiac disease, Type 1 diabetes

SLC22A4: Ergothioneine uptake, celiac disease, IBD

CYP1A1: Metabolism of exogenous substances; caffeine.

Pigmentation

SLC45A2, GRM5: Light skin pigmentation

HERC2/OCA2: Blue eye color

Immunity

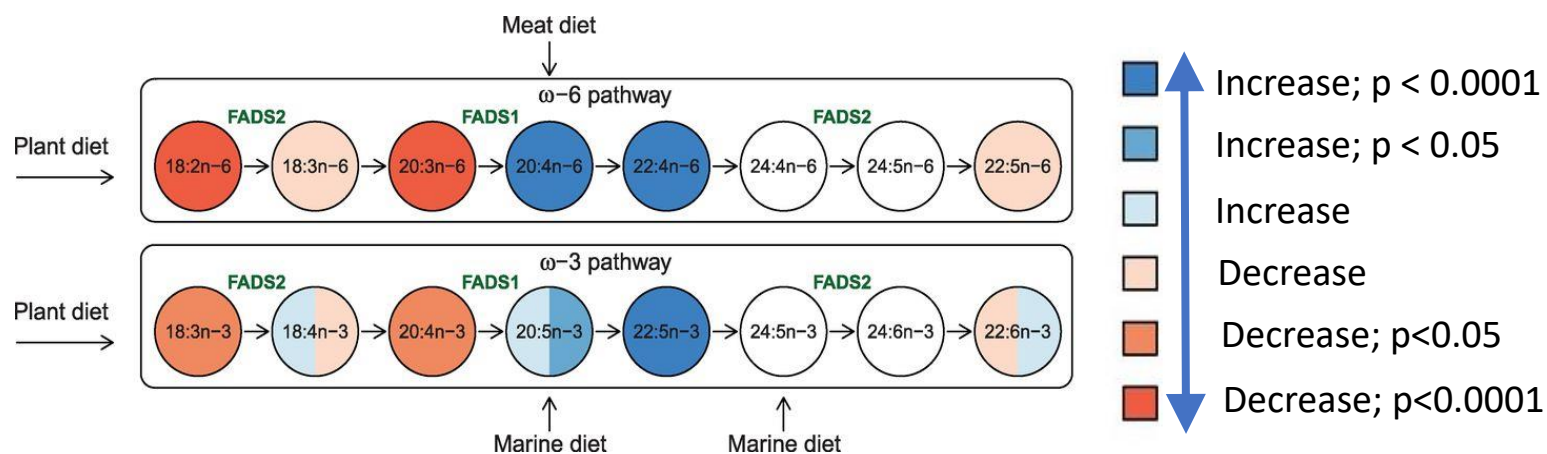
TLR1/6/10: Immunity, leprosy, TB and other mycobacterial resistance

OAS1/2/3: Viral resistance; Neanderthal introgressed haplotype

ZSCAN32: Autophagy

MHC: Immunity, everything.

What does the selected FADS allele do?



Fumagalli et al 2015

Top 10 UK Biobank PheWAS

Trait	p-value
Mean platelet (thrombocyte) volume	3.0477e-105
Red blood cell (erythrocyte) distribution width	5.1363e-93
Platelet count	1.256e-87
Red blood cell (erythrocyte) count	1.2592e-50
Haemoglobin concentration	5.6775e-40
Monocyte percentage	8.5623e-30
Platelet crit	2.7662e-25
Mean spheroid cell volume	4.3386e-25
Eosinophil count	5.2404e-25
Haematocrit percentage	1.8602e-23
Mean corpuscular volume	2.7039e-21

<http://geneatlas.roslin.ed.ac.uk>

One of the most significant genome-wide signals for lipids (Teslovitch et al. 2010)

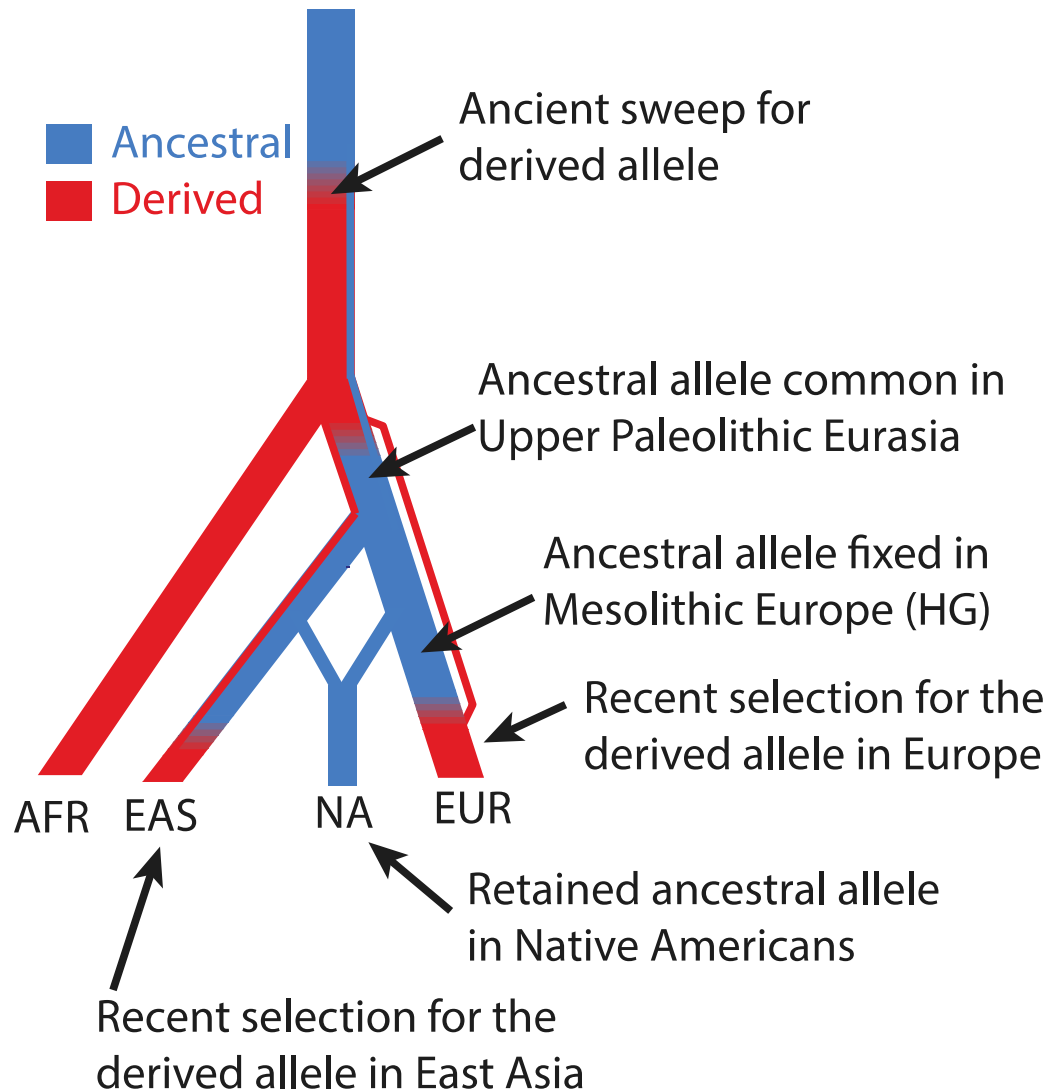
Other associations:

Sex-hormone binding globulin (P=10⁻²⁰)

Male testosterone (P=10⁻⁵)

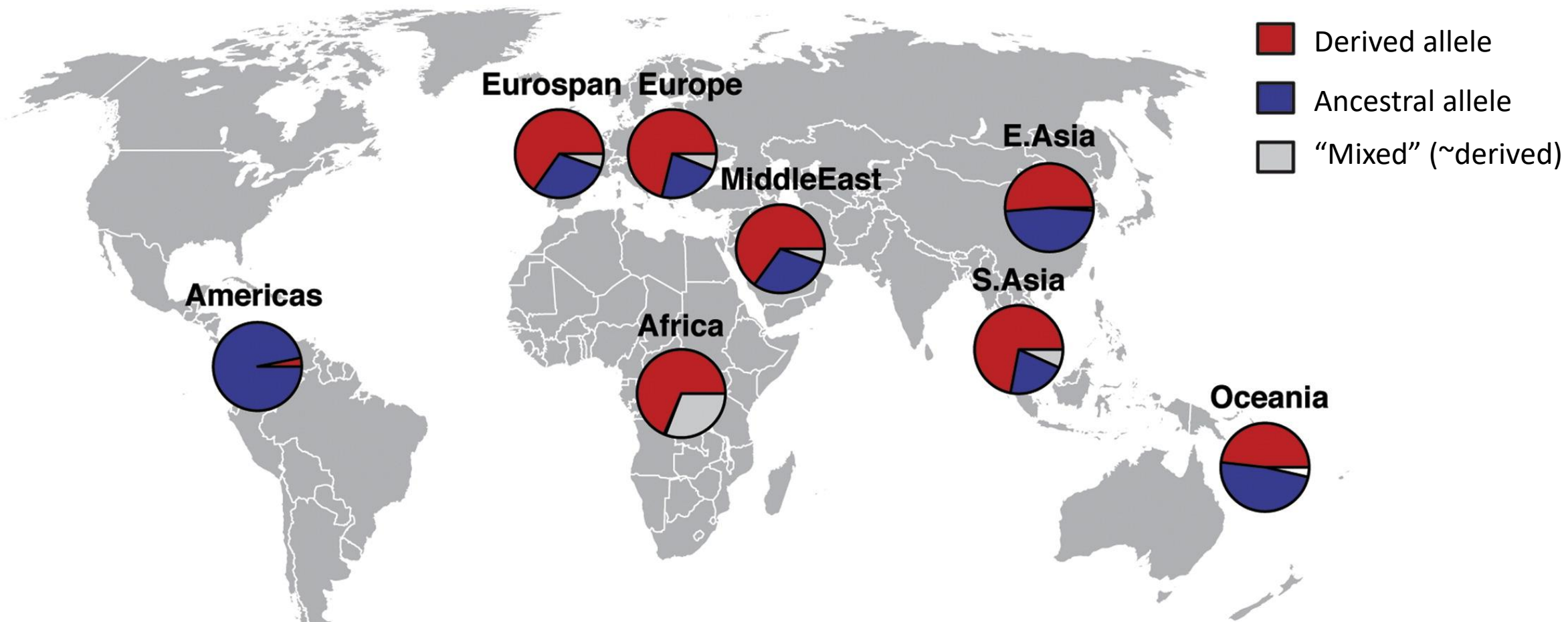
Male estradiol (P=10⁻⁴)

In fact, *FADS1* has been under selection for hundreds of thousands of years...

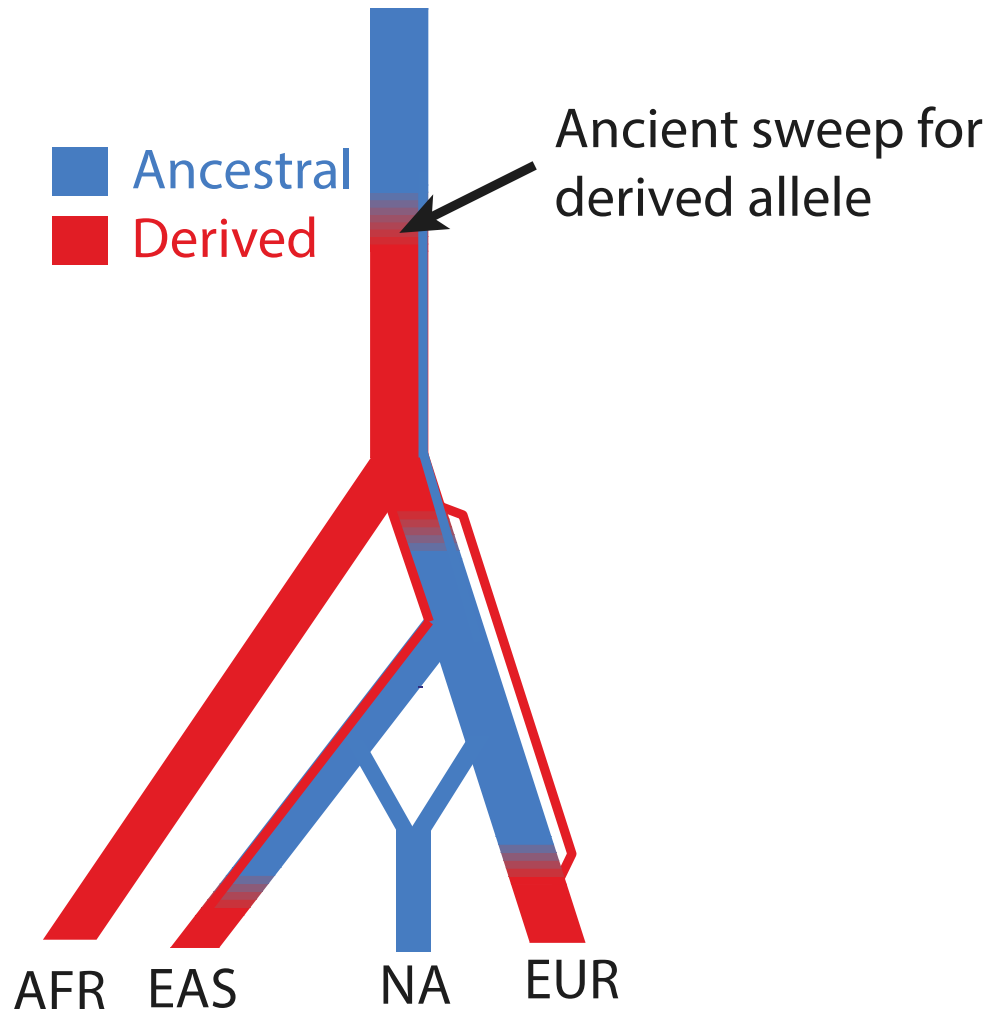


See also:
Harris et al. 2019
Hlusko et al. 2019
Mathieson & Mathieson 2018
Buckley et al. 2017
Ye et al. 2017
Amorim et al. 2017
Mathieson et al. 2015
Fumagalli et al. 2015
Mathias et al. 2012
Ameur et al. 2012

Mathieson (2020)



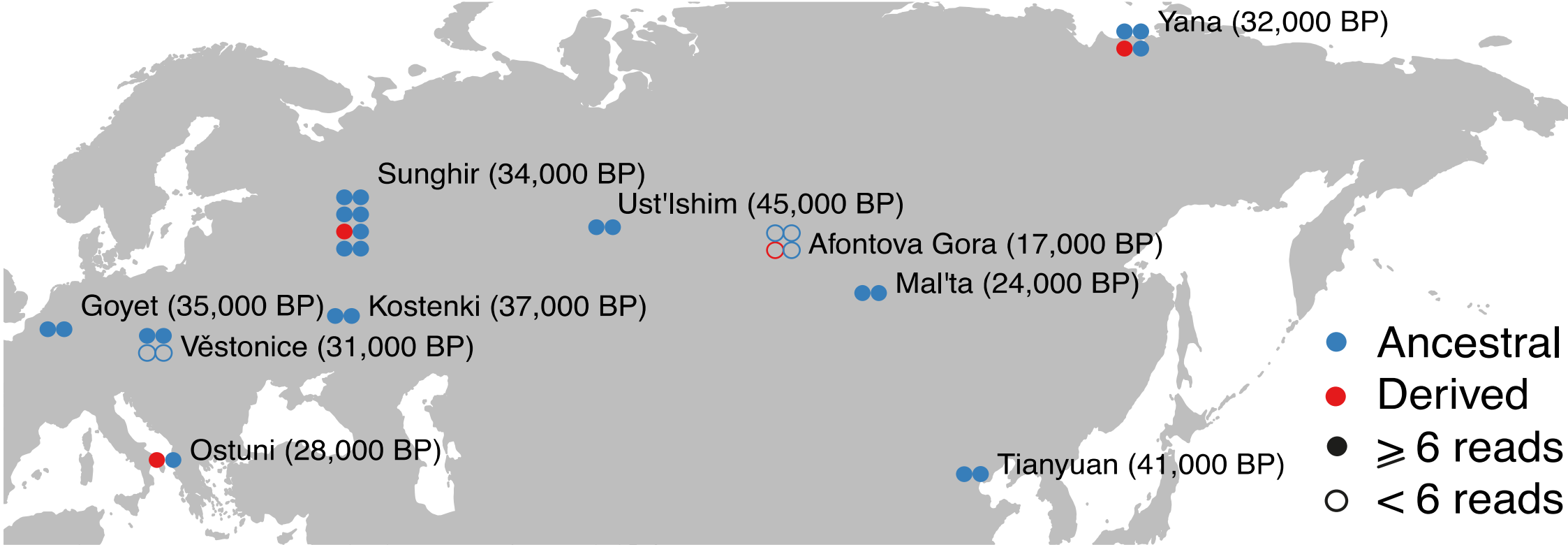
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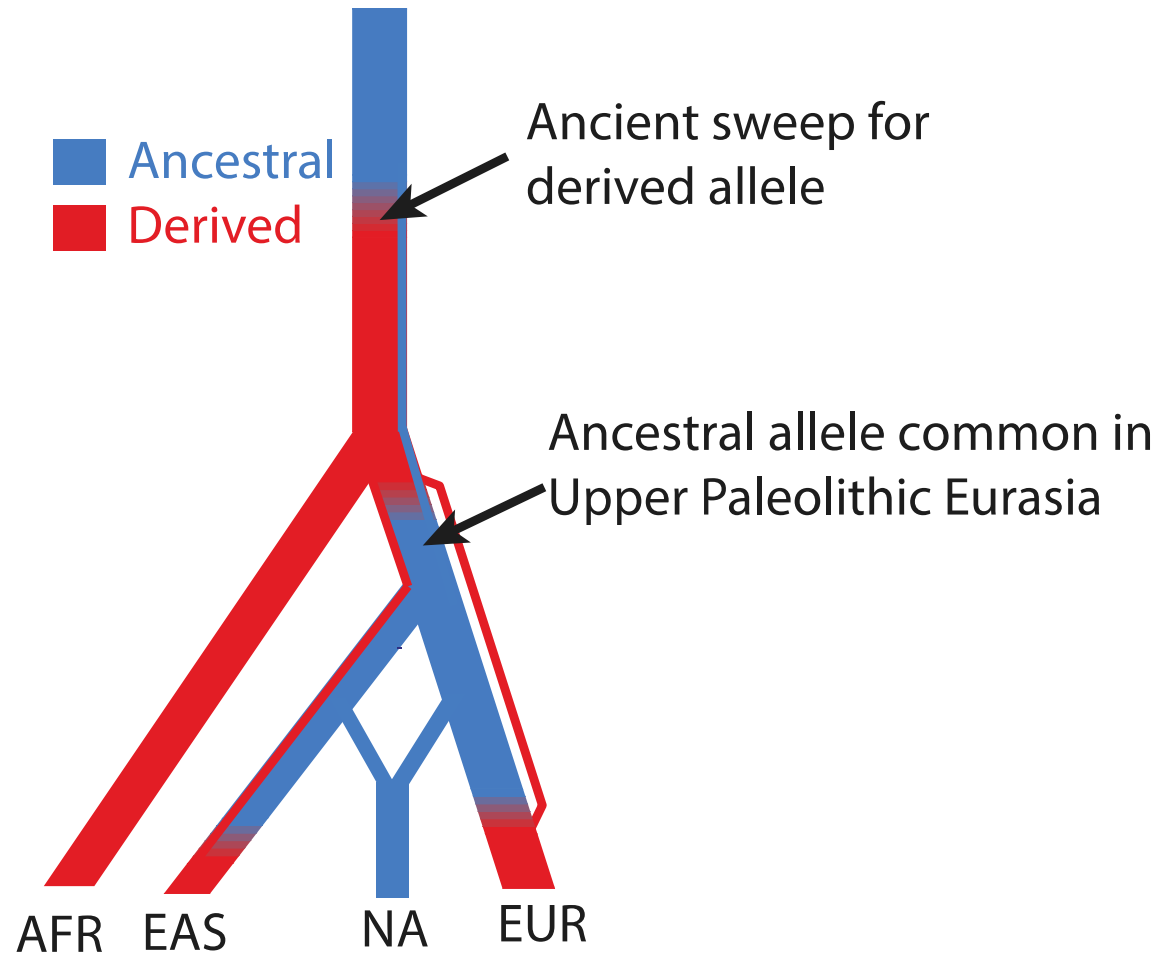
Mathieson (2020)

But.... the selected (ancestral) allele was already common before the split of Eurasian and Native American ancestors



(consistent with a meat-heavy Upper Paleolithic diet)

In fact, *FADS1* has been under selection for hundreds of thousands of years...

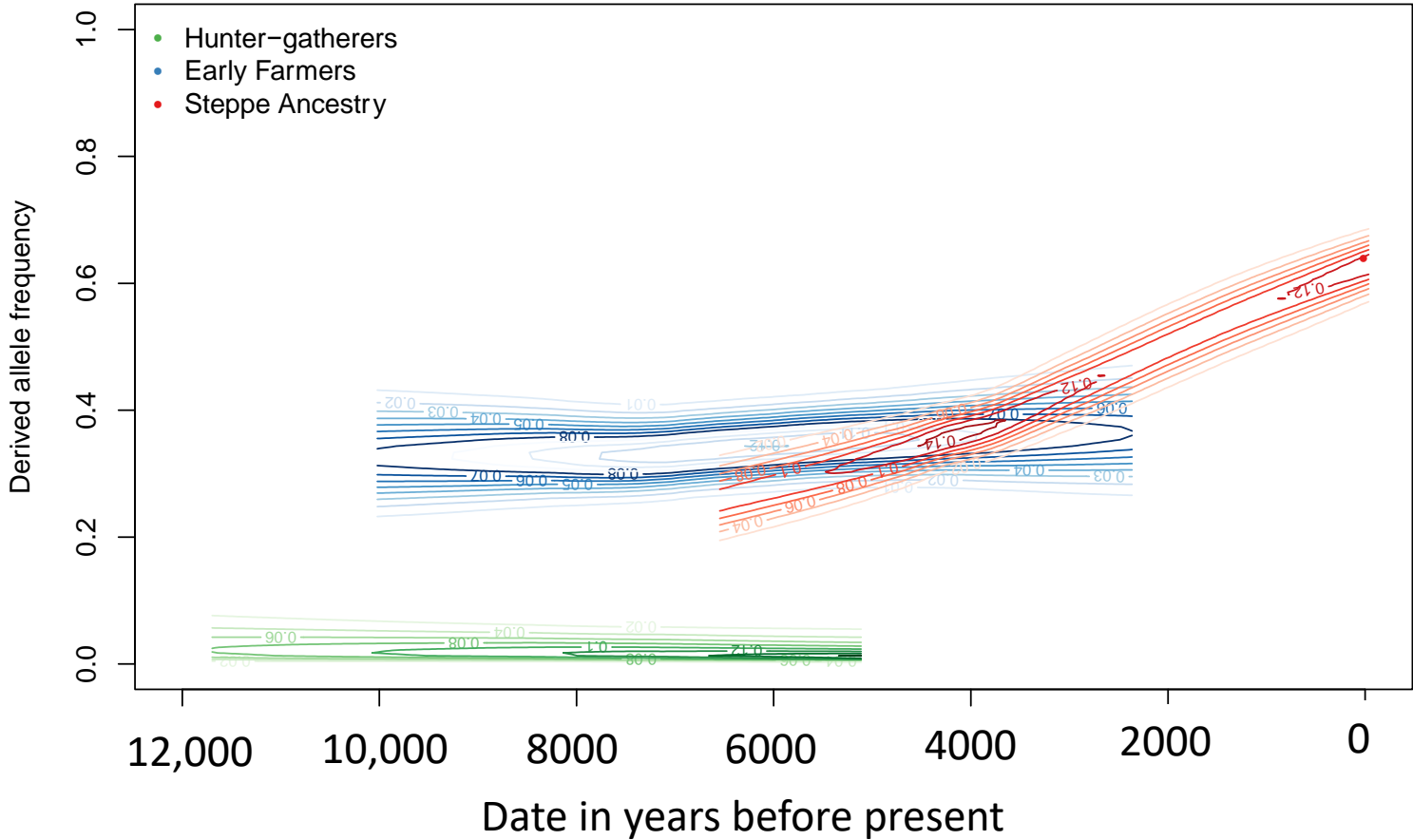


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Harris et al. 2019
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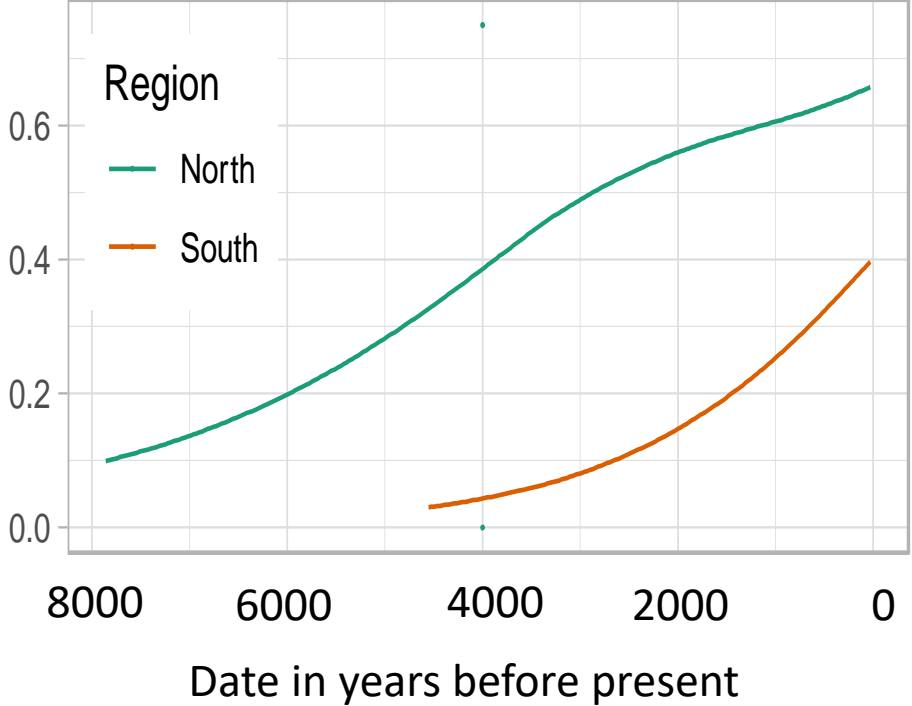
Mathieson (2020)

Direct evidence of selection on the derived allele

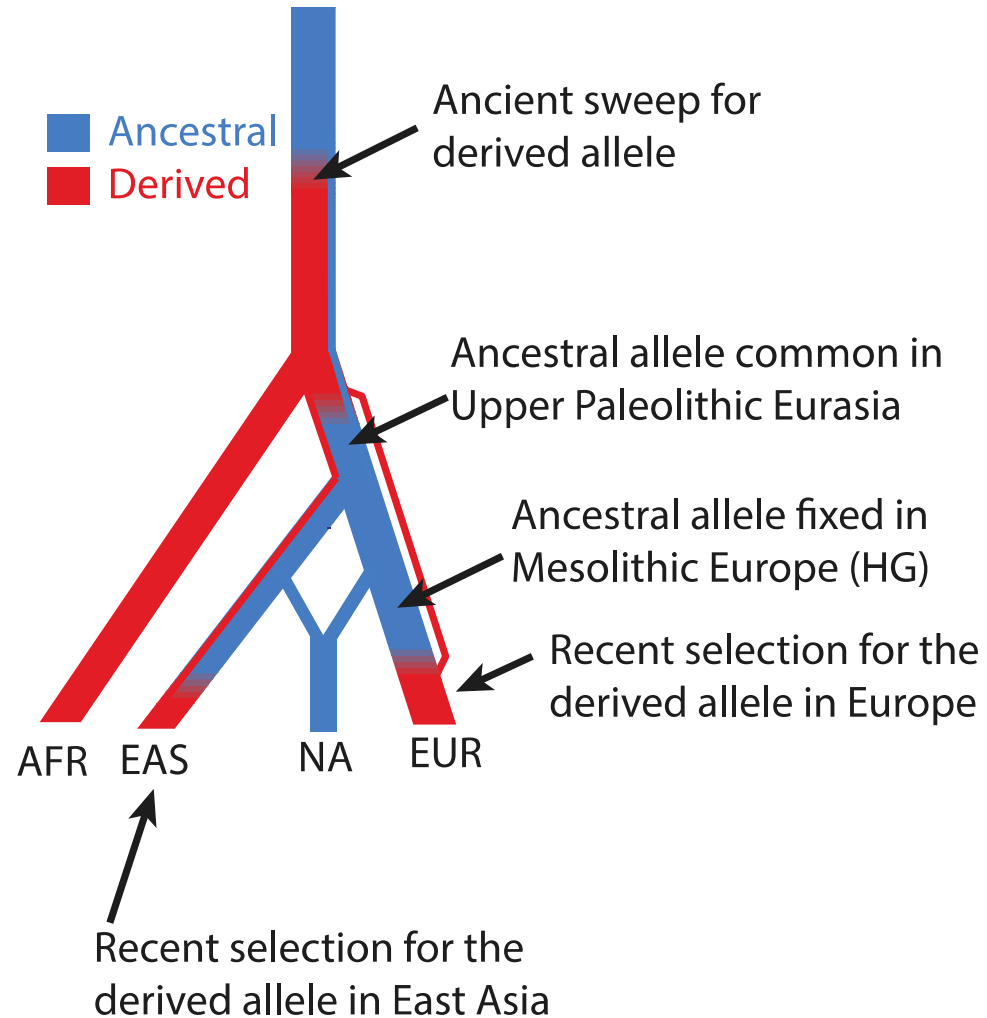
In Europe



In East Asia



In fact, *FADS1* has been under selection for hundreds of thousands of years...



See also:

Harris et al. 2019

Hlusko et al. 2019

Mathieson & Mathieson 2018

Buckley et al. 2017

Ye et al. 2017

Amorim et al. 2017

Mathieson et al. 2015

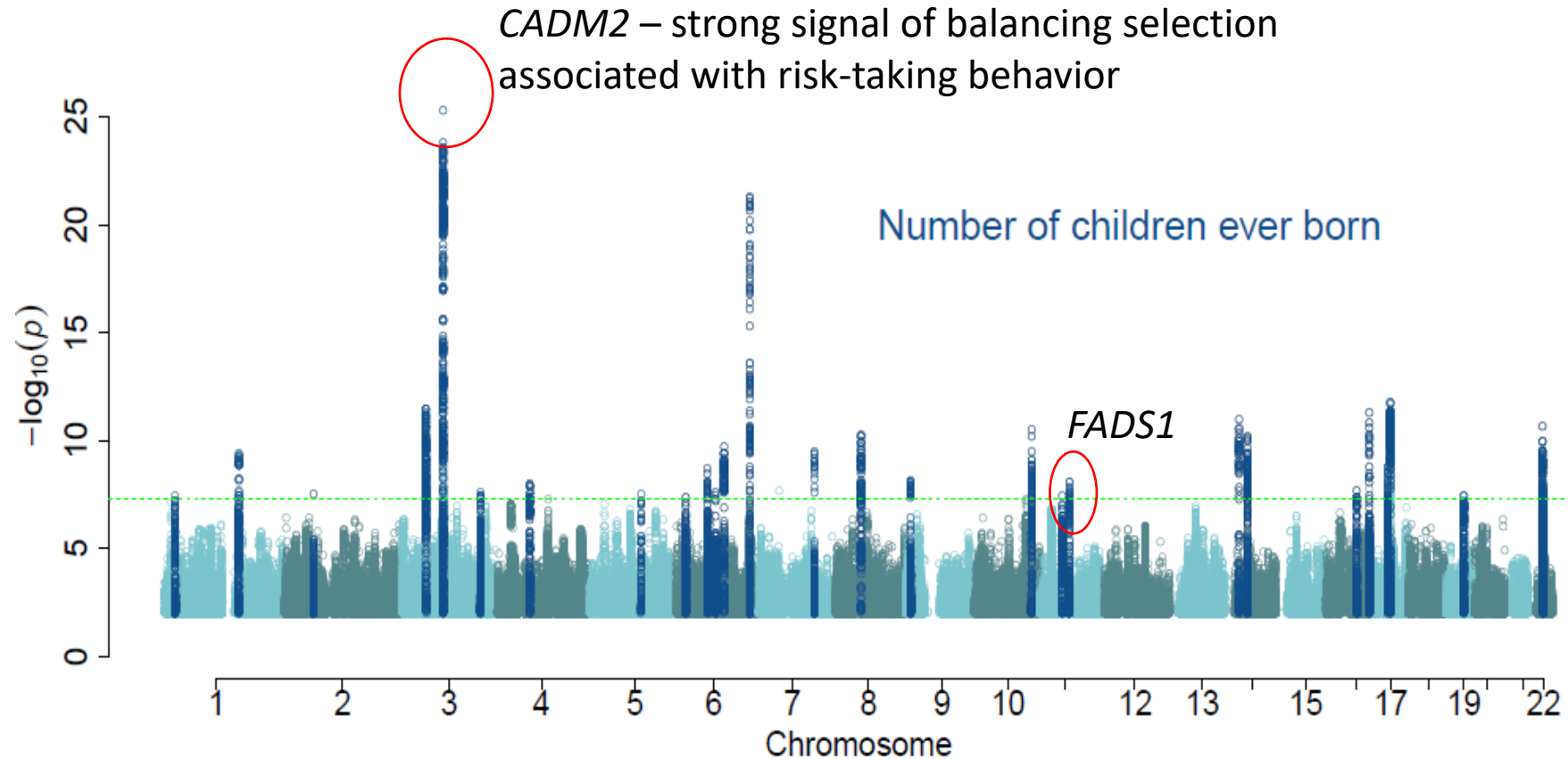
Fumagalli et al. 2015

Mathias et al. 2012

Ameur et al. 2012

Mathieson (2020)

... and may still be under selection today



Mathieson et al. (bioRxiv)
Genome-wide analysis identifies genetic effects on reproductive success and ongoing natural selection at the *FADS* locus.

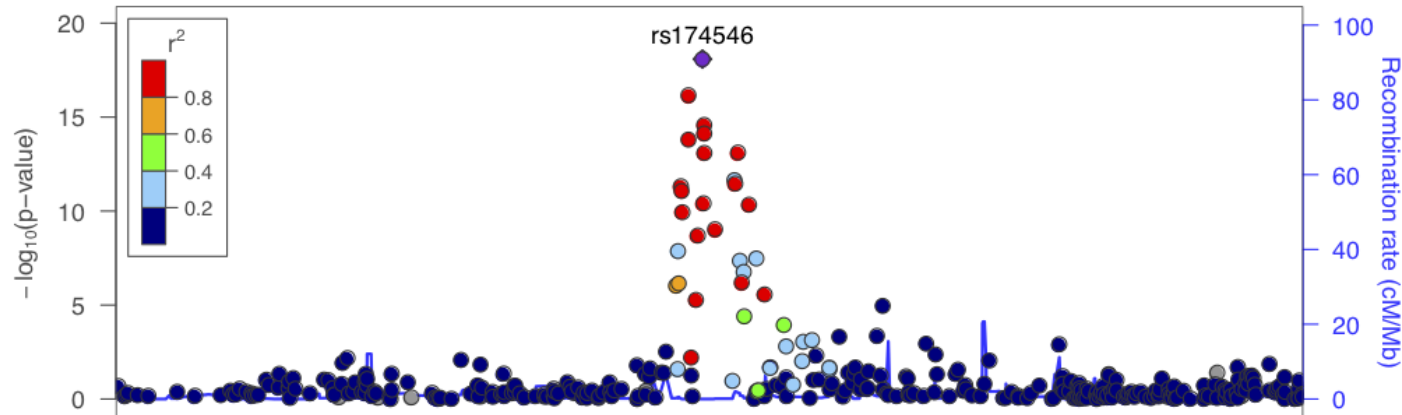


Melinda Mills

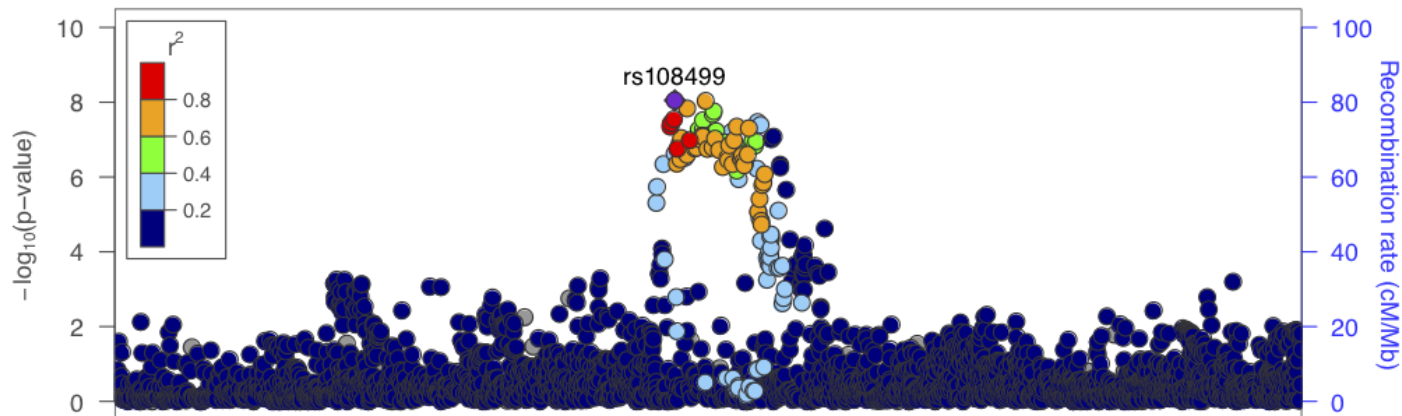


John Perry

... and may still be under selection today



Selection scan (past 10,000 years)
Mathieson et al. (2015); selection
coefficient estimated to be 0.78%

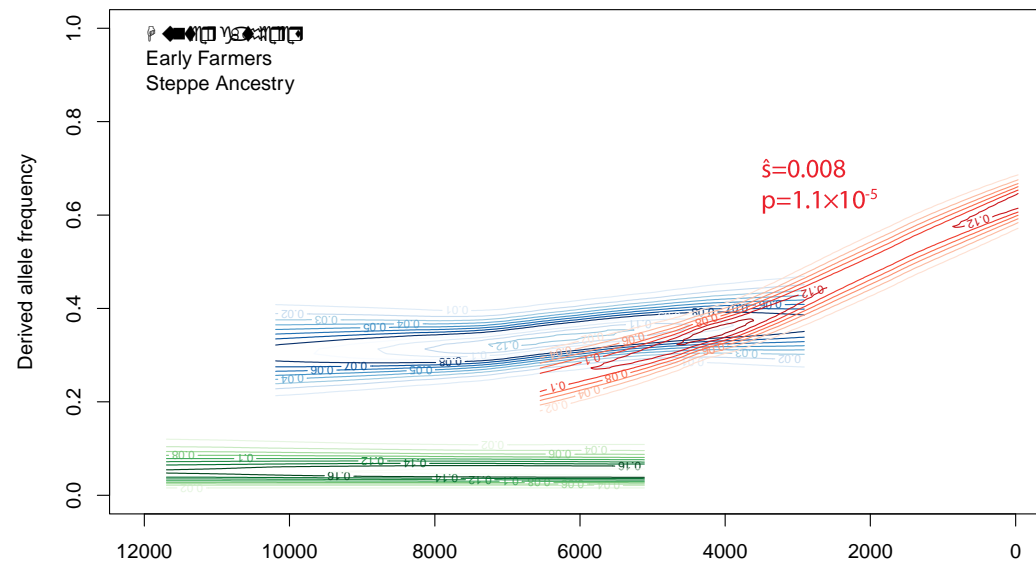


Genome-wide association study for fertility
Derived allele increases number of children
by ~ 0.013 , corresponding to a selection
coefficient of $\sim 0.74\%$

Mathieson et al. (bioRxiv)
Genome-wide analysis identifies genetic effects on reproductive
success and ongoing natural selection at the *FADS* locus.

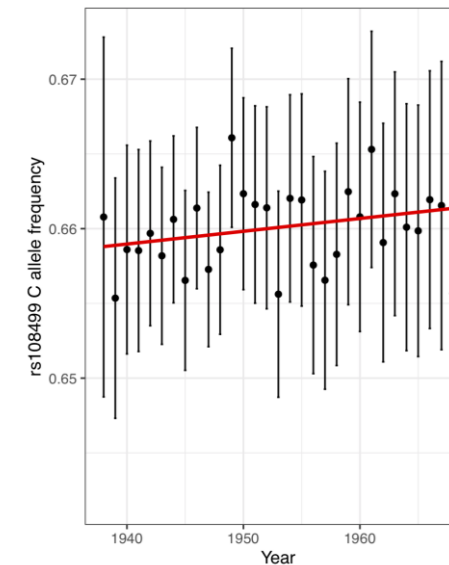
... and may still be under selection today

Increases in frequency by about 20% in 4,000 years
(0.005% per-year, correcting for changes in ancestry)



Mathieson & Mathieson 2018 Years BP

Increases by 0.009% per-birth-year
in UK Biobank (correcting for 10
PCs and assessment center)



Mathieson et al. bioRxiv

No other fertility GWAS signals overlap with historical selection scans (CMS, SDS or ancient DNA scans) (with the exception of *CADM2* which has a strong signal of long-term balancing selection)

- How did humans adapt to changes in environment and culture? Evolutionary change is one (but only one) aspect.
- Ancient DNA allows us to track the evolution of functional loci very precisely in time and space.
- The real goal here is to try to understand why these loci are under selection by integrating archaeological and biological evidence.
- The *FADS* locus is an extreme (perhaps unique) example of an allele that has been under selection, at different times and places, for hundreds of thousands of years.

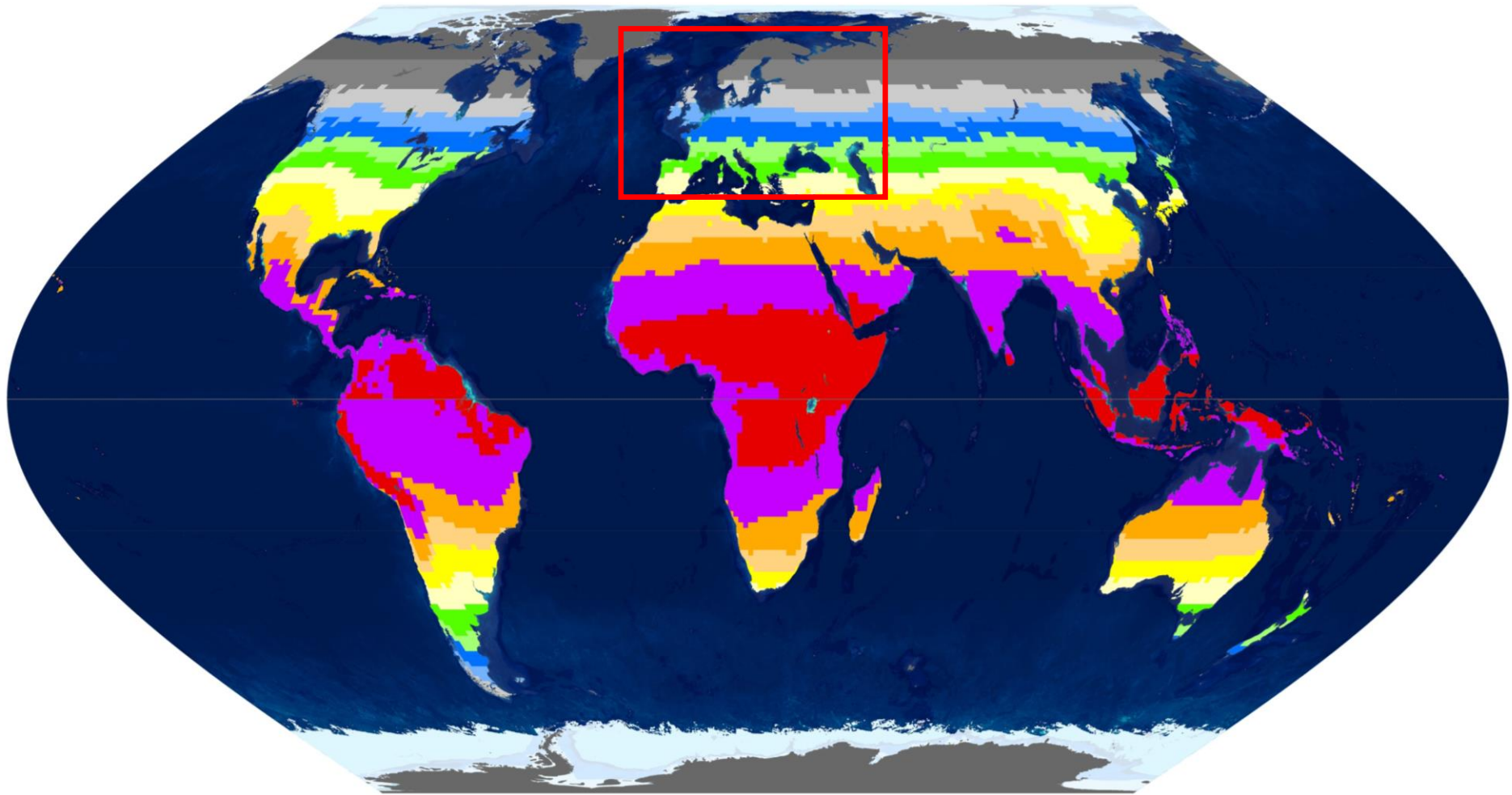
Selection on polygenic traits



Samantha Cox

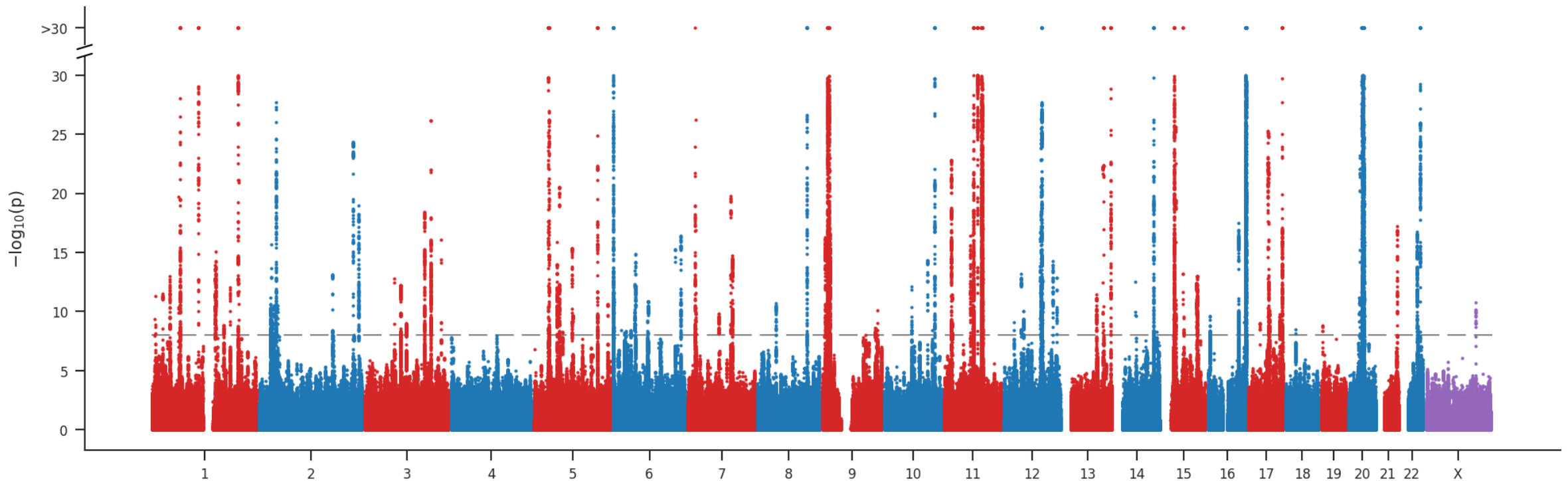


Dan Ju



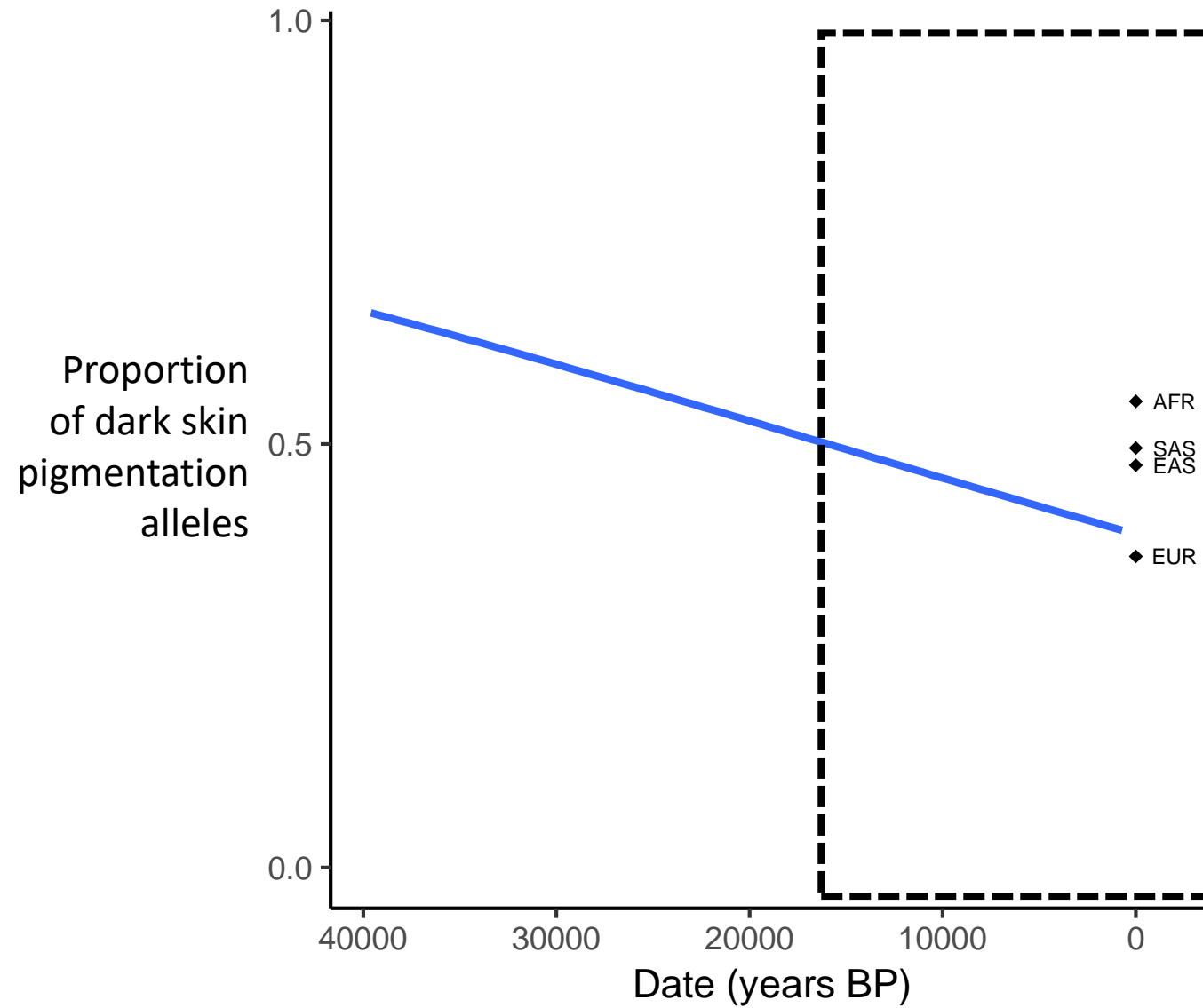
Jablonski & Chaplin 2009

~180 independent loci for skin pigmentation

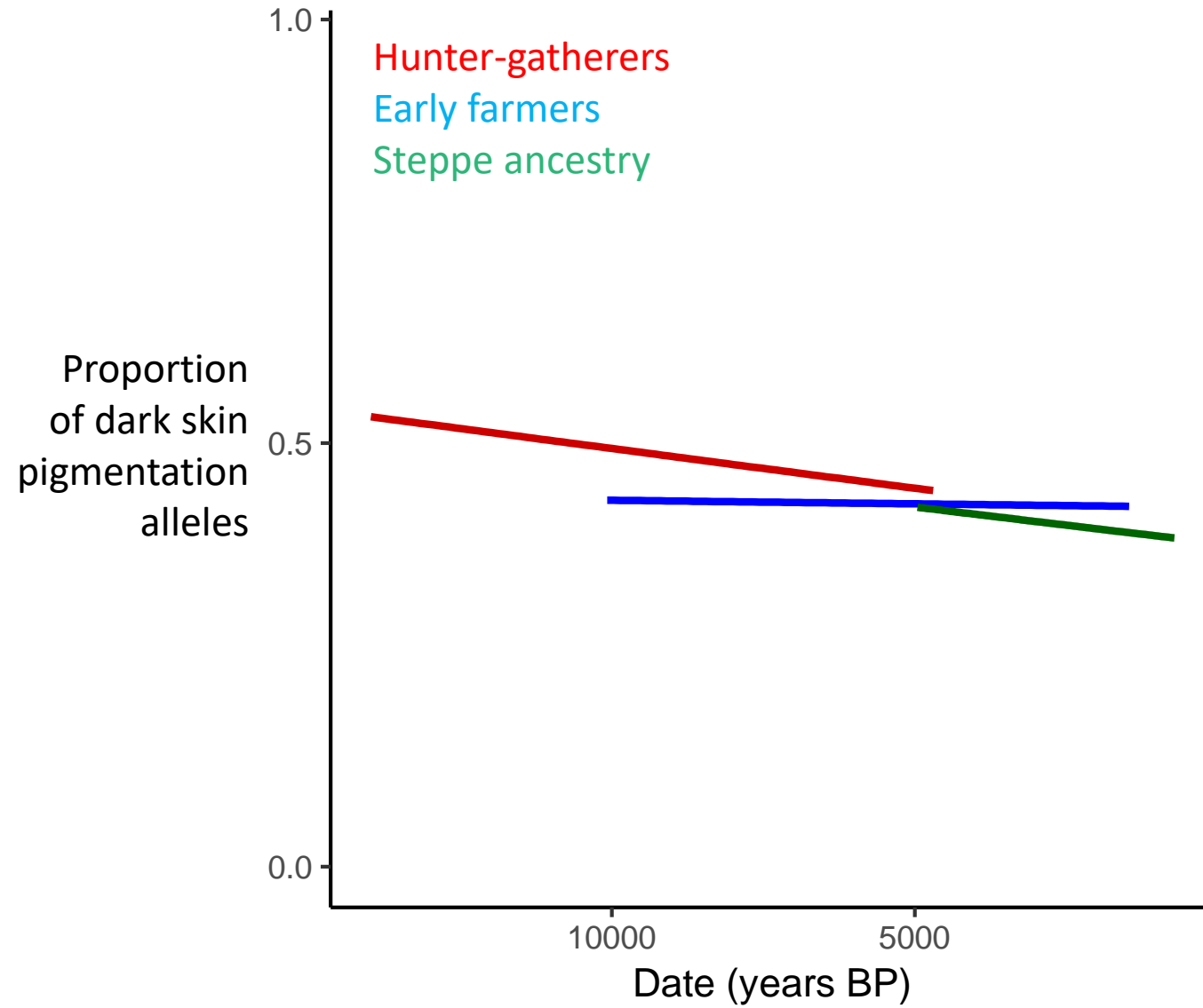


Data: UK Biobank; Visualization: <http://geneatlas.roslin.ed.ac.uk>

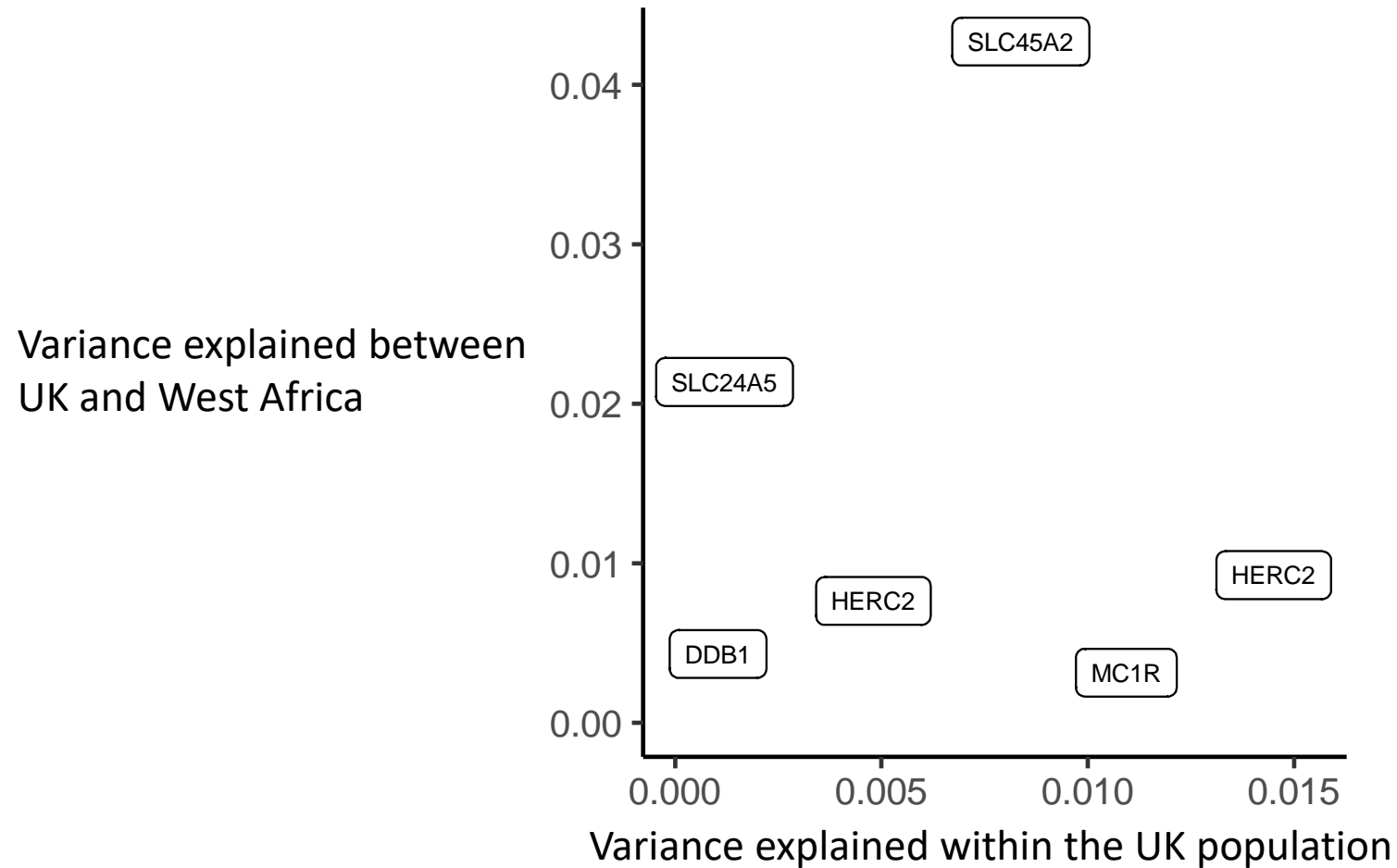
Dark skin pigmentation alleles were more common in the past



Dark skin pigmentation alleles were more common in the past



Selection driven by a relatively small number of variants



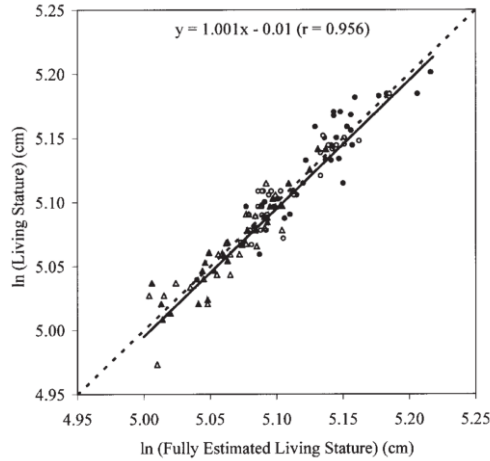
Alleles associated with lighter skin pigmentation were less common in the past

Selection on skin pigmentation likely drove frequency changes at 5-10 large-effect loci

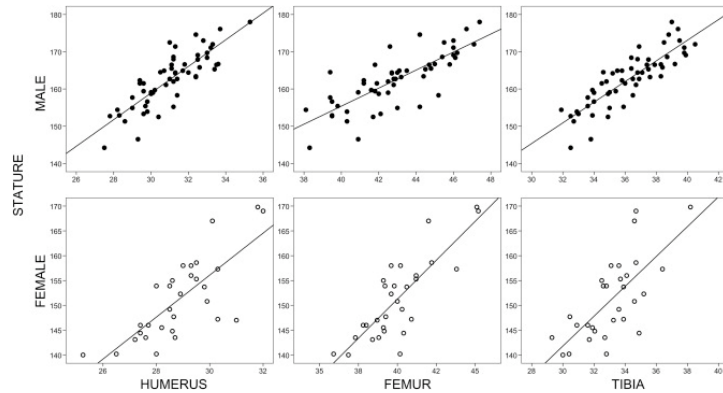
The data are consistent with constant selection over the past 45,000 years

Caution against interpreting these results as prediction of pigmentation in ancient populations.

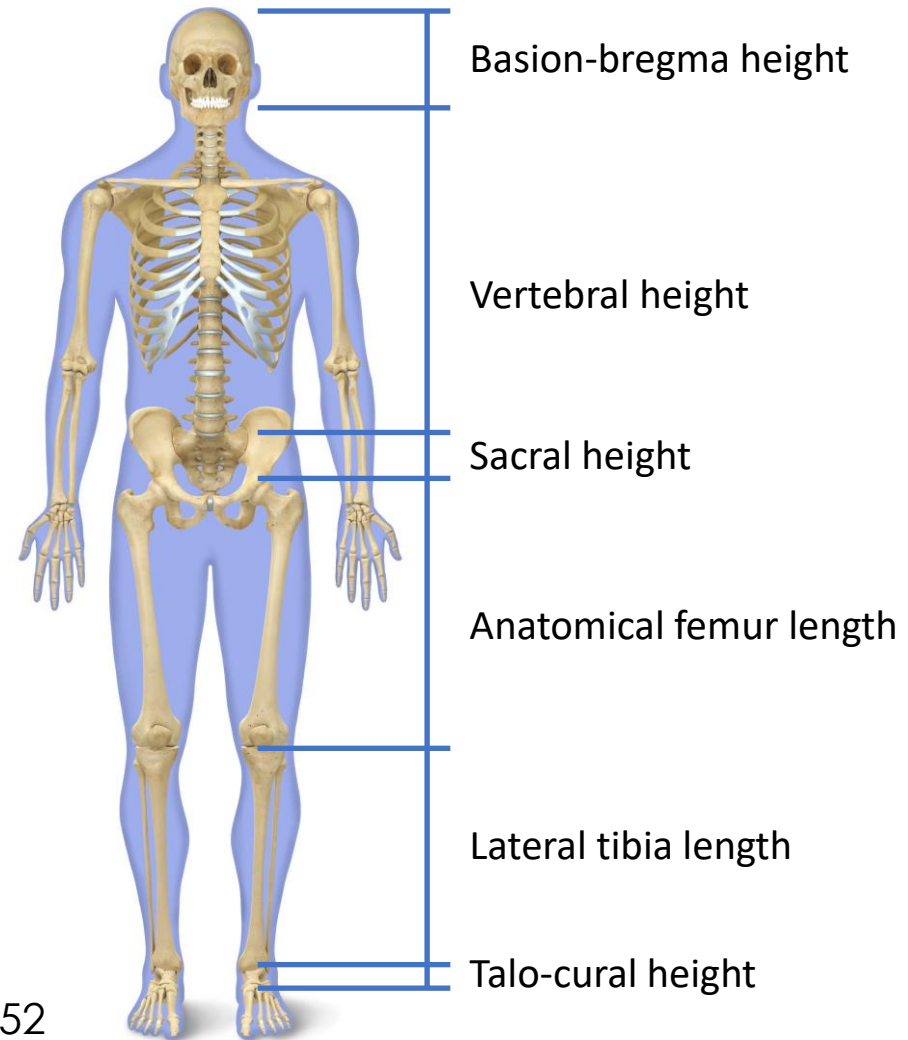
Stature estimation from skeletons



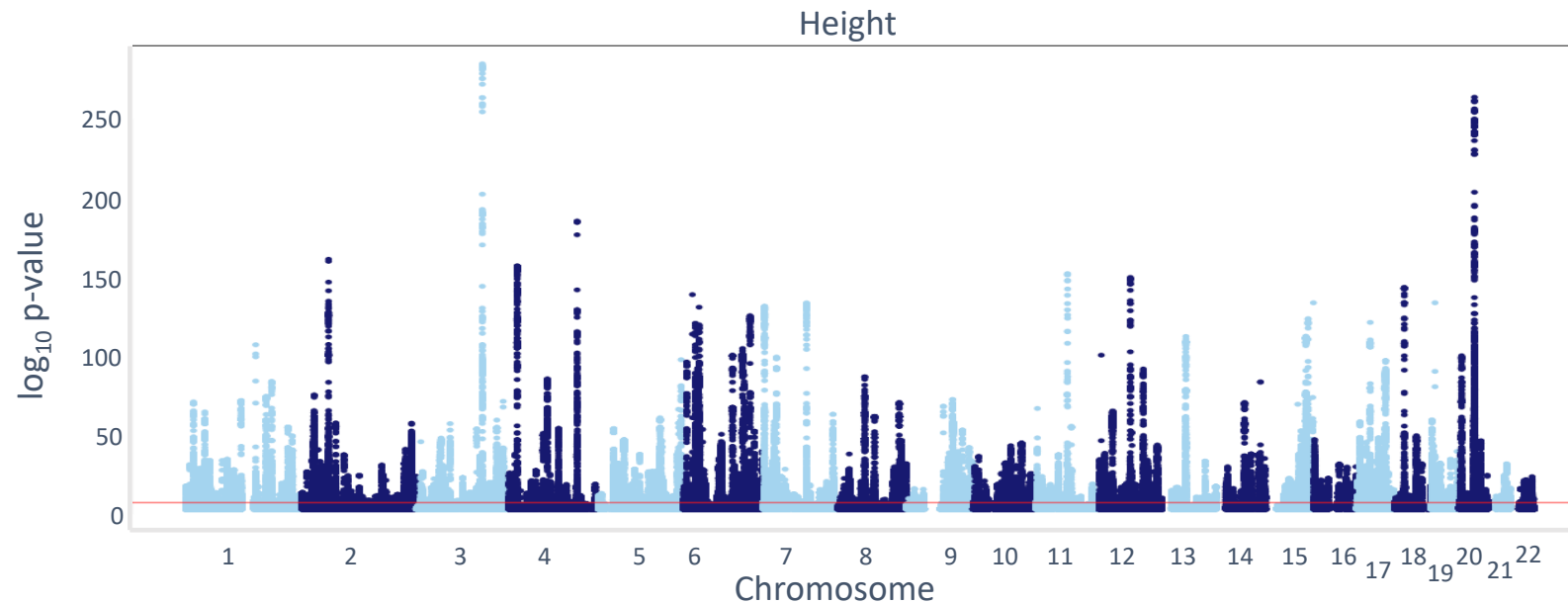
“Anatomical model” Fully 1956



“Mathematical model” Trotter & Gleser 1952



Genome-wide association studies for height



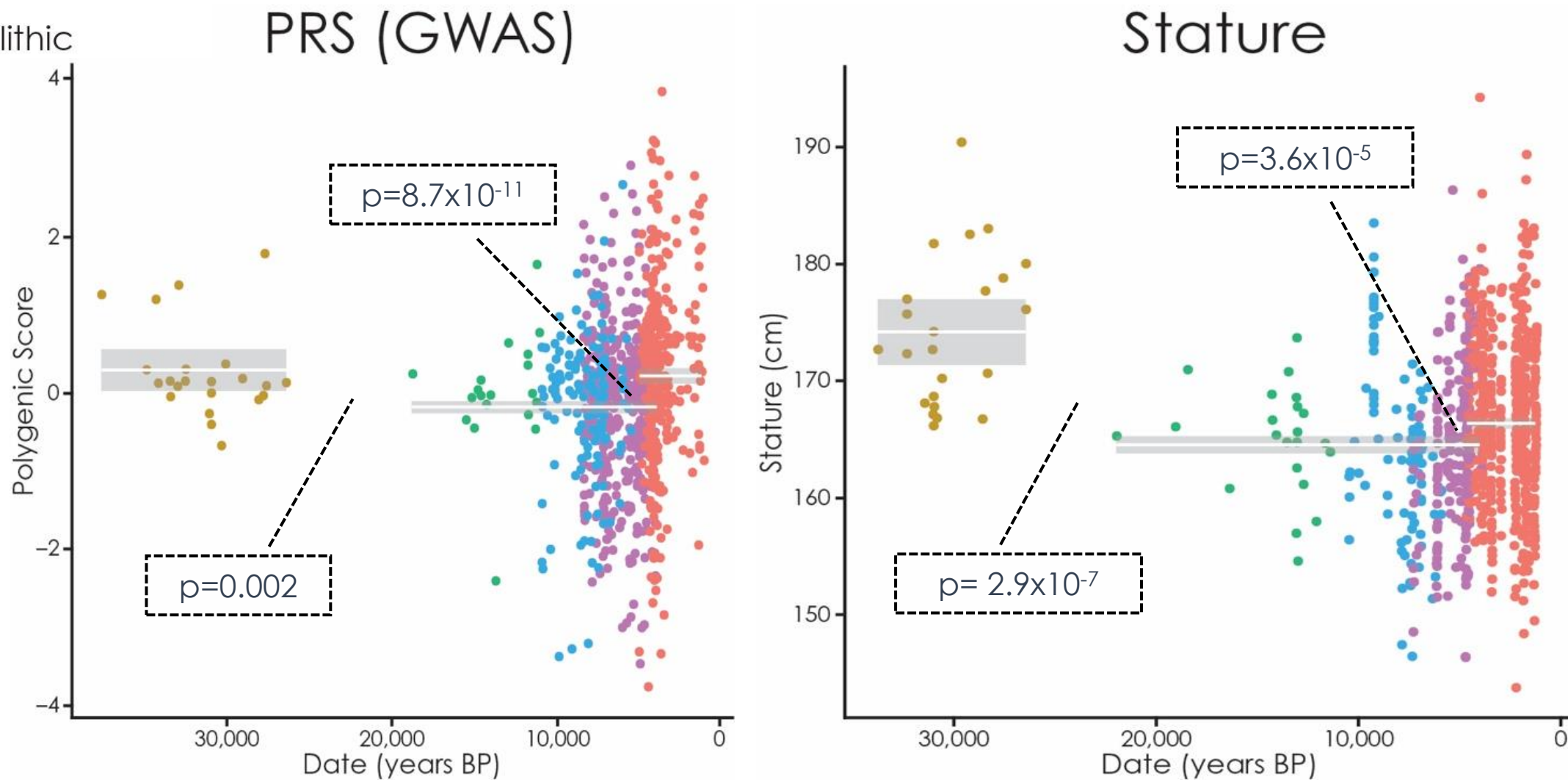
UK Biobank: ~3000 genome-wide significant loci

$$\text{Polygenic risk score (PRS)} = \sum_{SNPs} \beta_i X_i$$

For some set $\{i\}$ of SNPs, effect sizes β and genotypes X

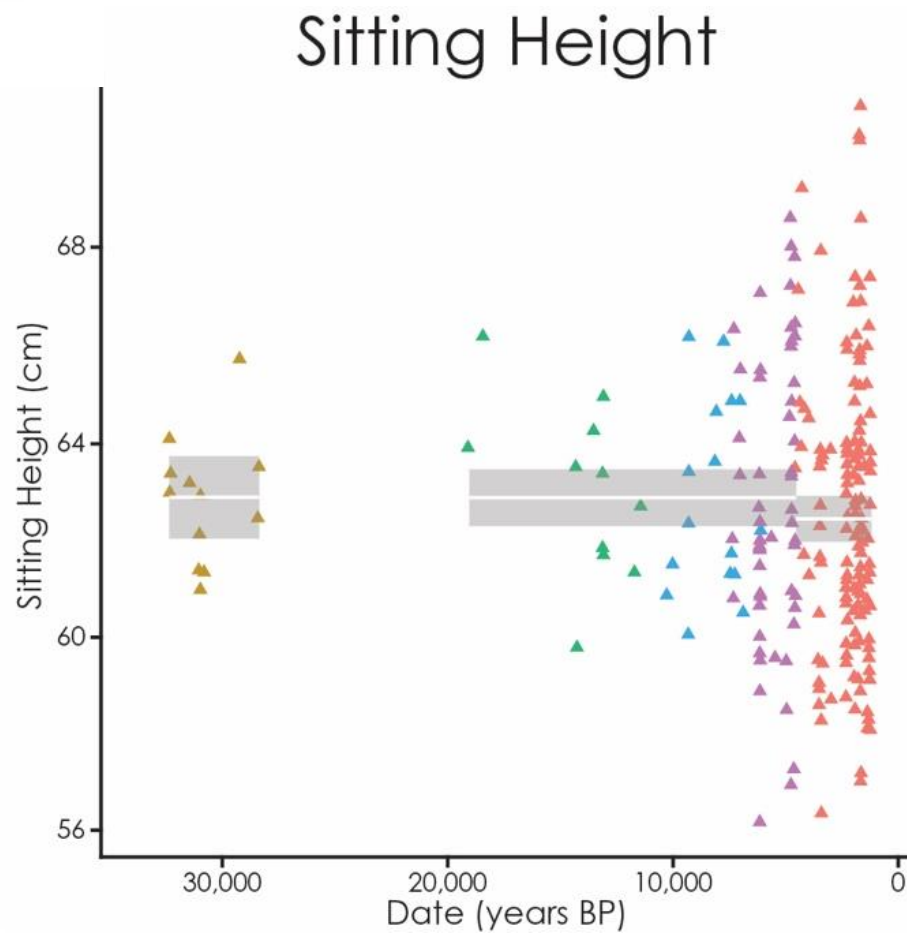
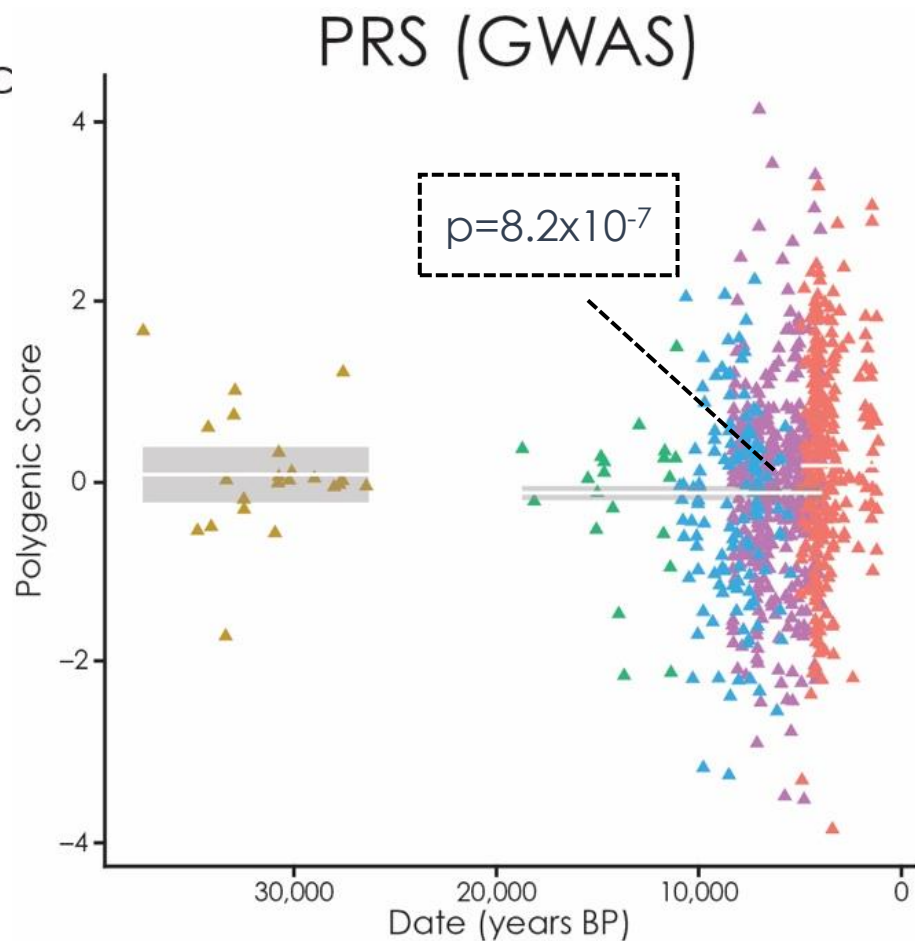
Height PRS predicts skeletal stature

- Early Upper Paleolithic
- Late Upper Paleolithic
- Mesolithic
- Neolithic
- post-Neolithic

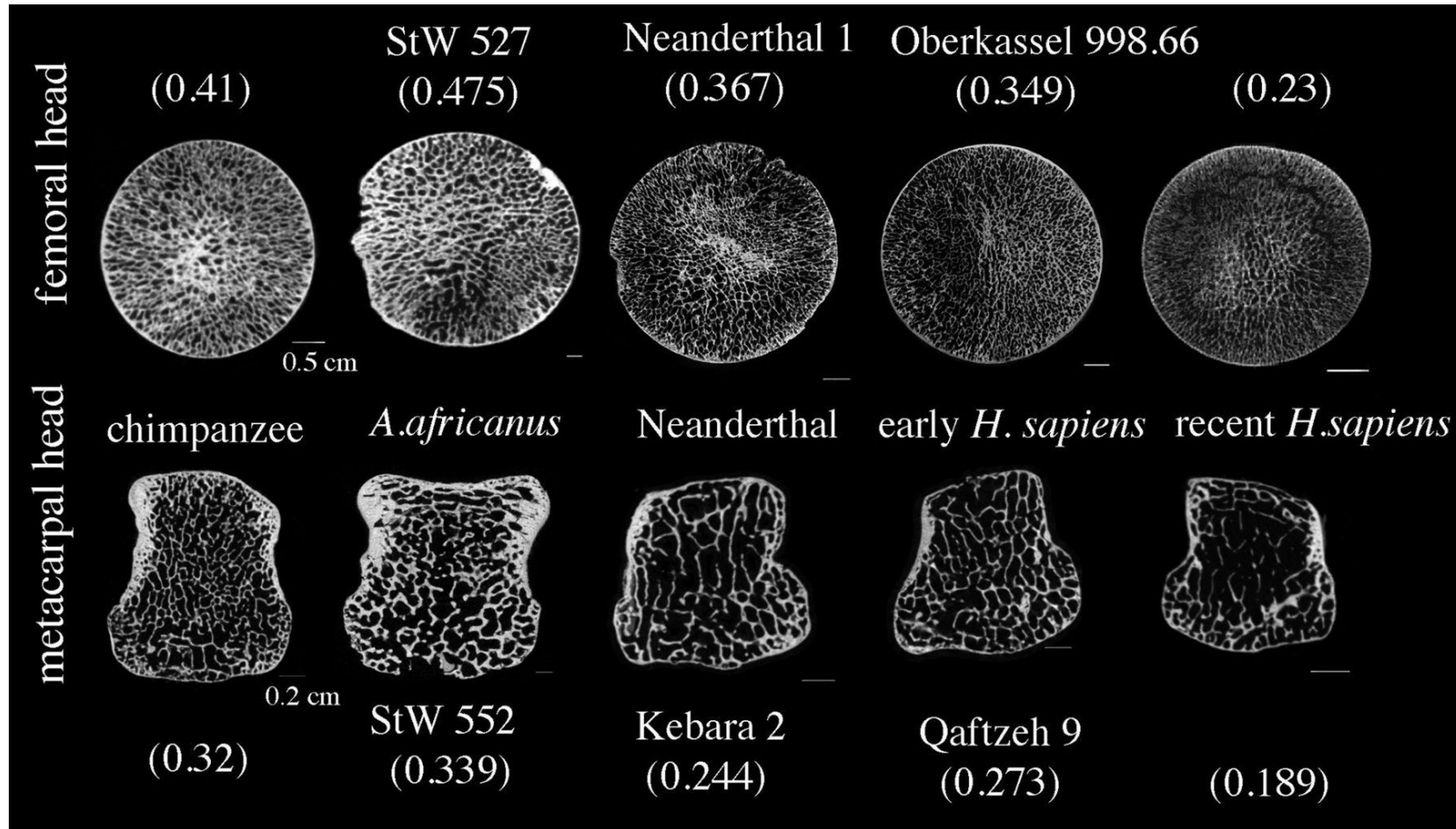


Sitting height remains nearly constant

- Early Upper Paleolithic
- Late Upper Paleolithic
- Mesolithic
- Neolithic
- post-Neolithic

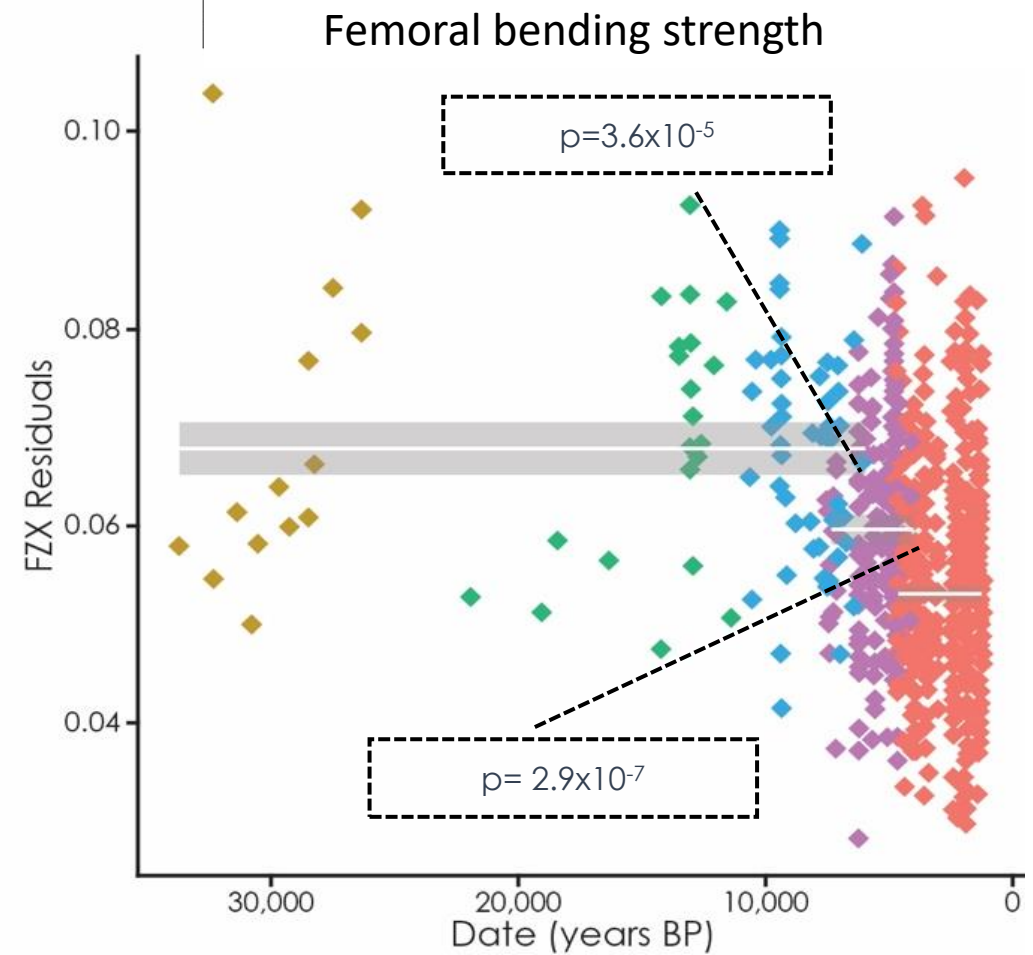
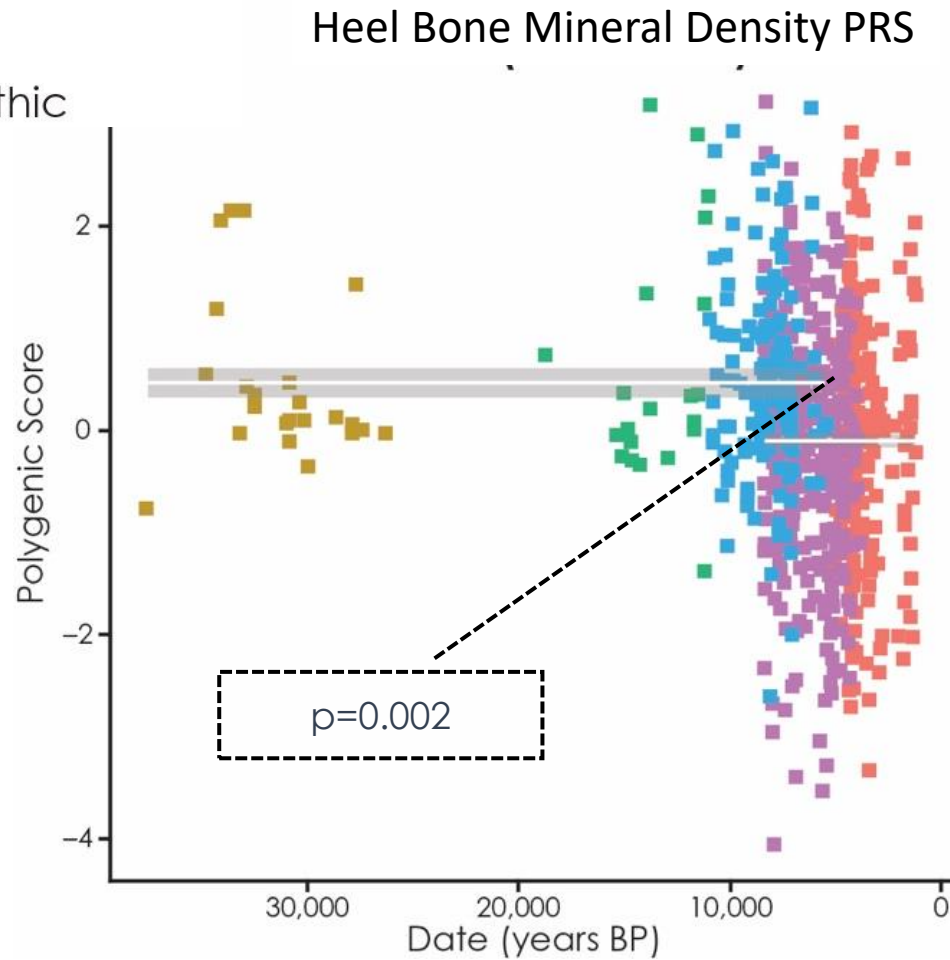


Recent decrease in bone density



Neolithic decrease in bone density and strength

- Early Upper Paleolithic
- Late Upper Paleolithic
- Mesolithic
- Neolithic
- post-Neolithic

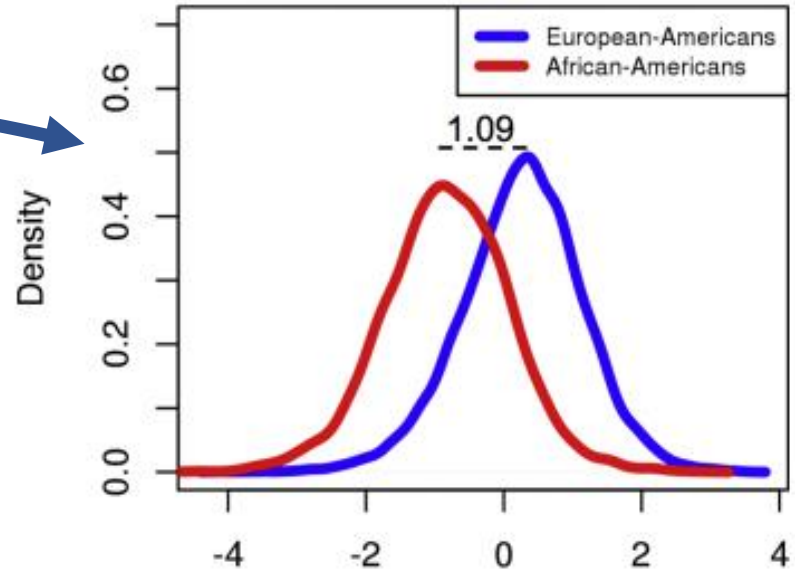


Stature certainly seems adaptive....

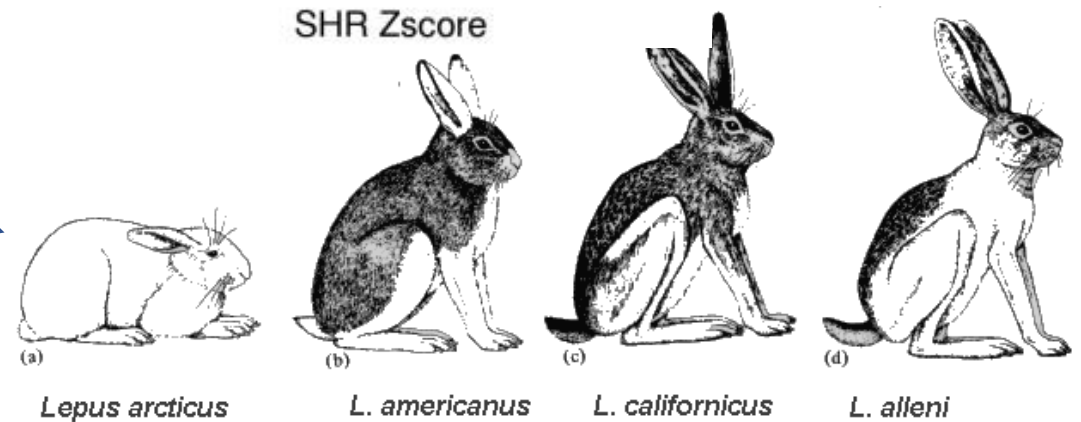
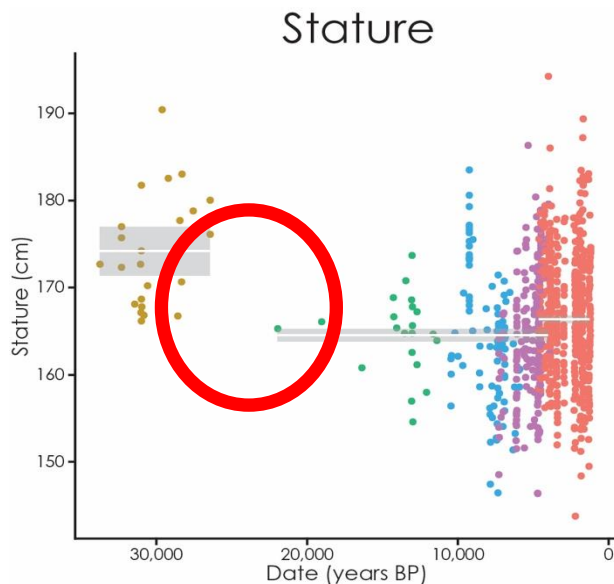
Decreasing limb length in paleolithic Europe may have a genetic basis

Reflects difference between present-day Northern and Tropical populations

An example of Allen's rule, driven by adaptation to climate?

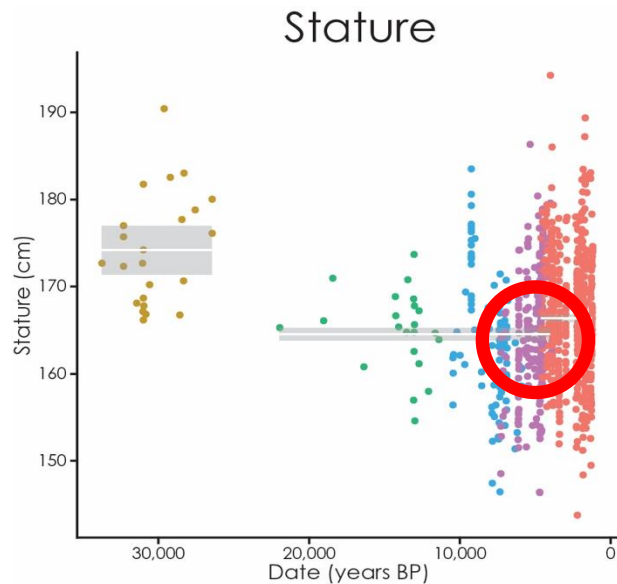


Chan et al. 2015



Stature certainly seems adaptive....

Increasing stature in Bronze Age Steppe ancestry populations contemporary with increasing social inequality, rapid population range expansions and increased male reproductive variance.

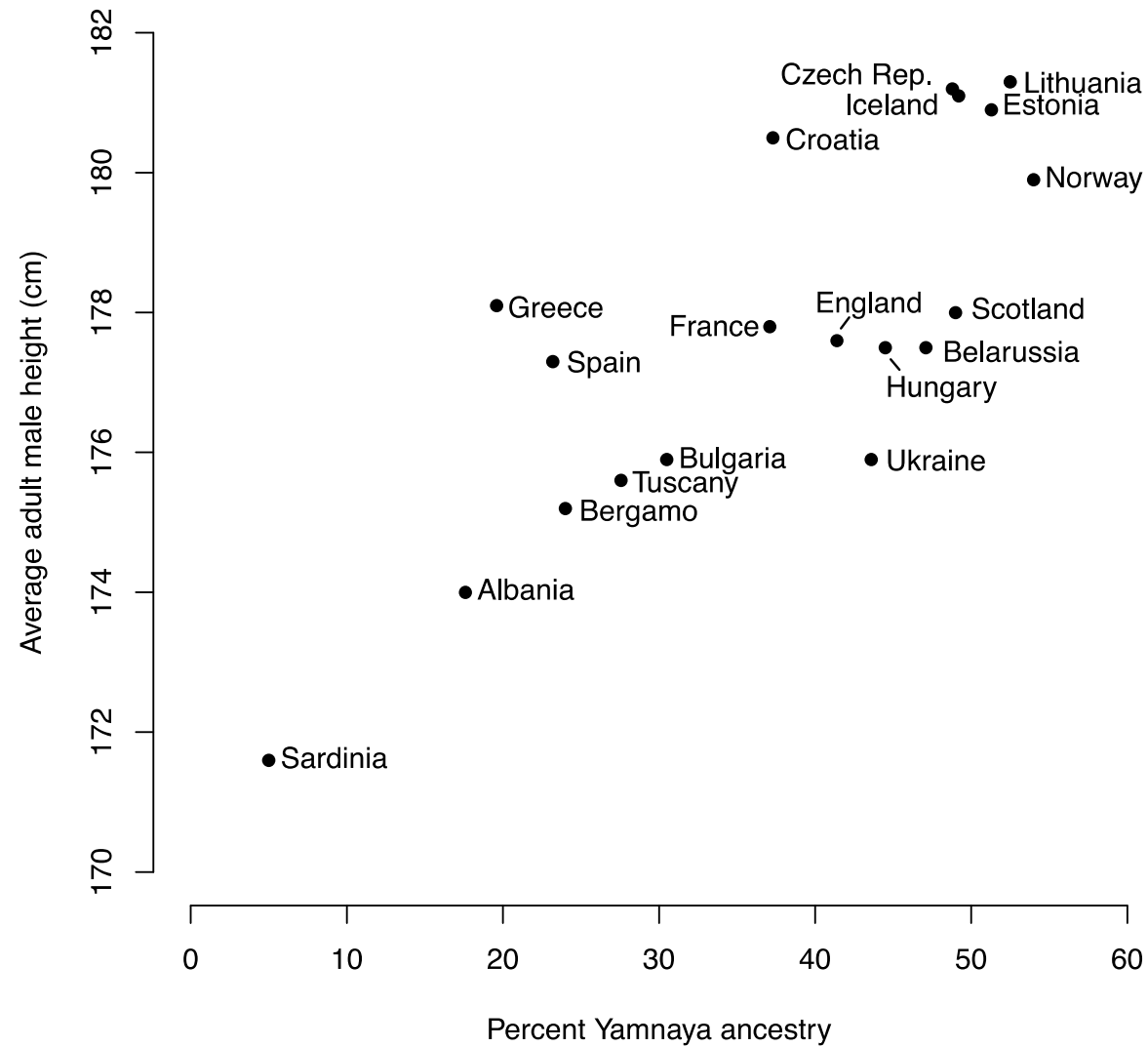


Varna Man - 6500 years ago

Buried with more gold than anyone ever had before

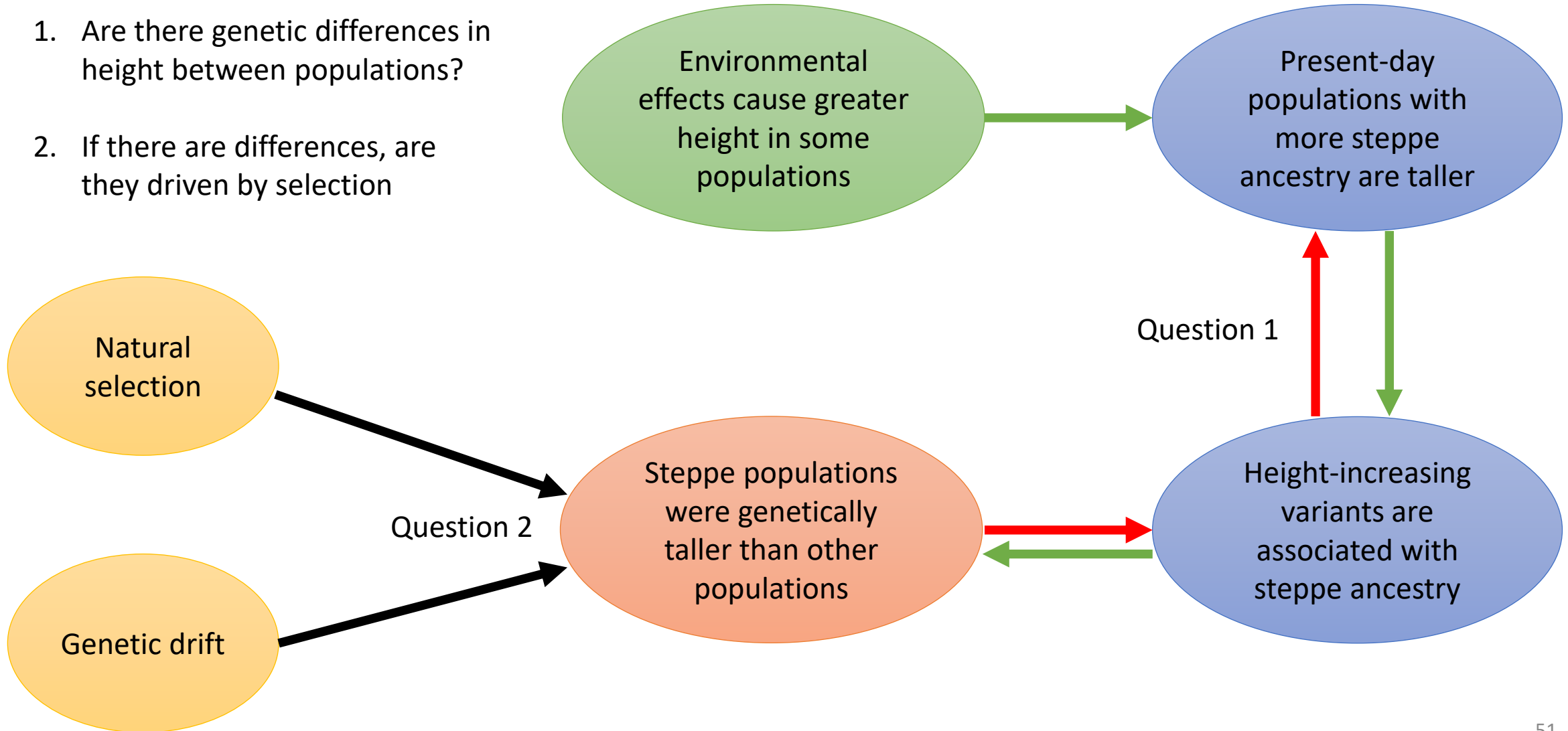


Steppe ancestry is fairly strongly correlated with stature...



...but the causality is unclear

1. Are there genetic differences in height between populations?
2. If there are differences, are they driven by selection?



- For skin pigmentation we can find robust evidence of polygenic selection. Ancient DNA allows us to identify the timing of selection, as for single loci.
- For height, we can actually measure the correlation with phenotypes, but the genomic evidence for selection is unclear. Technical issues such as population stratification in GWAS limit our ability to make inference
- Future program involves using ancient DNA to resolve the interaction of genetics and environment.

Acknowledgments

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Laura Colbran

Arslan Zaidi

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Sara Mathieson (Haverford)

Christopher Ruff (Johns Hopkins)

John Perry (Cambridge)

Melinda Mills (Oxford)



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Questions?