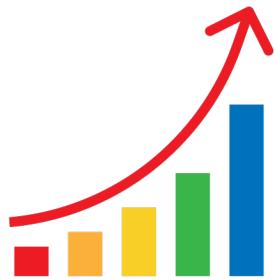


Temporal Selection

Detecting selection with ancient DNA time-series



Evan Irving-Pease
 @EvanIrvingPease

UNIVERSITY OF
COPENHAGEN



GEOGENETICS
LUNDBECK FOUNDATION CENTRE

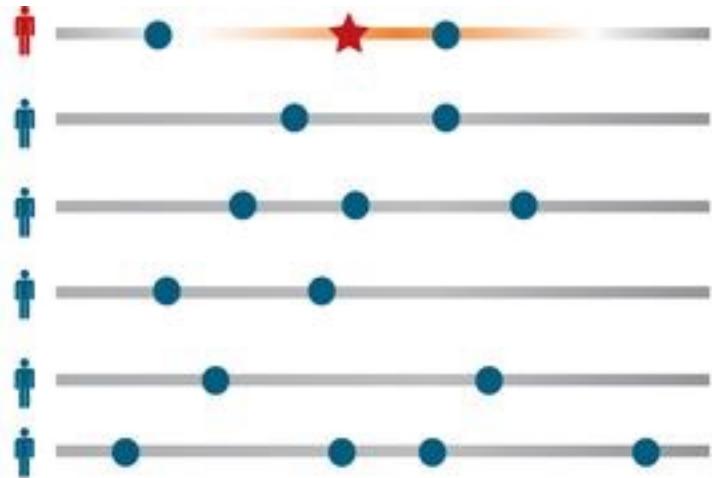


Signatures of selection in present-day genomes

- A. Hard sweep
- B. Soft sweep
- C. Polygenic adaptation
- D. Adaptive introgression

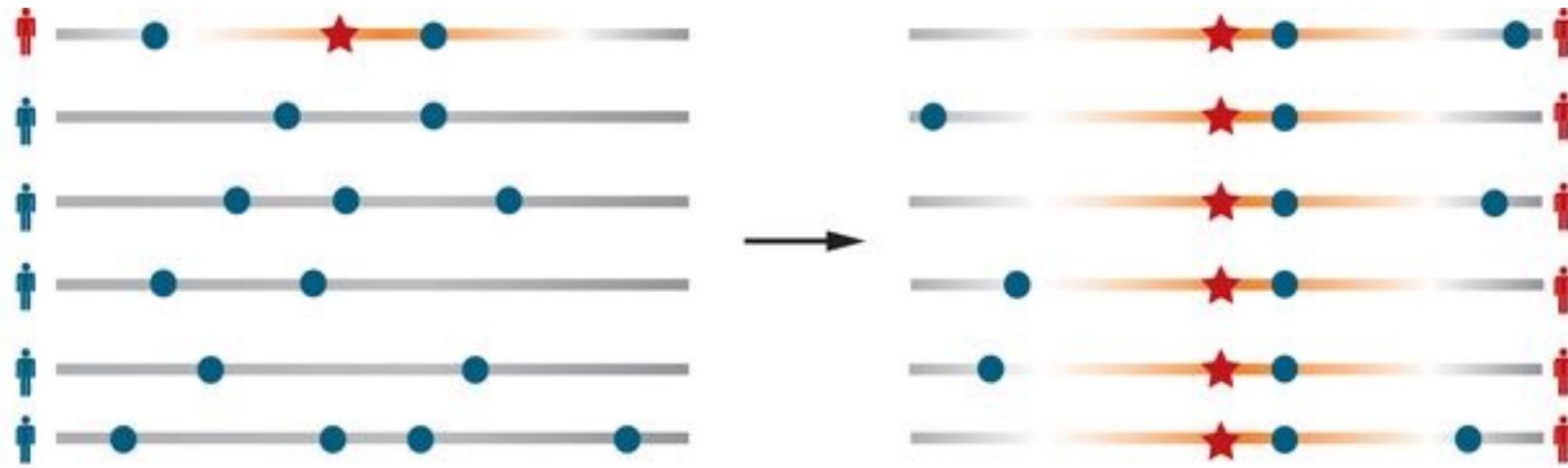
A

Hard
sweep



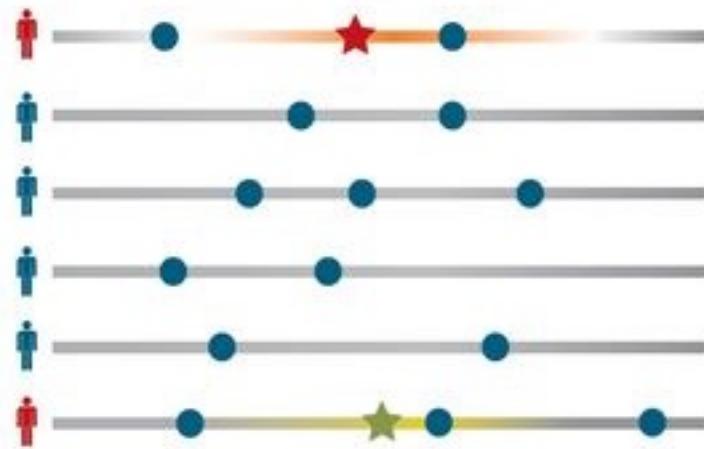
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Hard
sweep



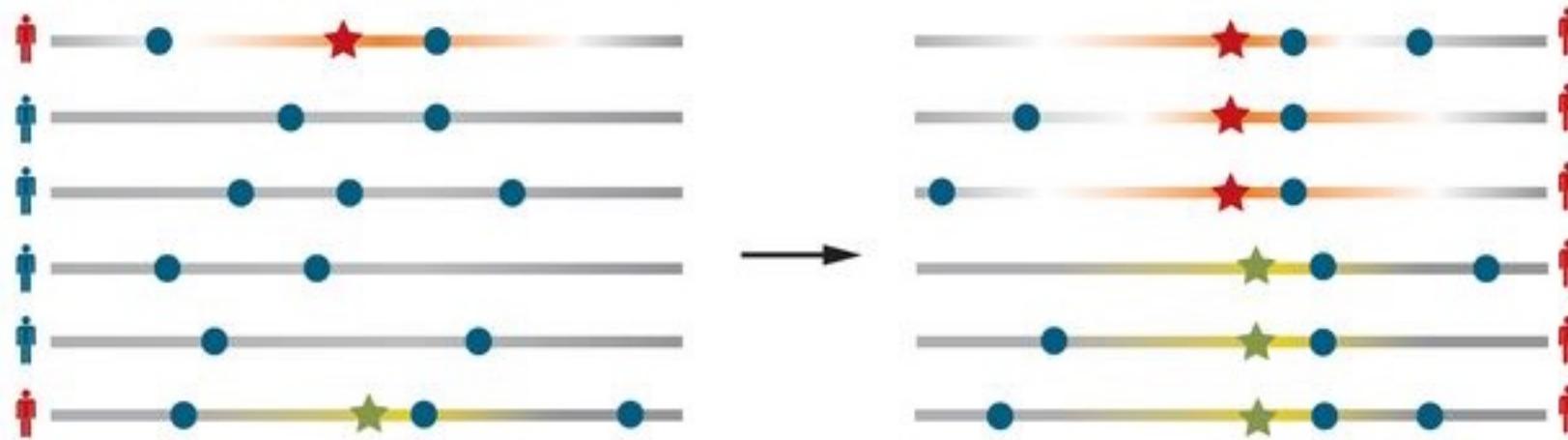
B

i) Selection on different de novo mutations

Soft
sweep

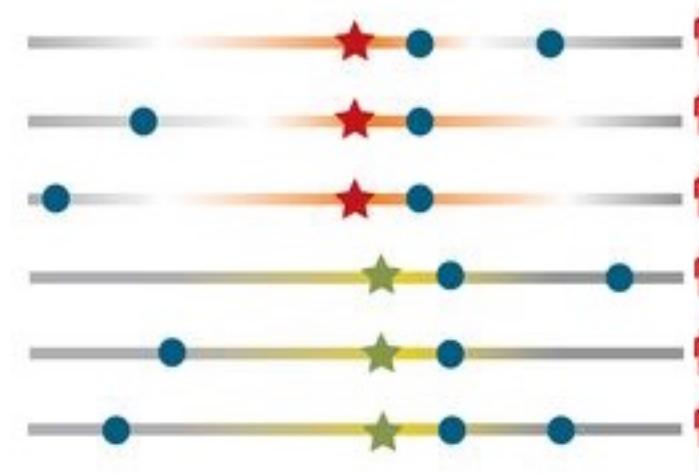
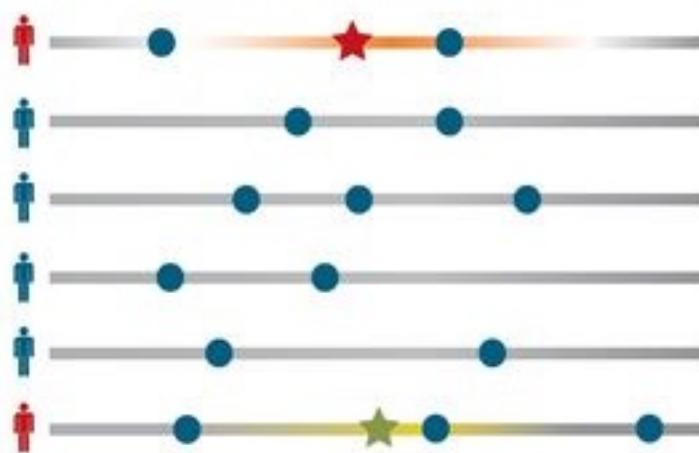
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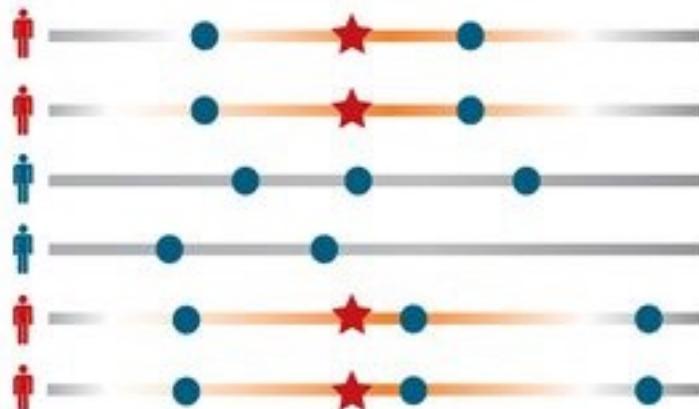
Soft
sweep

B

i) Selection on different de novo mutations

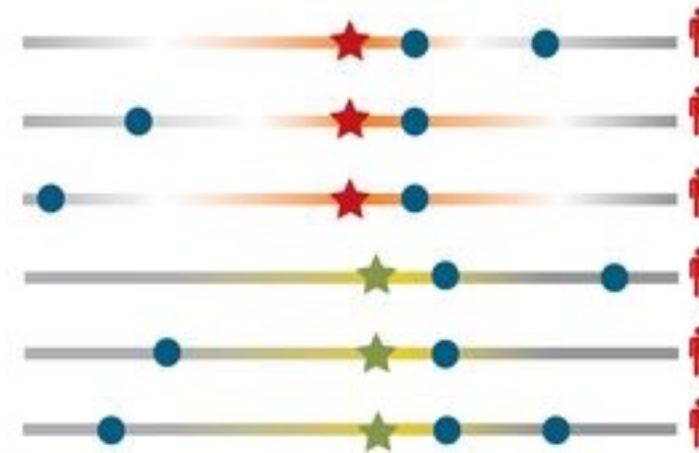
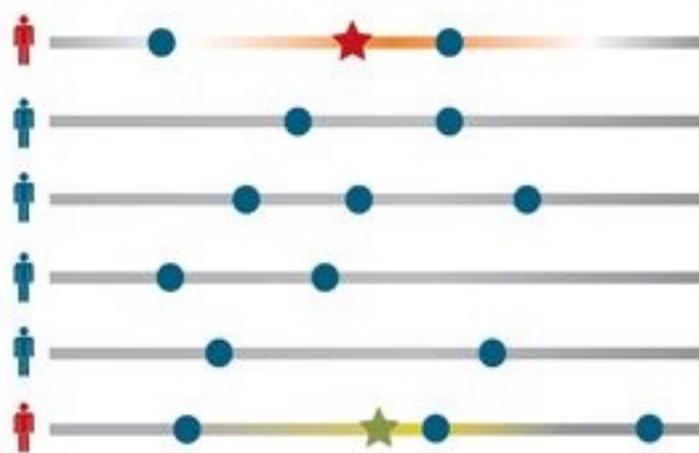
Soft
sweep

ii) Selection on standing variations

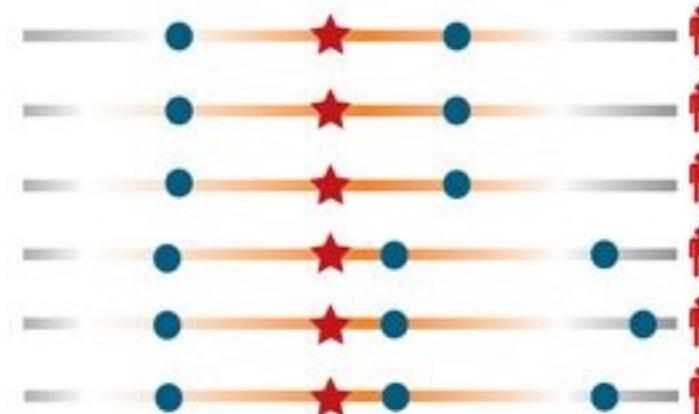
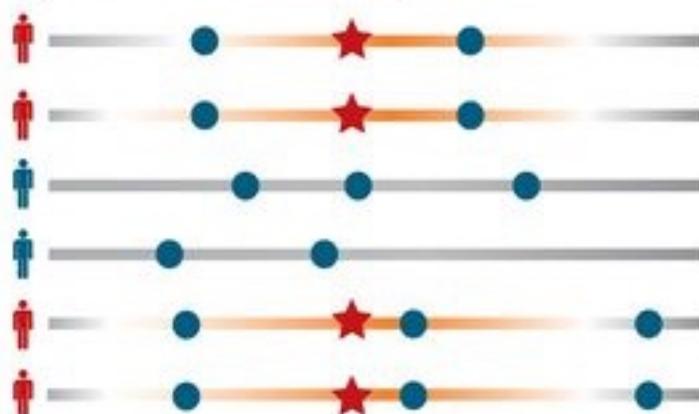


B

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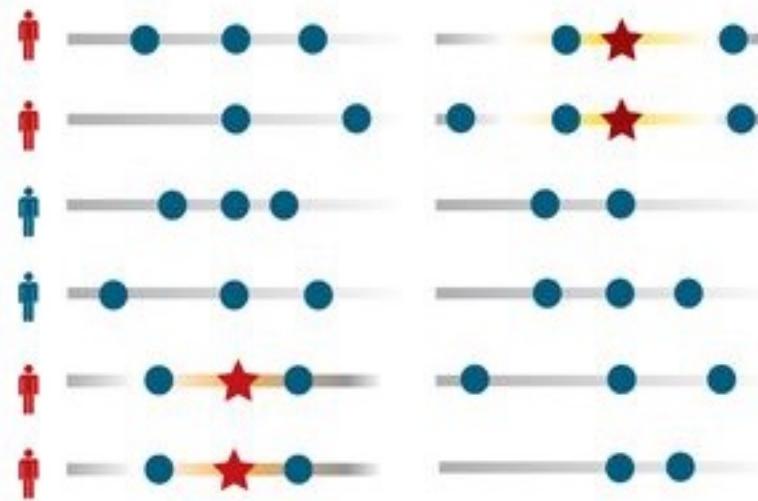
Soft
sweep

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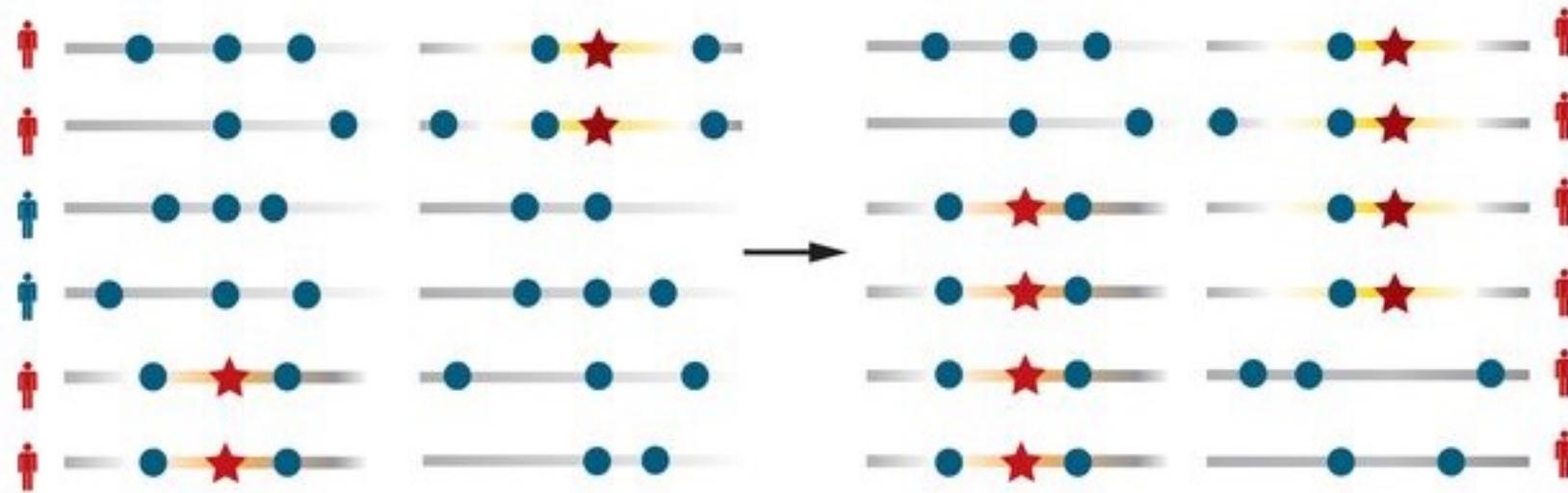
C

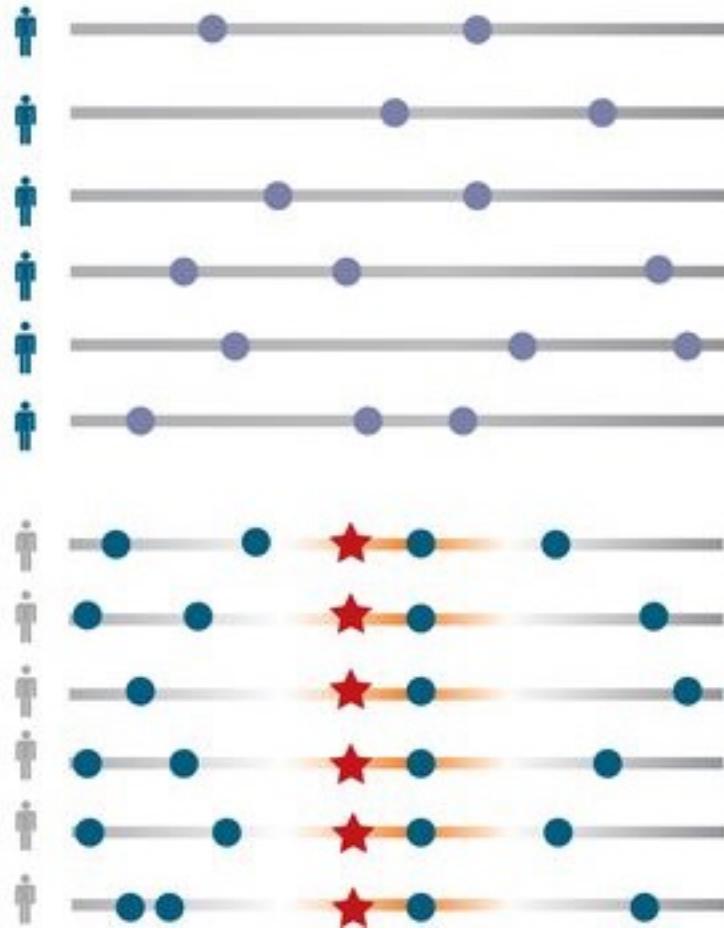
Polygenic
adaptation

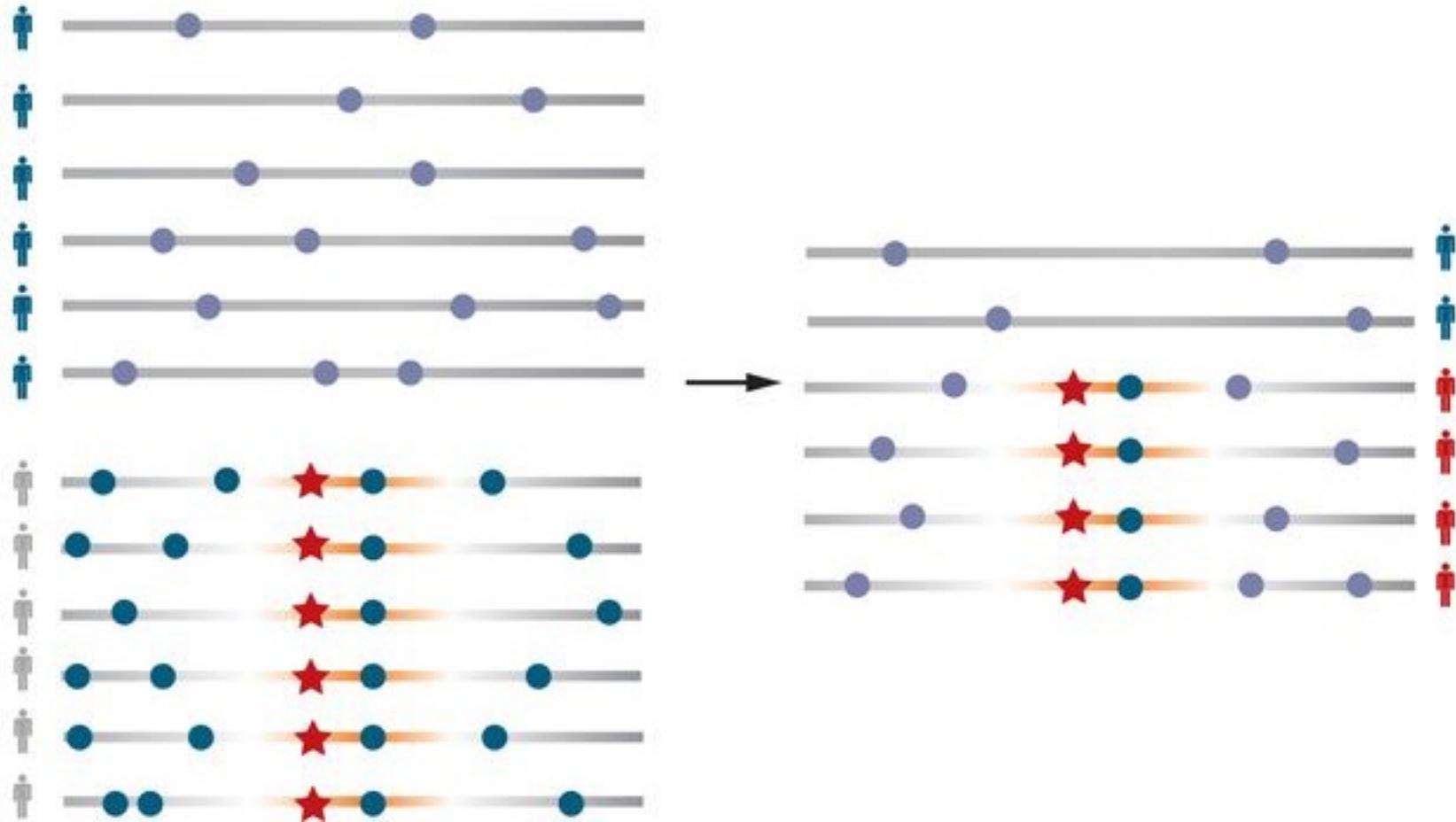


C

Polygenic
adaptation



DAdaptive
introgression

DAdaptive
introgression

Problems and issues

- Evolution is rarely as simple as our models assume

Problems and issues

- Evolution is rarely as simple as our models assume
- Genomes contain records of many different evolutionary processes, at different time scales

Problems and issues



palimpsest

/'palim(p)sɛst/

noun

a manuscript or piece of writing material on which later writing has been superimposed on effaced earlier writing.

- something reused or altered but still bearing visible traces of its earlier form.
"Sutton Place is a palimpsest of the taste of successive owners"

Problems and issues



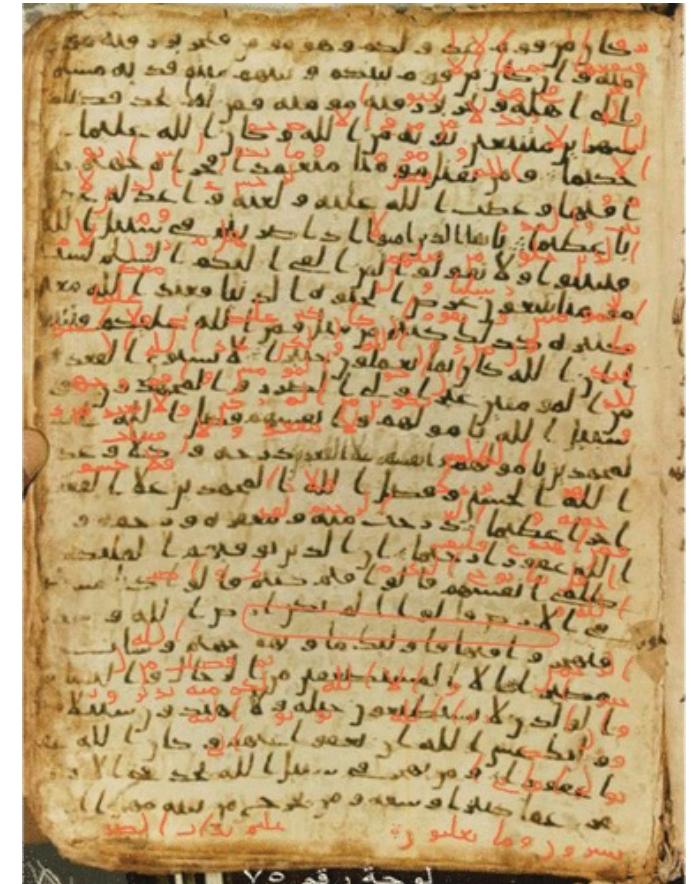
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Problems and issues



equifinality

/ˌekwɪˈfɪnəl(ə)lɪ/

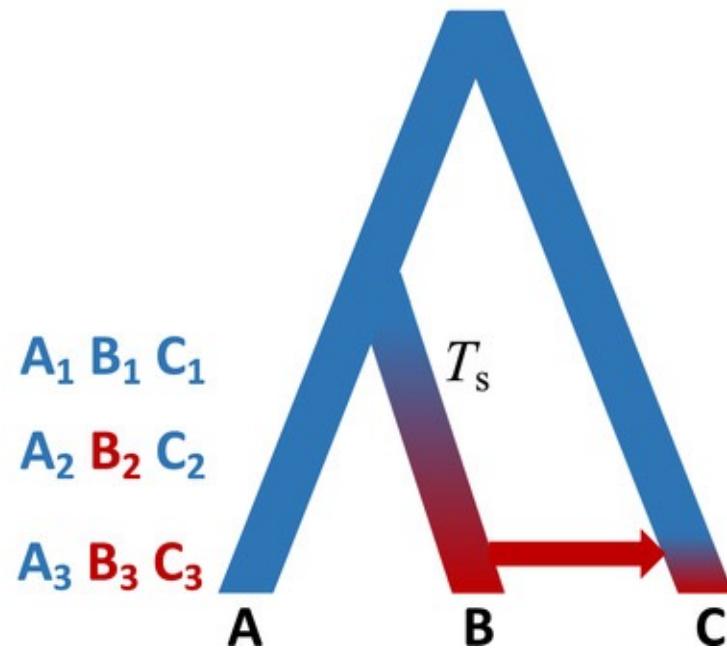
adjective TECHNICAL

adjective: **equifinal**

having the same end or result.

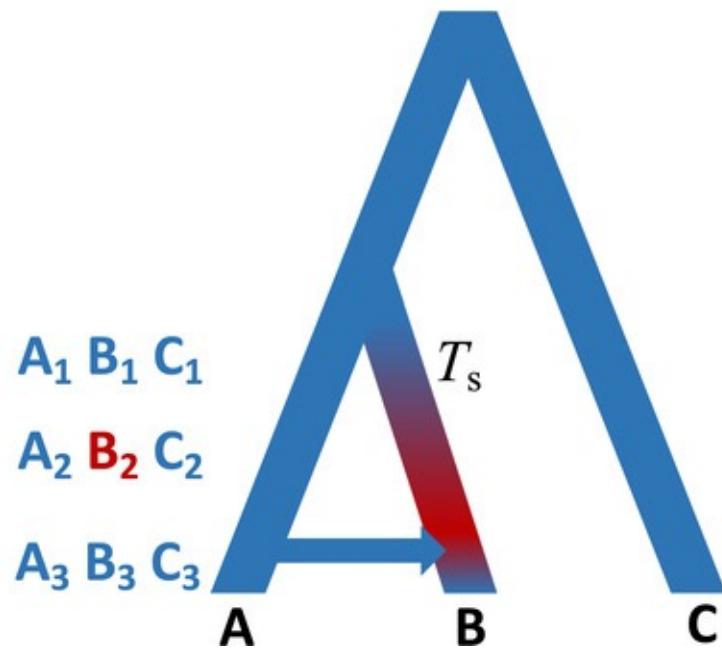
Problems and issues

i.



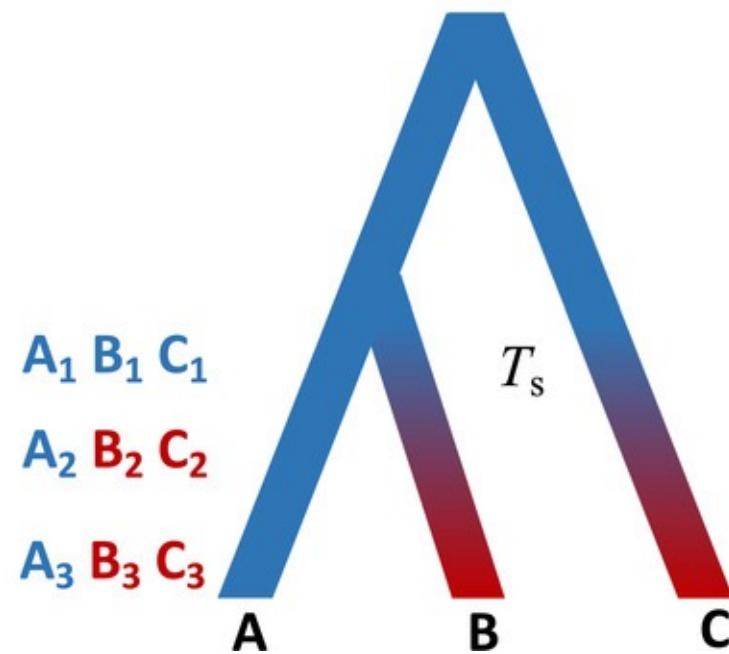
Problems and issues

ii.



Problems and issues

iii.



Gene-flow is pervasive across the tree of life

Gene-flow is pervasive across the tree of life

RESEARCH ARTICLE

A Genetic Atlas of Human Admixture History

Garrett Hellenthal¹, George B. J. Busby², Gavin Band³, James F. Wilson⁴, Cristian Capelli², Daniel Falush^{5,*}, Simon Myers^{3,6,...}

+ See all authors and affiliations

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Krzysztof M Kozak ✉, Mathieu Joron, W Owen McMillan, Chris D Jiggins | Author Notes

Genome Biology and Evolution, Volume 13, Issue 7, July 2021, evab099,
<https://doi.org/10.1093/gbe/evab099>

Published: 04 May 2021 | Article history ▾

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First published: 05 May 2012 | <https://doi.org/10.1111/j.1365-294X.2012.05614.x> | Citations: 96

 Amro Zayed, Fax: 416-736-5698; E-mail: zayed@yorku.ca

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Fine Scale Genomic Signals of Admixture and Alien Introgression among Asian Rice Landraces

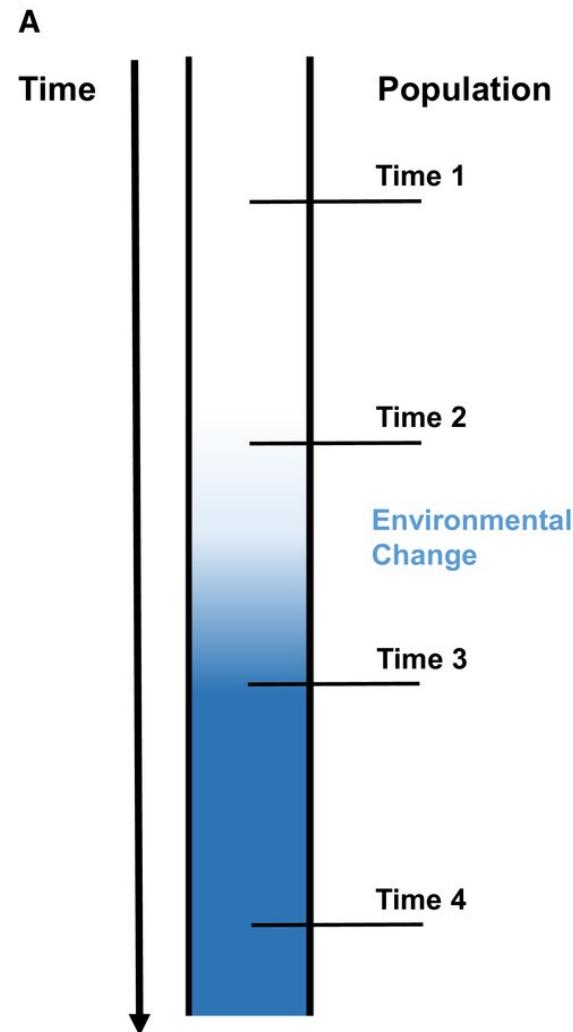
João D Santos, Dmytro Chebotarov, Kenneth L McNally, Jérôme Bartholomé, Gaëtan Droc, Claire Billot, Jean Christophe Glaszmann 

Genome Biology and Evolution, Volume 11, Issue 5, May 2019, Pages 1358–1373,
<https://doi.org/10.1093/gbe/evz084>

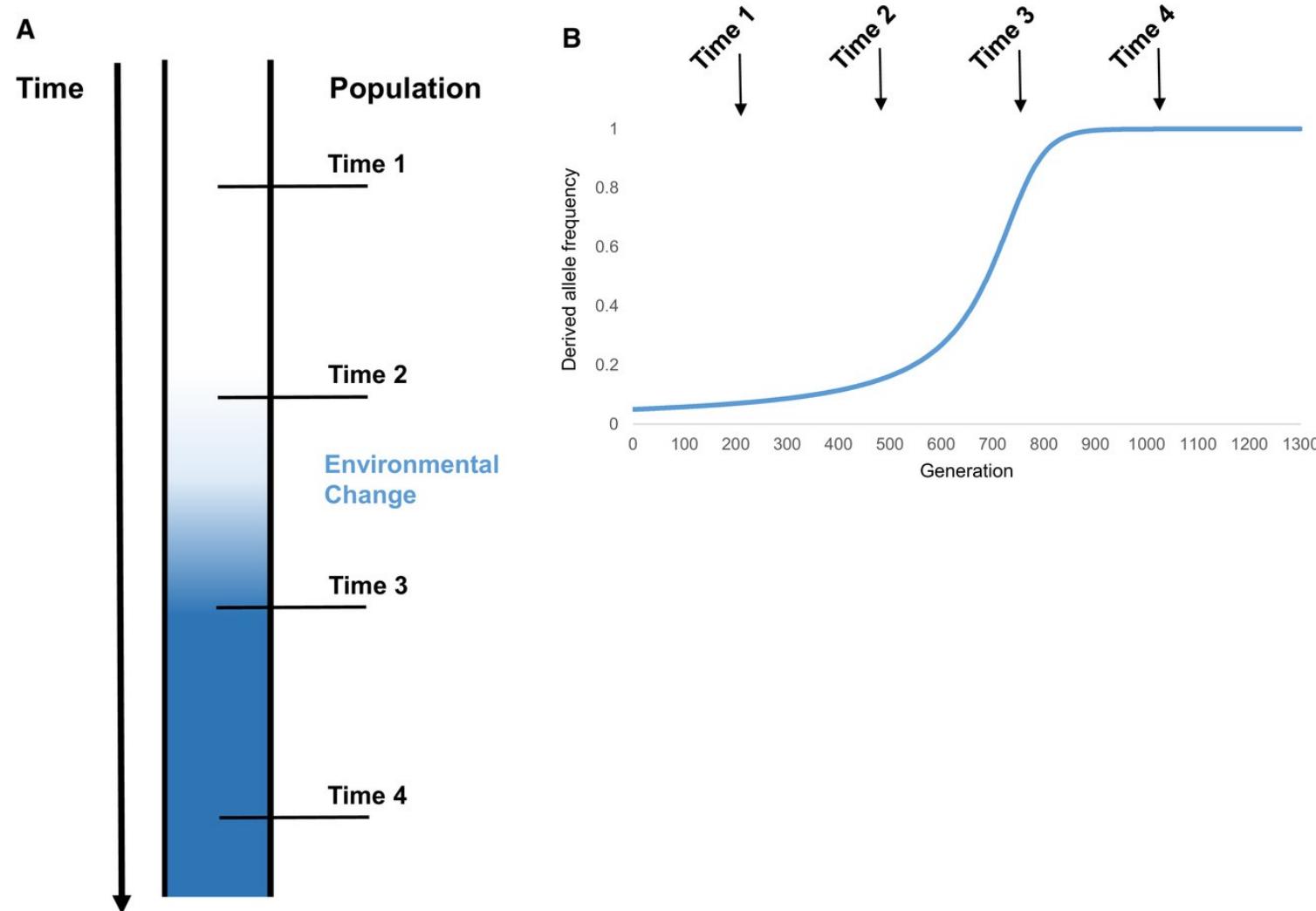
Published: 16 April 2019 | Article history ▾

Benefits of time-series sampling

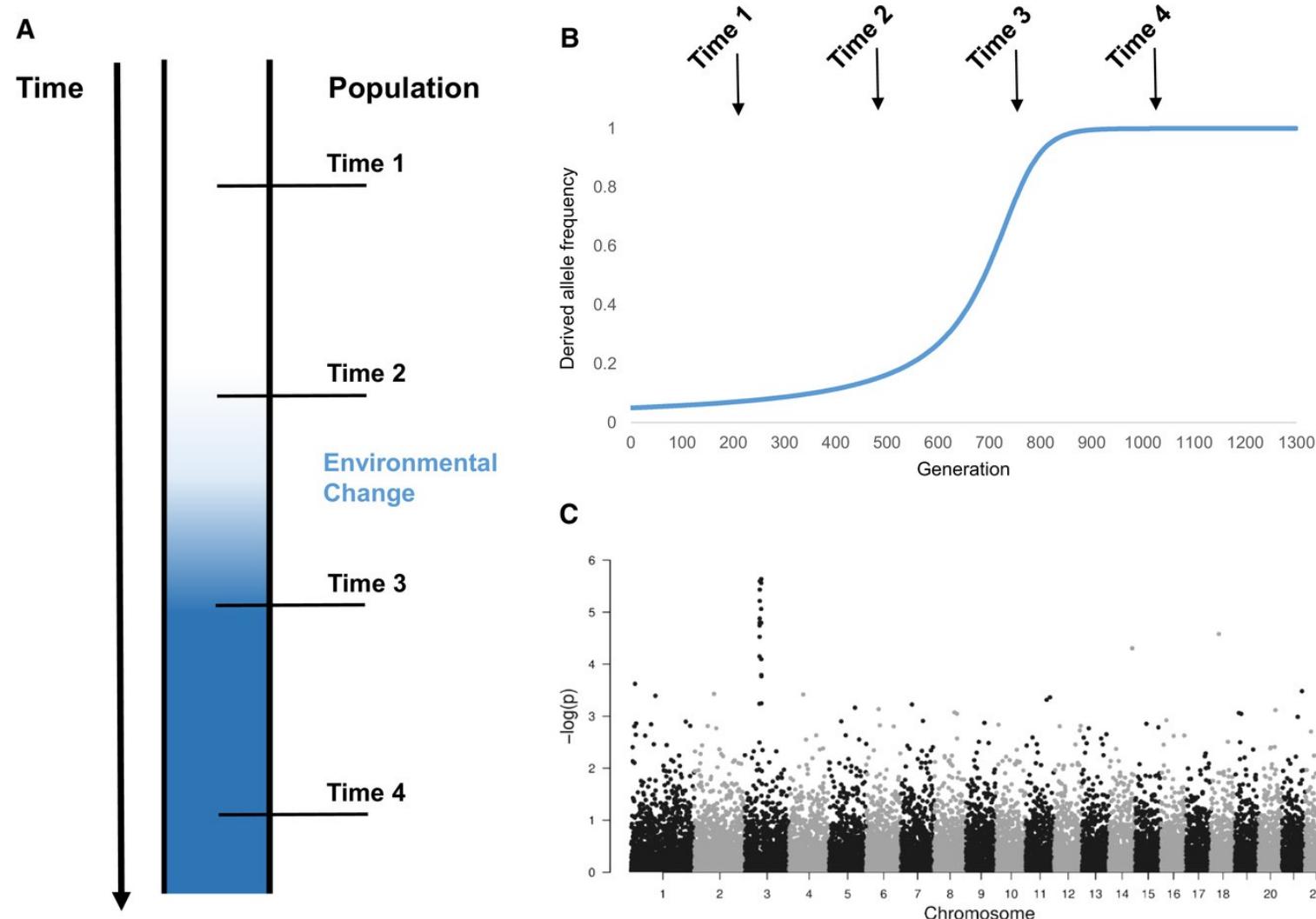
Benefits of time-series sampling



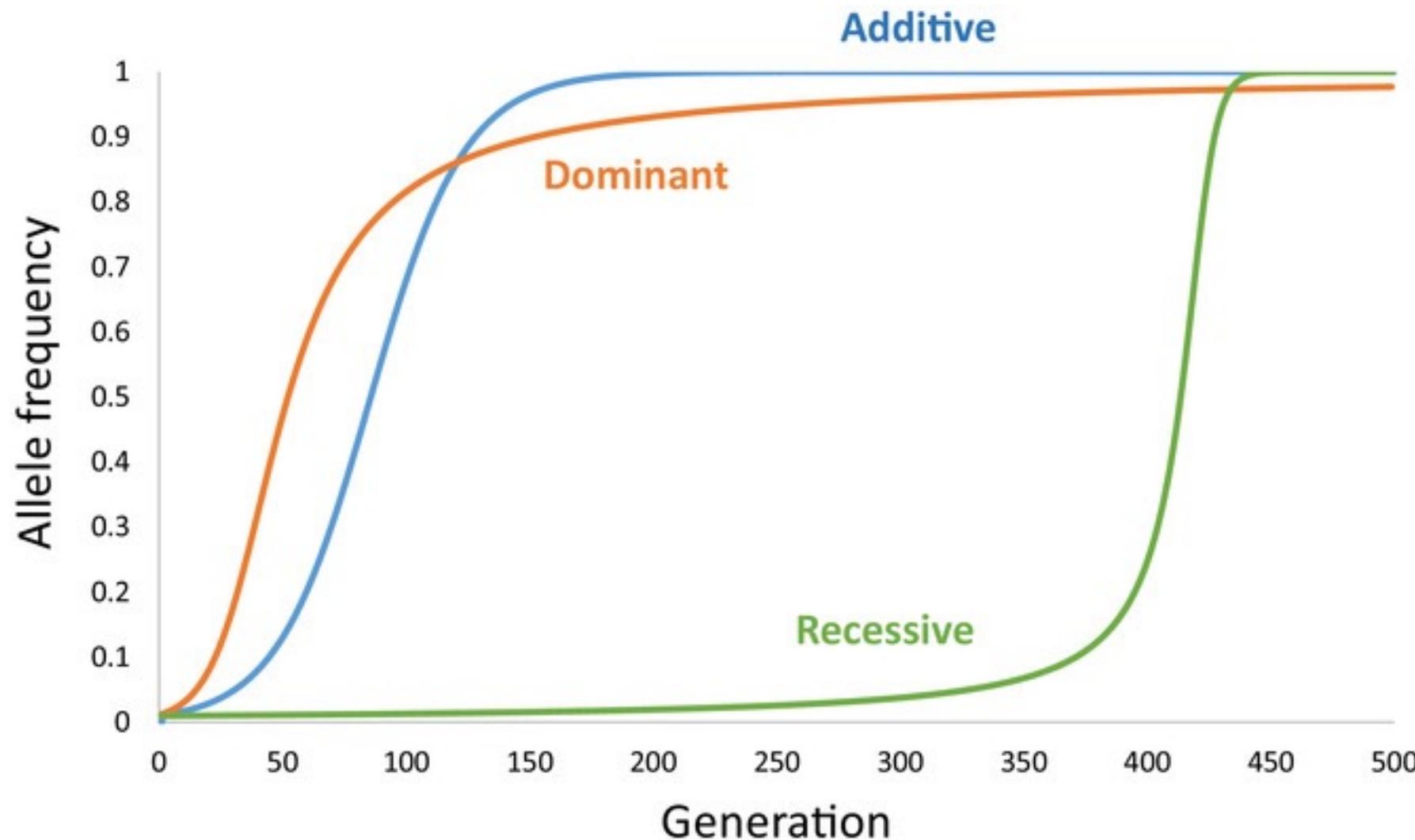
Benefits of time-series sampling



Benefits of time-series sampling



Benefits of time-series sampling



EXERCISE 1: Simulate selection trajectories

<https://cjabattey.shinyapps.io/driftR/>

Initial setup:

- Starting allele frequency A: 0.0001
- Mutation Rate 0
- Fitness of genotype AA 1
- Fitness of genotype AB 0.99
- Fitness of genotype BB 0.98
- Migration Rate 0
- Number of Populations 100
- Population Size 10000
- Number of Generations 1000

Try changing the initial settings and see what happens

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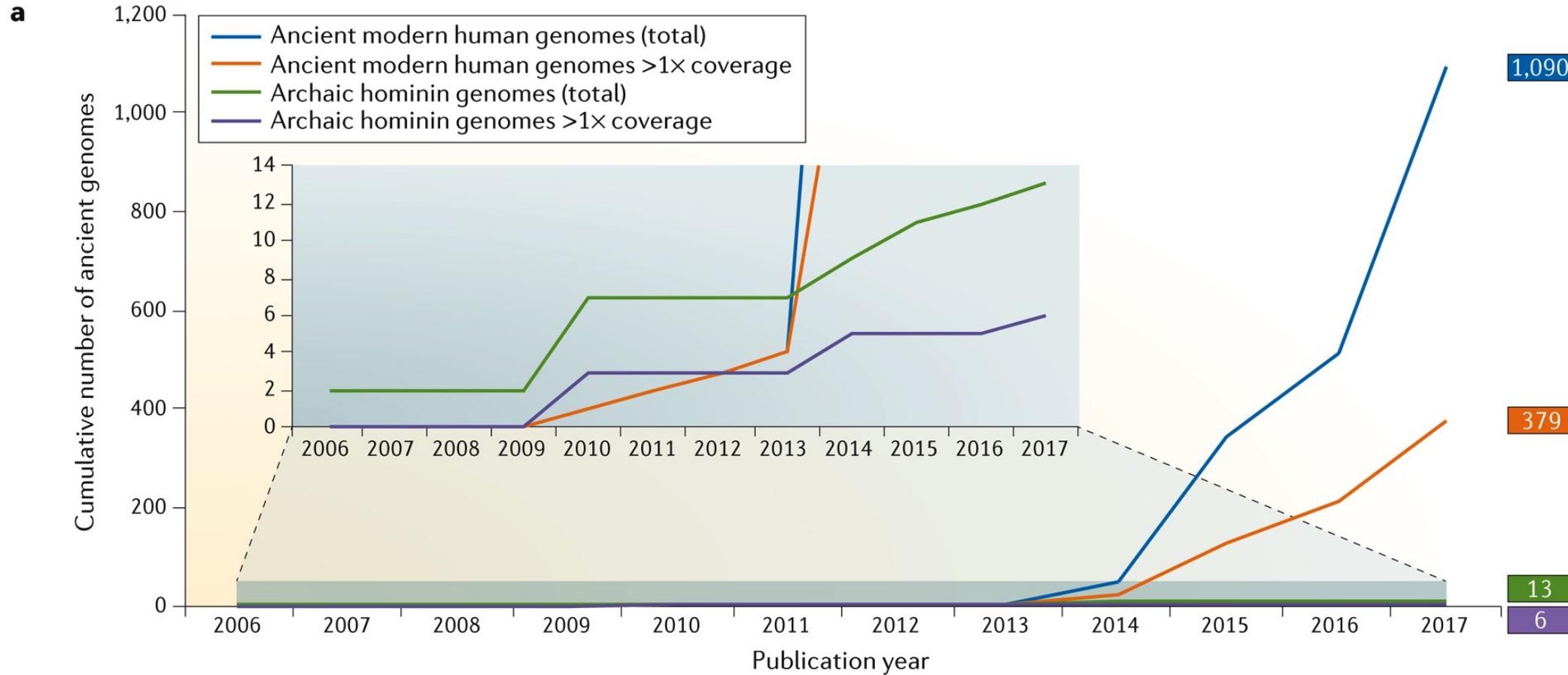
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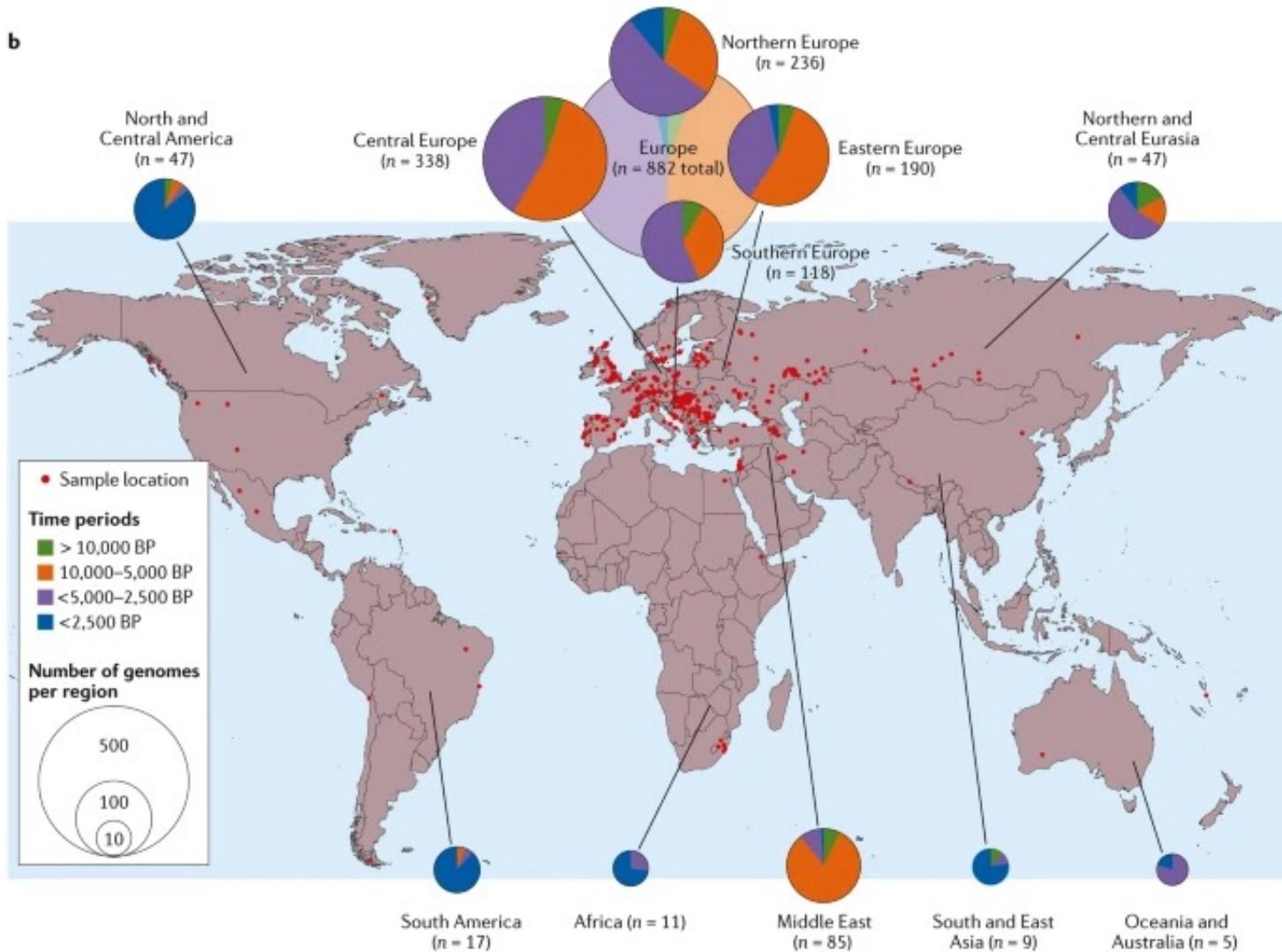
Questions

- What patterns do you observe in the simulated trajectories?
- How does the starting frequency affect survival of a selected allele?
- How does population size affect the trajectories?
- What happens when you allow migration between the populations?
- What about recurrent mutations?

Rapid growth in ancient human genomes



Rapid growth in ancient human genomes



CASE STUDY 1: Genome-wide selection in humans

nature

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[nature](#) > [articles](#) > [article](#)

Published: 23 November 2015

Genome-wide patterns of selection in 230 ancient Eurasians

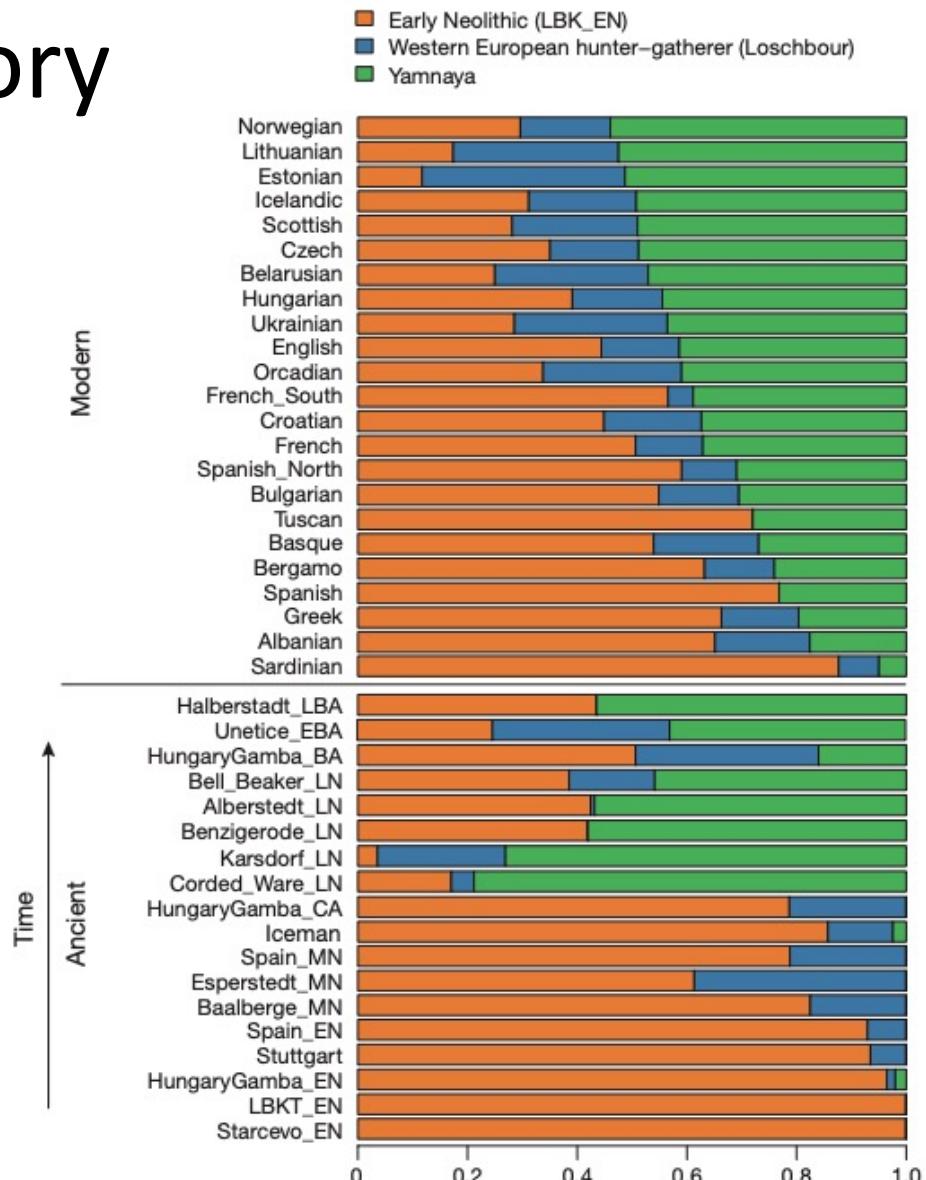
Iain Mathieson , Iosif Lazaridis, [...] David Reich 

Nature **528**, 499–503 (2015) | [Cite this article](#)

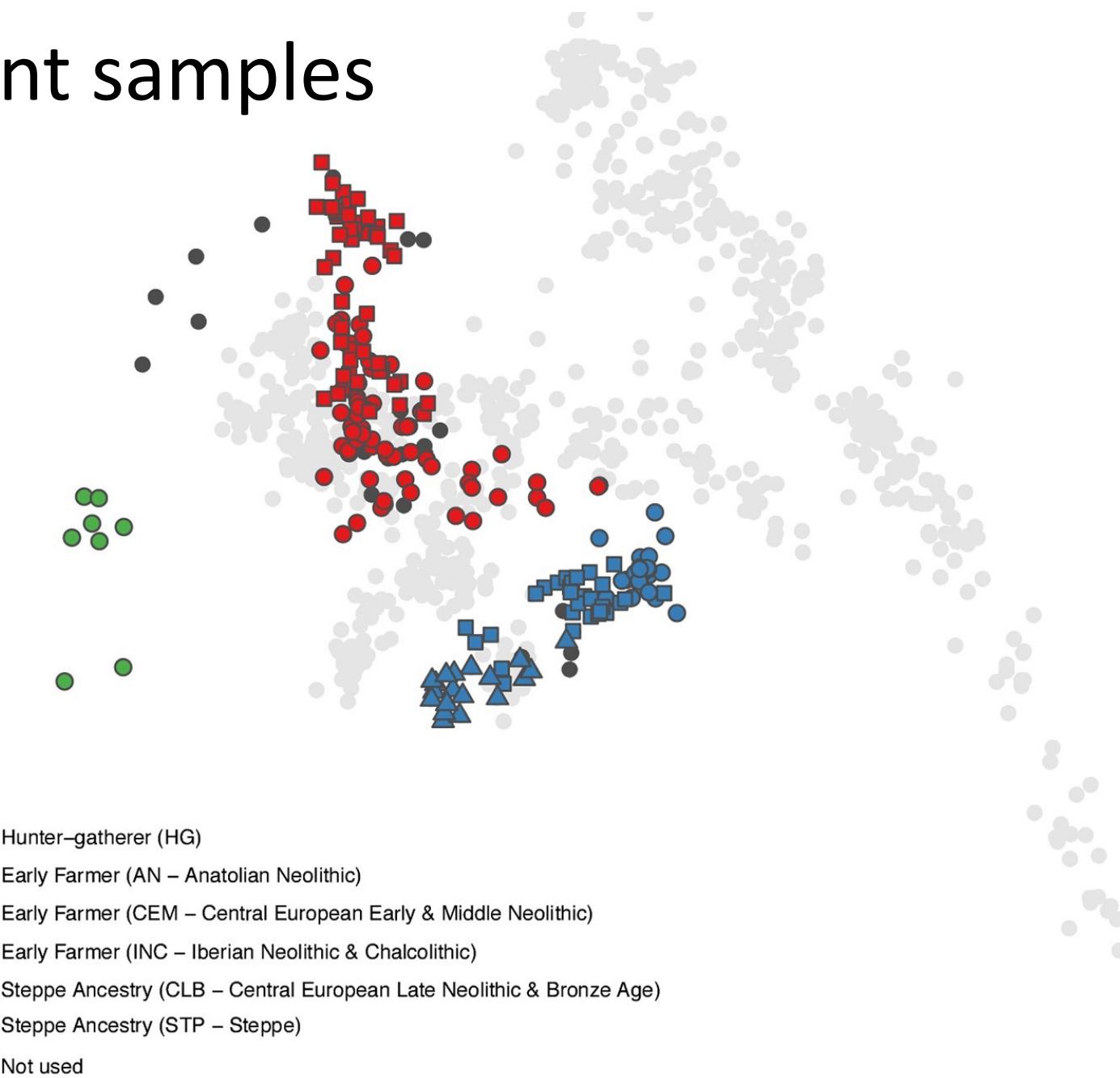
Admixture in European prehistory

Most present-day Europeans can be modelled as a combination of three highly differentiated ancestral populations:

- Early European farmers
- Western hunter-gatherers
- Steppe pastoralists



PCA of ancient samples



Genome-wide scan for selection

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- For each SNP, compute the likelihood of the allele frequency in each of the three ancestral populations

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Limitations

- Cannot infer the strength or timing of selection

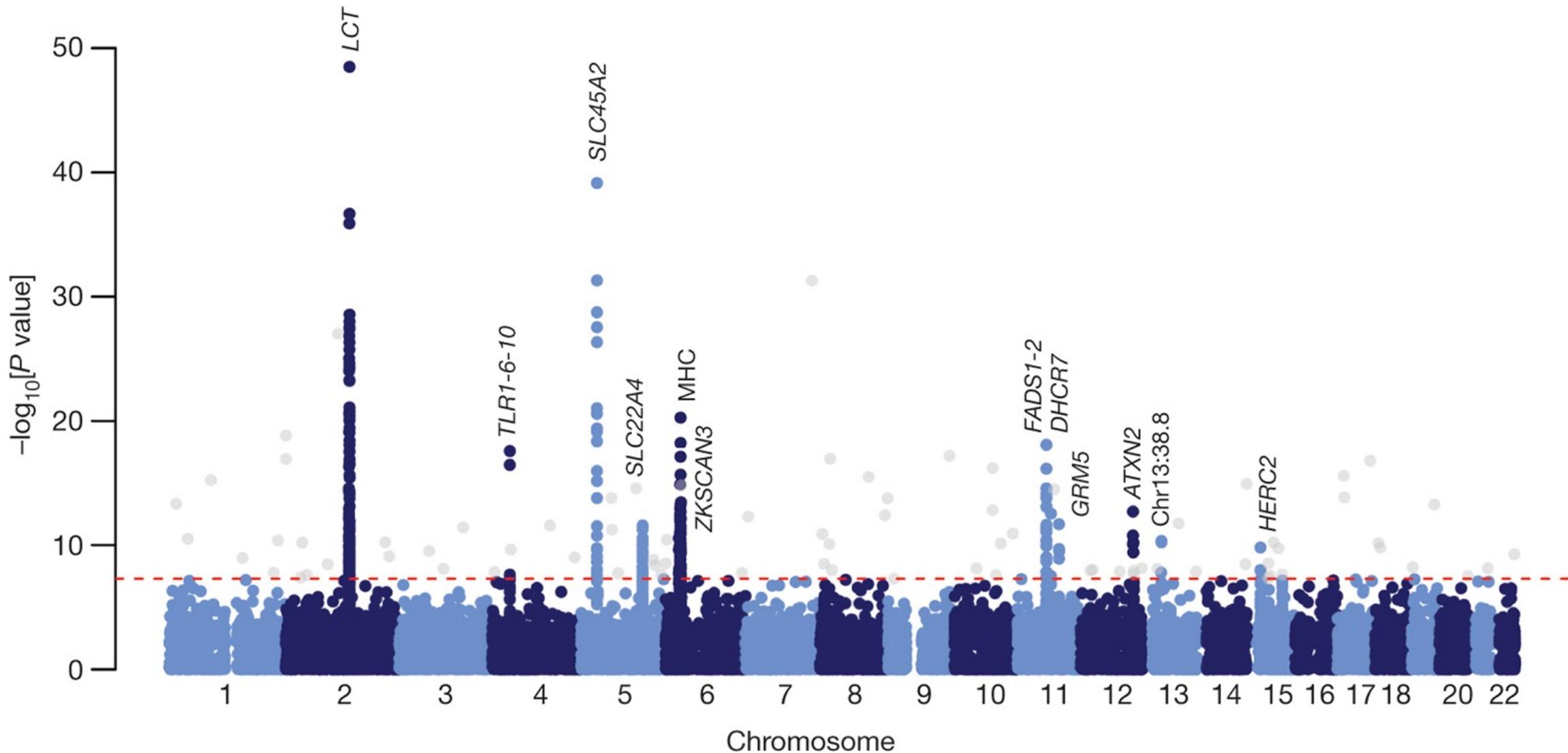
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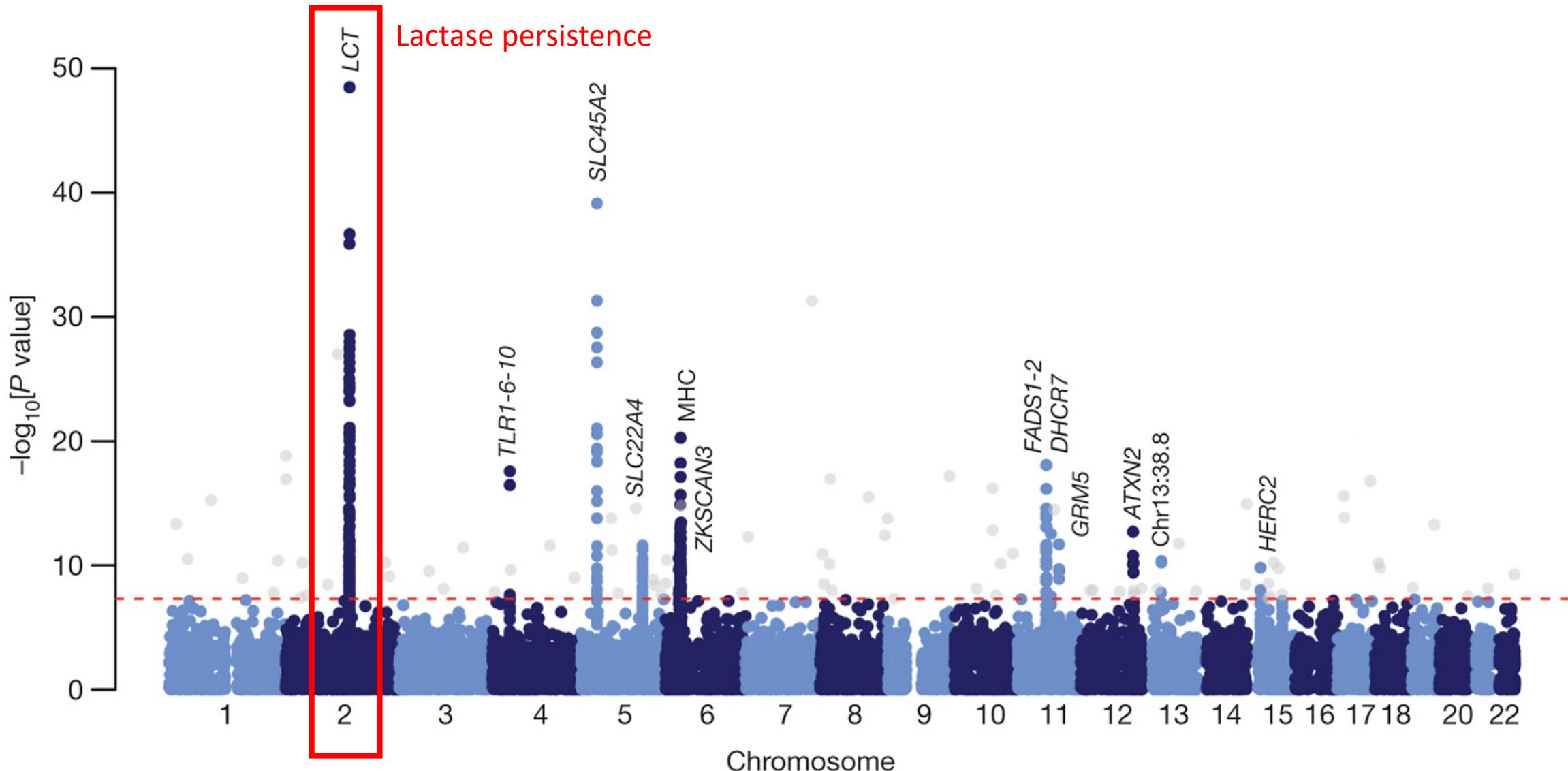
Limitations

- Cannot infer the strength or timing of selection
- Test is sensitive to misspecification of the ancestral populations and their mixture fractions

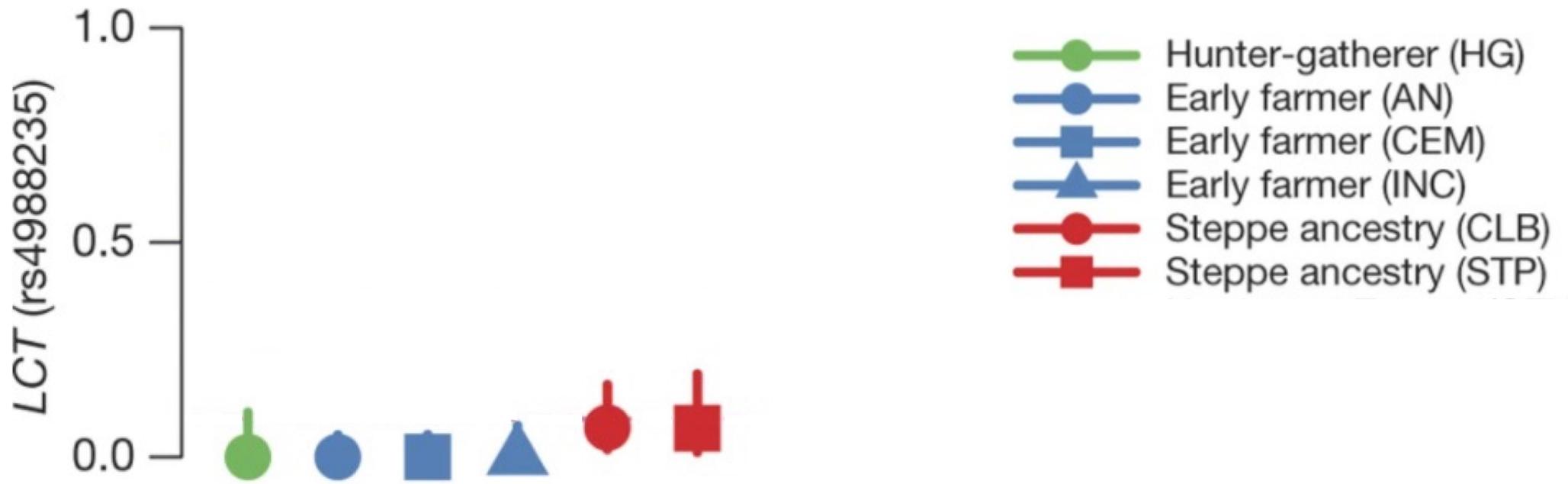
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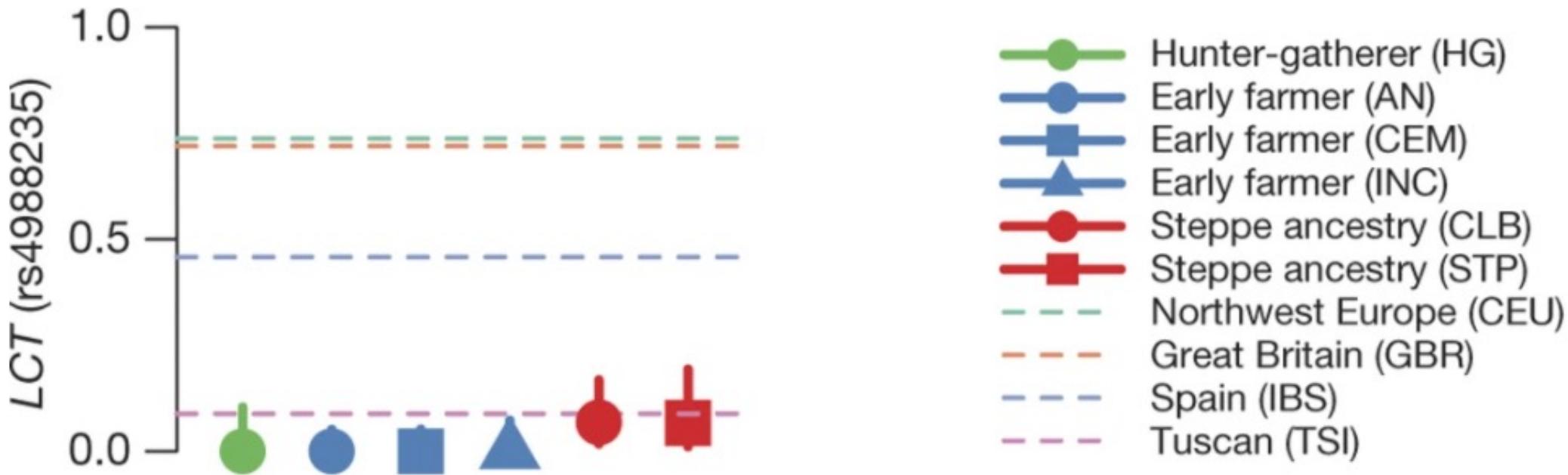
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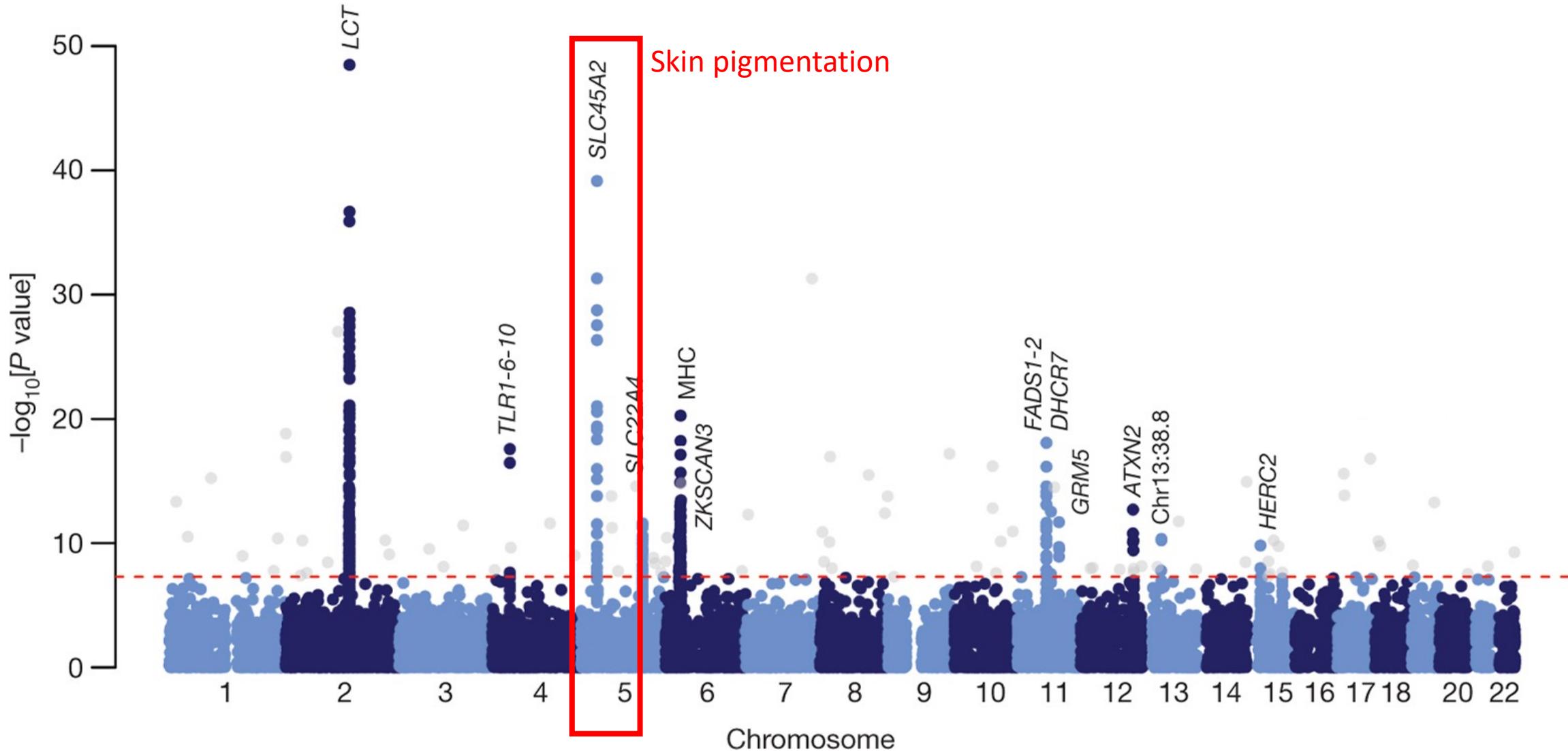
Lactase persistence



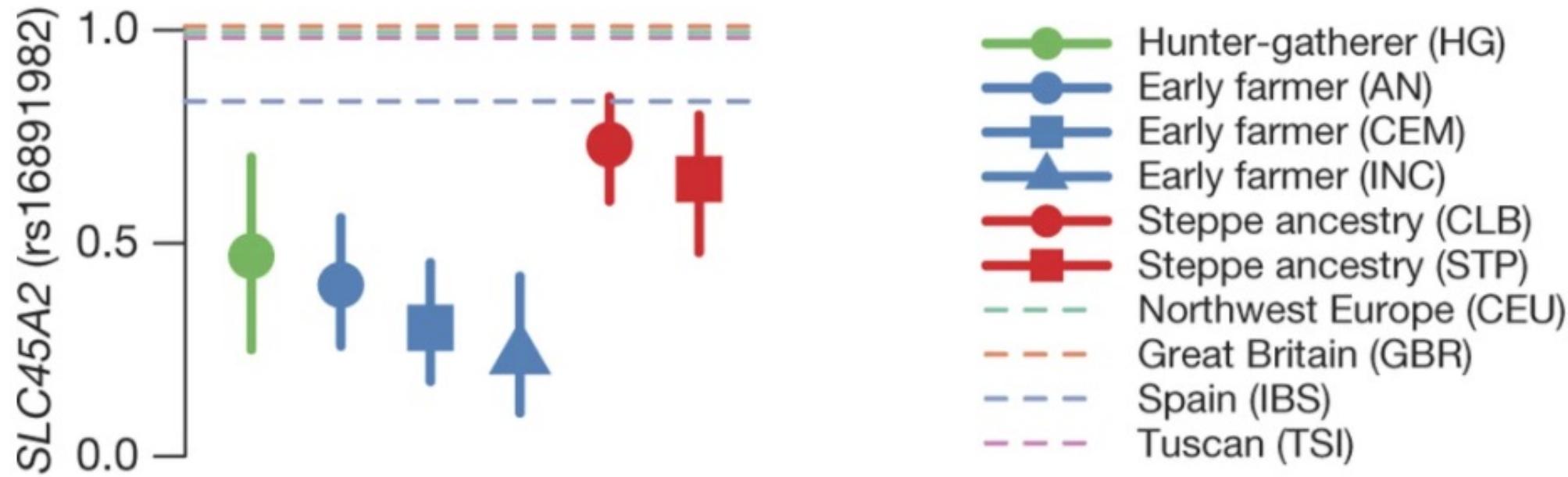
Lactase persistence



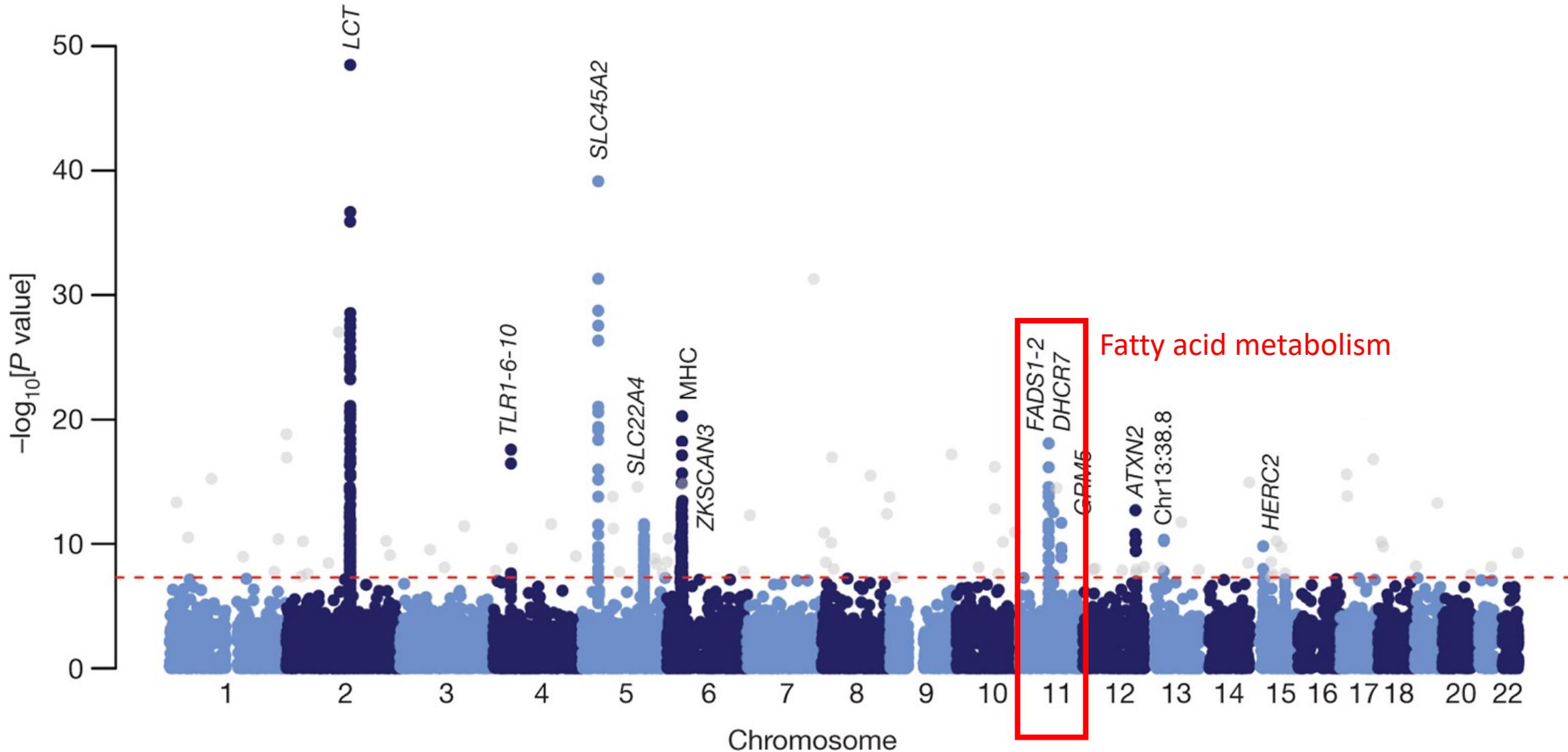
Genome-wide scan for selection



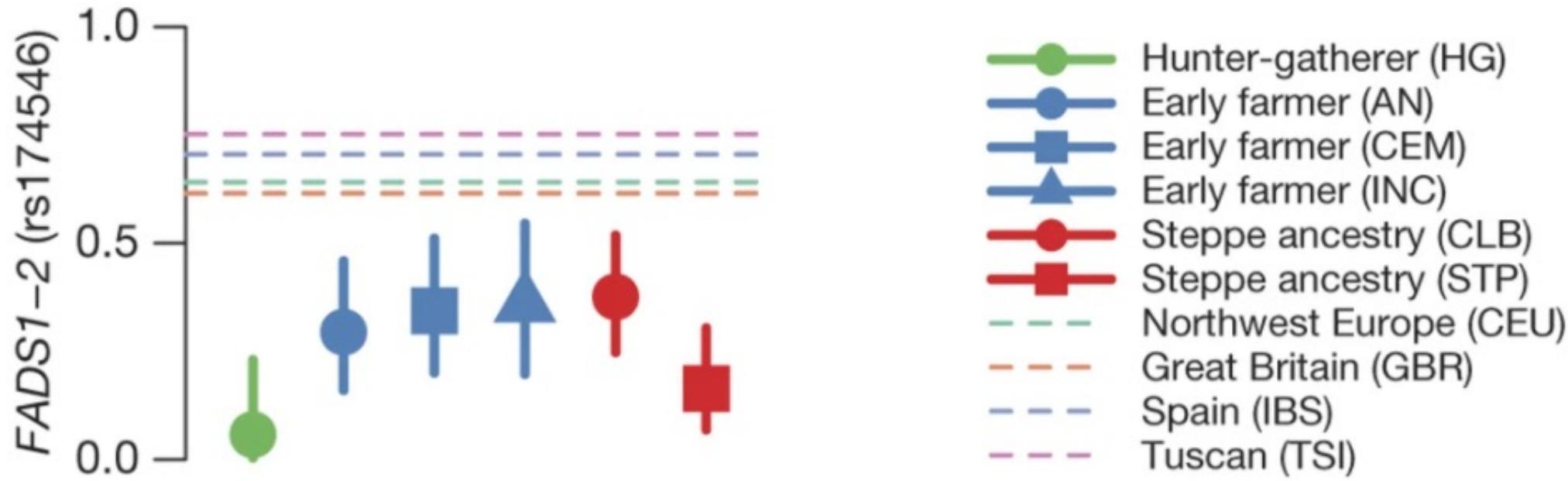
Skin pigmentation



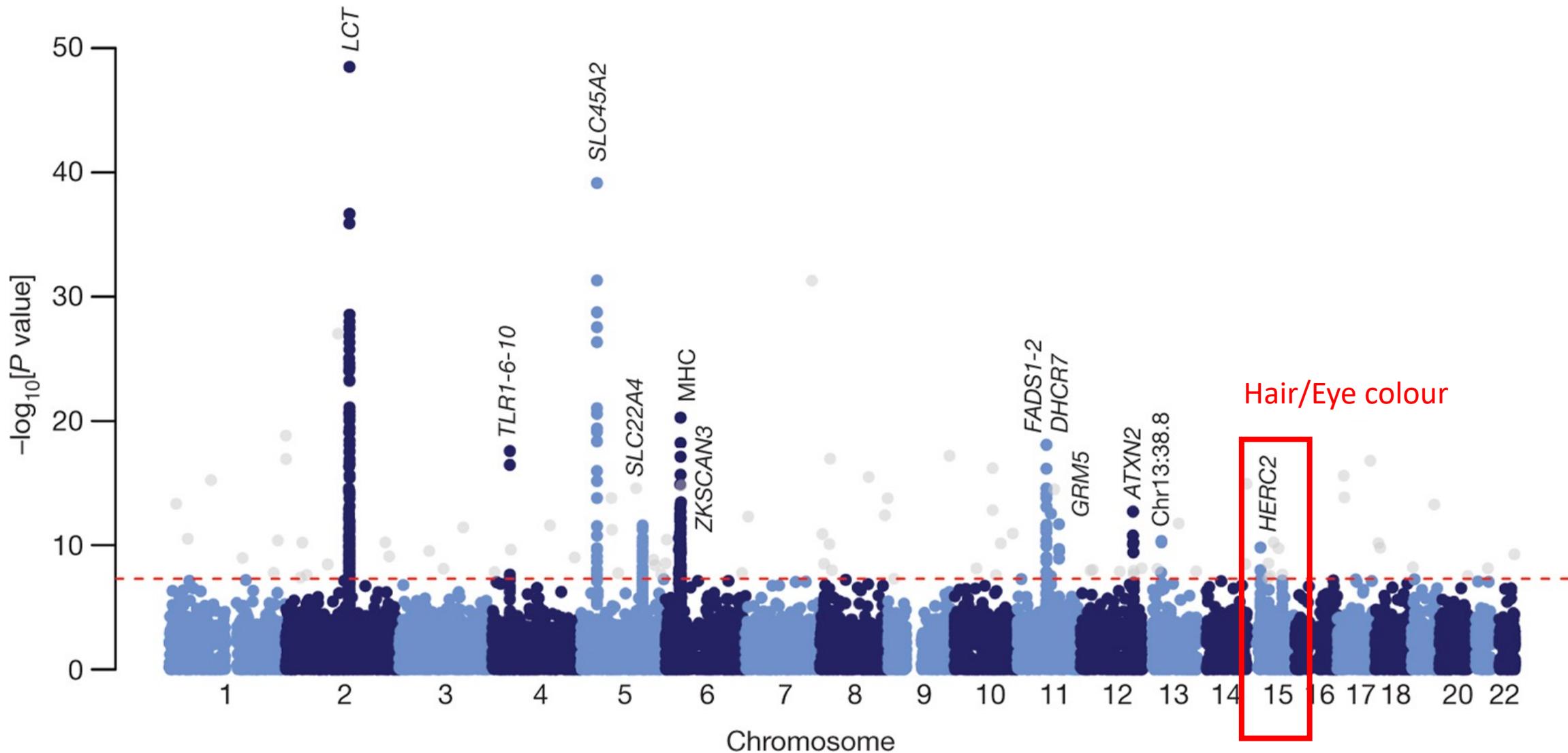
Genome-wide scan for selection



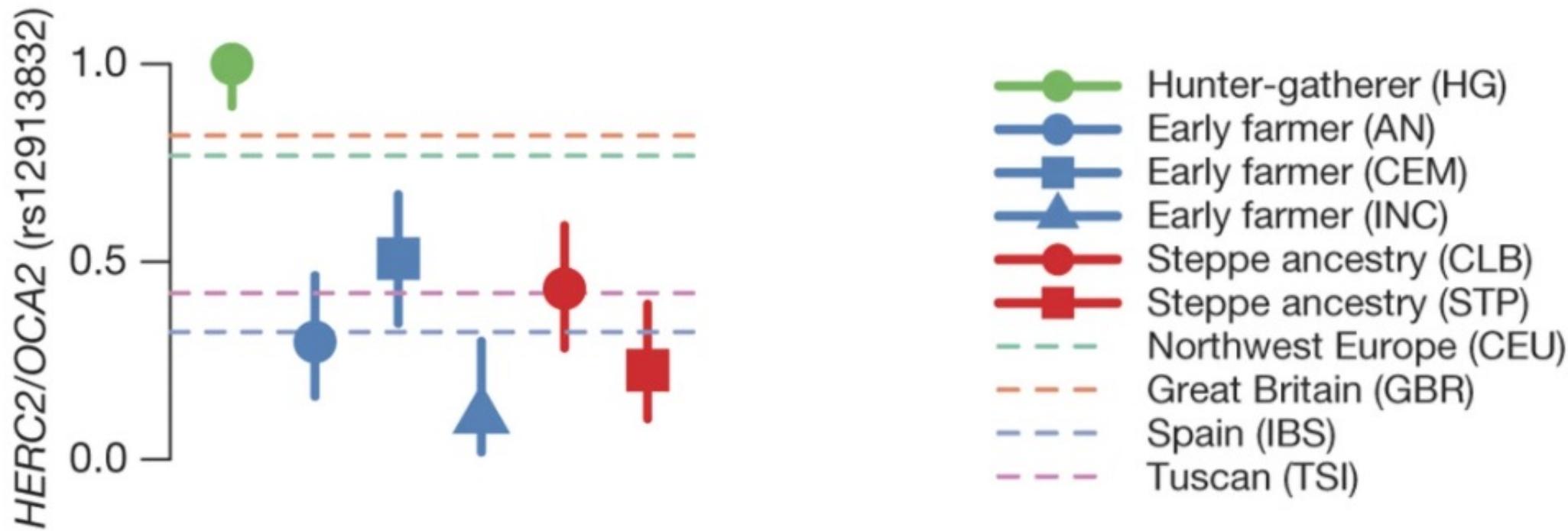
Fatty acid metabolism



Genome-wide scan for selection



Hair/Eye colour



CASE STUDY 2: Selection for coat colour in horses

Bayesian Inference of Natural Selection from Allele Frequency Time Series

Joshua G. Schraiber, Steven N. Evans and Montgomery Slatkin

GENETICS May 1, 2016 vol. 203 no. 1 493-511; <https://doi.org/10.1534/genetics.116.187278>

Inferring selection trajectories from time-series data

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- Assume that the time-series of samples are drawn from the same continuous population

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- Group samples into temporal bins, and calculate the frequency of the derived allele in each time bin

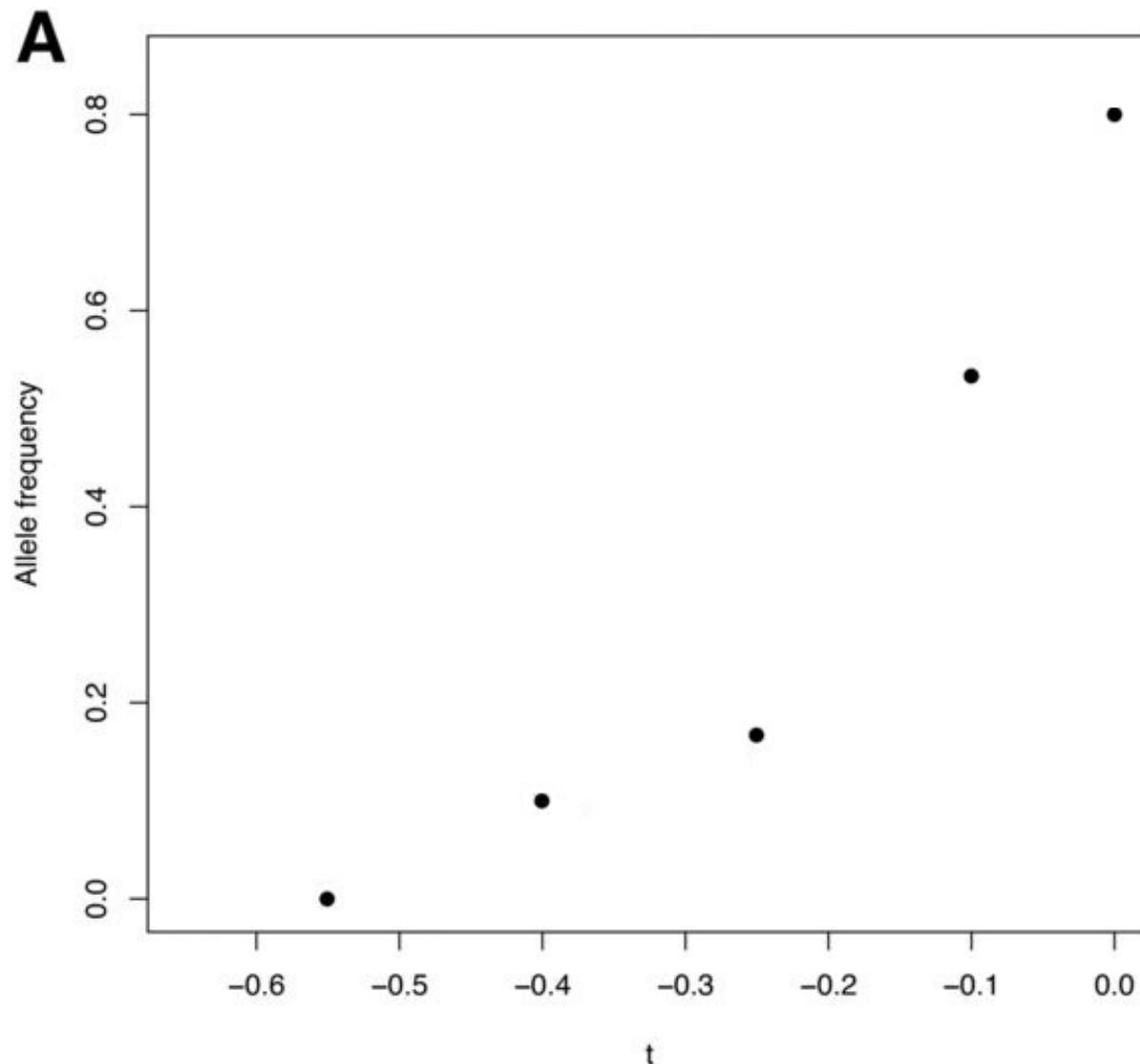
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- Use a Markov Chain Monte Carlo (MCMC) method to integrate over the space of allele frequency trajectories and selection coefficients consistent with the observed data

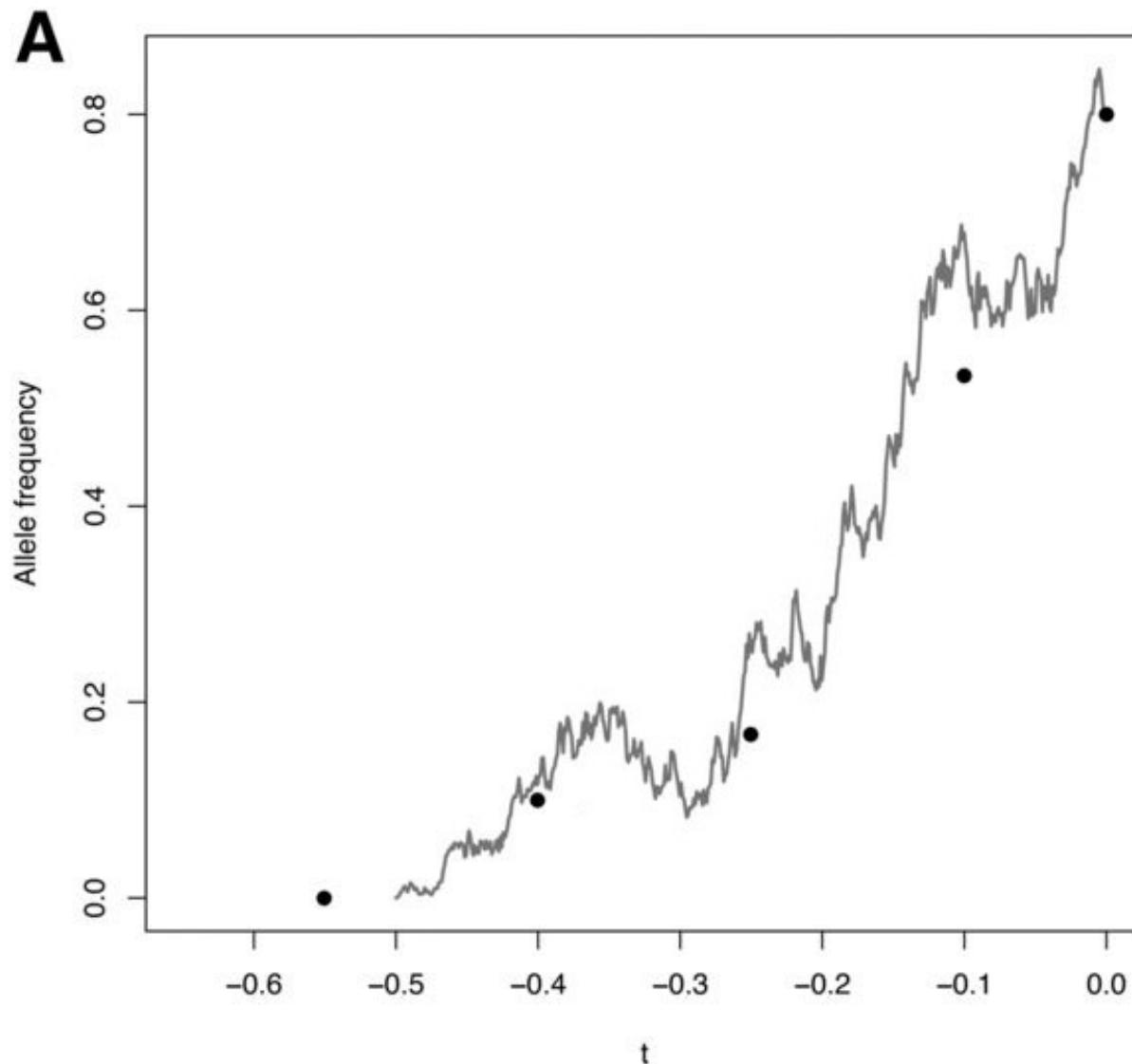
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- Resulting in Bayesian posterior distributions for the trajectory of an allele, and the strength of selection

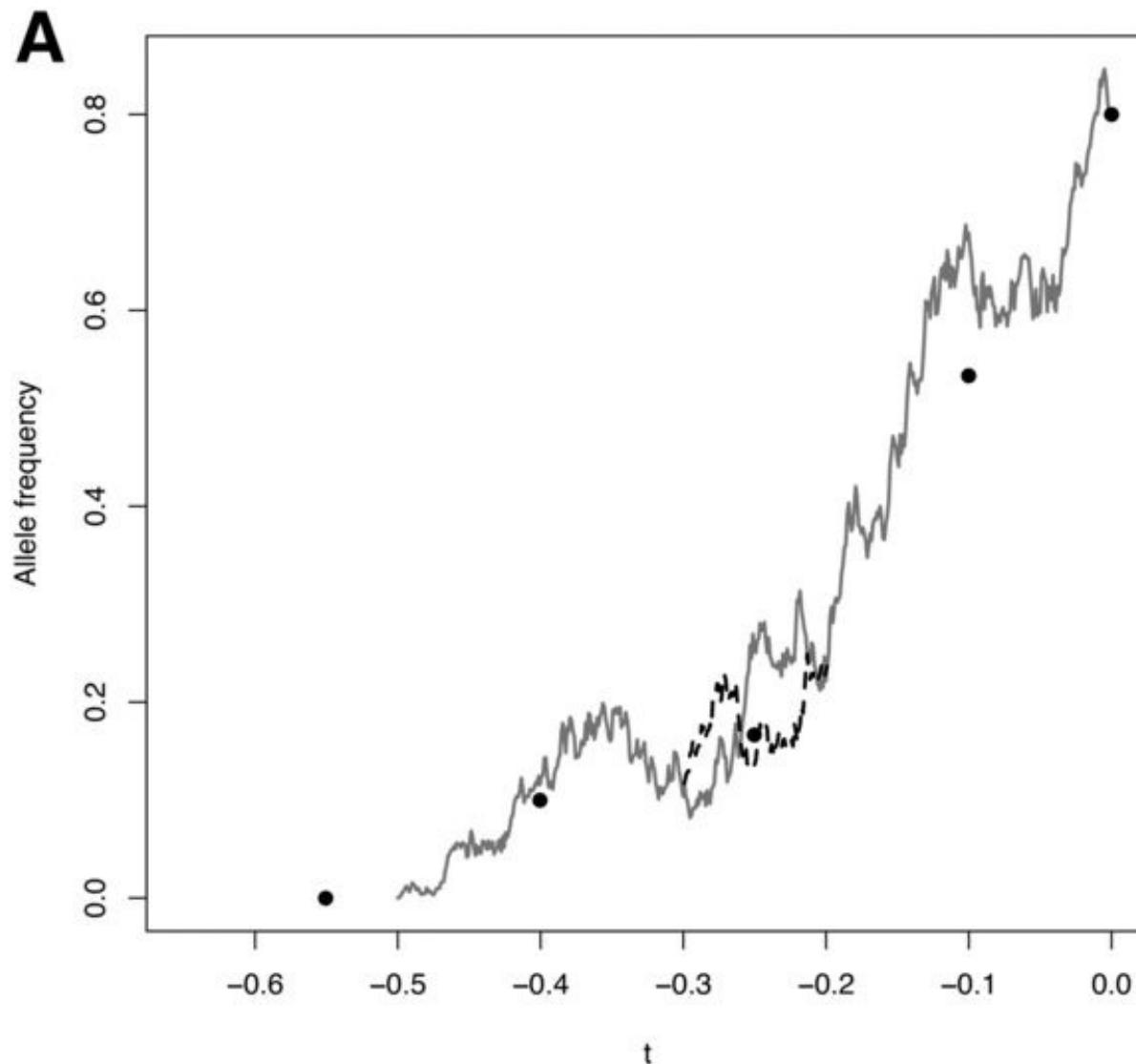
Sampling from the space of possible trajectories



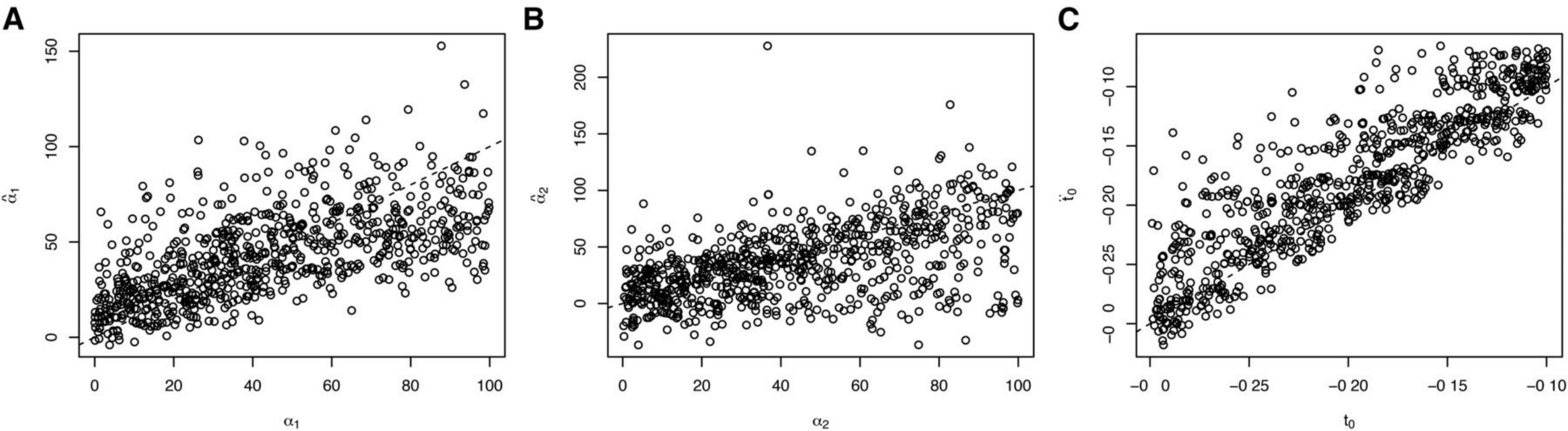
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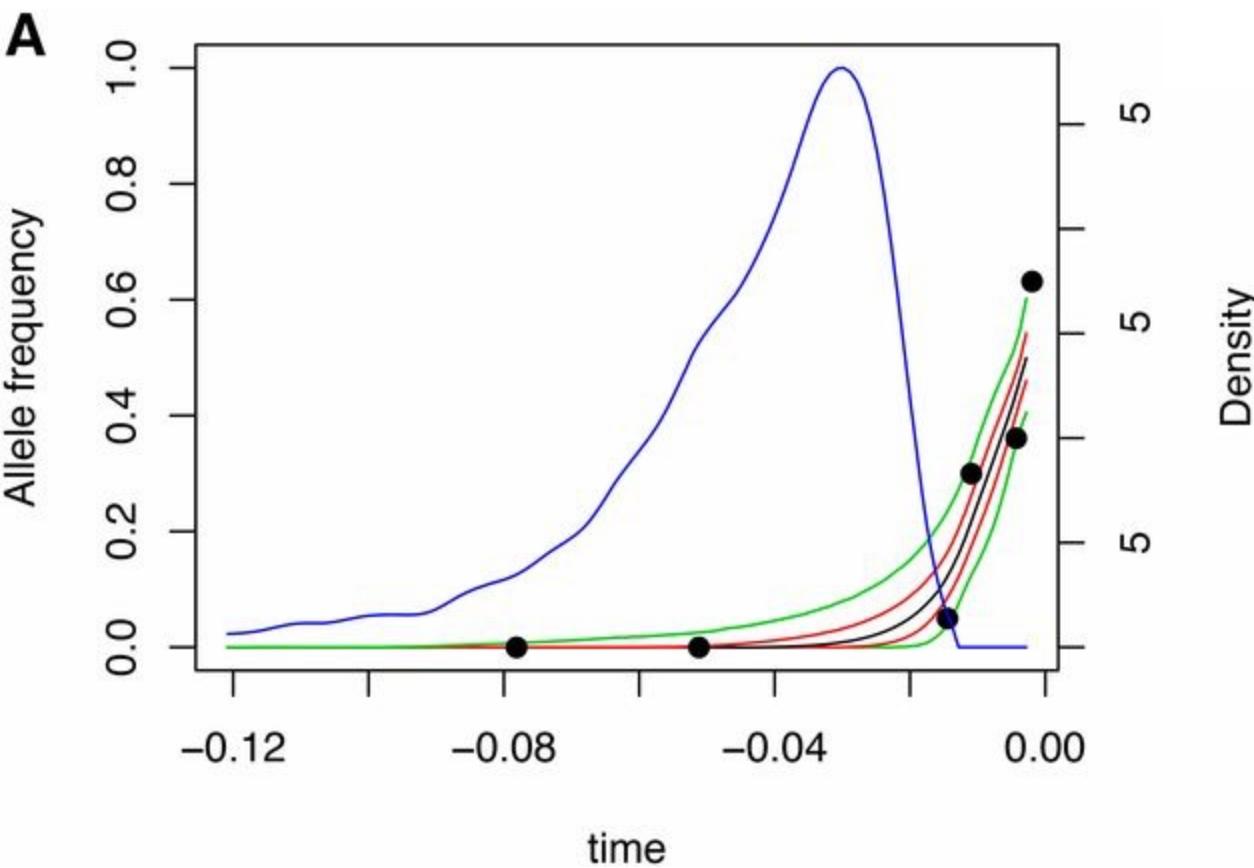


Maximum *a posteriori* estimates from simulations

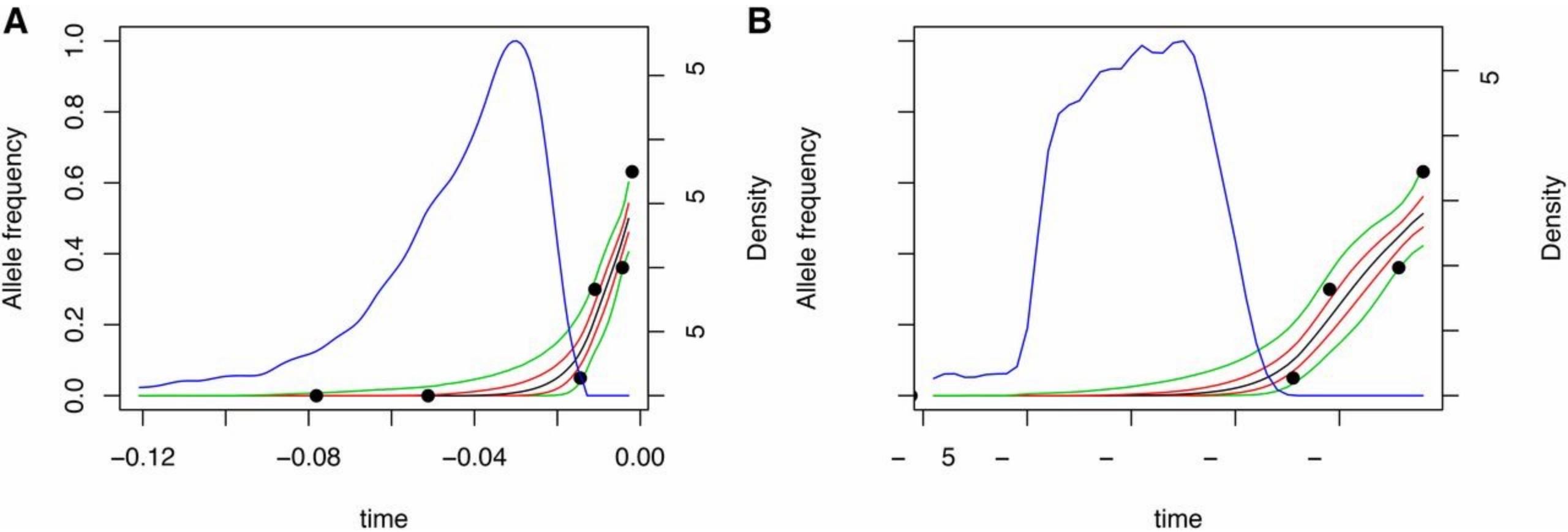


MC1R – Selection for horse coat colour

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EXERCISE 2: Infer a selection trajectory

<https://github.com/ekirving/temporal-selection/>

Follow the instructions to install the software and then to recreate the *MC1R* selection analysis

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Questions

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 - If not, what steps can we take to improve the ESS?
- Does your trajectory look the same as Figure 6A from the paper?
- Does it look the same as other students' in the class?
 - If not, why might this be?
- How does your estimates for the age of the *MC1R* allele compare to onset of domestication?

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Optional Extra

- What effect did including the full demography have on the ESS for the inferred params?
 - How might we improve on this?
- How did the posterior densities of the age of the allele, and the selection coefficients, differ from the constant population model?

CASE STUDY 3: Polygenic selection in humans

RESEARCH ARTICLE



The evolution of skin pigmentation-associated variation in West Eurasia

Dan Ju and Iain Mathieson

[+ See all authors and affiliations](#)

PNAS January 5, 2021 118 (1) e2009227118; <https://doi.org/10.1073/pnas.2009227118>

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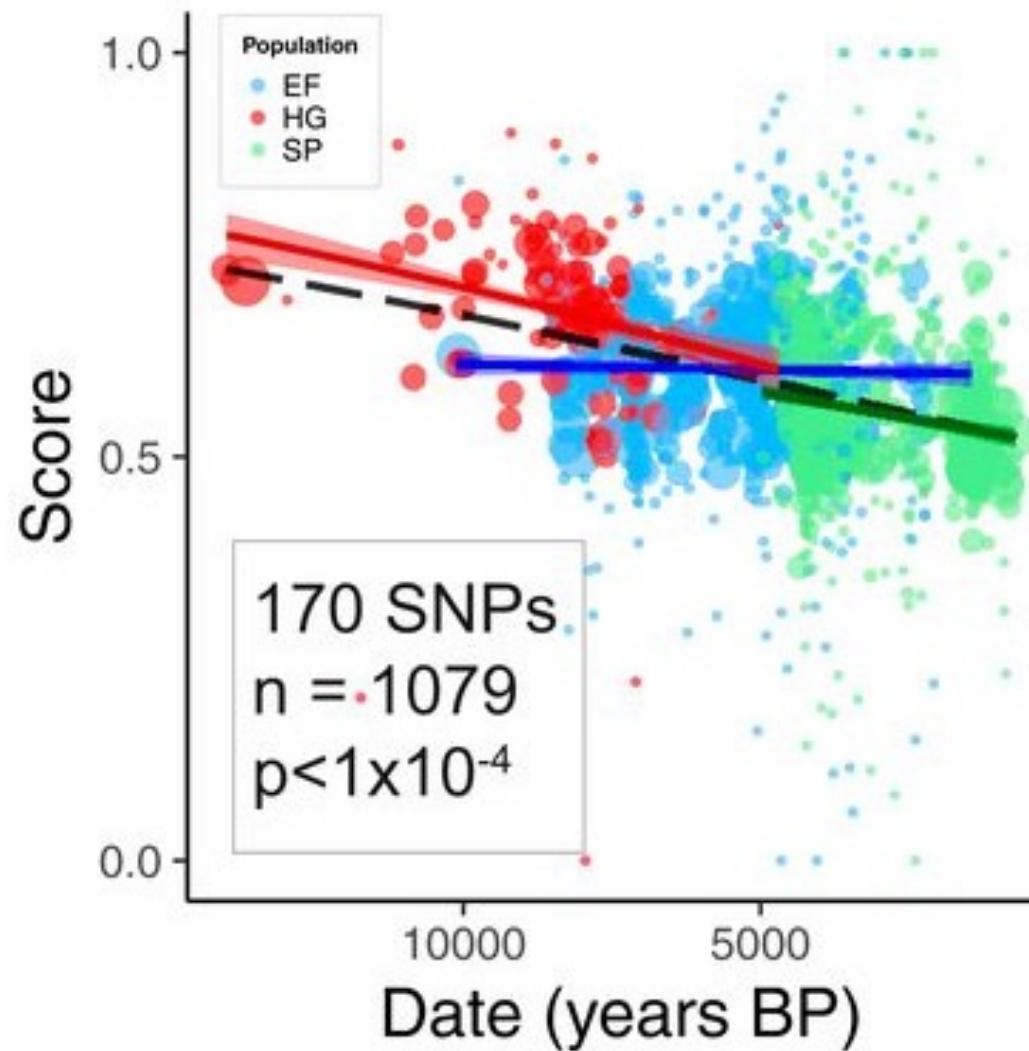
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Limitations

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- Estimated polygenic scores are very noisy and inherently unverifiable

Inferring polygenic adaptation in skin pigmentation



References

- Dehasque et al. 2020. Inference of natural selection from ancient DNA. *Evolution Letters* 4, 94–108. <https://doi.org/10.1002/evl3.165>
- Fan et al. 2016. Going global by adapting local: A review of recent human adaptation. *Science* 354, 54–59. <https://doi.org/10.1126/science.aaf5098>
- Haak et al. 2015. Massive migration from the steppe was a source for Indo-European languages in Europe. *Nature* 522, 207–211. <https://doi.org/10.1038/nature14317>
- Ju and Mathieson 2021. The evolution of skin pigmentation-associated variation in West Eurasia. *PNAS* 118. <https://doi.org/10.1073/pnas.2009227118>
- Malaspinas 2016. Methods to characterize selective sweeps using time serial samples: an ancient DNA perspective. *Mol Ecol* 25, 24–41. <https://doi.org/10.1111/mec.13492>
- Marciak and Perry 2017. Harnessing ancient genomes to study the history of human adaptation. *Nat Rev Genet* advance online publication.
<https://doi.org/10.1038/nrg.2017.65>
- Mathieson et al. 2015. Genome-wide patterns of selection in 230 ancient Eurasians. *Nature* 528, 499–503. <https://doi.org/10.1038/nature16152>
- Schraiber et al. 2016. Bayesian Inference of Natural Selection from Allele Frequency Time Series. *Genetics* 203, 493–511. <https://doi.org/10.1534/genetics.116.187278>