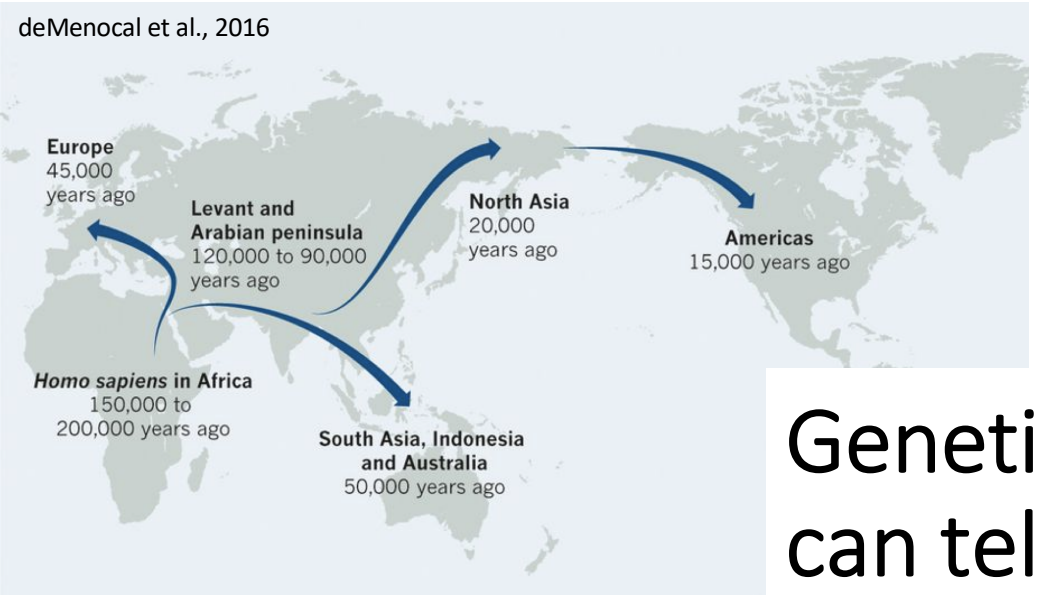
Learning about evolution by building coalescent trees

Simon Myers, Jasmin Rees, Leo Speidel

- This am: introductory lectures
- This pm: "Relate in the Prelate"
  - Running Relate on a human dataset of 130 different populations
  - Population structure and how it changes through time
  - Identifying directional selection

deMenocal et al., 2016



Genetic variation data can tell us about:

- Structure and migrations
- Population bottlenecks
- Admixture

- Mutation
- Recombination
- Selection
- etc

Step 1: Let's model these
Step 2: Inference

These might themselves evolve through time!

The genetic tree(s) relating humans (or any other species)

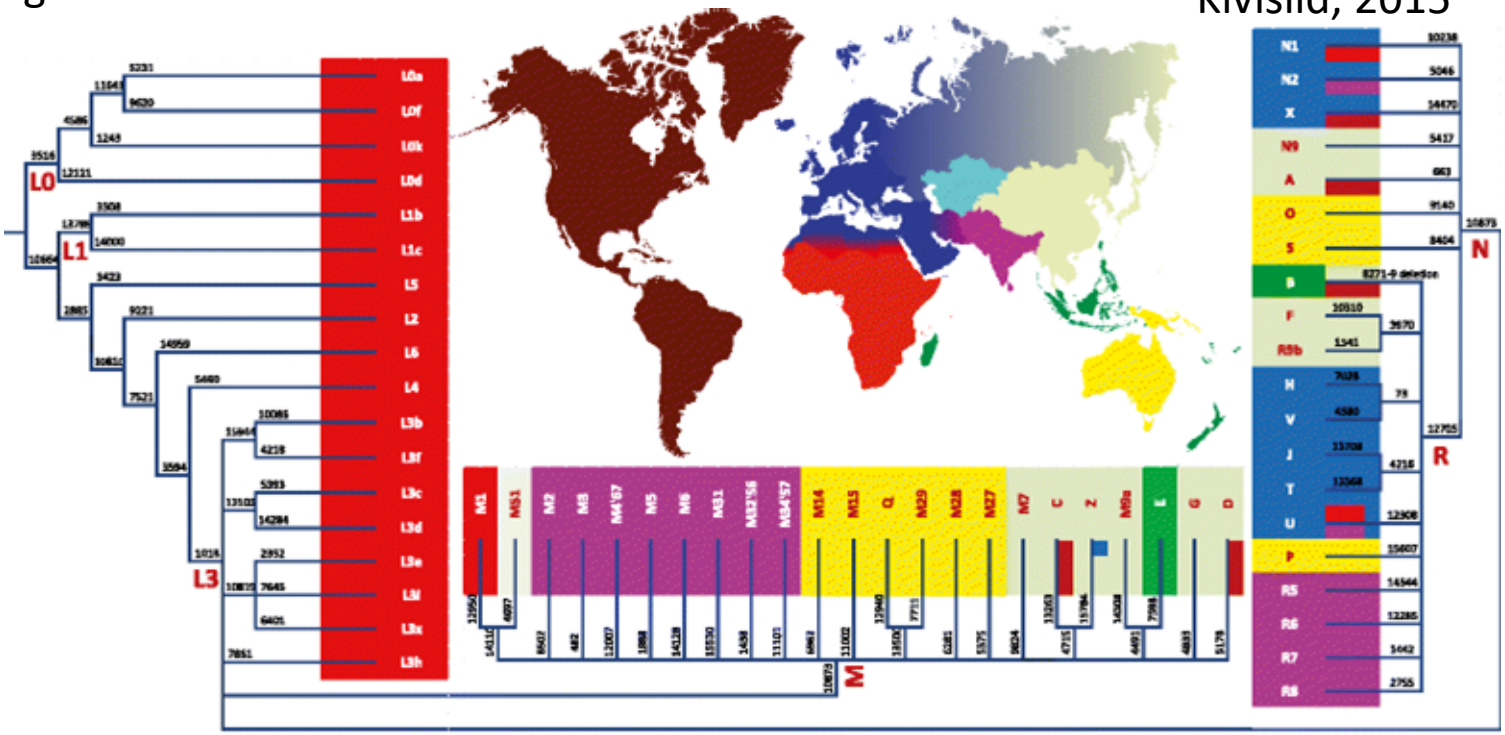
Reconstructing >100,000s years of evolution!

- 22 autosomal chromosomes
- 2 sex chromosomes
  - X chromosome
  - Y chromosome
- Mitochondrial genome

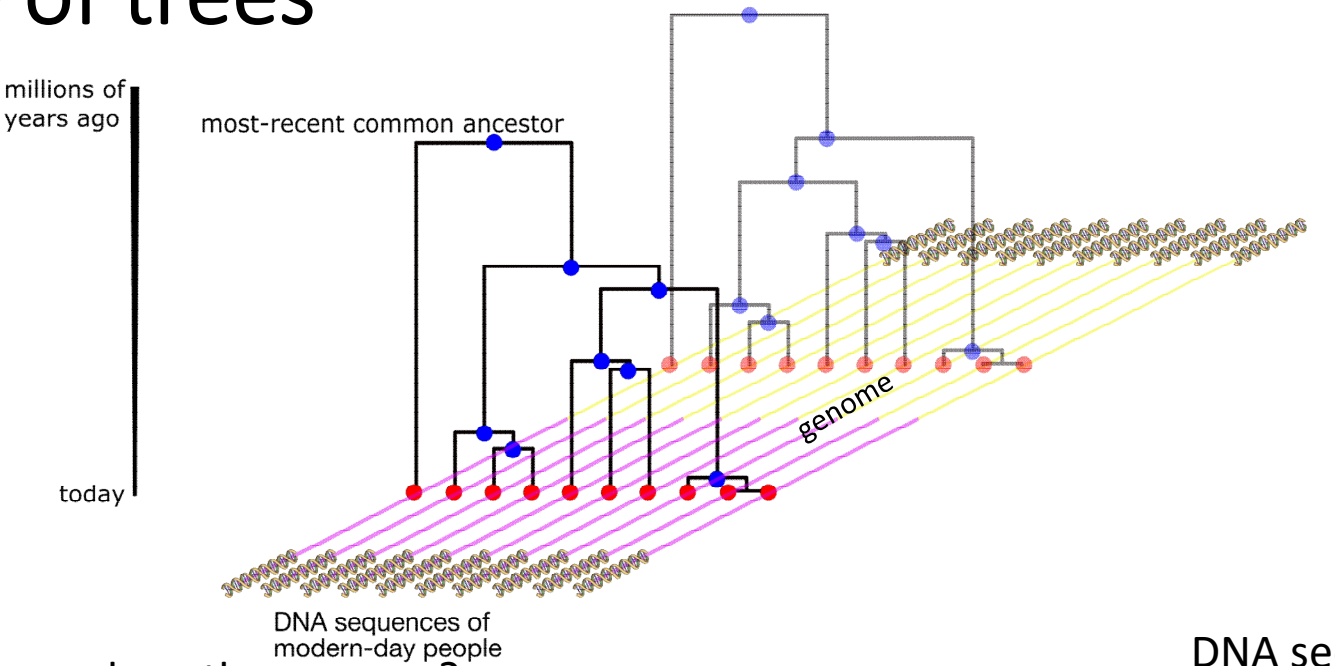
Different trees in different parts of the genome, due to recombination

1 tree each (maternal/paternal)

Kivisild, 2015

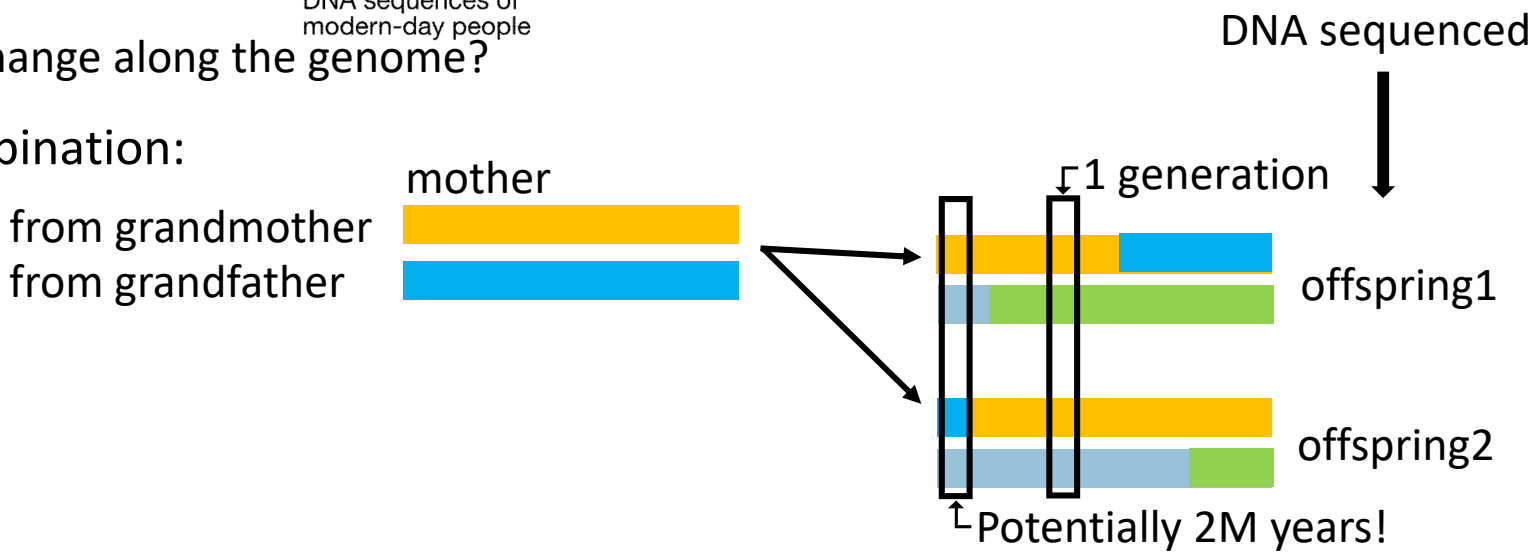


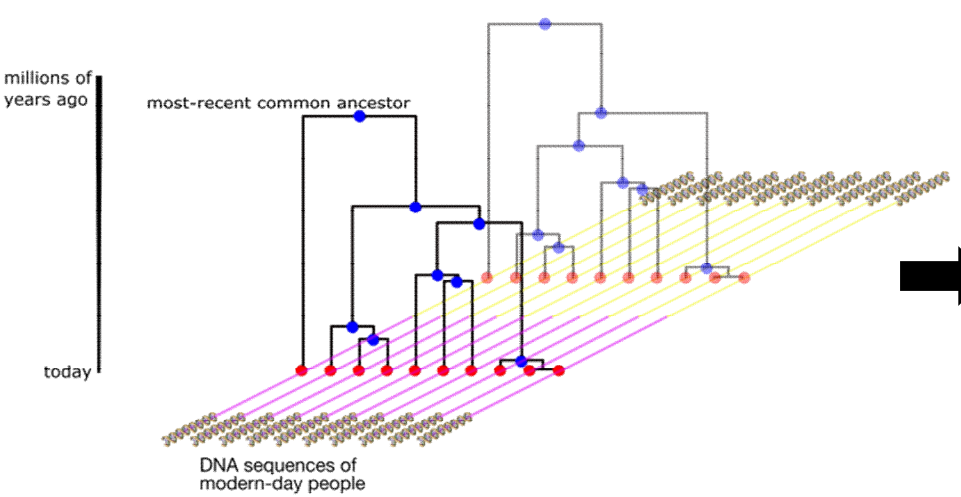
Key concept: Genealogies
We are genetically related through a sequence of trees

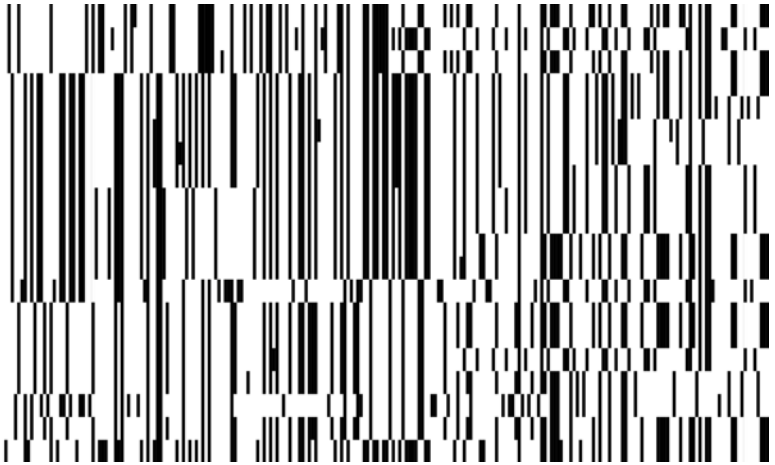


Why do trees change along the genome?

Recombination:



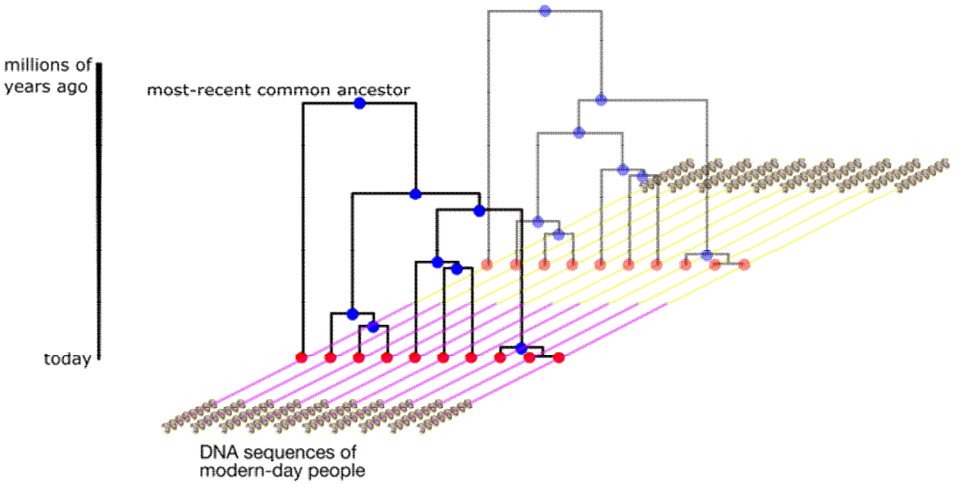


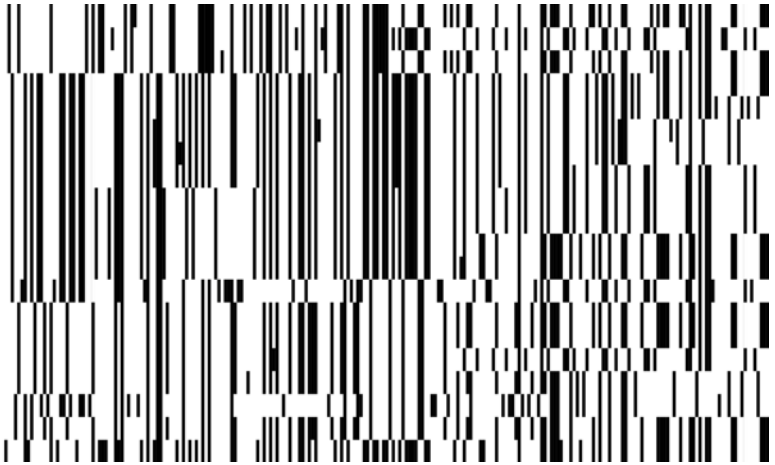


Demographic history
Genetic structure
Mutation, recombination,
etc.

Fundamental forces impact data (only) through underlying genealogies

Many canonical approaches

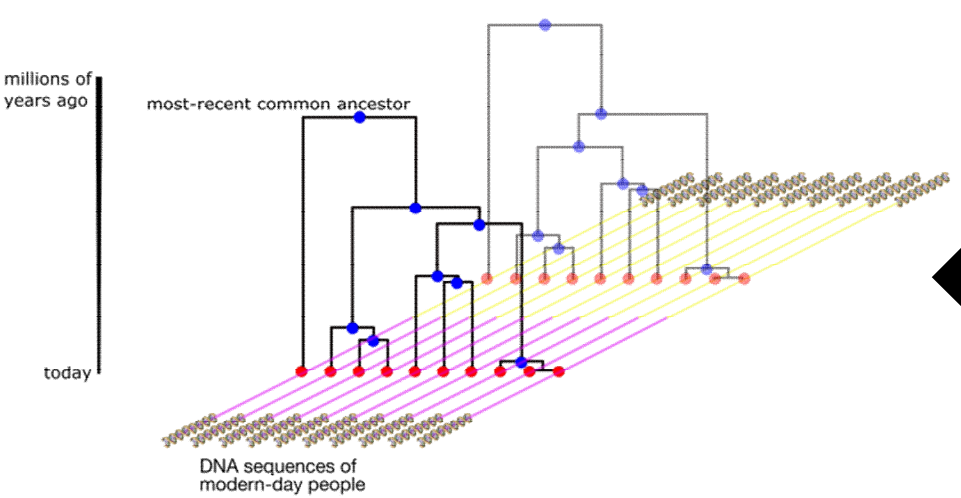


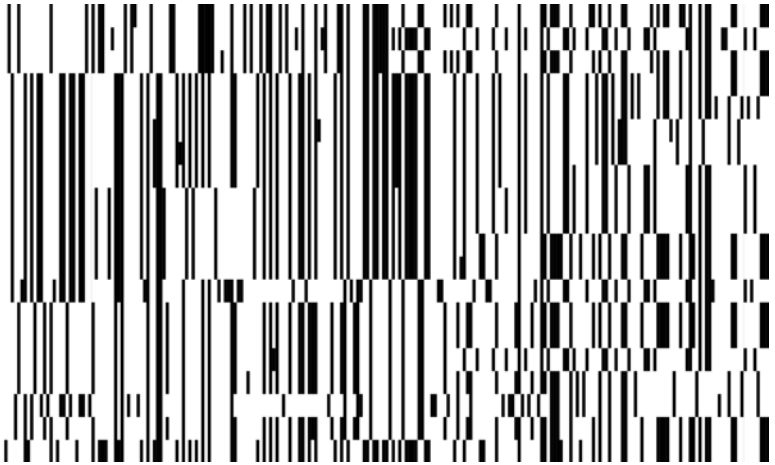


Demographic history
Genetic structure
Mutation, recombination, etc.

Invent informative statistics, simplify, "integrate out all possible histories“ (machine learning methods typically learn these statistics from the data)

Today's approach





Build (simple) statistics directly based on trees, to answer questions in population genomics

Demographic history
Genetic structure
Mutation, recombination,
etc.

In **principle**, trees capture **all the information** available from the data about these processes, allowing **self-consistent inference**

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

Inferring genealogies

Old problem, lots of methods, but few can scale:

- ARGweaver } Infers Ancestral Recombination Graphs
- Rent+
- Tsinfer+tsdate
- Relate
- ARG-Needle

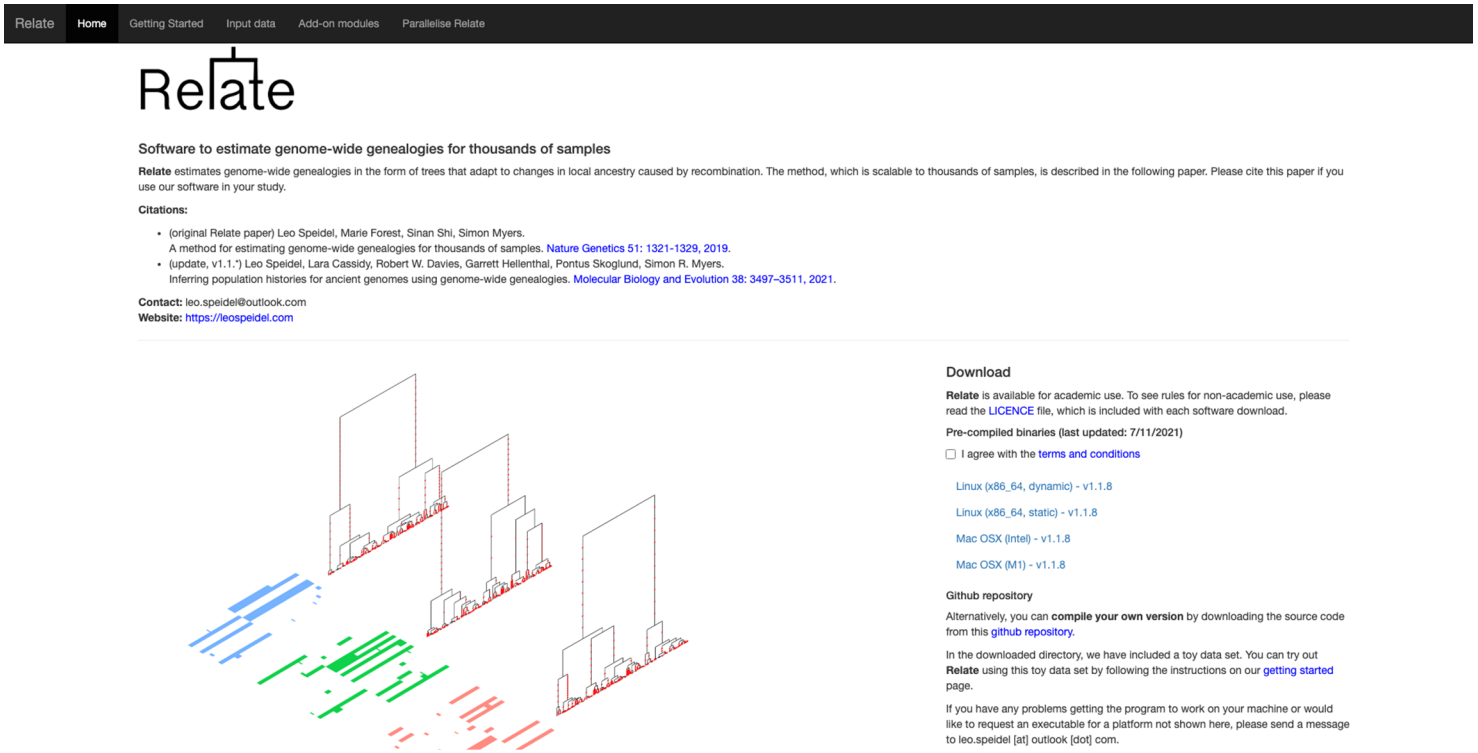
} Published since 2019, scale to large sample sizes

We will talk about Relate today – Georgia will introduce tsinfer tomorrow…..

but principles of tree-based inference apply more generally!

Relate

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

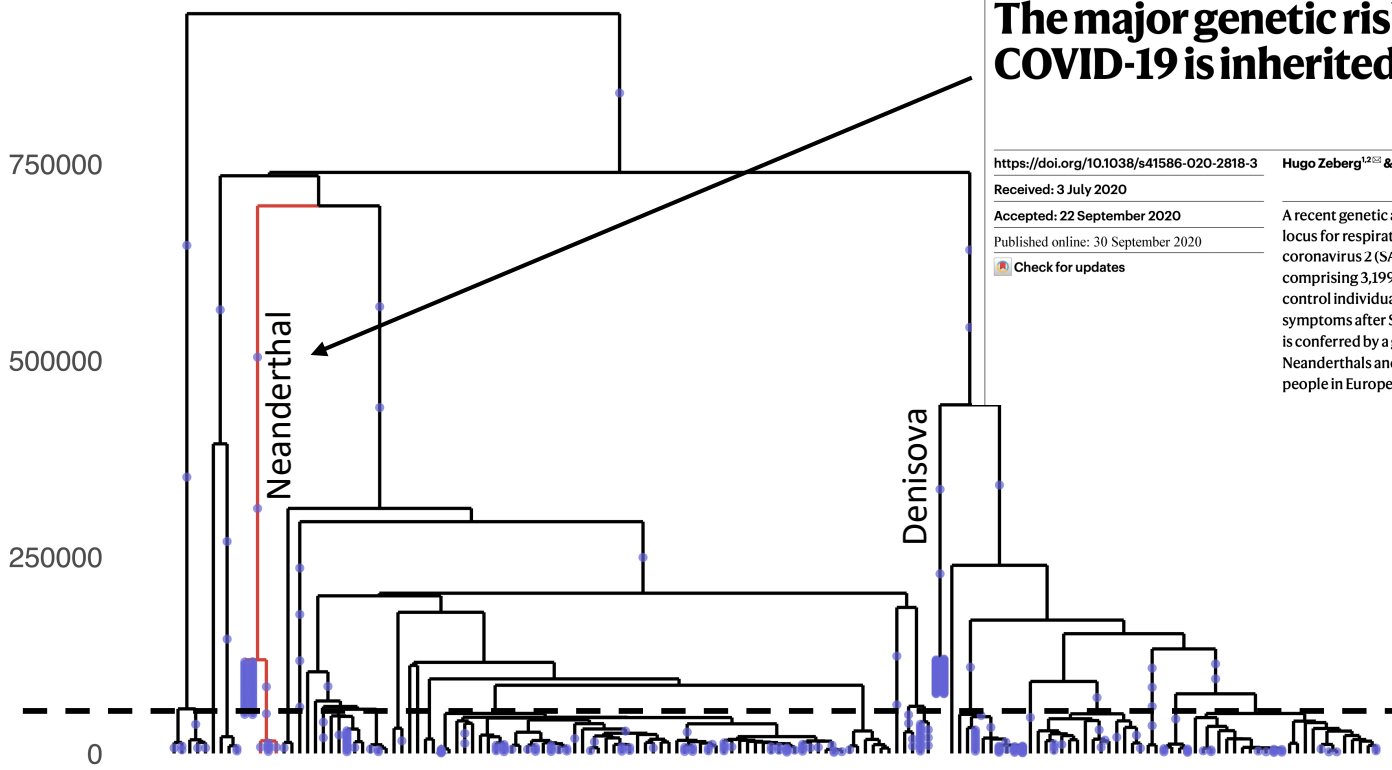


https://myersgroup.github.io/relate/

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

One locus can already tell us a lot about our history



Article

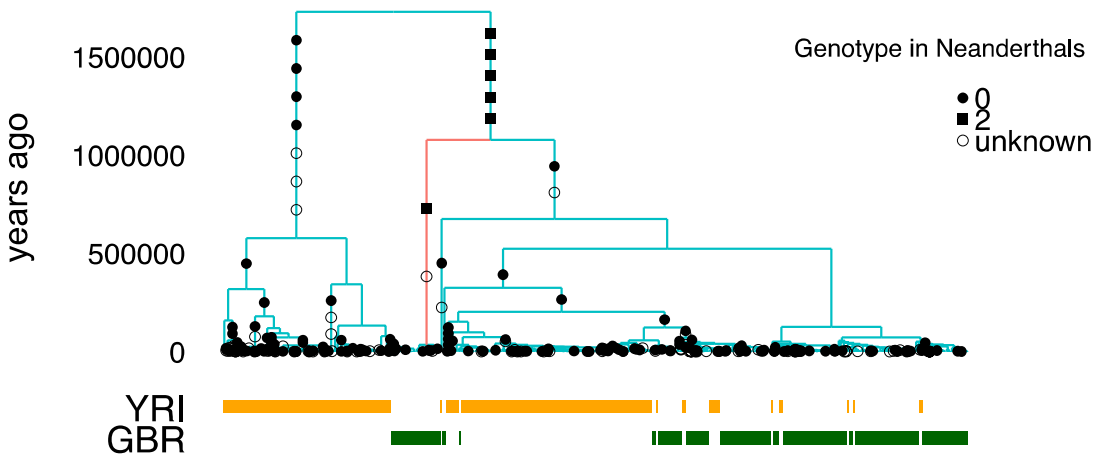
The major genetic risk factor for severe COVID-19 is inherited from Neanderthals

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

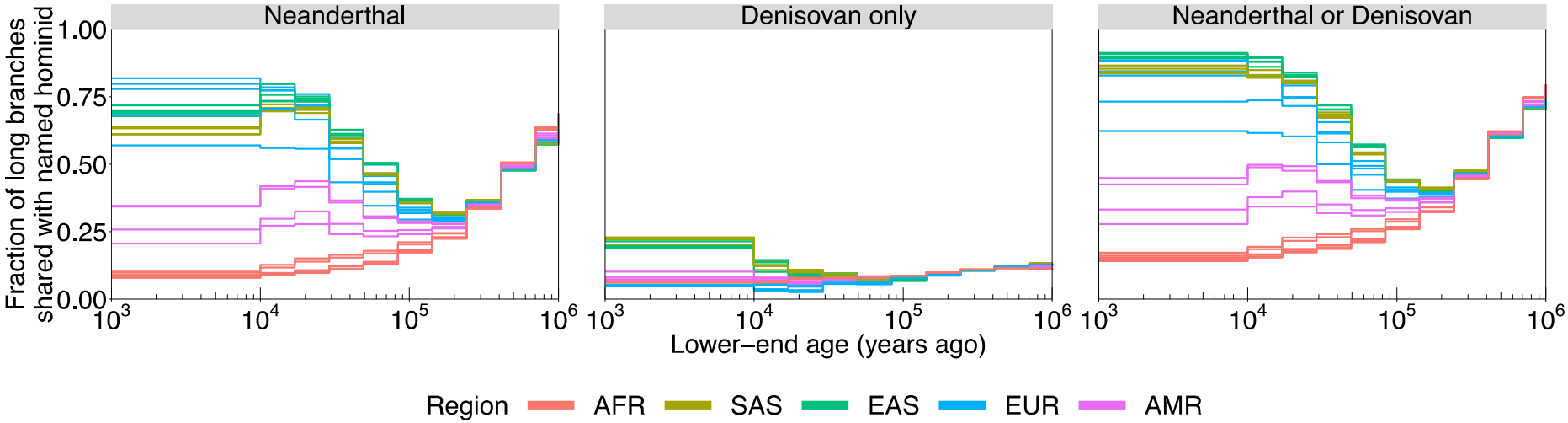
Hugo Zeberg[1,2] & Svante Pääbo[1,3]

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.

….combining across loci tells us much more (e.g. ancient introgression in non-Africans mainly from Neanderthal/ Denisovan relatives)

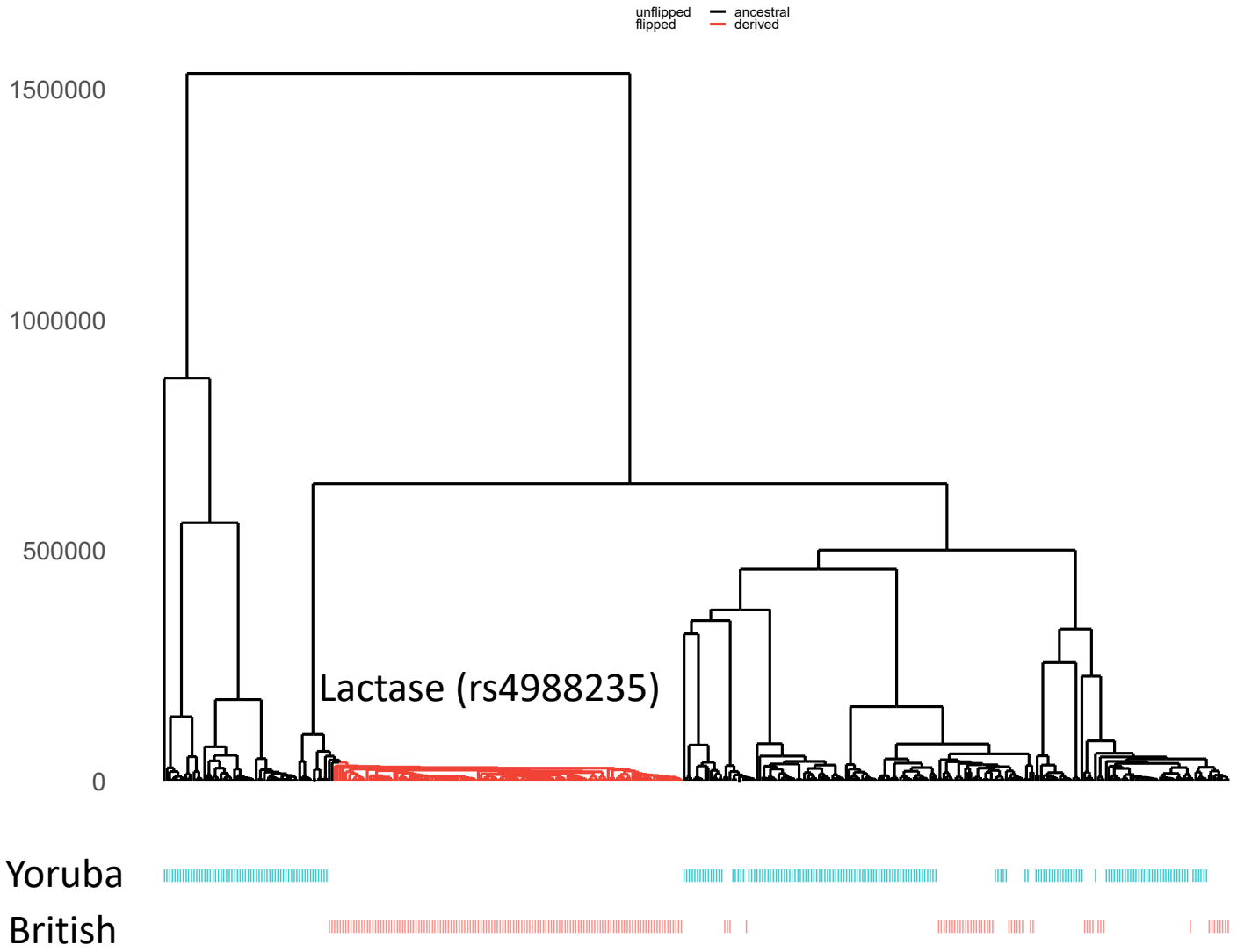


Fraction of **deep branches** shared with named hominid:
(Upper end > 1M years)

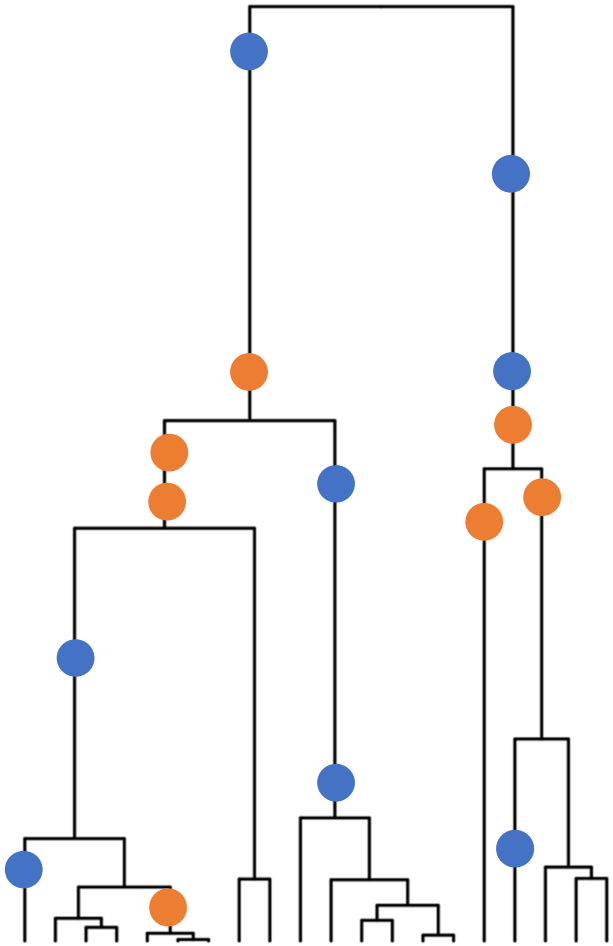


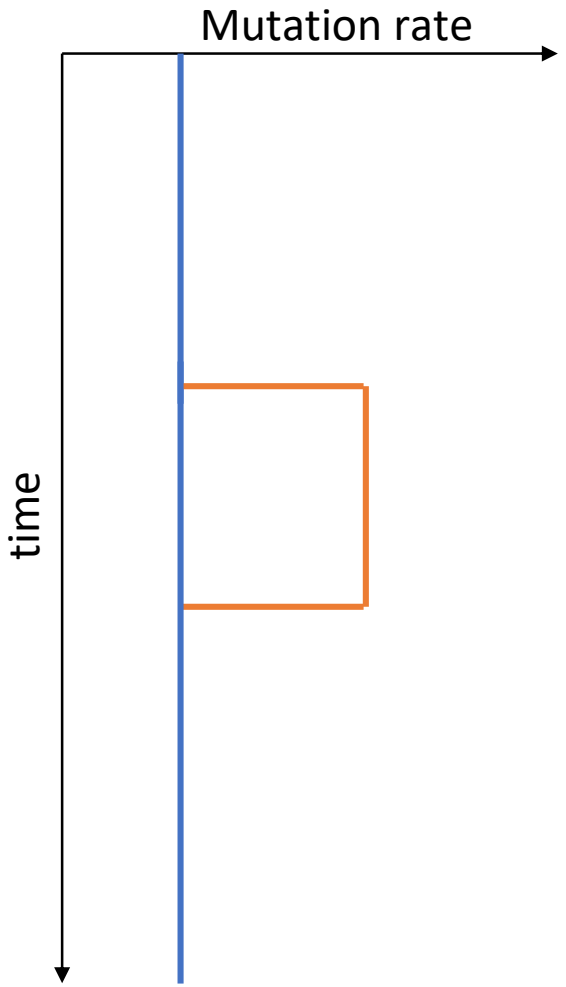
NB: Africa shows little Neanderthal or Denisovan introgression, but actually has a **huge excess** of long (unexplained) branches shared only within Africa

Example: Positive selection, rapidly spreading lineage



Example: clusters of mutations in time can capture changes in mutation rate





To actually do inference, we need to (re)visit the coalescent model to help:

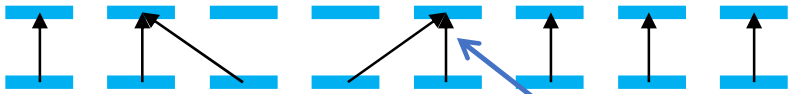
1) Create a method to build trees under a coalescent model, with varying population size, and allowing for recombination
2) Construct statistics to capture information from trees and either
   (i) Interpret parameters in the coalescent, e.g. coalescence rates
   (ii) Reject a null model, e.g. testing for selection

Revision of coalescent

The **Wright-Fisher model** is able to approximate more realistic models of populations, but is itself the "simplest possible model incorporating inheritance"

N individuals; each member of the current generation randomly chooses one of *2N* parent chromosomes and inherits their DNA

Some population members have 0 children, others more than 1 child:



Each haplotype chooses parent in previous generation totally at random

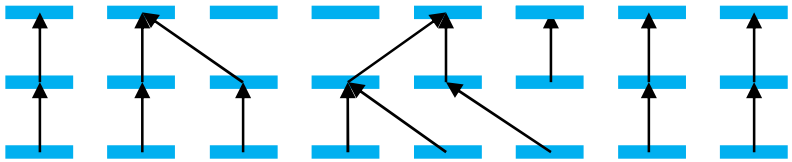
If haplotypes **share** a parent back in time, this is called a **coalescence event**

Revision of coalescent

Over many generations, the population evolves

Our DNA comes from our ancestors so we look back in time

In a single generation, chance two haplotypes choose the same parent is $1/2N$



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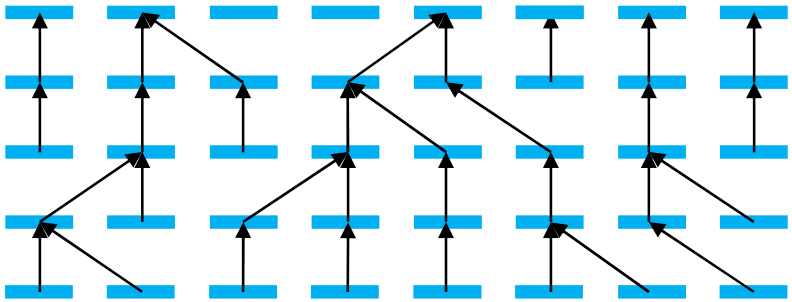

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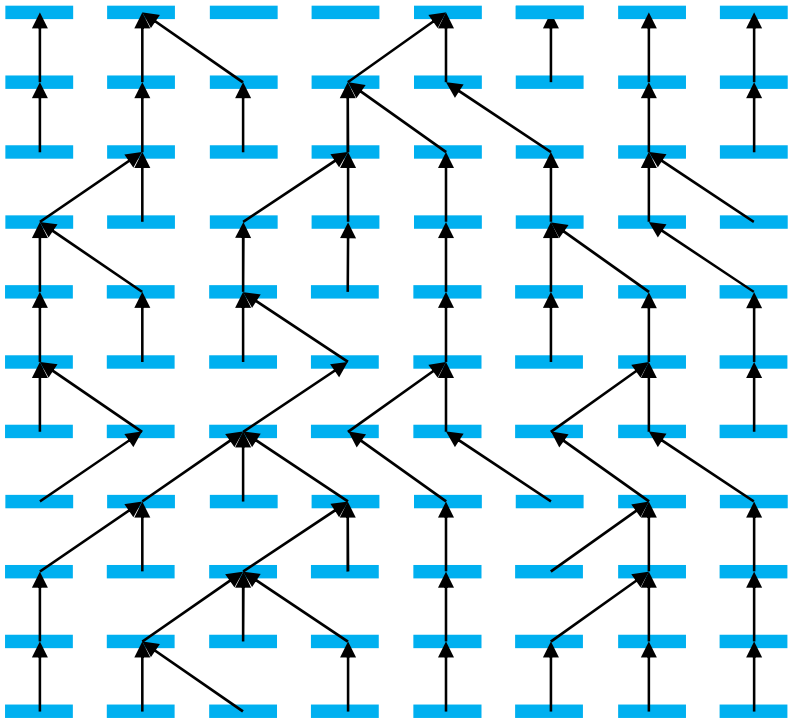

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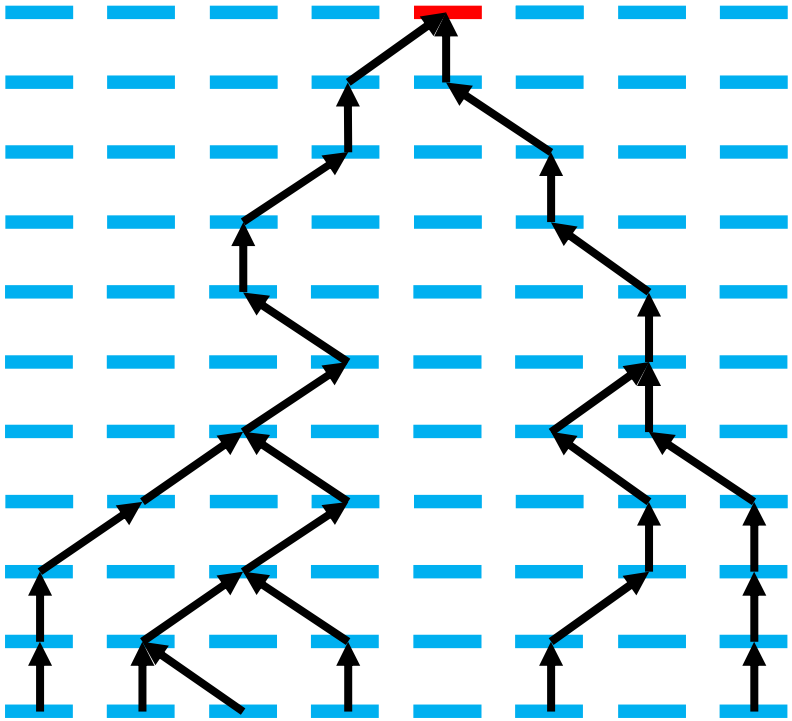
If haplotypes **share** a parent back in time, this is called a **coalescence event**

If we take a sample from the population, we can trace their ancestry: a random tree

In this tree, the number of ancestors decreases back in time from *n* to 1

Each pair of lineages has 1/2*N* coalescences per generation, so 1 coalescence per 2*N* generations



Sample of size *n*=6

N ~10-50,000 for all human

populations, highest in Africa

So a typical pair of human chromosomes share an ancestor on average around 2x20,000x28=1 million years ago

N varies dramatically across species
(Charlesworth, Nature Reviews Genetics 2009):

25,000,000 for *E.coli*

2,000,000 for fruit fly

D. Melanogaster

<100 for Salamanders
(Funk et al. 1999)

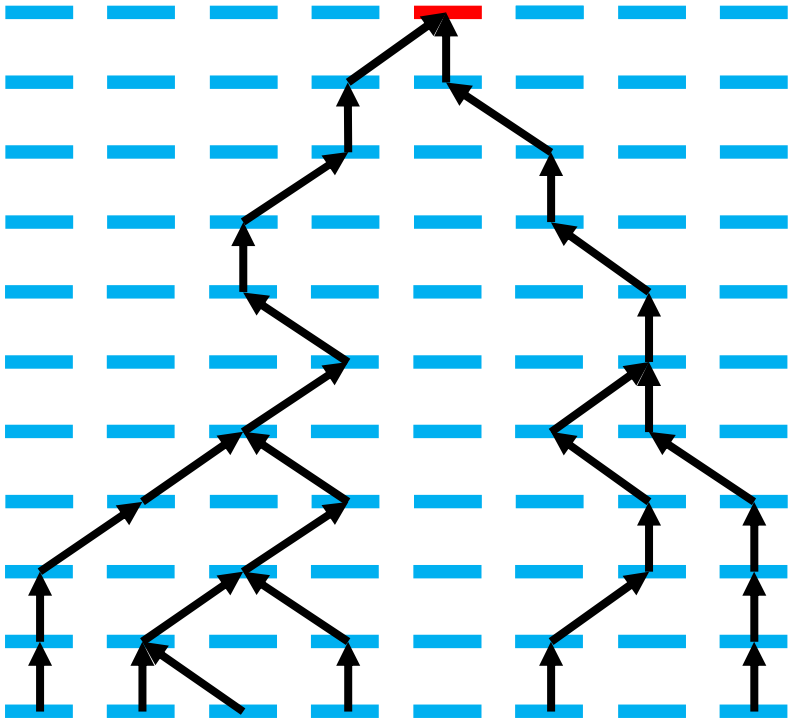
Let's not even talk about plankton!

Typically, as *N* is large we just model time as continuous

Any pair of lineages coalesces at rate 1/*2N*

Then while there are *j* lineages, there are $\binom{j}{2}$ pairs that can coalesce - so the rate at which a coalescence happens is just $\binom{j}{2}/2N$

[this leads to an exponential distribution of time until coalescence, with rate $\binom{j}{2}/2N$]

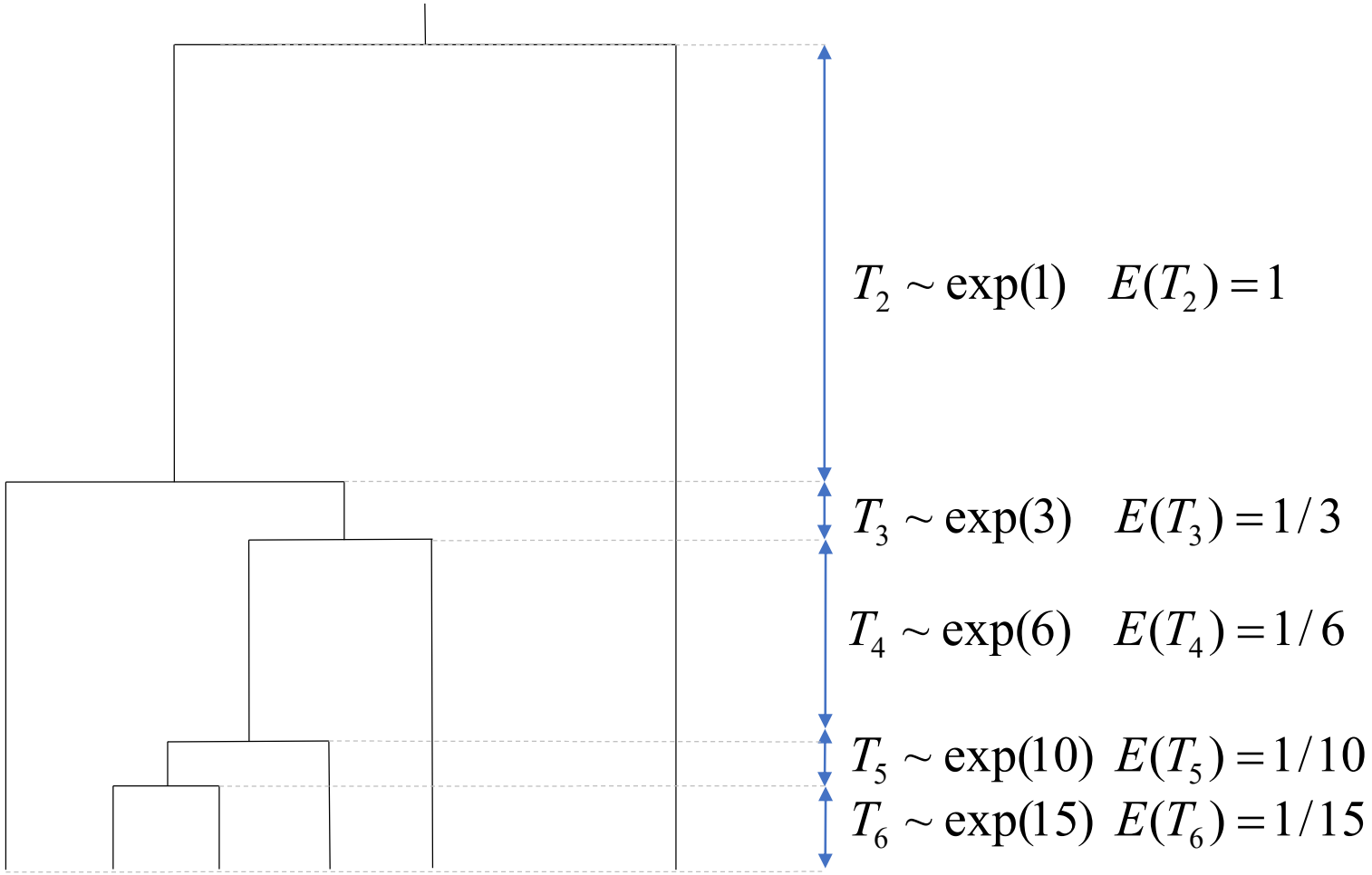


j=2, 1 pair

j=4, 6 pairs

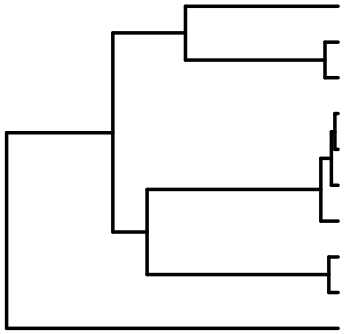
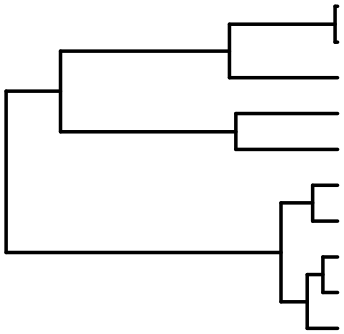
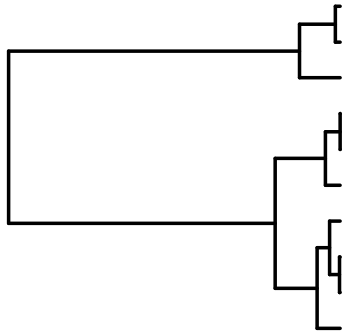
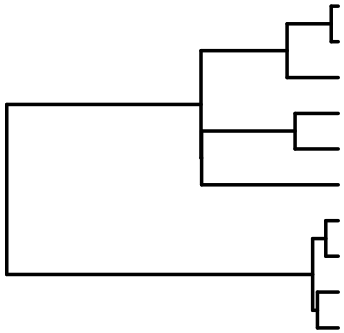
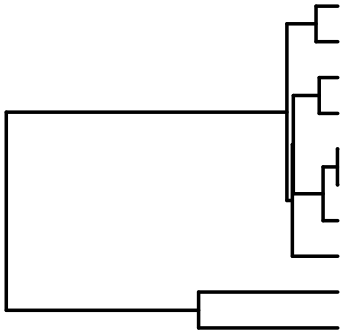
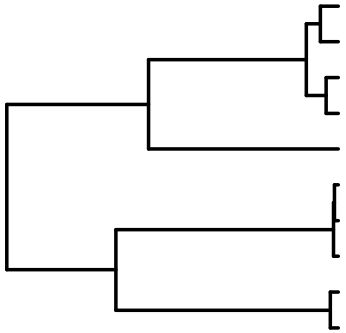
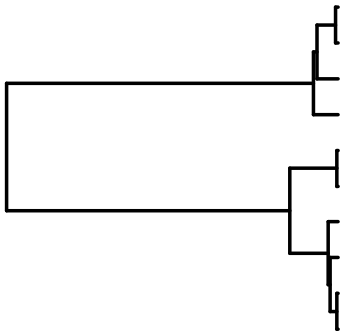
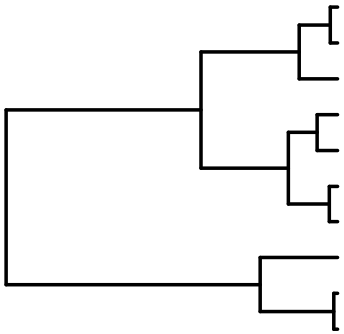
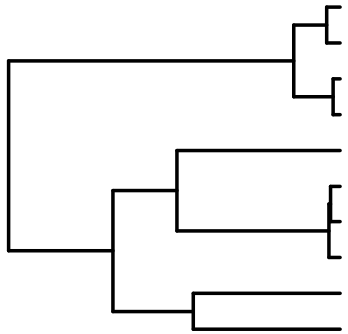
Sample of size *n*=6

We have come to a model – the Coalescent



n=6

(after scaling time by *M* generations)

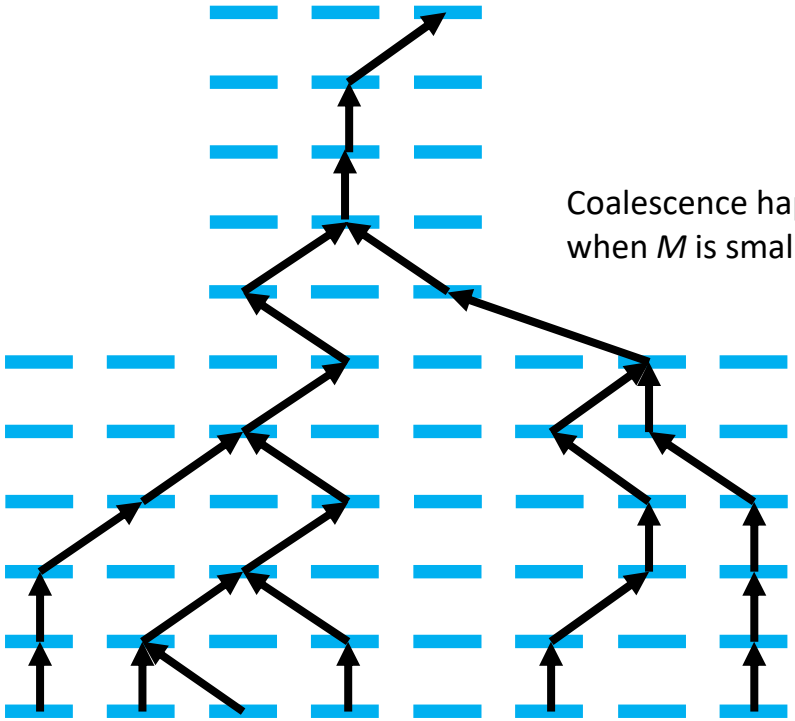










Varying population size

If N changes, so does the chance of coalescing

While there are *j* lineages, the rate at which a coalescence happens is just $\binom{j}{2}/2N(t)$ a time *t* ago

Shapes of trees can tell us about *N*(*t*)

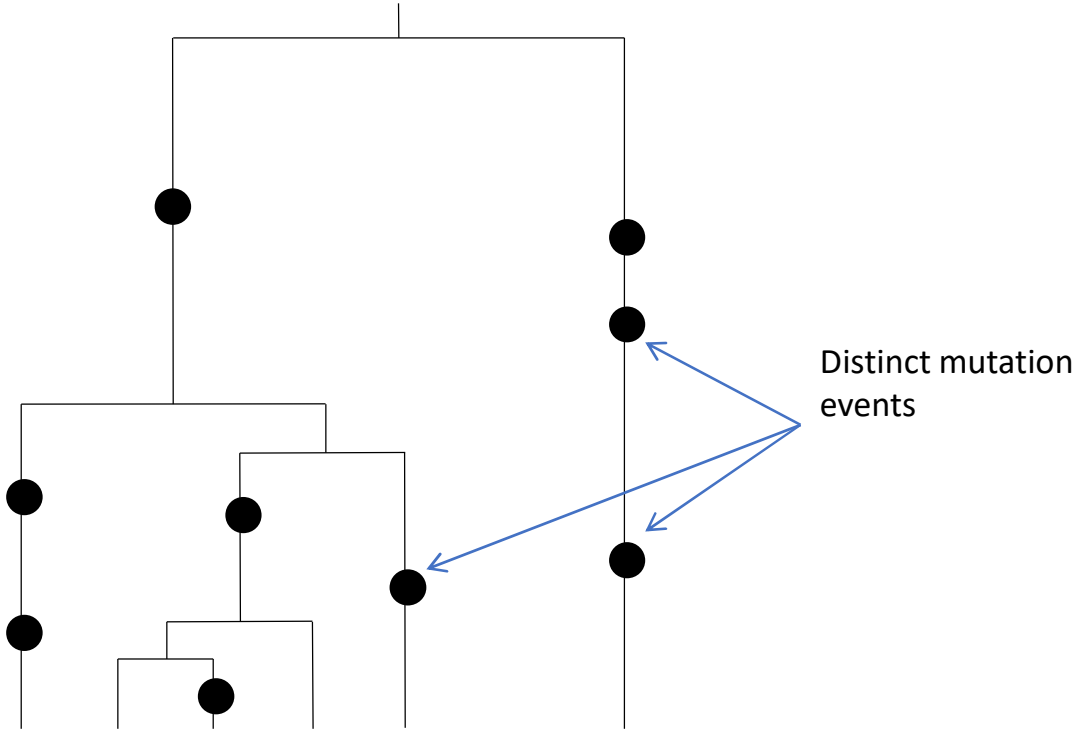


Coalescence happens faster when *M* is small

j=4

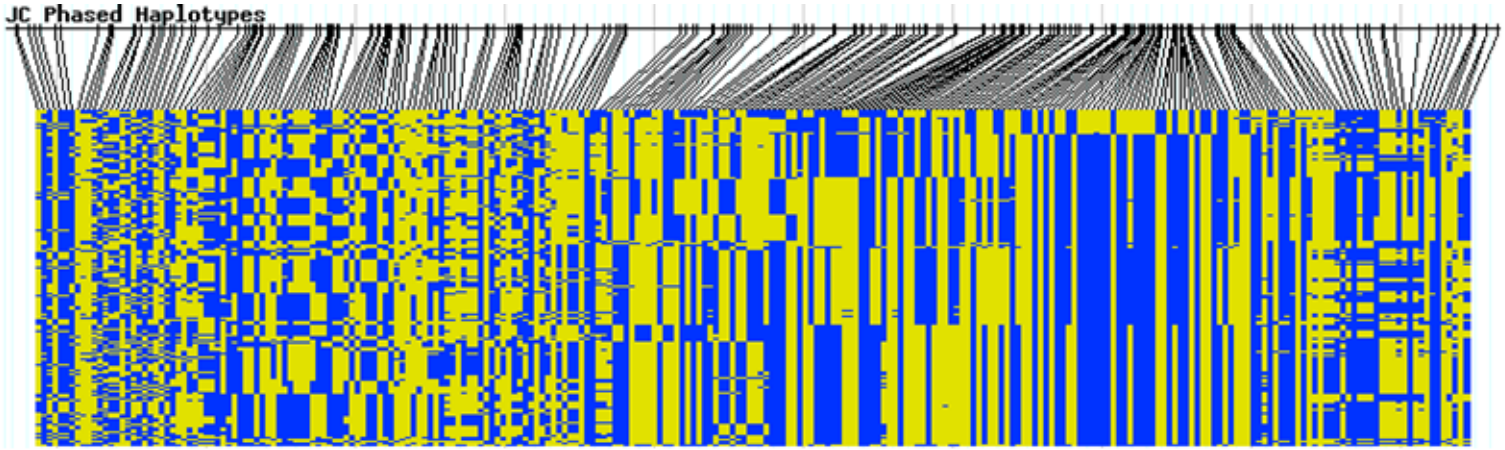
Sample of size *n*=6

Adding mutation to the mix

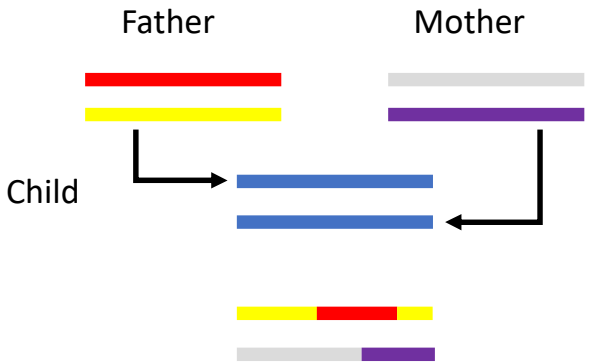


- Mutations are dropped randomly on the edges of the tree (e.g. in many simulation software packages)
- They are seen in descendants of this edge, so this totally specifies diversity patterns
- We will talk about some theory results about spread of mutations in the coalescent later

What about recombination?



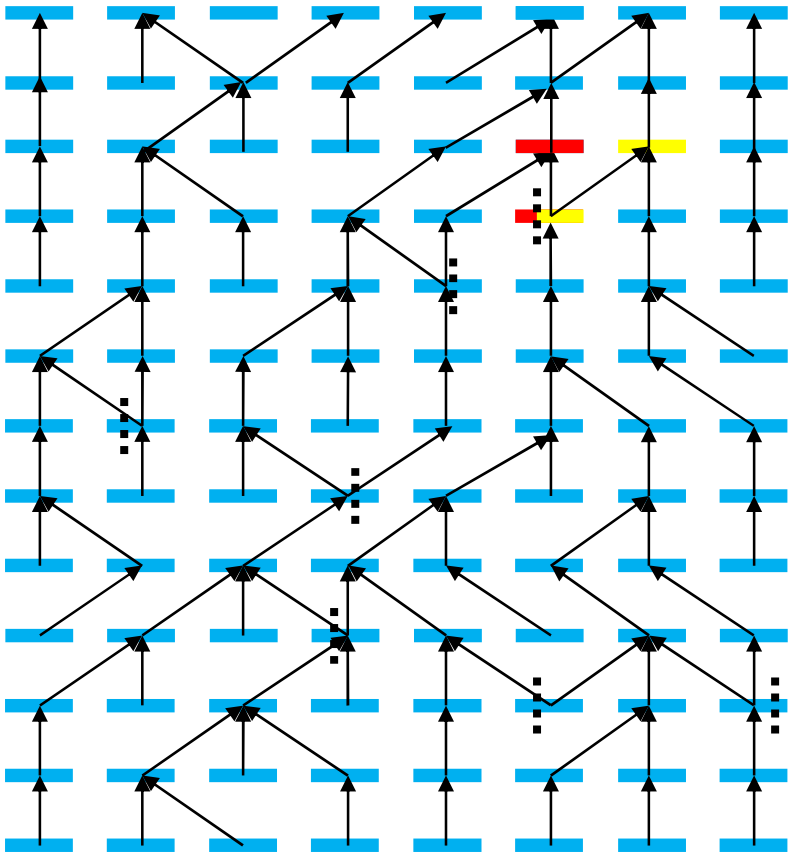
- Unlike mutation, recombination events actually **change the trees**



- One piece of DNA can be inherited from **two** different parental chromosomes, as a mosaic

Principles of adding recombination to the coalescent

In the Wright-Fisher model, if recombination occurs then a chromosomal segment has two parents



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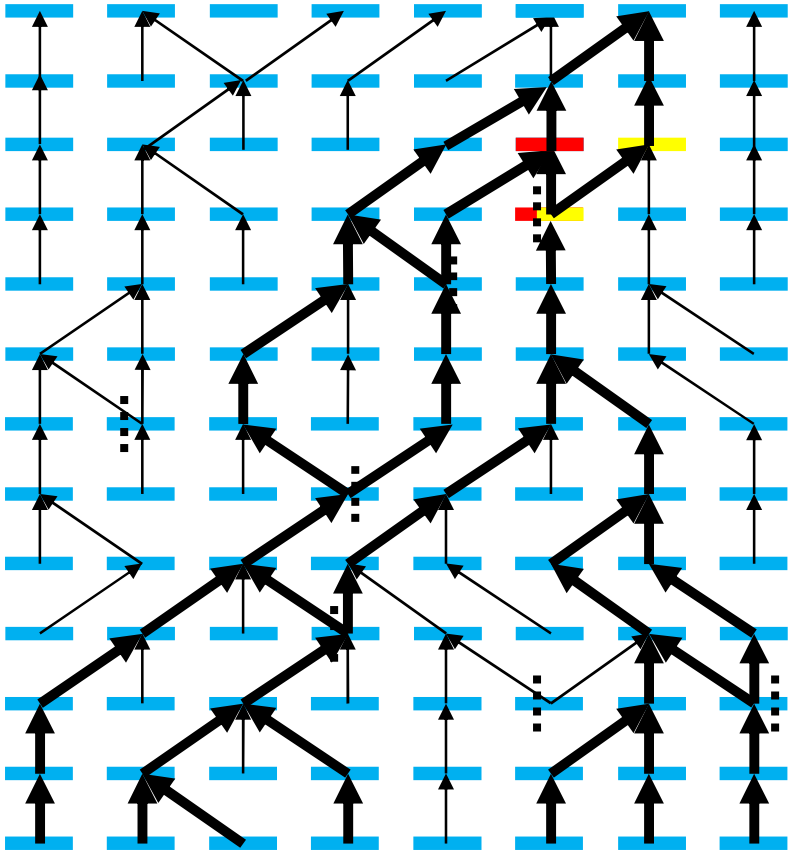
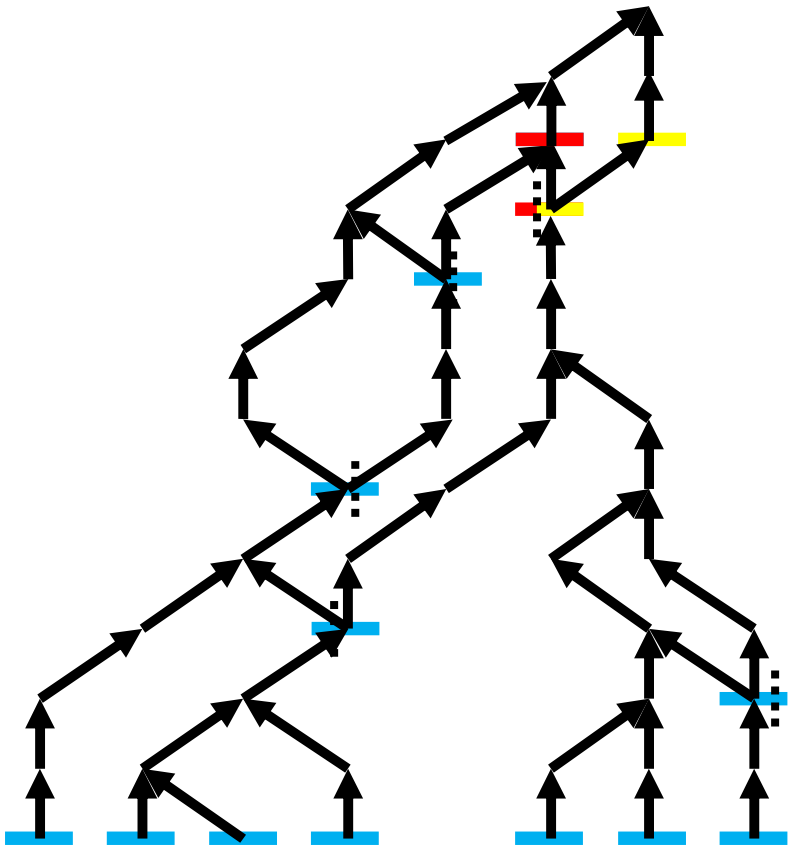
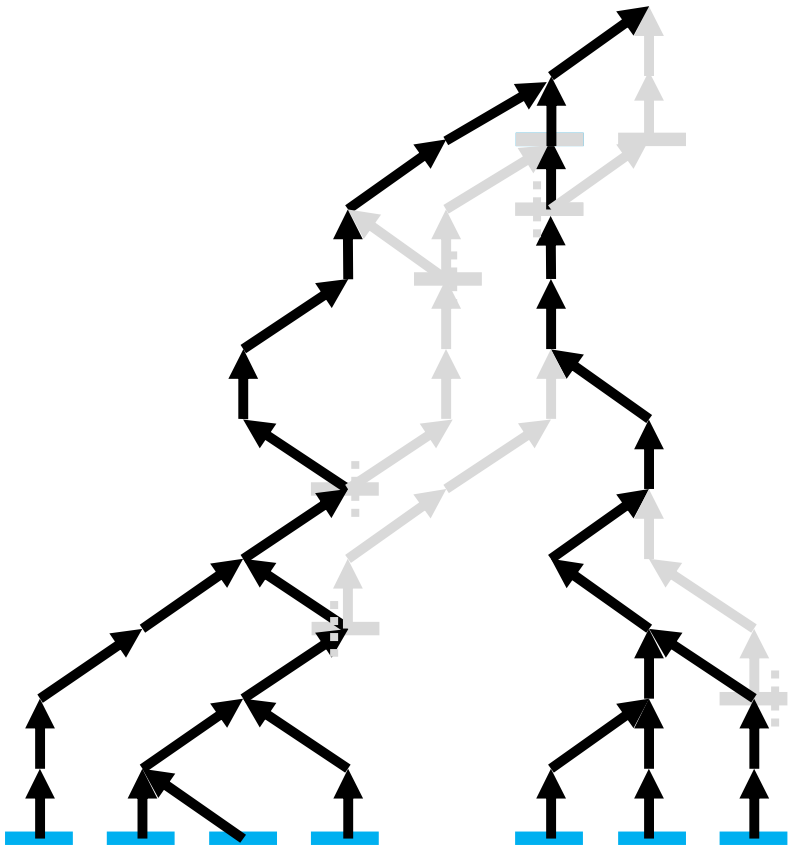


The ancestral recombination graph



The tree at the left-most position in the region

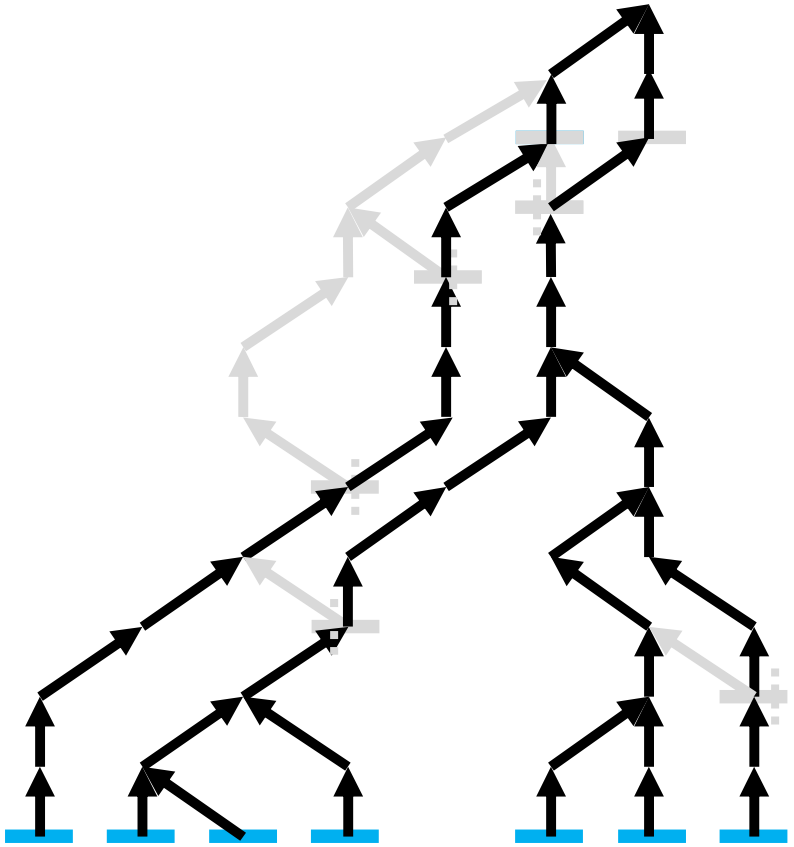
A small piece of DNA is not impacted by recombination, so the coalescent model still applies – with the same rates as usual



The tree at the right-most position in the region

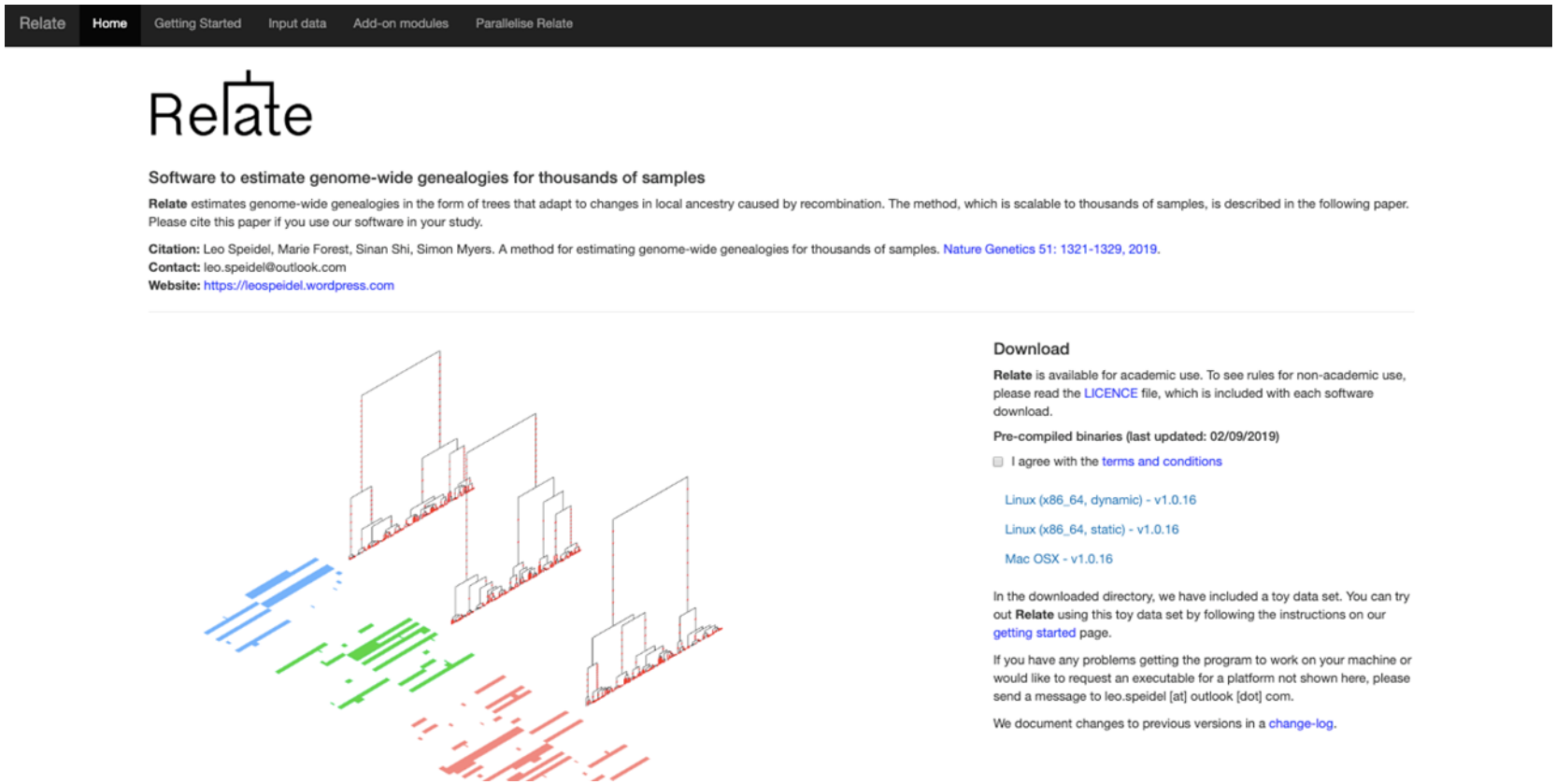
A small piece of DNA is not impacted by recombination, so the coalescent model still applies

The bases of the trees have less recombination so are more similar than the tops



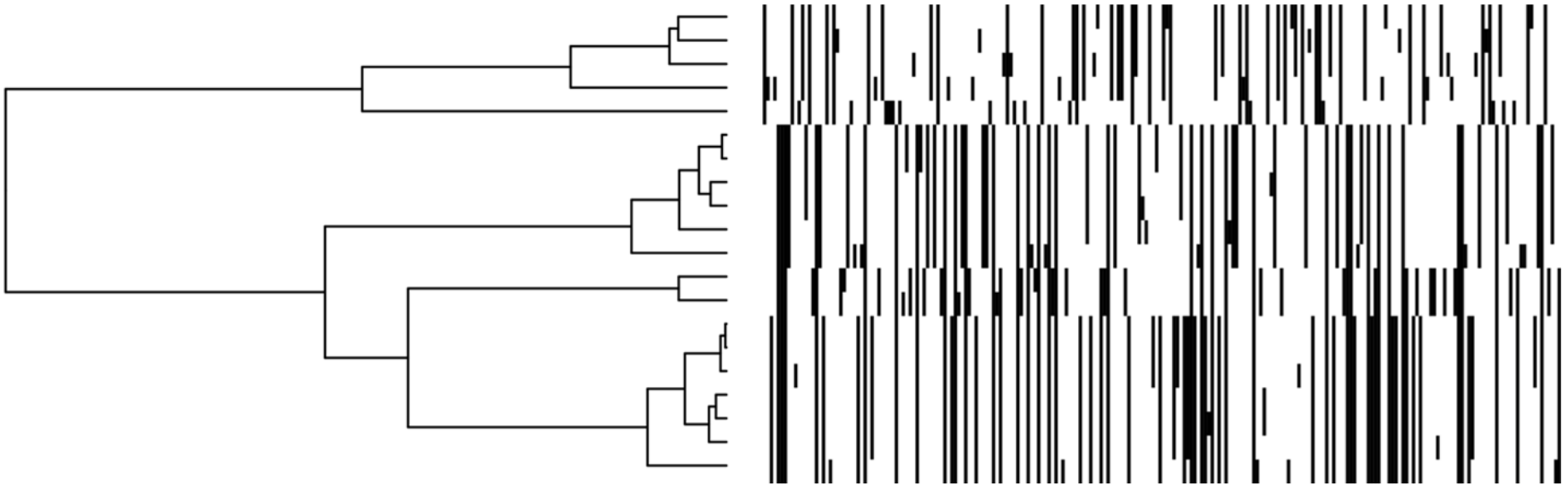
Building trees under this model – approximately – with Relate

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



L. Speidel, M. Forest, S. Shi, S. Myers. Nature Genetics 2019

Data, and the underlying tree structure



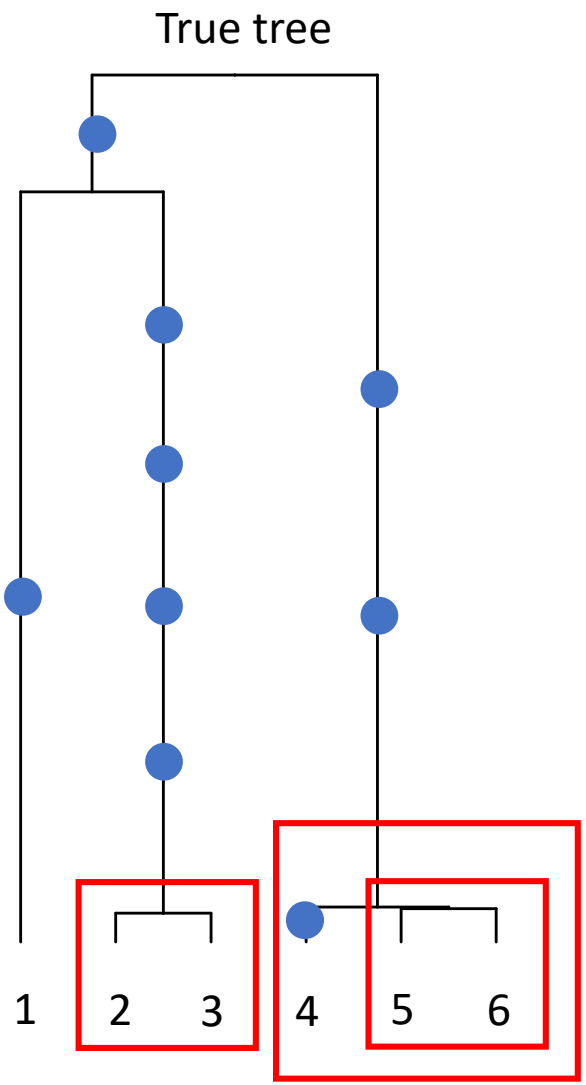
- This is a simulation without (for now) recombination
- Every mutation occurs only once on the tree….so
- **Every mutation shows the existence of a branch, suggesting we can build the tree given enough mutations**
- **Given the tree, we can uniquely map each mutation to its branch**

A basic tree-builder: UPGMA

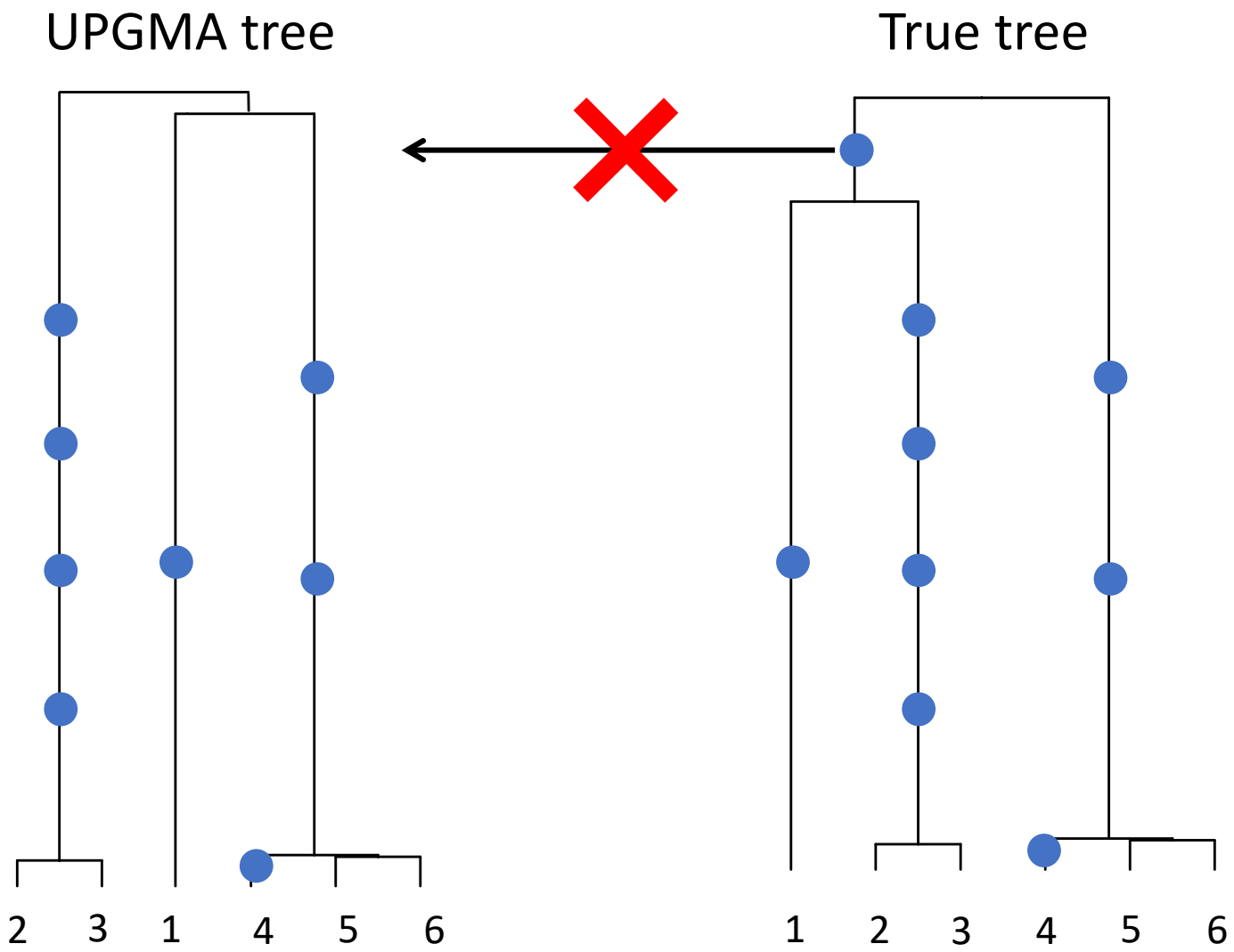
- We are confronted with variation data – how do we build a tree?
- UPGMA coalesces lineages with smallest number of (averaged) pairwise differences
- (2,3) and (5,6) are coalesced first
- (5,6) and 4 are coalesced

- Now, pairwise difference of
  1 and (2,3) is 5
  1 and (5,6) is 4
  1 and 4 is 5

→ 1 and (4,5,6) are coalesced next!



UPGMA tree cannot be correct, given the data



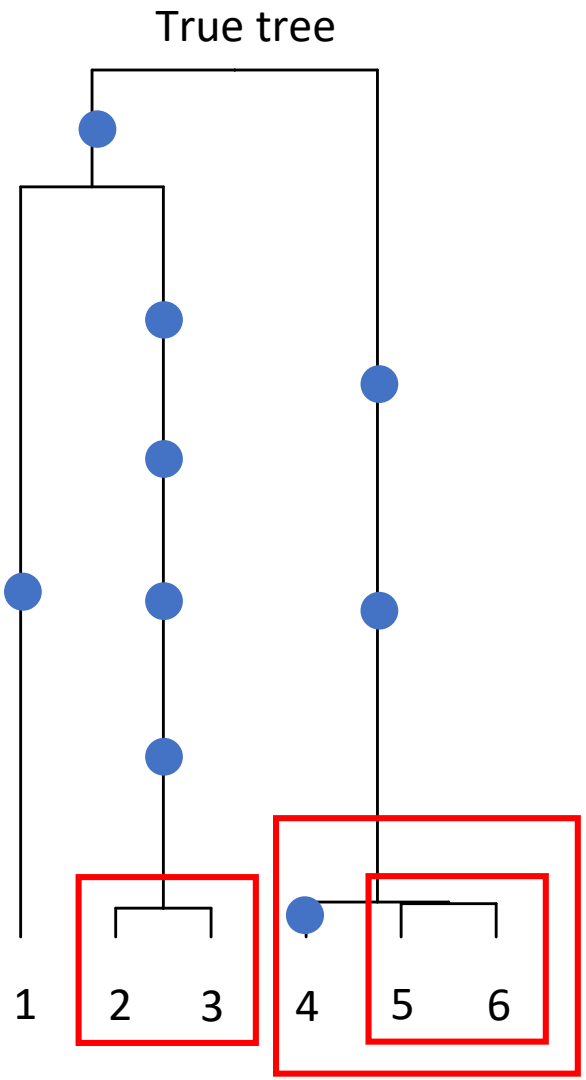
The UPGMA tree cannot be correct, because it does not include any branch whose descendants are sequences 1,2,3. How can we fix this?

Towards Relate: counting **derived** mutations to build the correct tree

relative to

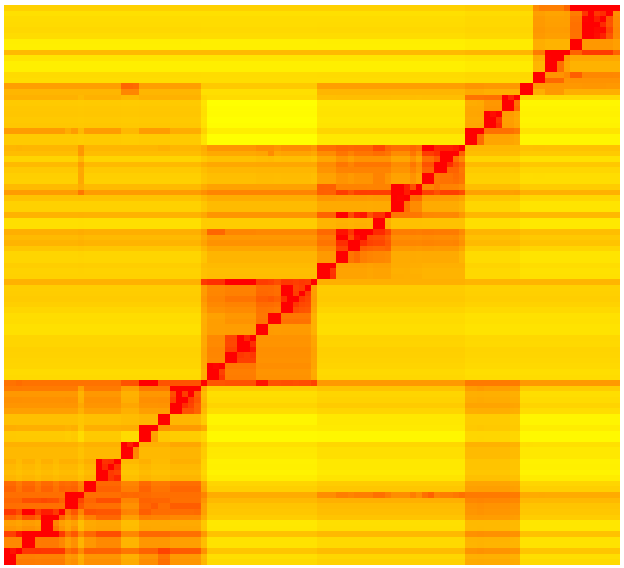
Mutation carrier	1	(2,3)	(4,5,6)
1	0	1	2
(2,3)	4	0	5
(4,5,6)	2	2	0

Avoids adding information of two branches!



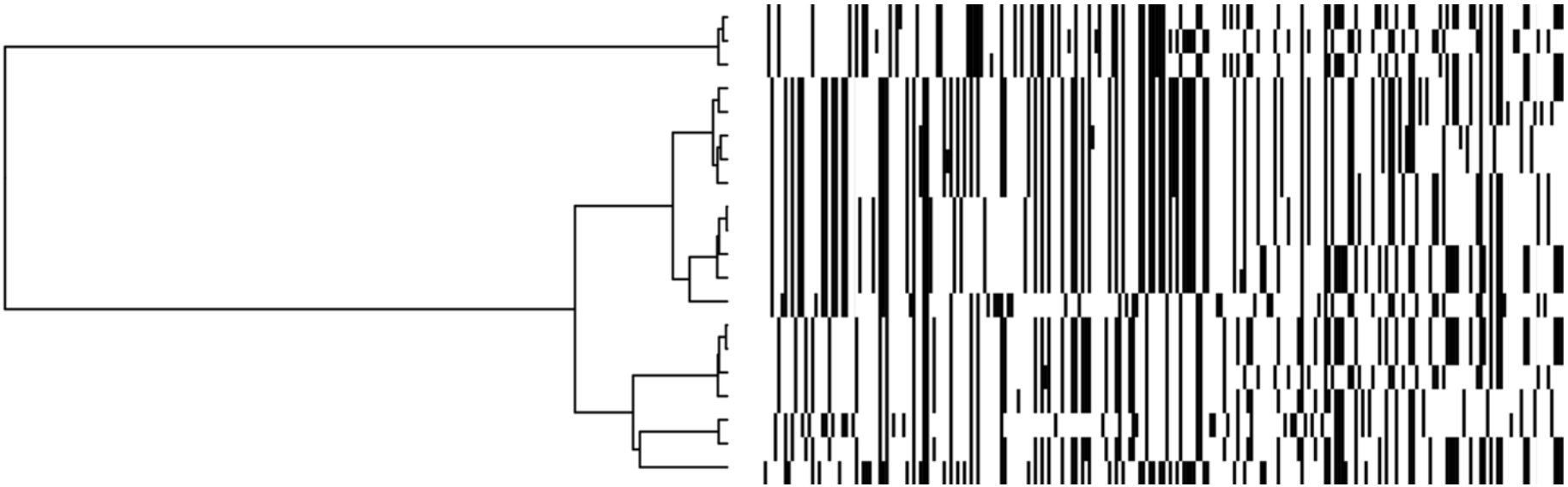
How does Relate work?

- In the **no-recombination** case, it first counts numbers of derived mutations for each pair:



- Performs coalescences between mutually most similar lineages
- Guaranteed to produce a tree matching the data!
- First builds a tree structure/topology (times are deferred for now)

Accounting for recombination

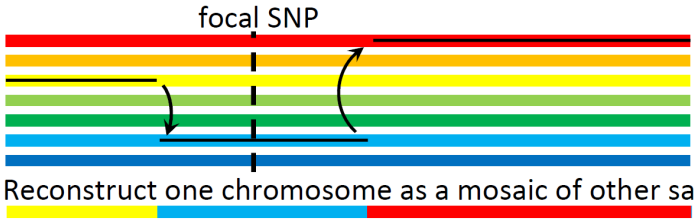


- Recombination means pairs of sequences are most similar for only **stretches of DNA**
- Use a HMM to (intuitively) identify these stretches, count derived mutations only within them, then proceed as for no-recombination case
- More formally, we use a modified version of Li+Stephens (Genetics, 2003) where we count differences

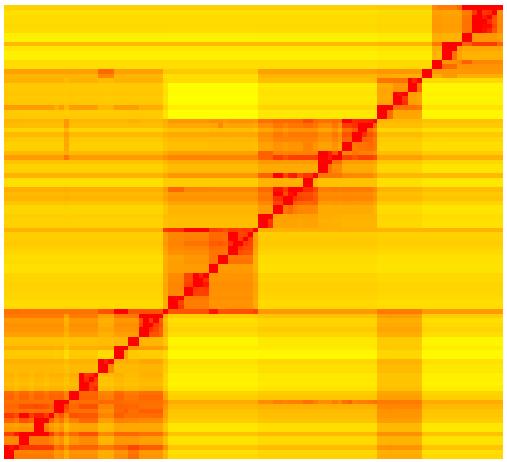
Summary of Relate pipeline

Hidden Markov model (HMM)

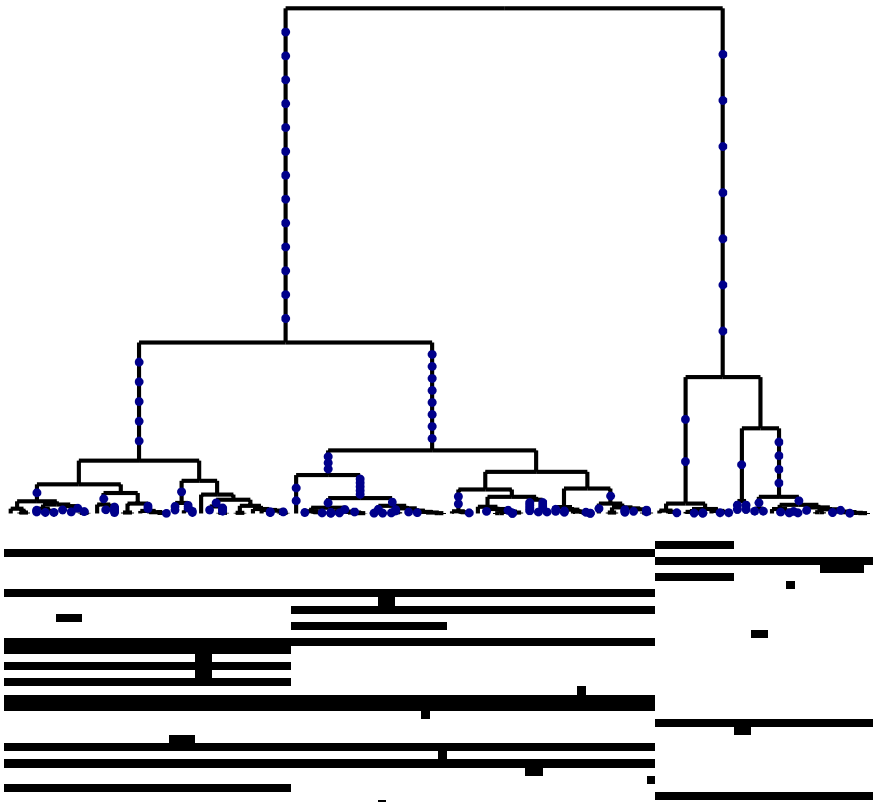
Li and Stephens, Genetics, 2003; Lawson et al., PLOS Genetics, 2012



Distance matrix for focal SNP



Hierarchical clustering
&
MCMC for branch lengths



haplotype data sorted using constructed tree

Coffee break!

After the break: branch lengths, variable population sizes, and applications of Relate

Branch lengths and population size are estimated jointly in an EM algorithm

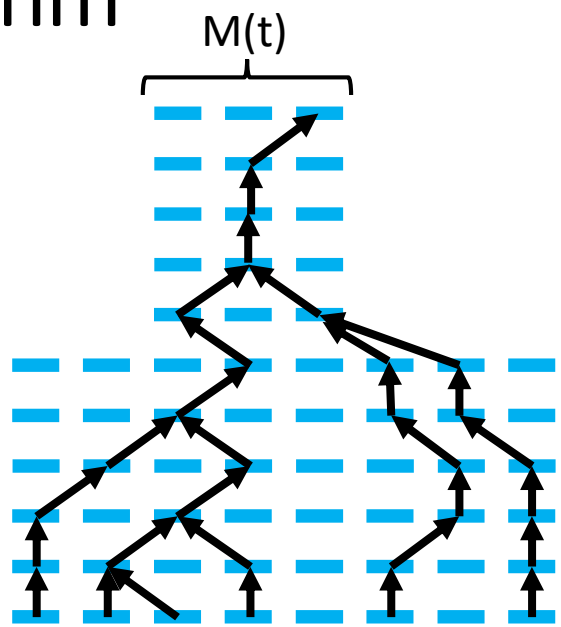
- Expected branch lengths depend on population size $N(t)$

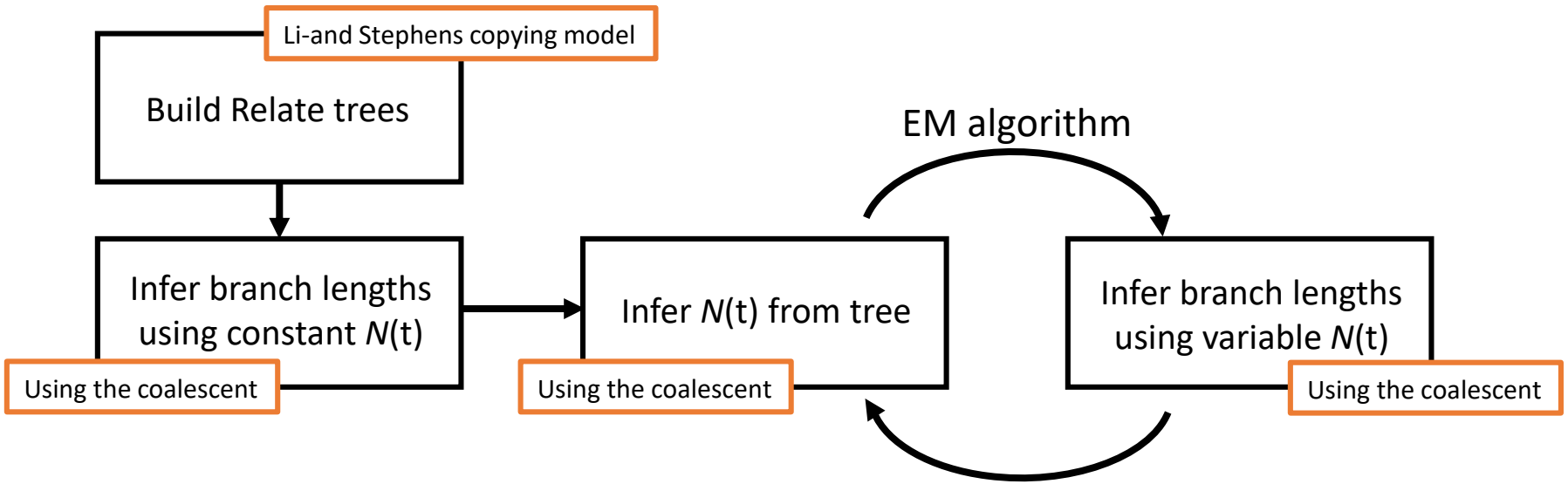
  (or coalescence rates $1/2N(t)$)

- While there are j lineages, the rate at which a coalescence happens is $\binom{j}{2}/2N(t)$ a time t ago

- Demography is shared genome-wide, so we average across trees

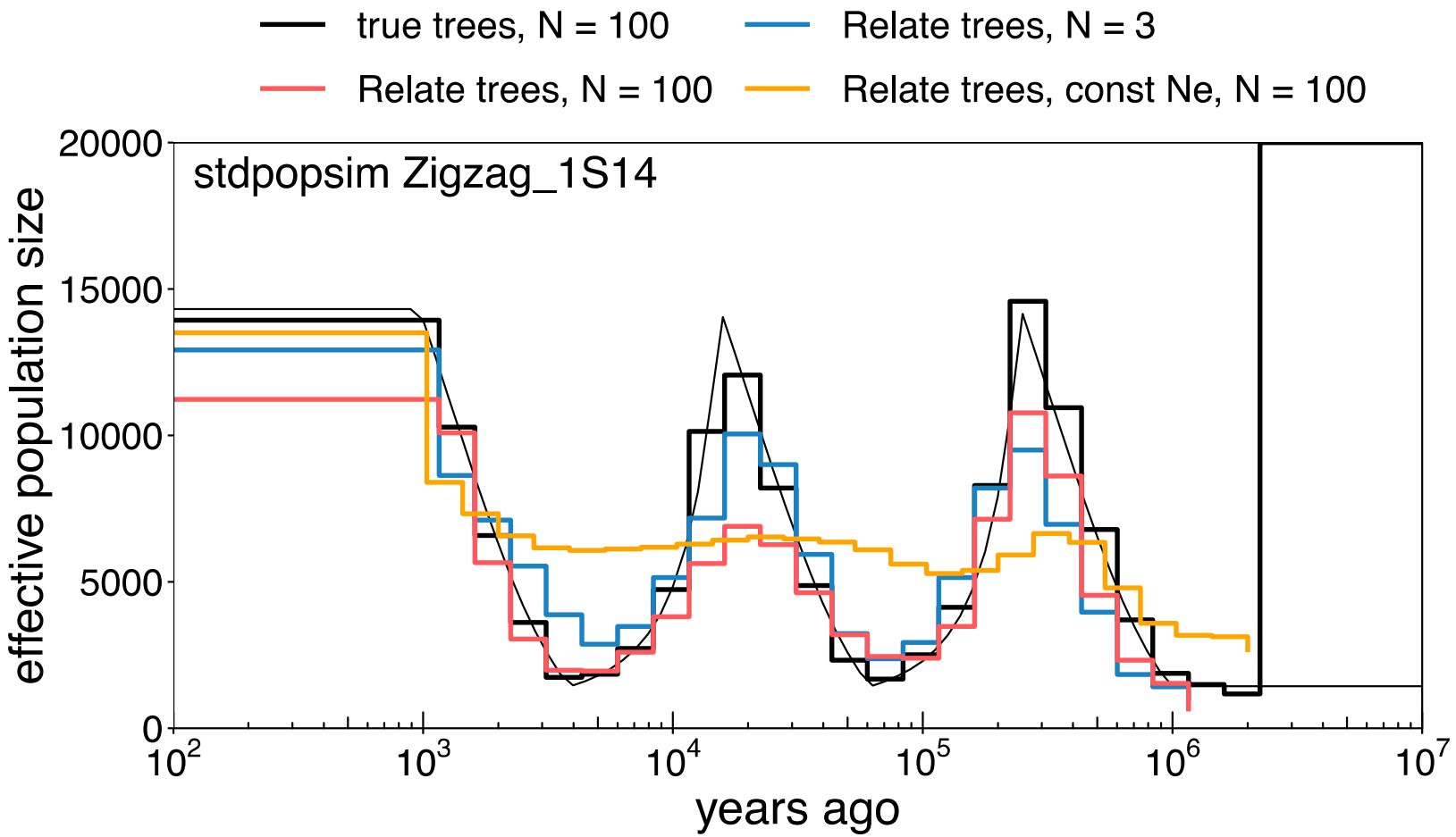
- So within a time interval, scaled fraction of trees where coalescence occurs is inversely proportional to $N(t)$





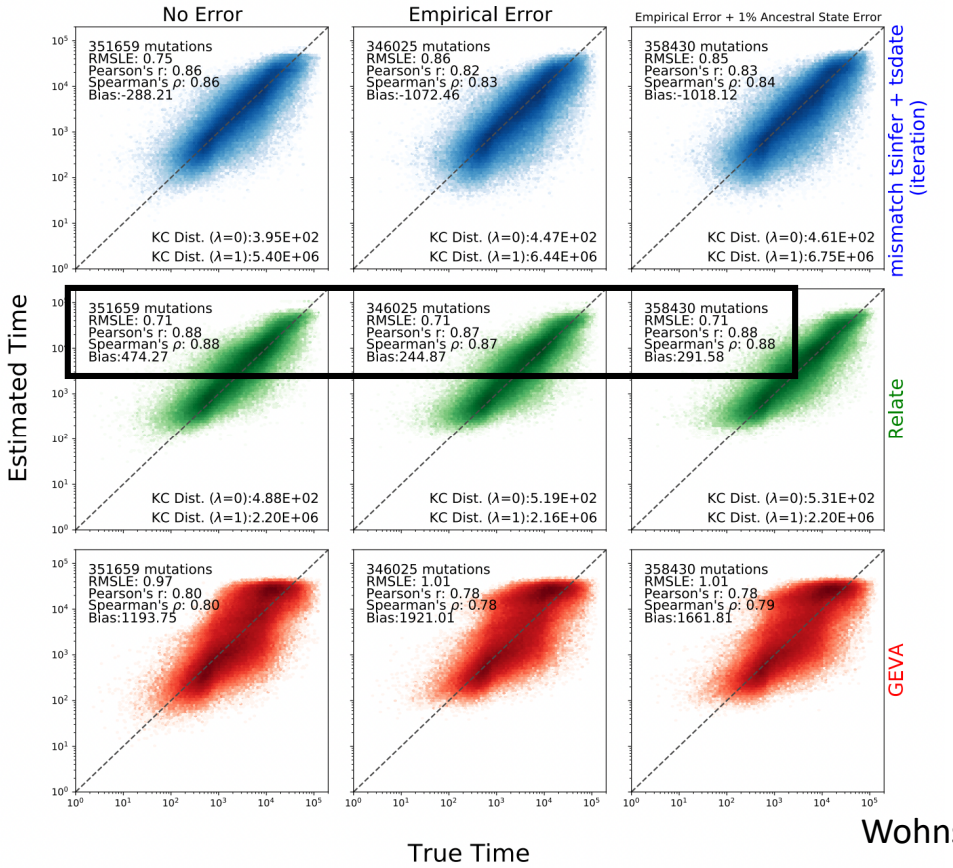
Simulation: population size changes through time

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



Speed and accuracy of Relate

- About 14,000 times faster than previous method, ARGWEAVER (1 min. vs. 200 hours), slower than tsinfer + tsdate
- Builds “correct” tree if no recombination
- Accurate, robust to data errors
- Can sample posterior branch lengths



Wohns et al. Science 2022

Example I: 1000 Genomes Project data:

- 4956 haplotypes from 26 populations
- ~71,000,000 biallelic SNPs
- ~93% of SNPs map uniquely to a tree (80% for CpG mutations due to repeat mutations)

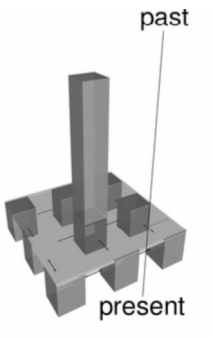
Run time: ~4 days on 300 cores

Genealogy-based inference of human evolutionary history

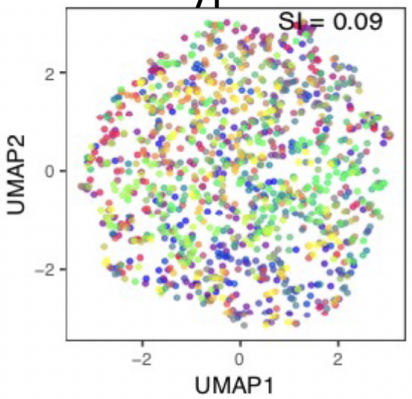
One reconstruction of history, many applications that are **self consistent**

Inferring fine-scale population structure and how it changed through time

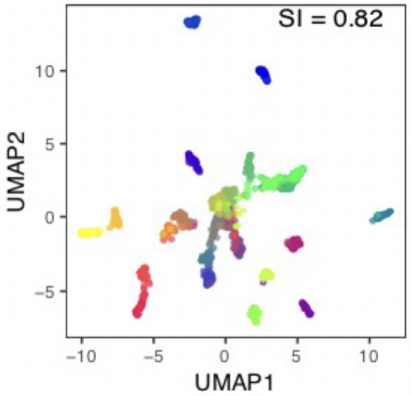
Fan, Mancuso, Chiang, bioRxiv, 2021



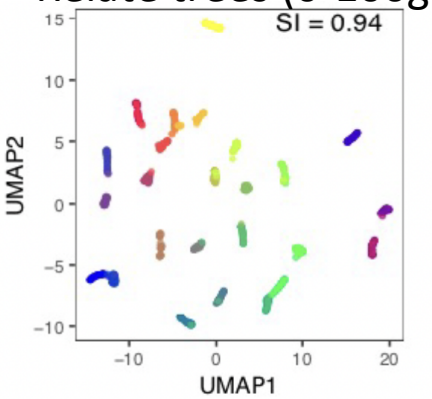
Genotype matrix

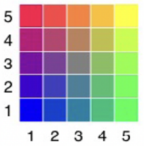


Relate trees

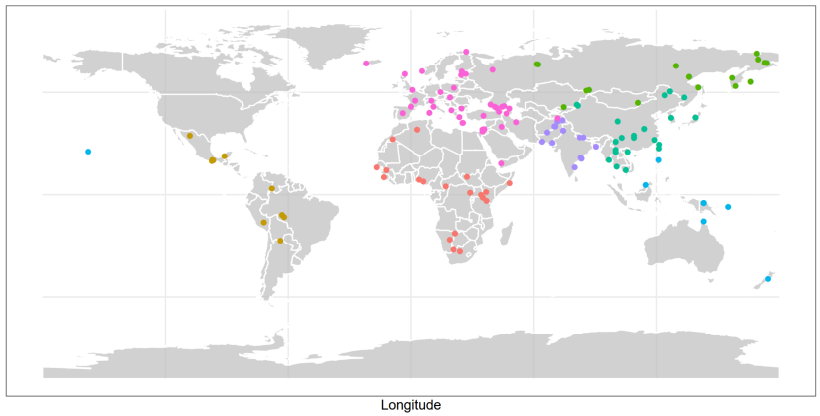


Relate trees (0-100gen)

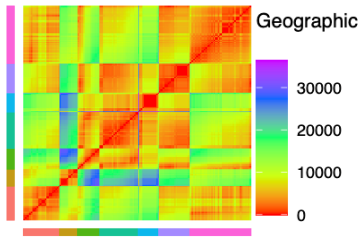


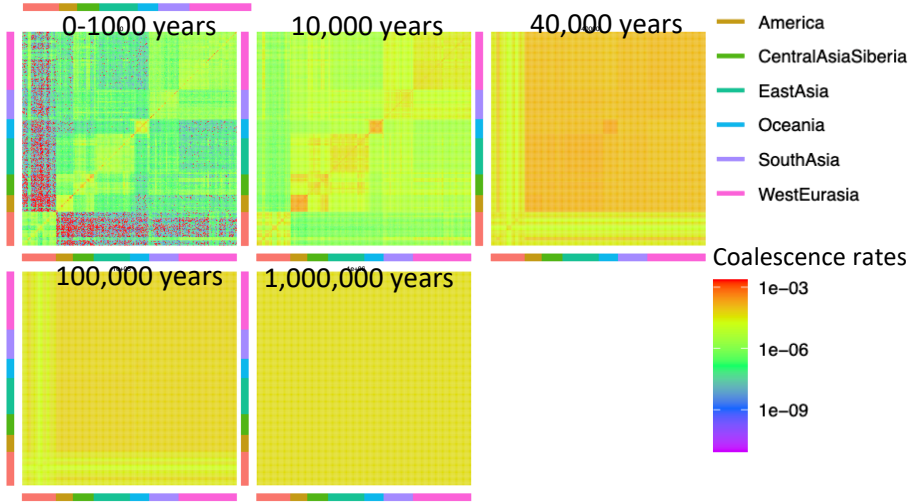


Simons Genome Diversity Project

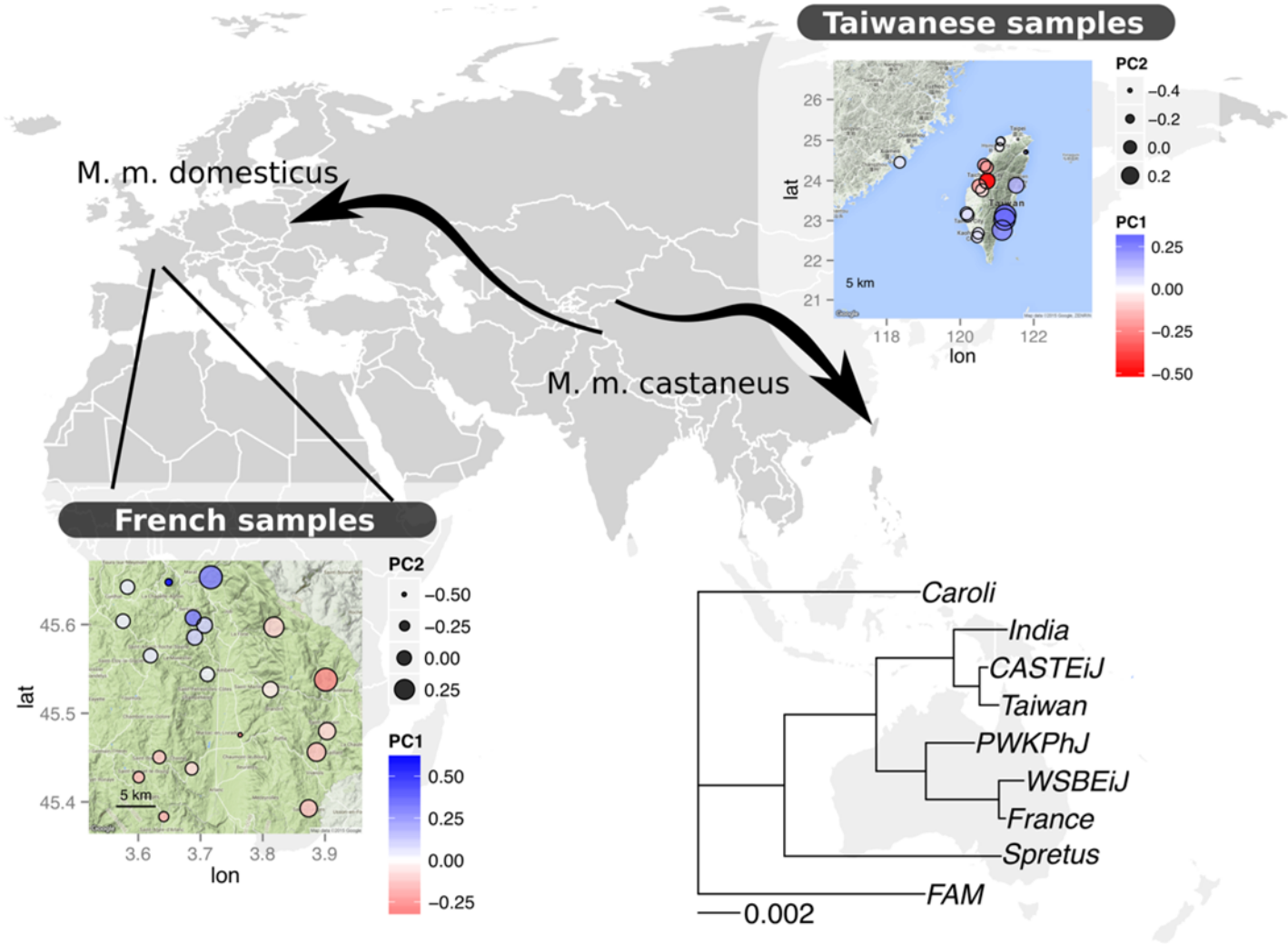


Speidel et al, MBE, 2021



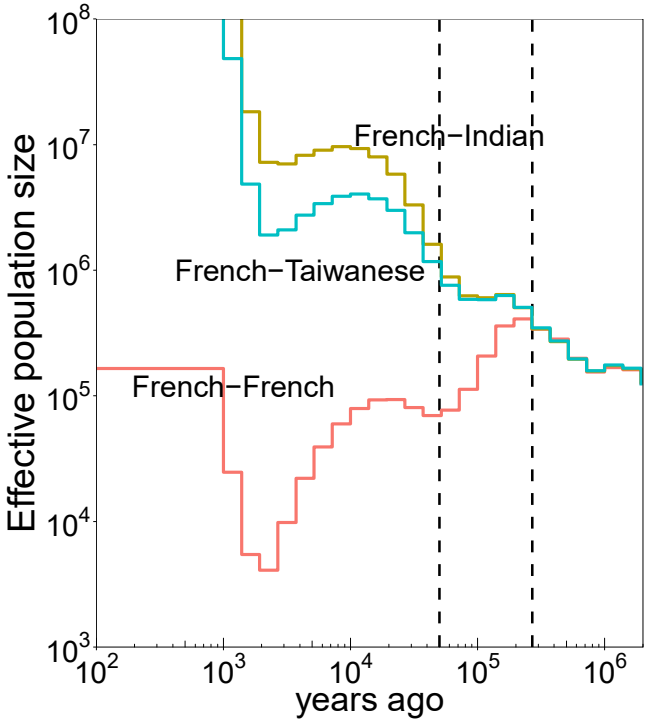


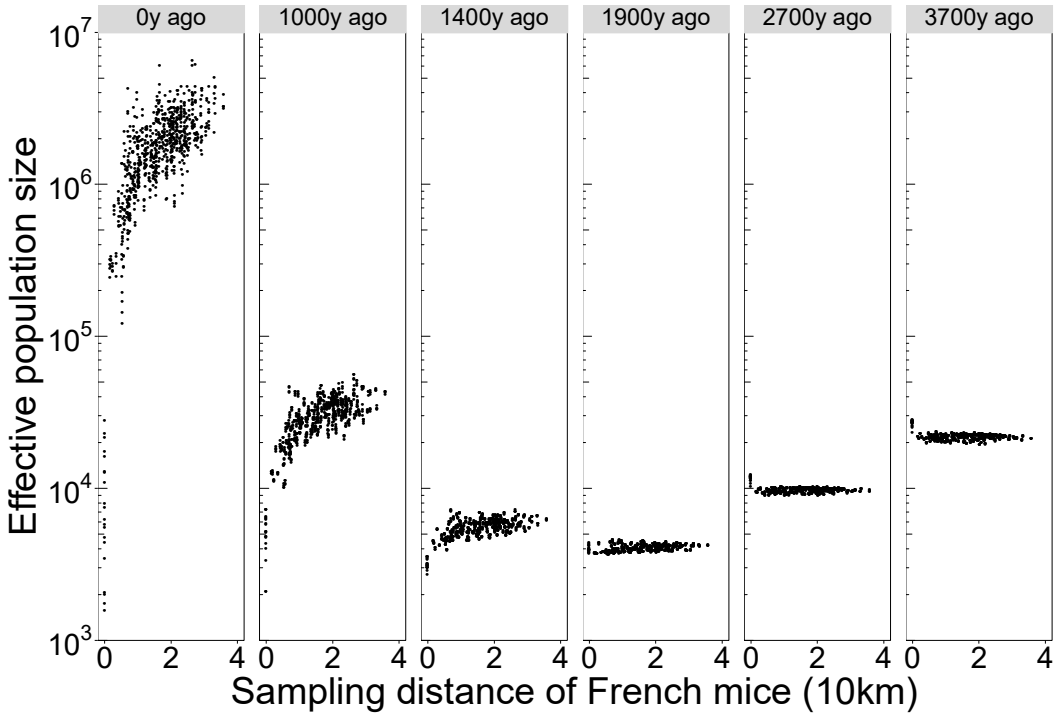
Relate applied to 50 wild mice sampled in India, Taiwan, and France



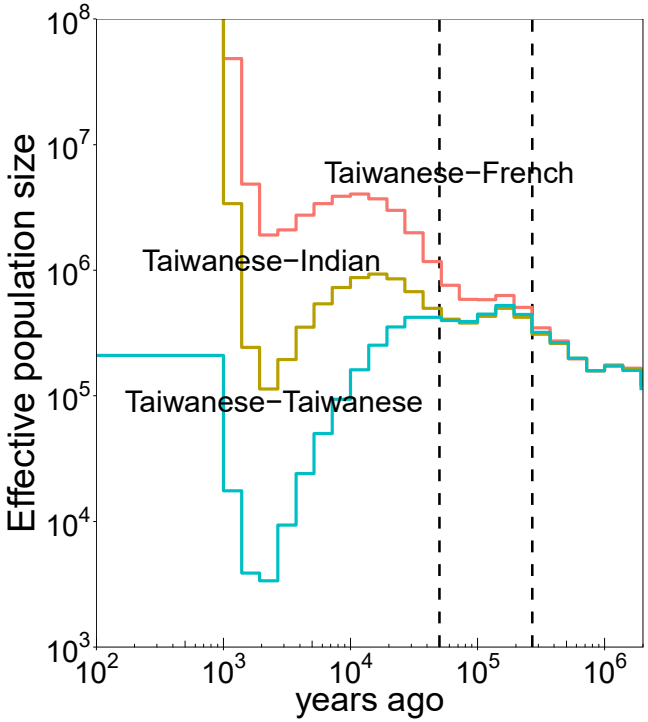
Runtime: 17 CPU hours for 19 chromosomes, Memory usage < 2.5 Gb

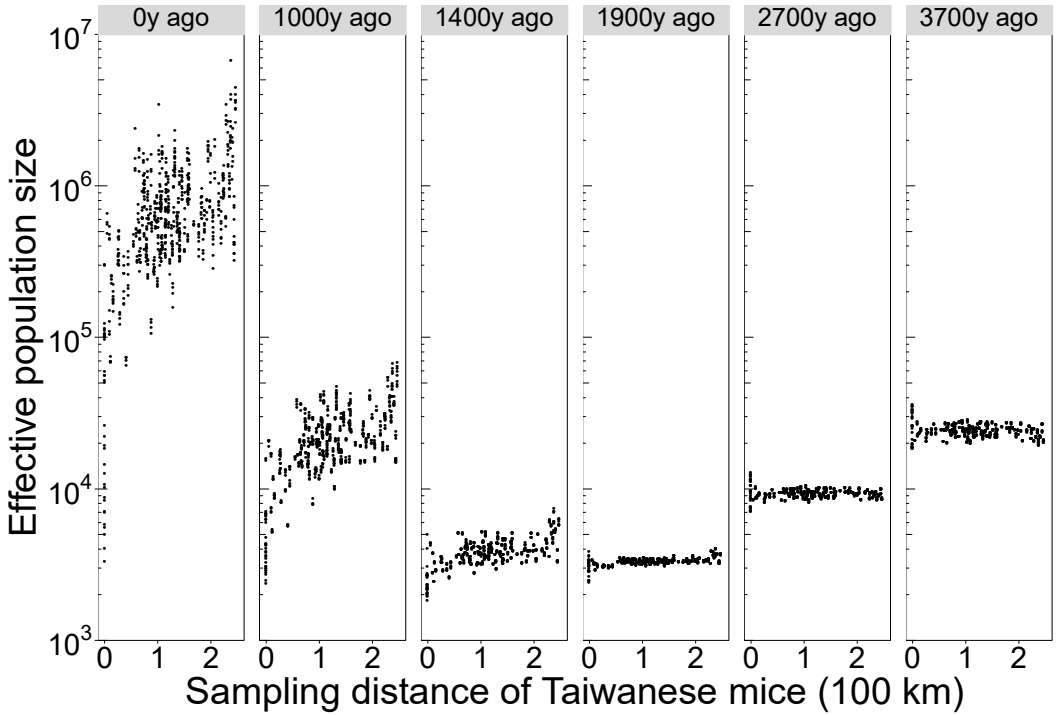
Population structure through time in French mice





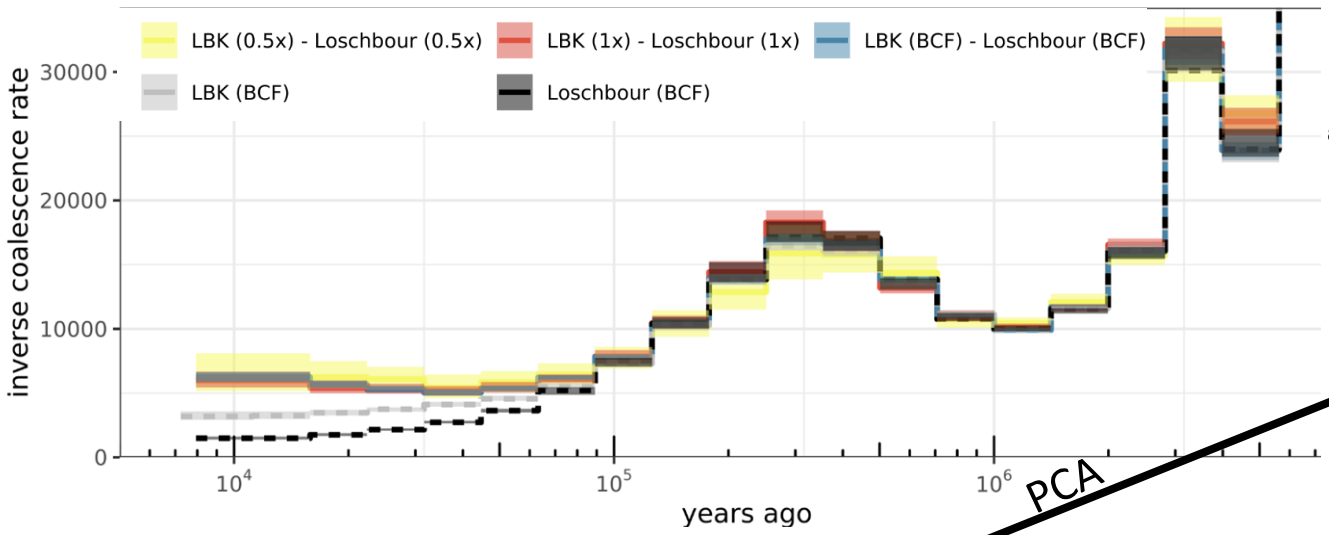
Population structure through time in Taiwanese mice

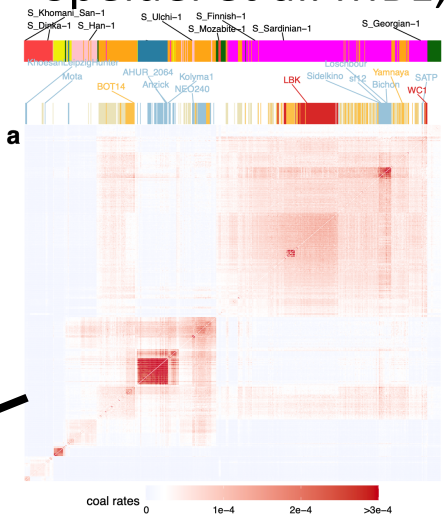




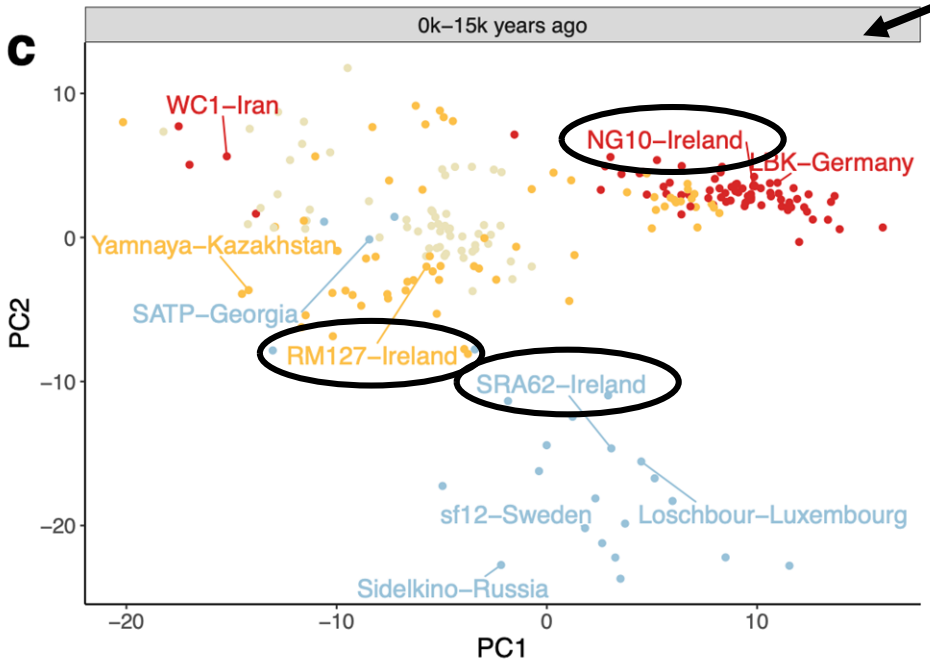
Colate: Inferring coalescence rates for low-coverage, unphased (ancient) genomes

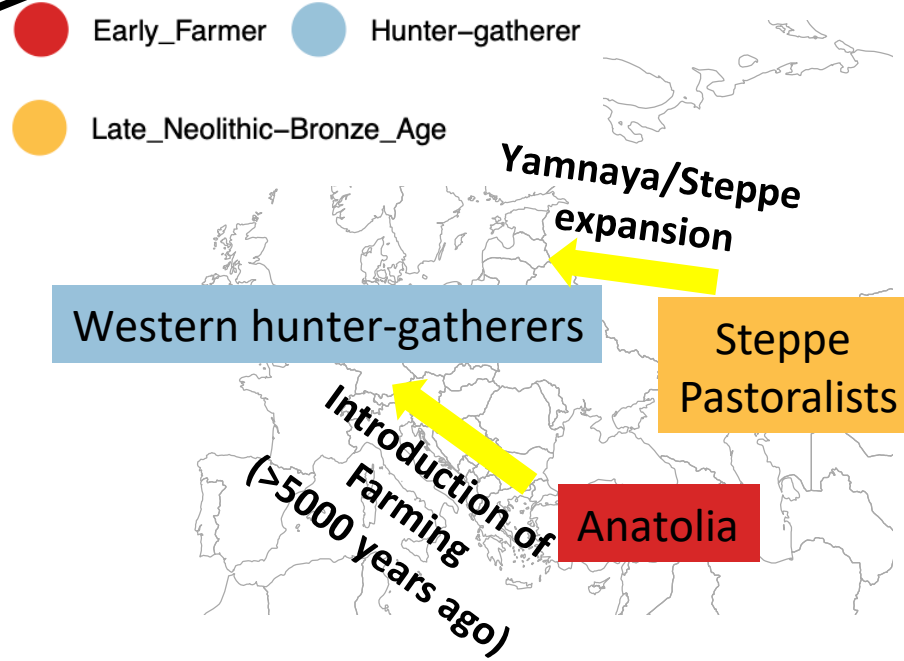
Speidel et al. MBE, 2021



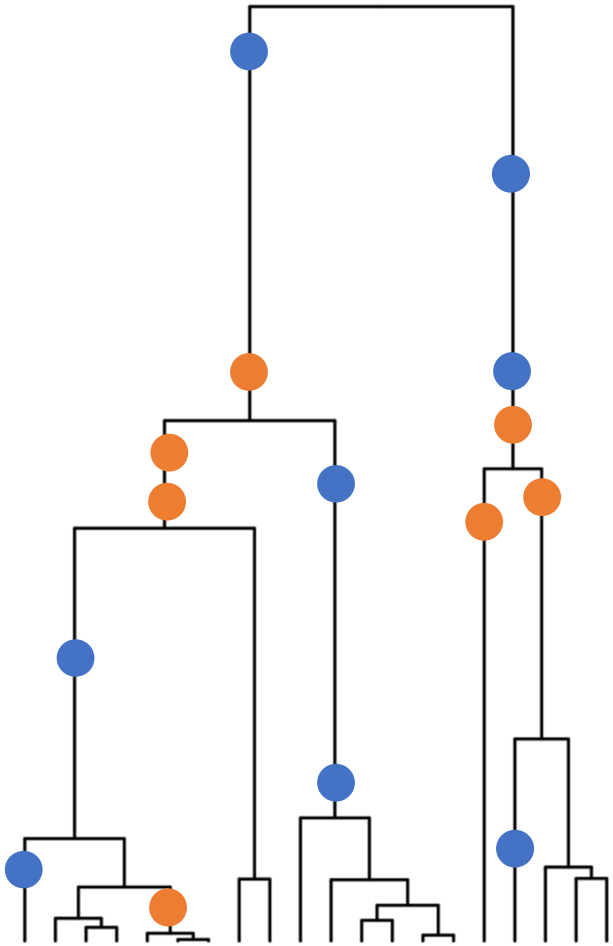


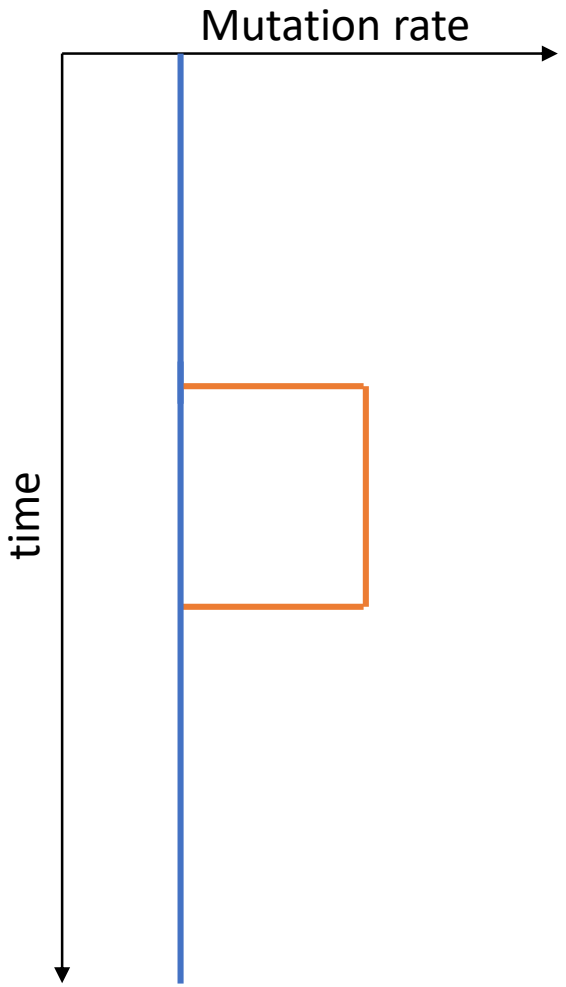
PCA





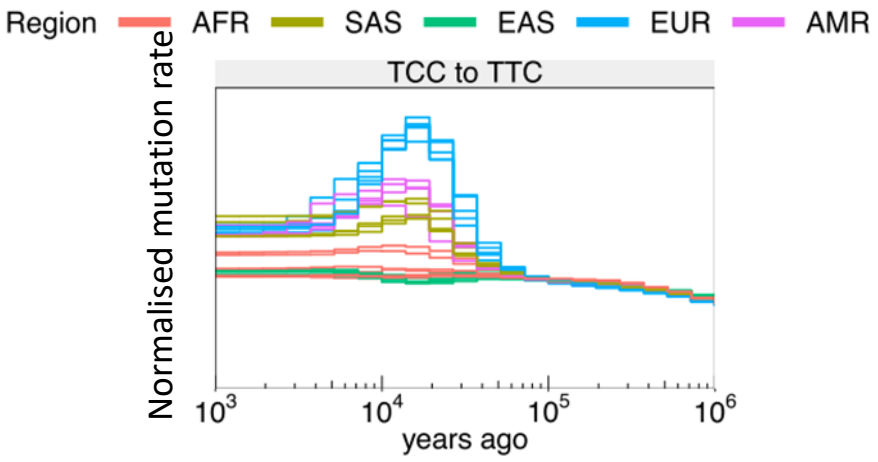
Reminder: Clusters of mutations in time can capture changes in mutation rate

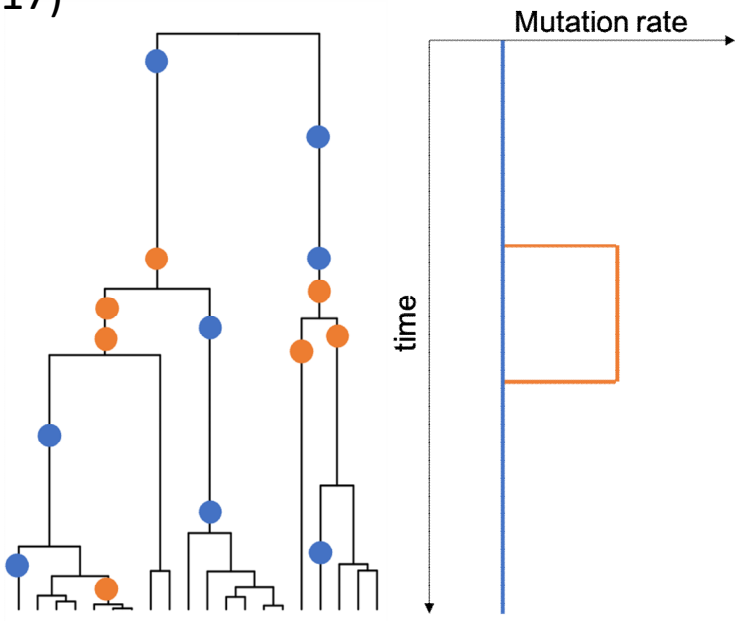




TCC/TTC mutation rates experienced a strong increase in the Upper Paleolithic

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

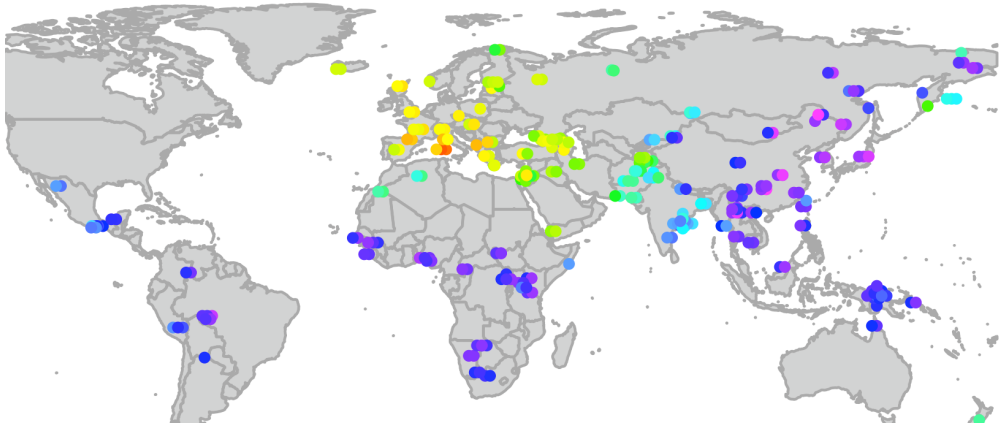




Speidel, Nature Genetics, 2019

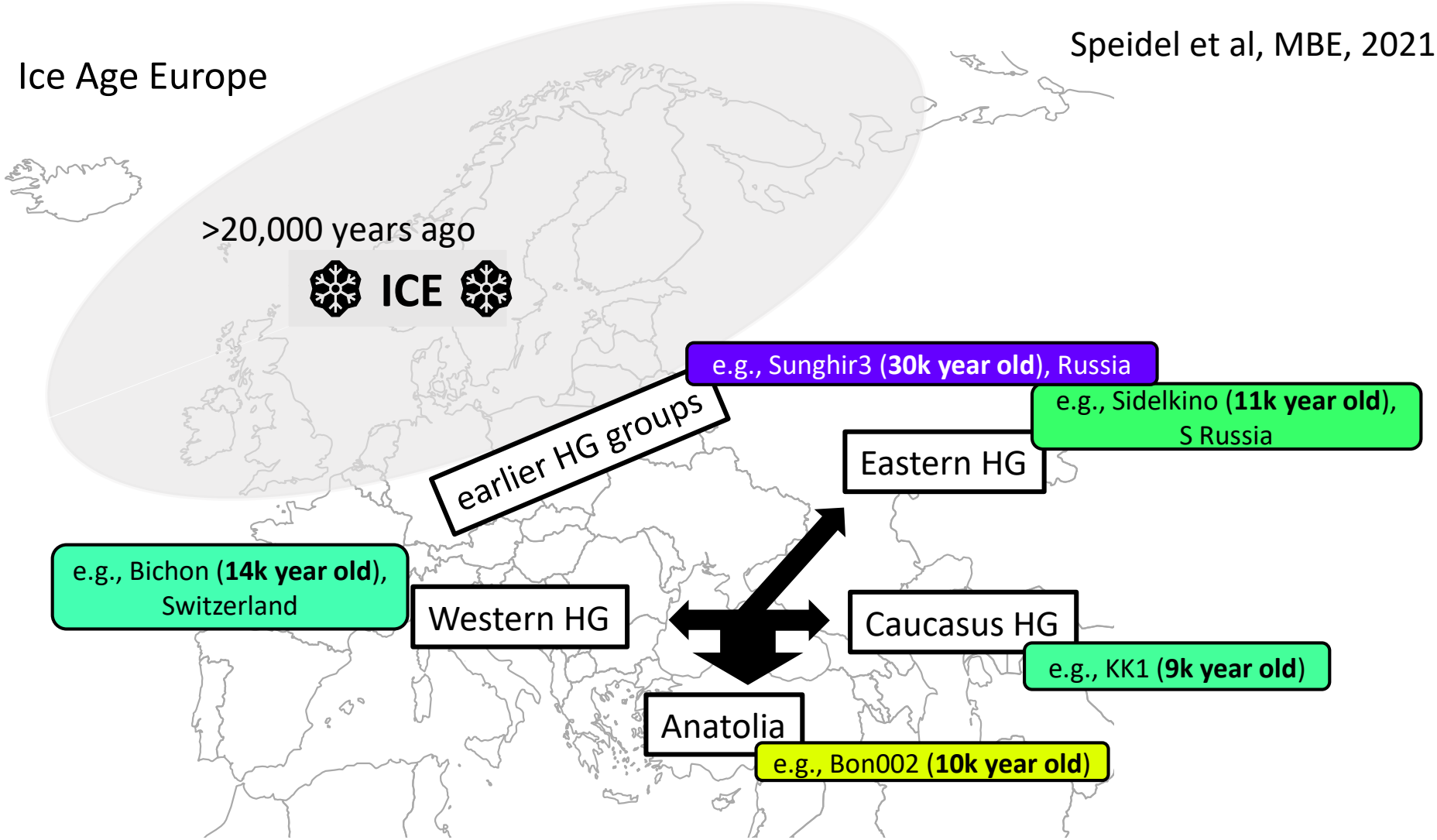
How did this spread to all West Eurasians today?

Colour shows strength of elevation in TCC/TTC mutation rates

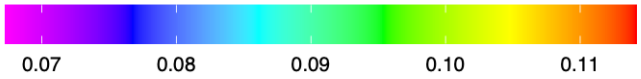


TCC/TTC mutation rate increase happened >15k years ago, and spread among hunter-gatherers before farming

Speidel et al, MBE, 2021

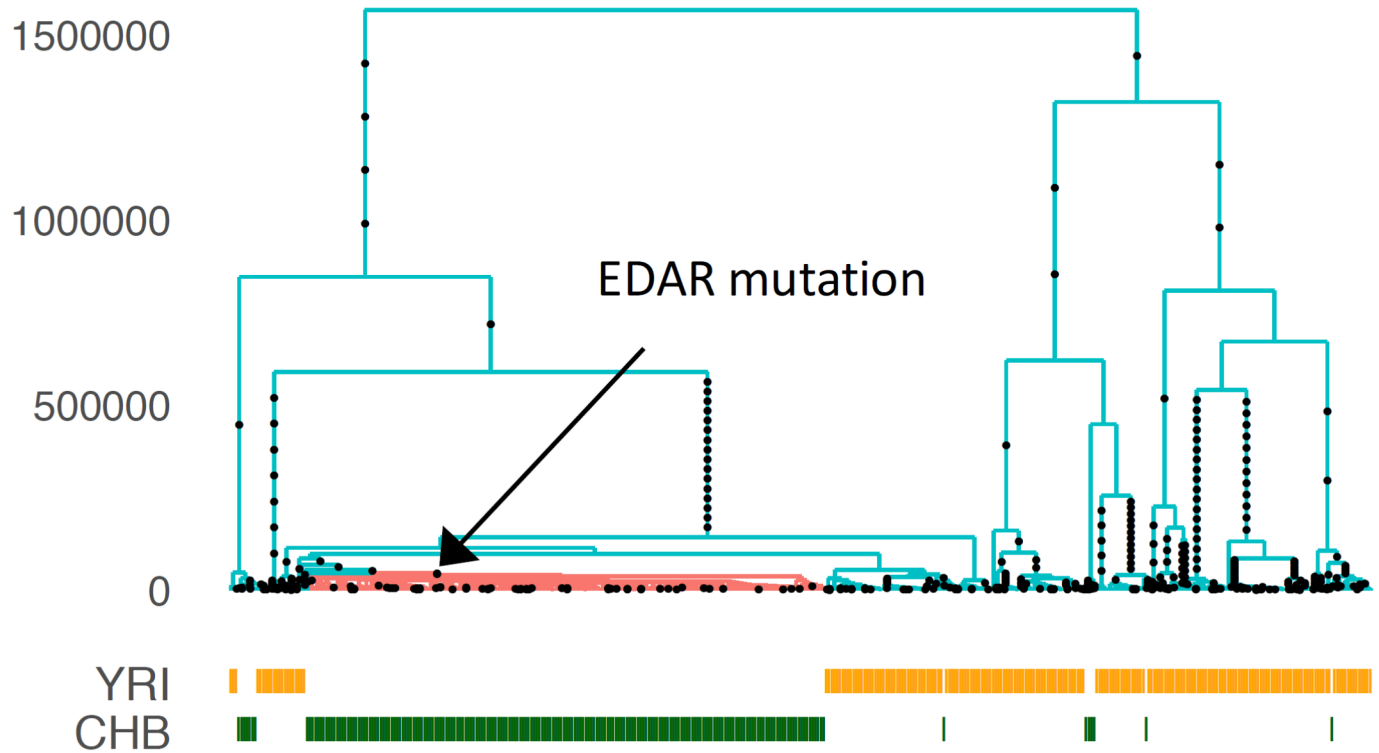


Colour shows strength of elevation in TCC/TTC mutation rates

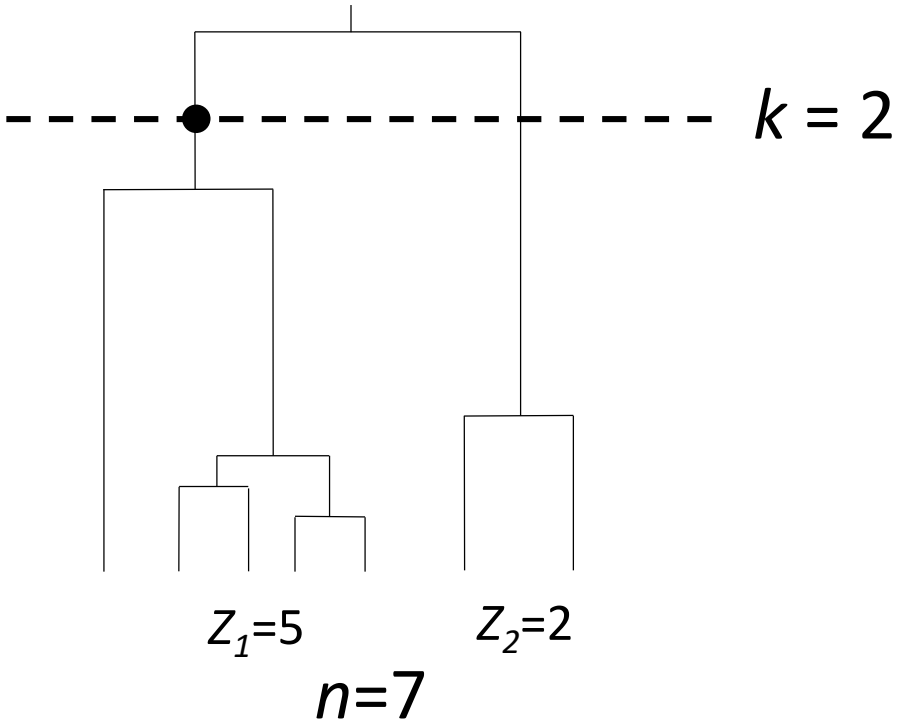


Detecting signals of positive selection

- First, consider 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?

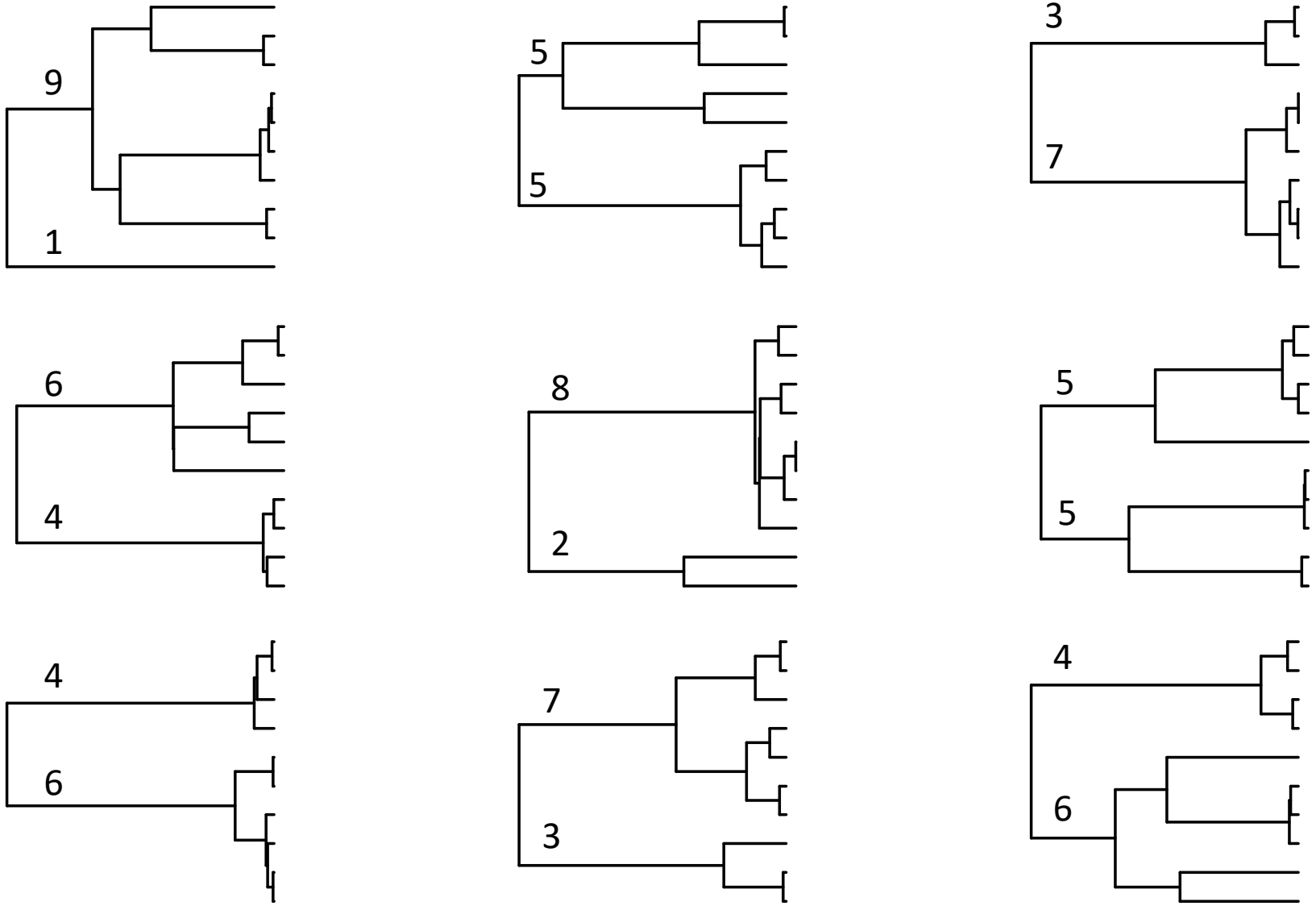


The coalescent is simple so it is possible to analytically write down the probability a mutation arising while *k* lineages are in the tree has at least some number of descendants: yields a **p-value, testing a null hypothesis of no selection**

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

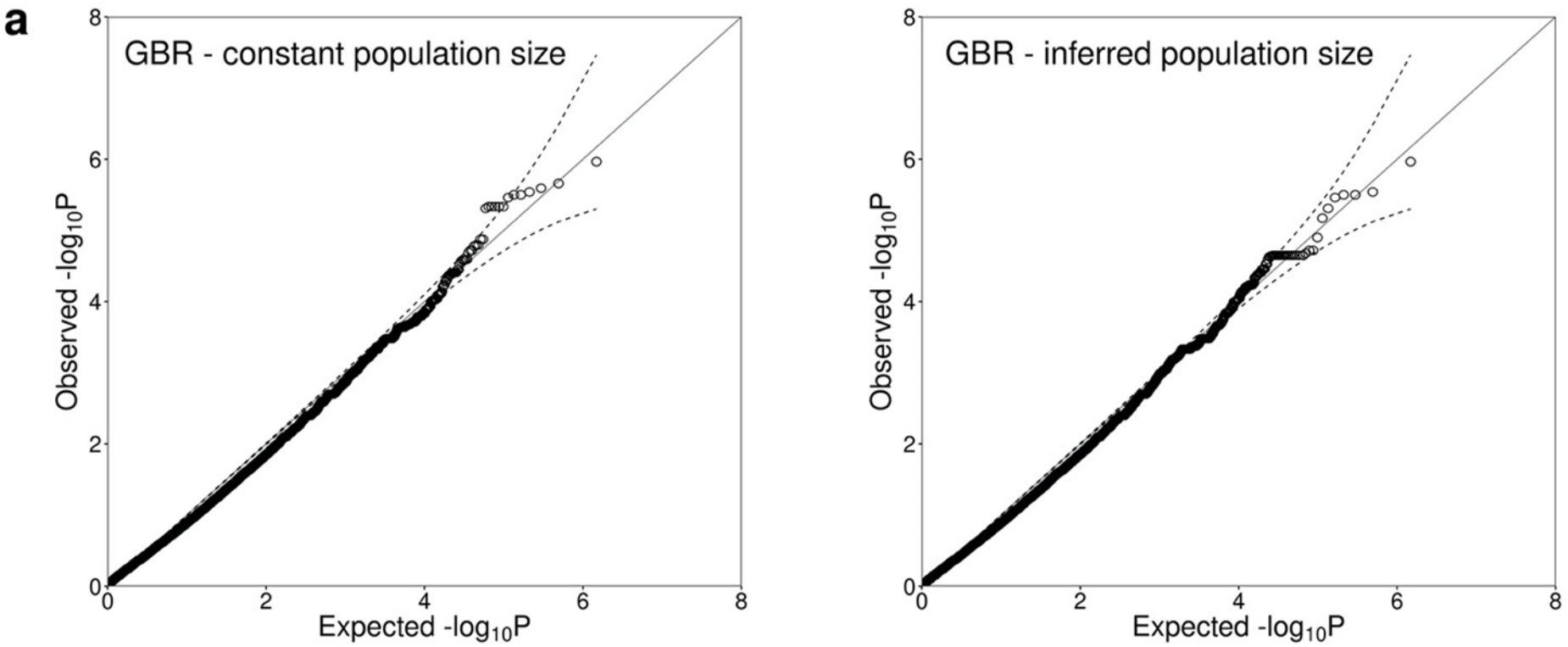
P(5 descendants)=1/6; ***P***=P(5 or more descendants)=1/3

The k=2 case

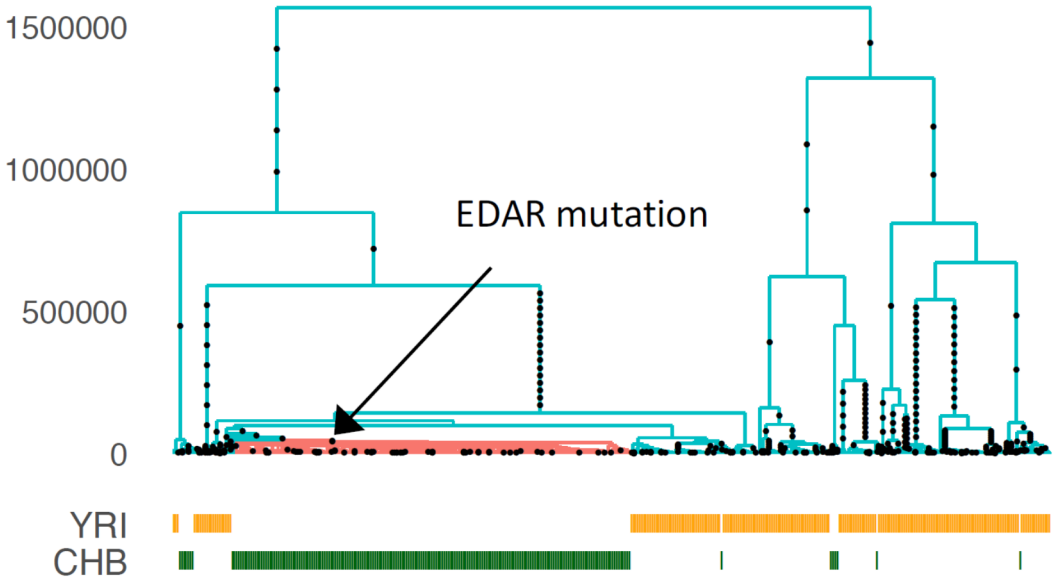


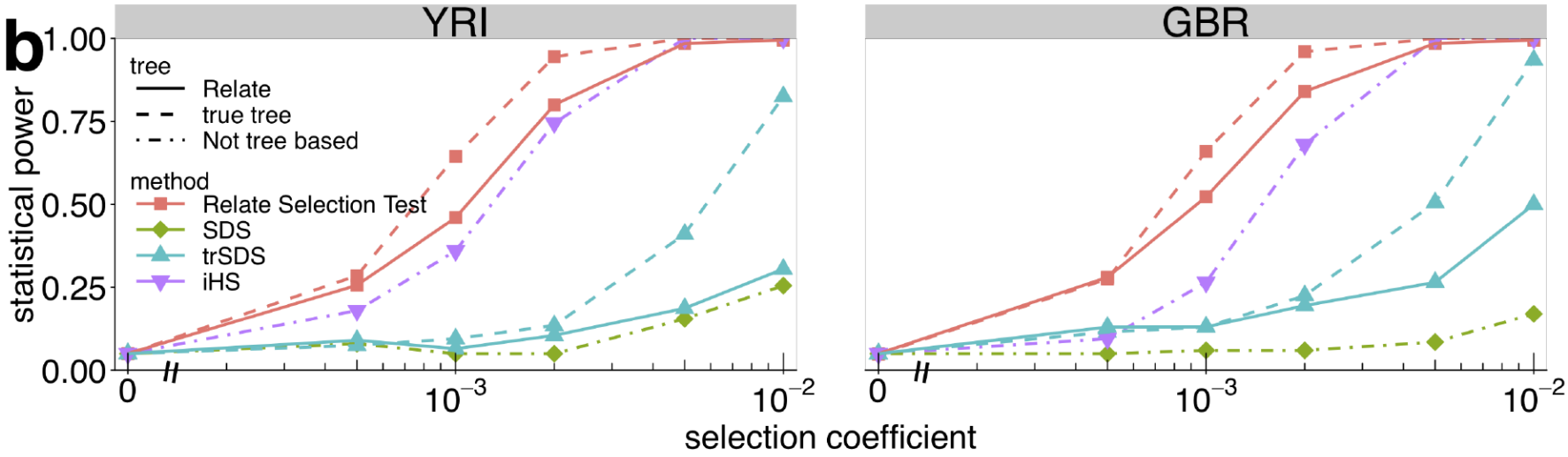
P-values: very well calibrated under null simulations of no selection

N=1000, 250Mb
Bottleneck population size



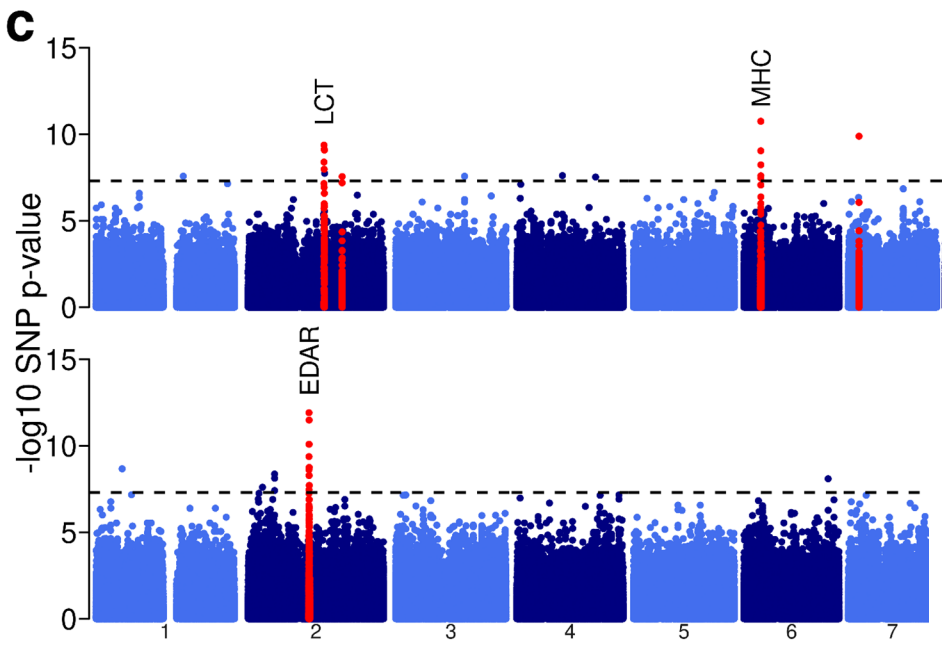
Improved power to see weak selection than existing approaches



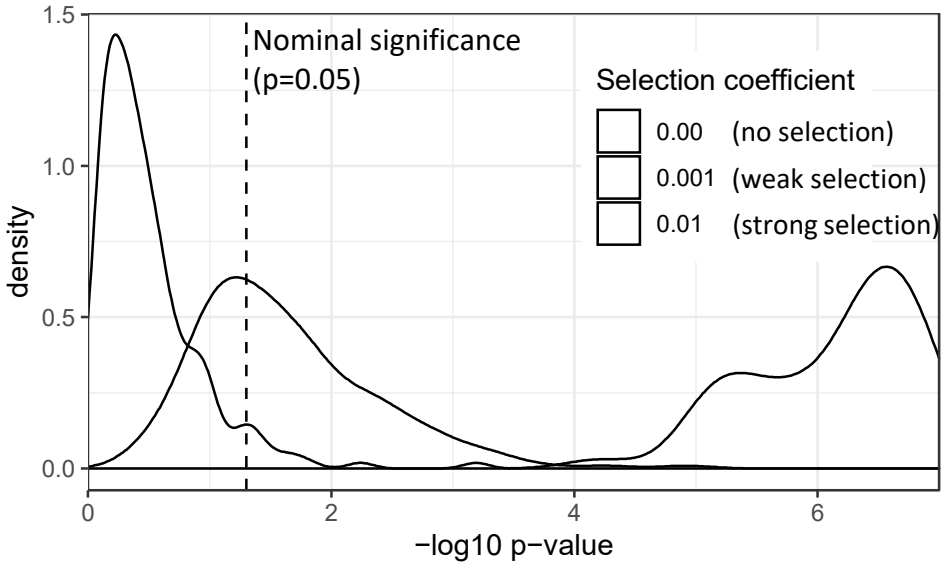


Genome-wide selection p-values

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

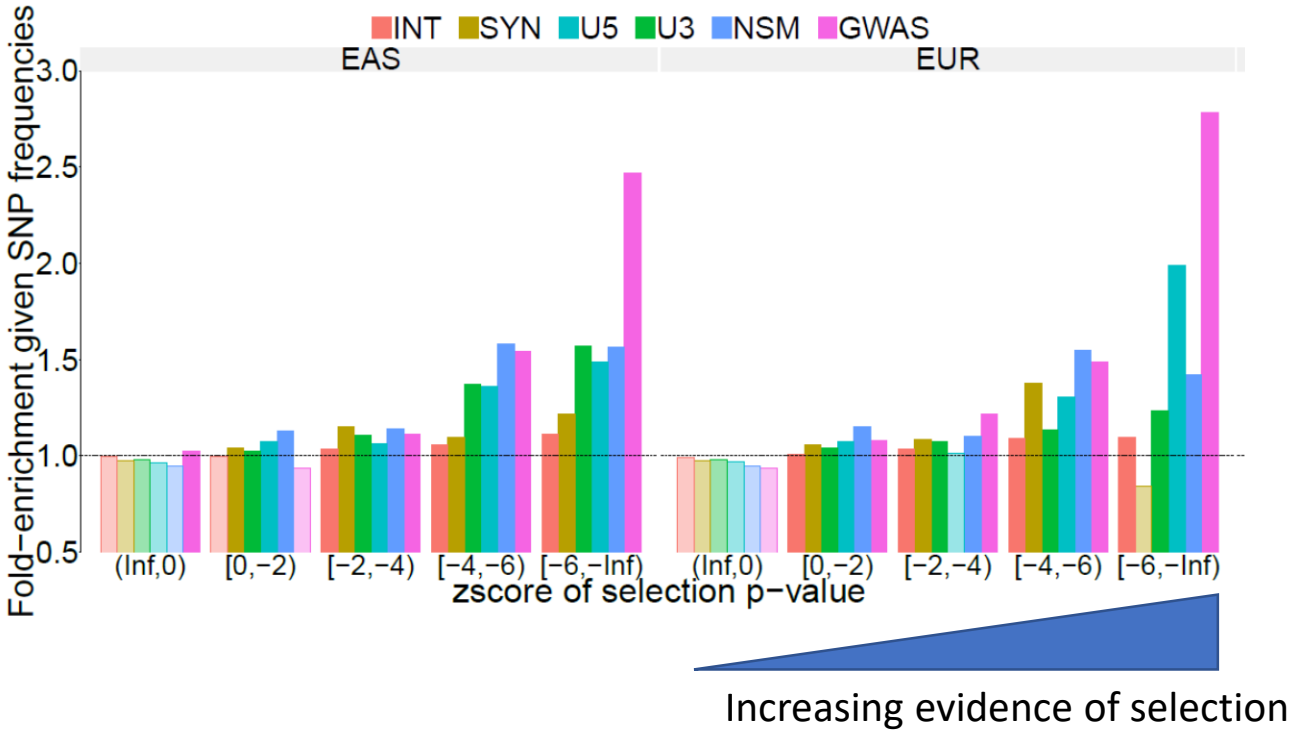


Weak selection on individual mutations is hard to detect, compared to shifts in distributions



How does weak selection evidence vary <u>by trait</u>?

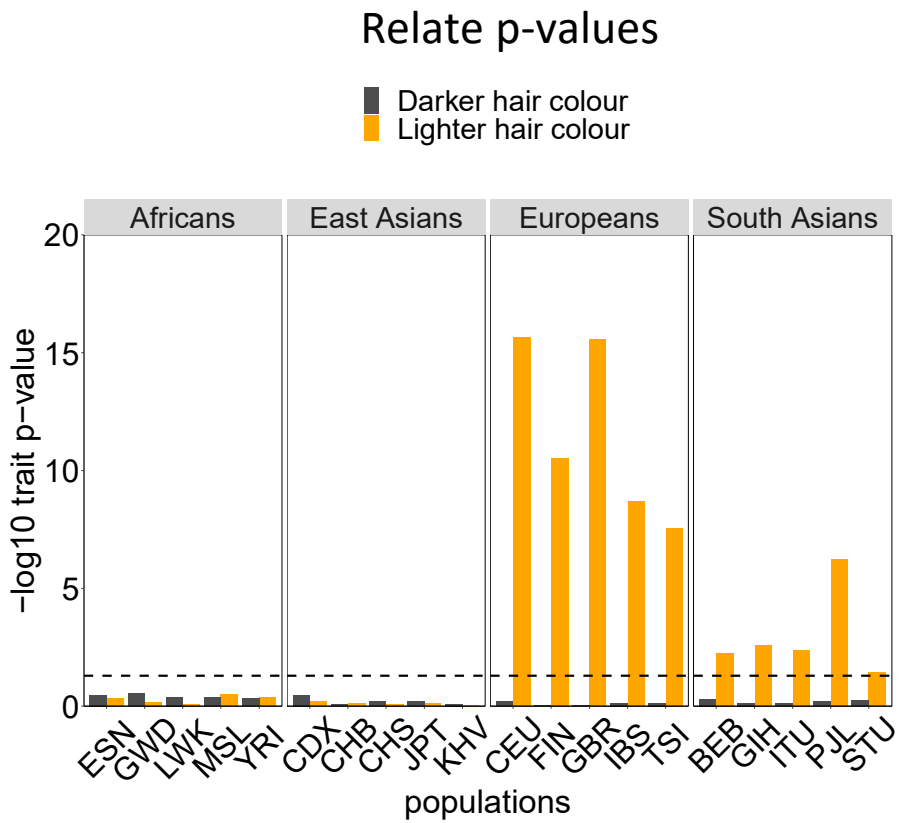
GWAS hits are most enriched, among selection signals we observe

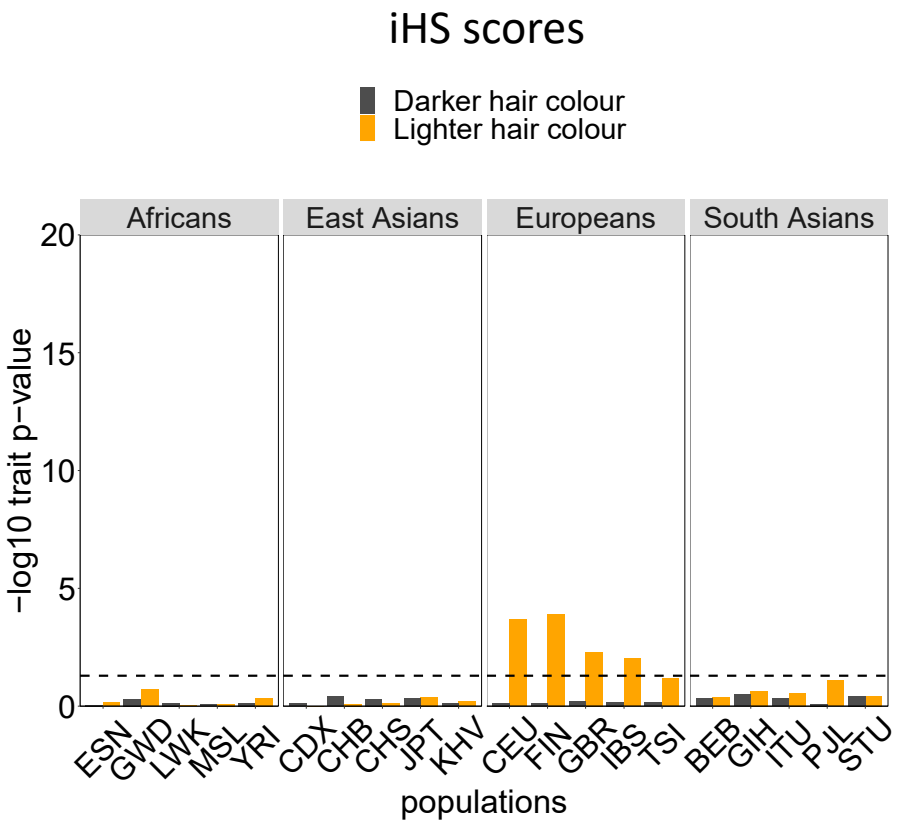


INT	Intronic SNP
SYN	Synonymous coding SNP
U5	5' untranslated region
U3	3' untranslated region
NSM	Non-synonymous coding SNP
GWAS	Genome-wide significant GWAS hits

Evidence of selection on a trait: hair colour

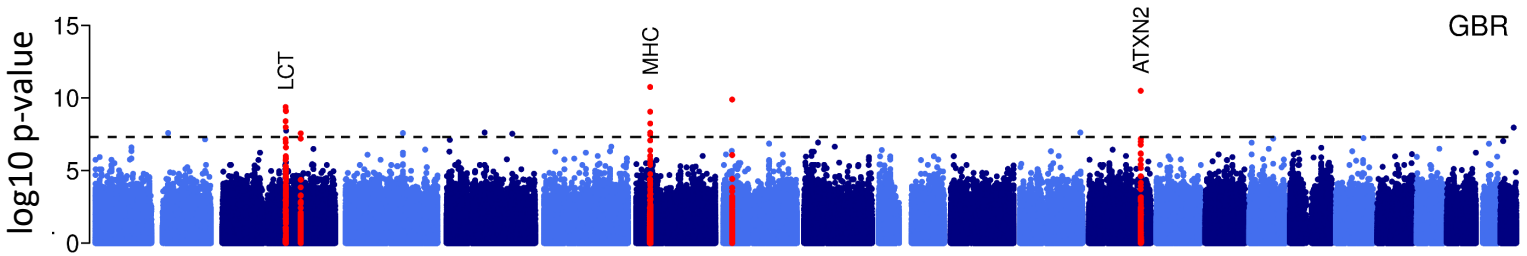
1. Use **effect direction** of ”genome-wide significant” associations
2. Compare selection p-values to frequency matched random SNPs (Wilcoxon rank-sum test)



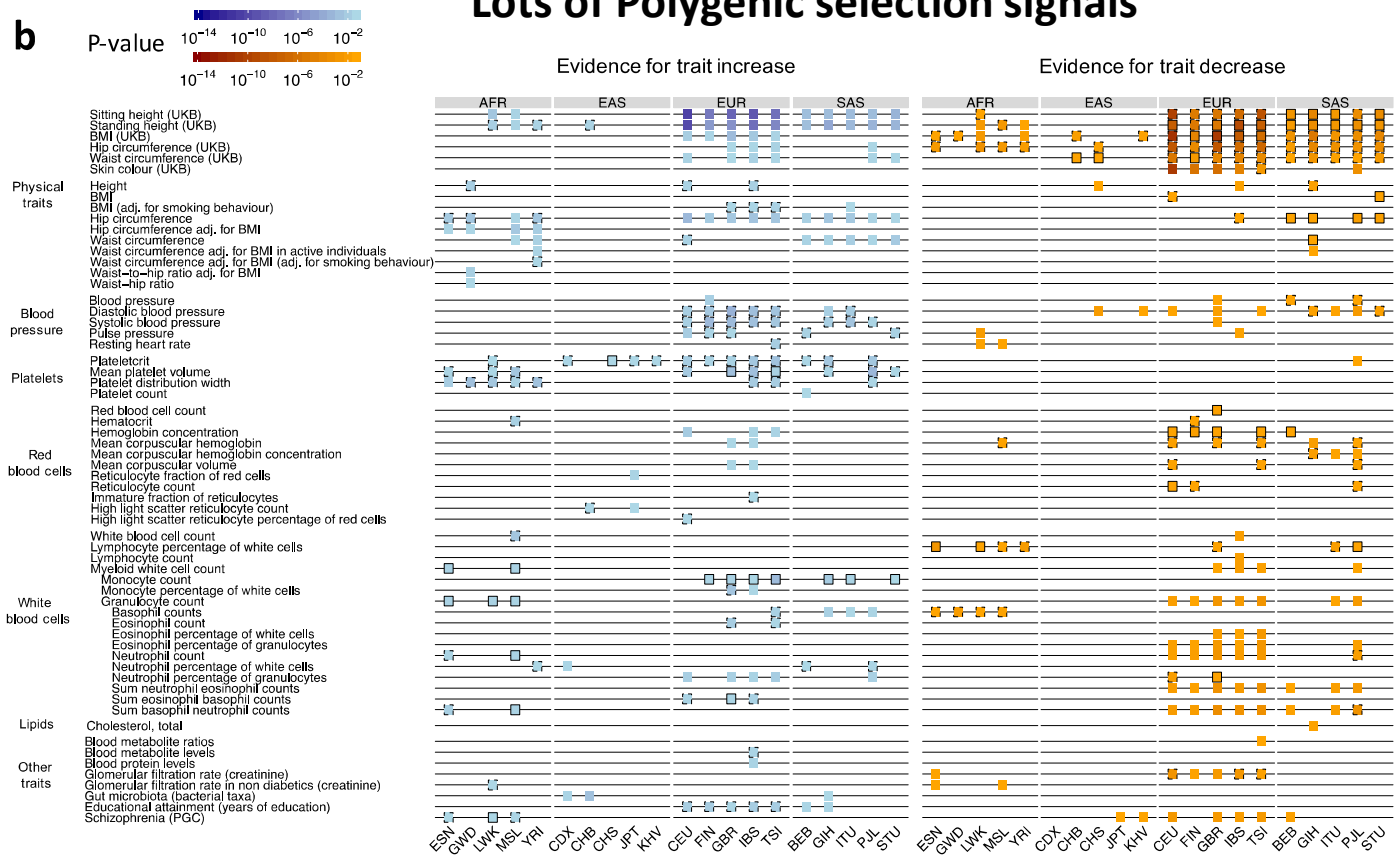


Many key events in our evolutionary history are only implicated as subtle

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



Lots of Polygenic selection signals



Blood pressure
↑ (EUR, SAS)

Hip circumference
↓ (SAS)

Plateletcrit
↑ (AFR, EAS, EUR, SAS)

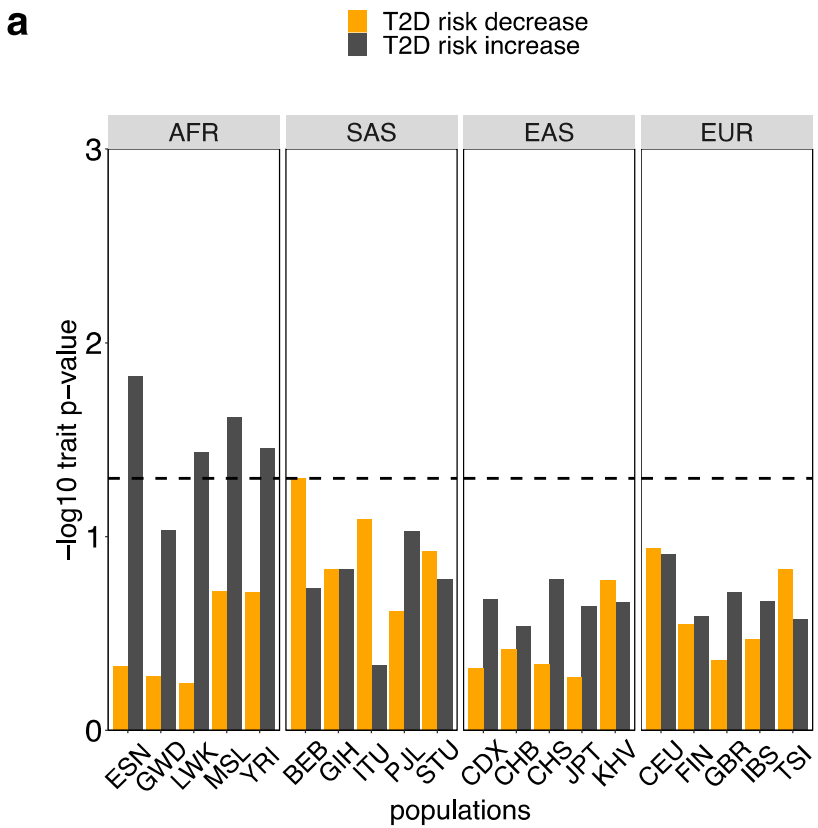
Hemoglobin
↓ (EUR, SAS)

Granulocyte
↑ (AFR) ↓ (EUR)

Evidence for selection increasing risk of T2D in African-ancestry people

Nature Genetics (2022), with Anubha Mahajan (Oxford), Mark McCarthy (Genentech)

- 171,262 cases and 1,075,072 controls from diverse ancestries
- 337 independent loci with T2D risk associations
- 209 (MSL) – 297 (FIN) segregating hits per population



- Correlated phenotypes
- Pleiotropy (in T2D, risk increase is fully explained by mutations associated with changes in body fat composition)
- Biased effect sizes (e.g., due to genetic structure)
- Unbalanced power for different ancestries

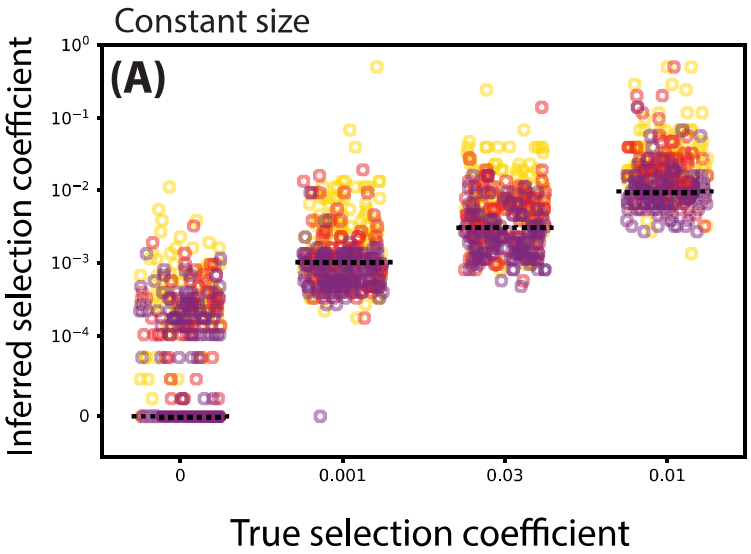
CLUES: Importance-sampling based method for inferring selection coefficients

Aaron Stern

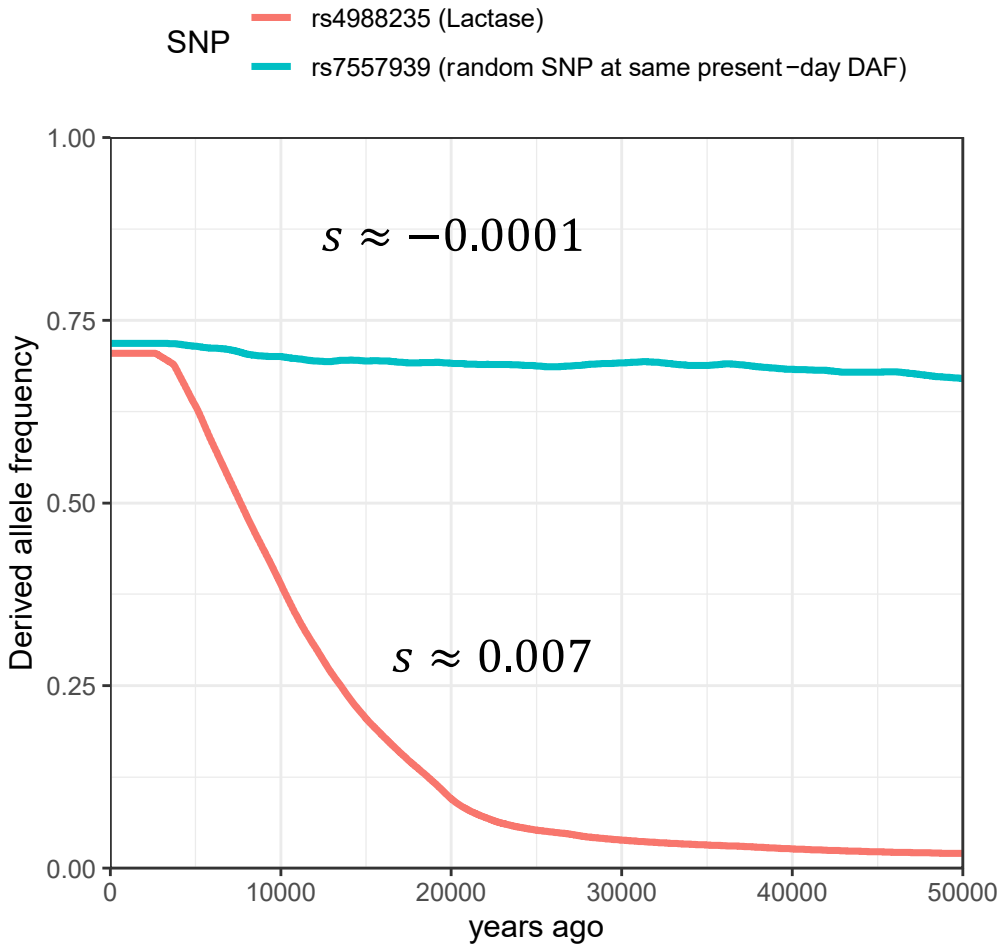
Aaron J. Stern, Peter R. Wilton, Rasmus Nielsen. **PLOS Genetics, 2019**.

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

Simulations:



1000 Genomes Project British:



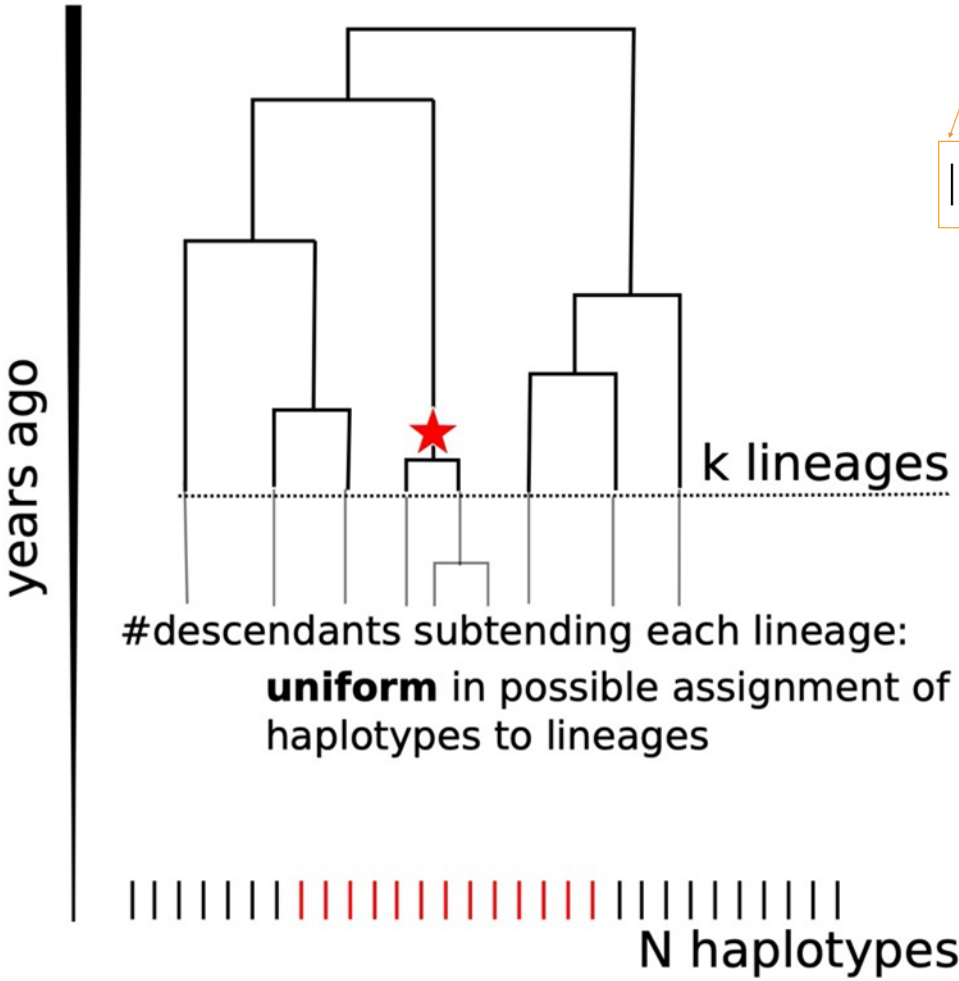
Summary & outlook

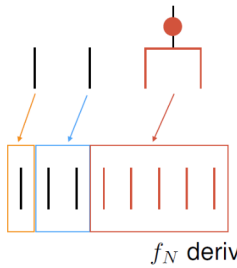
- It is now possible to build genealogical trees for huge datasets, in humans and other species (currently 10,000 individuals or more)
  - Humans (ancient and present)
  - Dogs and wolves
  - Mice
  - Bacteria
  - Atlantic cod, Cichlids
  - Waterhemp, Arabidopsis
- These trees capture information about 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!

P-value for evidence of positive selection

- How much has a mutation out-competed other mutations?
- Robust to population size history





k lineages when mutation had frequency 2

N haplotypes

f_N derived allele carriers

$$P(f_N|k) = \frac{\binom{f_N-1}{2-1}\binom{N-f_N-1}{(k-2)-1}}{\binom{N-1}{k-1}}$$

$$\text{p-value} = \sum_{f=f_N}^{N-k+2} P(f|k)$$