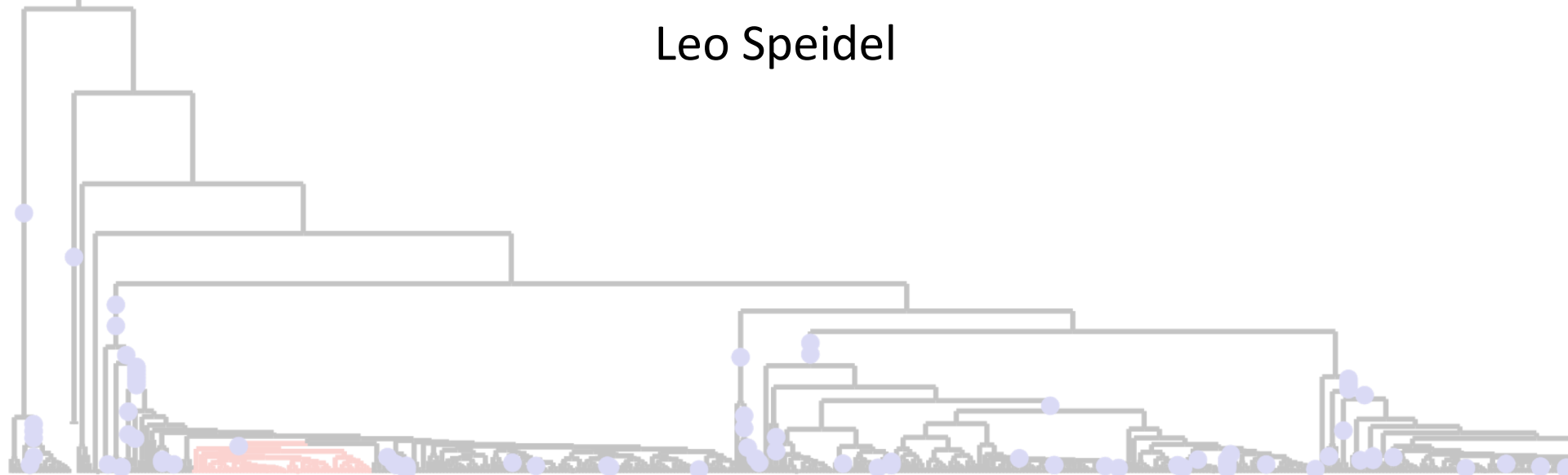
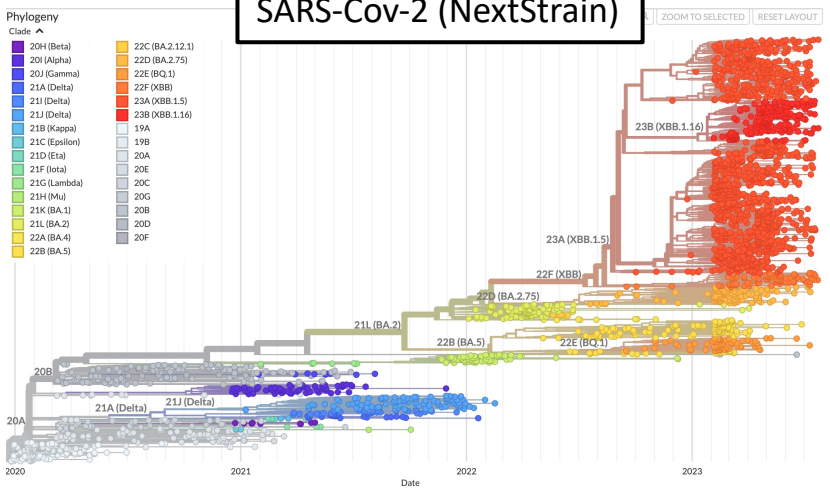

# Learning about evolution by building coalescent trees

Leo Speidel

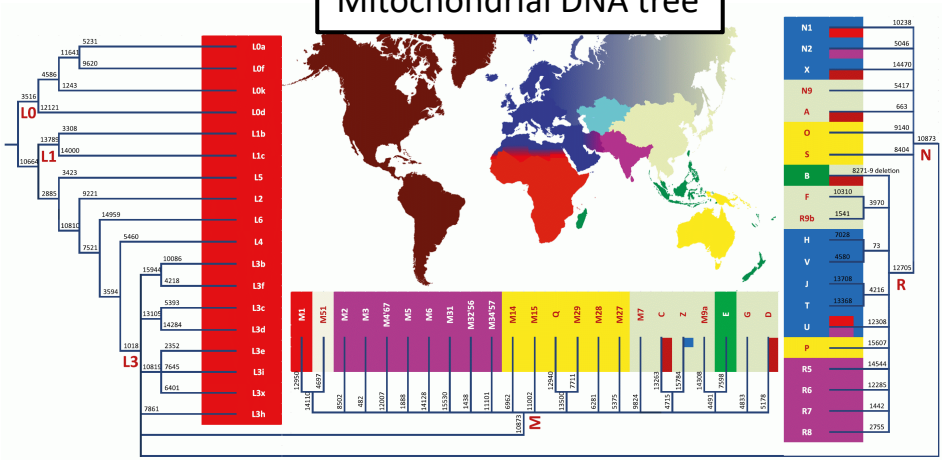


# Trees are central to evolutionary biology

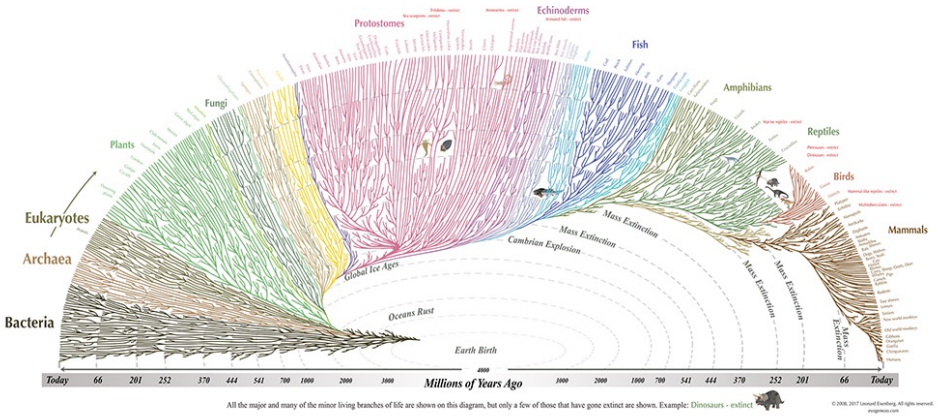
SARS-Cov-2 (NextStrain)




Mitochondrial DNA tree



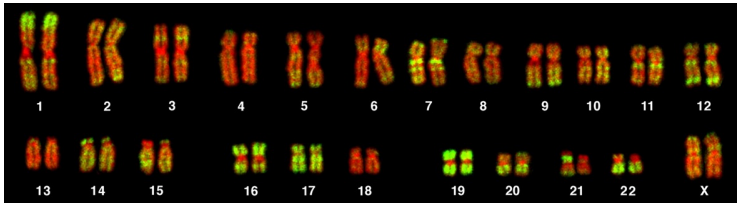

Species tree of life



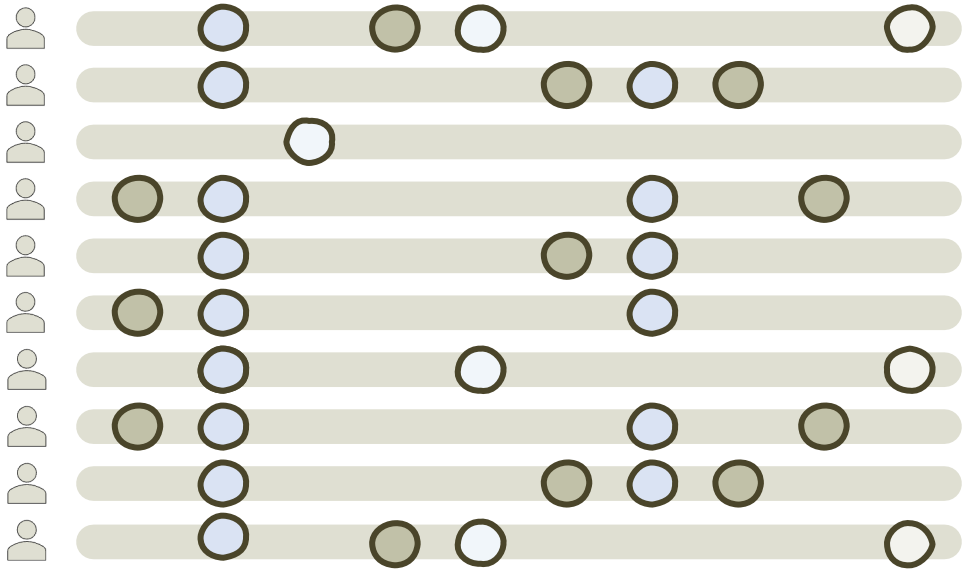

Autosomal DNA trees

?

22 chromosomes

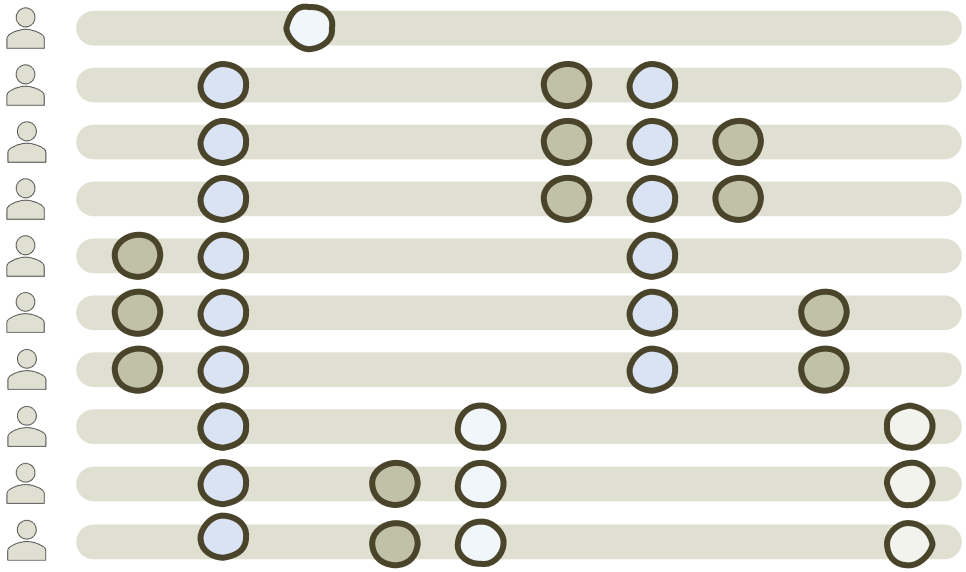


# Building trees from mutation sharing



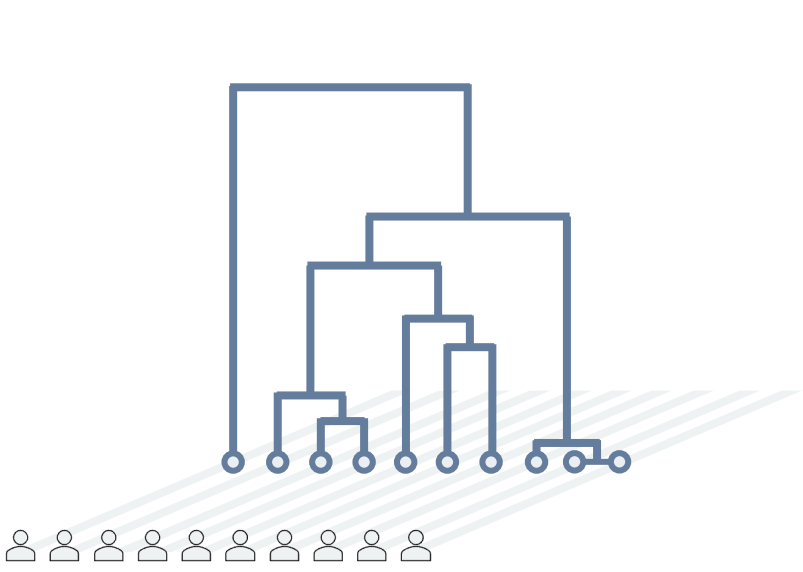
Credit: Aina Colomer

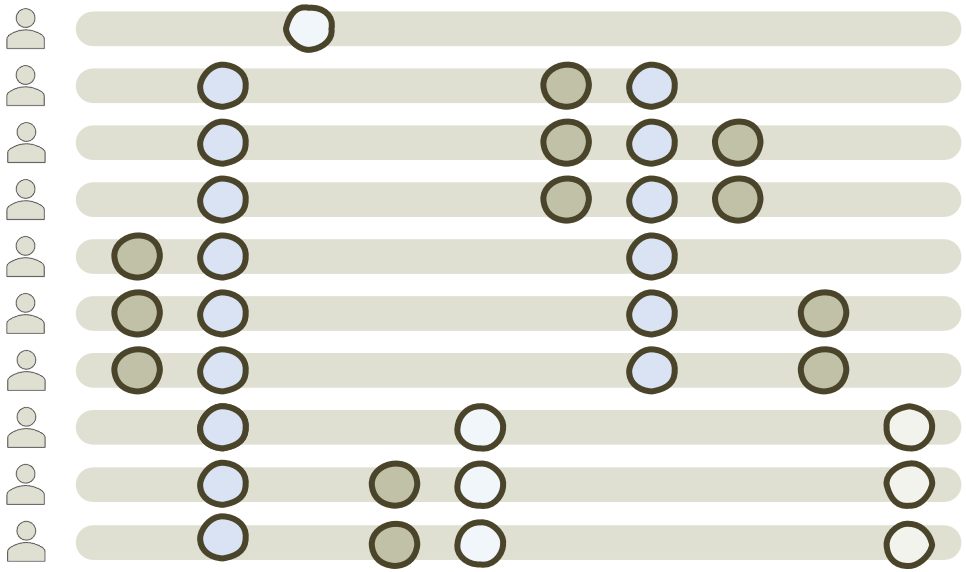
# Building trees from mutation sharing



Credit: Aina Colomer

# Building trees from mutation sharing



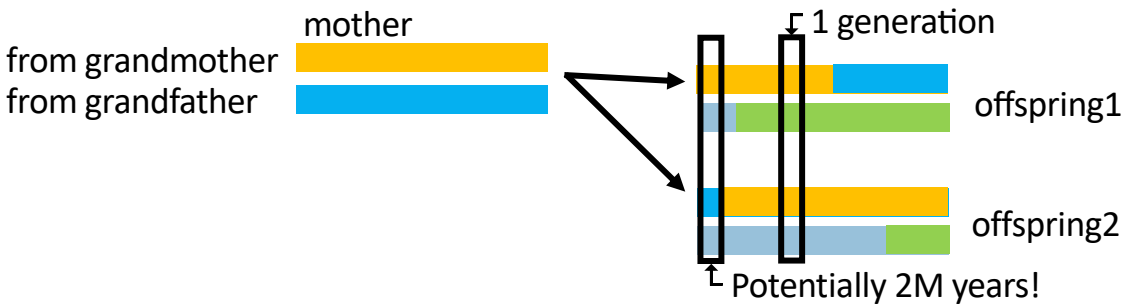


Credit: Aina Colomer

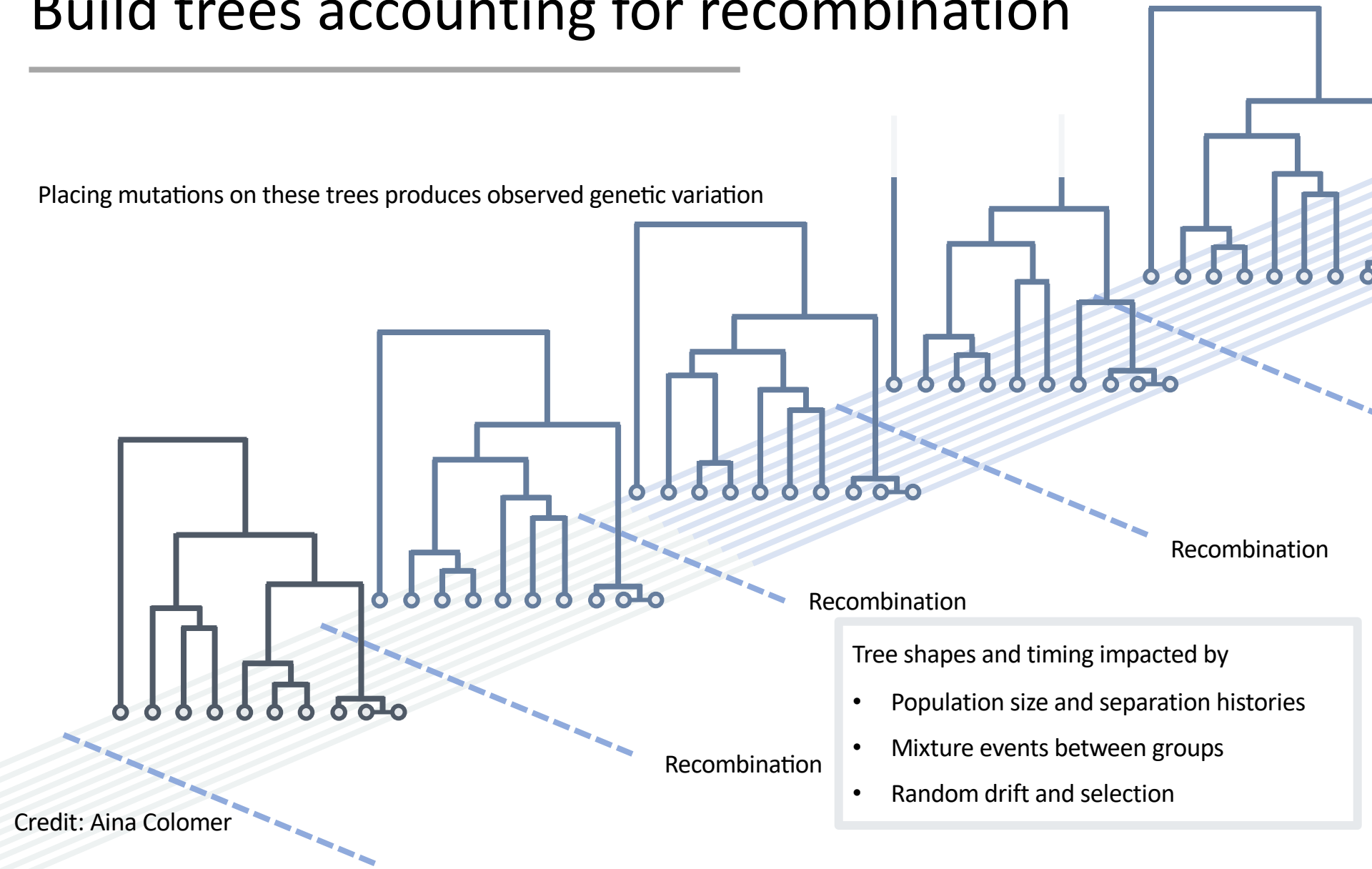
# Recombination

Shuffling of our genetic material in every generation

→ We're differently related to each other in different parts of our genomes



# Build trees accounting for recombination



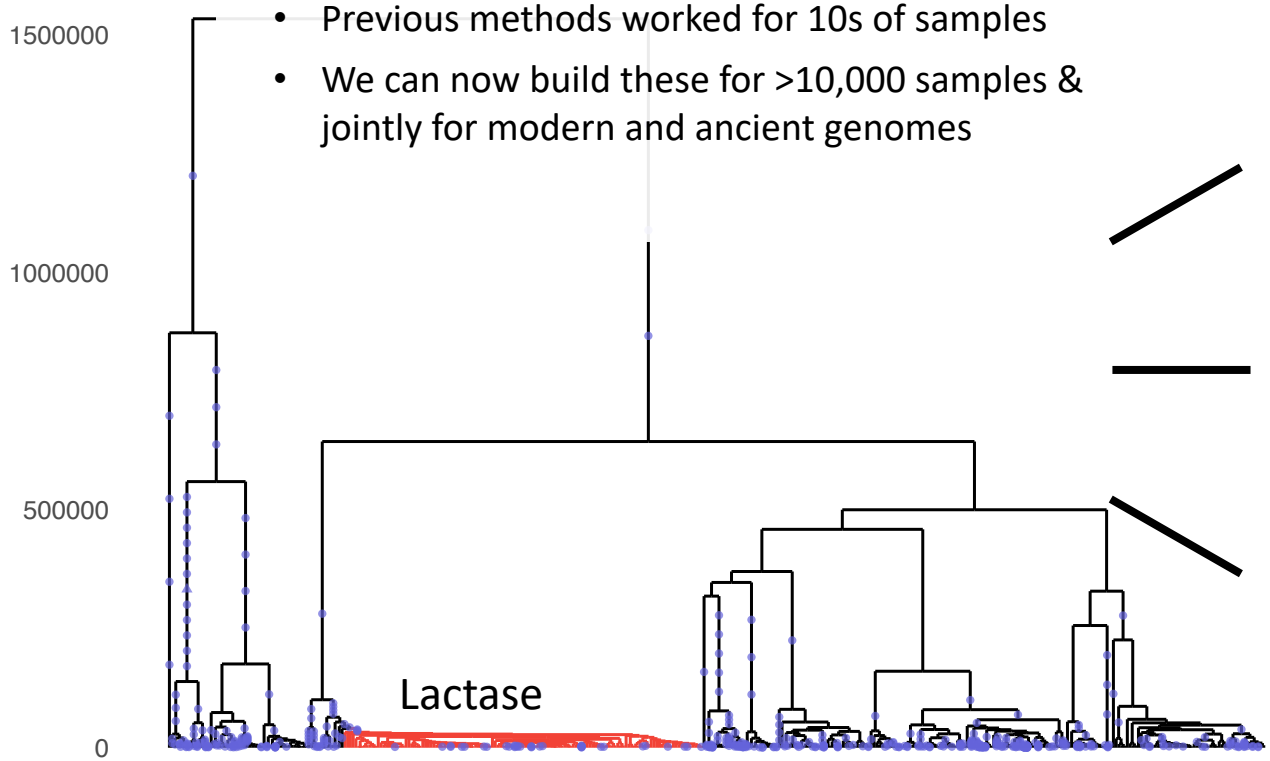

Tree shapes and timing impacted by

- Population size and separation histories
- Mixture events between groups
- Random drift and selection

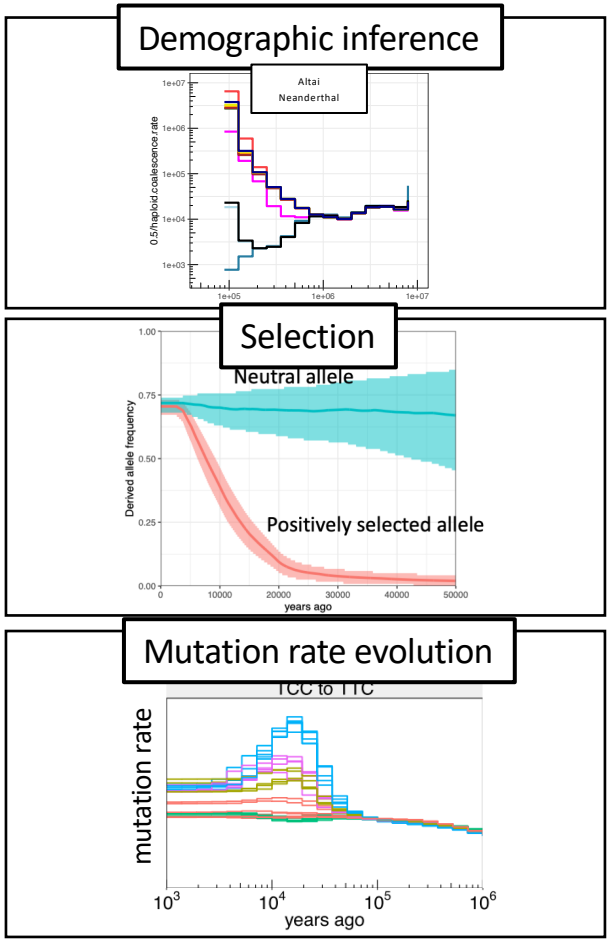
# We can now infer genealogical trees across the genome!

**Relate** (Speidel et al, Nat. Genetics 2019/MBE 2021 ), **Tsinfer** (Kelleher et al, Nat. Genetics 2019, Wohns et al, Science 2022), **ARG-Needle** (Zhang et al, Nature Genetics 2023)

- Many previous attempts since the 90s!
- Previous methods worked for 10s of samples
- We can now build these for >10,000 samples & jointly for modern and ancient genomes



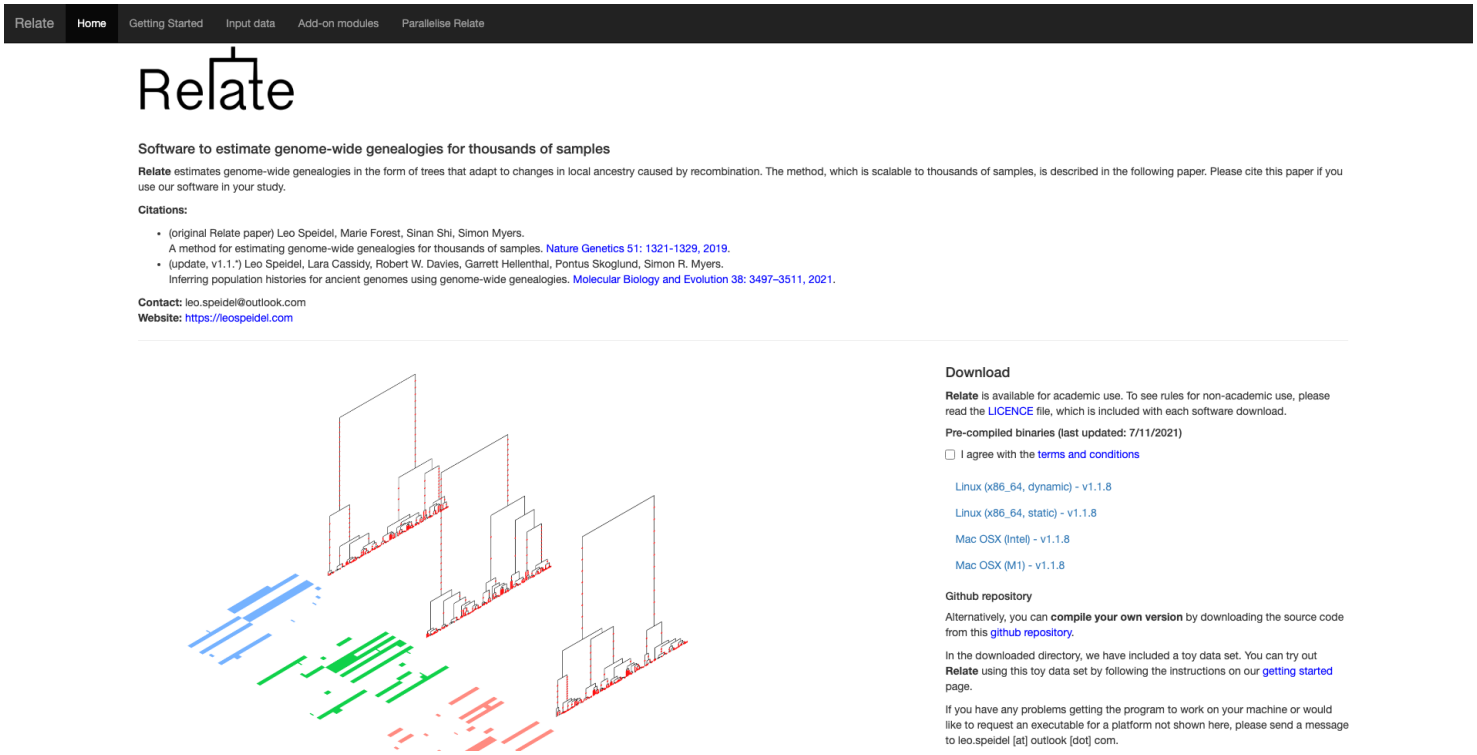

Applied to hundreds of studies on humans, apes, dogs, birds, fish, plants, bacteria etc!




We will talk about Relate, but principles of tree-based inference applies more generally!

# Relate

Speidel, Forest, Shi, Myers. Nature Genetics 2019
Speidel, Cassidy, Davies, Hellenthal, Skoglund, Myers, MBE, 2021

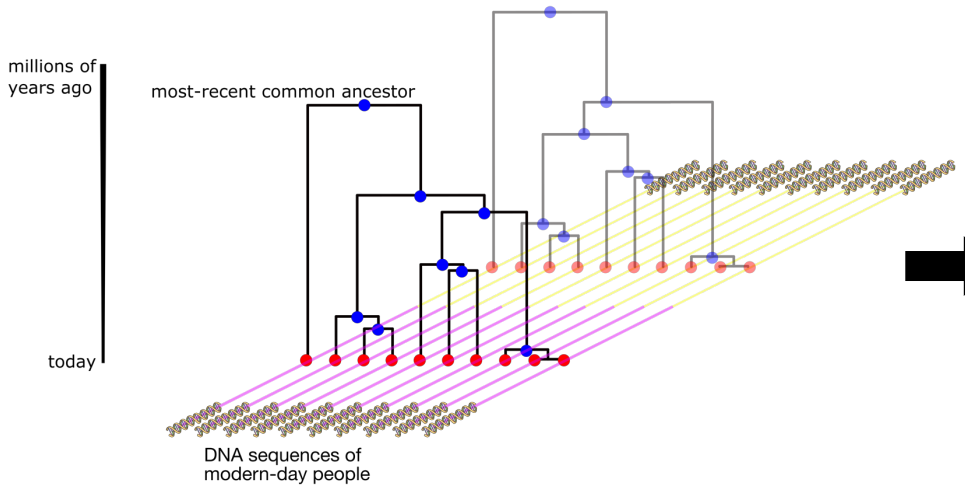



https://myersgroup.github.io/relate/

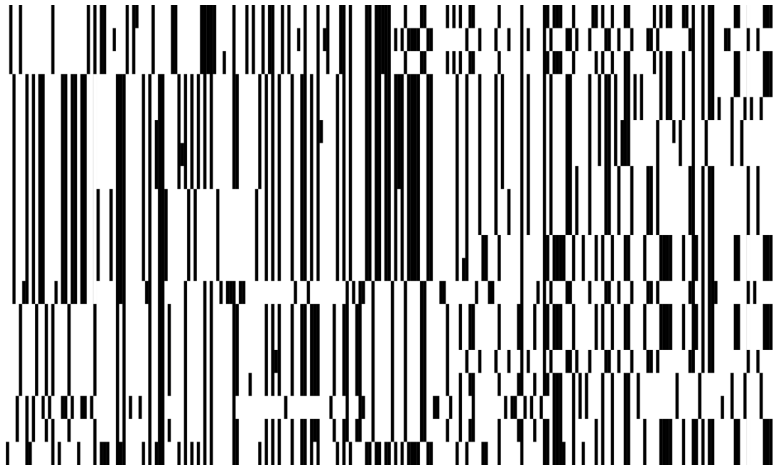
**Key features:**

- Fast & accurate
- Robust to errors!
- Jointly infers branch lengths and demographic history
- Moderns and ancients
- Lots of add-on tools for various types of analyses

# Fundamental forces impact data (only) through underlying genealogies

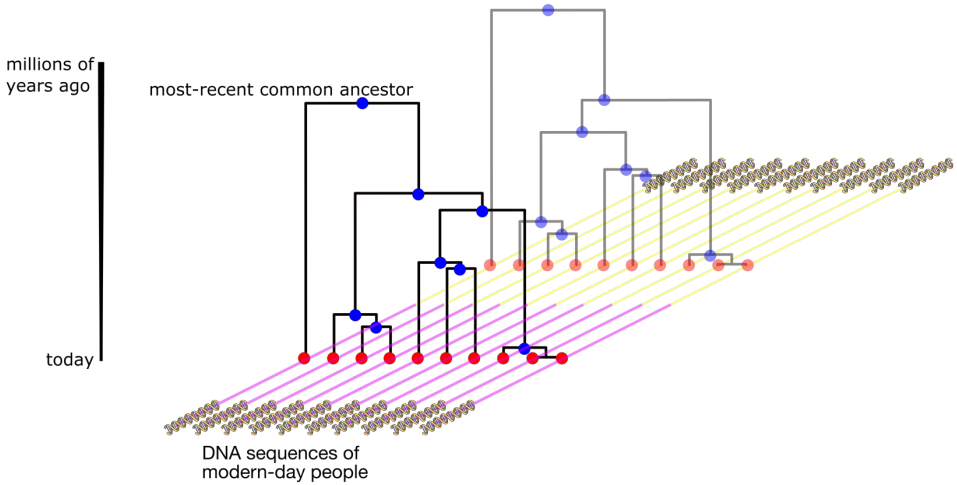



polymorphic sites

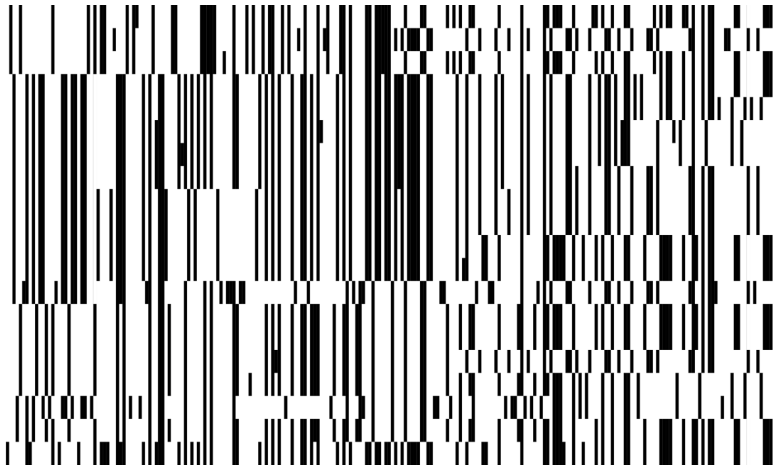



Demographic history
Genetic structure
Admixture
Selection, etc.

# Many canonical approaches




polymorphic sites

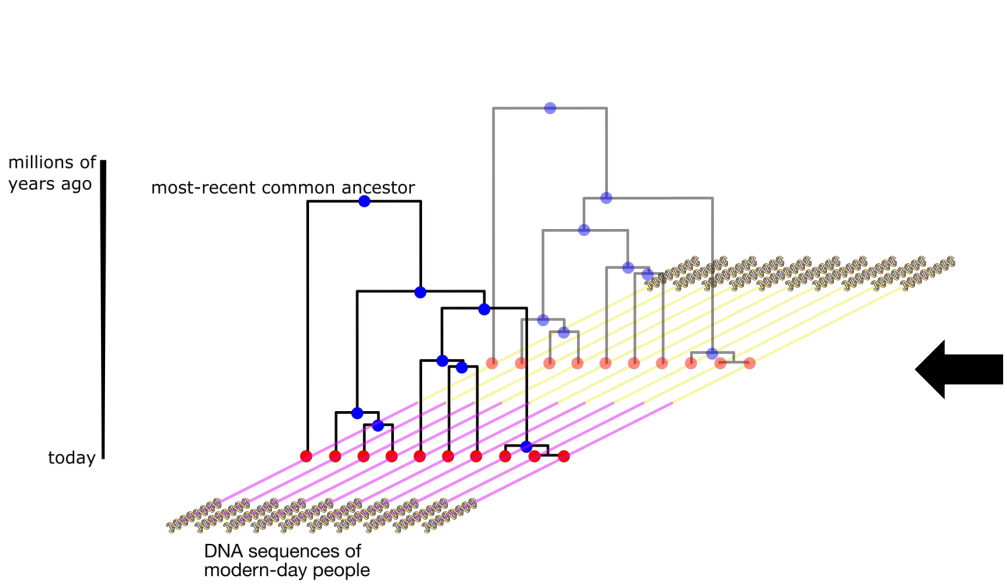


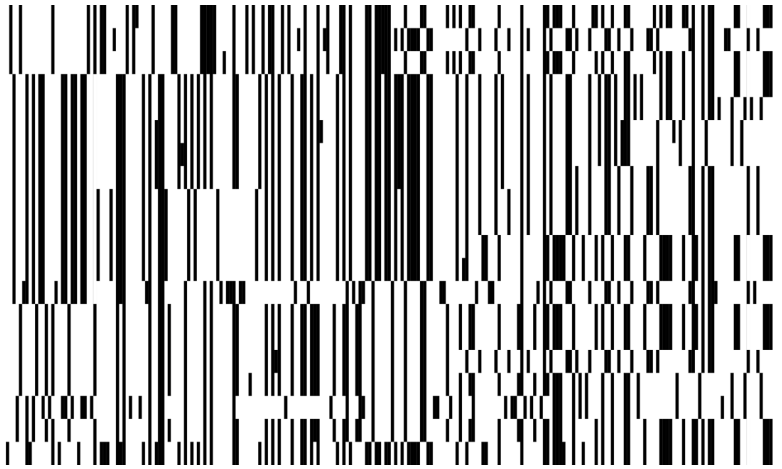

Demographic history
Genetic structure
Admixture
Selection, etc.

Invent informative statistics, simplify, "integrate out all possible histories"

- Allele frequency-based methods
- Local haplotype sharing
- Mutation sharing (e.g., f statistics)

# Genealogies are the “unobserved link” between evolutionary processes and genetic variation




Demographic history
Genetic structure
Admixture
Selection, etc.

Invent informative statistics, simplify, "integrate out all possible histories”

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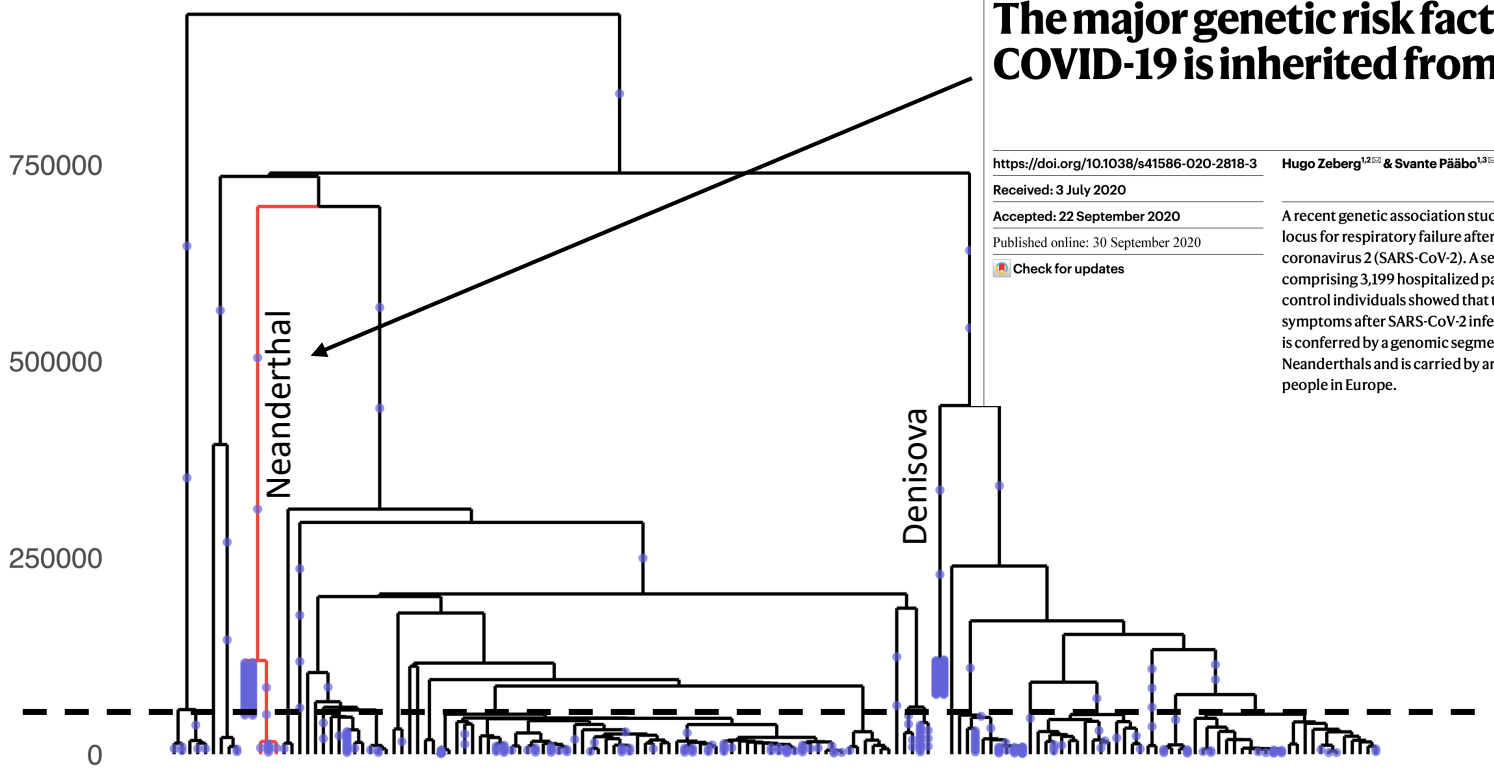
**Challenges**: computationally very challenging to sample trees from the data, and modern datasets can contain >50,000 individuals and >100,000,000 mutations

# One locus can already tell us a lot about our history




Article

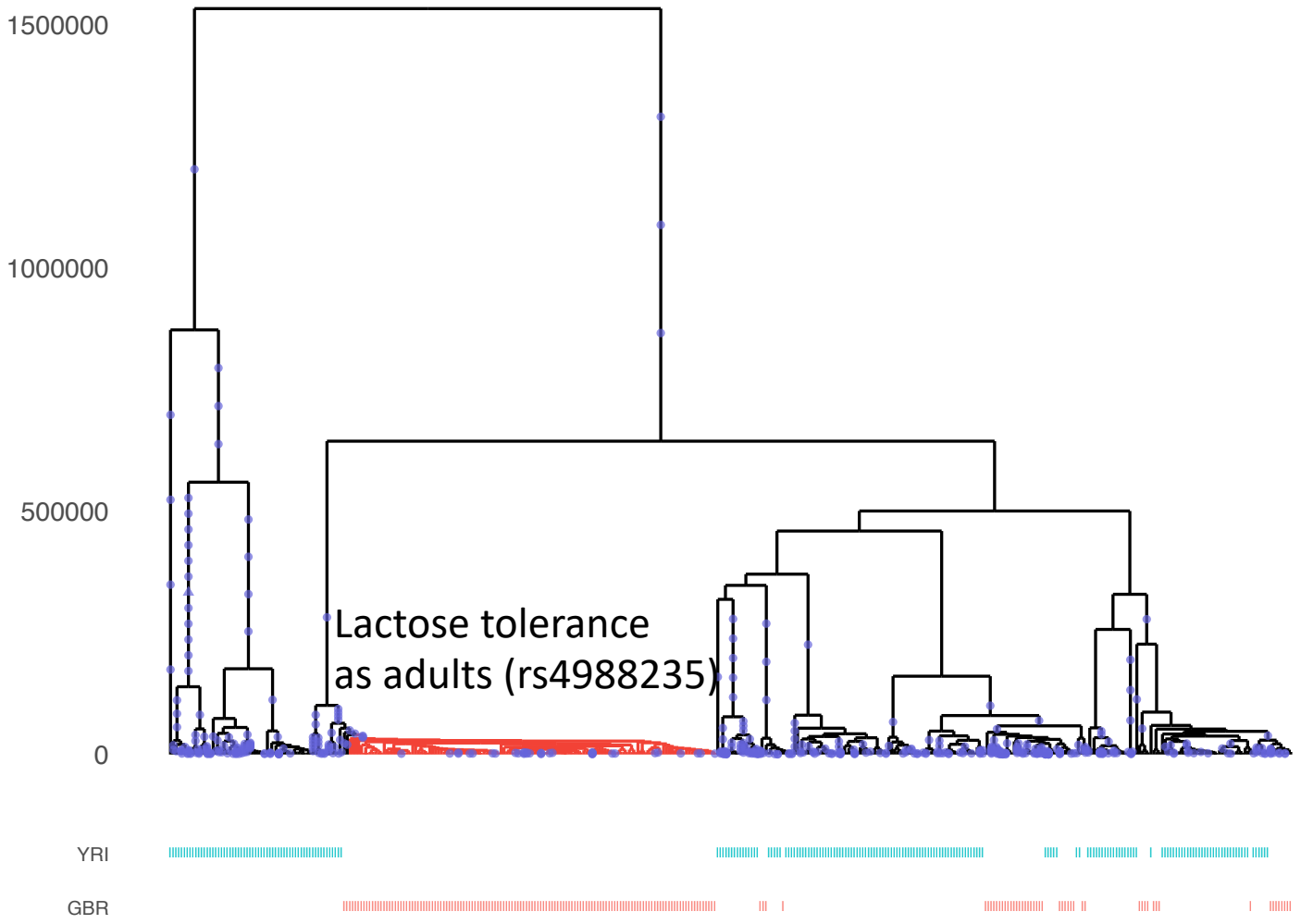
## The major genetic risk factor for severe COVID-19 is inherited from Neanderthals

https://doi.org/10.1038/s41586-020-2818-3
Received: 3 July 2020
Accepted: 22 September 2020
Published online: 30 September 2020
Check for updates

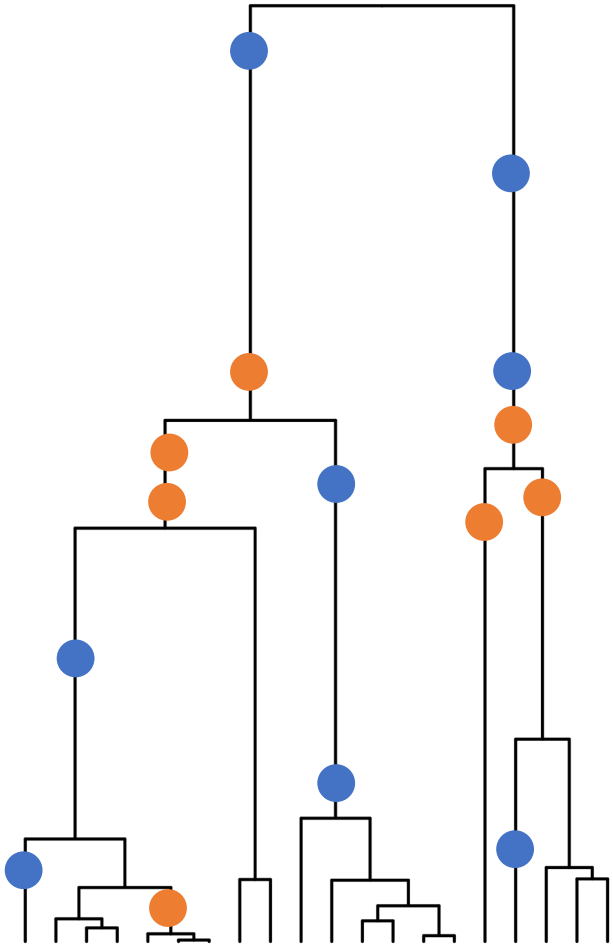
Hugo Zeberg[1,2] & Svante Pääbo[1,3]

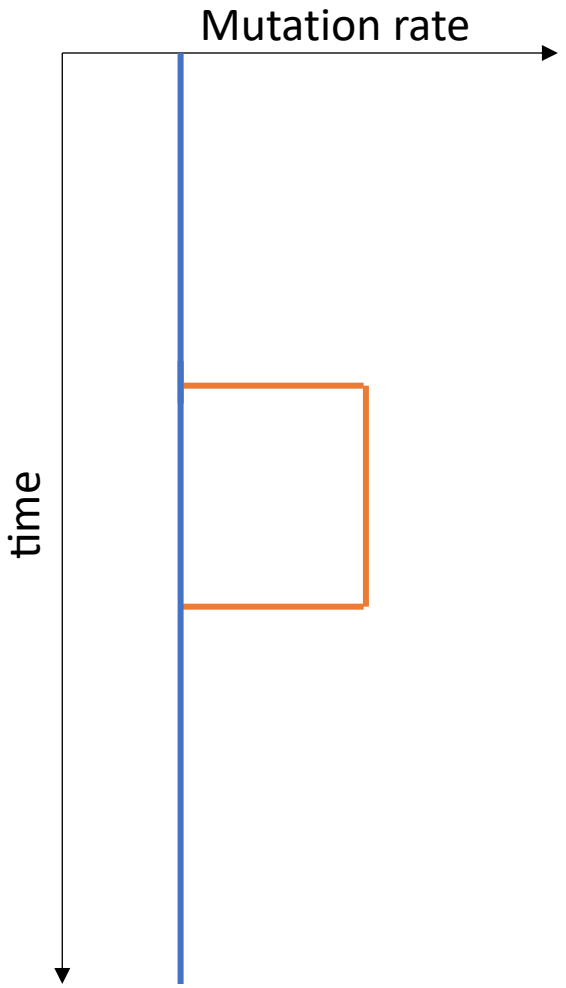
A recent genetic association study[1] identified a gene cluster on chromosome 3 as a risk locus for respiratory failure after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A separate study (COVID-19 Host Genetics Initiative)[2] comprising 3,199 hospitalized patients with coronavirus disease 2019 (COVID-19) and control individuals showed that this cluster is the major genetic risk factor for severe symptoms after SARS-CoV-2 infection and hospitalization. Here we show that the risk is conferred by a genomic segment of around 50 kilobases in size that is inherited from Neanderthals and is carried by around 50% of people in south Asia and around 16% of people in Europe.

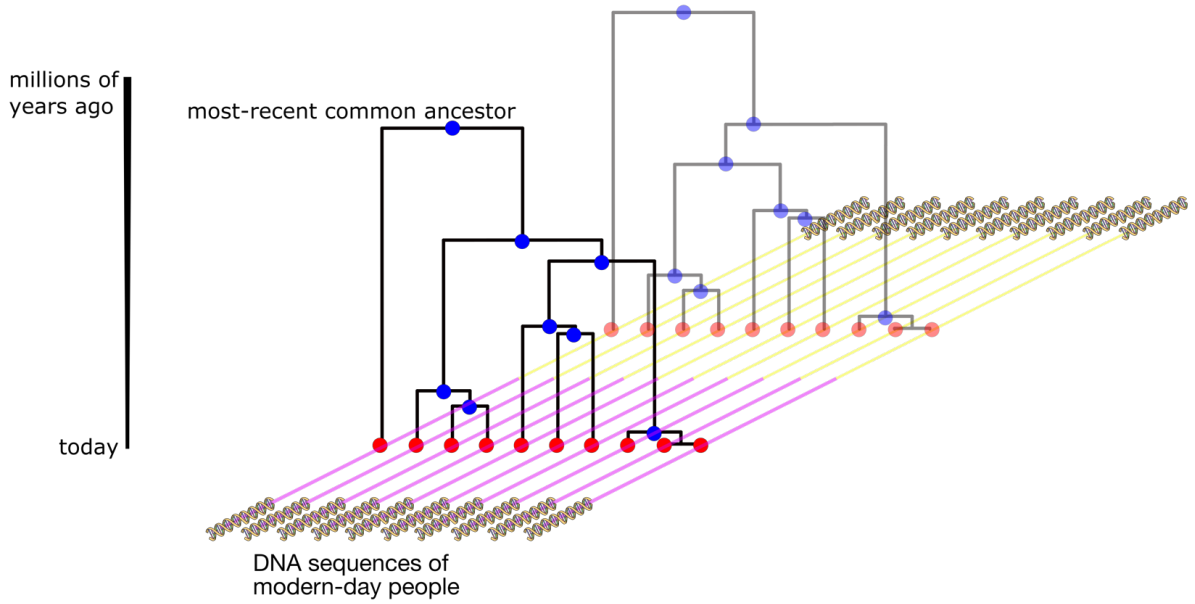
# Positive selection: rapidly spreading lineage



# Clusters of mutations in time can capture changes in mutation rate

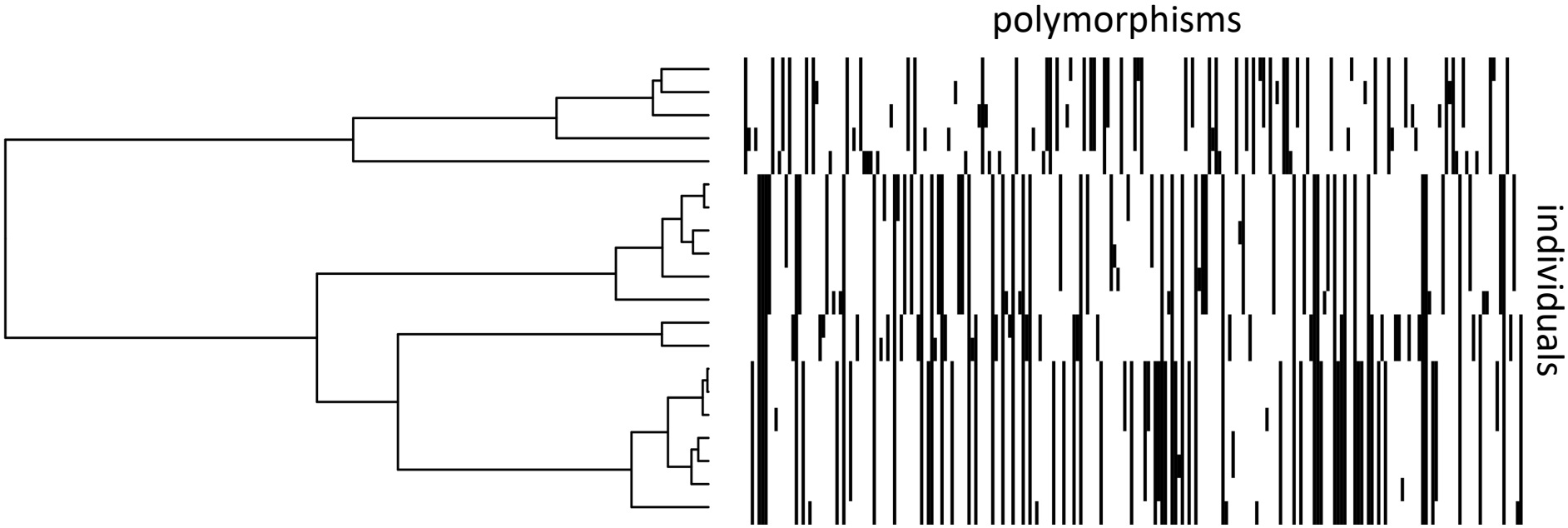







# Inferring genealogies from genetic variation

# Data and the underlying tree structure

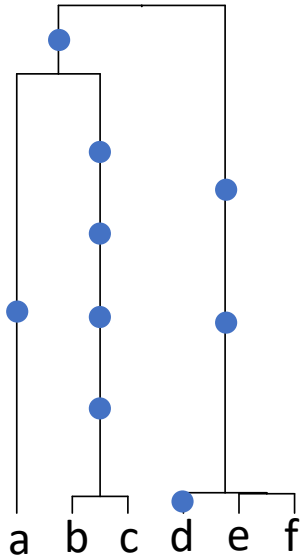



- **Every mutation shows the existence of a branch**
- Mutations are “ordered by inclusion”
- No two branches (mutations) ever show only partial overlap

# Count derived mutations to reconstruct tree topology

**For tree topology, we want to quantify the order in which we are related to others**

1. Count number of "derived mutations" to get order of coalescences
   - E.g., sequence a has 1 derived mutation to (b,c)
     2 derived mutation to (d,e,f)
2. Coalesce mutually closest lineages

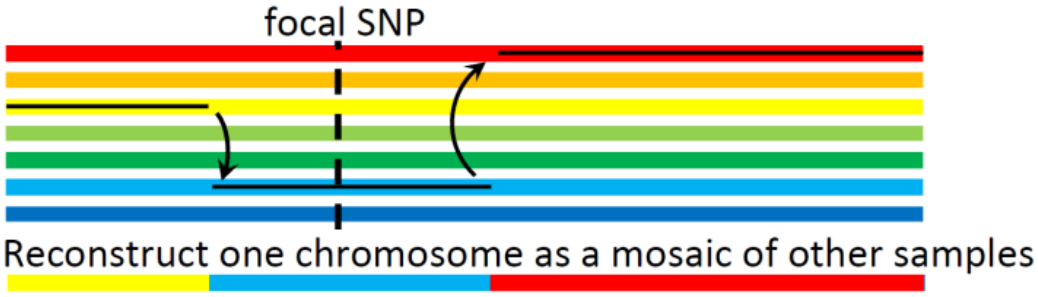



- No recombination: Guaranteed to build tree consistent with data
- This is not the case if we use "pairwise differences" (UPGMA)
  - a and (d,e,f) are closer than a and (b,c)

- Use **chromosome painting** to count derived mutations accounting for recombination

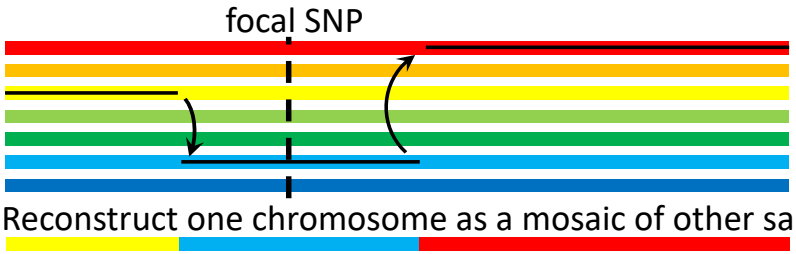
**Hidden Markov model (HMM)**

Li and Stephens, Genetics, 2003; Lawson et al., PLOS Genetics, 2012

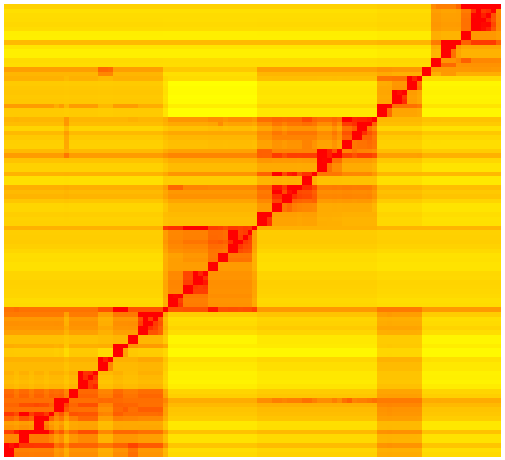


# Summary of Relate

Hidden Markov model (HMM)

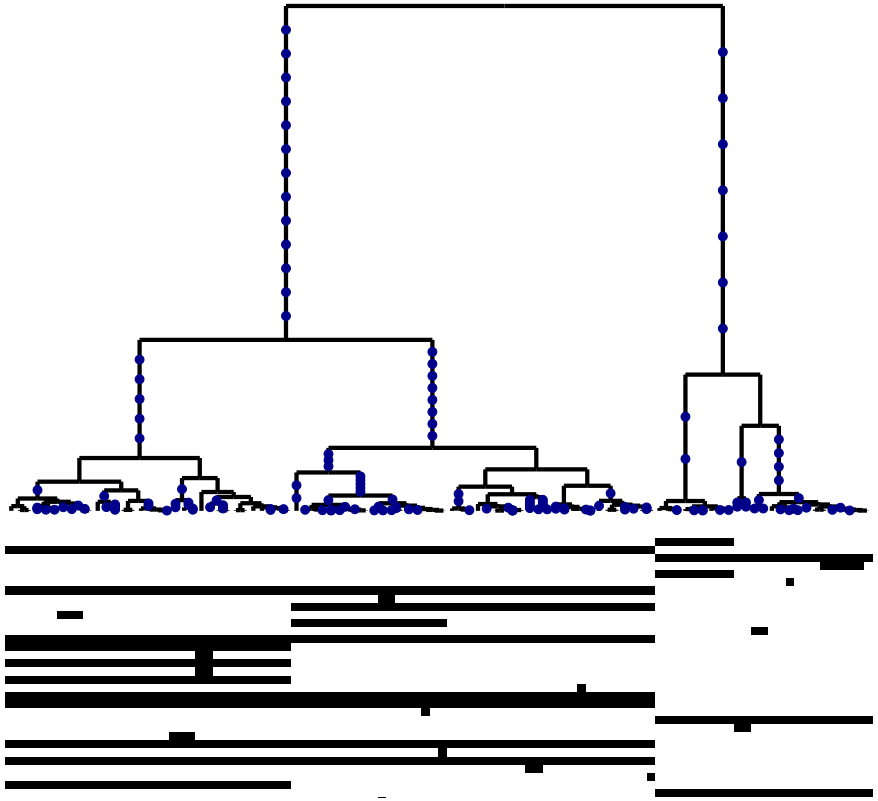



Distance matrix for focal SNP



"number of derived mutations"

Hierarchical clustering
&
MCMC for branch lengths

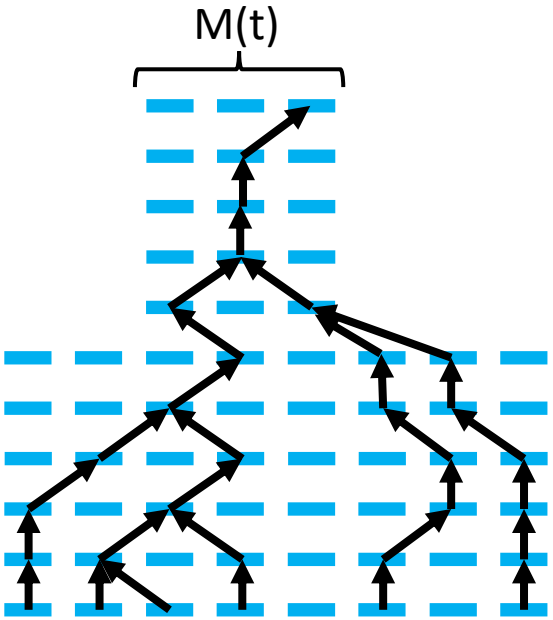


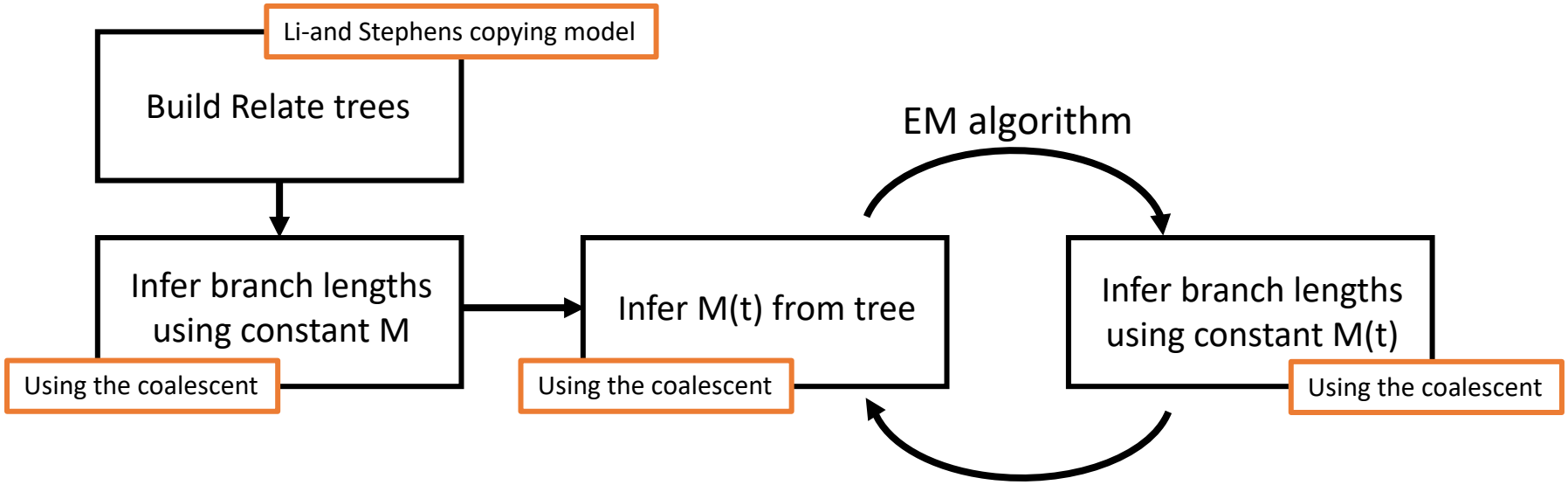
haplotype data sorted using constructed tree

# Branch lengths and population size is estimated jointly in an EM algorithm

- Expected branch lengths depend on population size M(t)

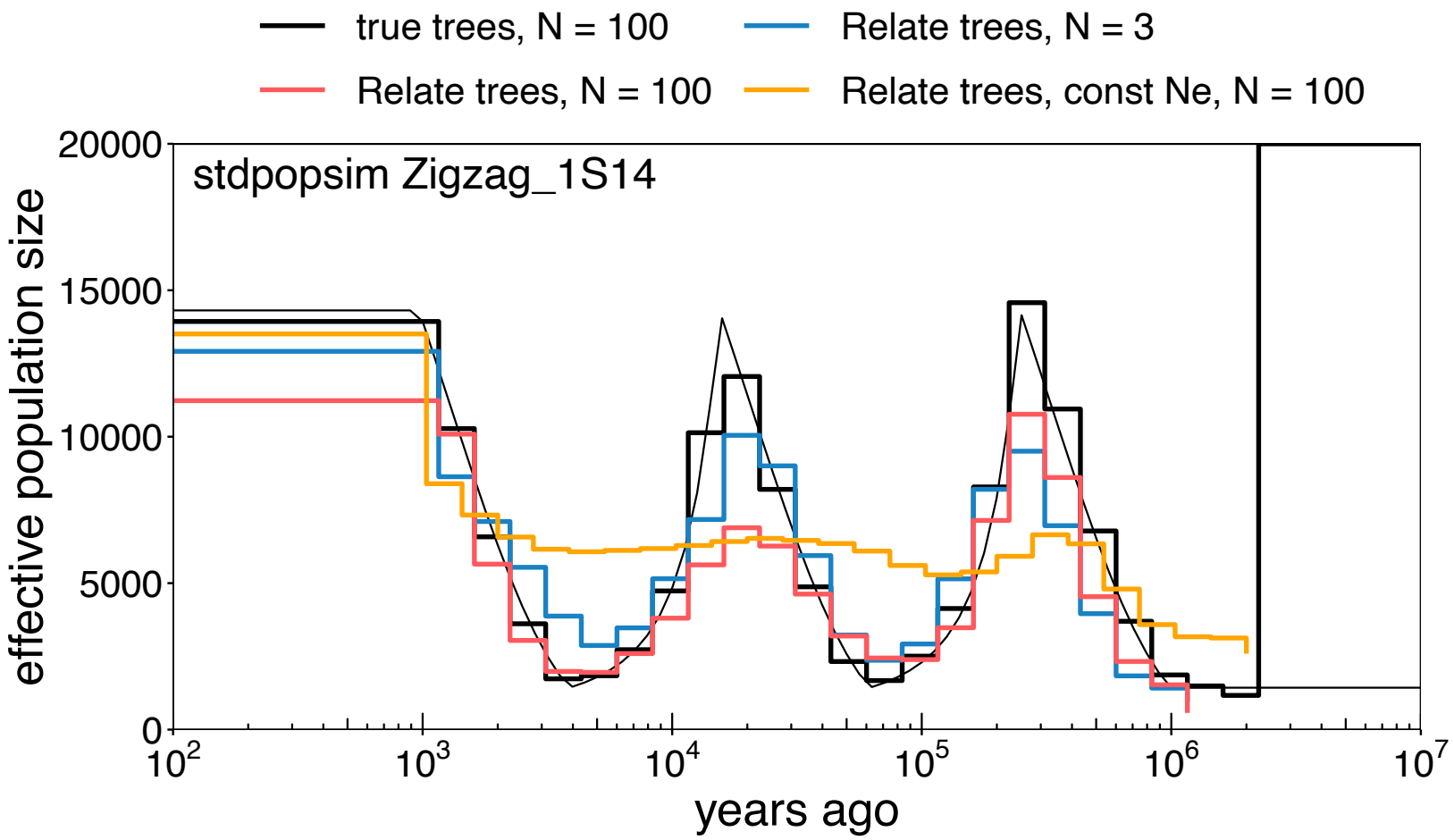
  (or coalescence rates 1/M(t))
- While there are *j* lineages, the rate at which a coalescence happens is $\binom{j}{2}/M(t)$ a time *t* ago
- Demography is shared genome-wide, so we average across trees
- So within a time interval, scaled fraction of trees where coalescence occurs is inversely proportional to M(t)

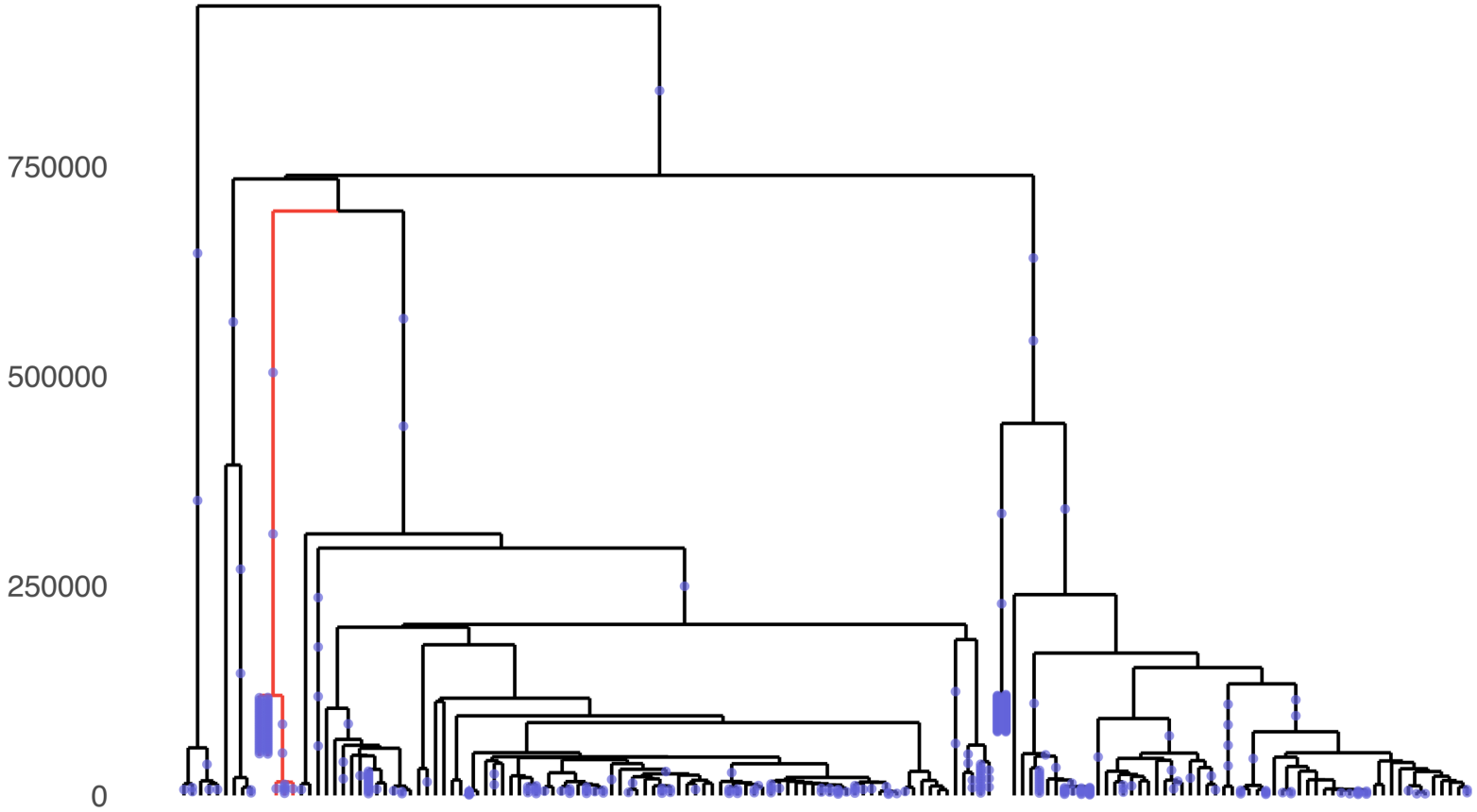


# Population size changes through time are jointly inferred in Relate

- Effective population size = inverse coalescence rate
- N: number of diploid samples

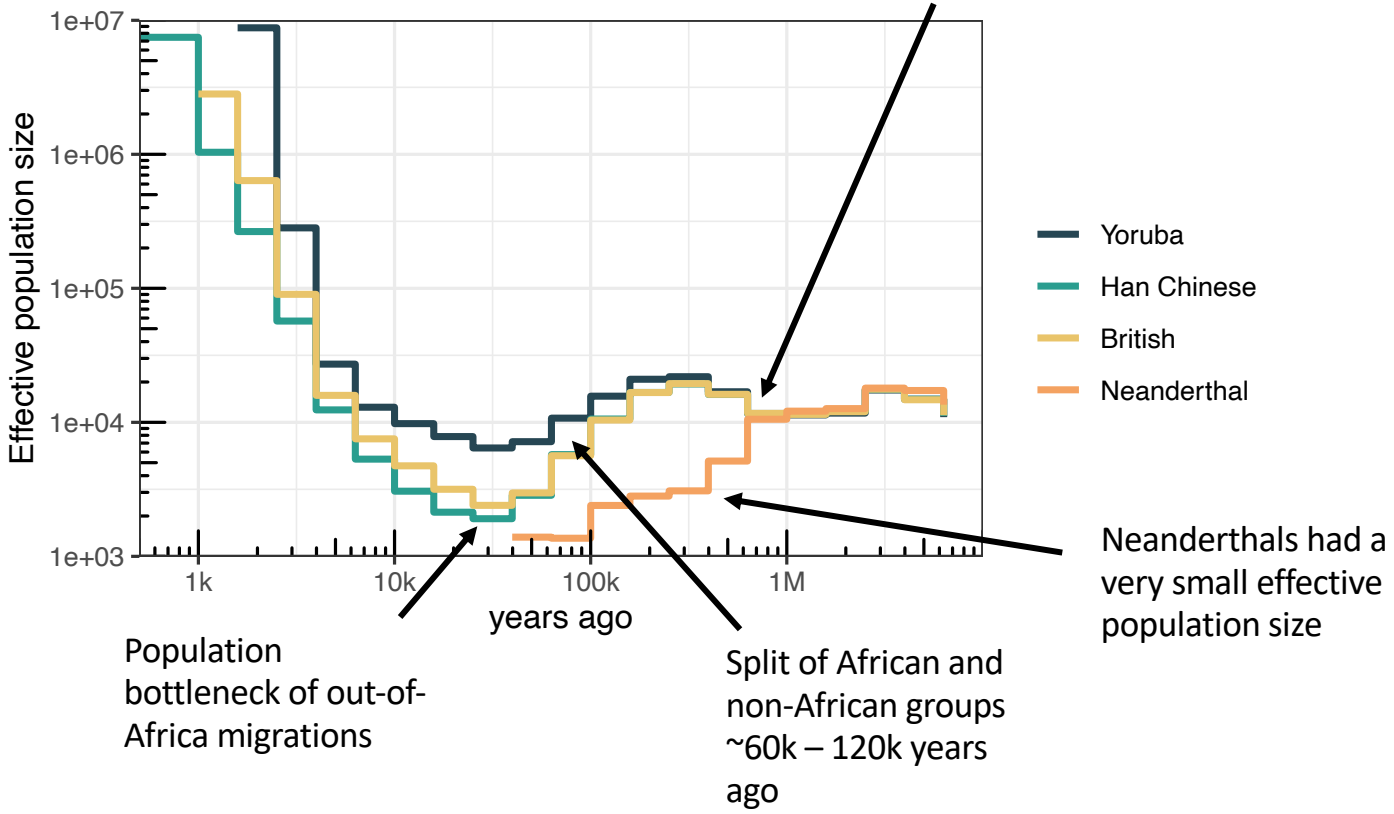





# Genealogy-based inference of human evolutionary history

One reconstruction of history, many applications that are self consistent

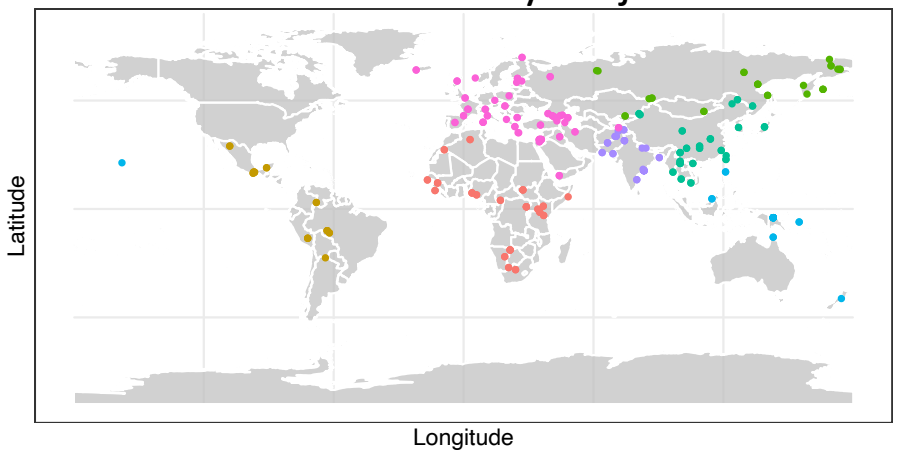
# Human diversity through time



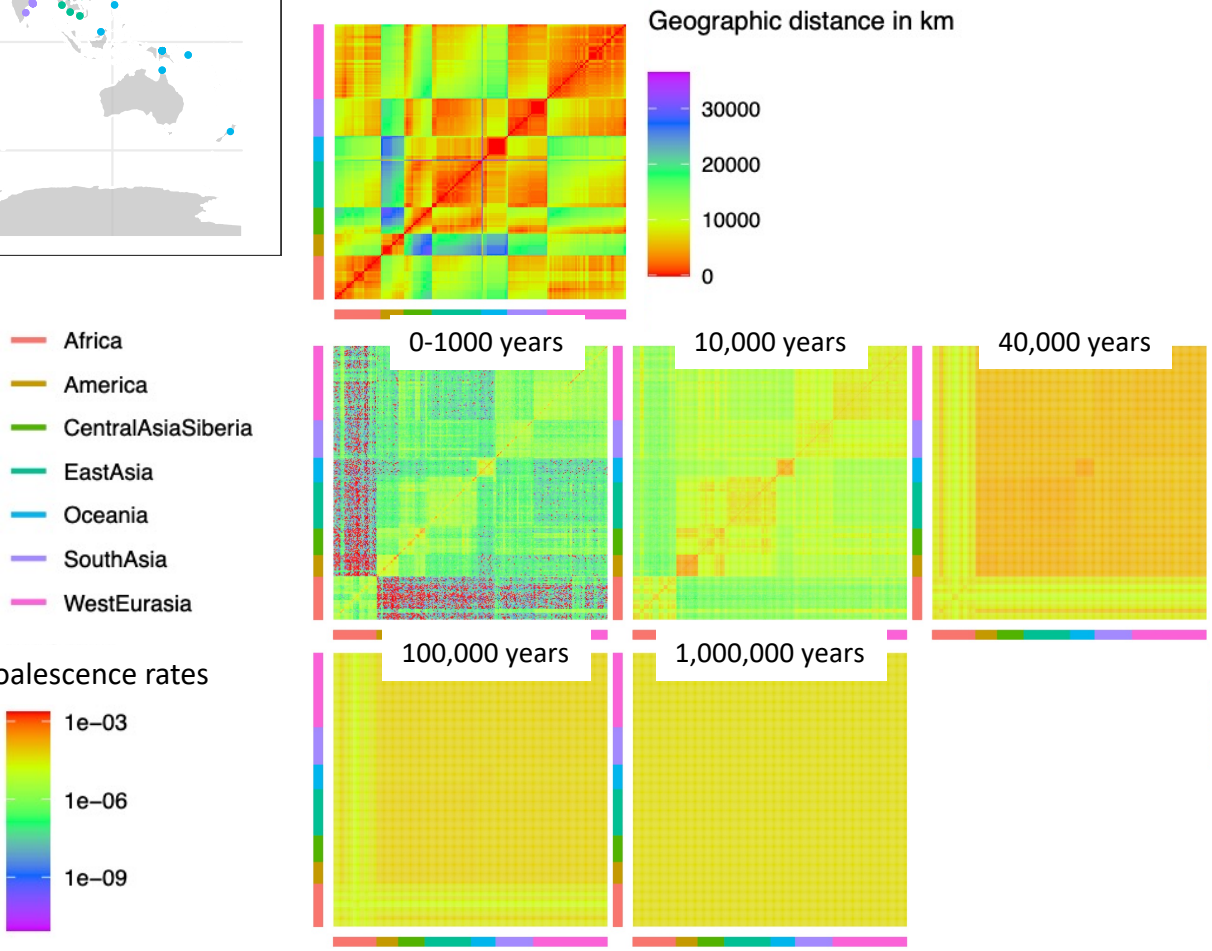

Li and Durbin Nature 2011
Speidel Nature Genetics 2019

# Population structure at different time depths

Simons Genome Diversity Project



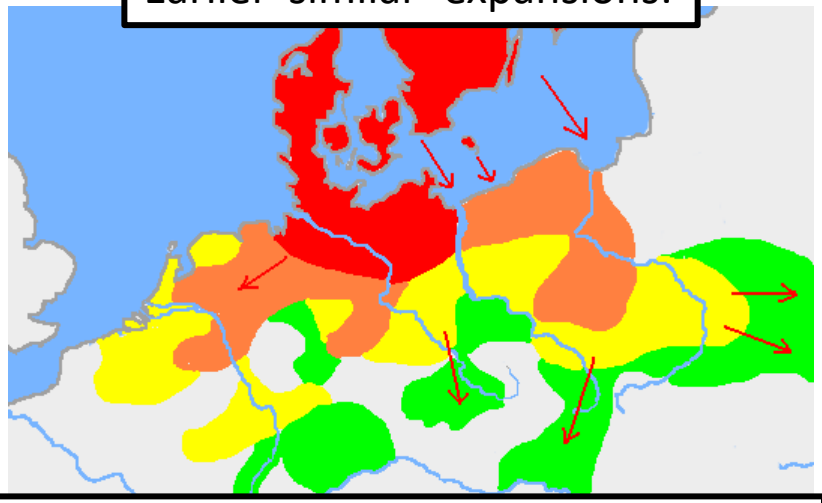

Speidel et al, MBE, 2021



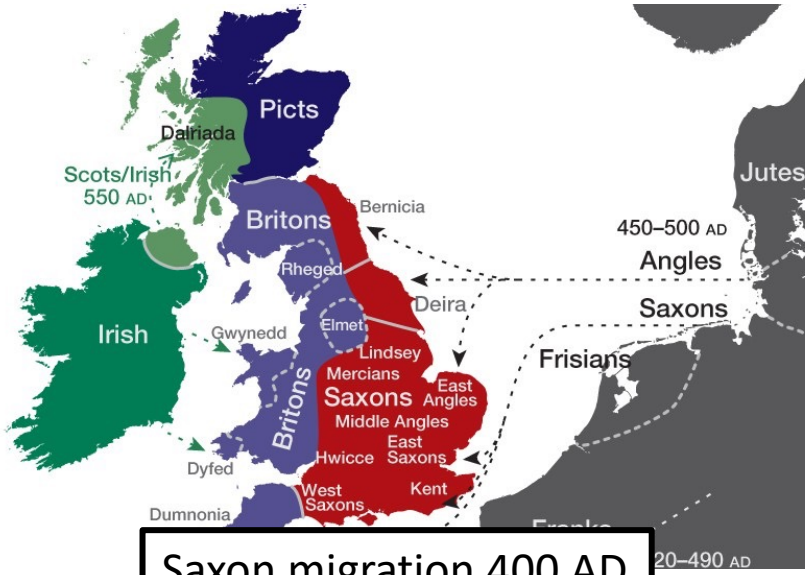
# Robust fine-scale admixture inference

Viking voyages 750AD – 1100AD


Earlier 'similar' expansions:



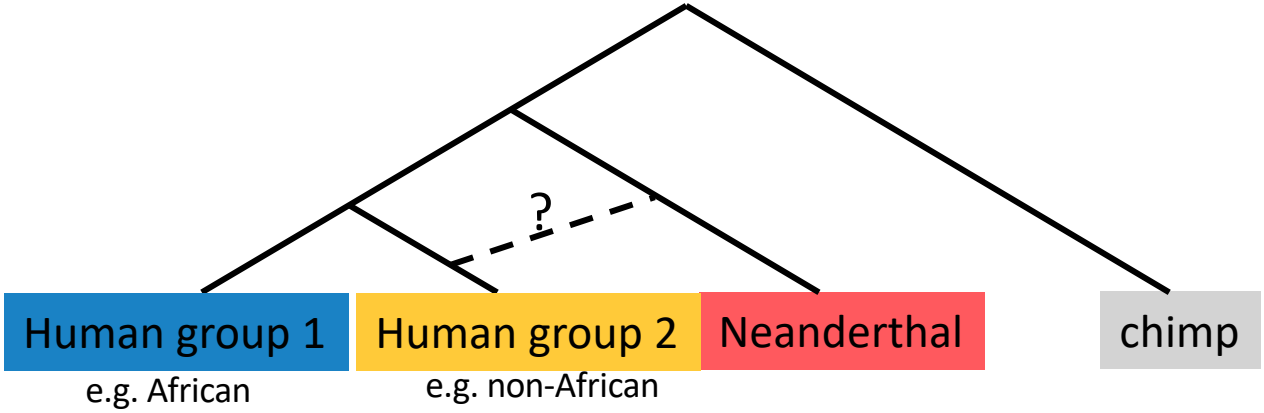
Expansion of Germanic tribes from 500BC

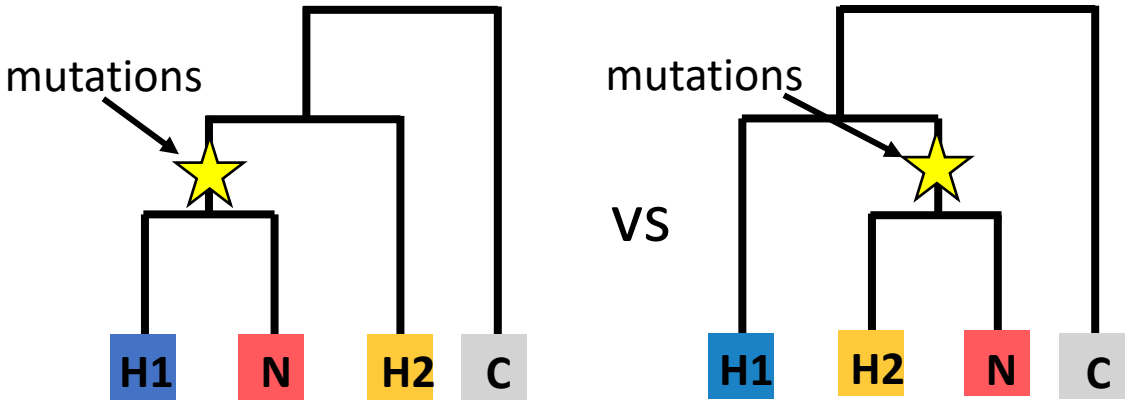



Saxon migration 400 AD

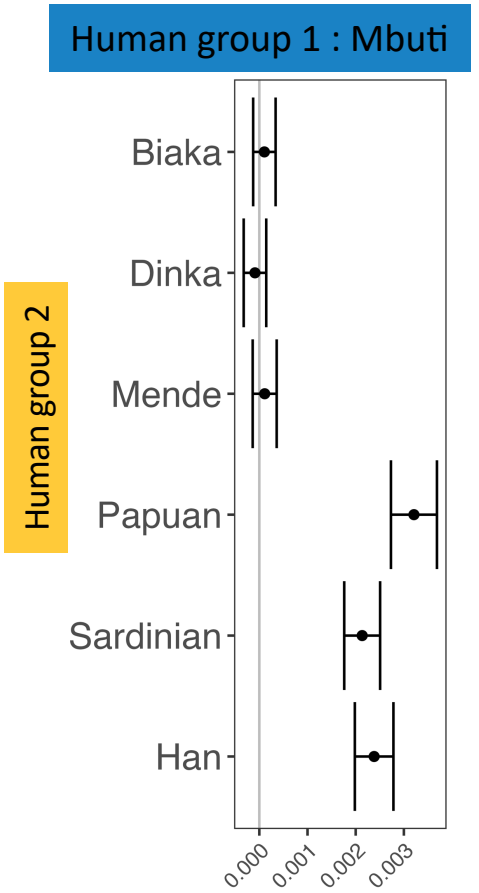
# The textbook f4-statistic example…

Test for excess clustering of human group 2 with Neanderthals?



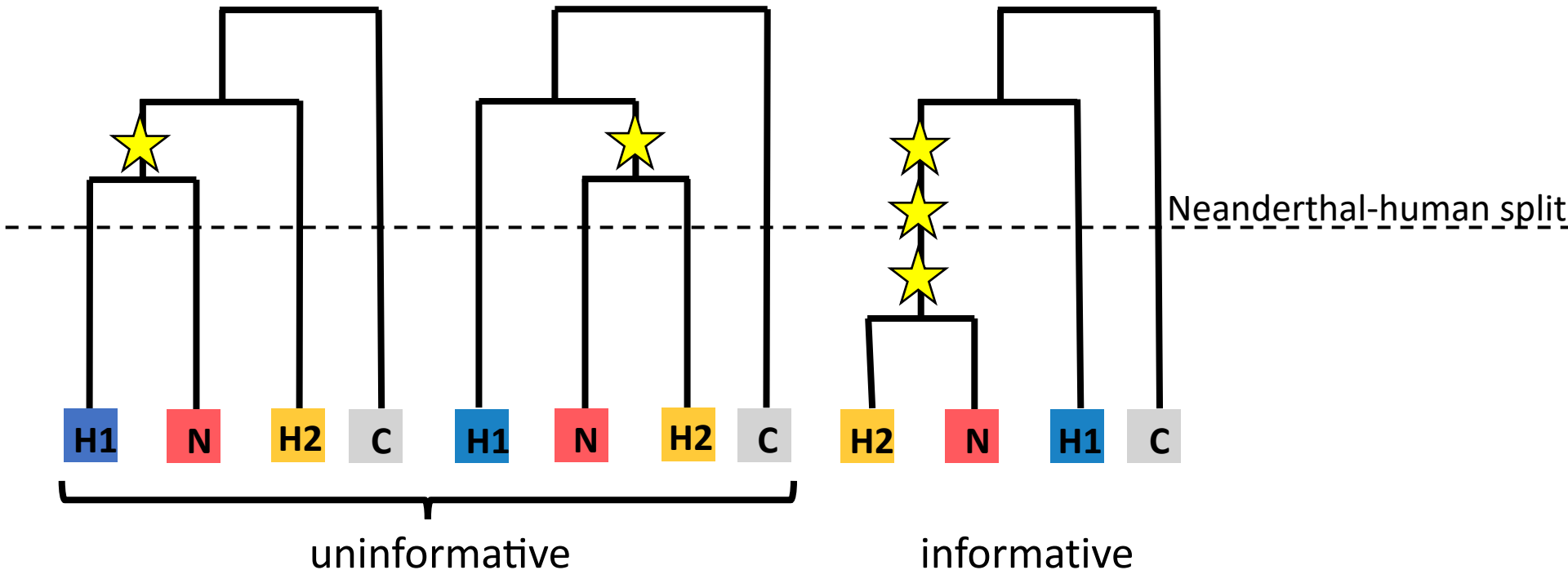




Gene trees (local genealogies)




Patterson Genetics 2012

# Discard uninformative coalescence events

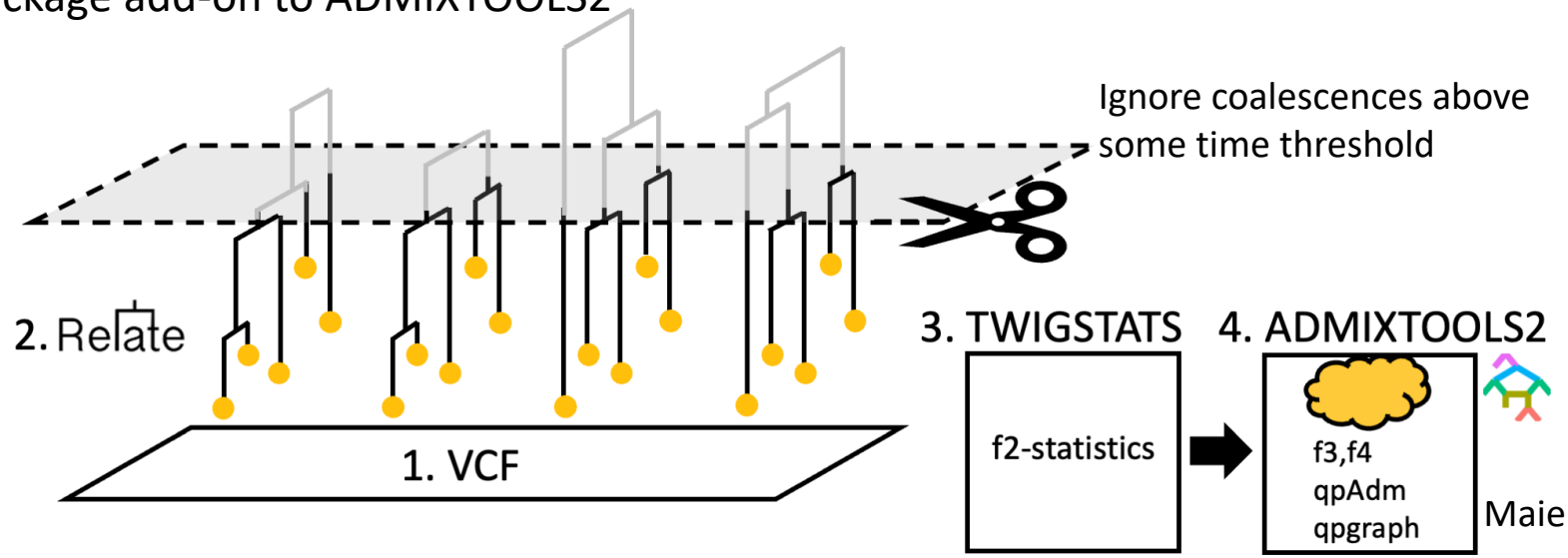



**Discard coalescences exceeding the source split times!**

# Twigstats: F-statistics on recent coalescences

**https://leospeidel.github.io/twigstats**

R package add-on to ADMIXTOOLS2

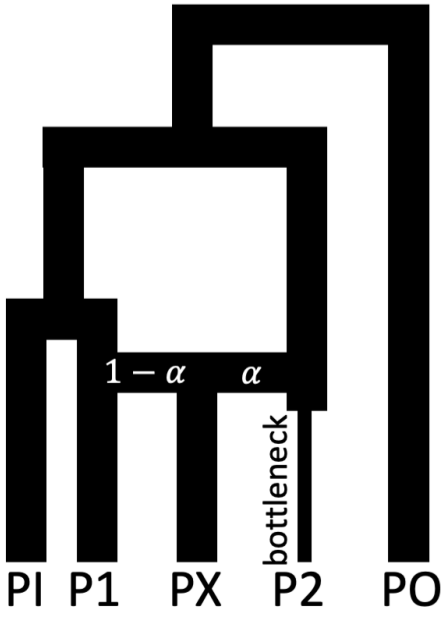



Maier, Elife, 2023

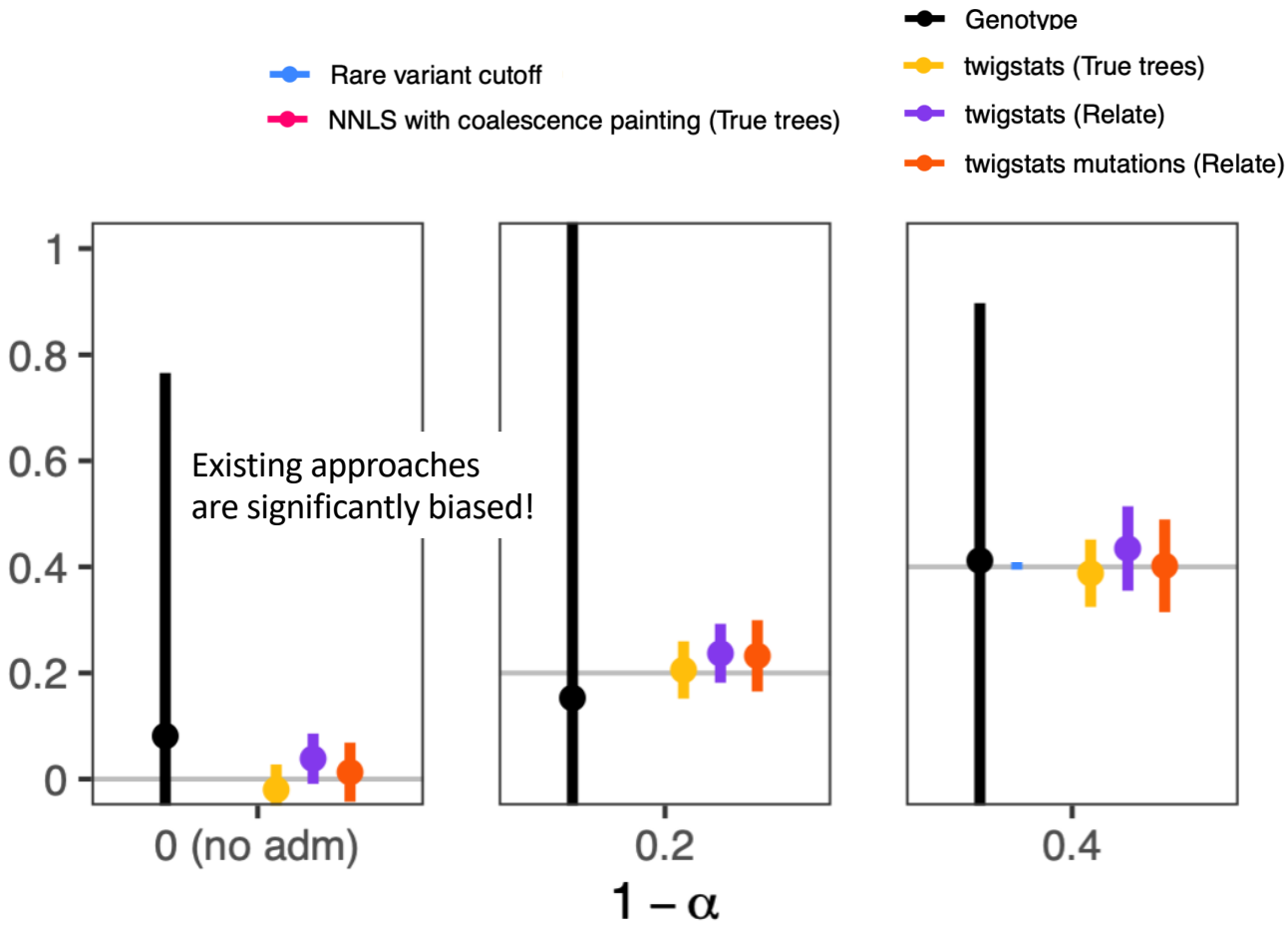
In theory, twigstats ascertainment

- Removes all uninformative coalescences
- Is unbiased
- Flexible:
  Use genealogy directly (aDNA built into genealogy) or ascertain mutations (aDNA external to genealogy)

# Unbiased ancestry inference in simulations

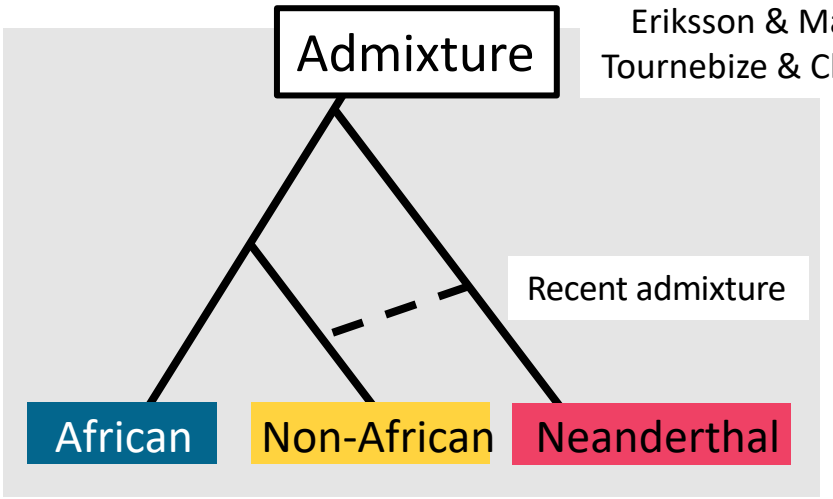


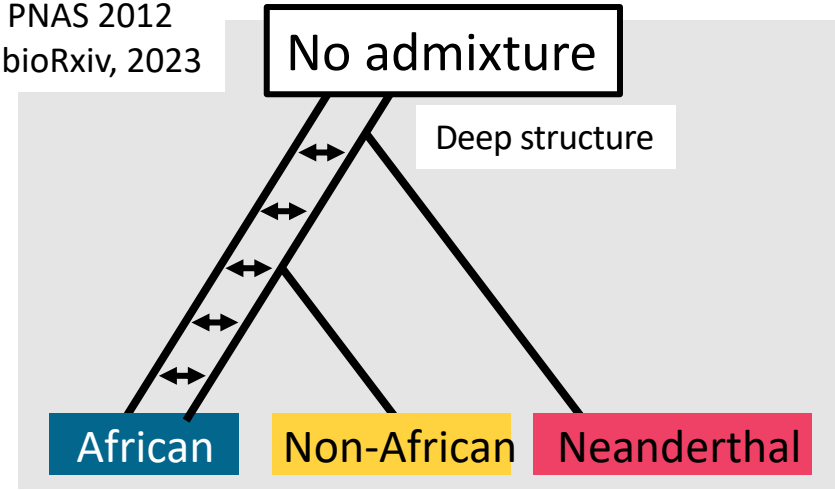

$$\alpha = \frac{F_4(PO, PI, PX, P1)}{F_4(PO, PI, P2, P1)}$$

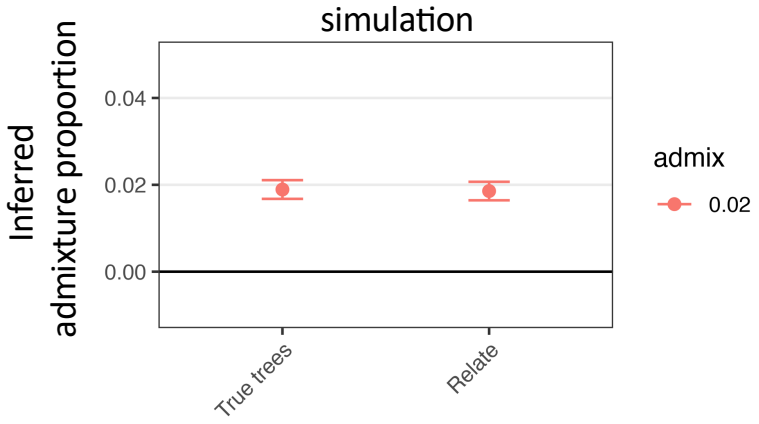


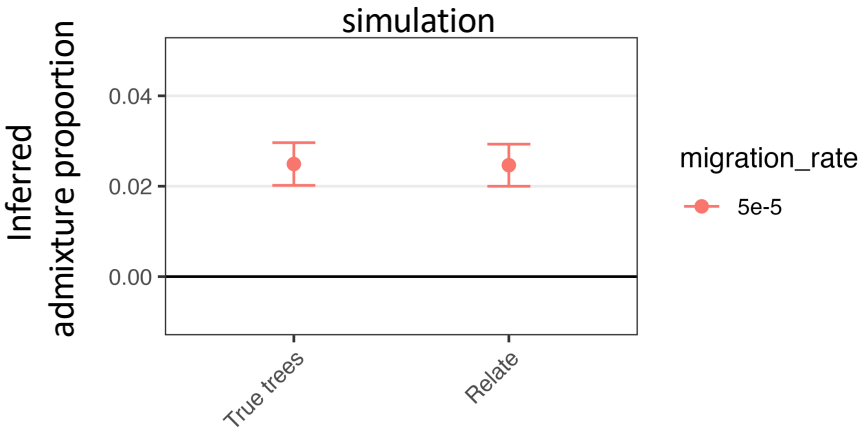
# Can deep structure explain Neanderthal admixture signals?

Green et al, Science 2010
Eriksson & Manica, PNAS 2012
Tournebize & Chikhi, bioRxiv, 2023

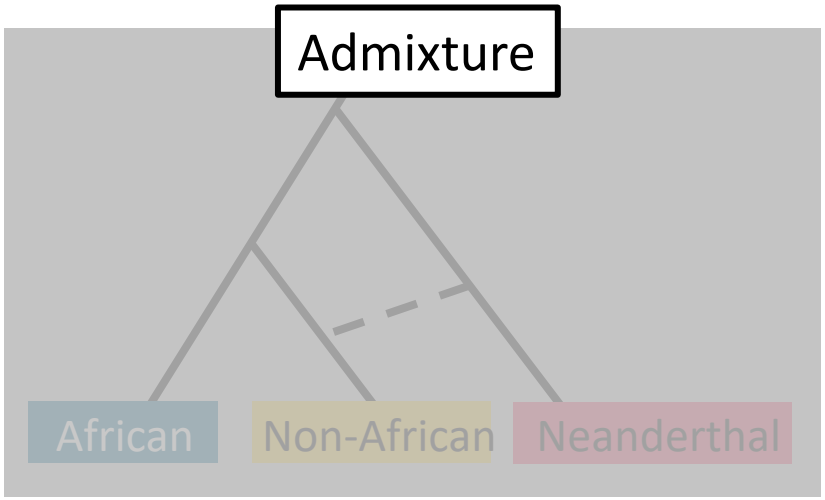


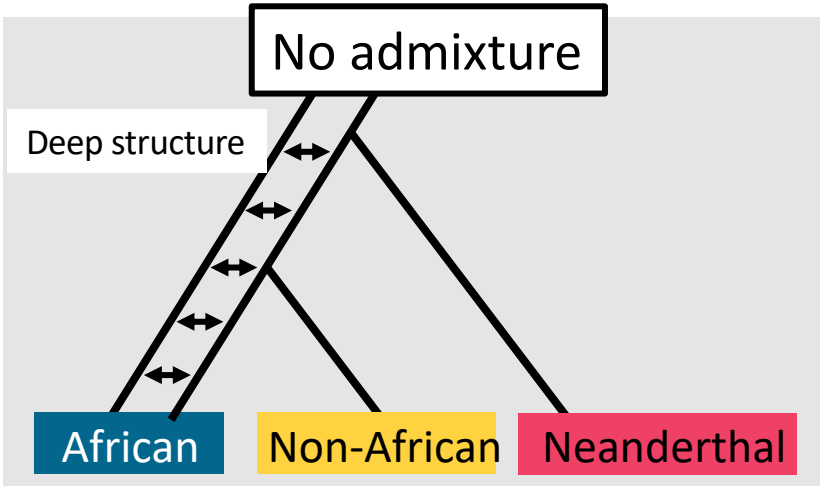



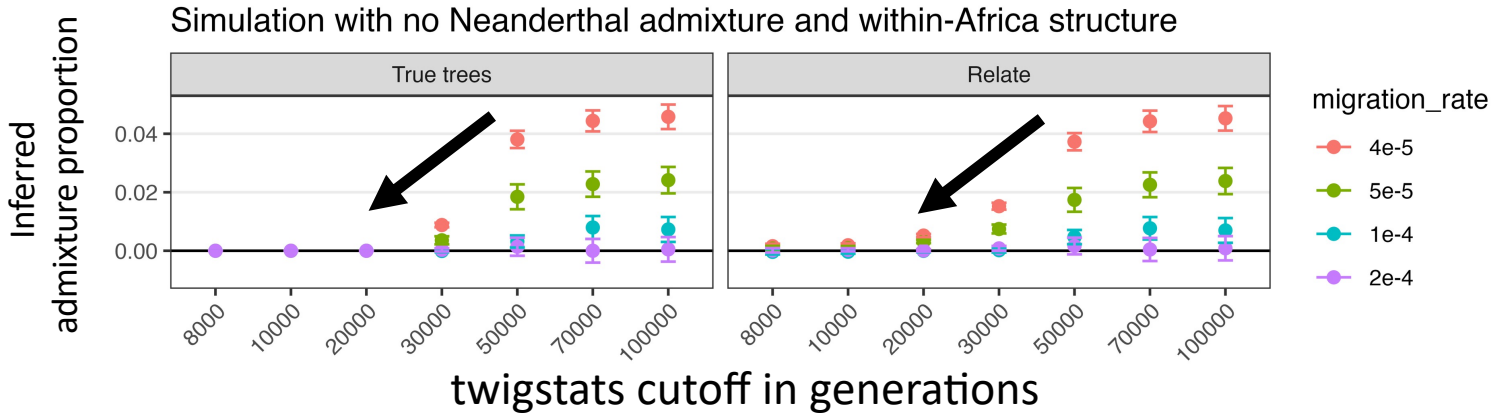



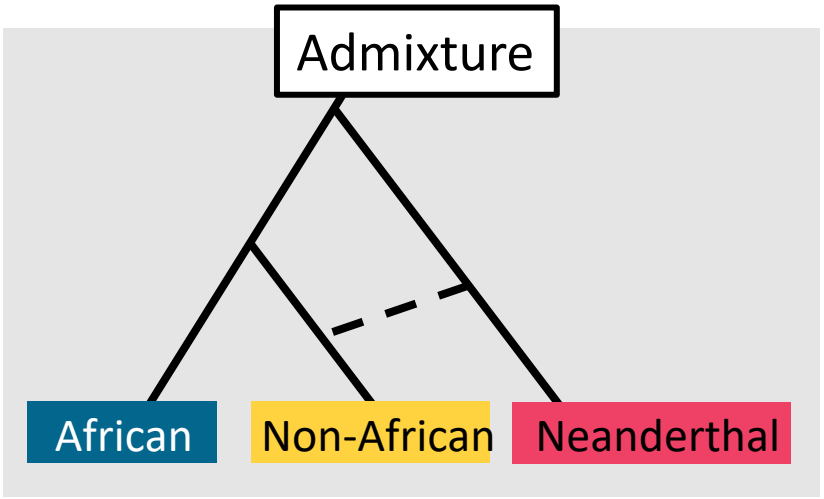
# Ascertaining recent coalescences removes deep structure signal

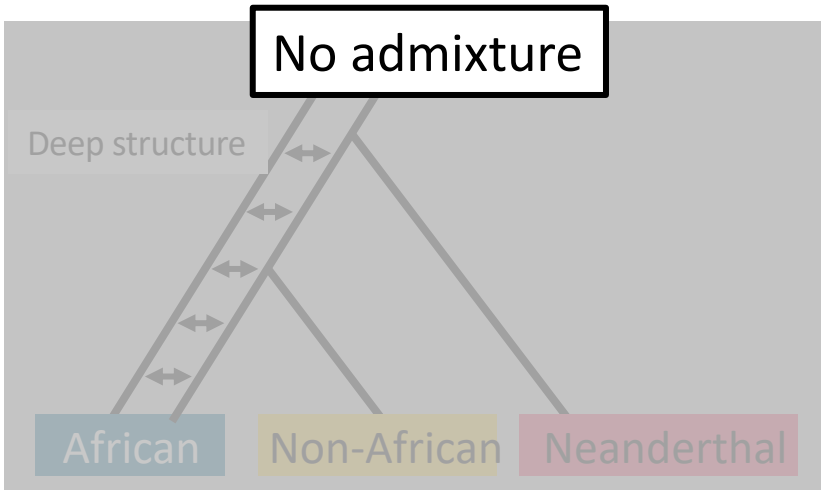


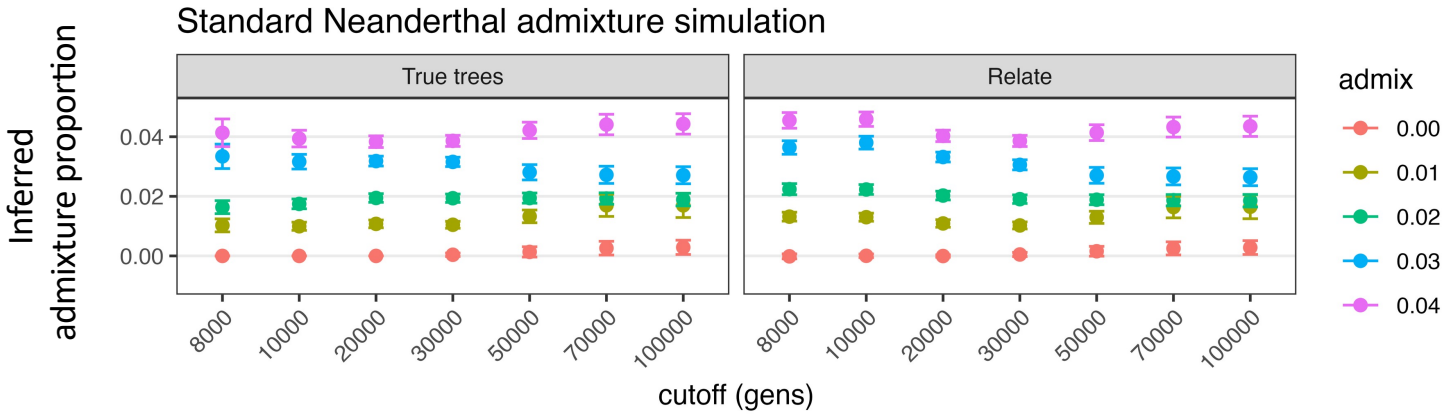



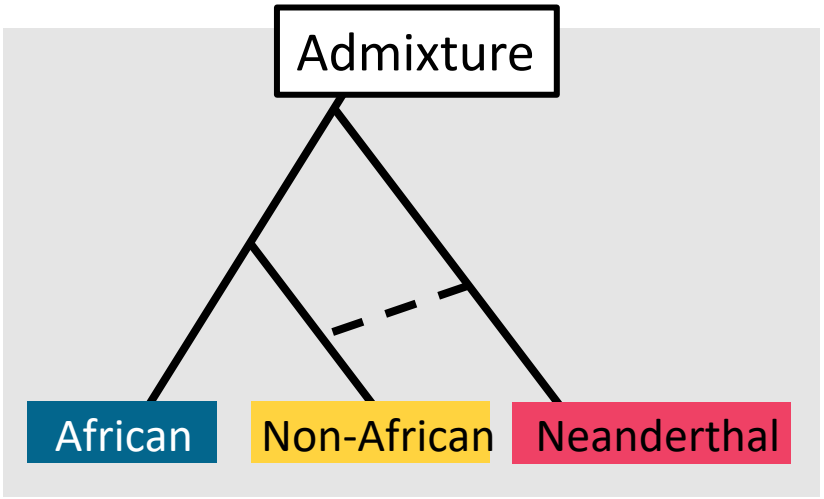
# But doesn’t remove recent Neanderthal admixture

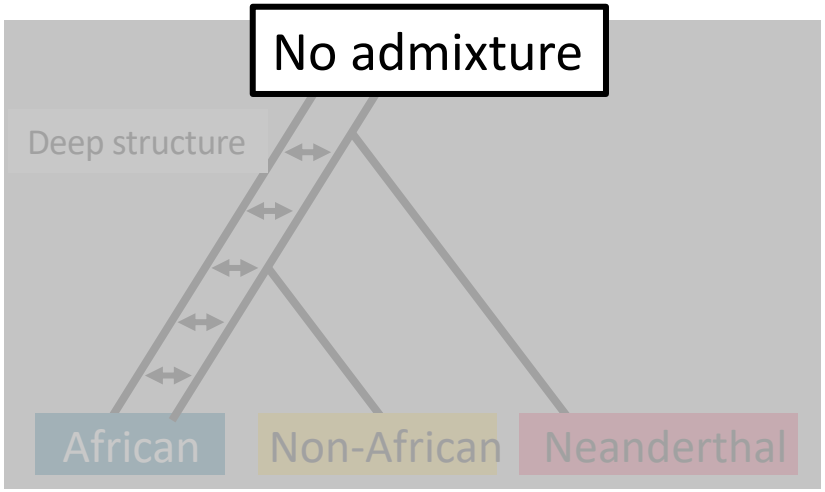


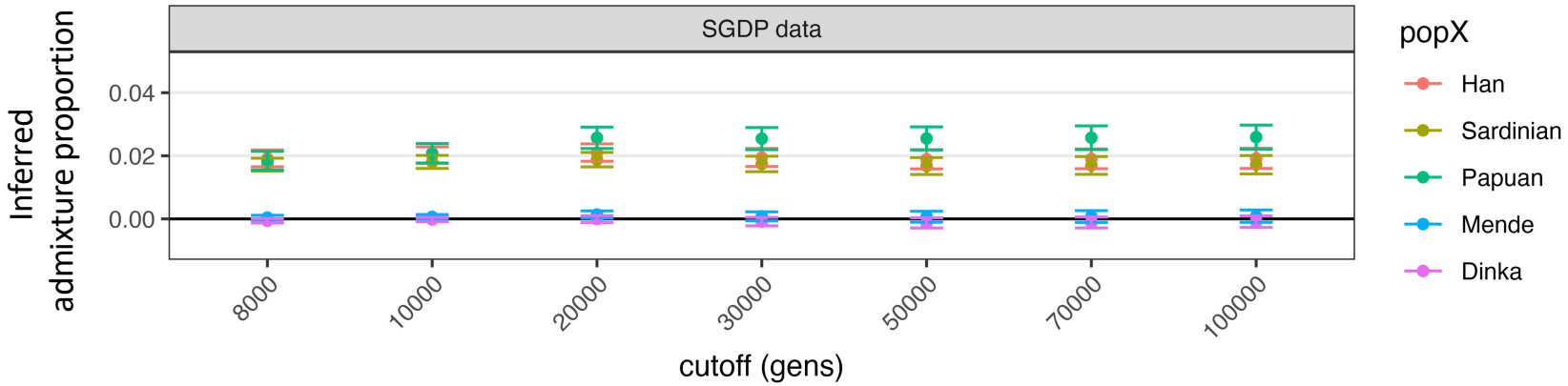



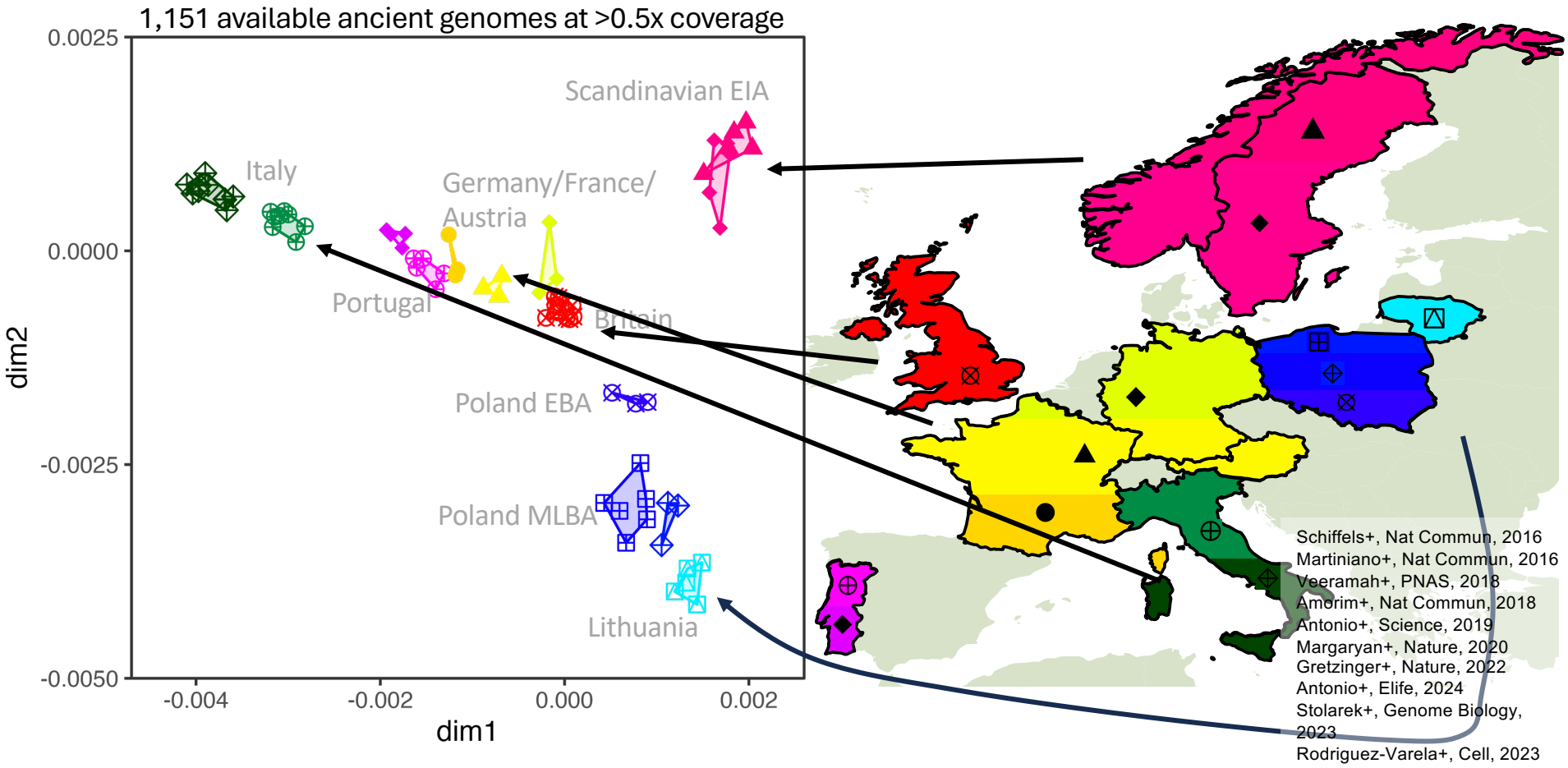
# Real data is consistent with recent Neanderthal admixture



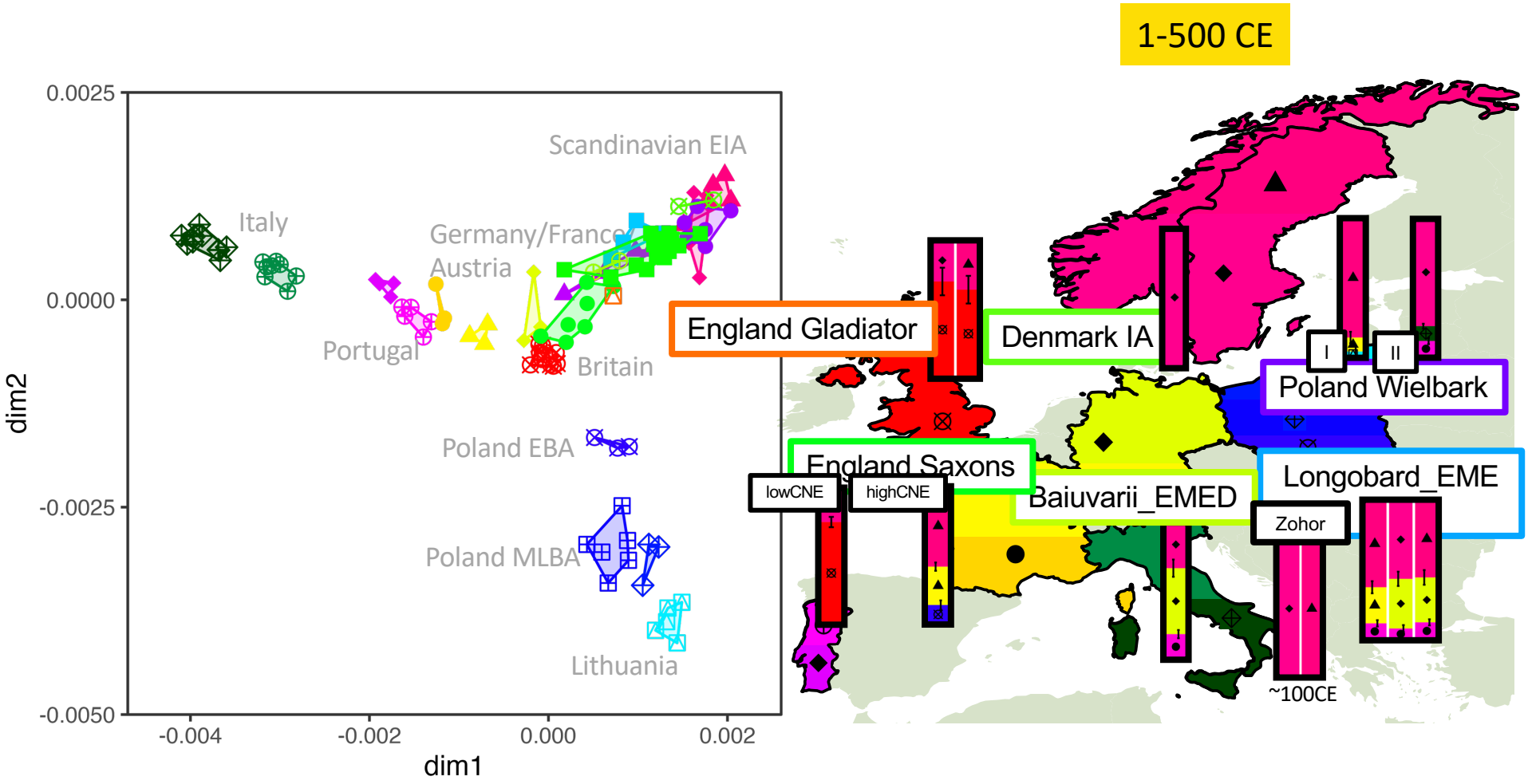



# Fine-scale population structure in Iron and Roman Age Europe

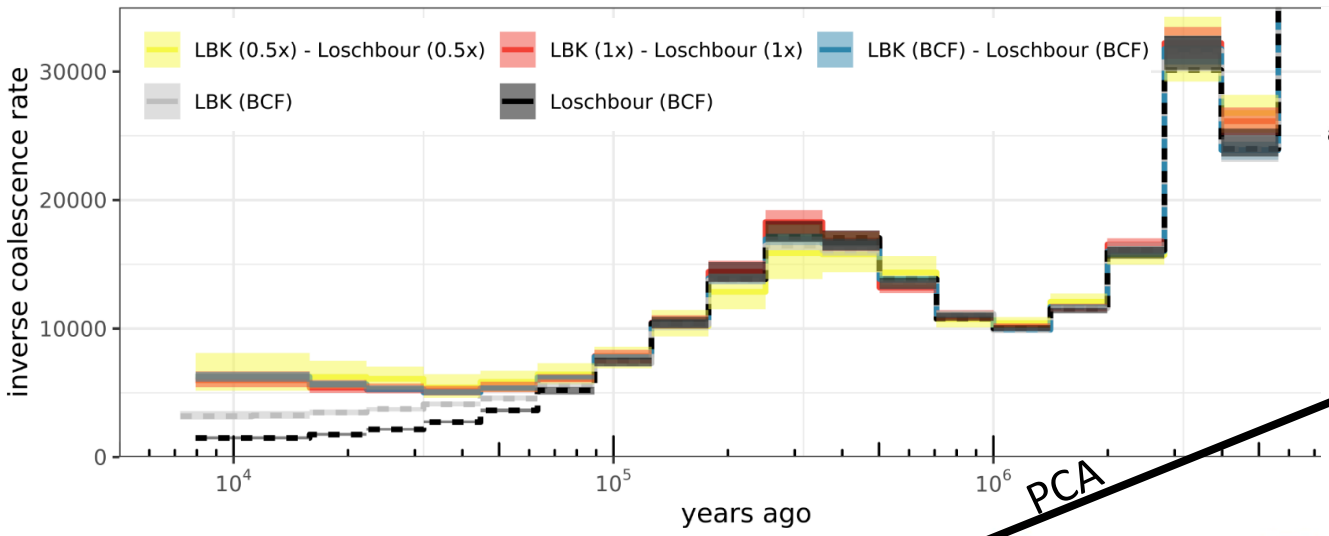


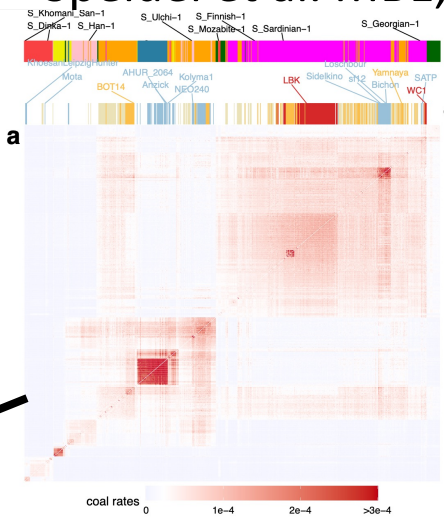
# Major expansions originating in Northern Europe in the early historical period



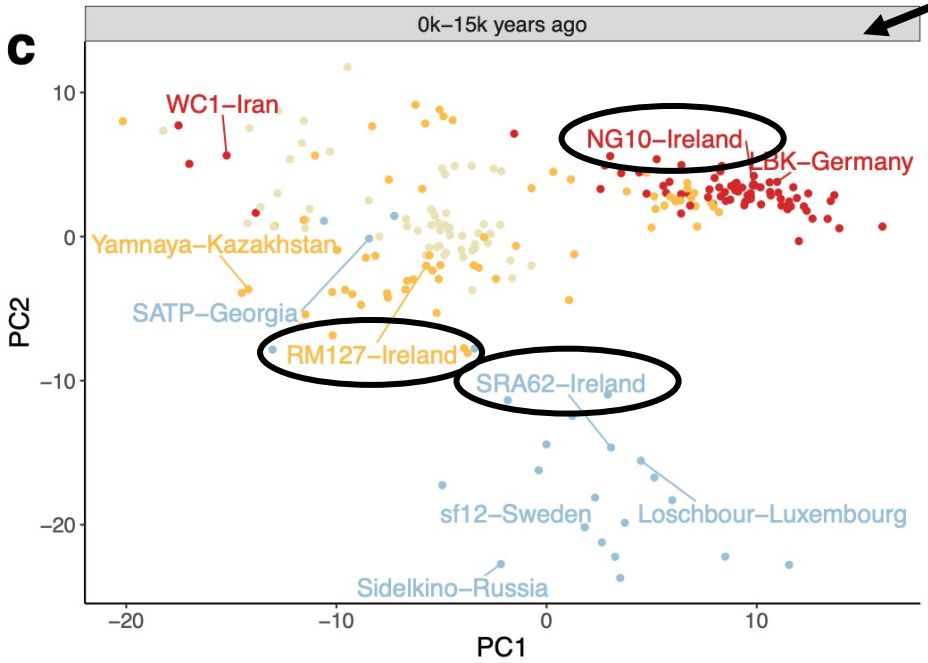
# Colate: Inferring coalescence rates for low-coverage, unphased (ancient) genomes

Speidel et al. MBE, 2021

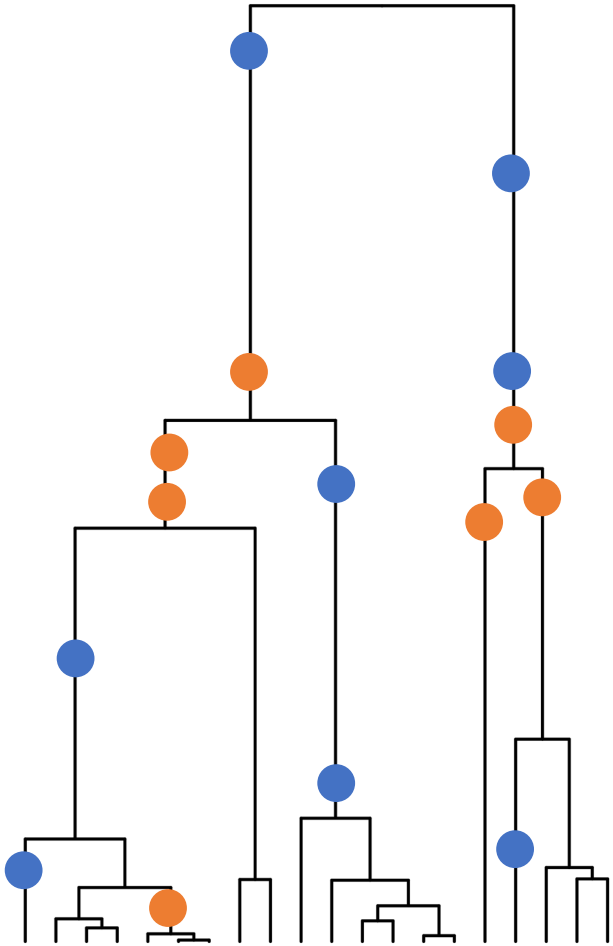


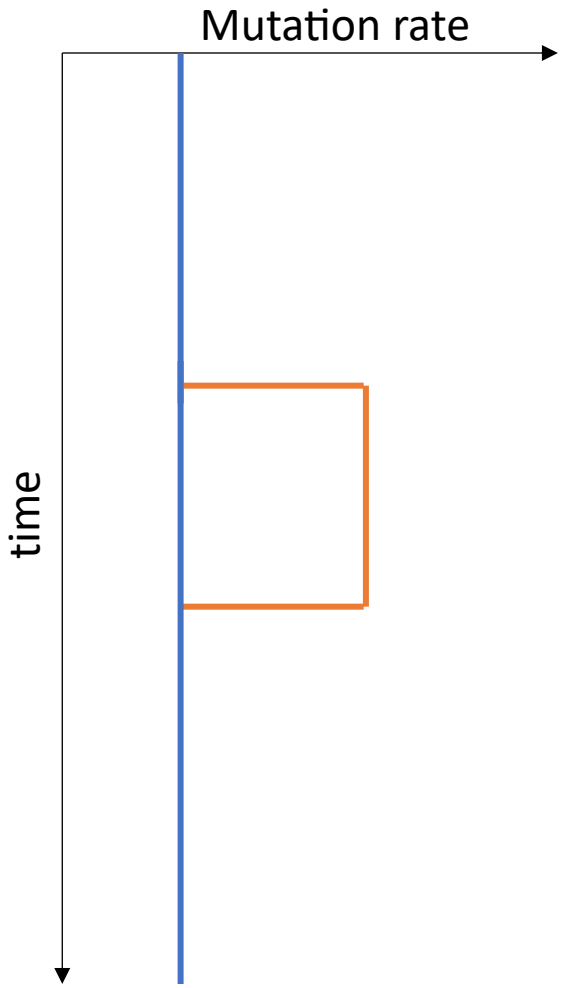




PCA



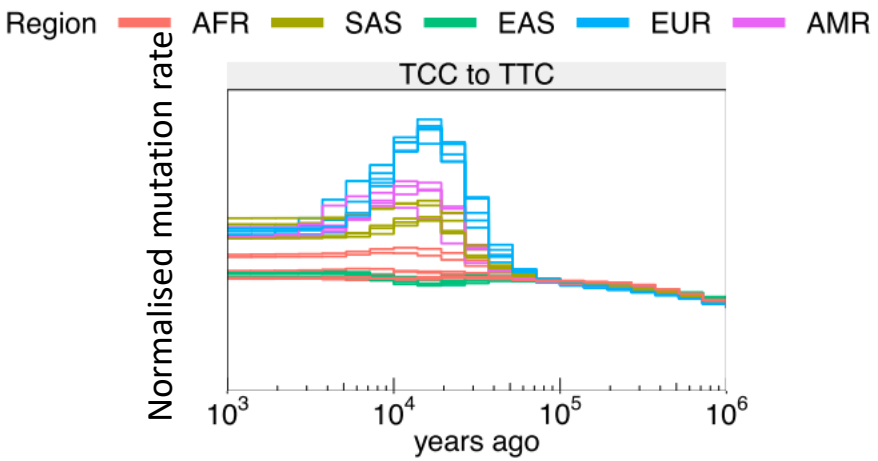

# Clusters of mutations in time can capture changes in mutation rate

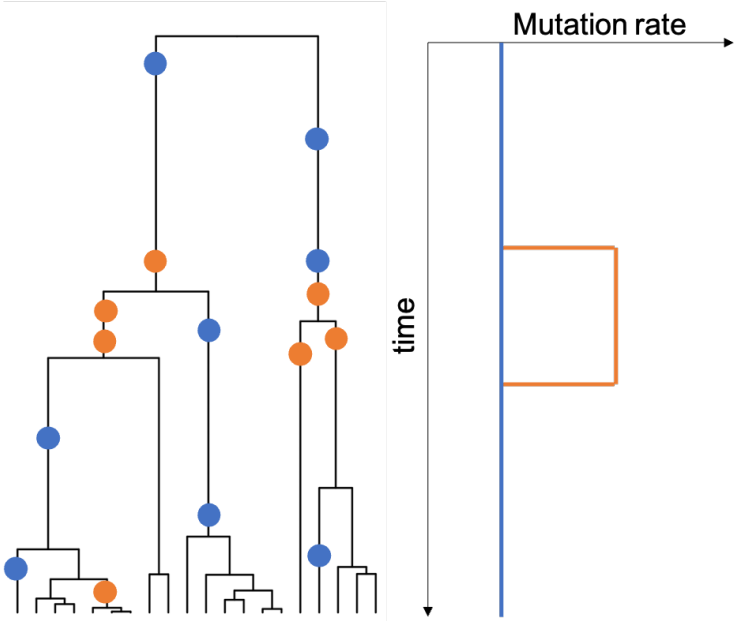




# TCC/TTC mutation rates have experienced a strong pulse in the Upper Paleolithic

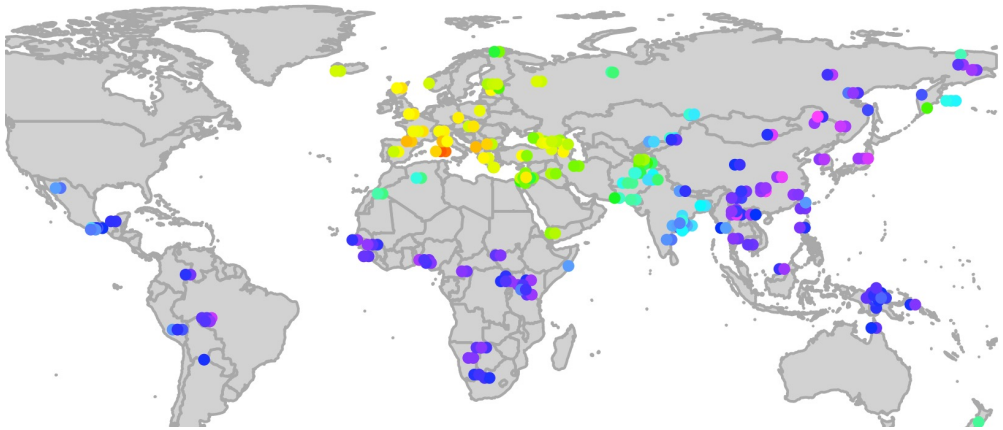
- First reported by Kelley Harris (PNAS 2015, eLife 2017)
- Unknown cause (genetic?, environmental?)
- Previously mainly studied in modern groups



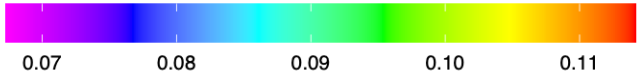




Speidel, Nature Genetics, 2019

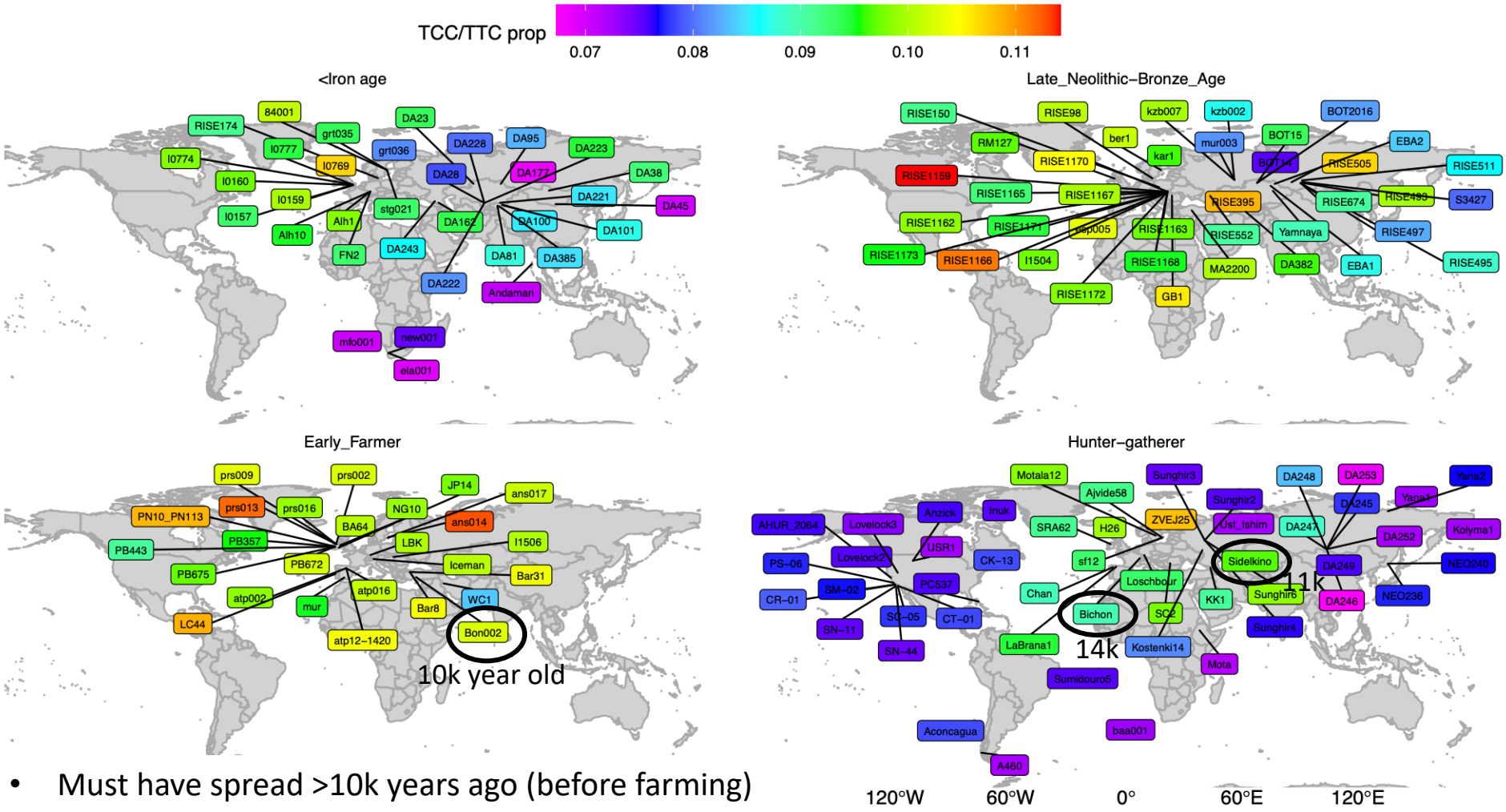
## How did this spread to all West Eurasians today?



Colour shows strength of elevation in TCC/TTC mutation rates

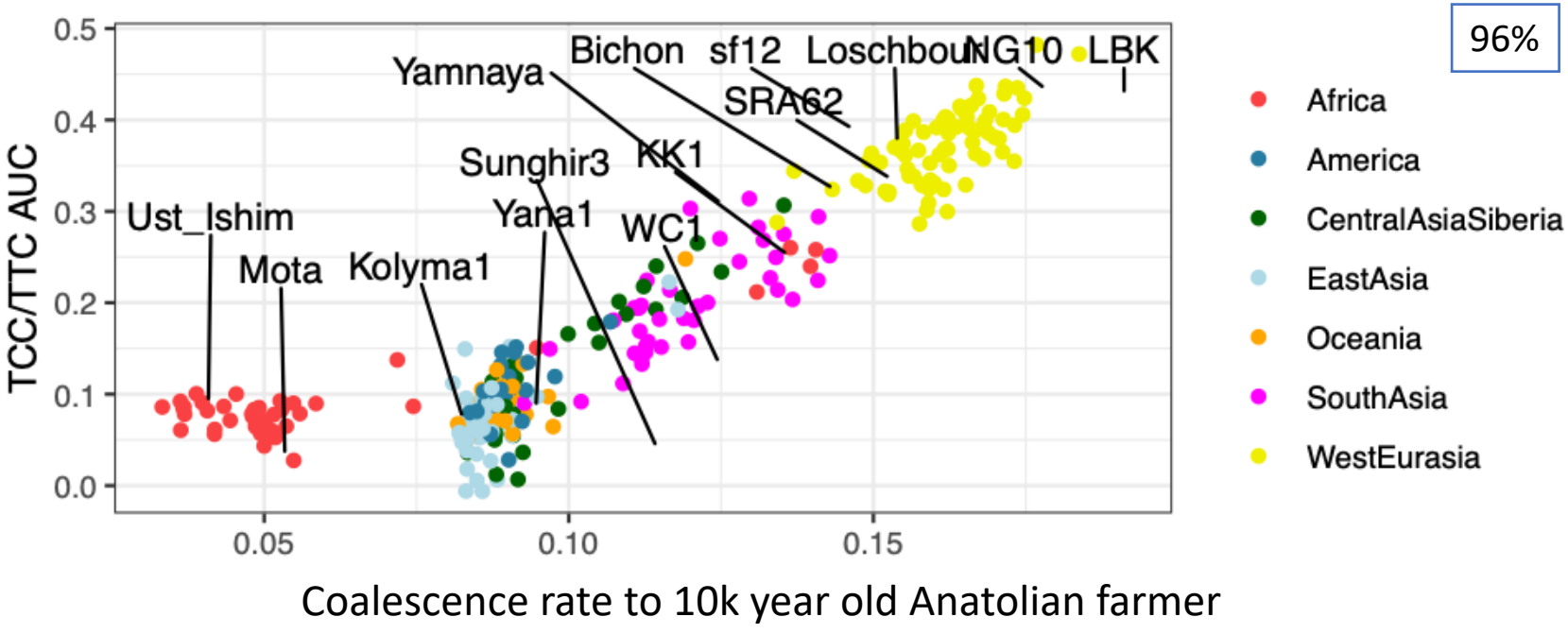


# Signal quantified in 161 ancients shows it was already widespread among European hunter-gatherers



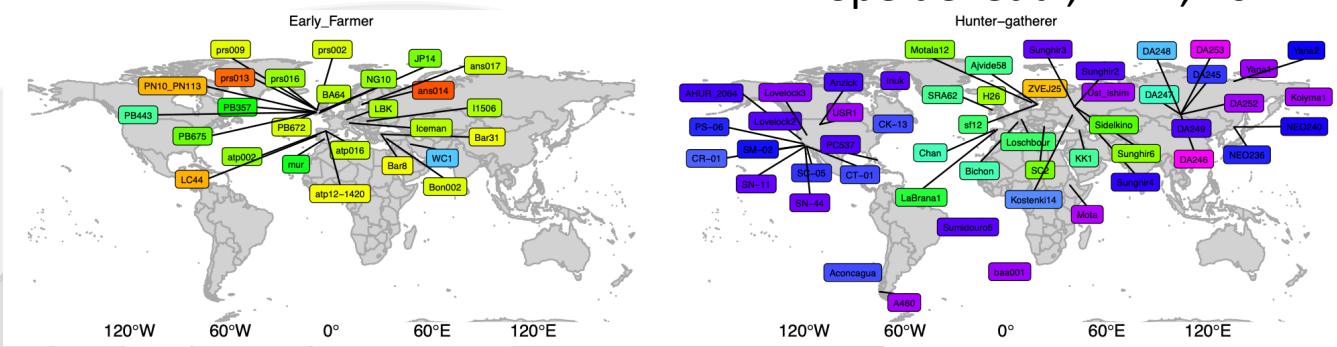

- Must have spread >10k years ago (before farming)
- How could it have spread to these samples? (environment/genetics)

# Very high correlation between signal strength and recent ancestry from Anatolia



# TCC/TTC mutation rate increase happened and spread before farming, >15k years ago!

Speidel et al, MBE, 2021




Ice Age Europe

>20,000 years ago

**ICE**

e.g., Sunghir3 (**30k year old**)

earlier HG groups

e.g., Sidelkino (**11k year old**)

Eastern HG

e.g., Bichon (**14k year old**)

Western HG

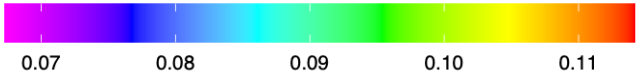
Caucasus HG

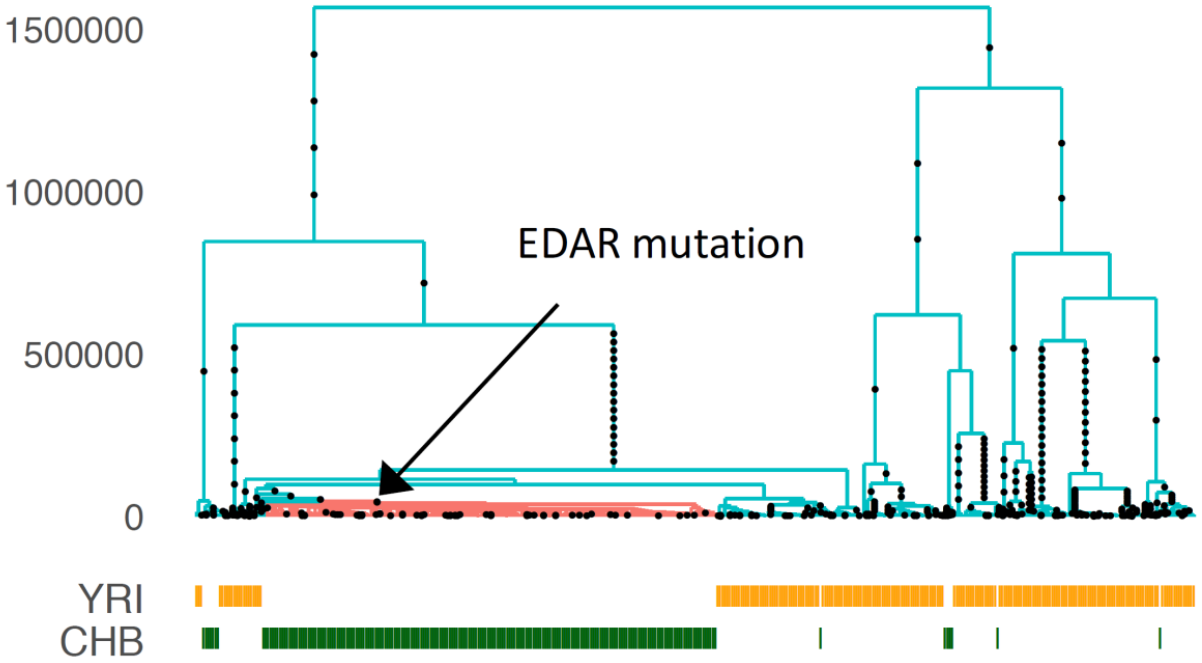
e.g., KK1 (**9k year old**)

Anatolia

e.g., Bon002 (**10k year old**)

Colour shows strength of elevation in TCC/TTC mutation rates

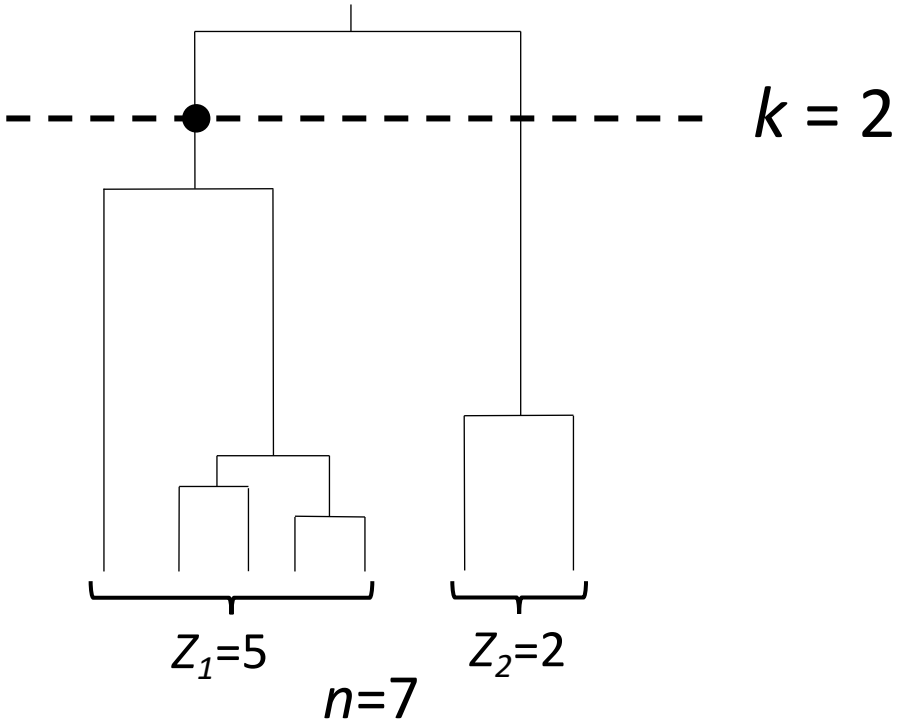





# Quantifying positive natural selection on a single mutation

- Genetic adaptations to changing environment, diet, lifestyles,…
- Use trees incorporating demographic history

# How quickly does a mutation spread in the neutral case?



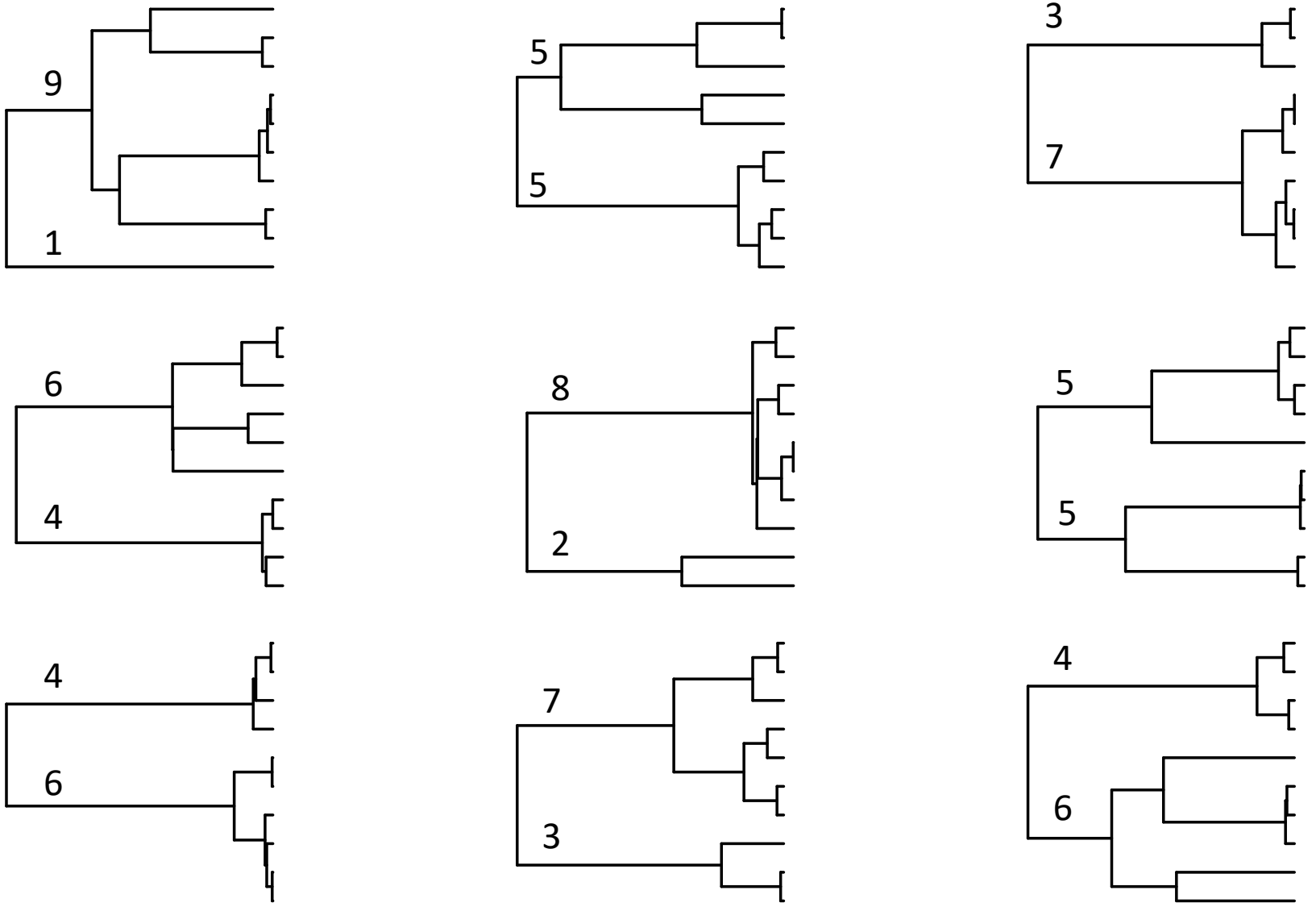

We can write down the analytical distribution for the number of descendants of a mutation arising while k lineages remain

Example: if *k*=2, this is just a **uniform distribution**

P(5 descendants)=1/6

# The k = 2 case

We expect “unbalanced” tree shapes!

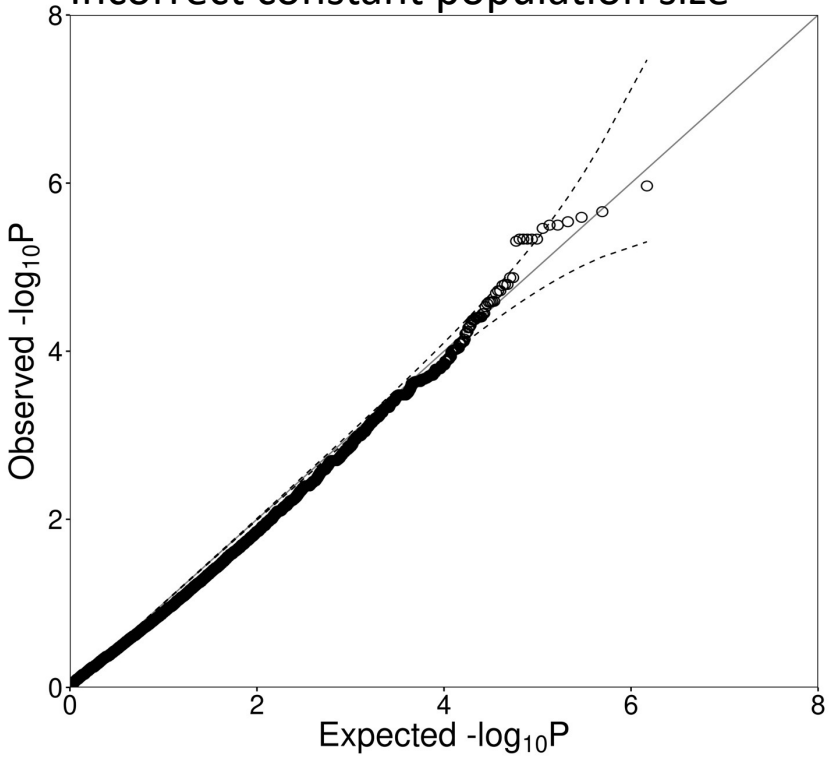


# P-values: very well calibrated under null simulations of no selection

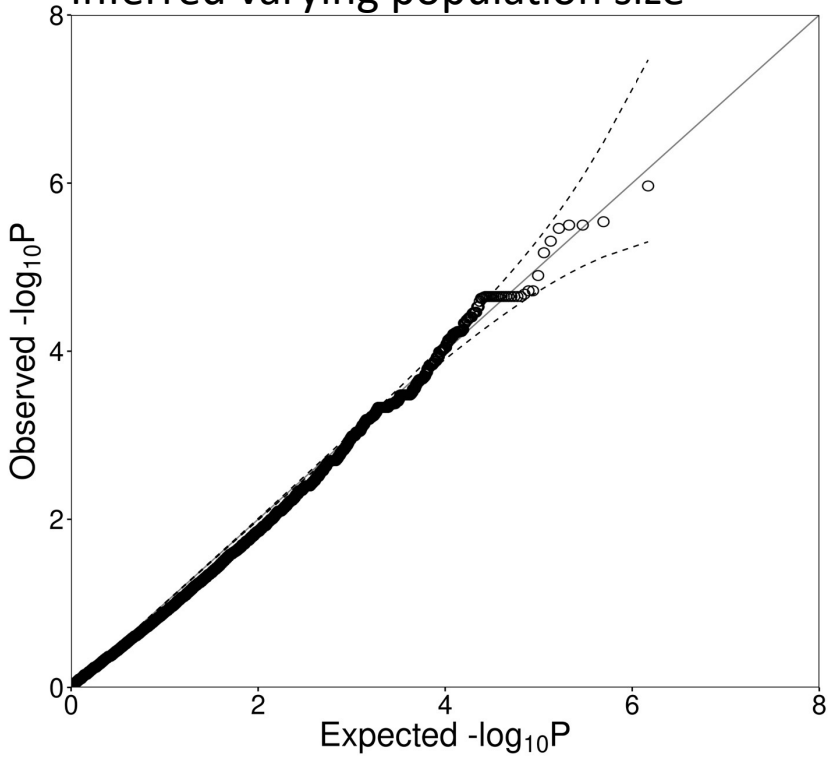
N=1000, 250Mb
Bottleneck population size

Quantile-quantile plot:

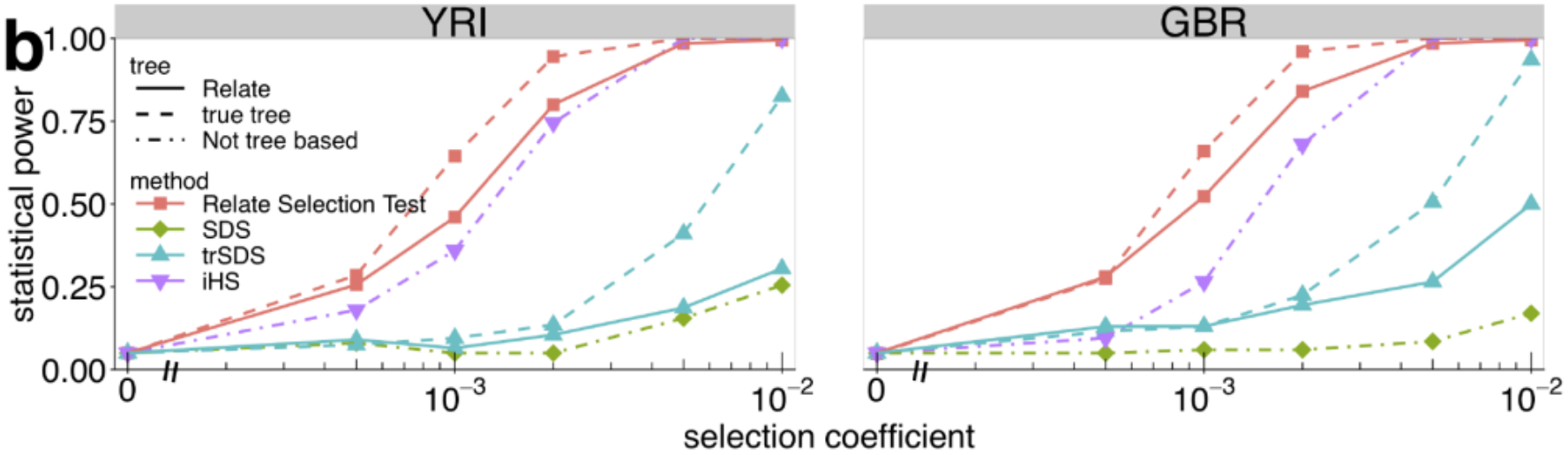
Incorrect constant population size




Inferred varying population size

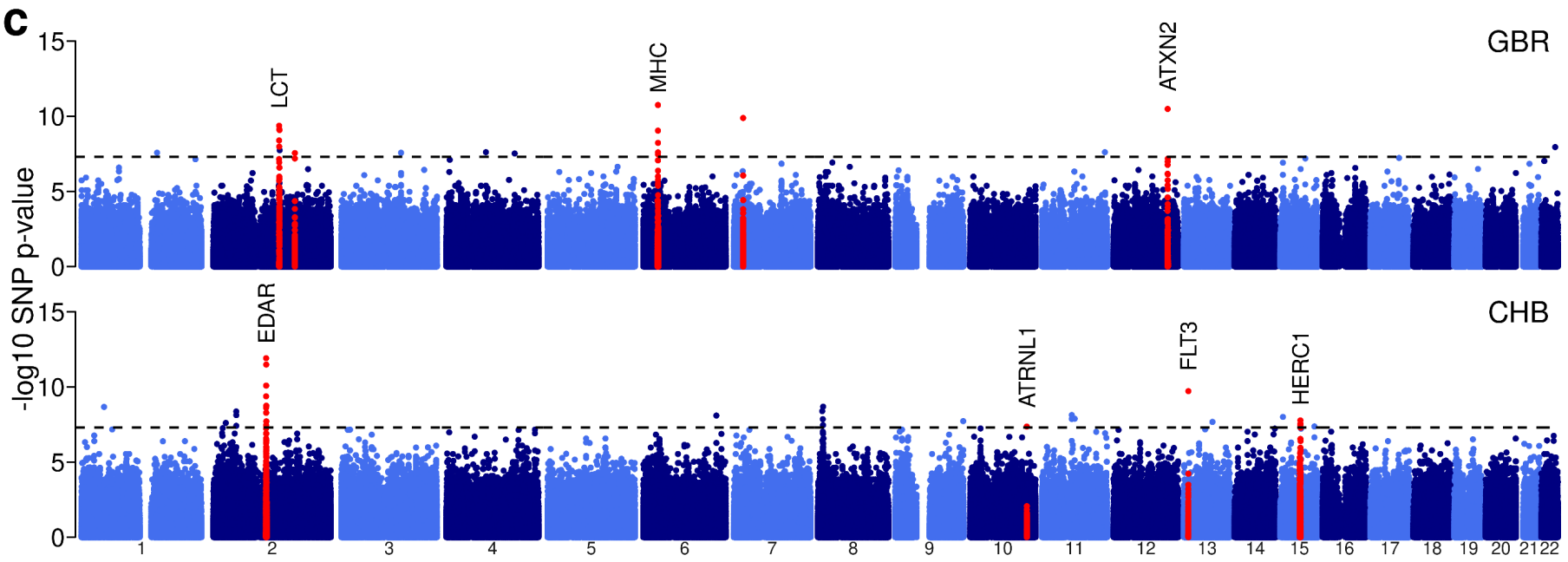


# Improved power to see weak selection



# Genome-wide selection p-values

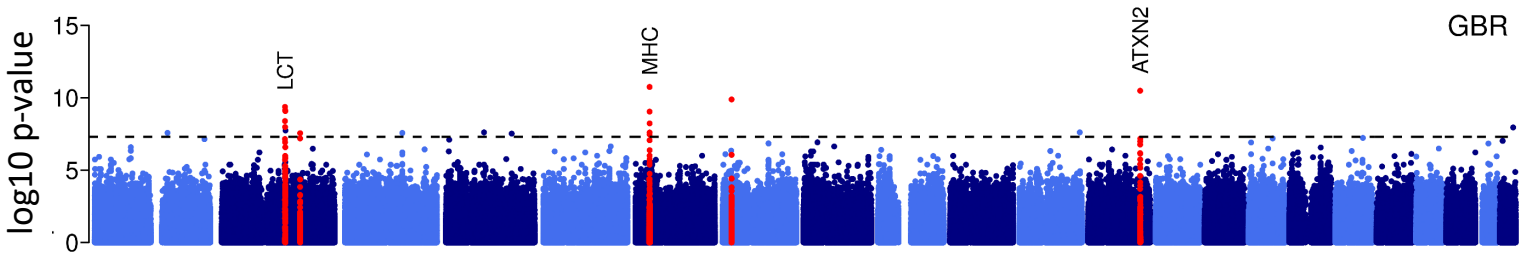
Given most traits are highly polygenic, expect mainly weak, polygenic selection



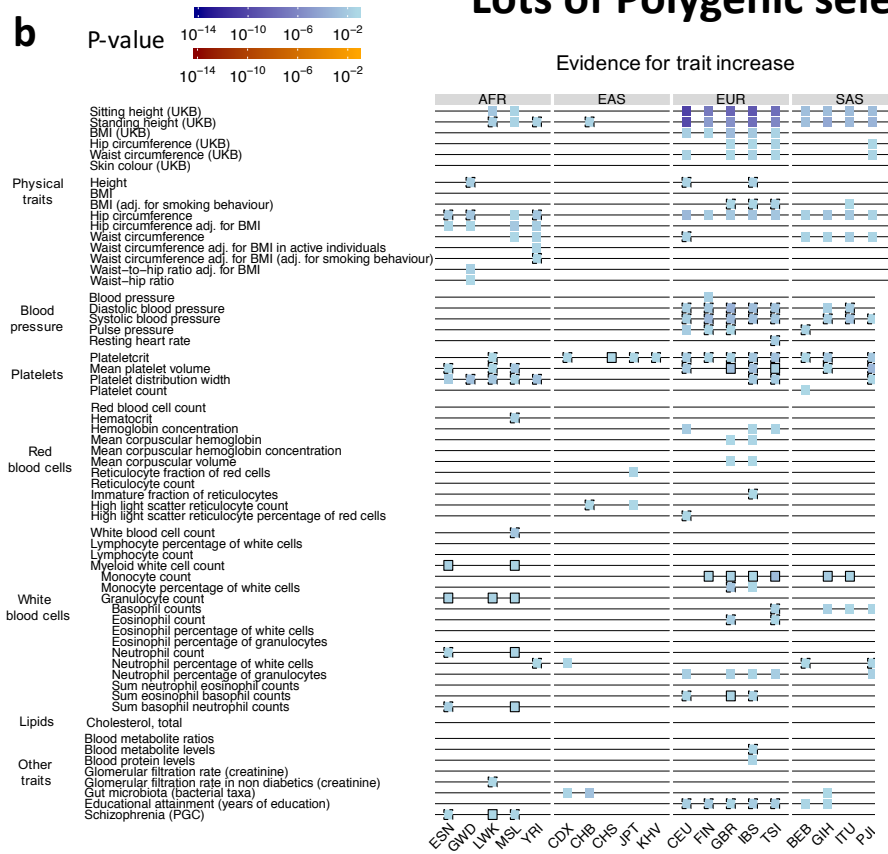

How does weak selection evidence vary by trait?

# Many key events in our evolutionary history are only implicated as subtle effects in our genomes

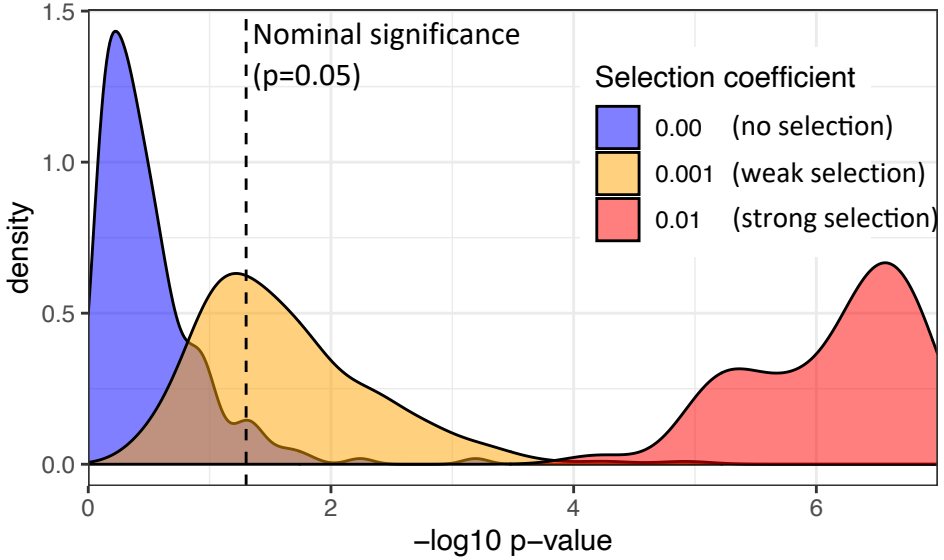
## Selection p-values: only a handful of "genome-wide significant" loci




## Lots of Polygenic selection signals

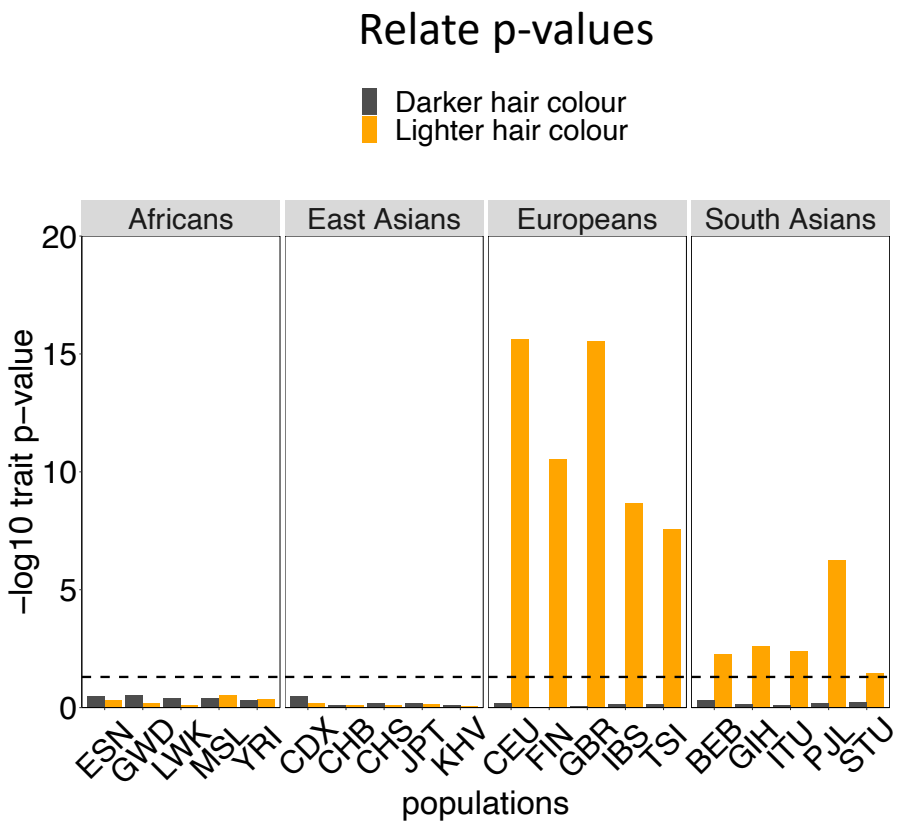


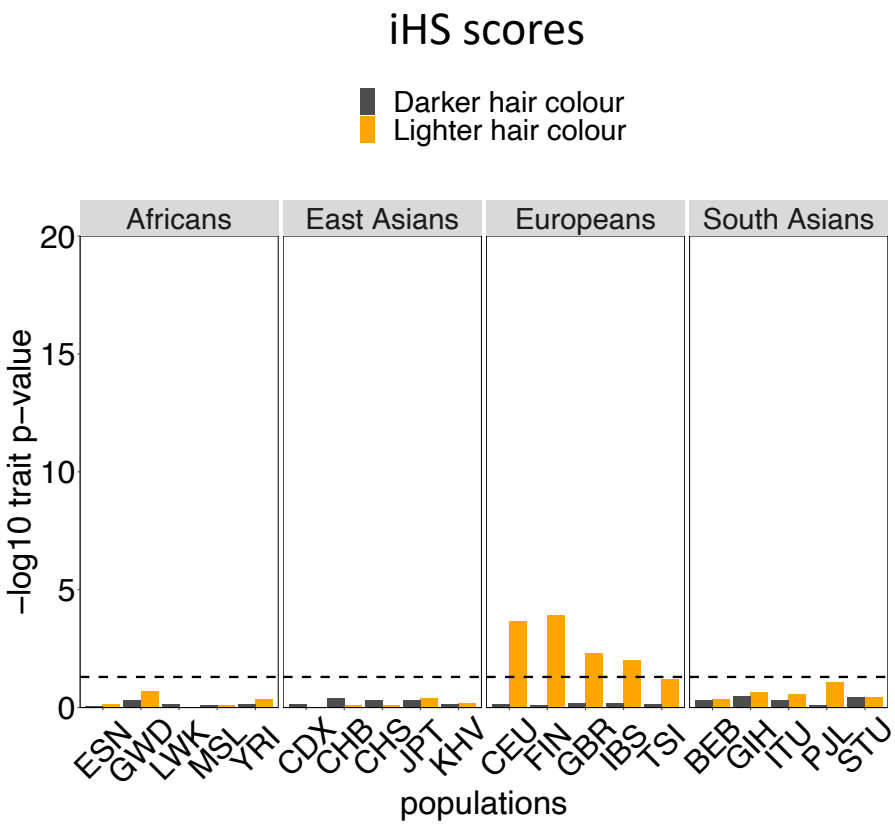

Weak selection on individual mutations is hard to detect, compared to shifts in distributions



# Evidence of selection on a trait: hair colour

1. Use **effect direction** of ”genome-wide significant” associations
2. Compare selection p-values to frequency matched random SNPs (Wilcoxon rank-sum test)



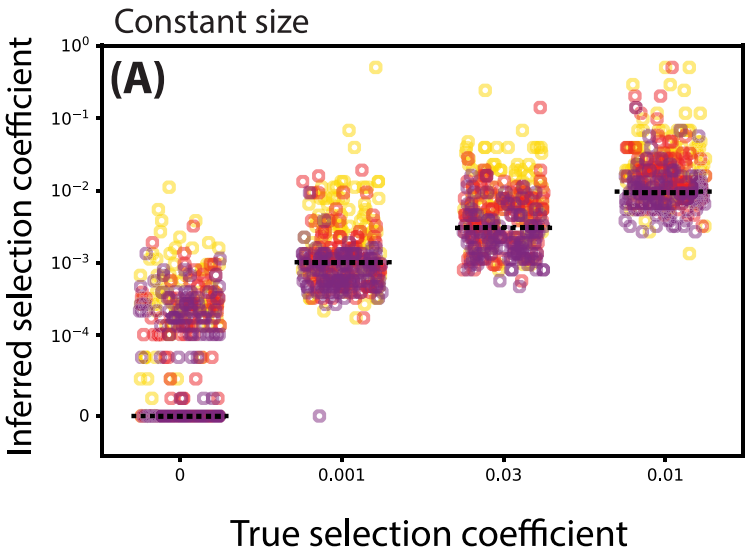
# **CLUES:** Importance-sampling based method for inferring selection coefficients

Aaron Stern

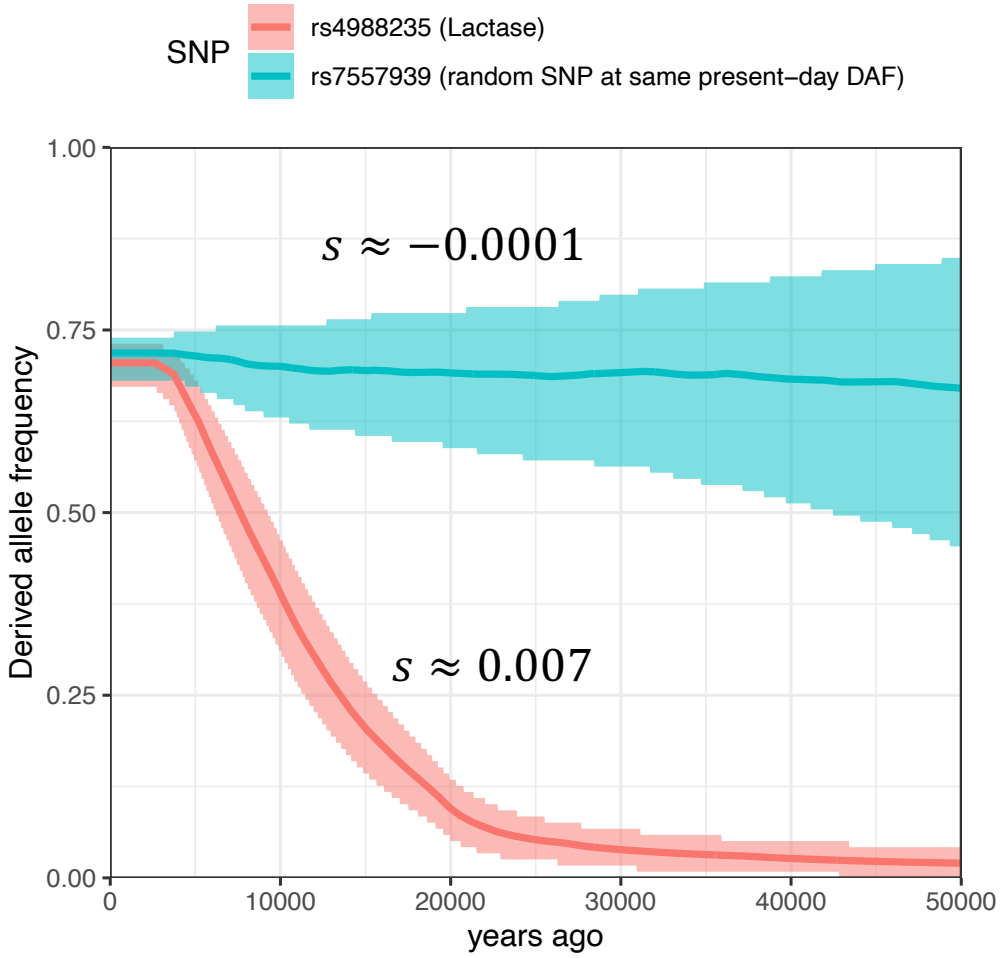
Aaron J. Stern, Peter R. Wilton, Rasmus Nielsen. **PLOS Genetics, 2019**.

Aaron J. Stern, Leo Speidel, Noah A. Zaitlen, Rasmus Nielsen. **AJHG 2021**

**Simulations:**




**1000 Genomes Project British:**



# Summary & outlook

- It is now possible to build genealogical trees for huge datasets, in humans and other species (currently 10,000 individuals or more)
  - Humans (ancient and present)
  - Dogs and wolves
  - Mice
  - Bacteria
  - Atlantic cod, Cichlids
  - Waterhemp, Arabidopsis
- These trees capture information about many processes including
  - Migrations and ancient introgression
  - Mutation rate evolution
  - Trait evolution
  - (and many more things)
- Lots of scope for more methods using inferred genealogies under development

….creative approaches to leverage trees to answer biological questions!