

# Archaic human introgression

**Population Genetics 2025**

**Martin Petr**

[mp@bodkan.net](mailto:mp@bodkan.net)

February 26, 2025

# 1856: Discovery of a ‘new man’



<https://www.donsmaps.com/neanderthaloriginal.html>



<https://twitter.com/Qafzeh/status/805339276334333953>

# 1856: Discovery of a ‘new man’



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**Neander's valley**

# 1856: Discovery of a ‘new man’



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<https://twitter.com/Qafzeh/status/805339276334333953>

## Neander's valley

valley = Thal in German

# 1856: Discovery of a ‘new man’



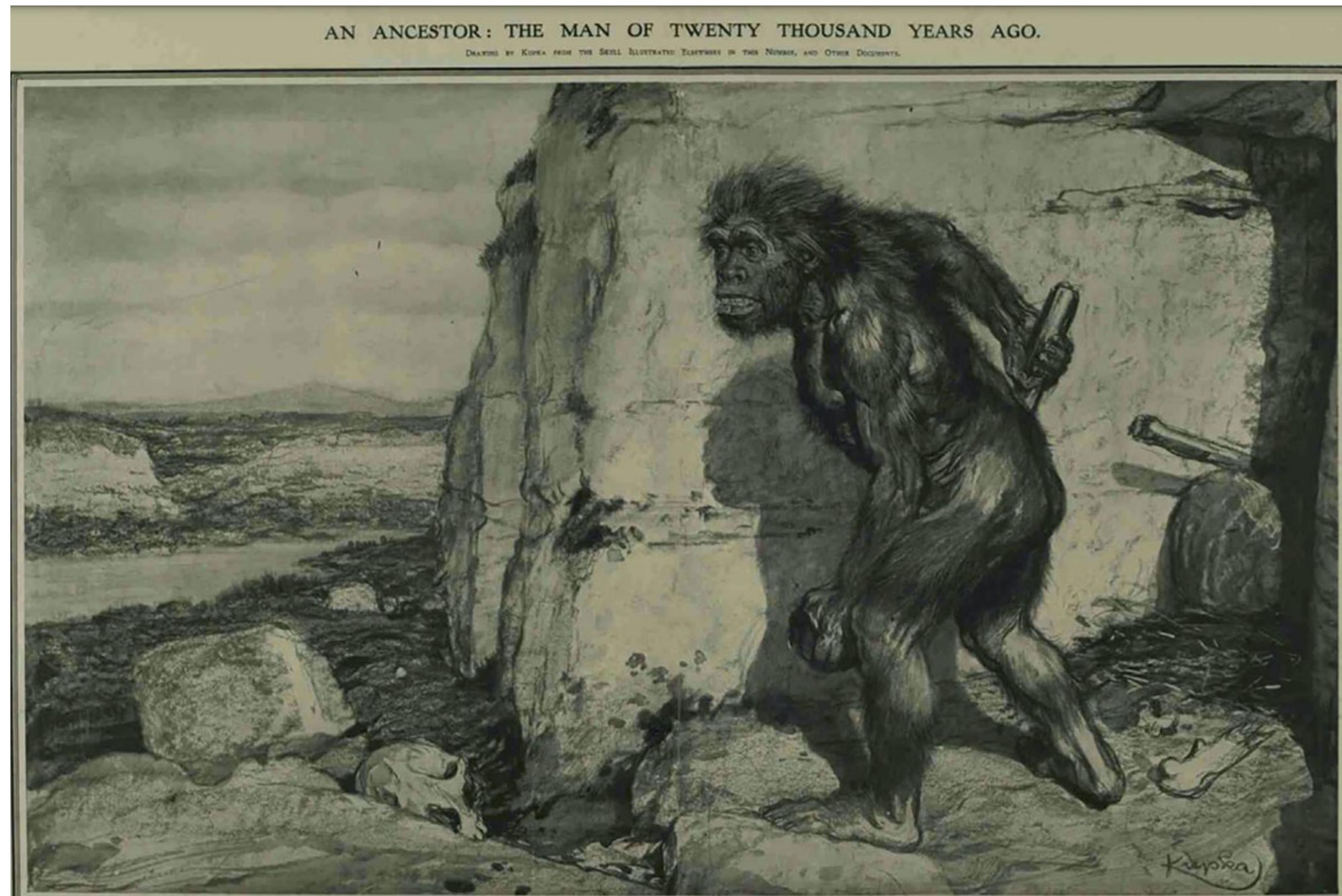
<https://www.donsmaps.com/neanderthaloriginal.html>

**Neander's valley**  
valley = Thal in German



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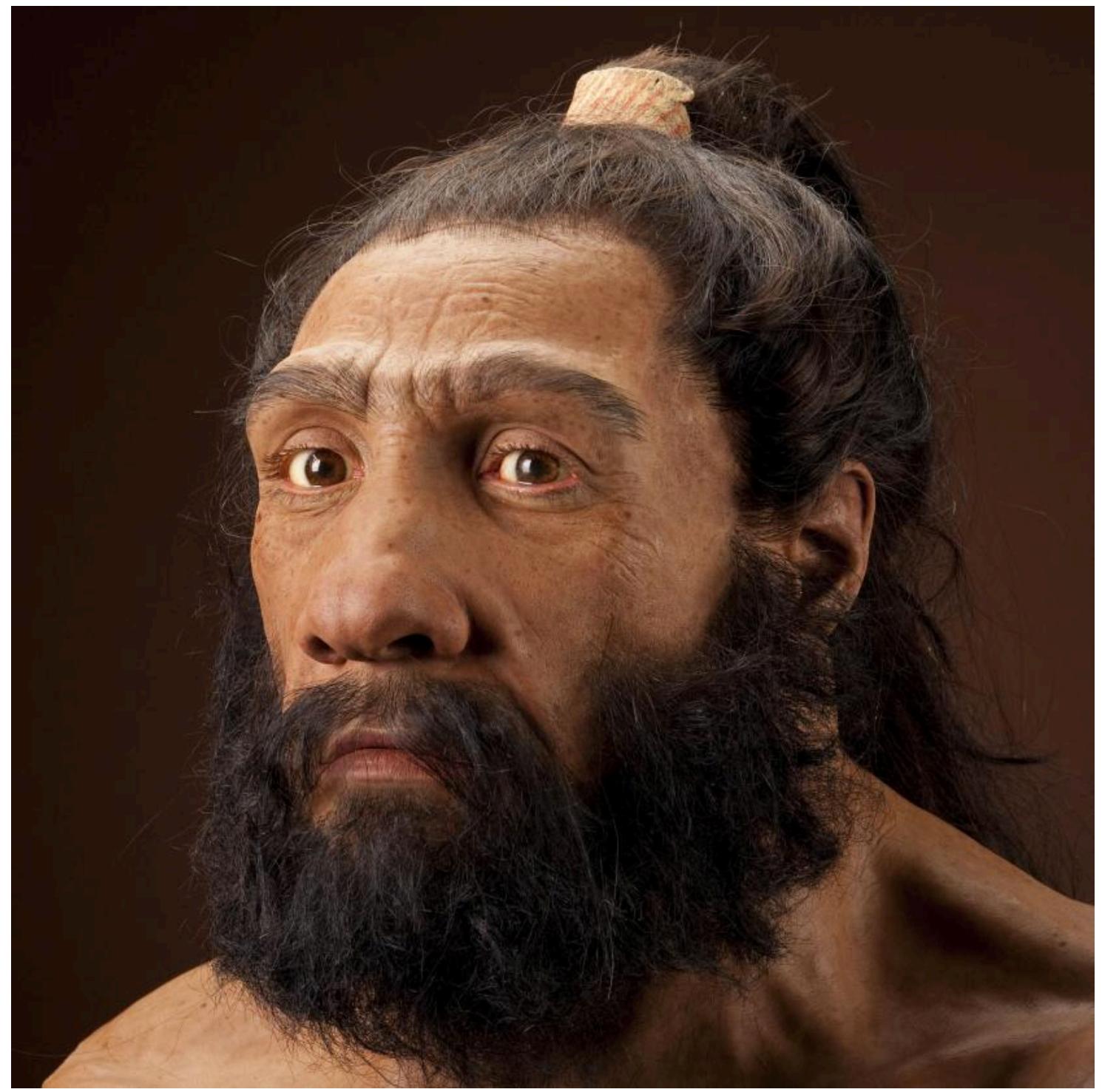
**Neanderthal**



The Illustrated London News, 1909



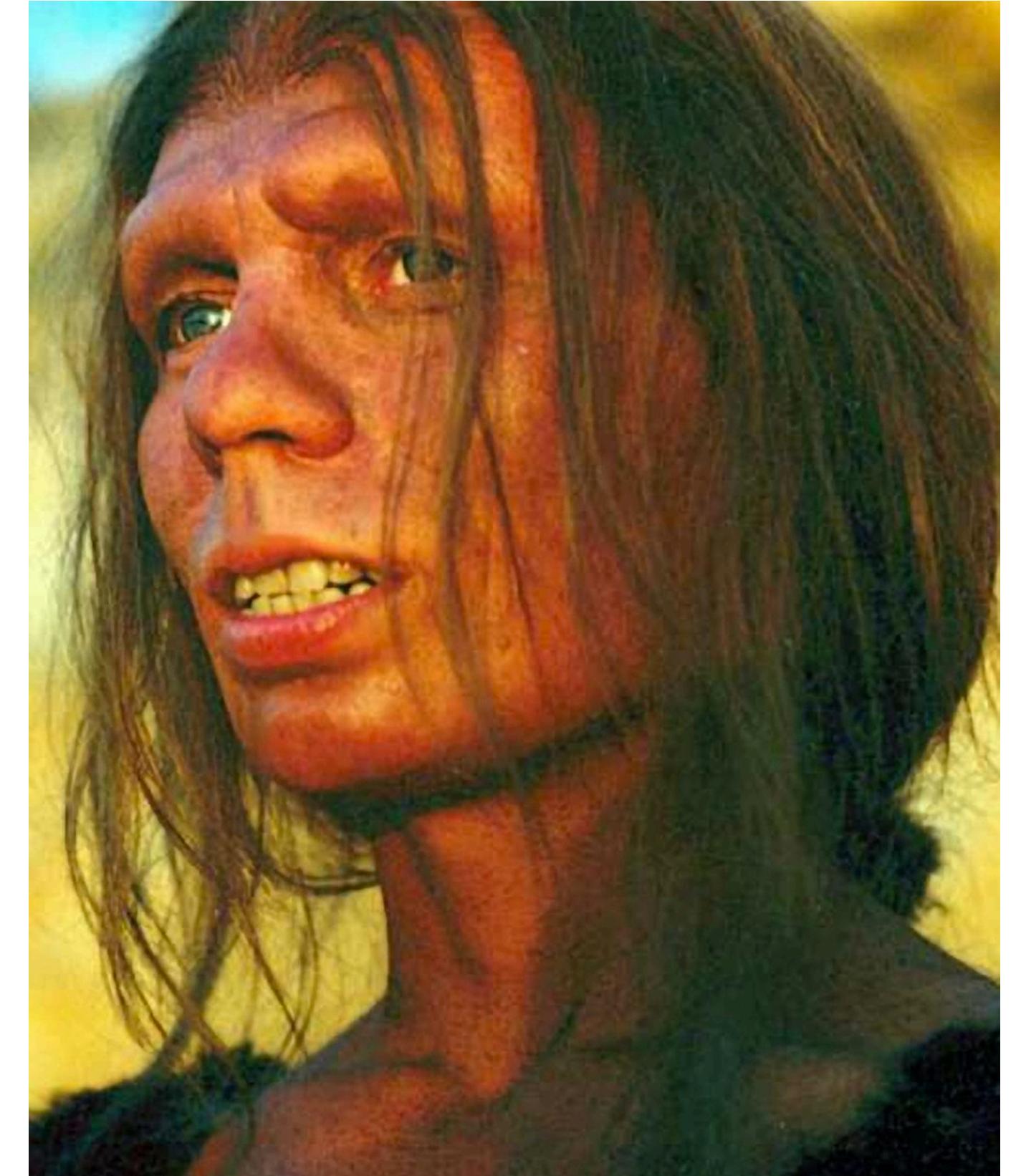
The Neanderthal Man movie poster, 1953



<http://humanorigins.si.edu/evidence/human-fossils/species/homo-neanderthalensis>



<https://www.neanderthal.de>



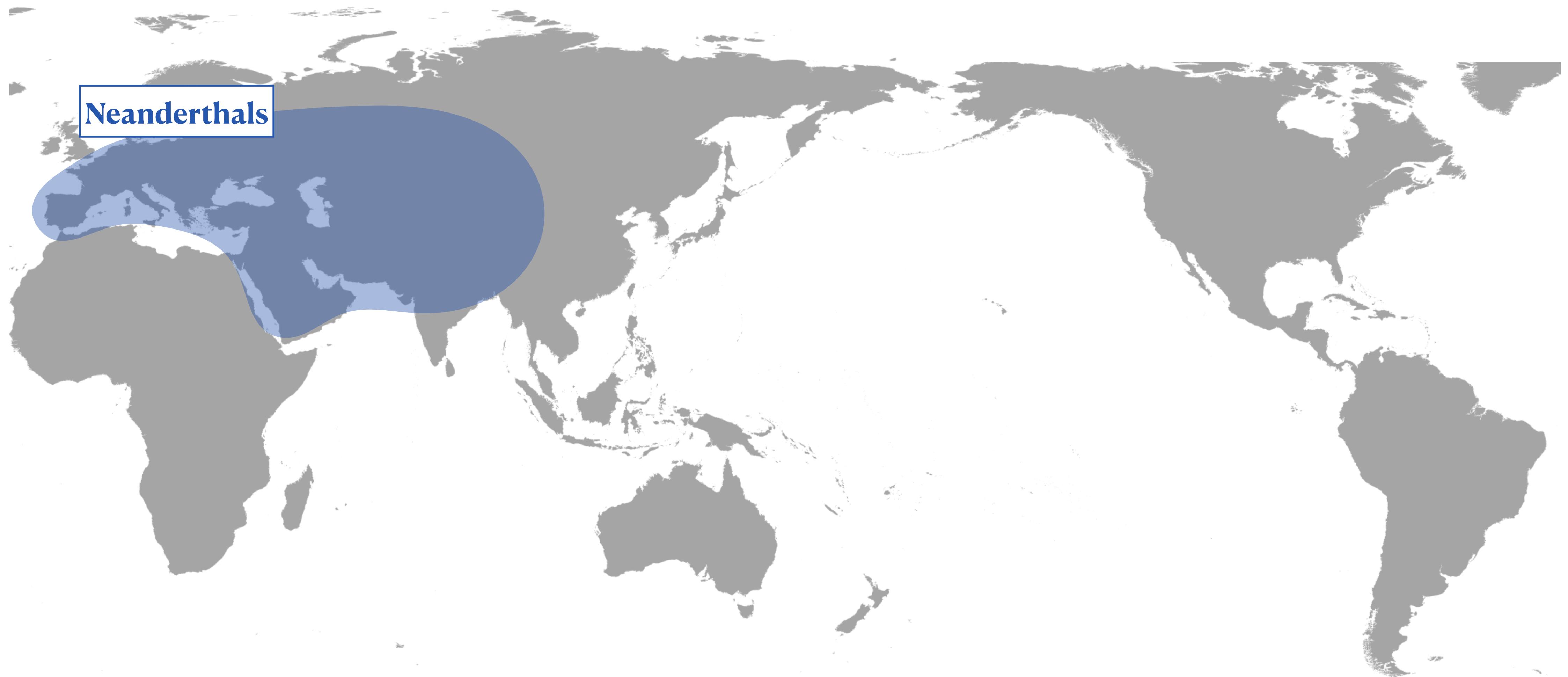
<https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.0020449>



Neanderthal Museum, Mettmann, Germany

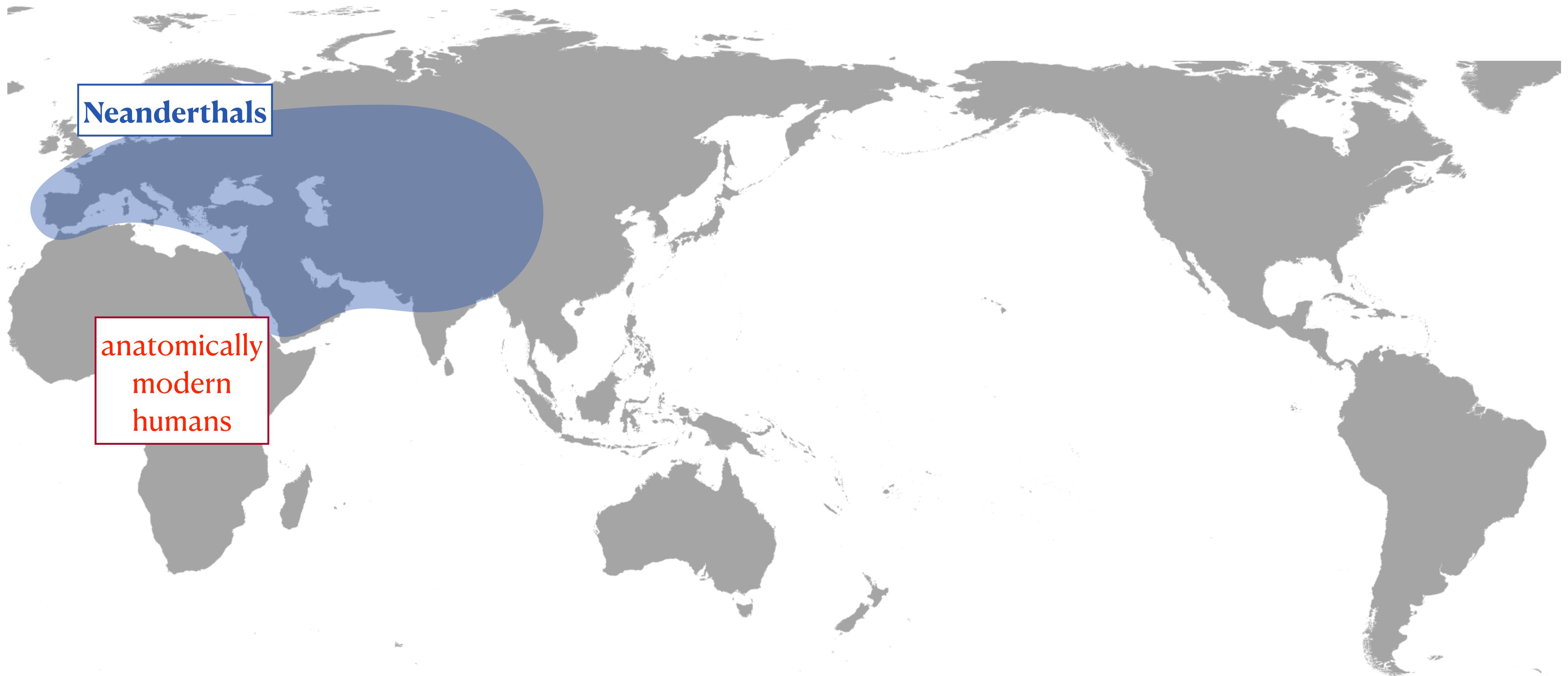


# ~600 kya B.P.: Neanderthals in Eurasia



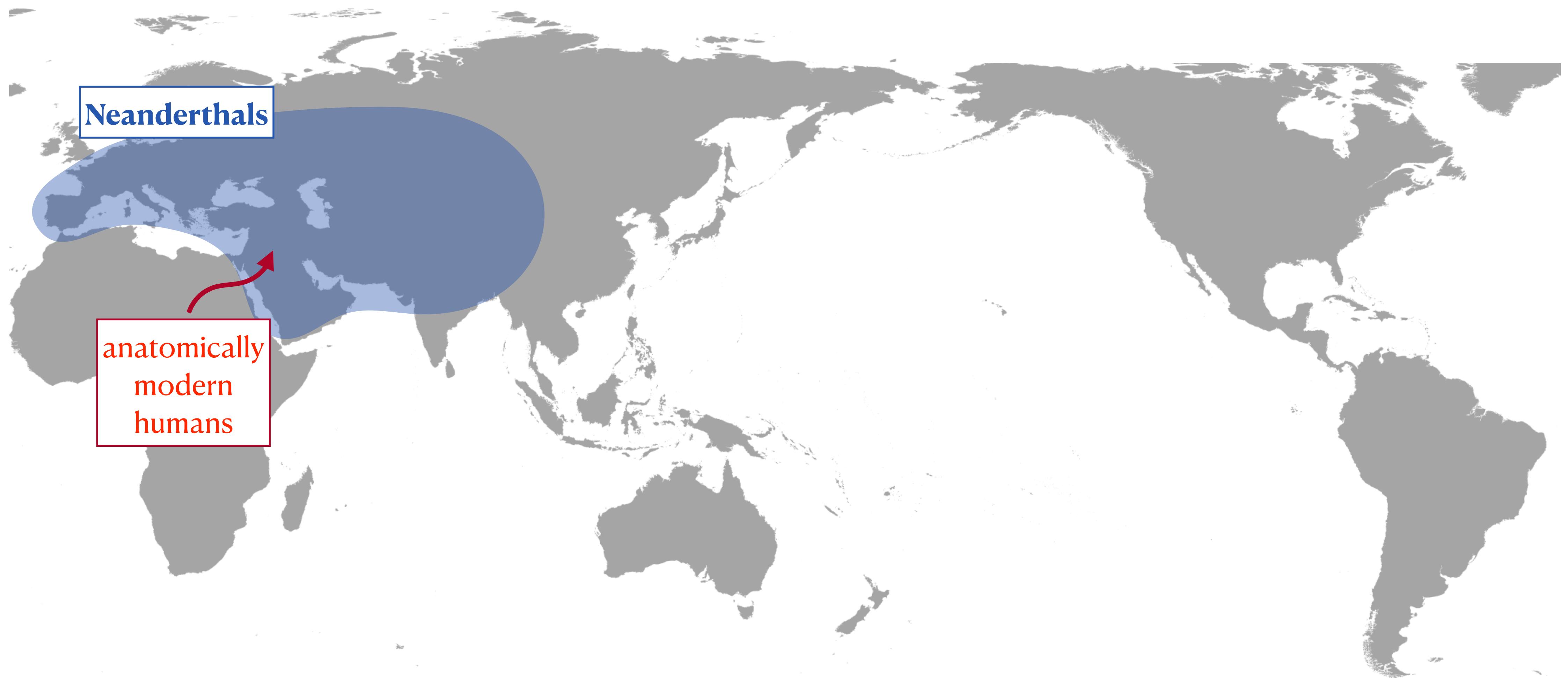
B.P. = "before present"

# **~300 kya B.P.: anatomically modern humans in Africa**



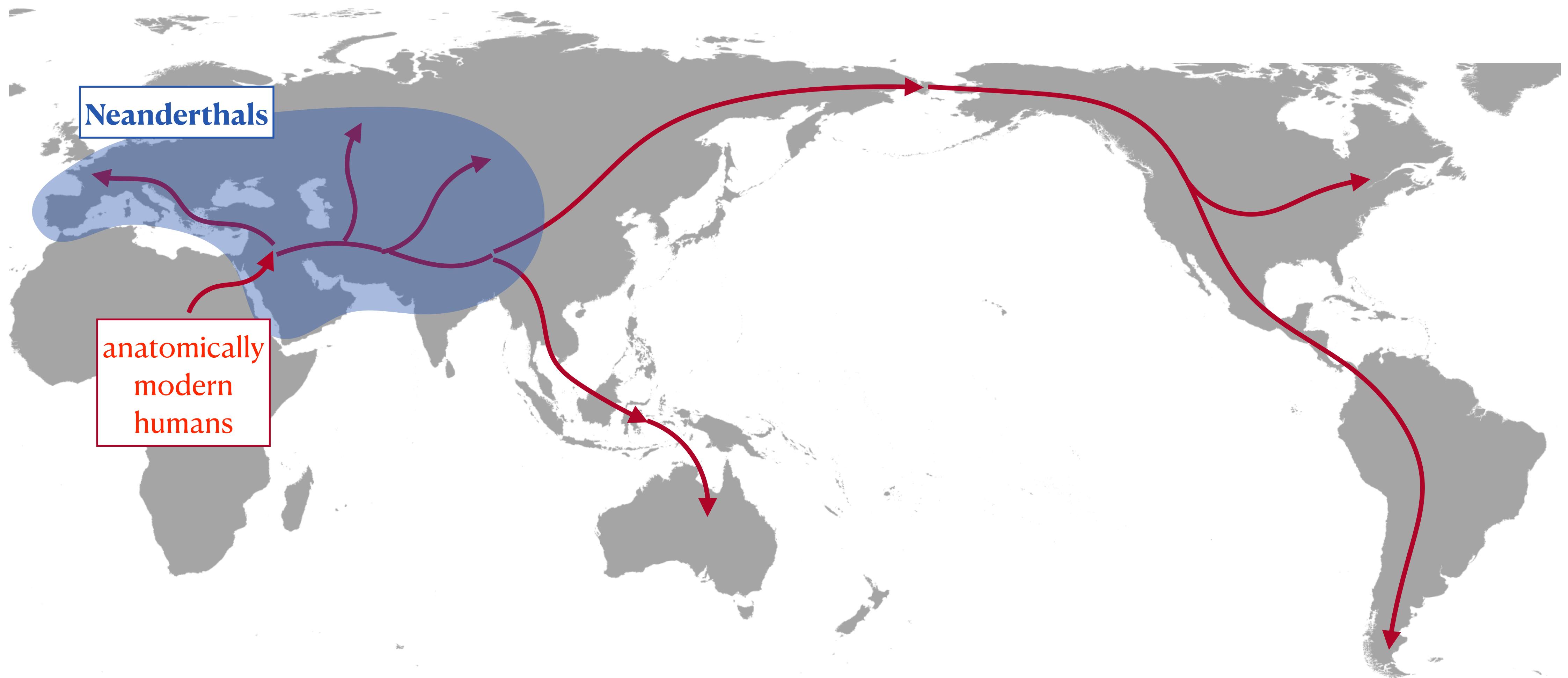
B.P. = "before present"

# **~70 kya B.P.: modern humans migrated out of Africa**



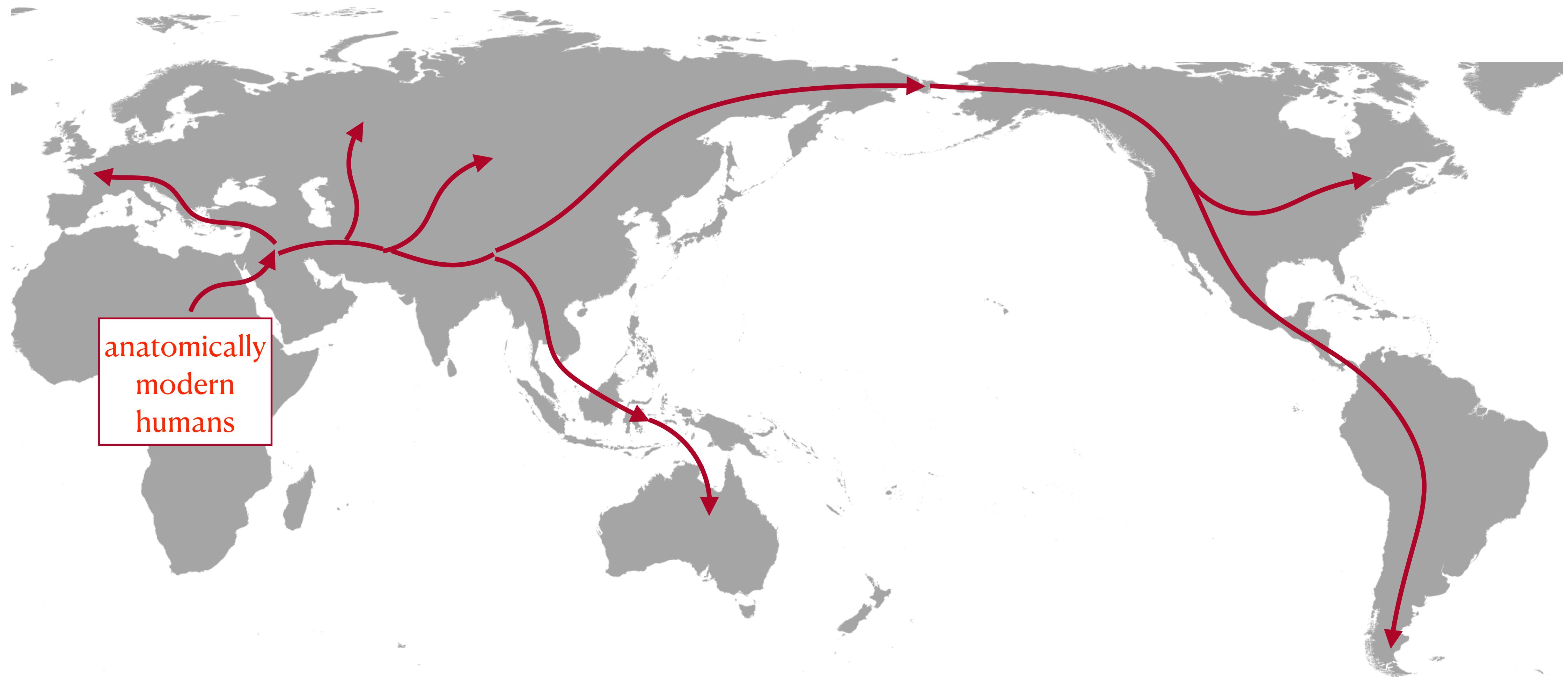
B.P. = "before present"

# **~70 kya B.P.: modern humans migrated out of Africa ...and colonized the entire world**



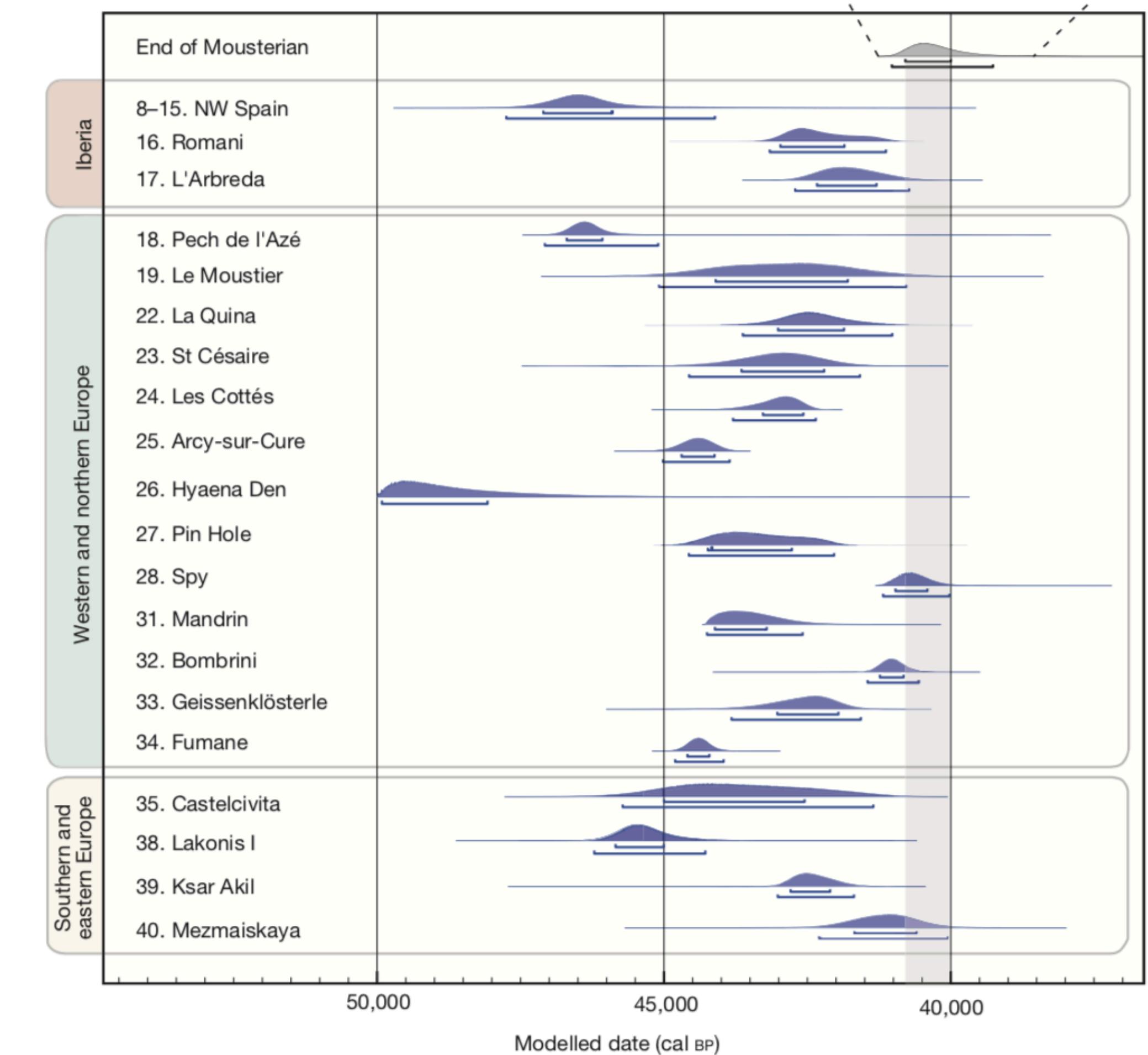
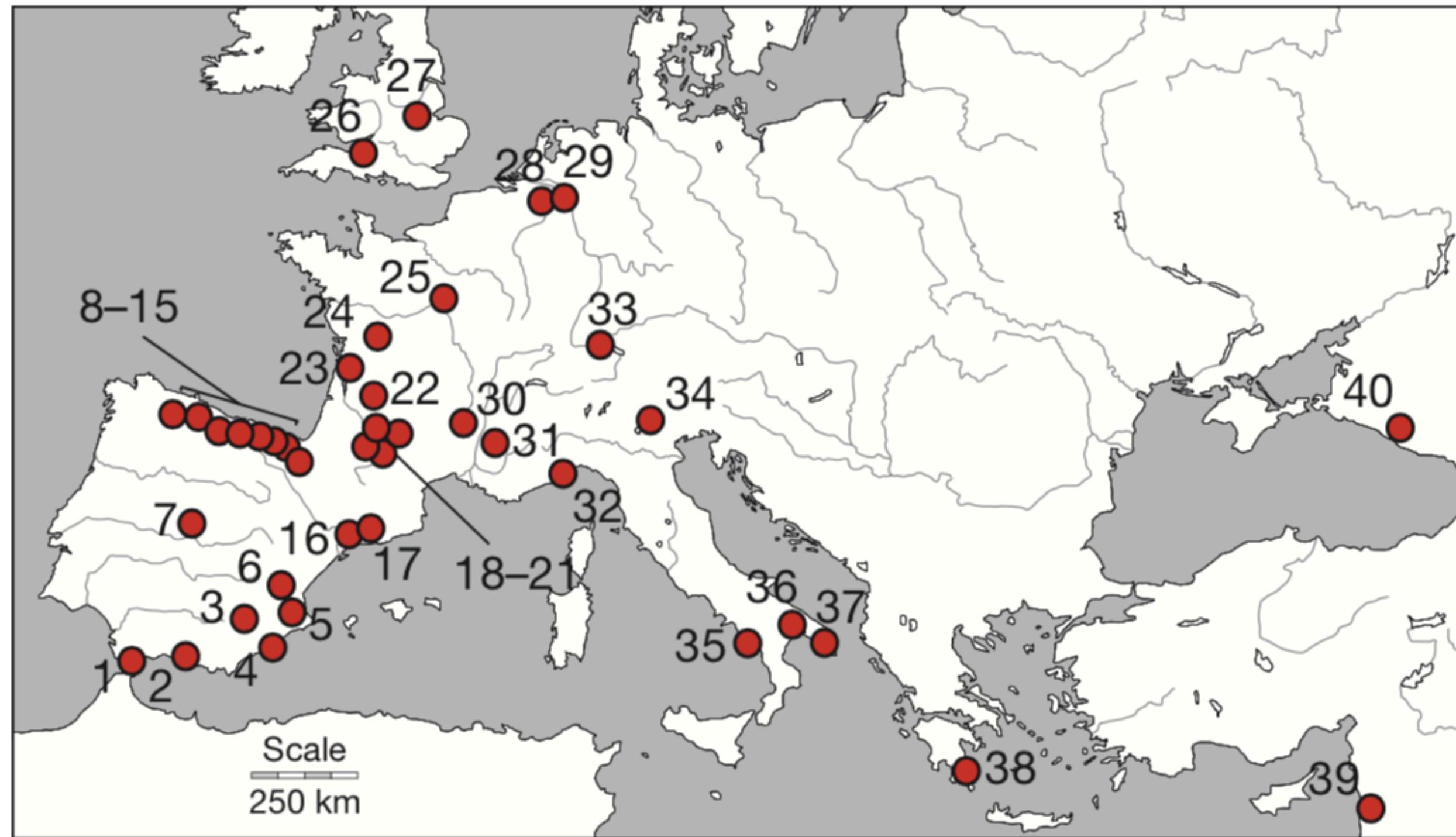
B.P. = "before present"

# $\sim$ 40 kya: Neanderthals vanished

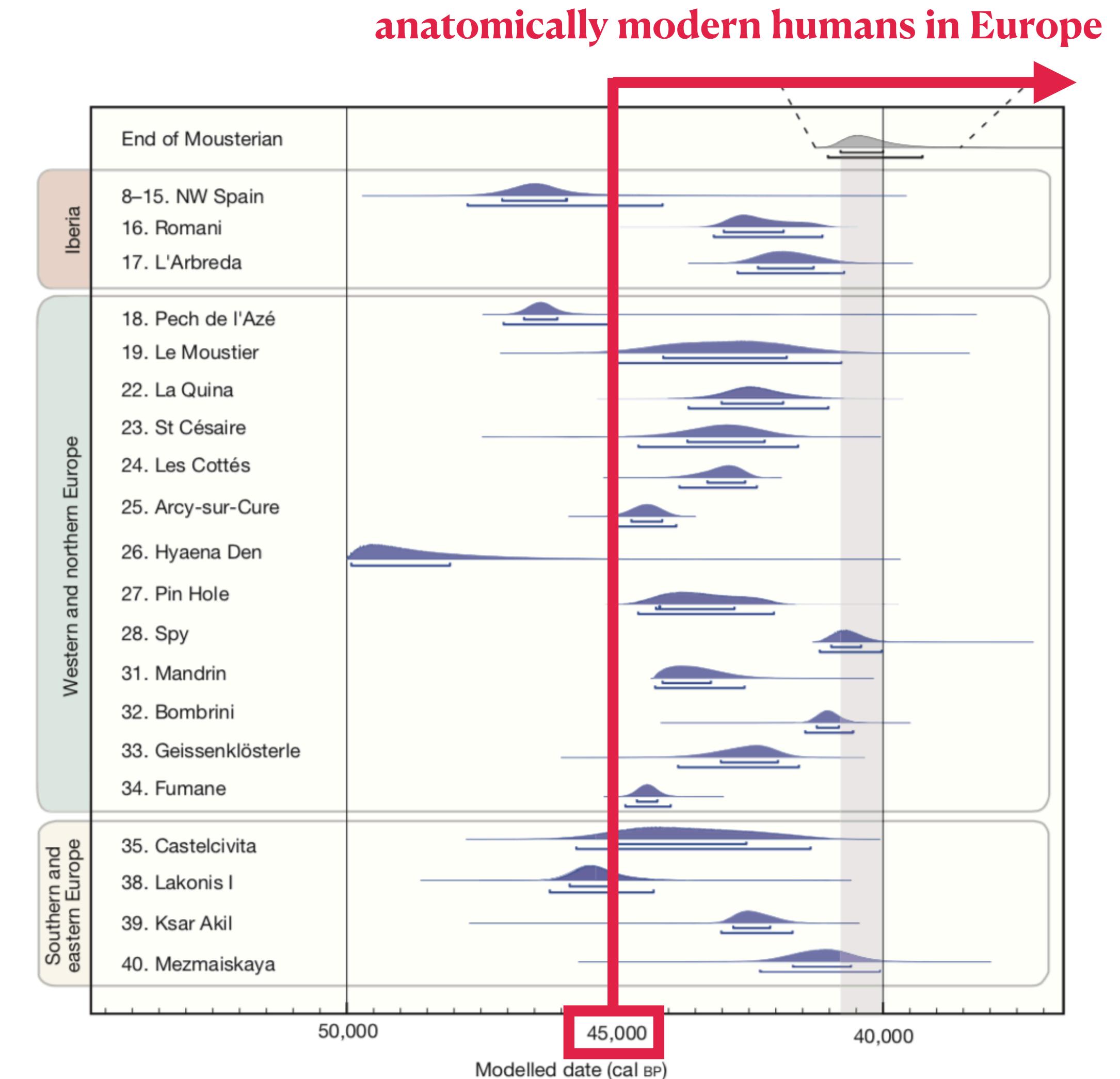
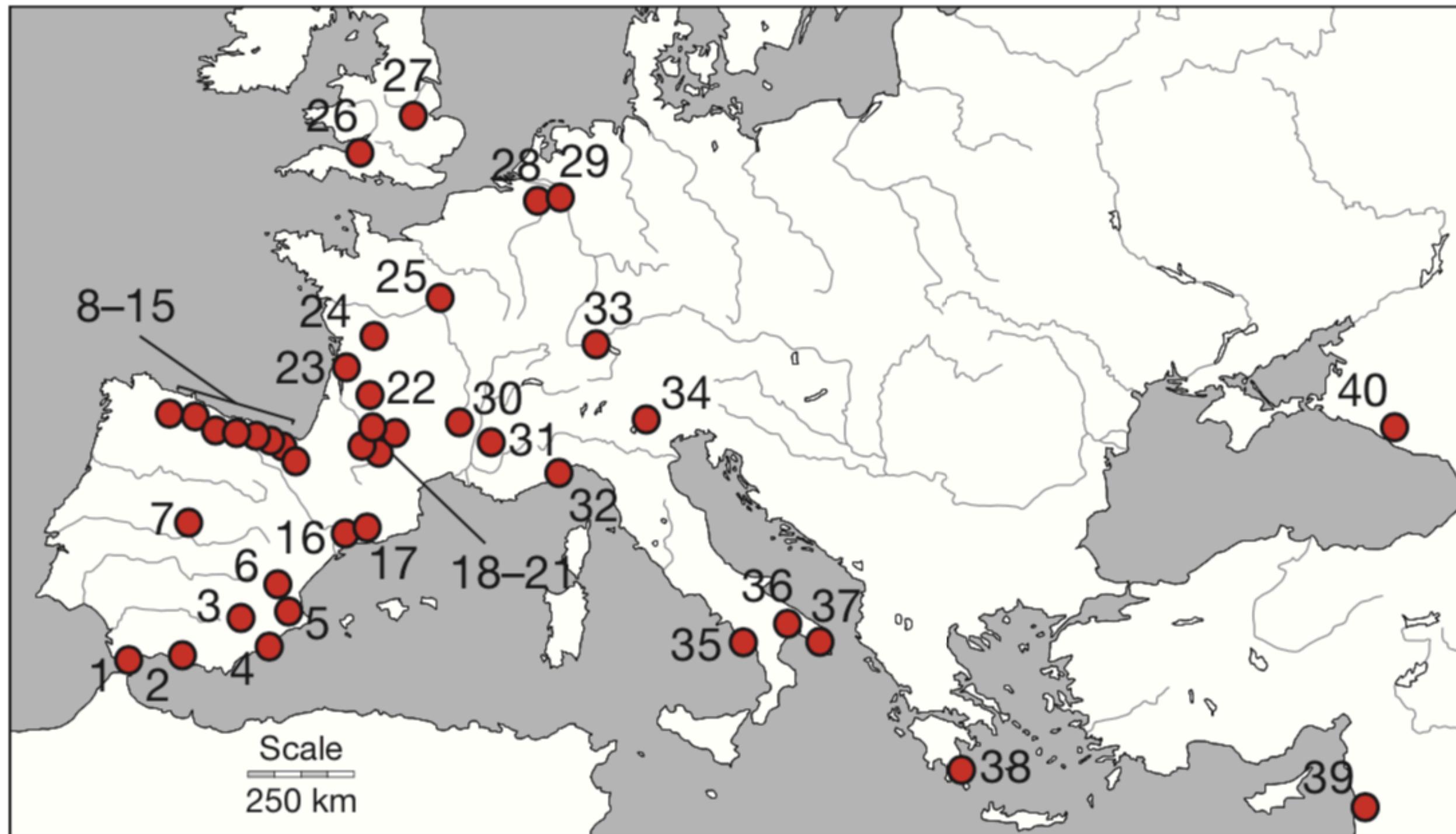


B.P. = "before present"

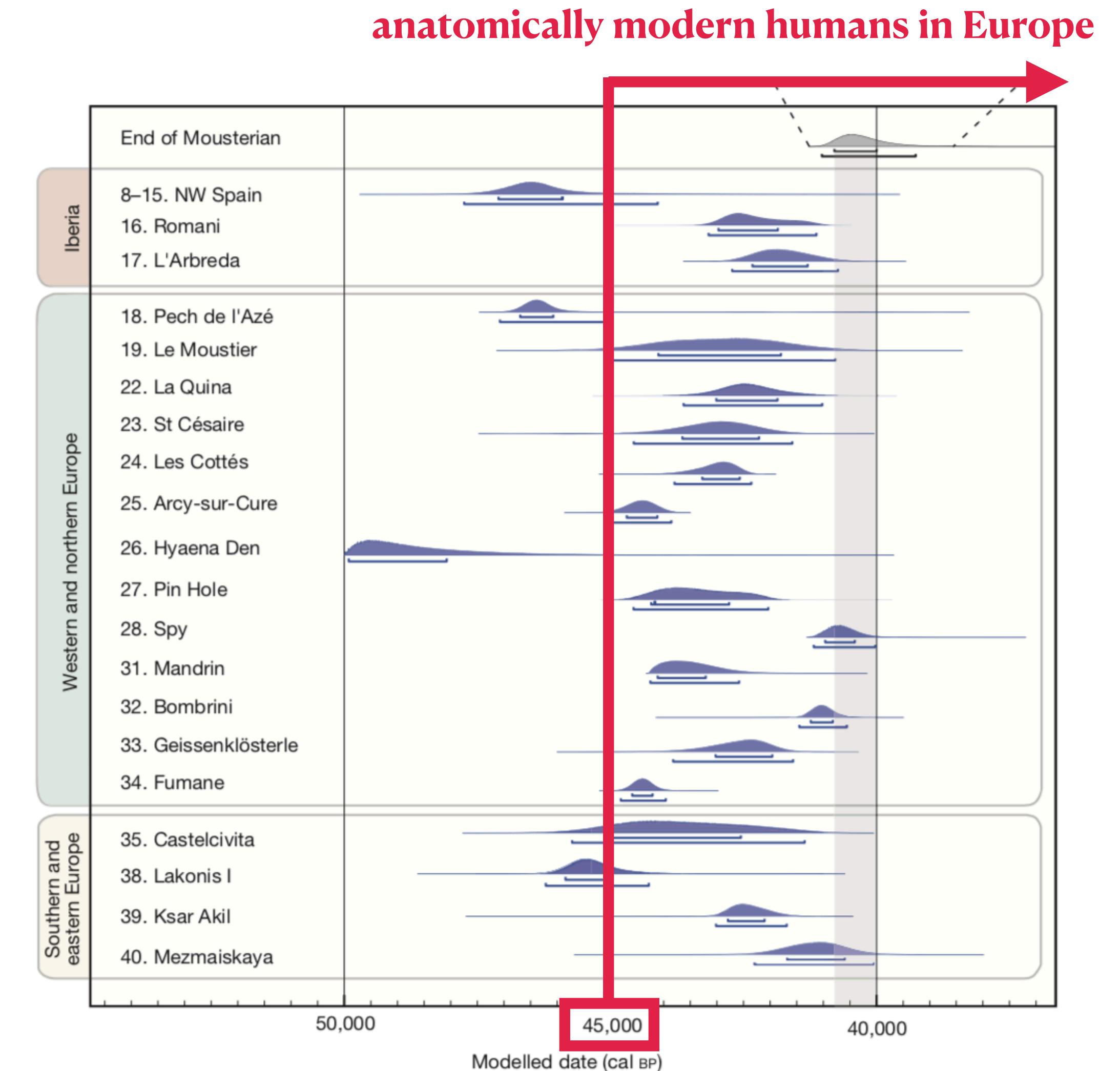
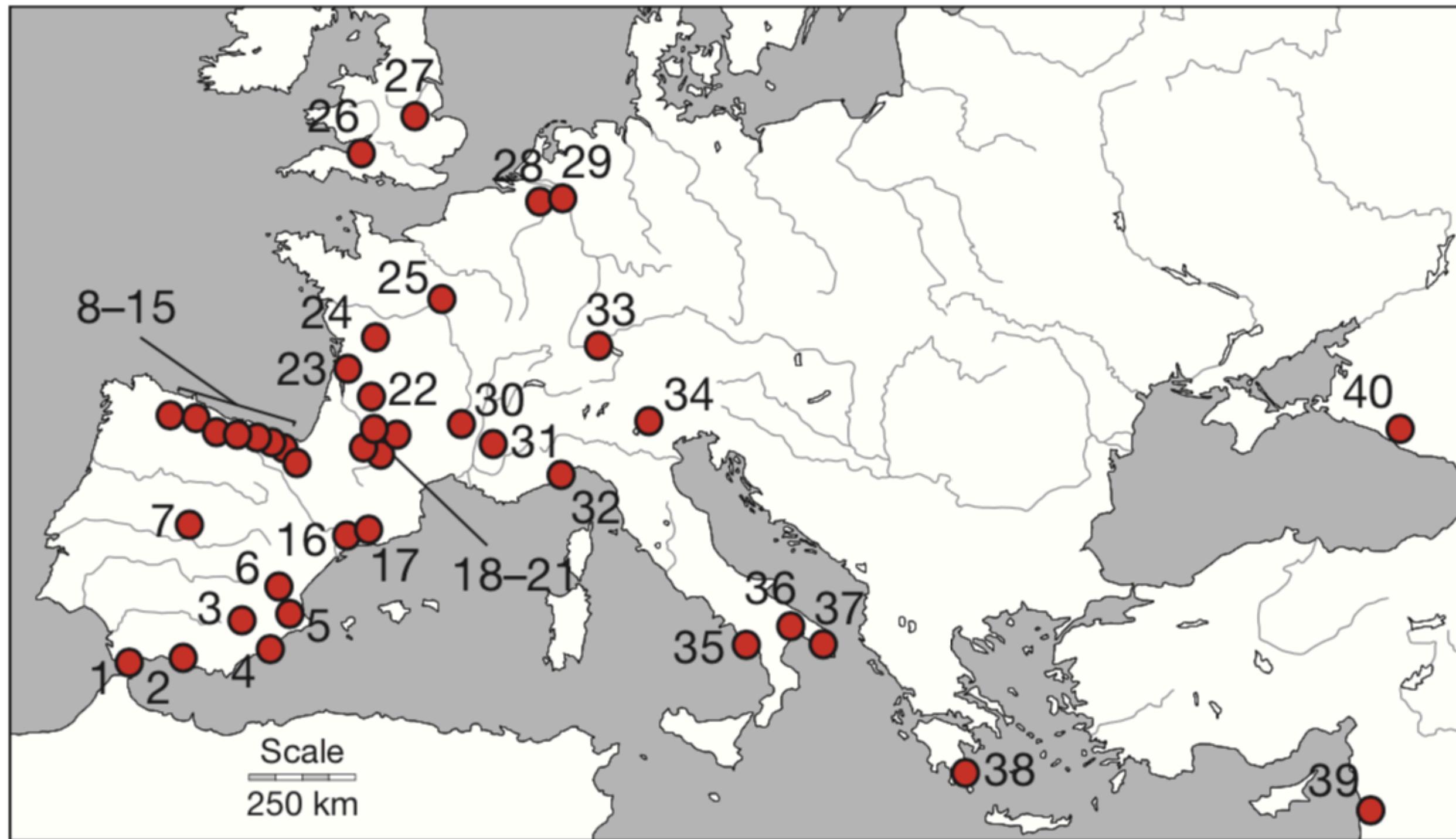
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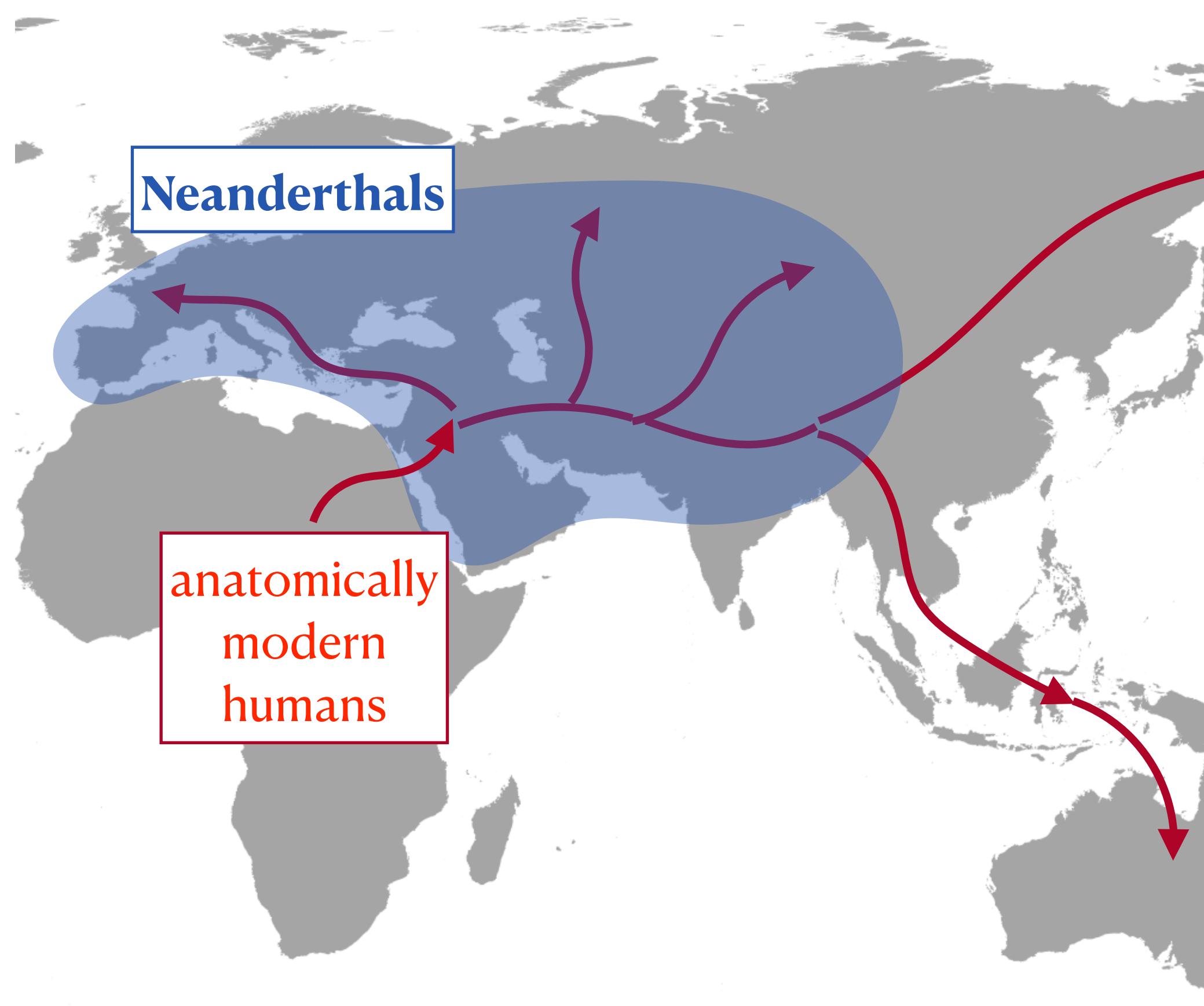
# ~40 kya: Neanderthals vanished



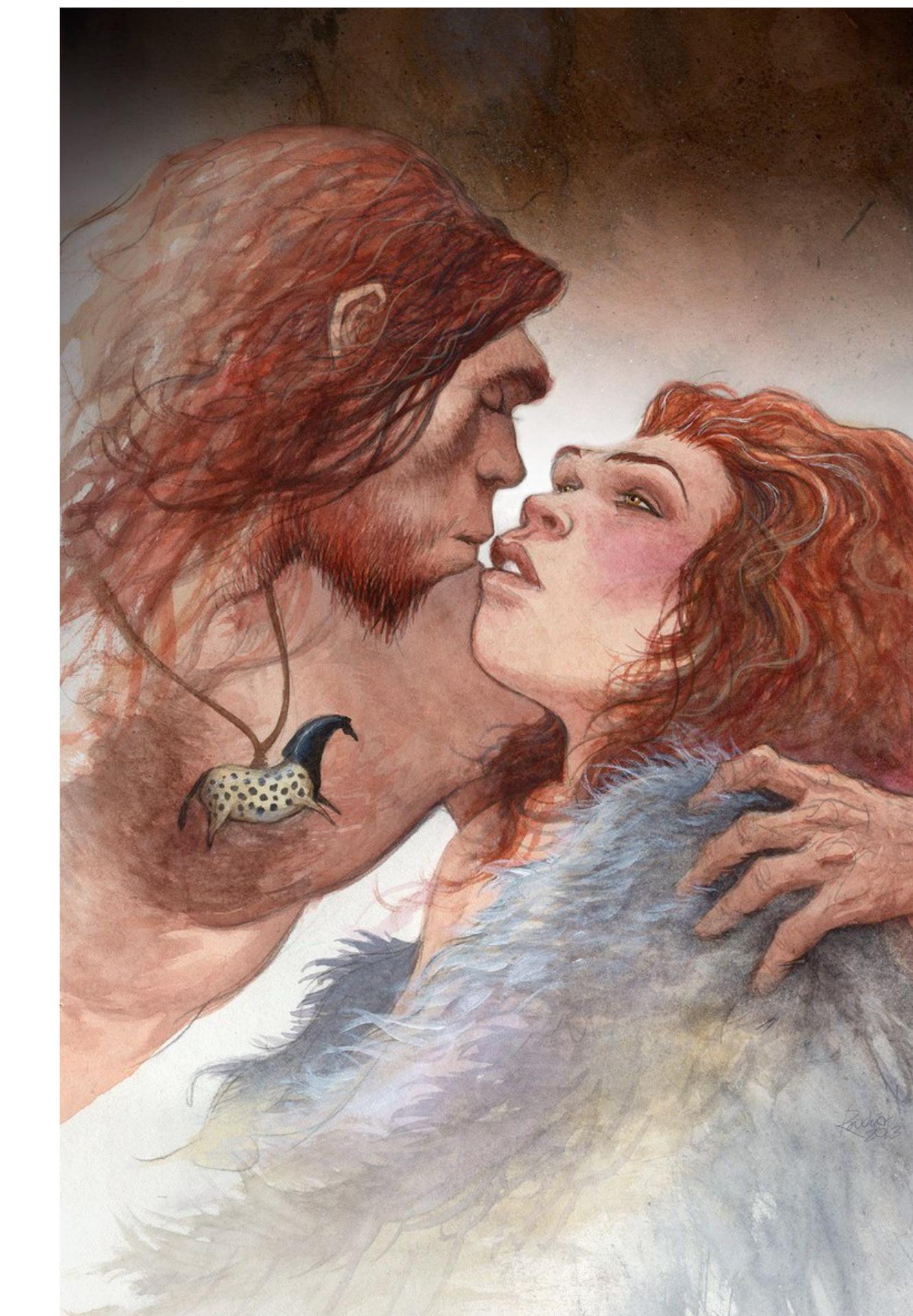
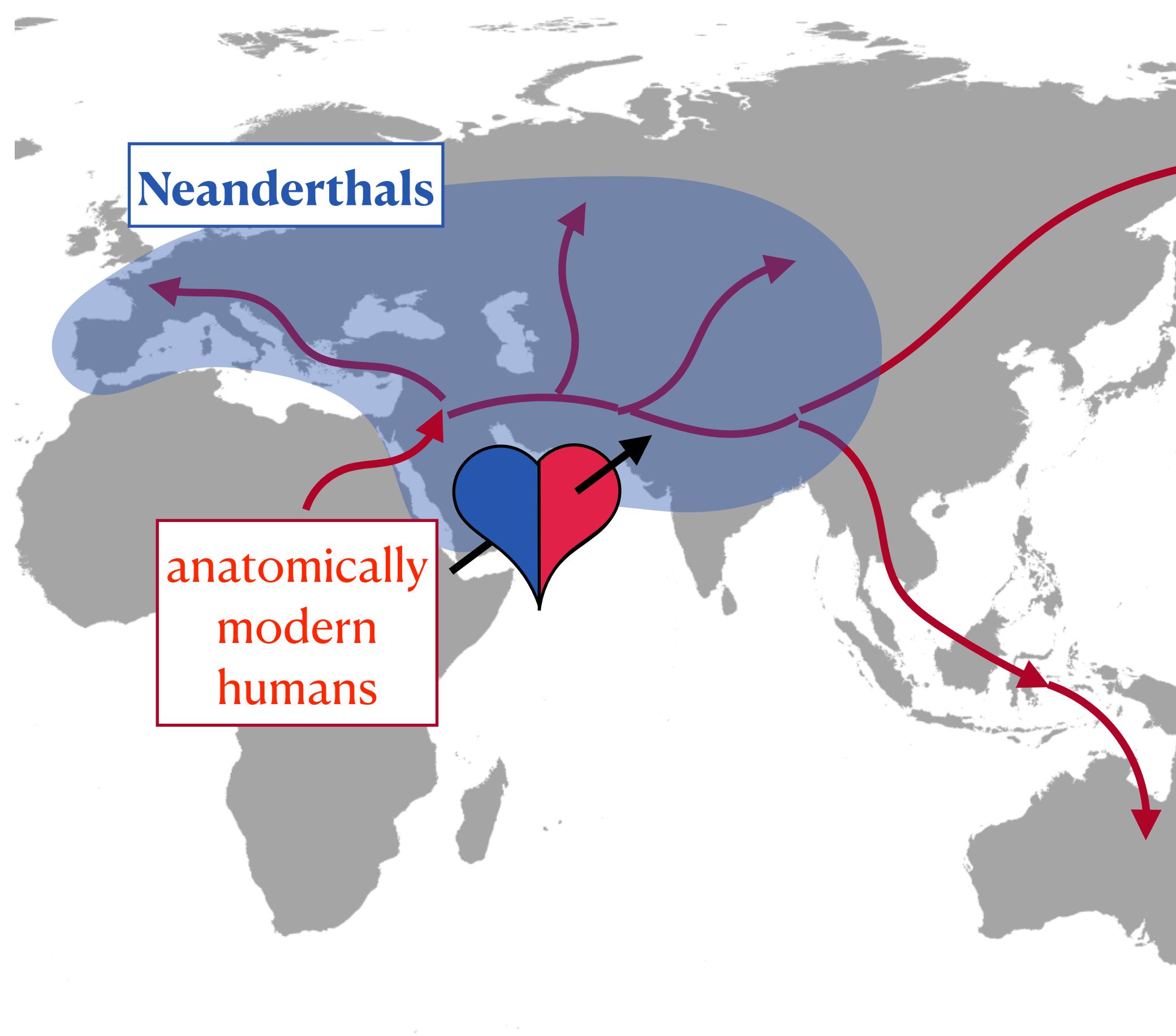
# What happened in the few thousand years of overlap?



# What happened in the few thousand years of overlap?



# Introgression / gene flow / admixture?



<https://twitter.com/ijhublin/status/739866080764628993>

# Morphological evidence?



**~40 thousand years old  
remains of a modern human  
Peștera cu Oase, Romania**

# Neanderthal DNA? (ancient DNA, aDNA)



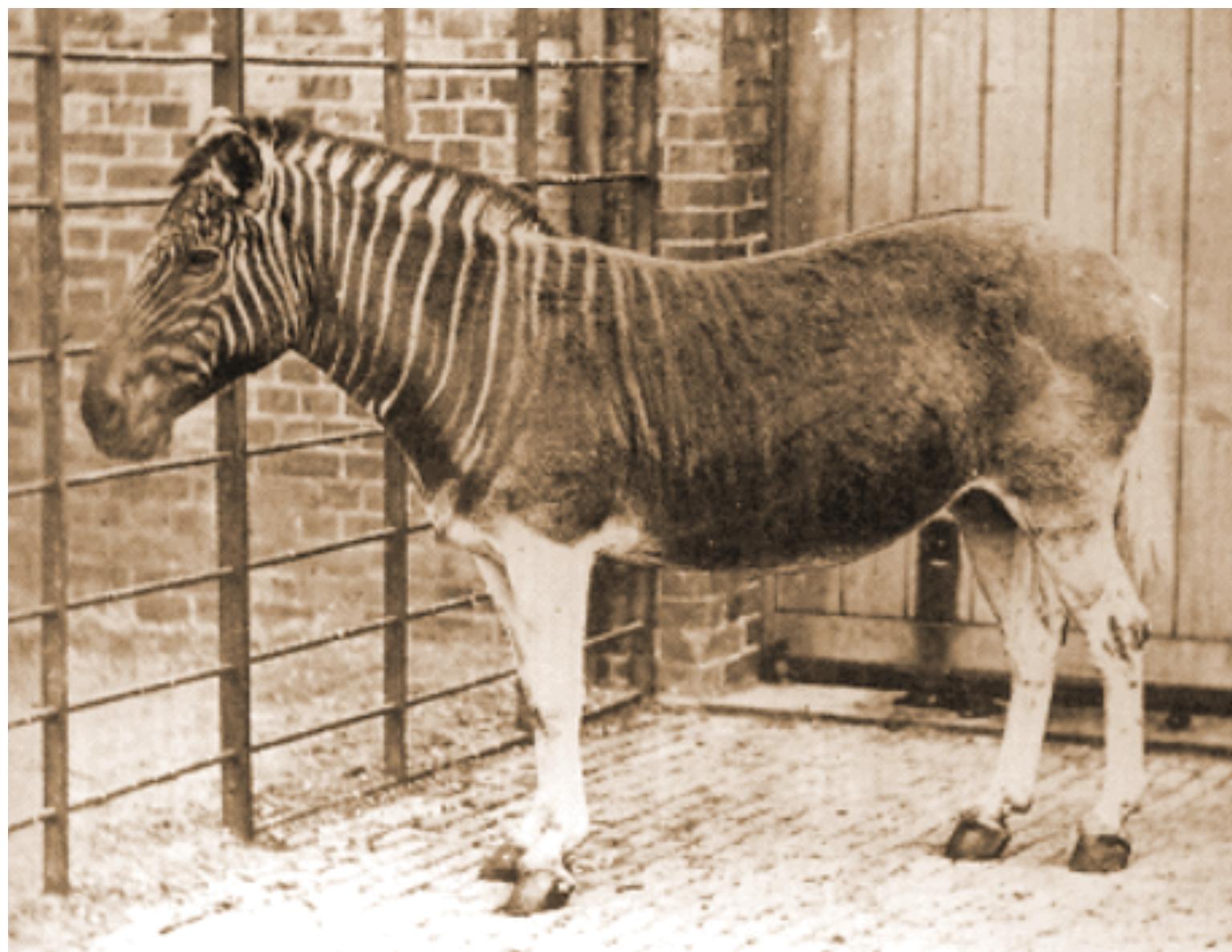
# 1984

## DNA sequences from the quagga, an extinct member of the horse family

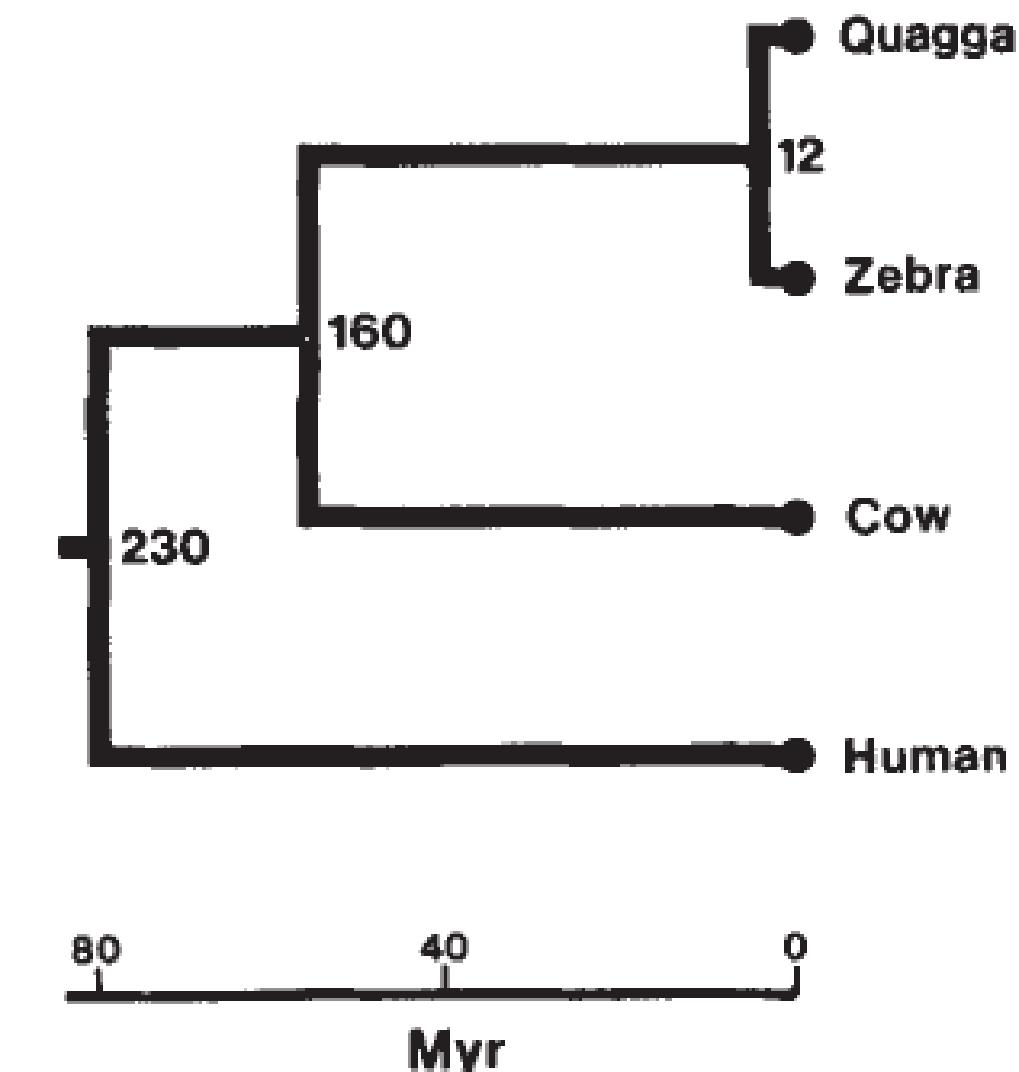
Russell Higuchi\*, Barbara Bowman\*, Mary Freiberger\*,  
Oliver A. Ryder† & Allan C. Wilson\*

\* Department of Biochemistry, University of California, Berkeley,  
California 94720, USA

† Research Department, San Diego Zoo, San Diego,  
California 92103, USA



- 150 years old tissue from a museum specimen
- 229 bp mitochondrial DNA



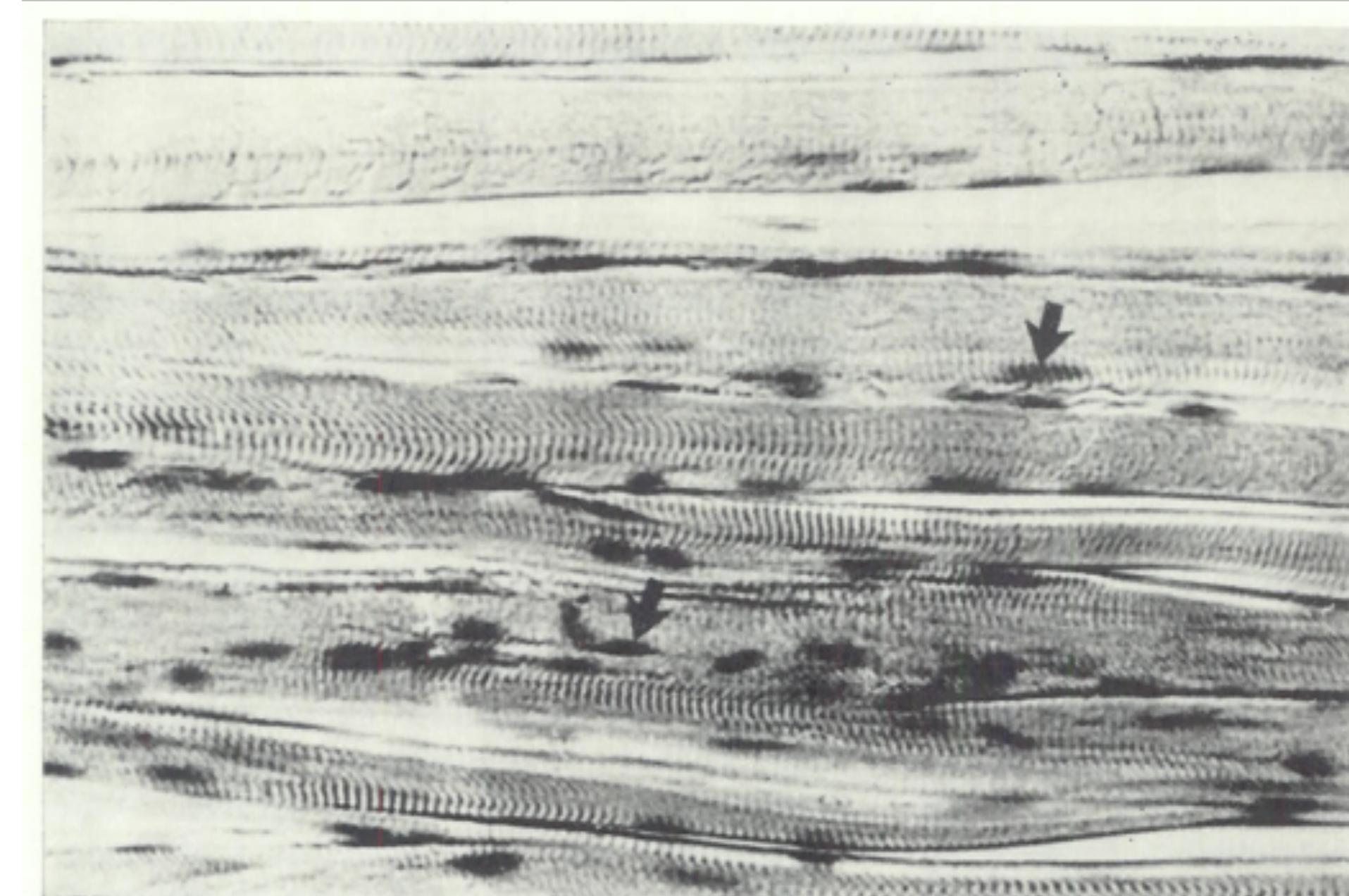
# 1985

## Molecular cloning of Ancient Egyptian mummy DNA

Svante Pääbo

Department of Cell Research, The Wallenberg Laboratory,  
University of Uppsala, Box 562, S-75122 Uppsala, Sweden and  
Institute of Egyptology, Gustavianum, University of Uppsala,  
S-75120 Uppsala, Sweden

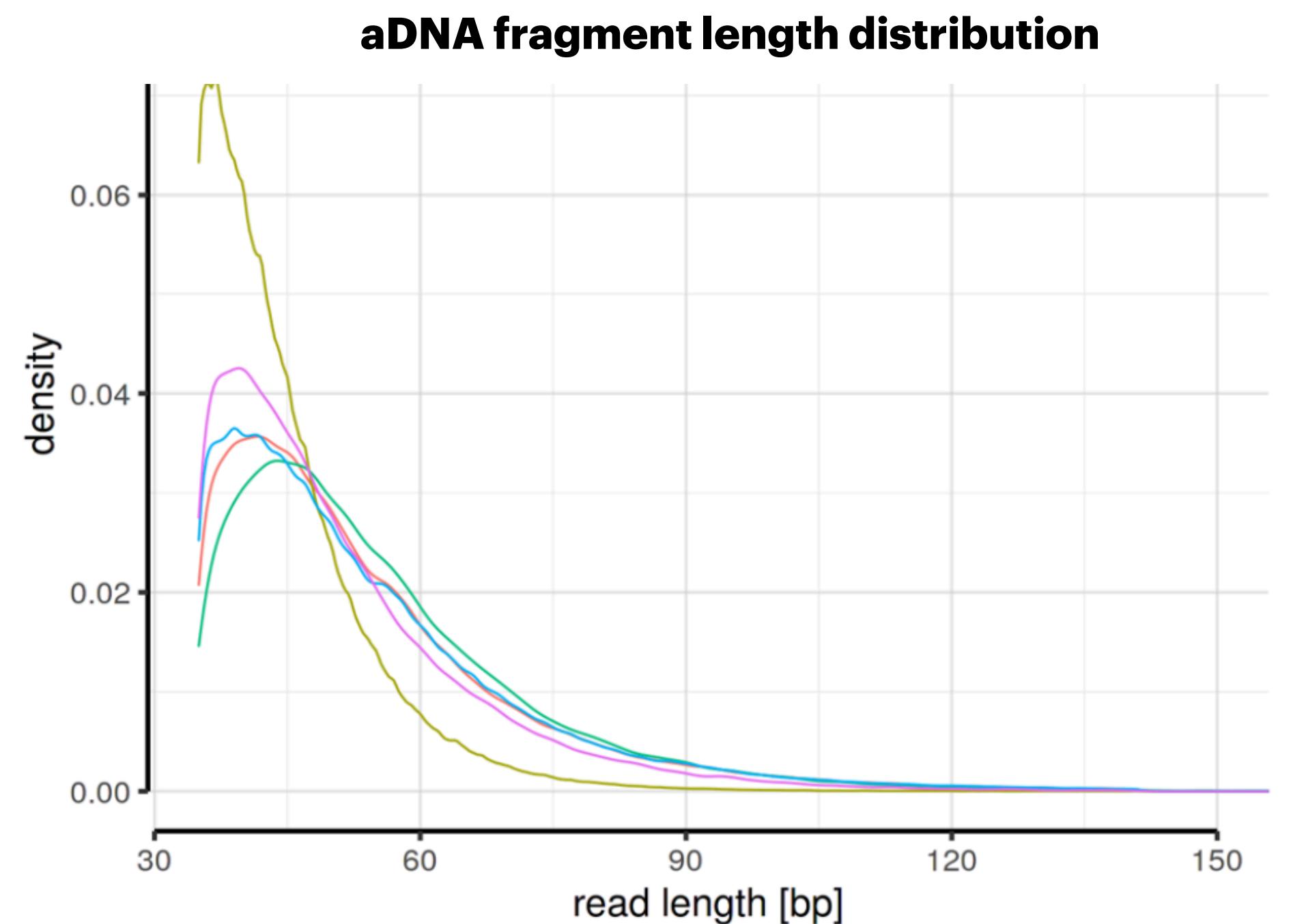
- ~2400 years old mummy
- 3400 bp nuclear DNA



# Molecular characteristics of aDNA

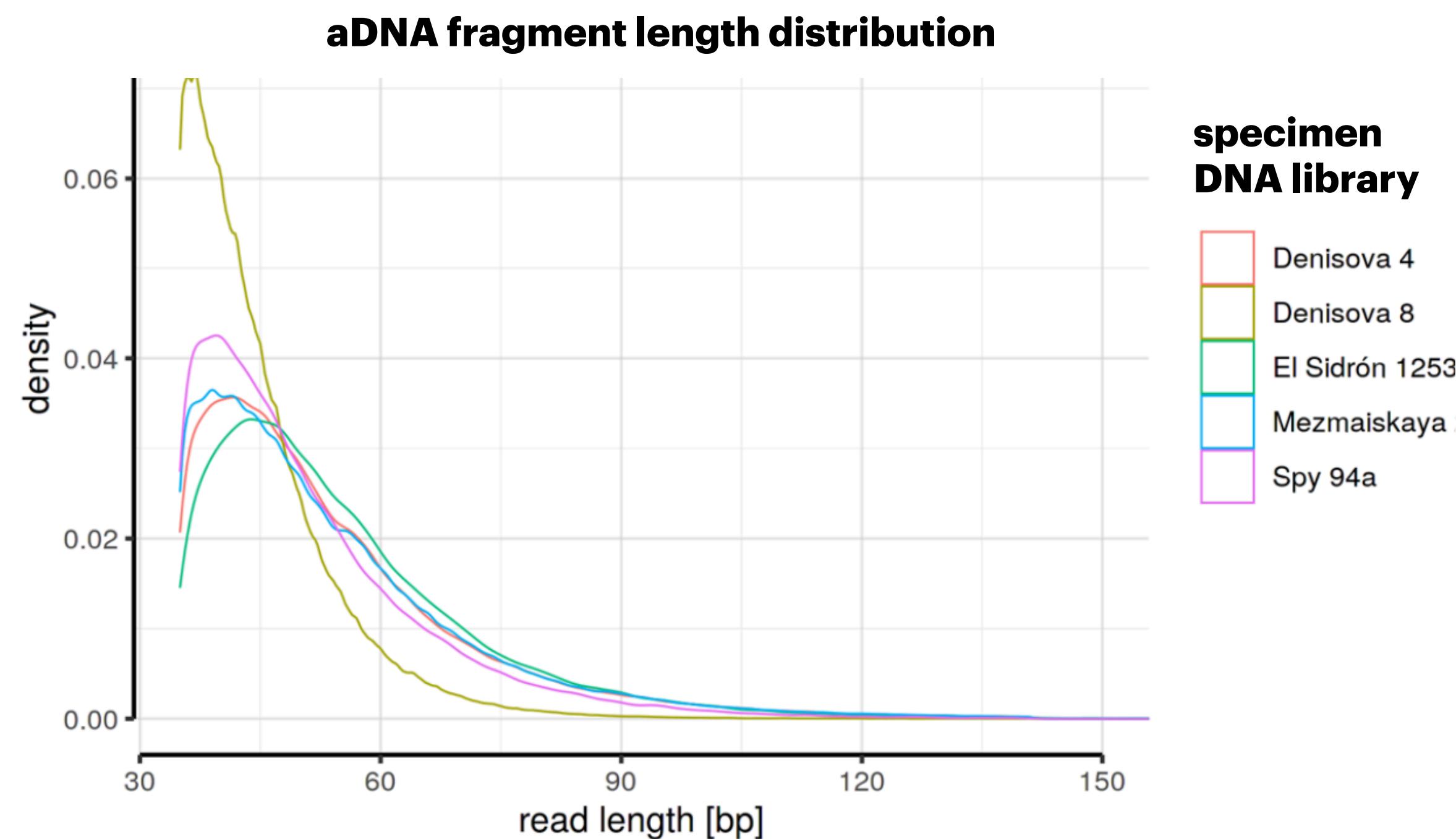
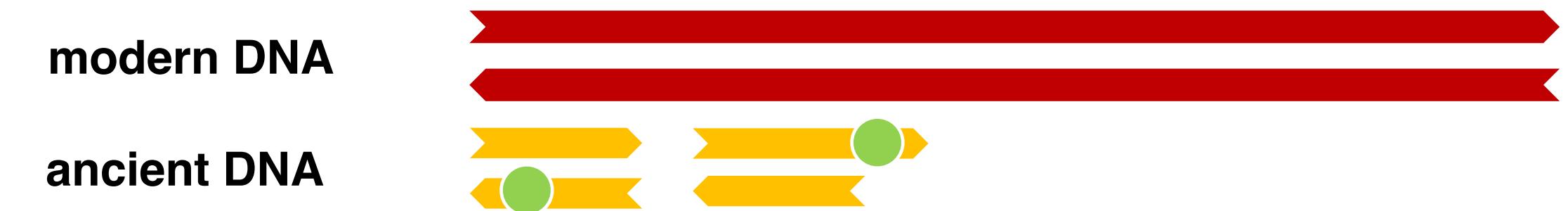
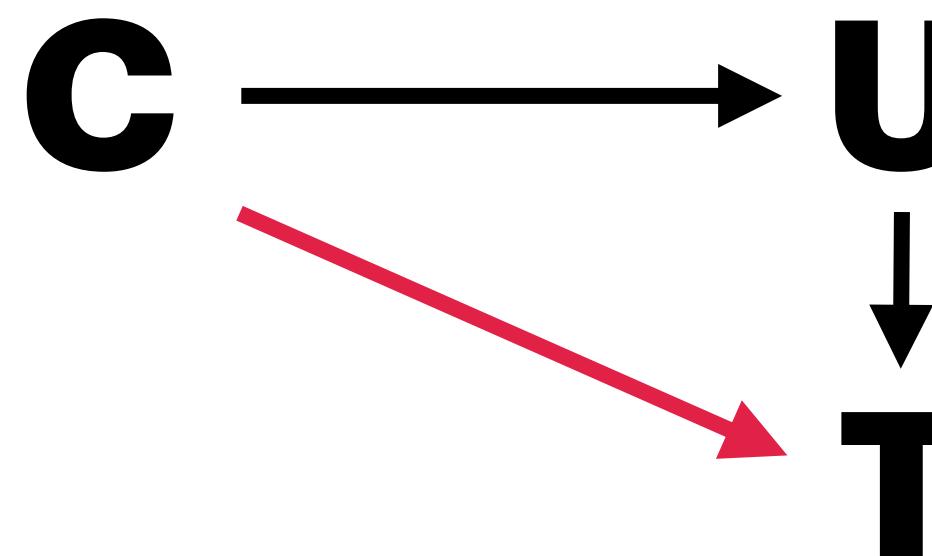
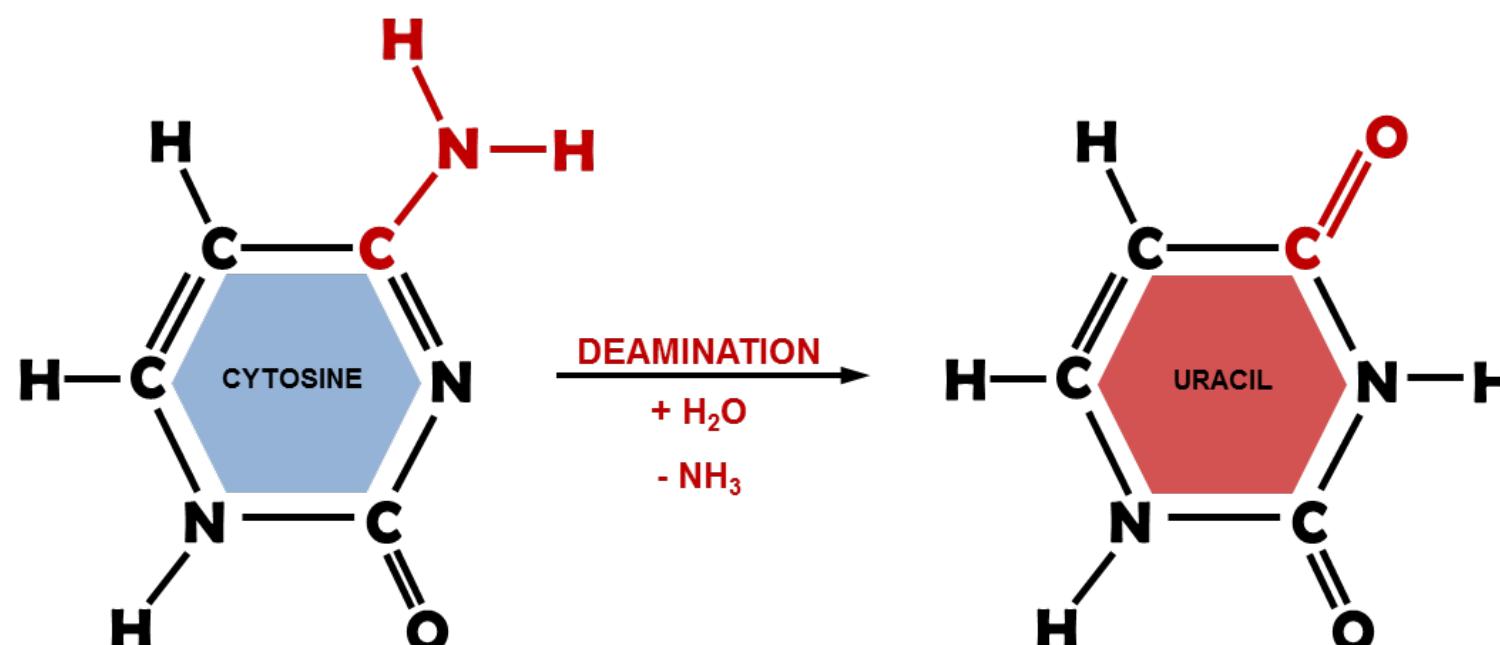
# Molecular characteristics of aDNA

- highly fragmented



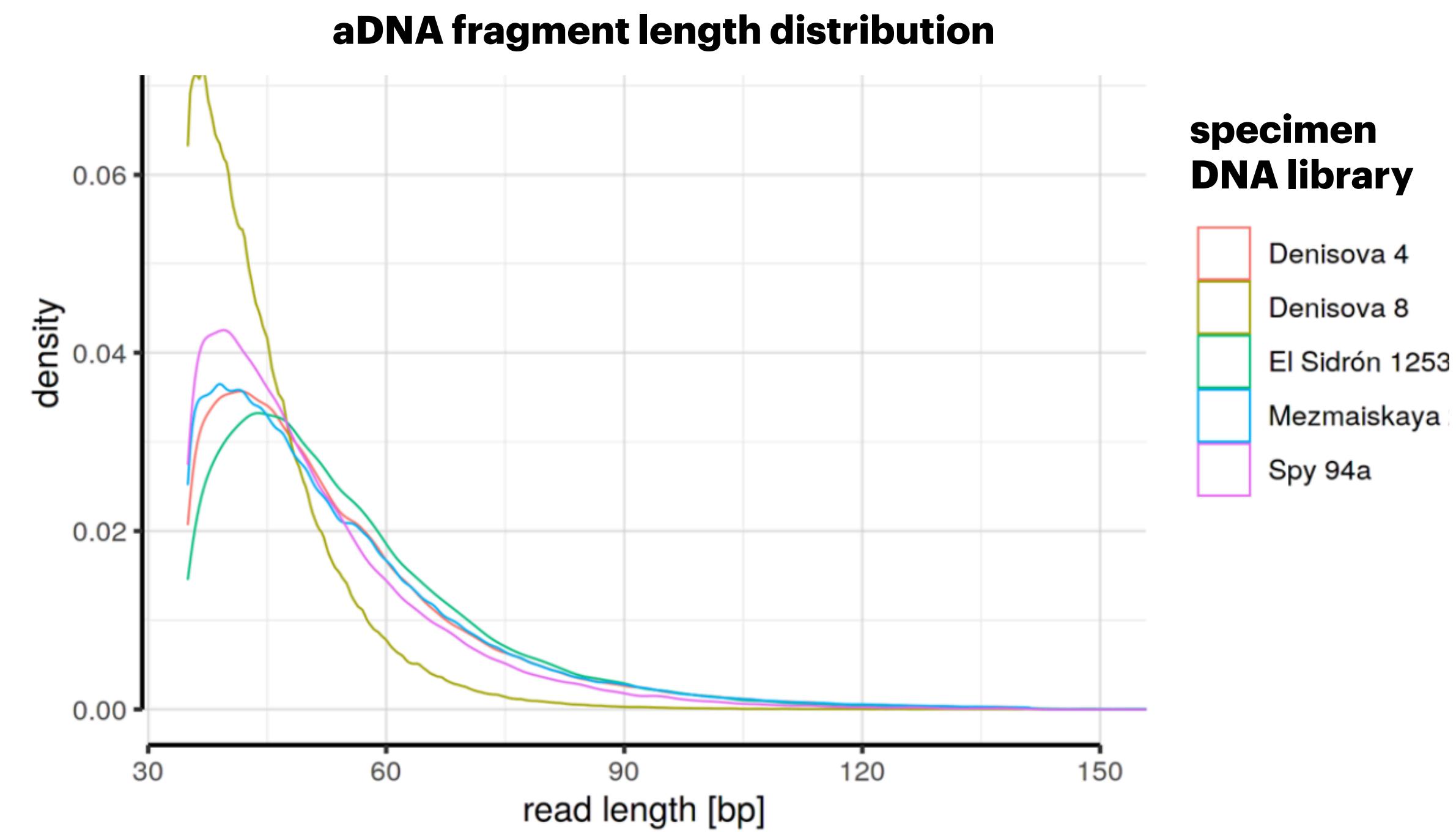
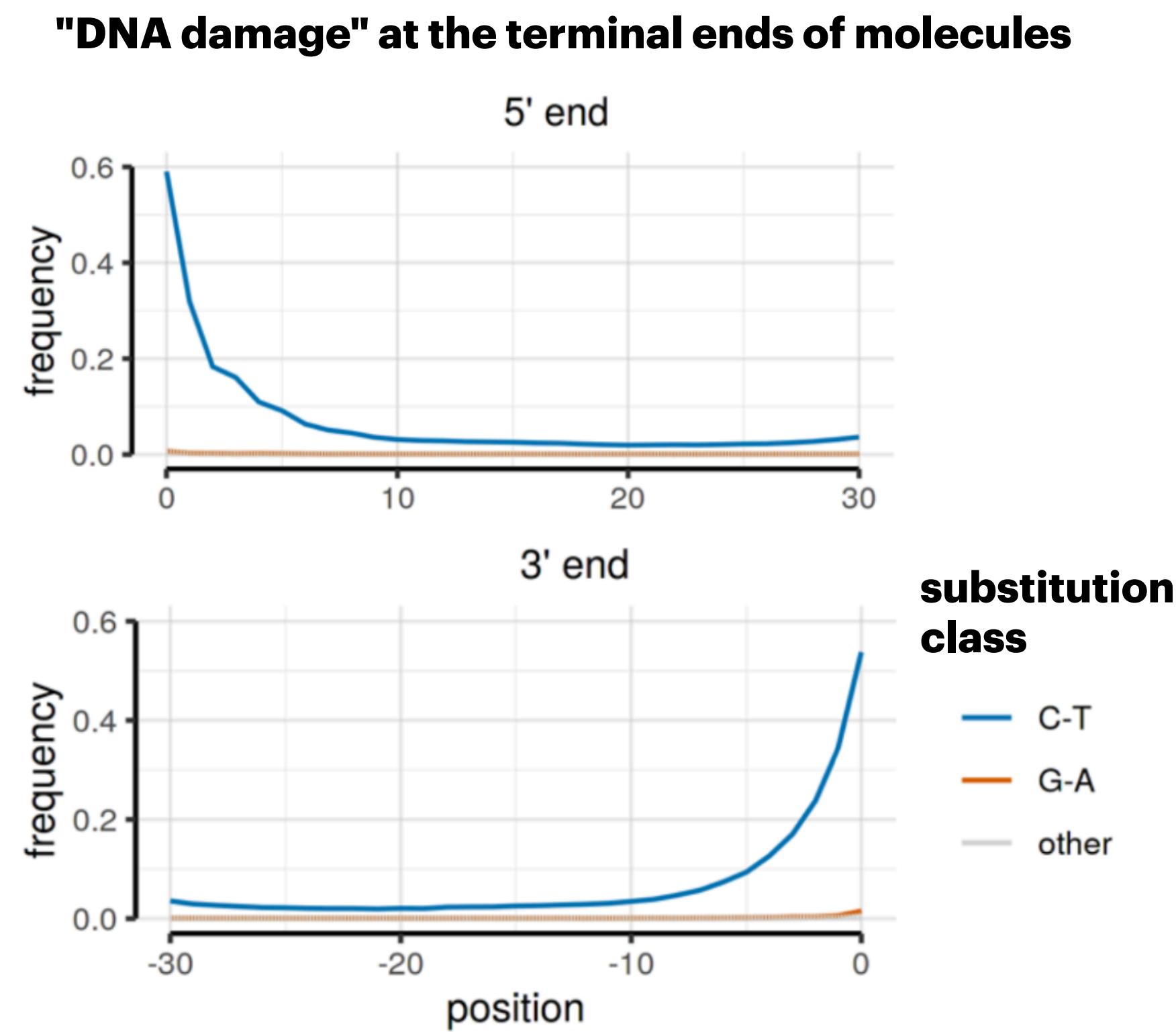
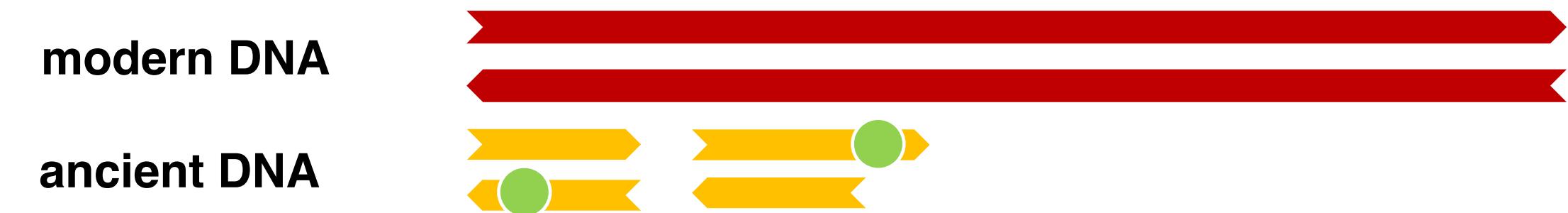
# Molecular characteristics of aDNA

- highly fragmented
- post-mortem chemical modifications



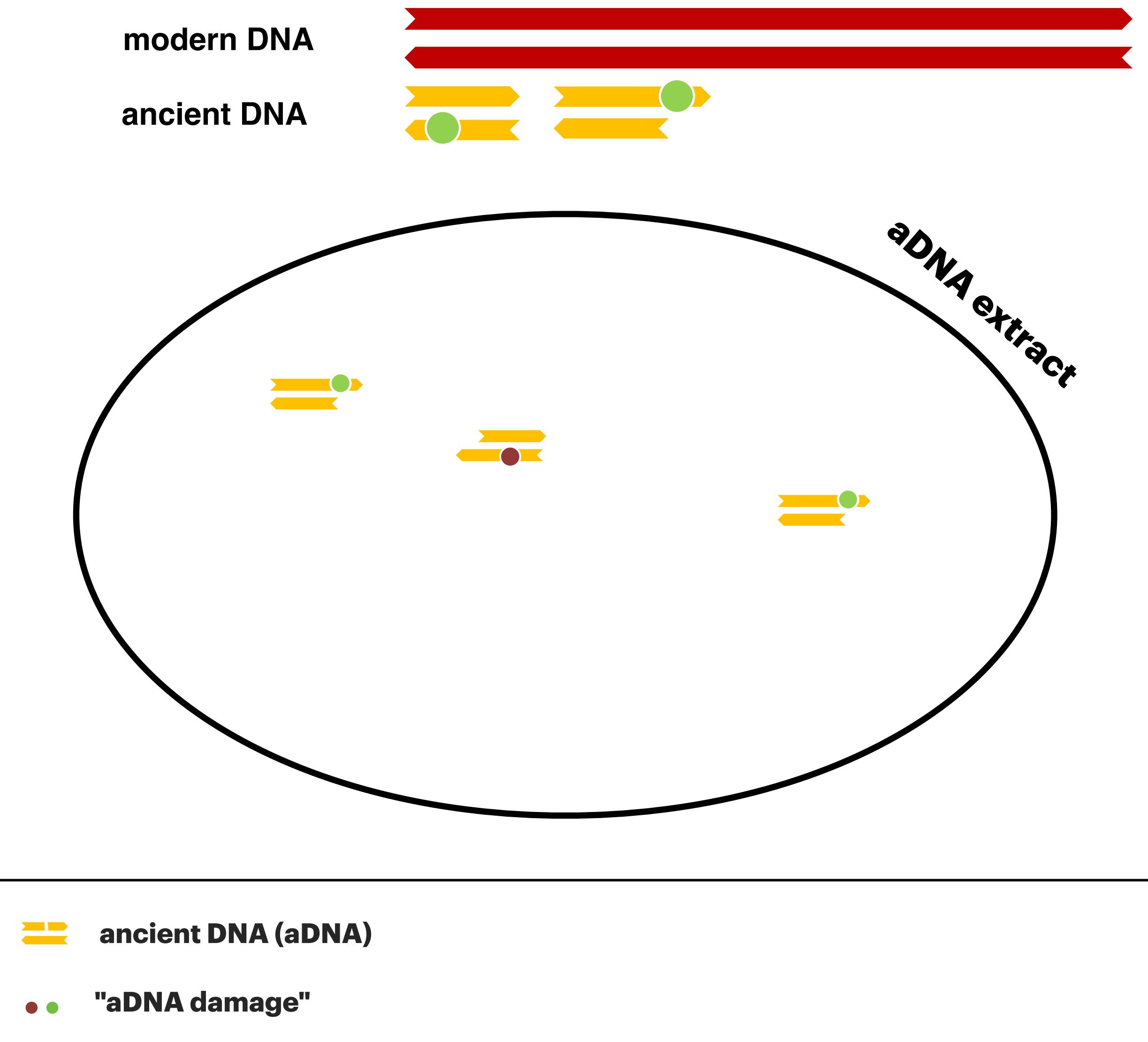
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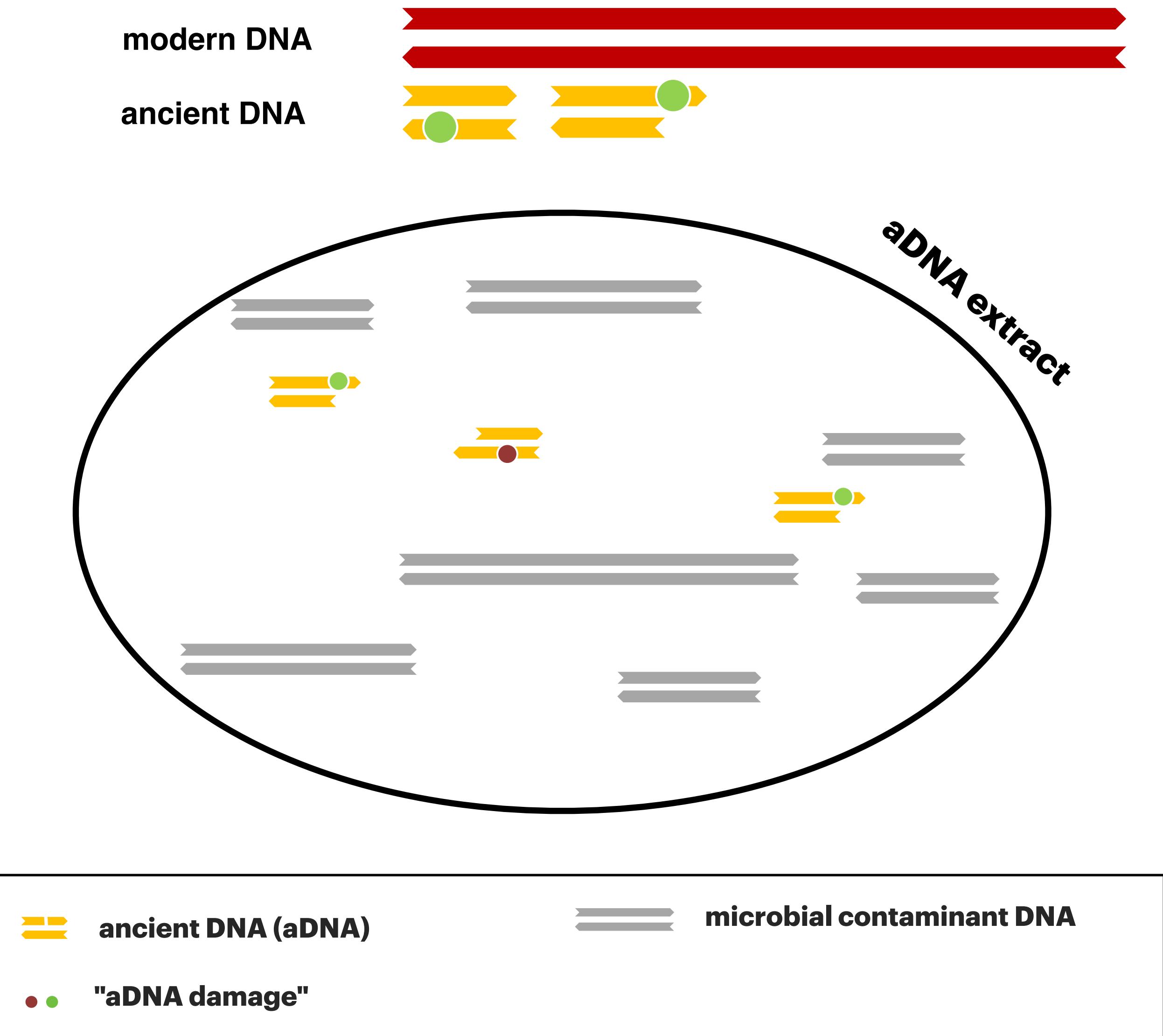
# Molecular characteristics of aDNA

- highly fragmented
- post-mortem chemical modifications
- contamination:
  - microbial DNA
  - human DNA (excavation, museum, lab)



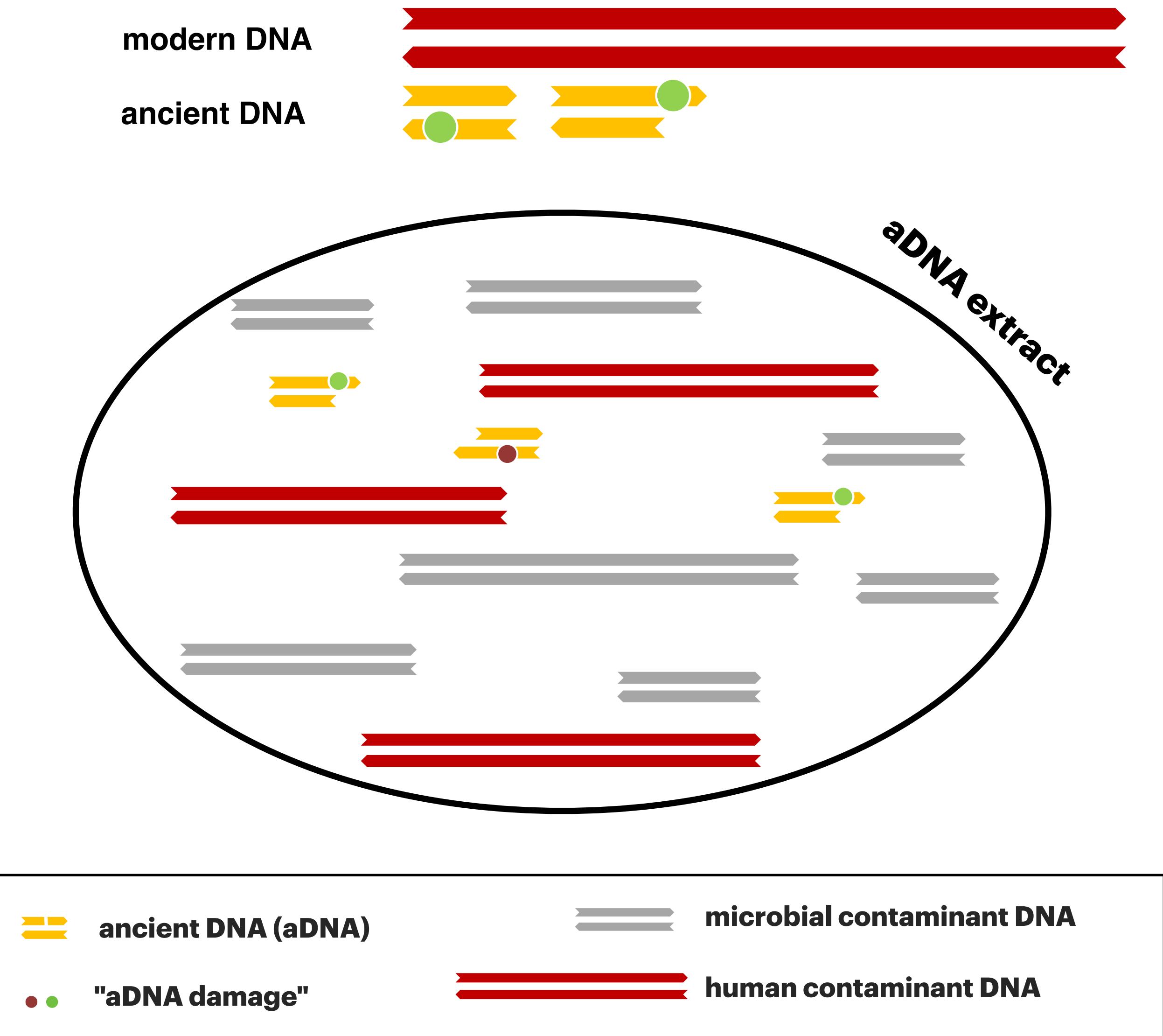
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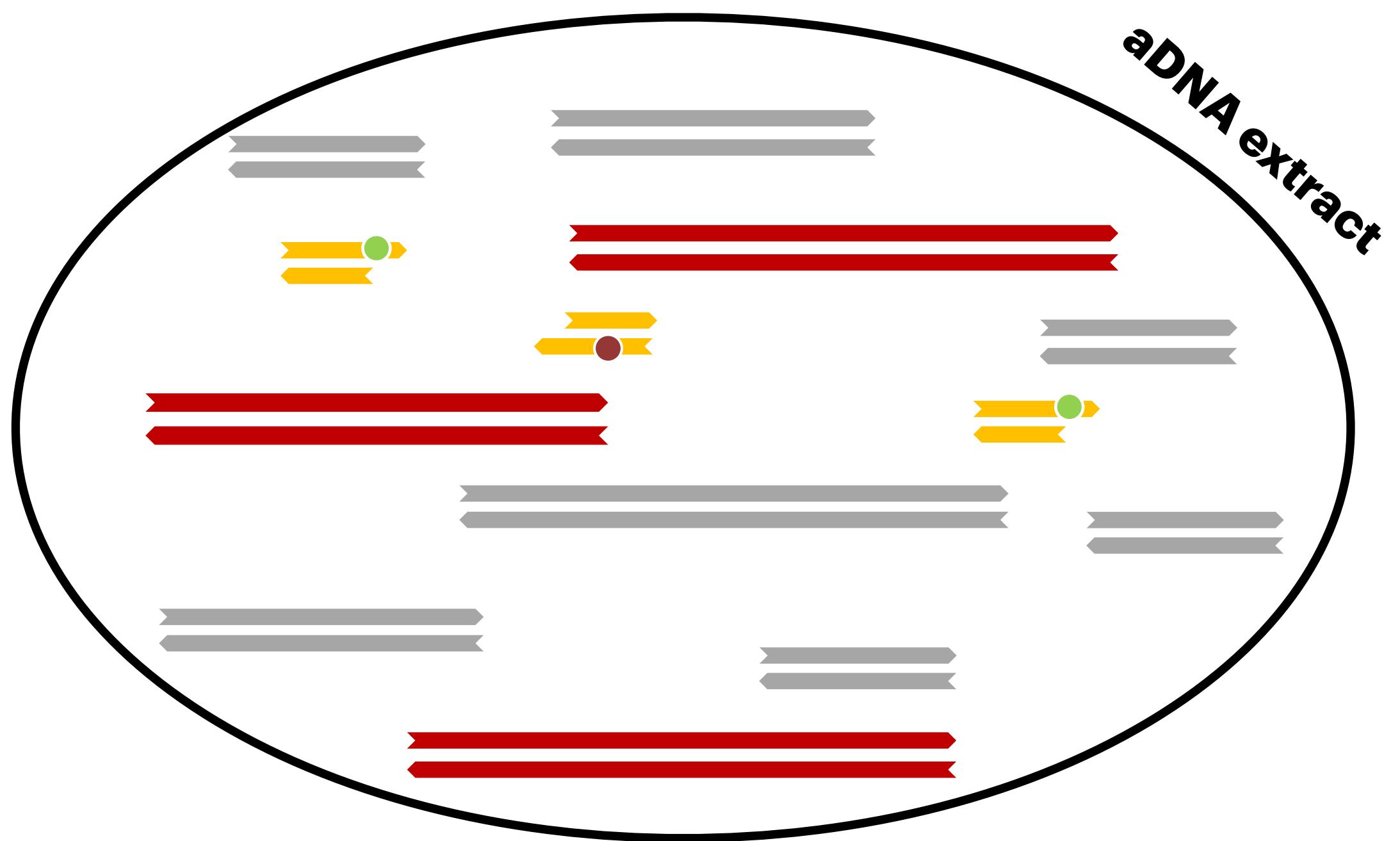
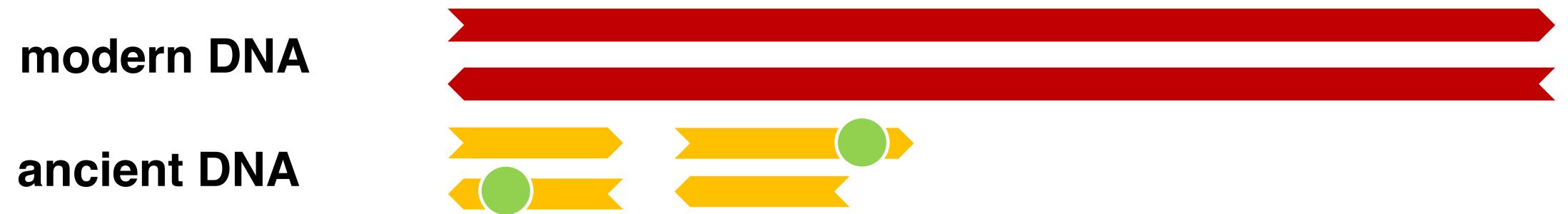


# Molecular characteristics of aDNA

- highly fragmented
- post-mortem chemical modifications
- contamination:
  - microbial DNA
  - human DNA (excavation, museum, lab)

aDNA extract

often < 1% endogenous DNA



ancient DNA (aDNA)

"aDNA damage"

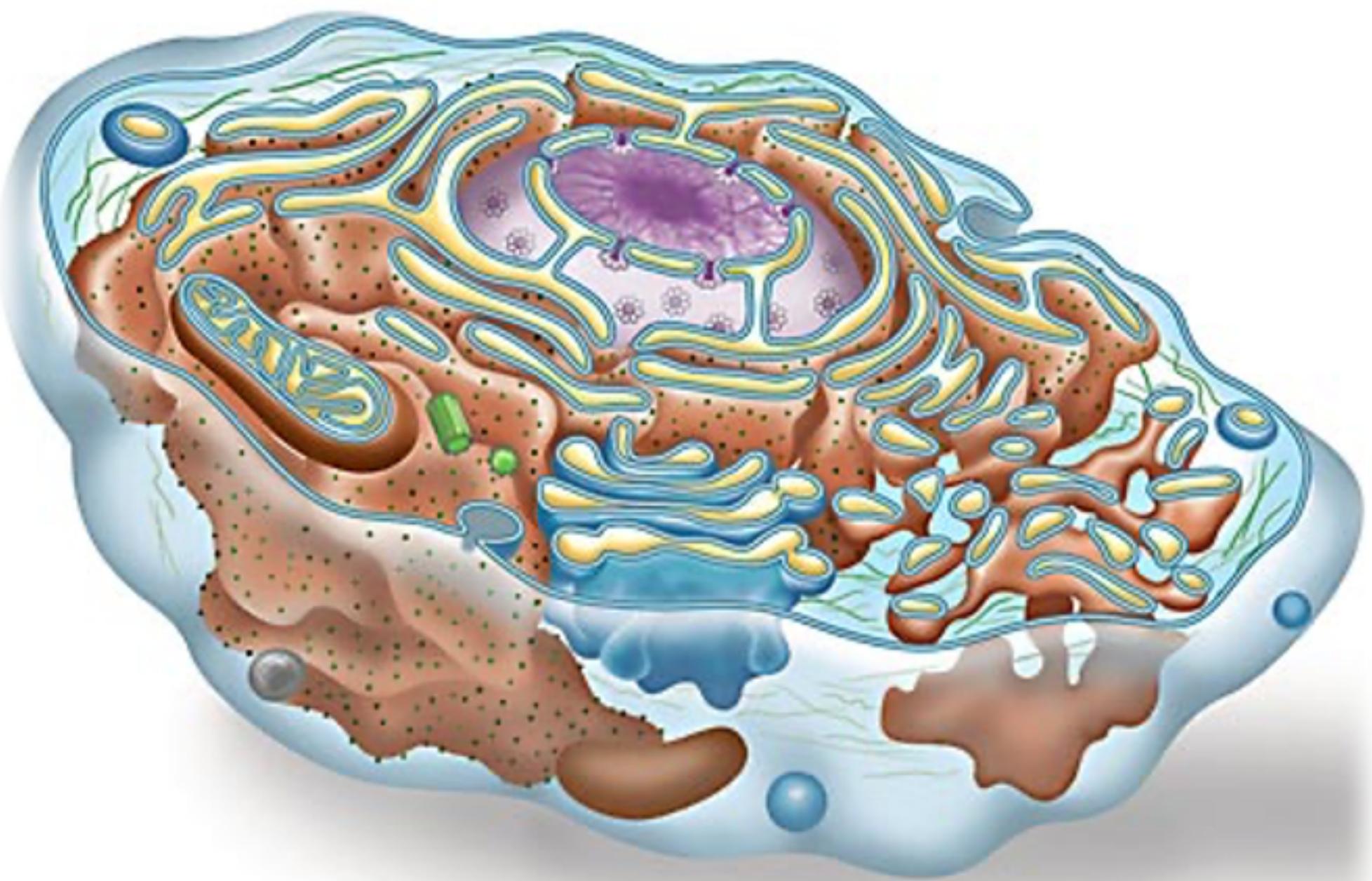
microbial contaminant DNA

human contaminant DNA

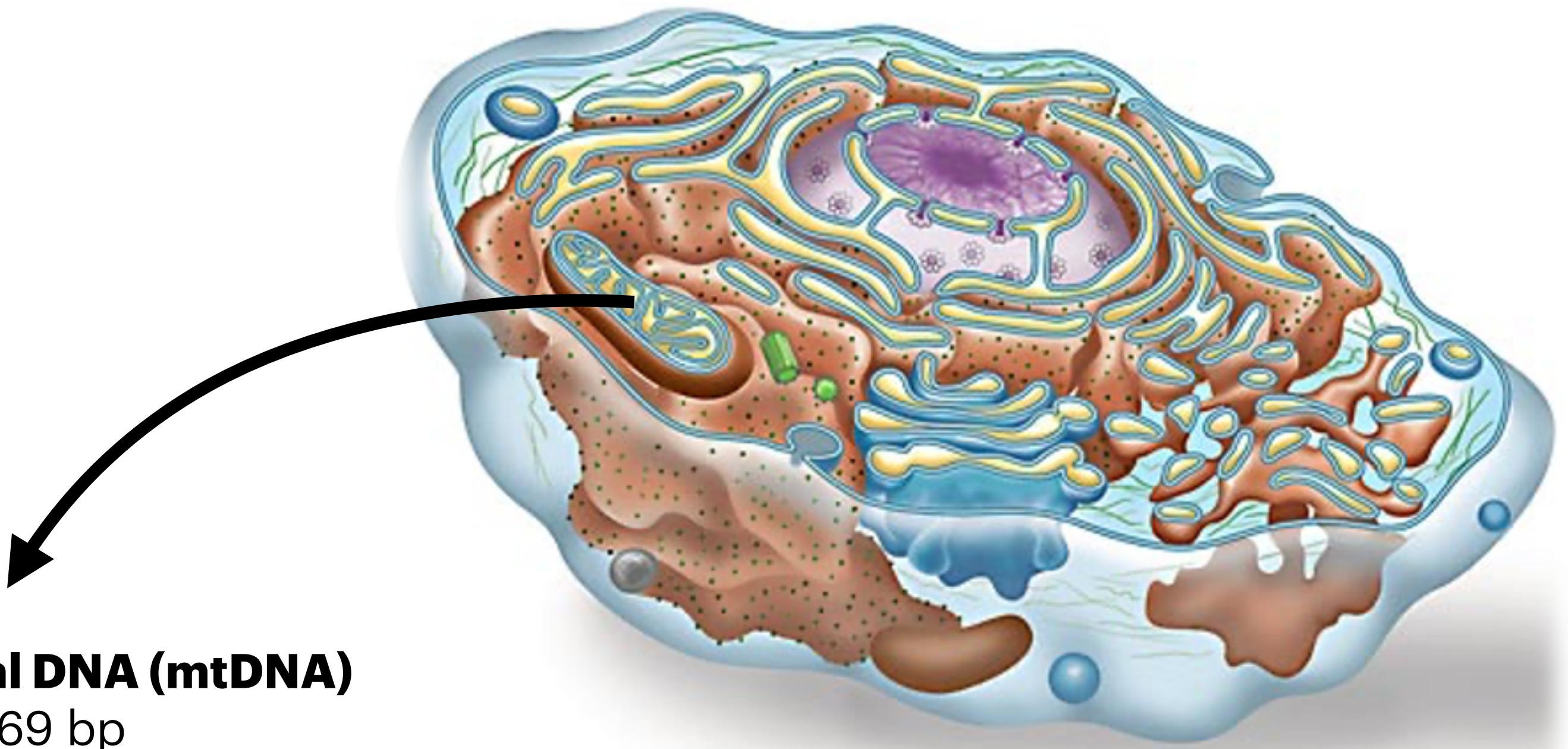
# Neanderthal DNA?



# Two sources of DNA



# Two sources of DNA

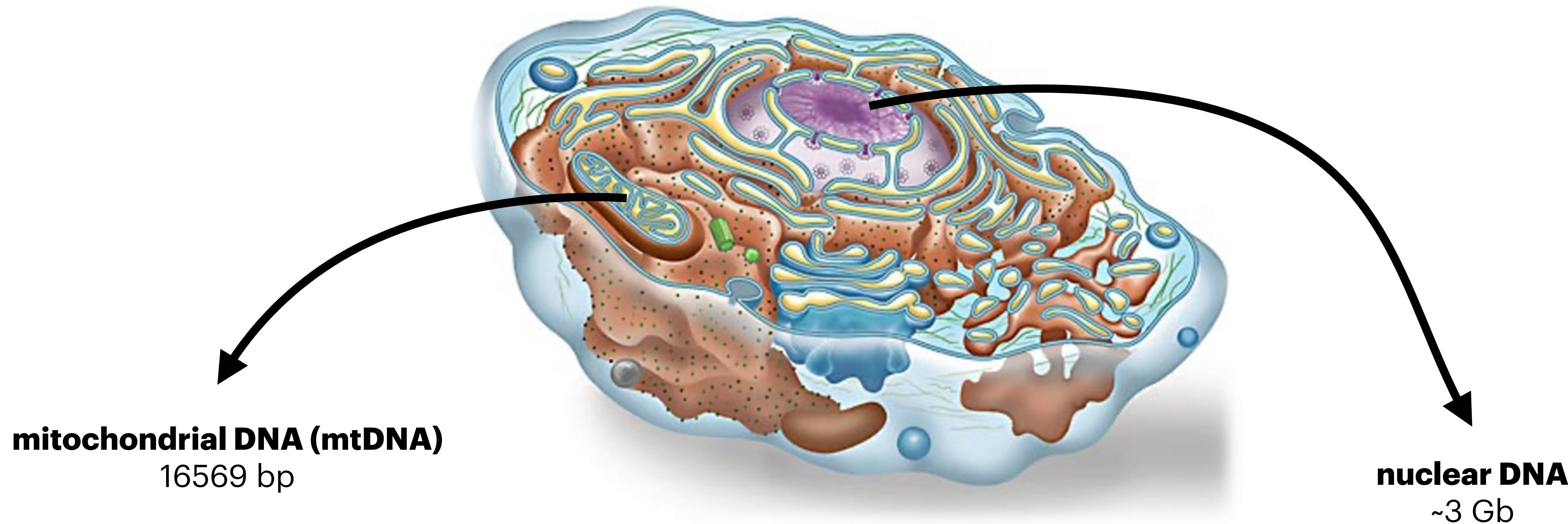


## mitochondrial DNA (mtDNA)

16569 bp

- just one locus
- transmitted along maternal line
- fast mutation rate
- **thousands of copies in a cell**

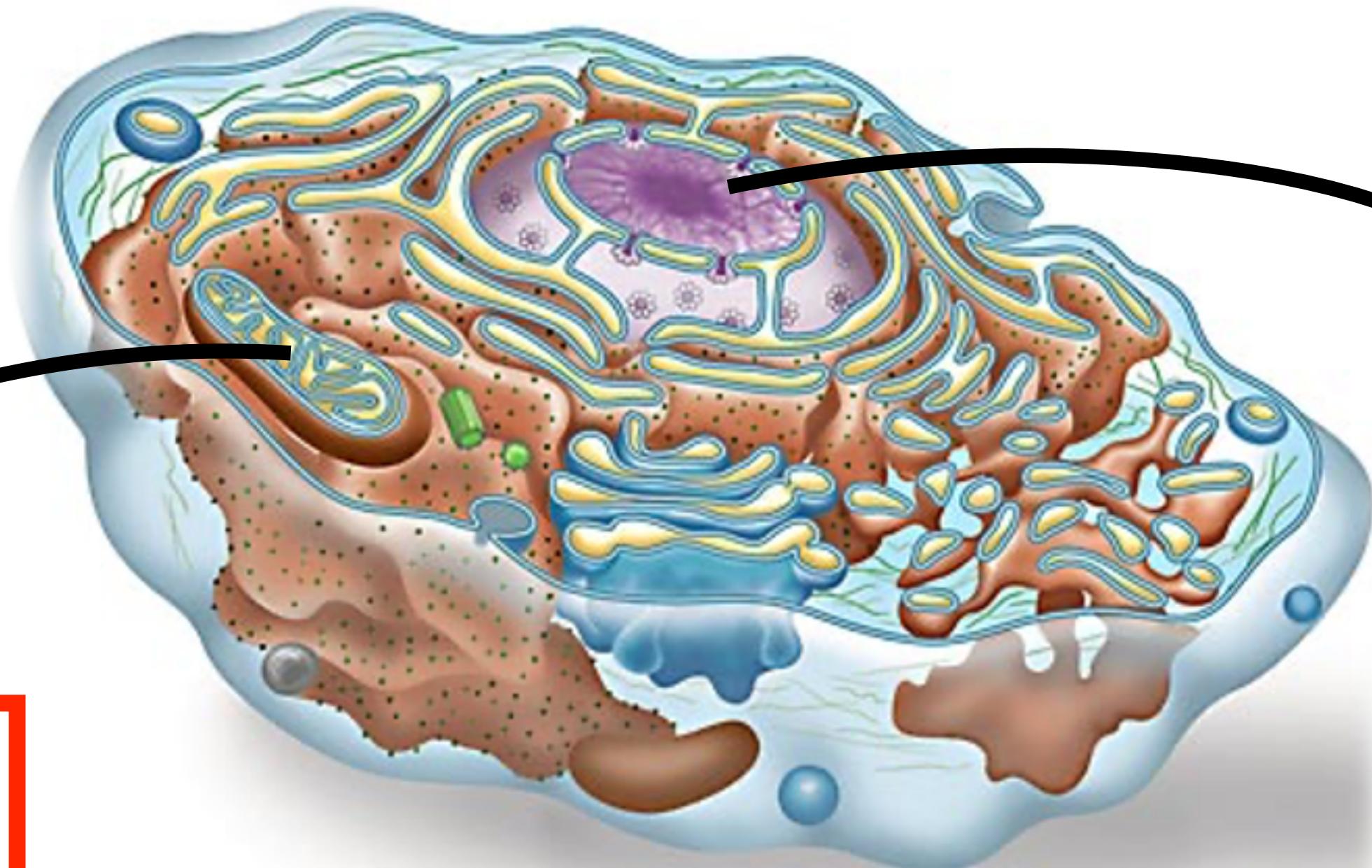
# Two sources of DNA



- just one locus
- transmitted along maternal line
- fast mutation rate
- **thousands of copies in a cell**

- thousands of loci due to recombination
- complex mosaic of genetic history
- **two copies in a human cell**

# Two sources of DNA



## mitochondrial DNA (mtDNA)

16569 bp

- just one locus
- transmitted along maternal line
- fast mutation rate
- **thousands of copies in a cell**

## nuclear DNA

~3 Gb

- thousands of loci due to recombination
- complex mosaic of genetic history
- **two copies in a human cell**

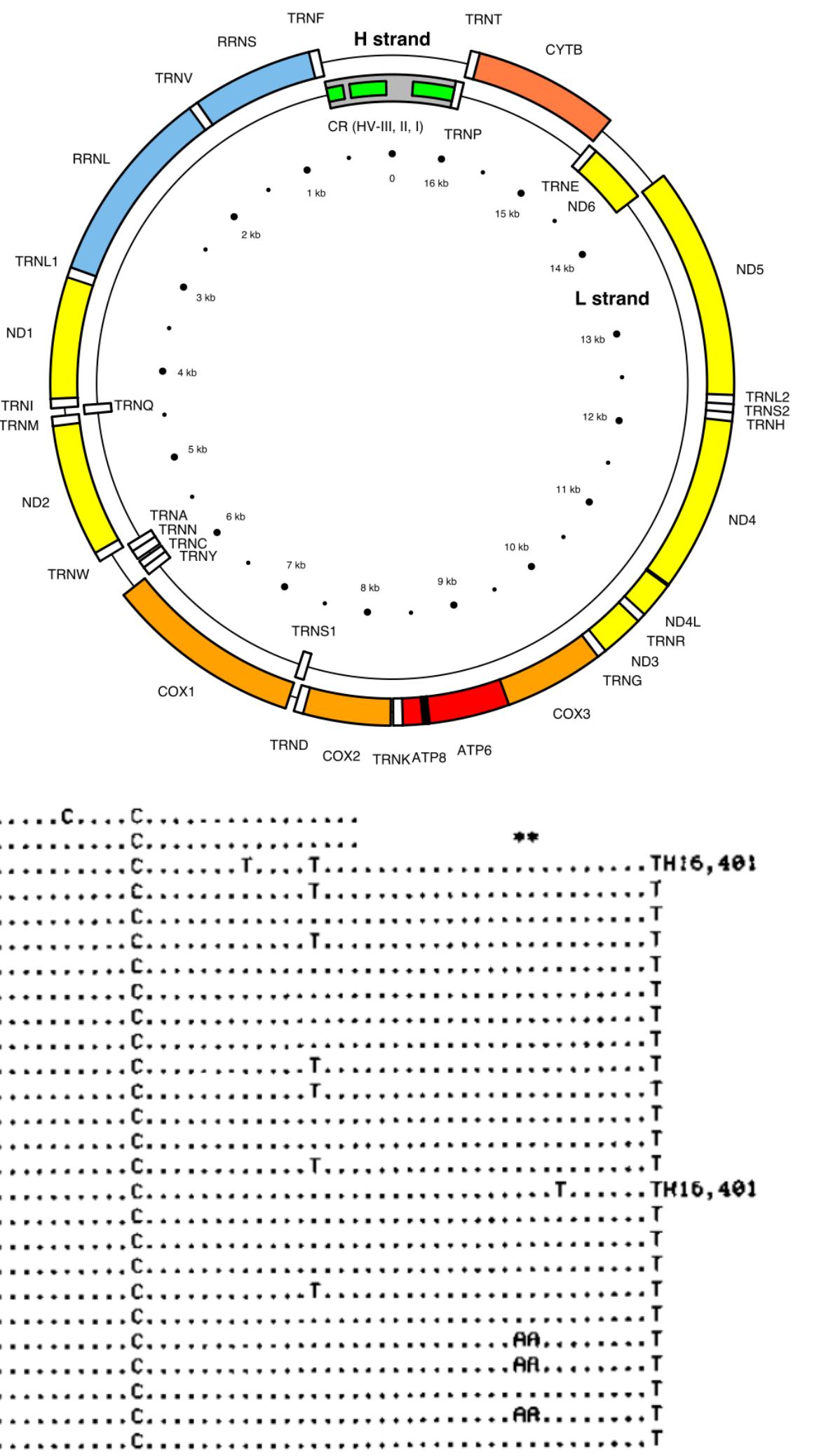
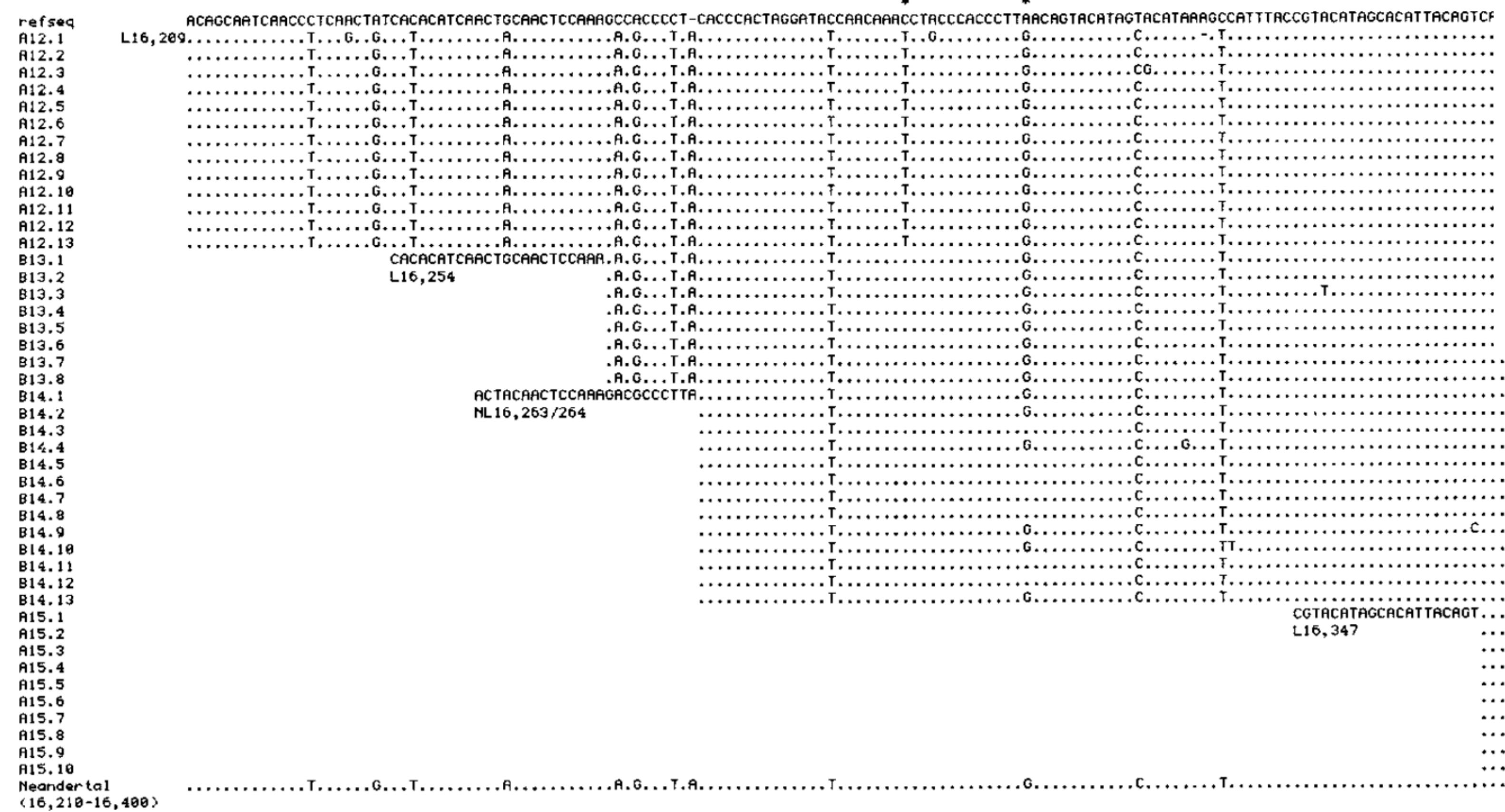
# 1997: Neanderthal mitochondrial DNA!

Cell, Vol. 90, 19–30, July 11, 1997, Copyright ©1997 by Cell Press

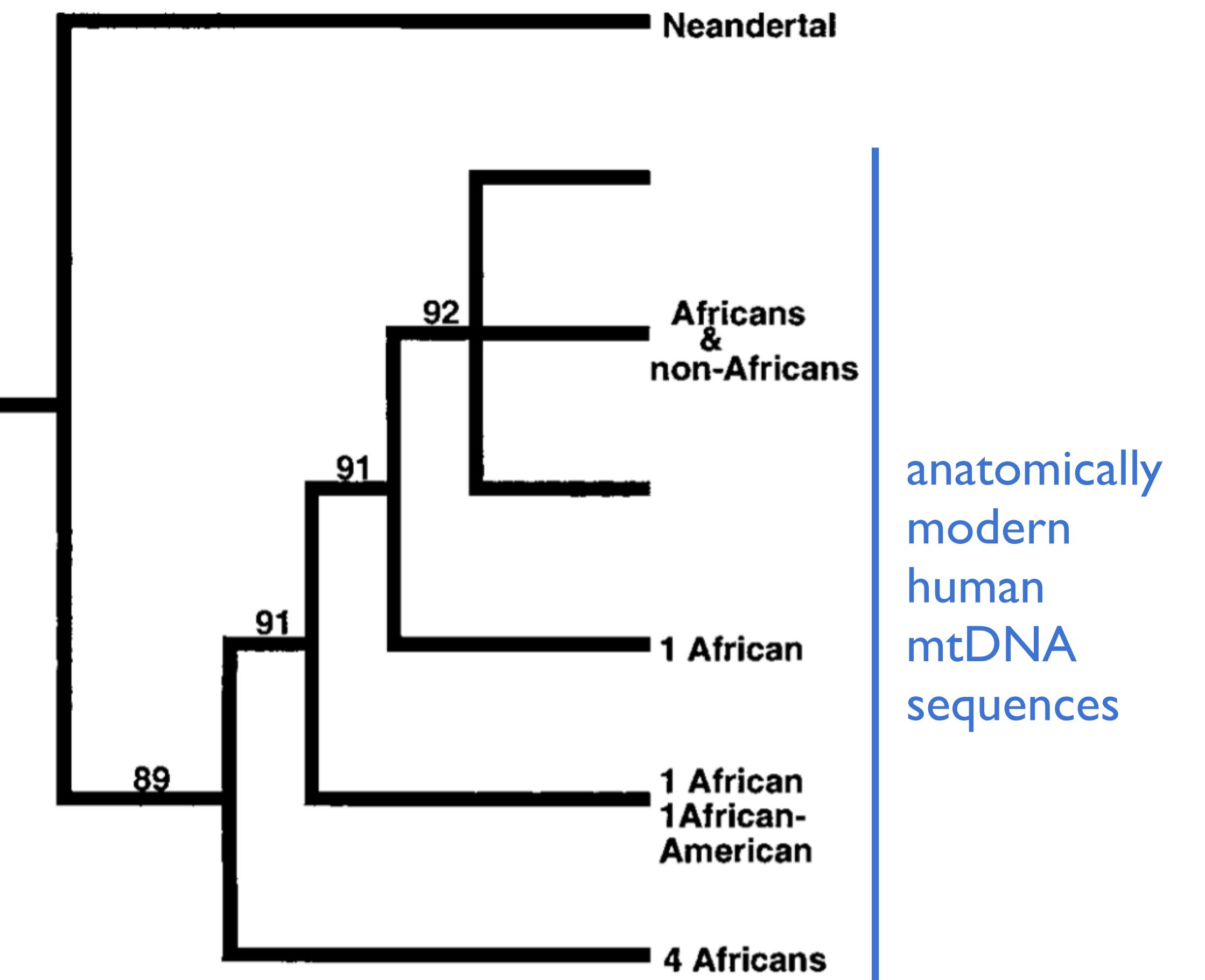
## Neandertal DNA Sequences and the Origin of Modern Humans

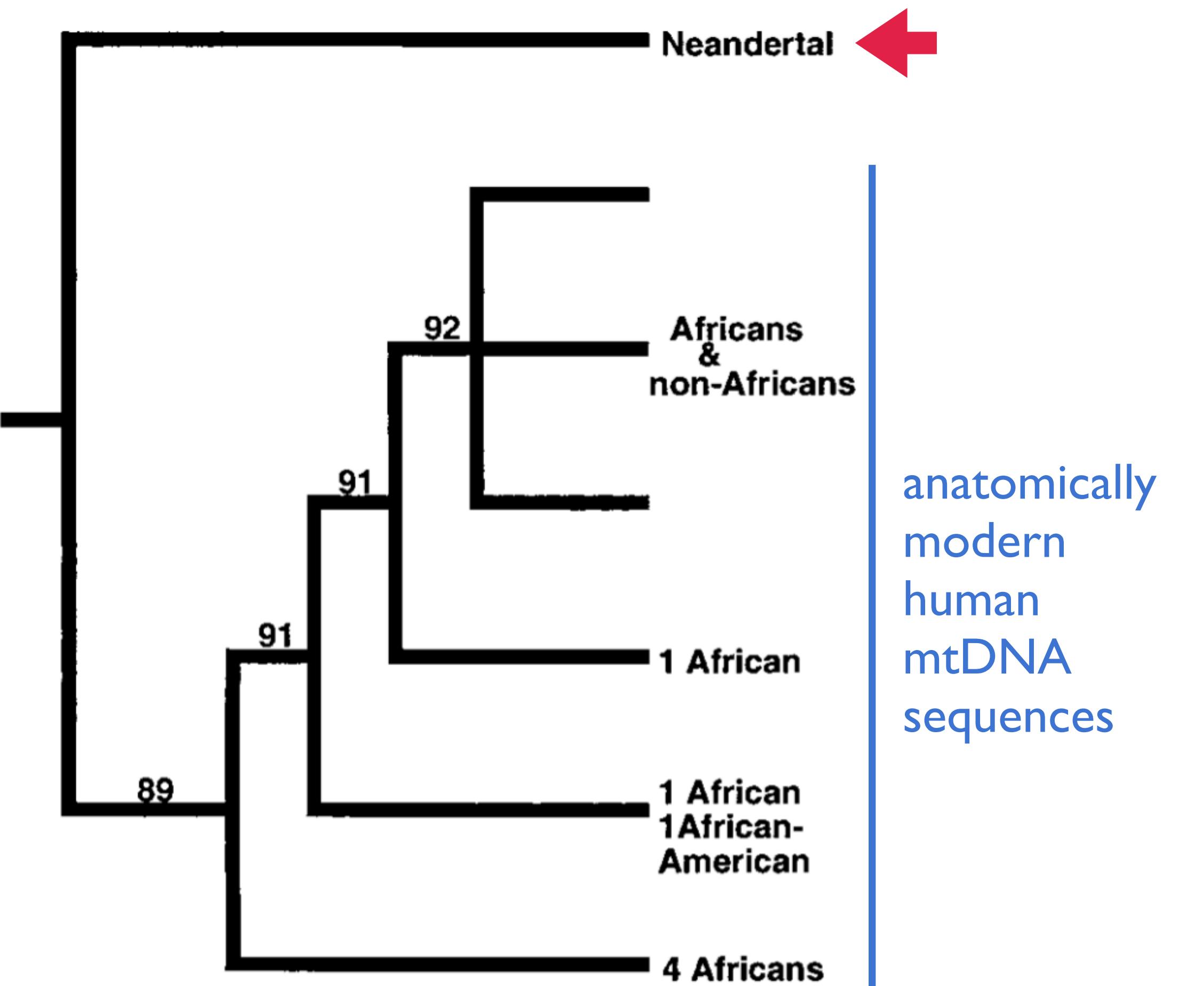
Matthias Krings,\* Anne Stone,† Ralf W. Schmitz,‡  
Heike Krainitzki,§ Mark Stoneking,† and Svante Pääbo\*



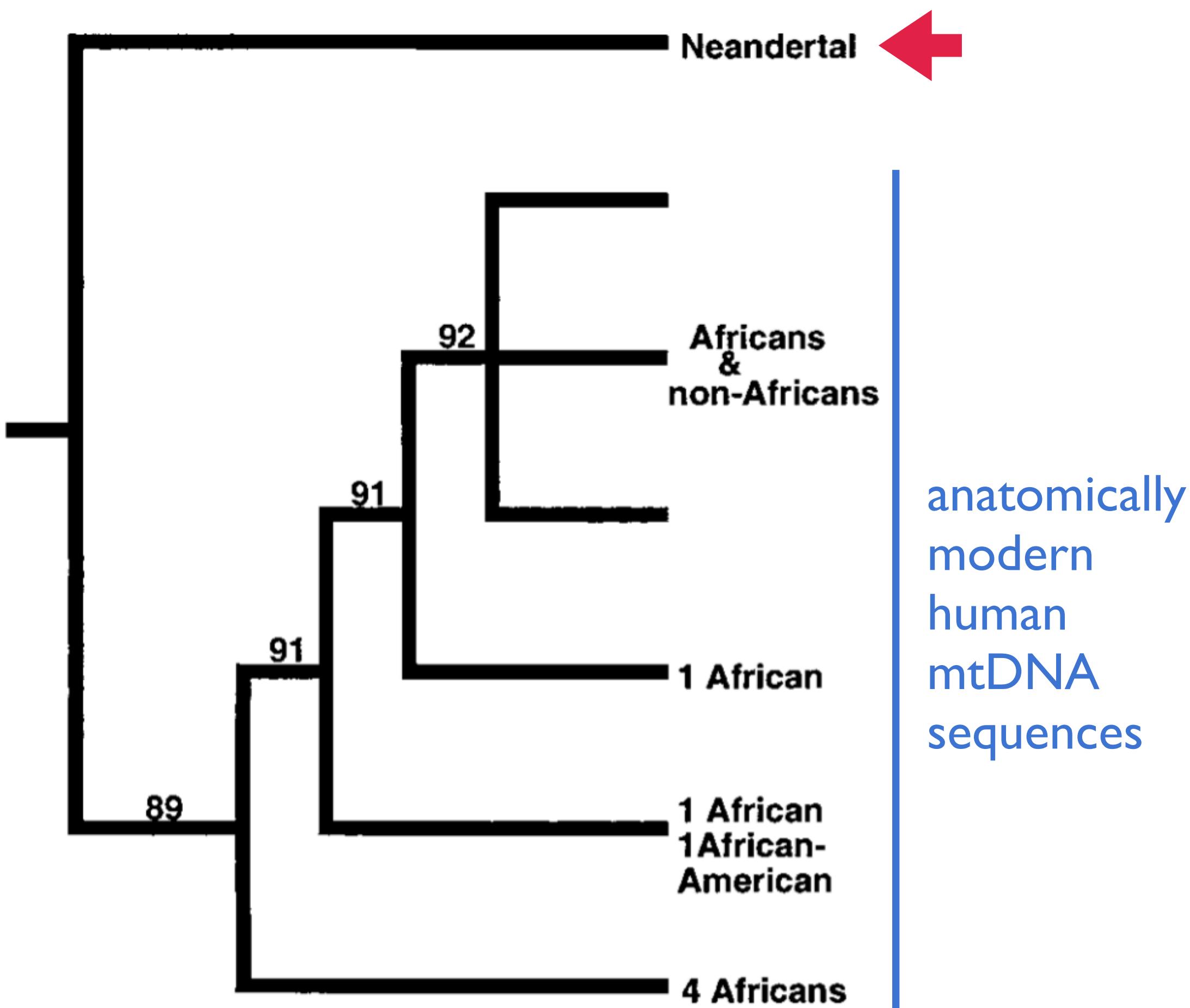


**Figure 5. The DNA Sequences of Clones Used to Infer the Sequence of the Hypervariable Region I of the Neandertal Individual**



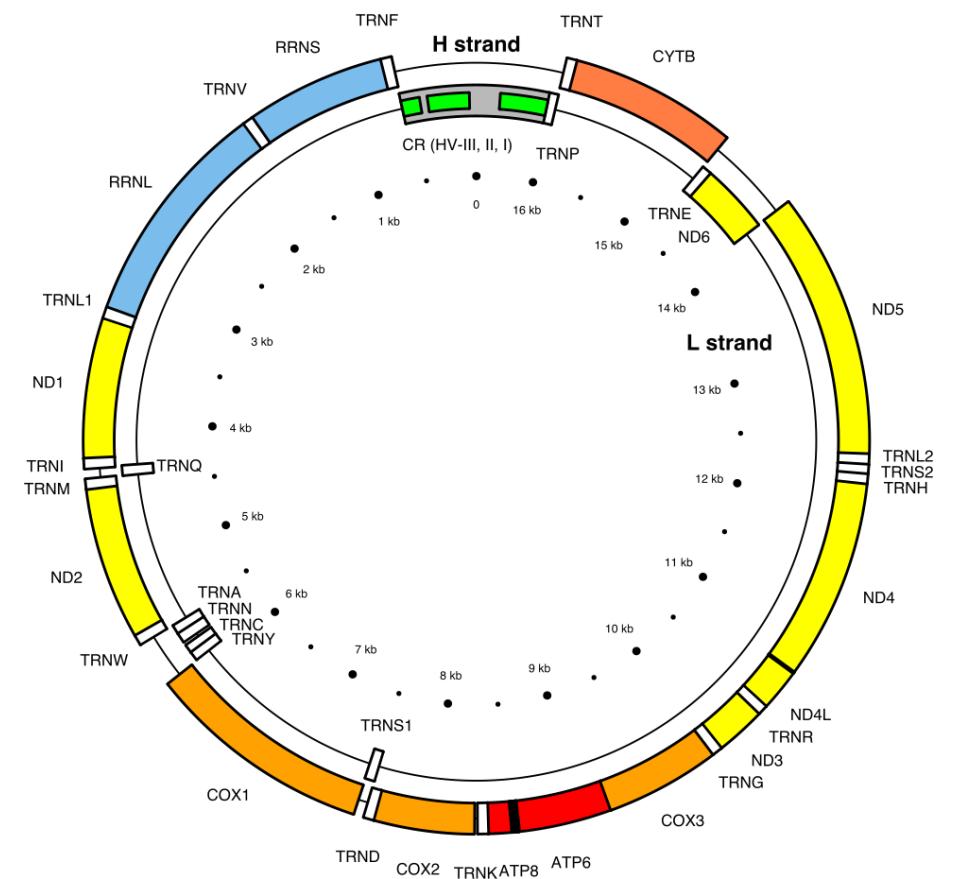


# No introgression?

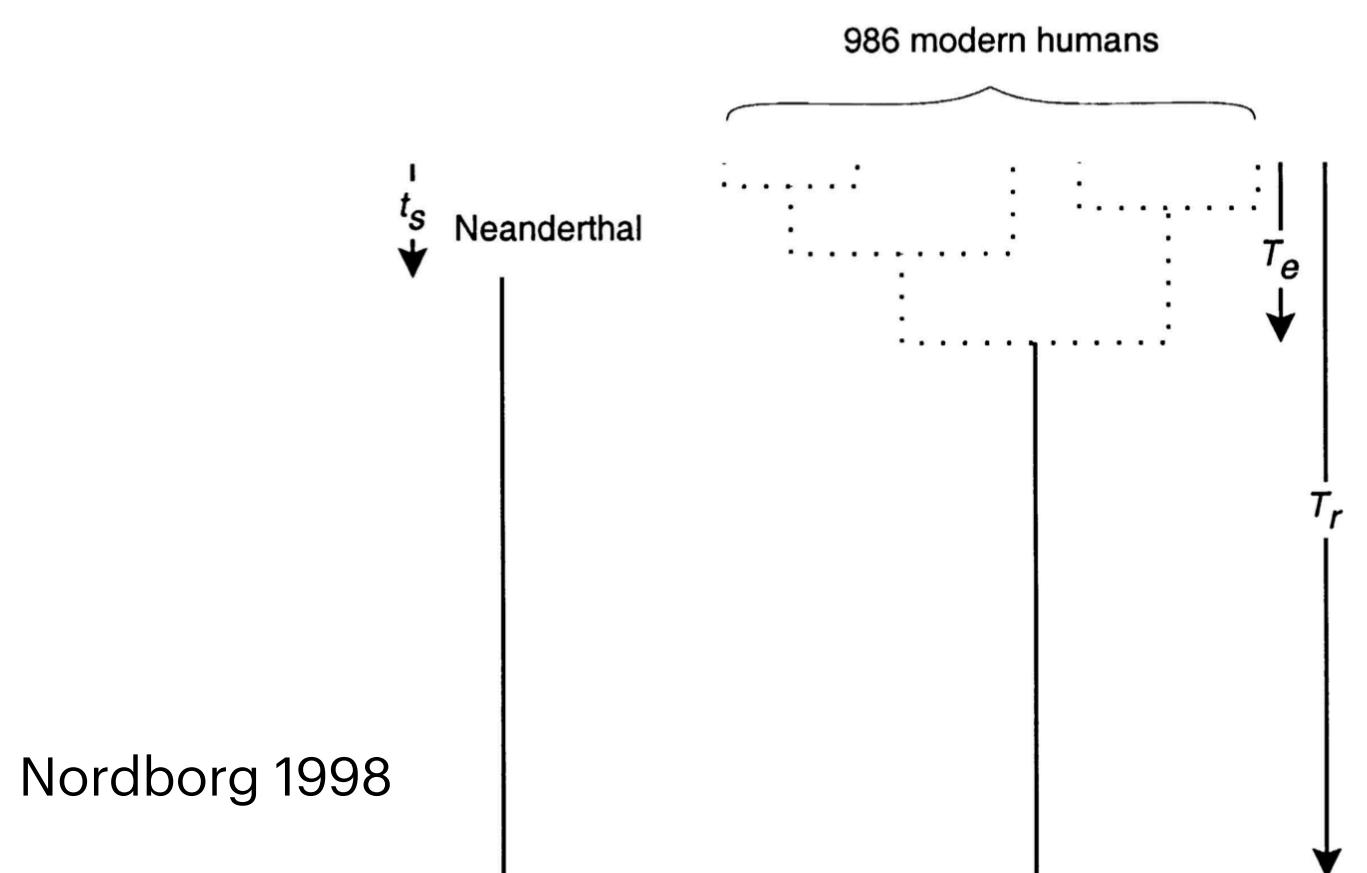


When the Neandertal mtDNA sequence is used to root a neighbor joining tree of modern human mtDNA sequences (Figure 7a), the first three branches consist exclusively of African sequences. The Neandertal mtDNA sequence thus supports a scenario in which modern humans arose recently in Africa as a distinct species and replaced Neandertals with little or no interbreeding.

# mitochondrial DNA



16 kb

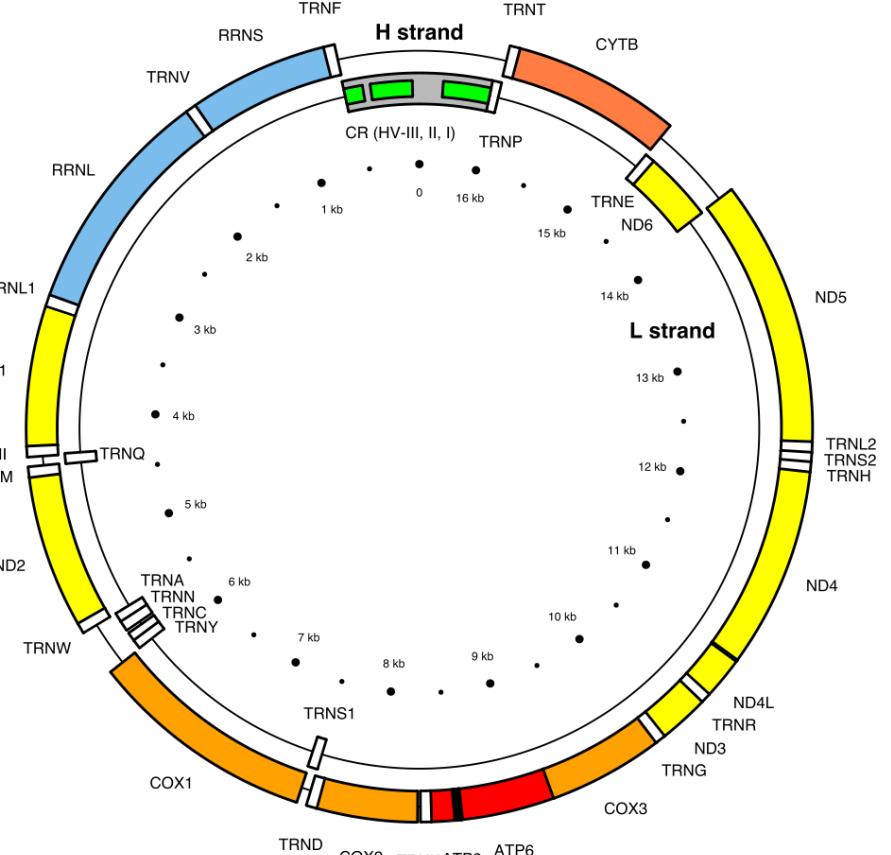


**one mtDNA phylogenetic tree**  
(maternal history)

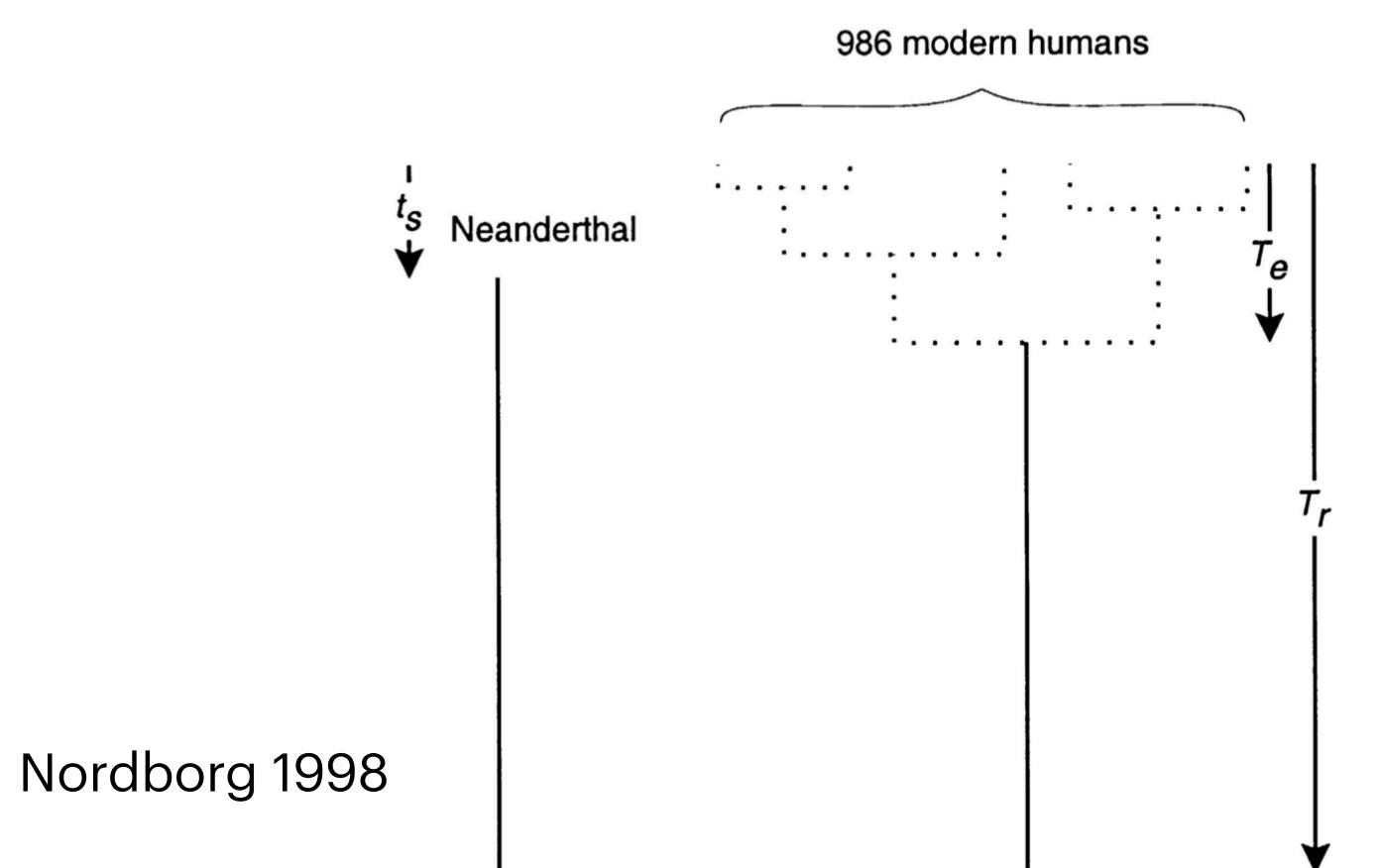
# mitochondrial DNA

**vs**

# nuclear DNA

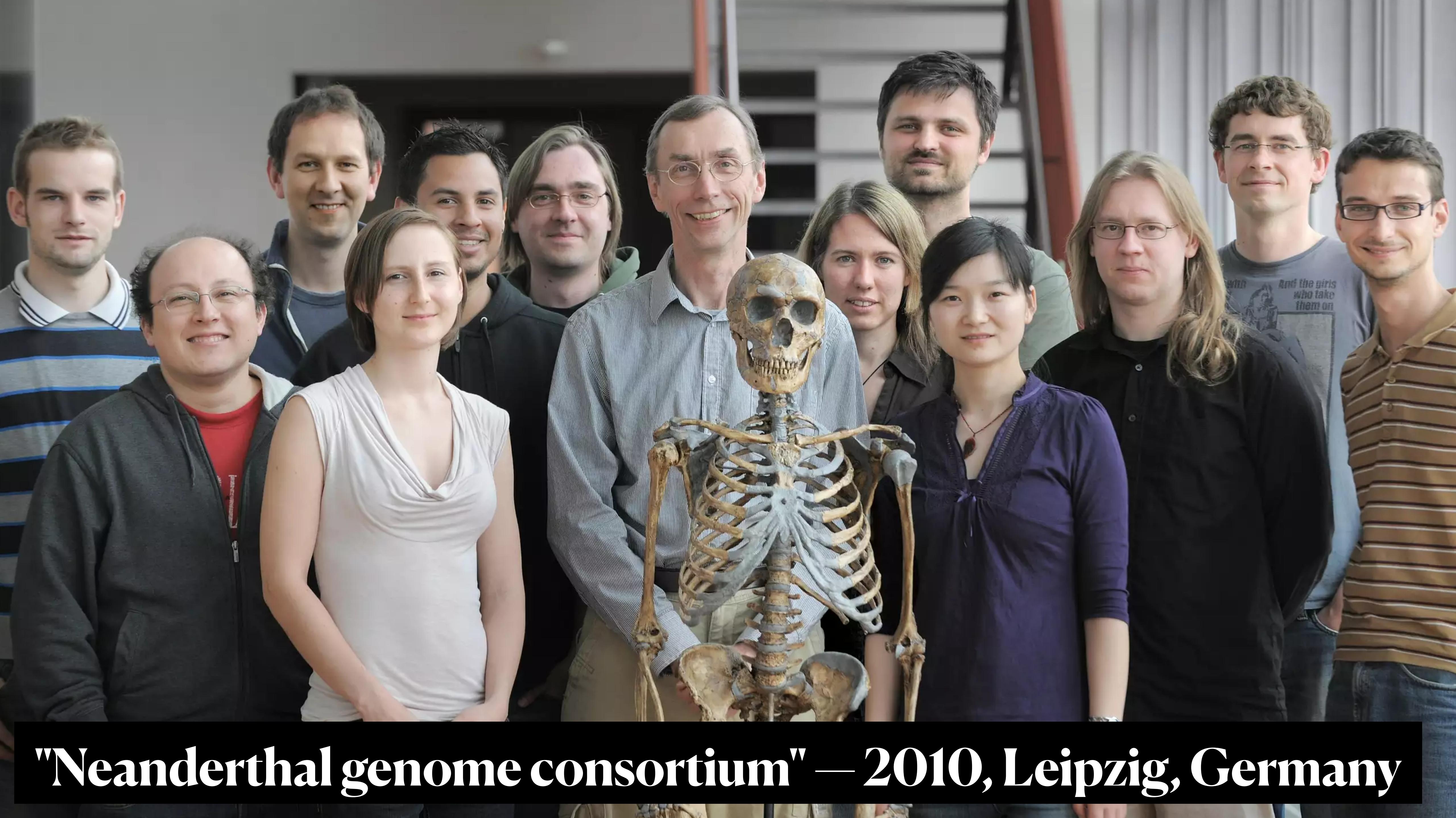


**3 Gb**



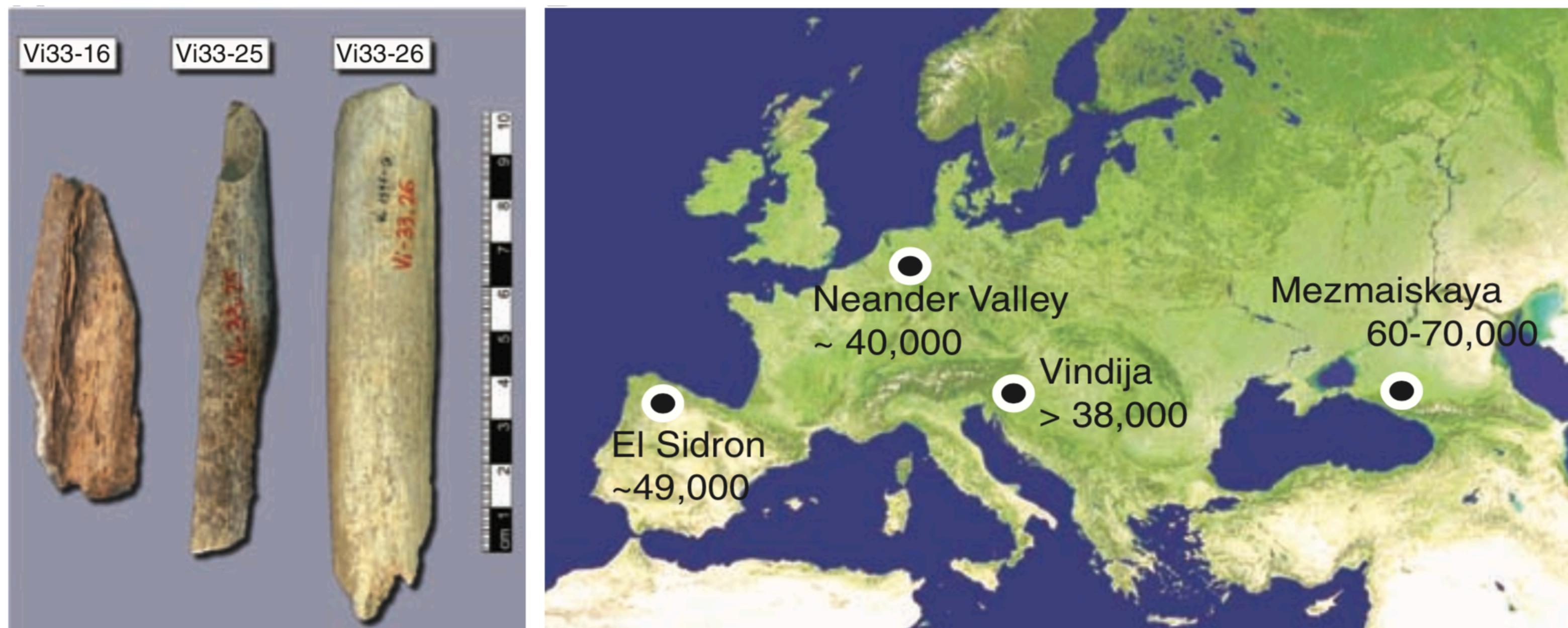
**one mtDNA phylogenetic tree**  
(maternal history)

**thousands of trees along the nuclear genome**  
(result of recombination)



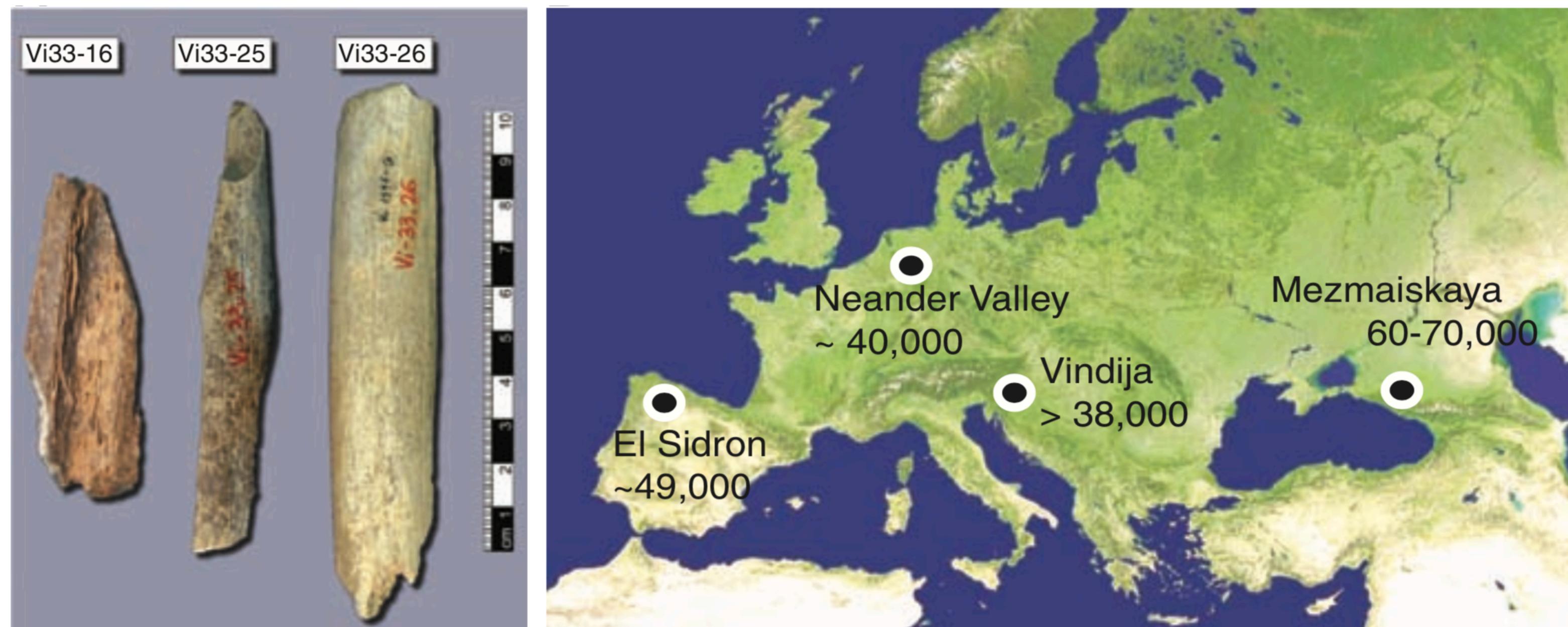
"Neanderthal genome consortium" – 2010, Leipzig, Germany

# 2010: "draft" Neanderthal genome



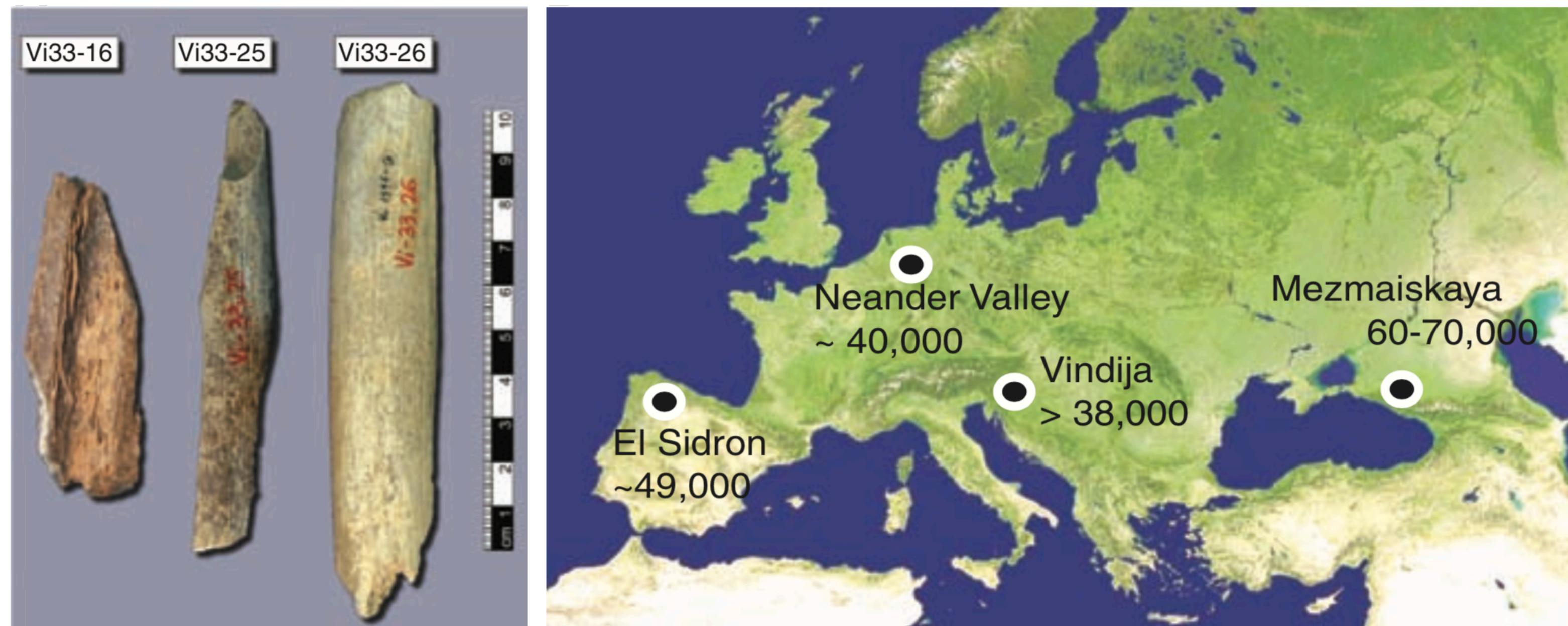
- DNA extracted from bone powder of three bones

# 2010: "draft" Neanderthal genome



- DNA extracted from bone powder of three bones
- ~1.3X coverage genome (on average, each position in the genome covered by 1.3 fragments)

# 2010: "draft" Neanderthal genome



- DNA extracted from bone powder of three bones
- ~1.3X coverage genome (on average, each position in the genome covered by 1.3 fragments)
  - to this date four more high-coverage archaic genomes up to ~40X

# Typical aDNA workflow



# Typical aDNA workflow



**dentist  
drill**

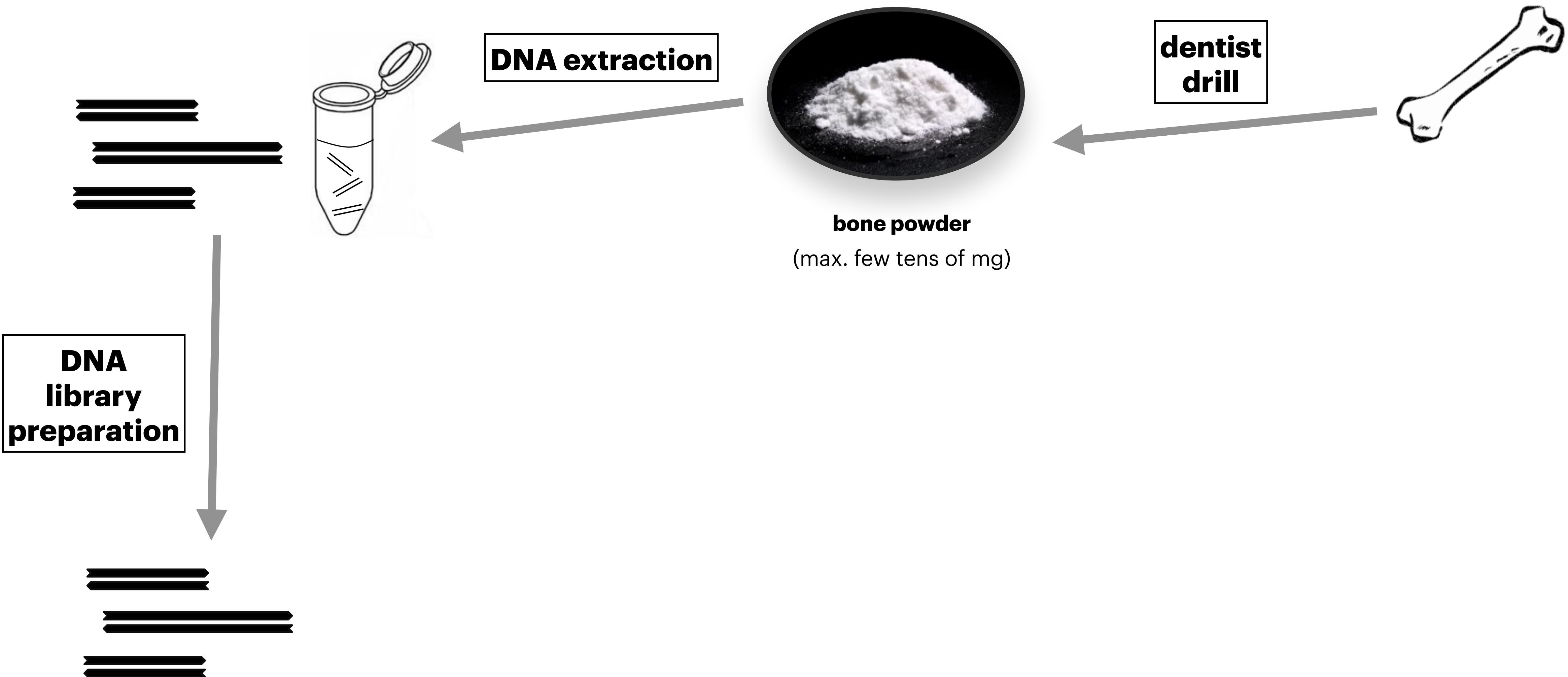


**bone powder**  
(max. few tens of mg)

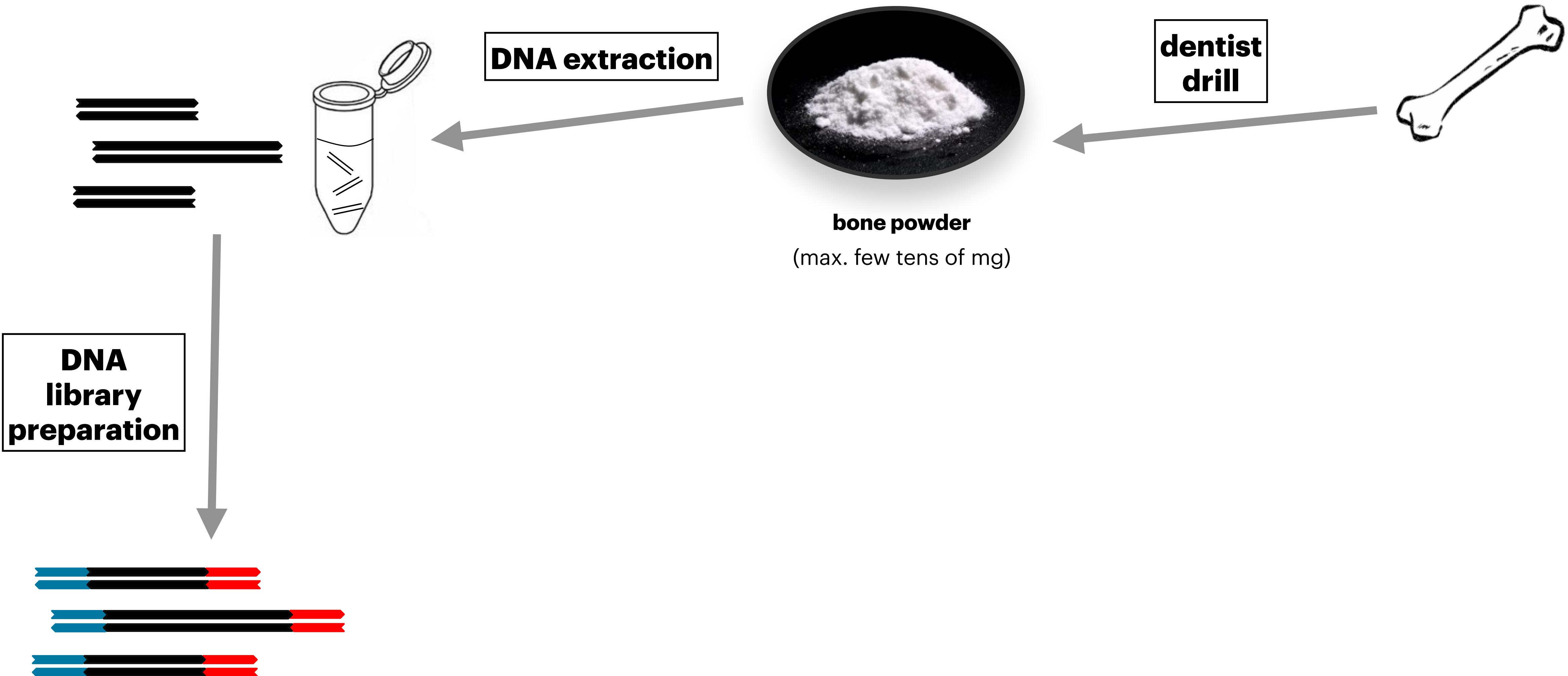
# Typical aDNA workflow



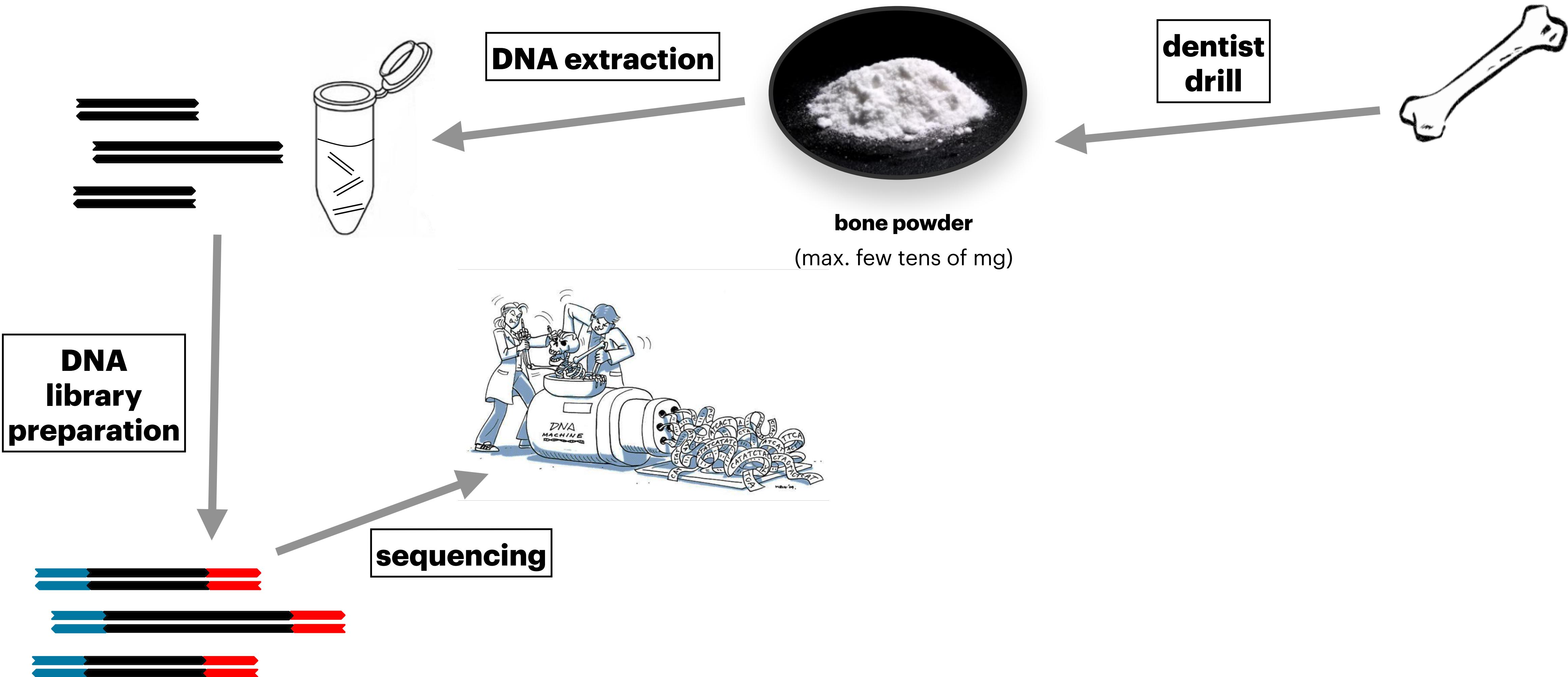
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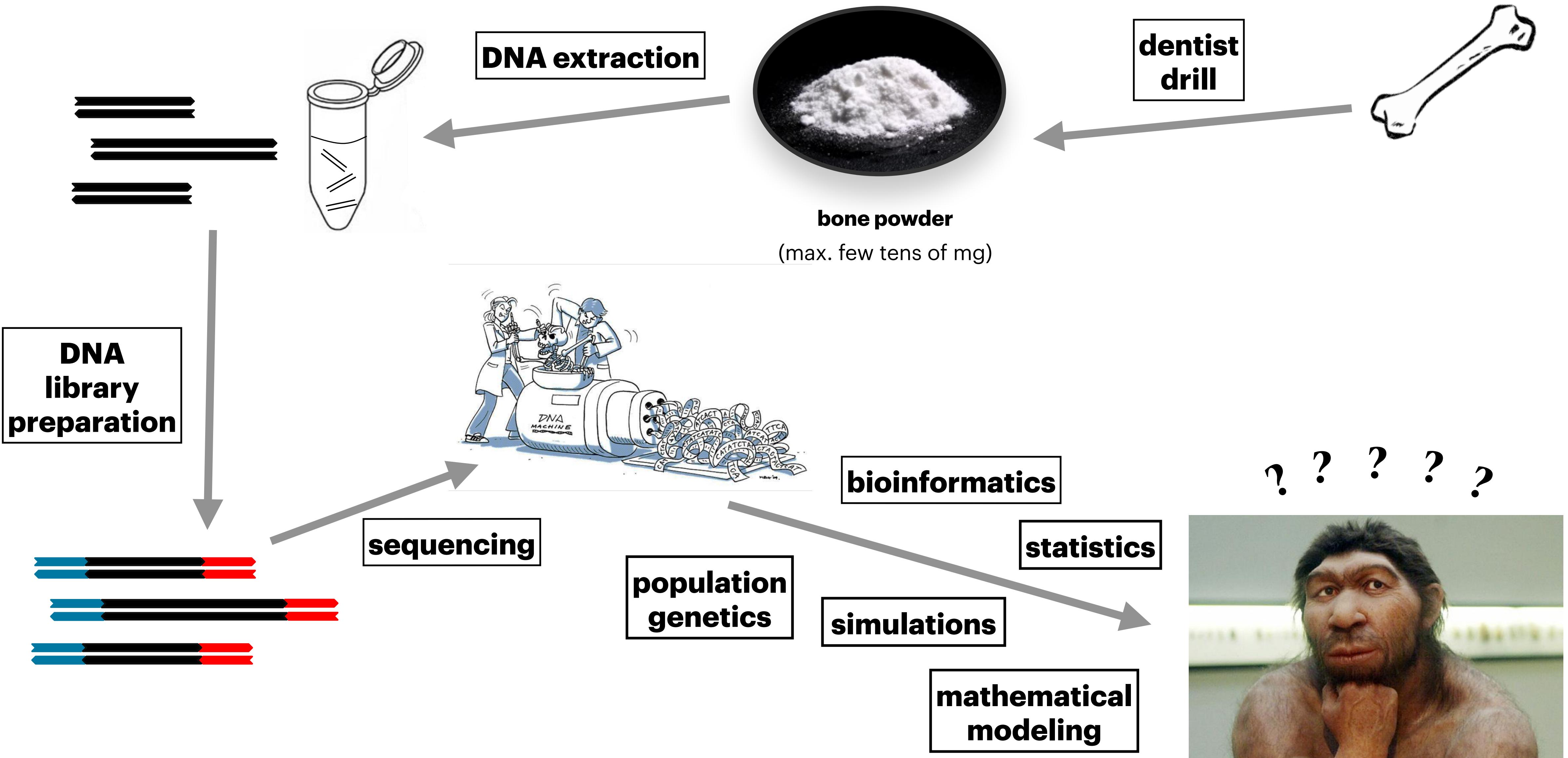
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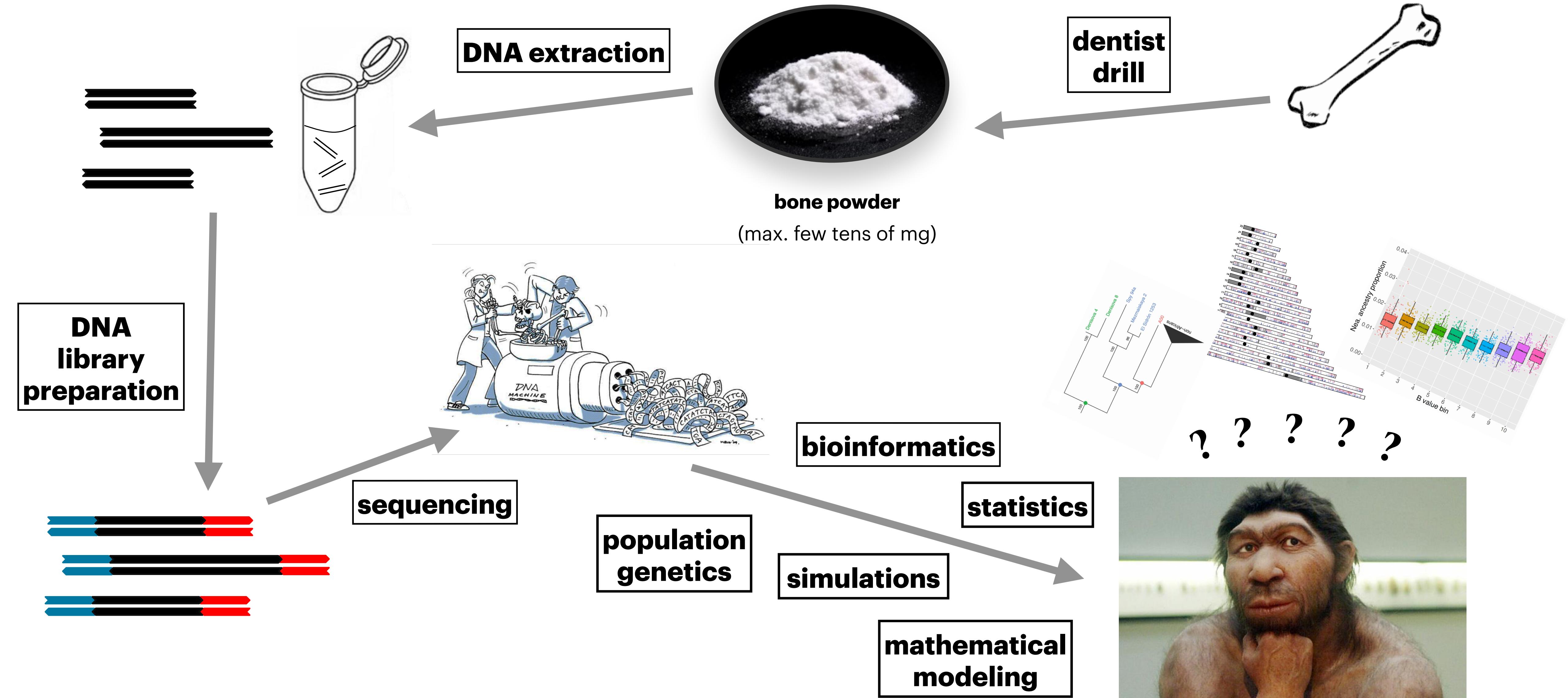
# Typical aDNA workflow



# Typical aDNA workflow



# Typical aDNA workflow



# So we have a Neanderthal genome...

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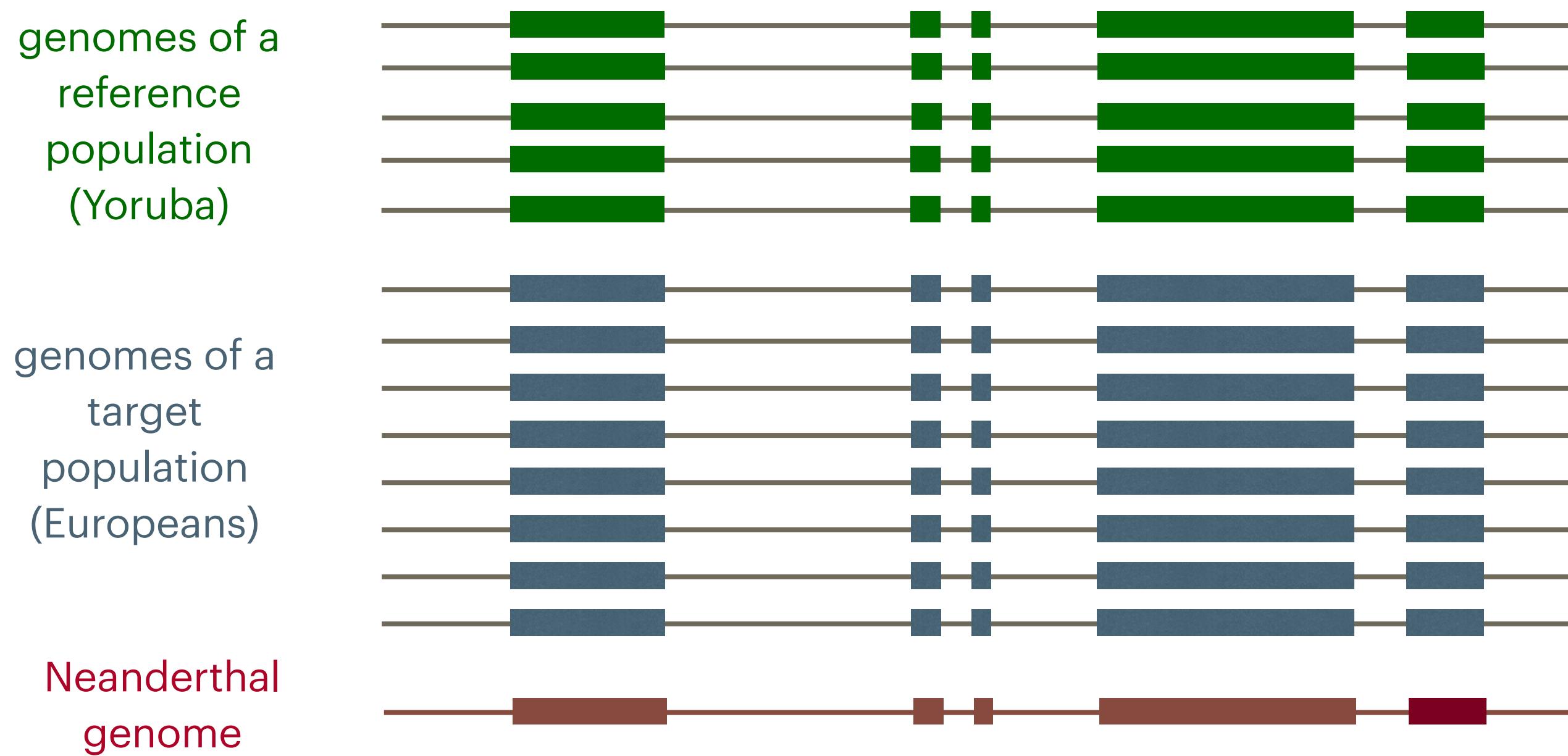


# ...how to test the gene-flow hypothesis?

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# How to test the gene-flow hypothesis?



David Reich



Nick Patterson



Green et al. (Science 2010)

# How to test the gene-flow hypothesis?



David Reich

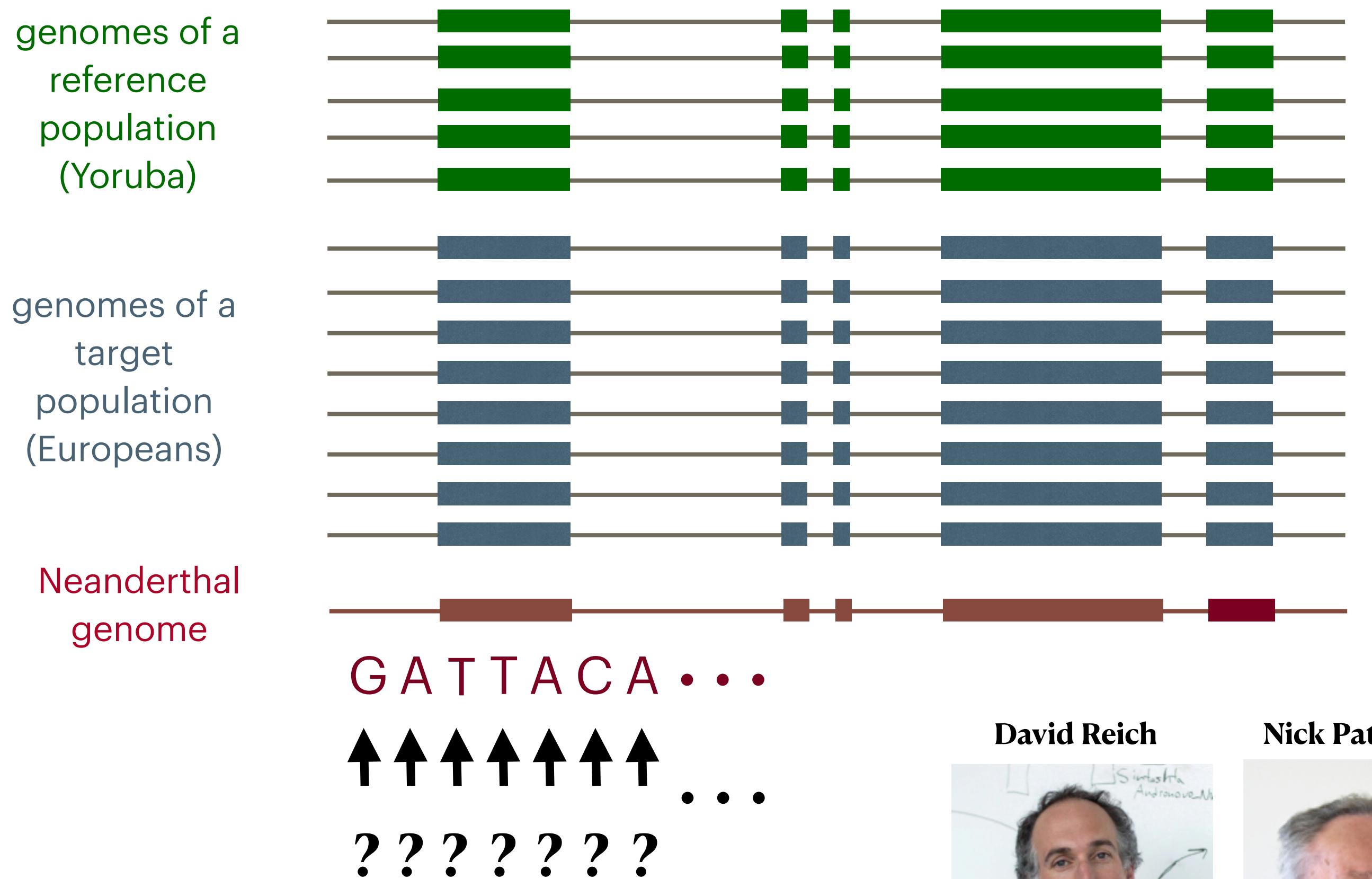


Nick Patterson



Green et al. (Science 2010)

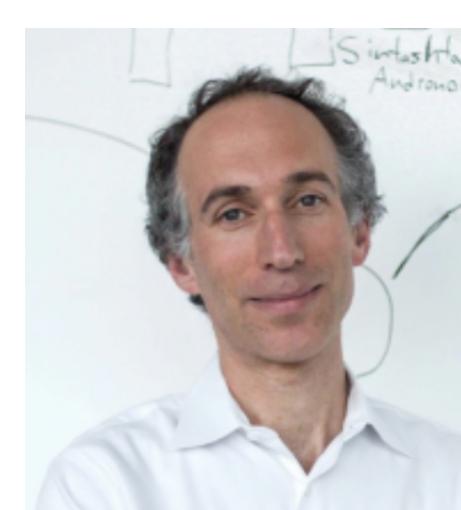
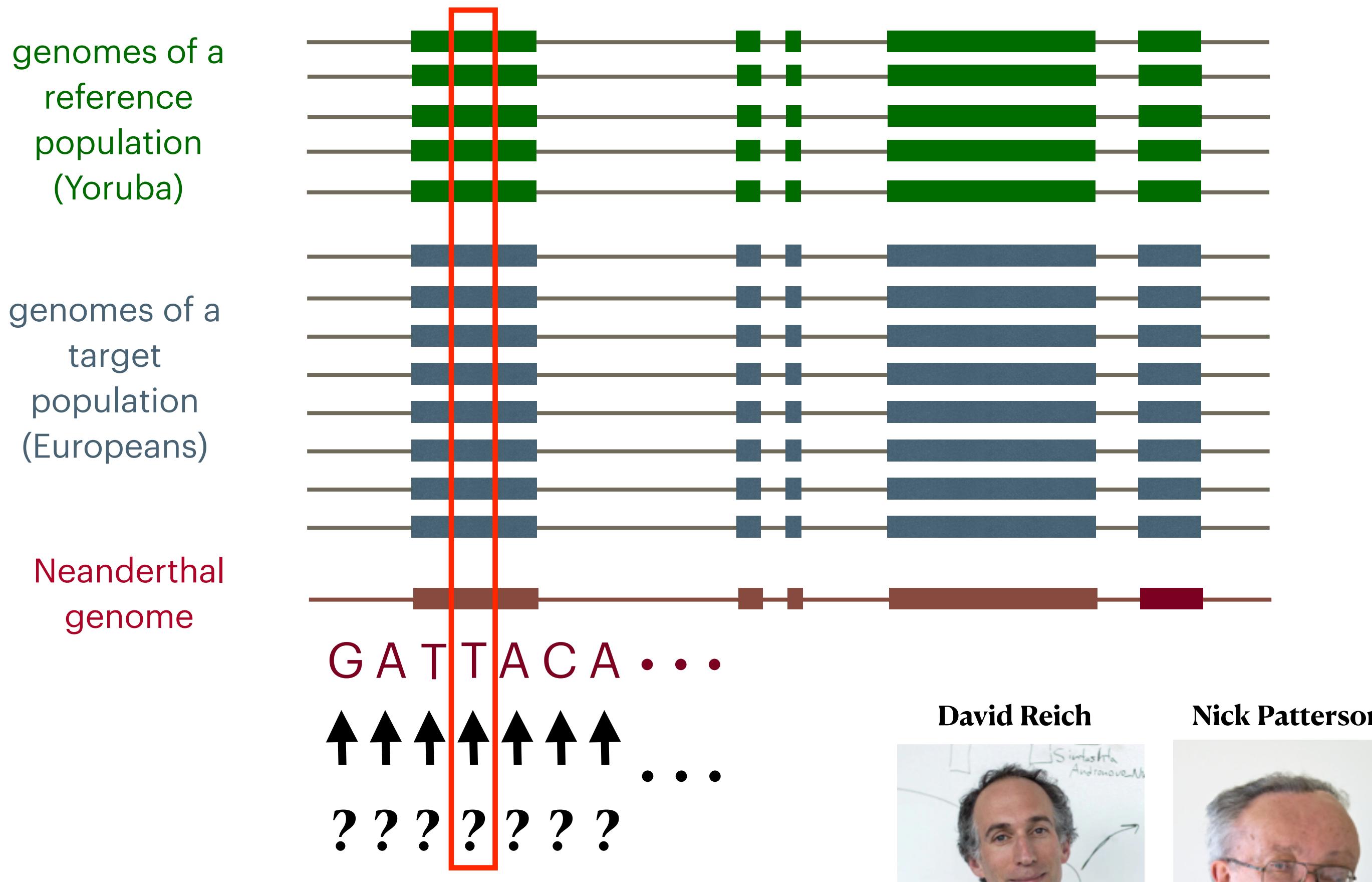
# How to test the gene-flow hypothesis?



Green et al. (Science 2010)

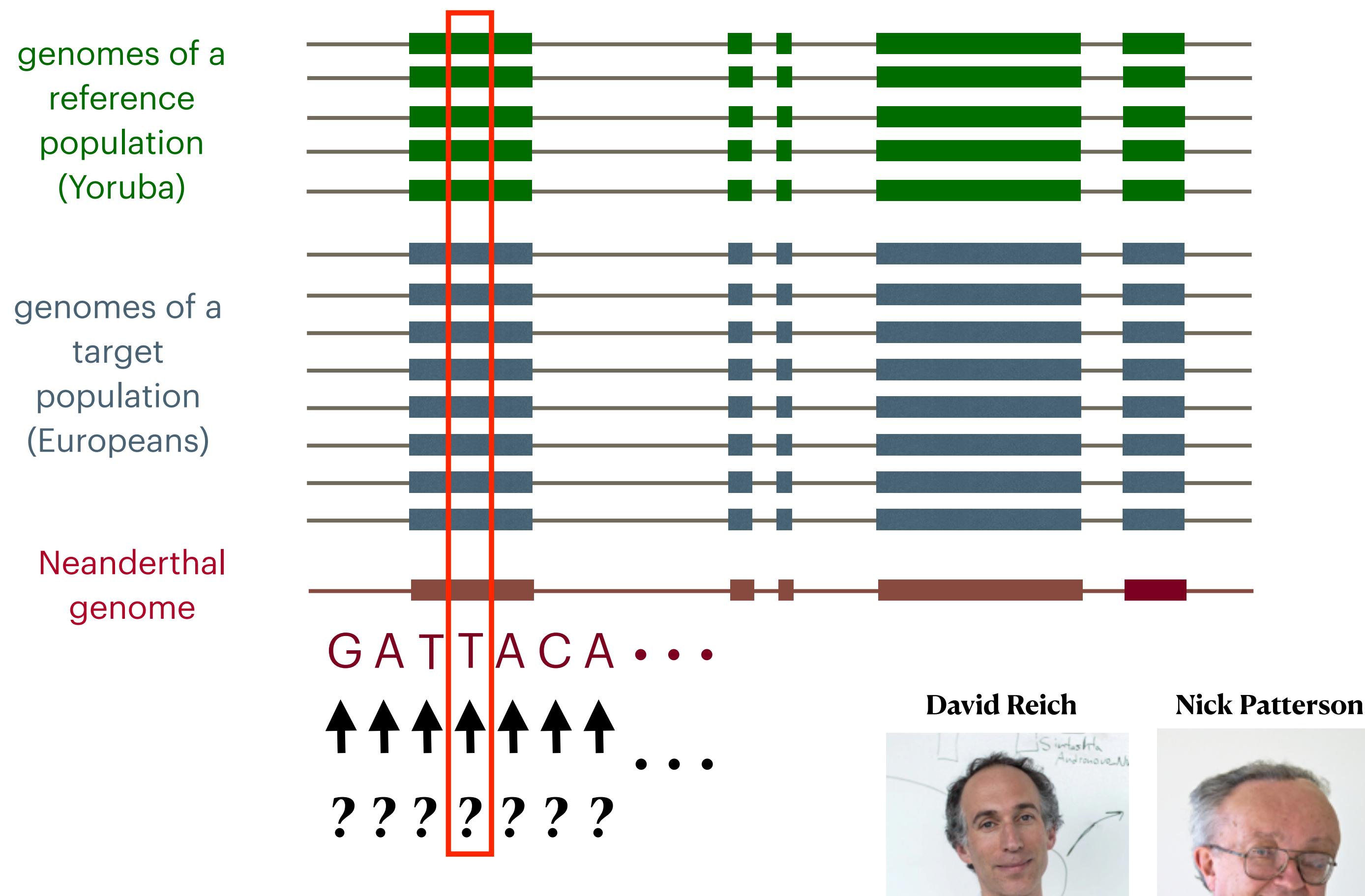
# How to test the gene-flow hypothesis?

**Situation at one locus...**



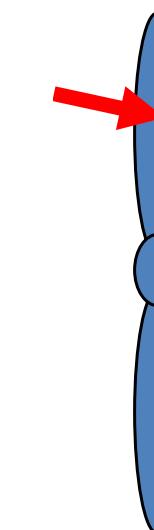
Green et al. (Science 2010)

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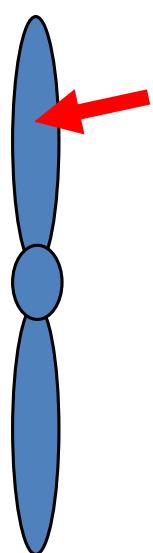


Situation at one locus...

person of an African ancestry



person of a non-african ancestry (i.e. European)

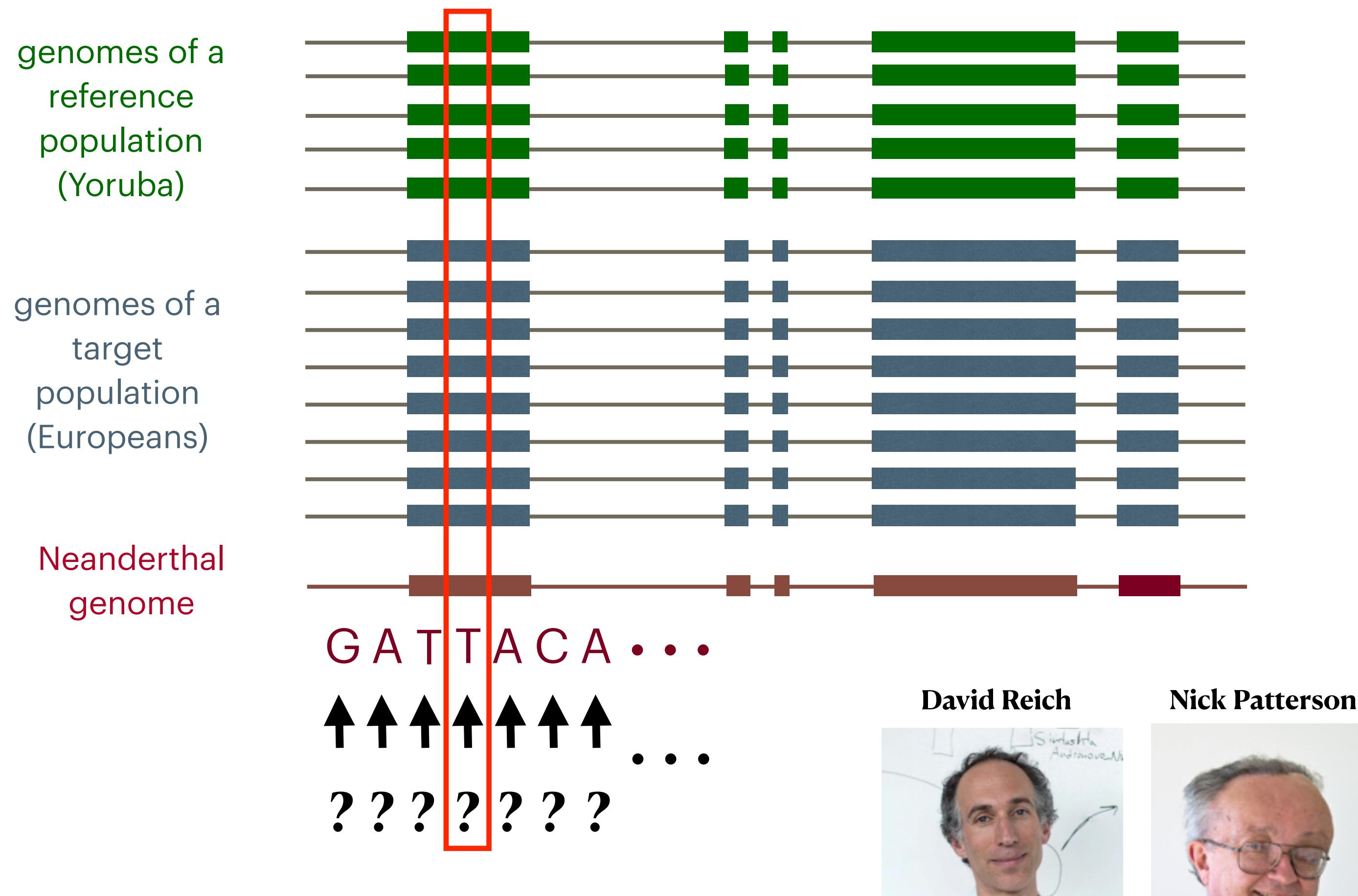


Neanderthal



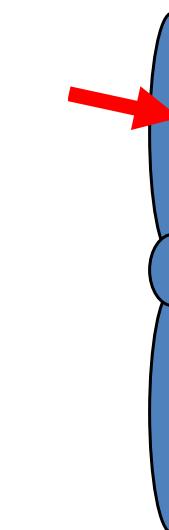
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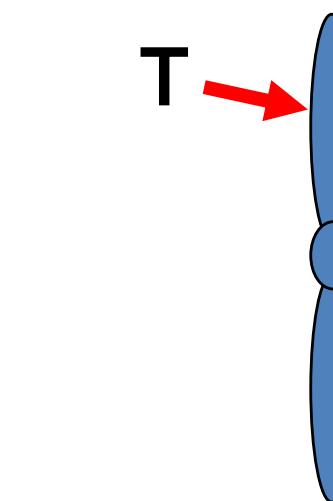
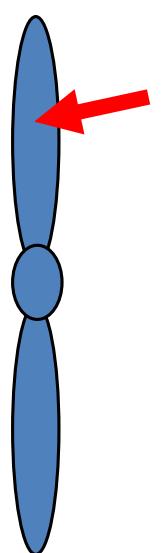


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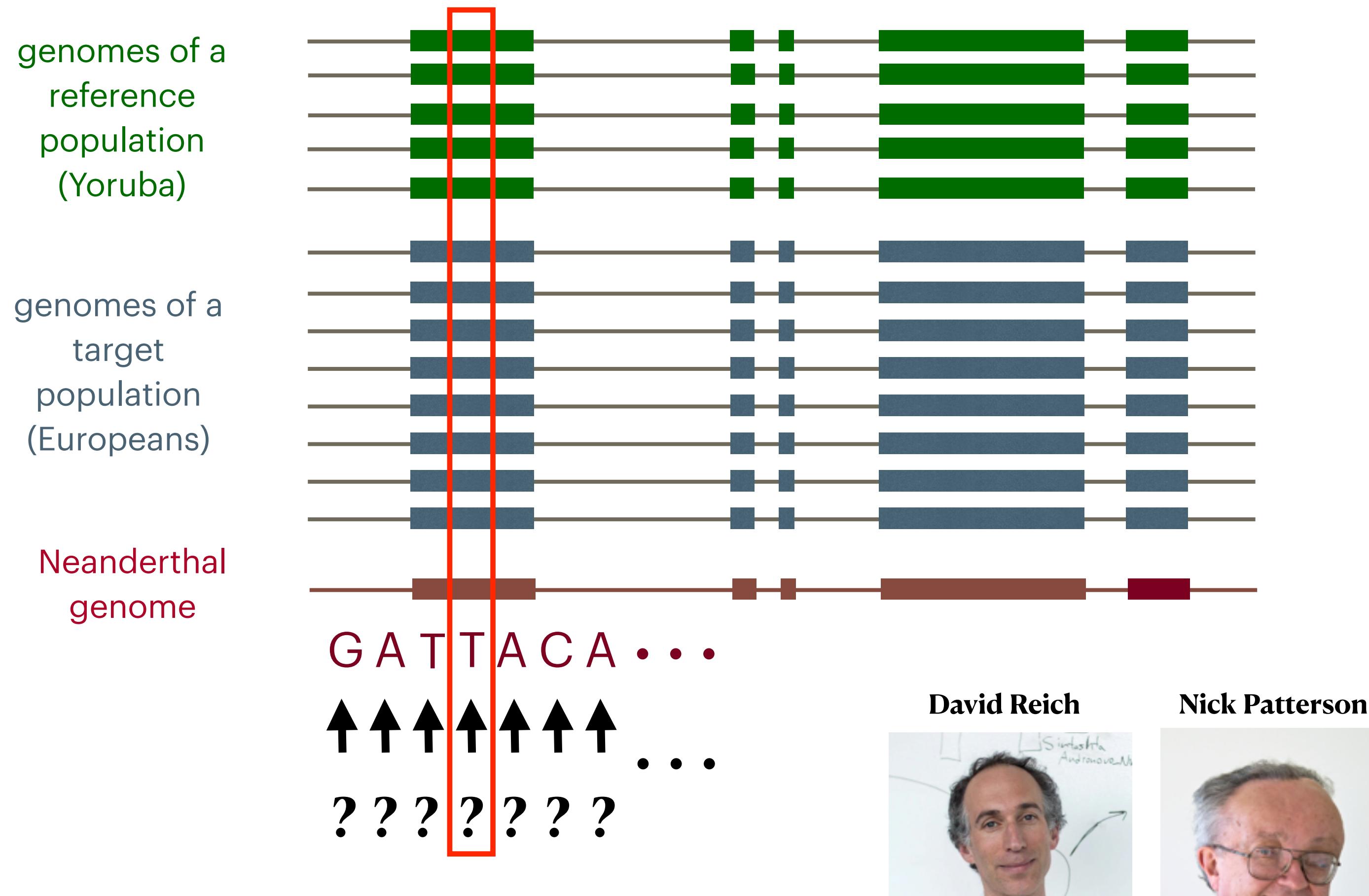


Neanderthal



Green et al. (Science 2010)

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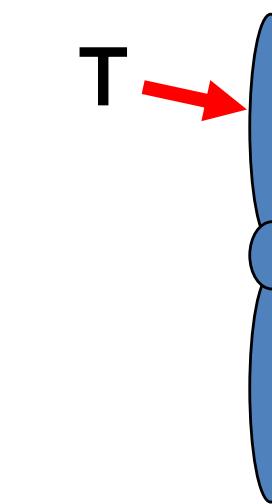
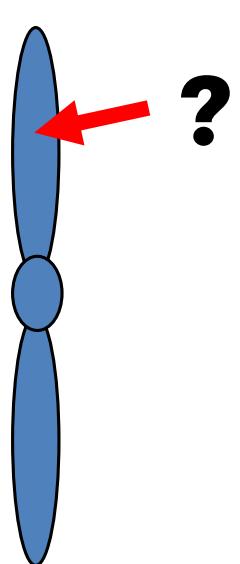


Situation at one locus...

person of an African ancestry



person of a non-african ancestry (i.e. European)



Neanderthal



Green et al. (Science 2010)

# Formal test of introgression

## $f_4$ statistic

Given a set of 4 samples,  $f_4$  compares counts of observed **BABA** vs **ABBA** site patterns.

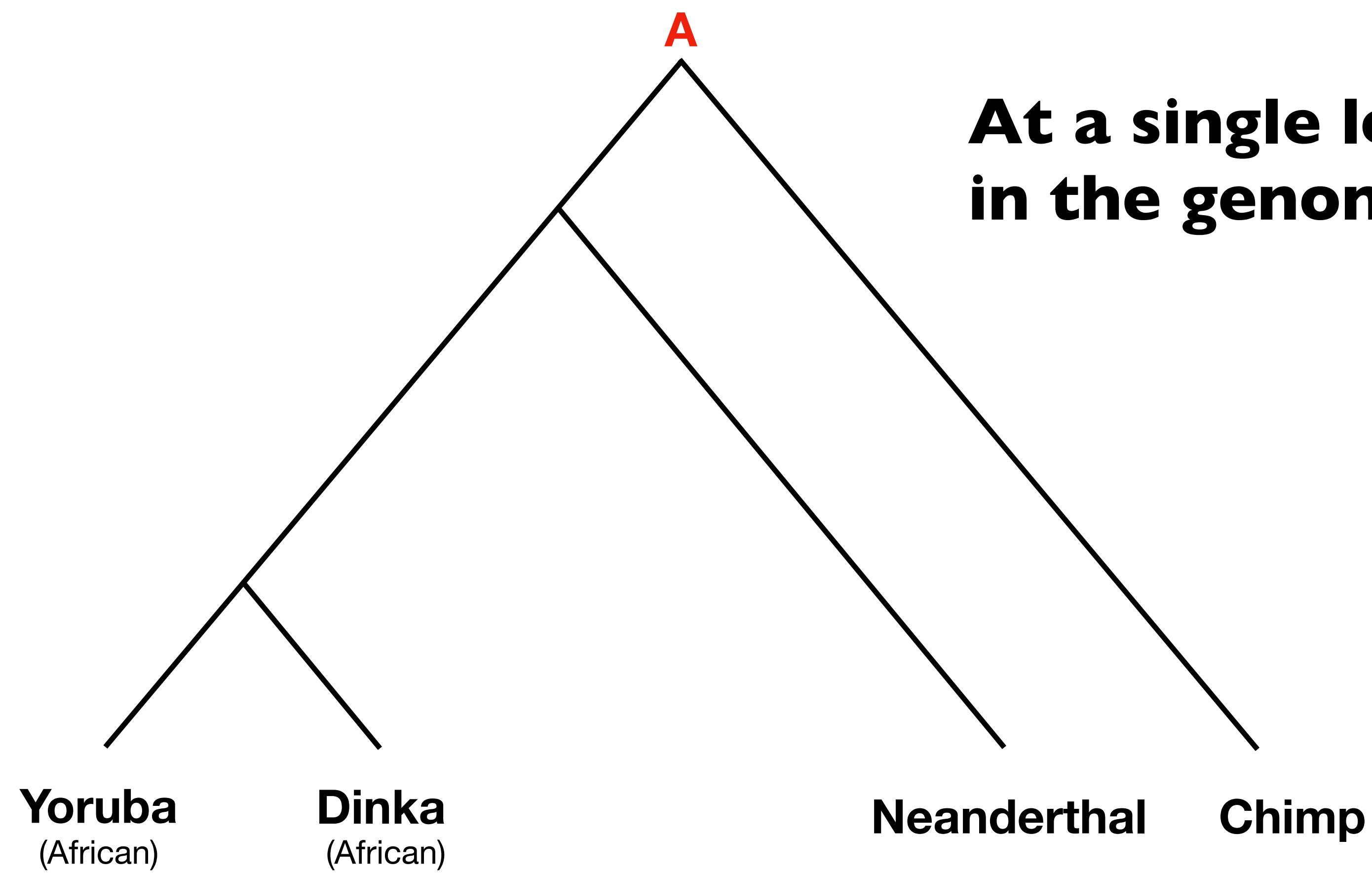
Nick Patterson



David Reich

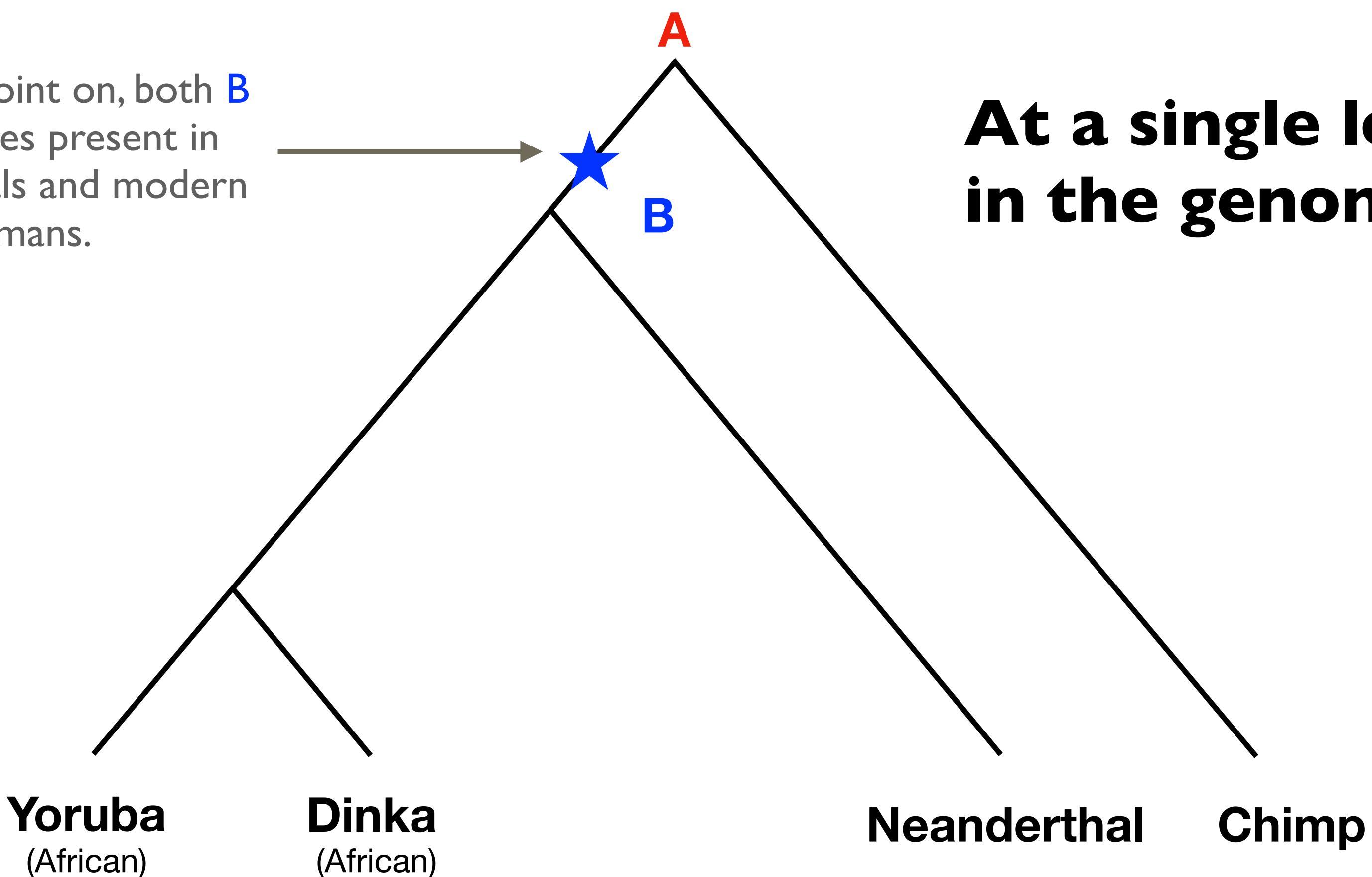


A variant of this statistic that is used equally often is known as **D statistic**.



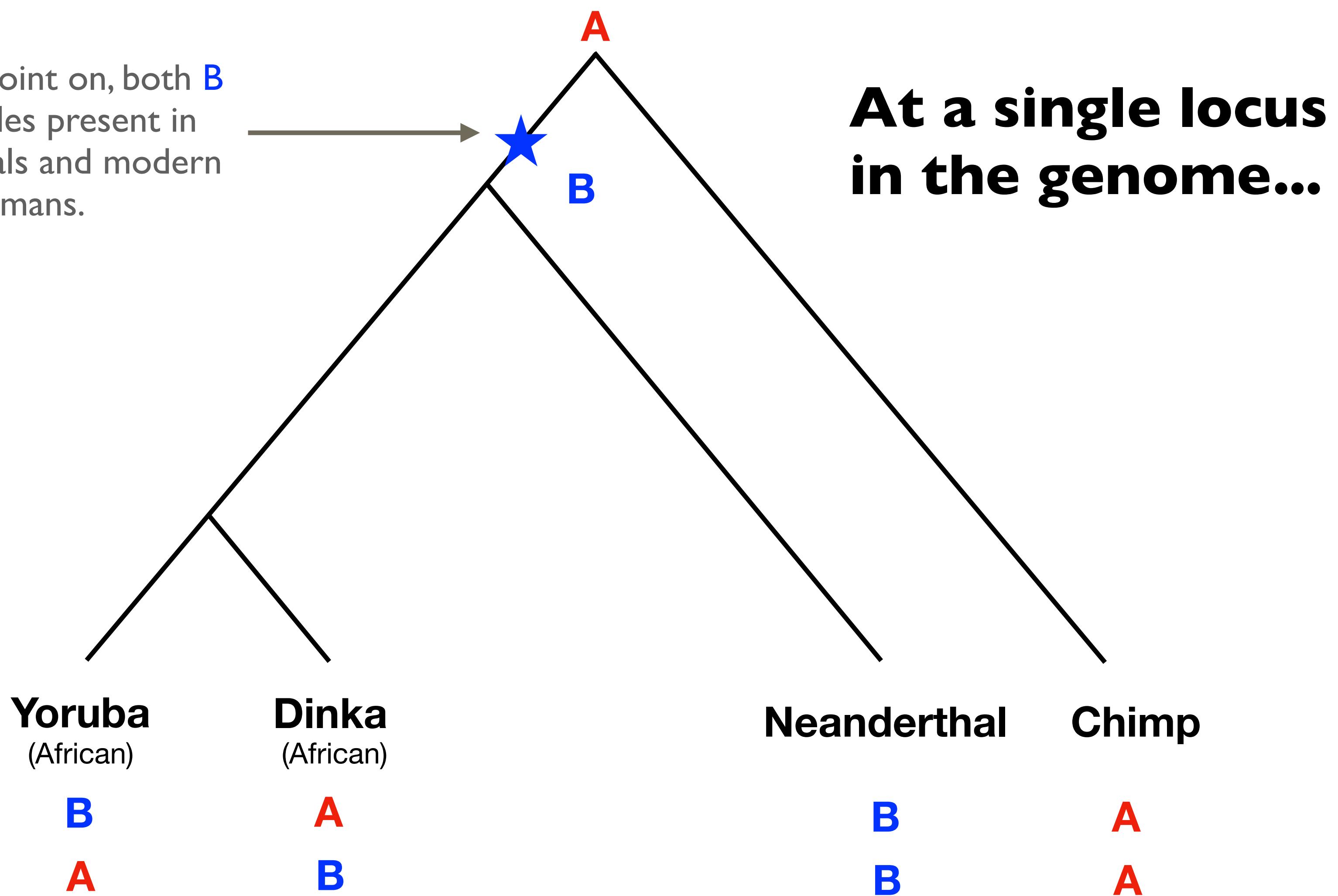
**At a single locus  
in the genome...**

From this point on, both **B** and **A** alleles present in Neanderthals and modern humans.

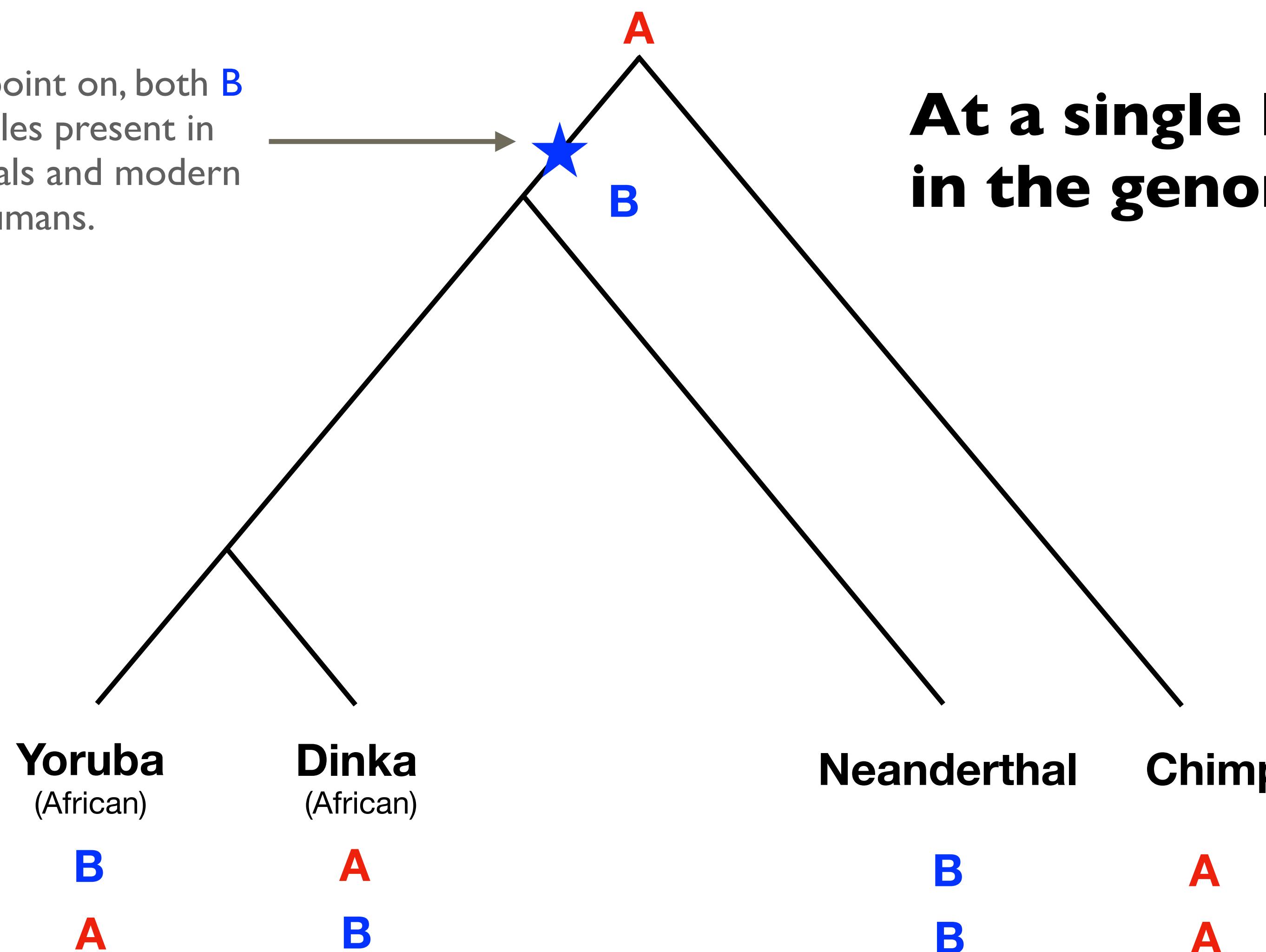


**At a single locus  
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From this point on, both **B** and **A** alleles present in Neanderthals and modern humans.



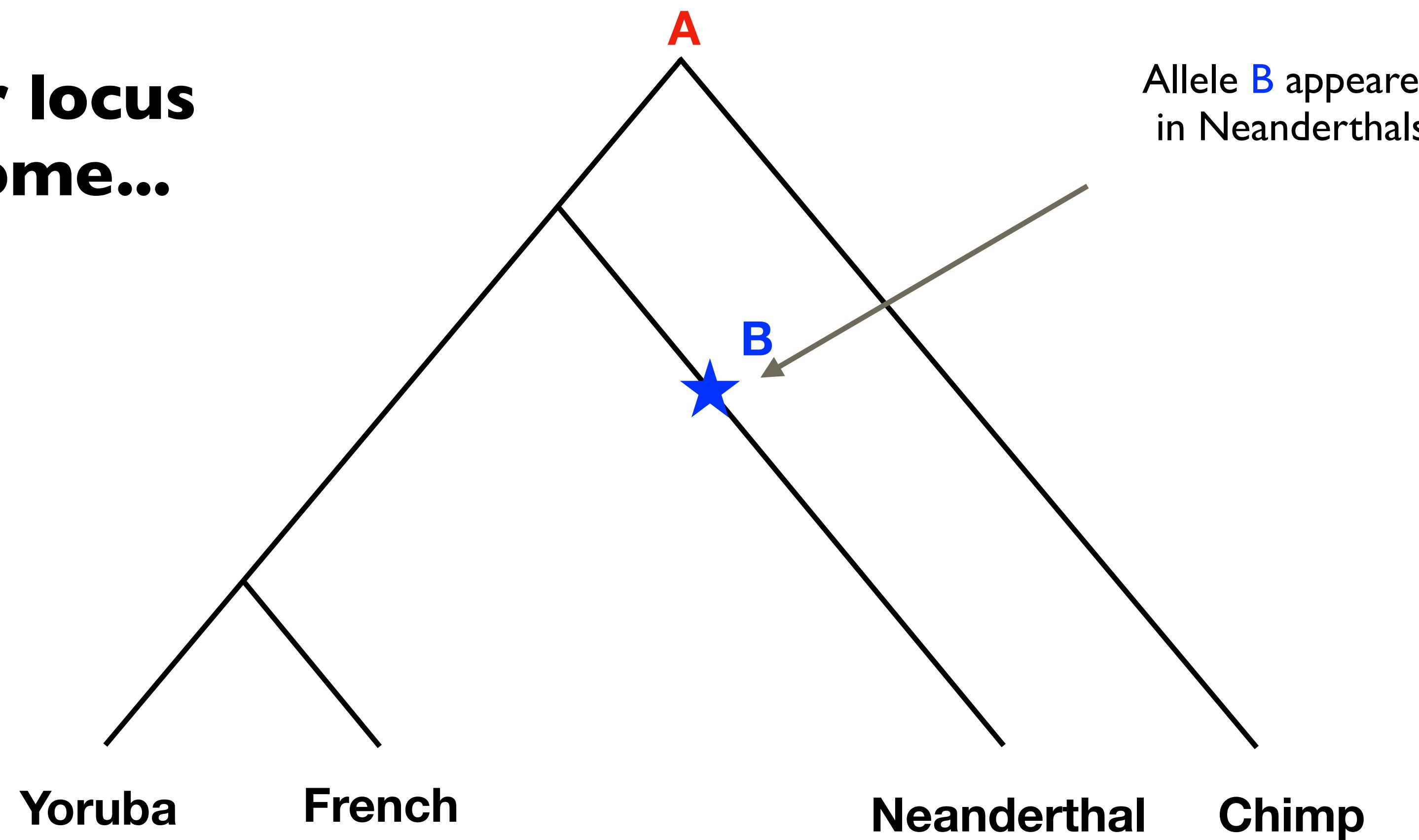
From this point on, both **B** and **A** alleles present in Neanderthals and modern humans.



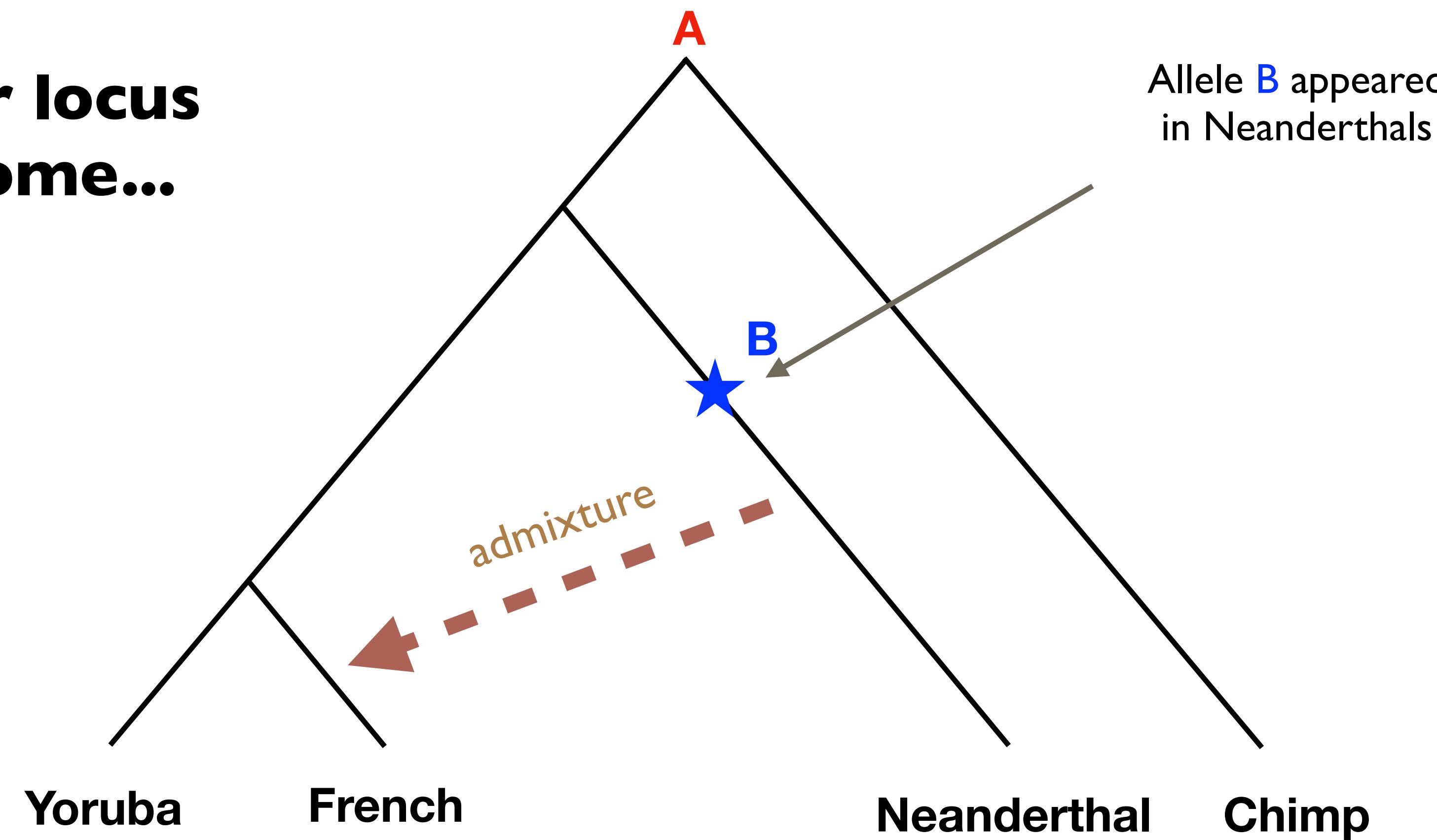
**At a single locus  
in the genome...**

**No introgression: *f4 statistic* = (# BABA - #ABBA) / # SNPs ~ 0**

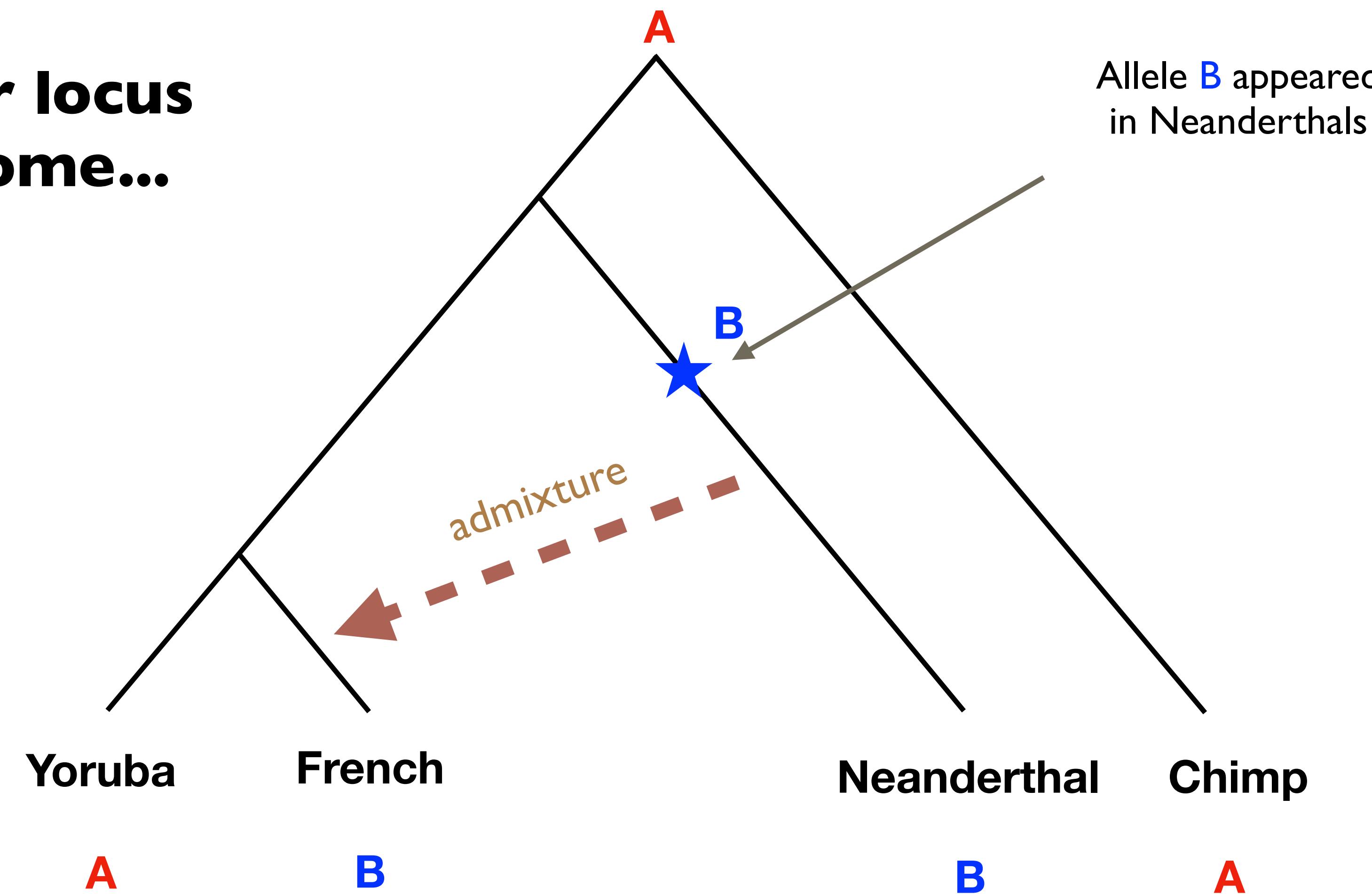
**At another locus  
in the genome...**



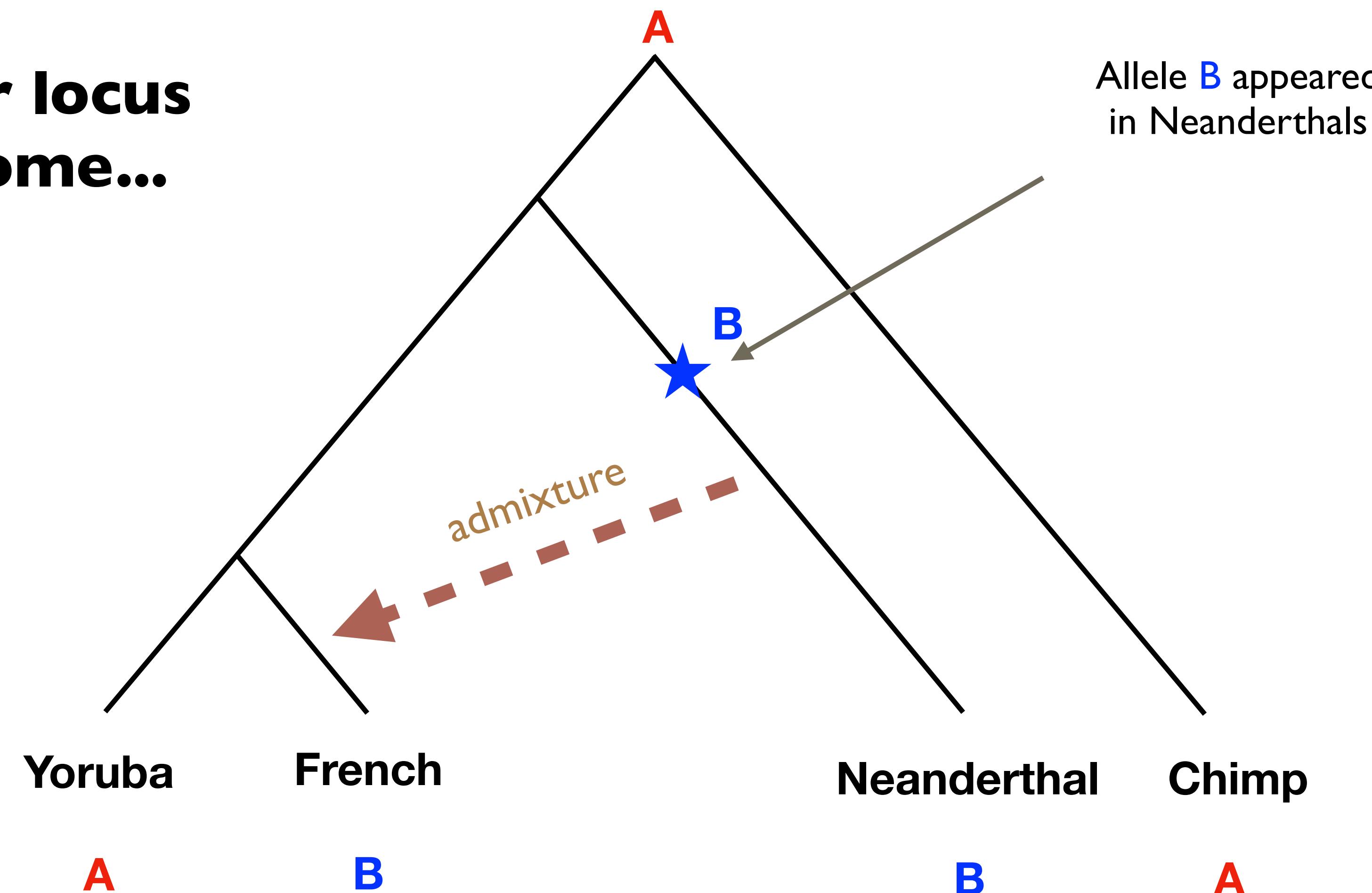
**At another locus  
in the genome...**



**At another locus  
in the genome...**

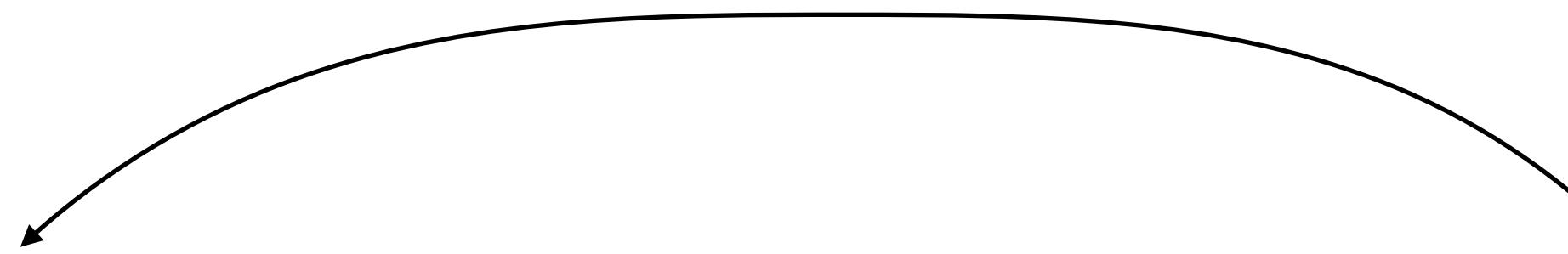


**At another locus  
in the genome...**



**Introgression: *f4 statistic* = (# BABA - # ABBA) / # SNPs < 0**

# Test of Neanderthal admixture in practice



$f_4(\text{Yoruba}, \mathbf{X}; \text{Neanderthal}, \text{Chimp}) \dots$  where  $\mathbf{X} = \text{Dinka or French}$

# Test of Neanderthal admixture in practice

$f_4(\text{Yoruba}, X; \text{Neanderthal}, \text{Chimp}) \dots$  where  $X = \text{Dinka or French}$

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X	#BABA	#ABBA	#total	f4
<b>French</b>	44409	46865	1436967	-0.0017
<b>Dinka</b>	43025	43182	1436978	-0.0001

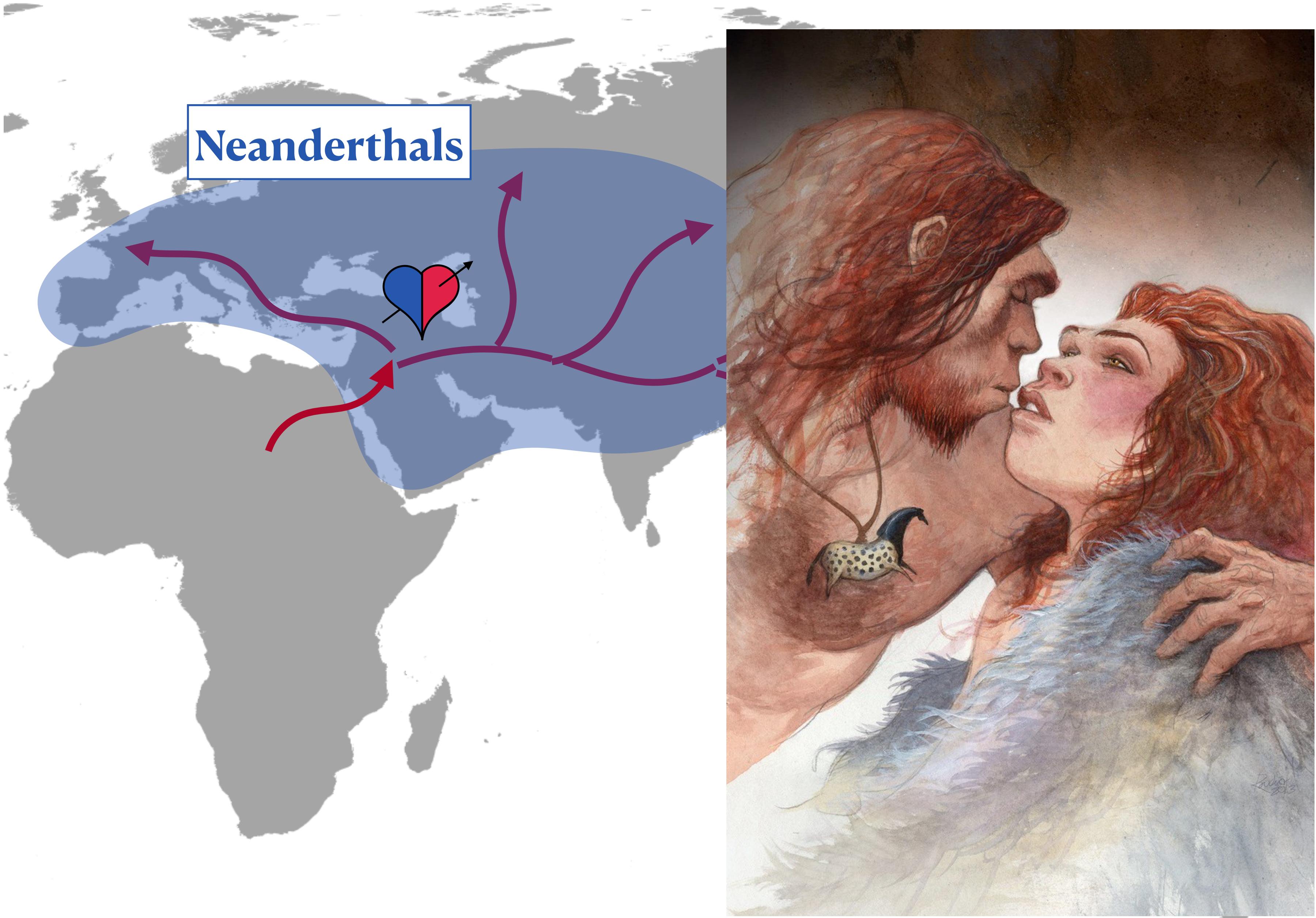
# Test of Neanderthal admixture in practice

$f_4(\text{Yoruba}, X; \text{Neanderthal}, \text{Chimp}) \dots$  where  $X = \text{Dinka or French}$

$$f_4 = (\# \text{BABA} - \# \text{ABBA}) / \# \text{SNPs}$$

X	#BABA	#ABBA	#total	f4	Z
<b>French</b>	44409	46865	1436967	-0.0017	-7.83
<b>Dinka</b>	43025	43182	1436978	-0.0001	-0.72

$|Z \text{ score}| > 3$  considered significant



# What about the proportion of Neanderthal ancestry?

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We compare the rate of allele sharing of X and a Neanderthal, with the rate of sharing between two Neanderthals (Altai and Vindija).

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X	#BABA	#ABBA	#sites	f4
<b>French</b>	44409	46865	1436967	-0.0017
<b>Dinka</b>	43025	43182	1436978	-0.0001
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# What about the proportion of Neanderthal ancestry?

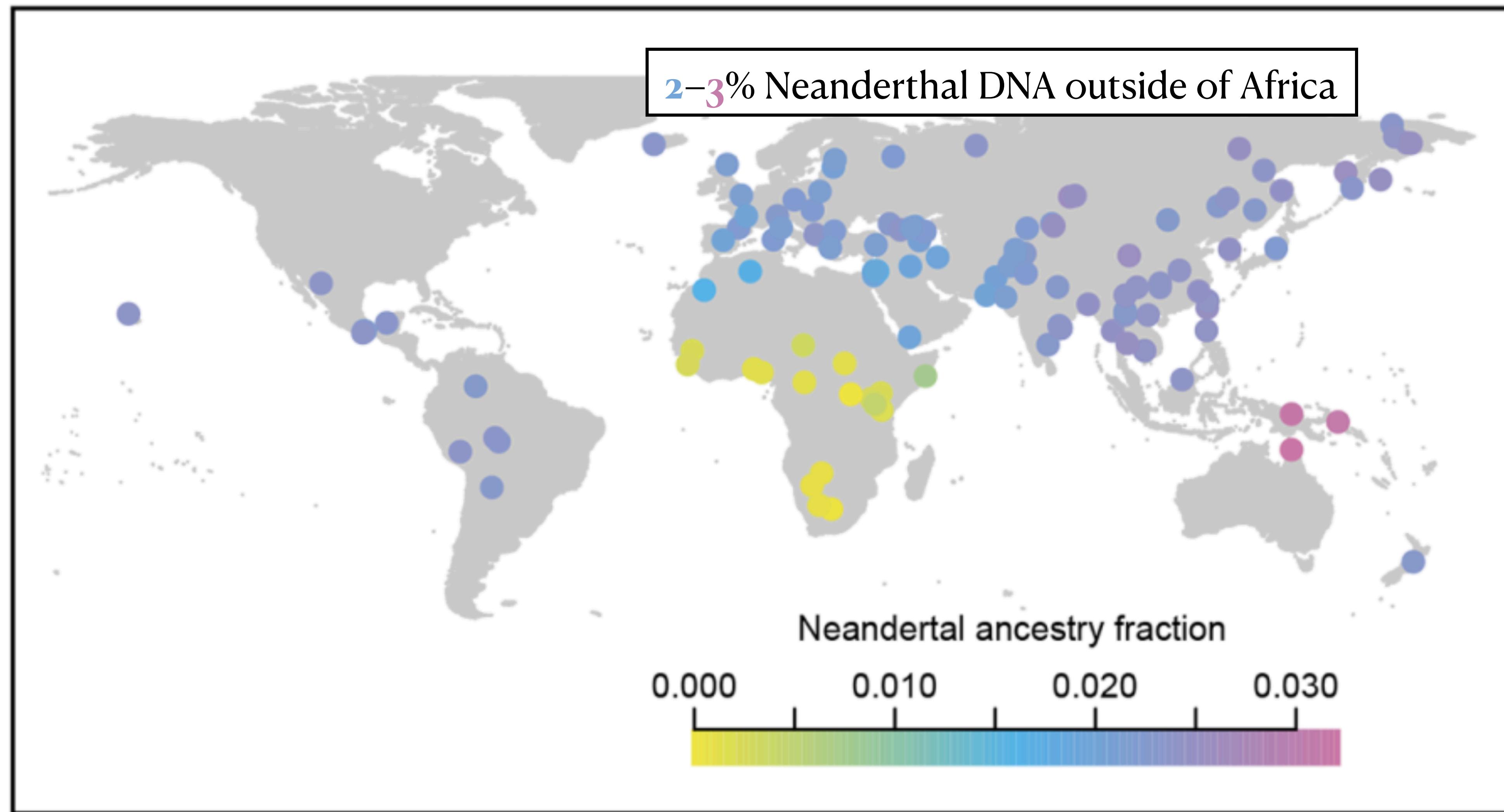
We compare the rate of allele sharing of X and a Neanderthal, with the rate of sharing between two Neanderthals (Altai and Vindija).

$f4(\text{Yoruba}, \mathbf{X}; \text{Altai}, \text{Chimp}) / f4(\text{Yoruba}, \mathbf{Vindija}; \text{Altai}, \text{Chimp})$

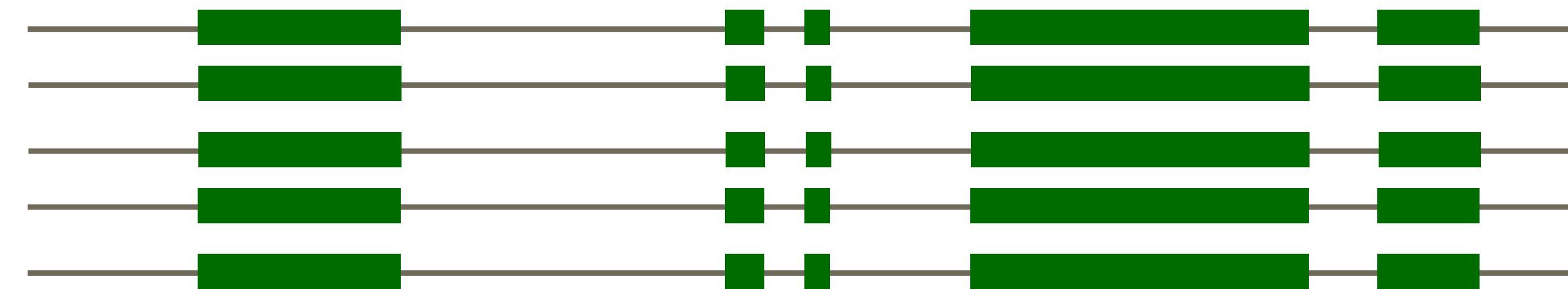


X	#BABA	#ABBA	#sites	f4	ratio
French	44409	46865	1436967	-0.0017	2.2%
Dinka	43025	43182	1436978	-0.0001	0.1%
Vindija	7337	118956	1436703	-0.0777	100%

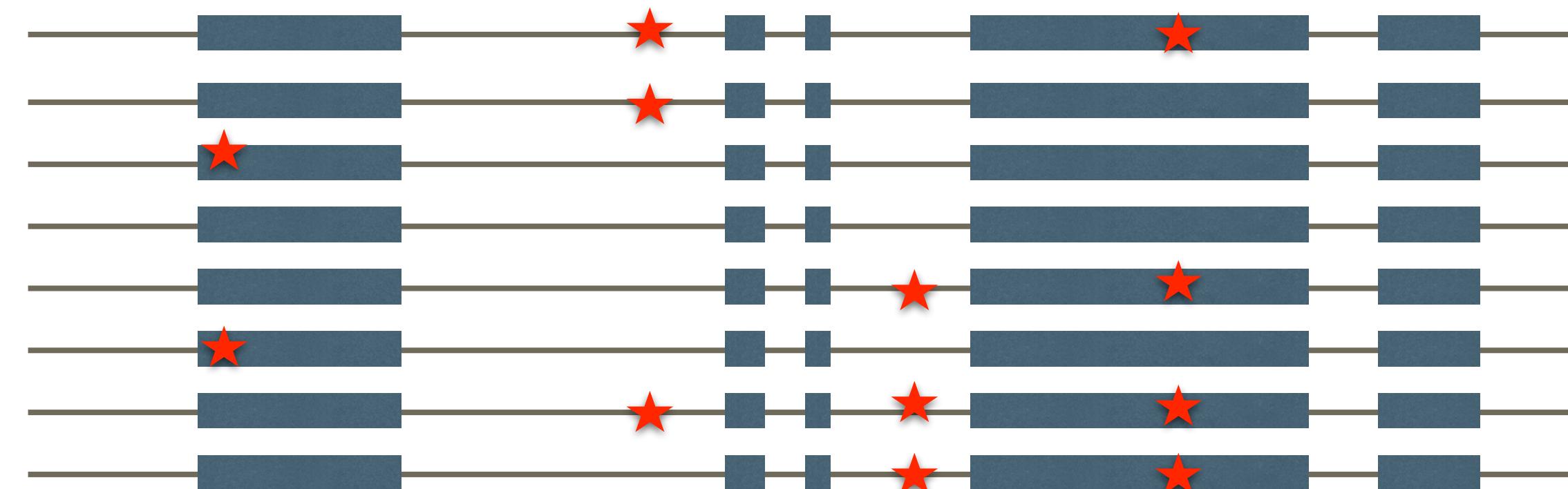
# Proportion of Neanderthal DNA in humans today



# We can go from detecting SNPs of Neanderthal origin...



genomes of a  
reference population  
(Yoruba)



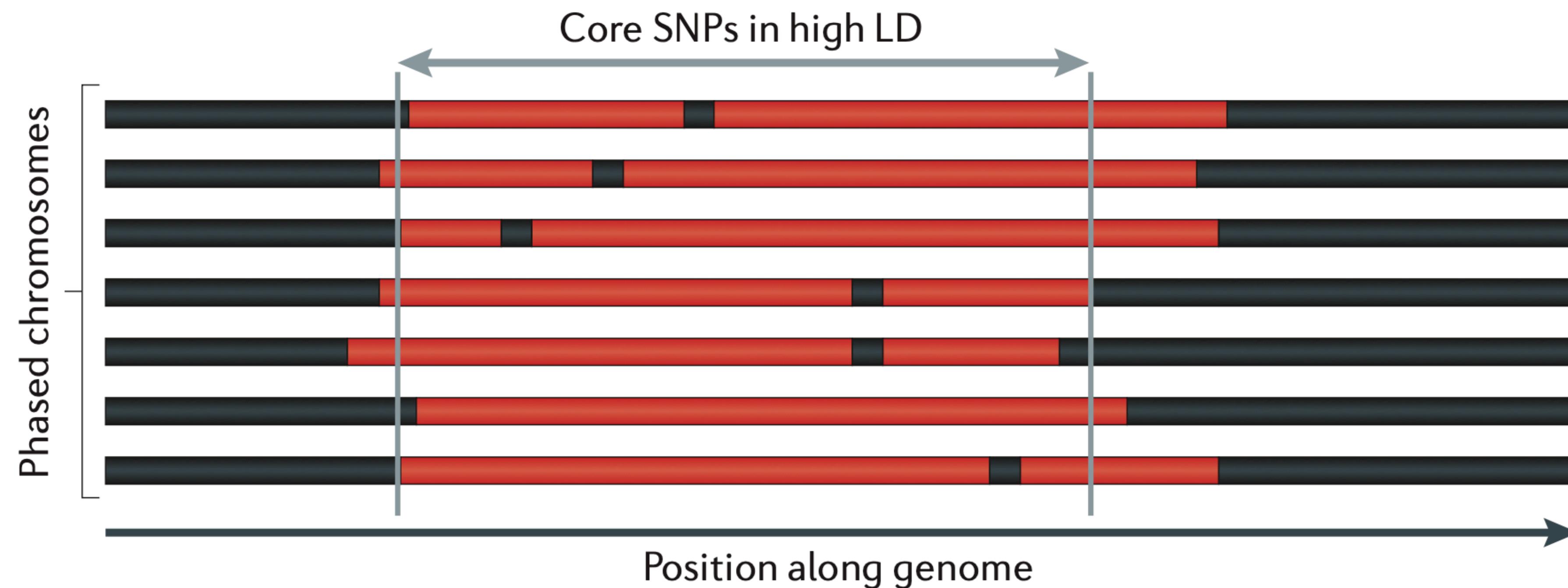
genomes of a  
target population  
(Europeans)



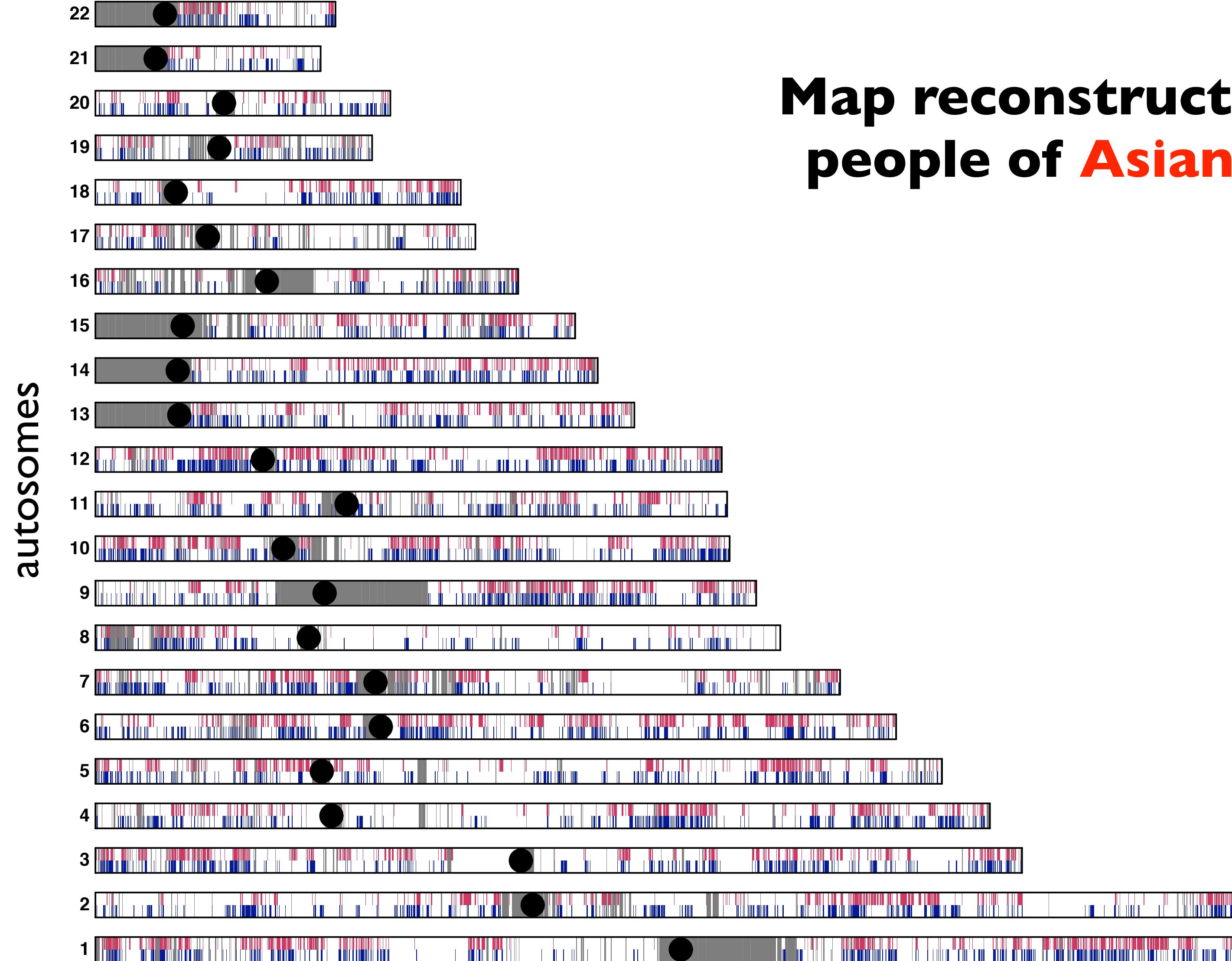
Neanderthal  
genome

★ = Neanderthal-derived mutation

# ...to continuous segments of Neanderthal DNA

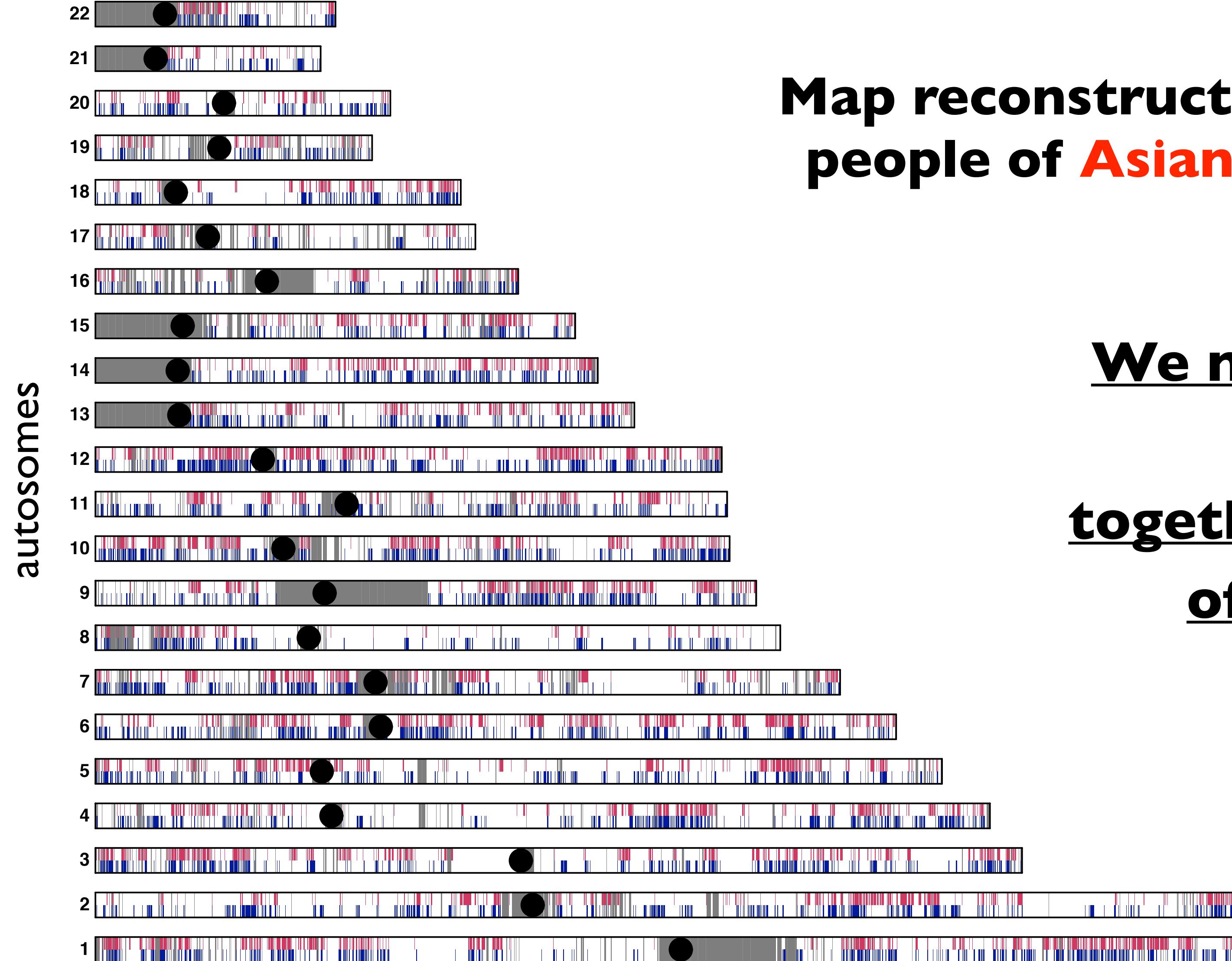


# Genomic maps of Neanderthal DNA today



**Map reconstructed from genomes of 700 people of Asian and European ancestry.**

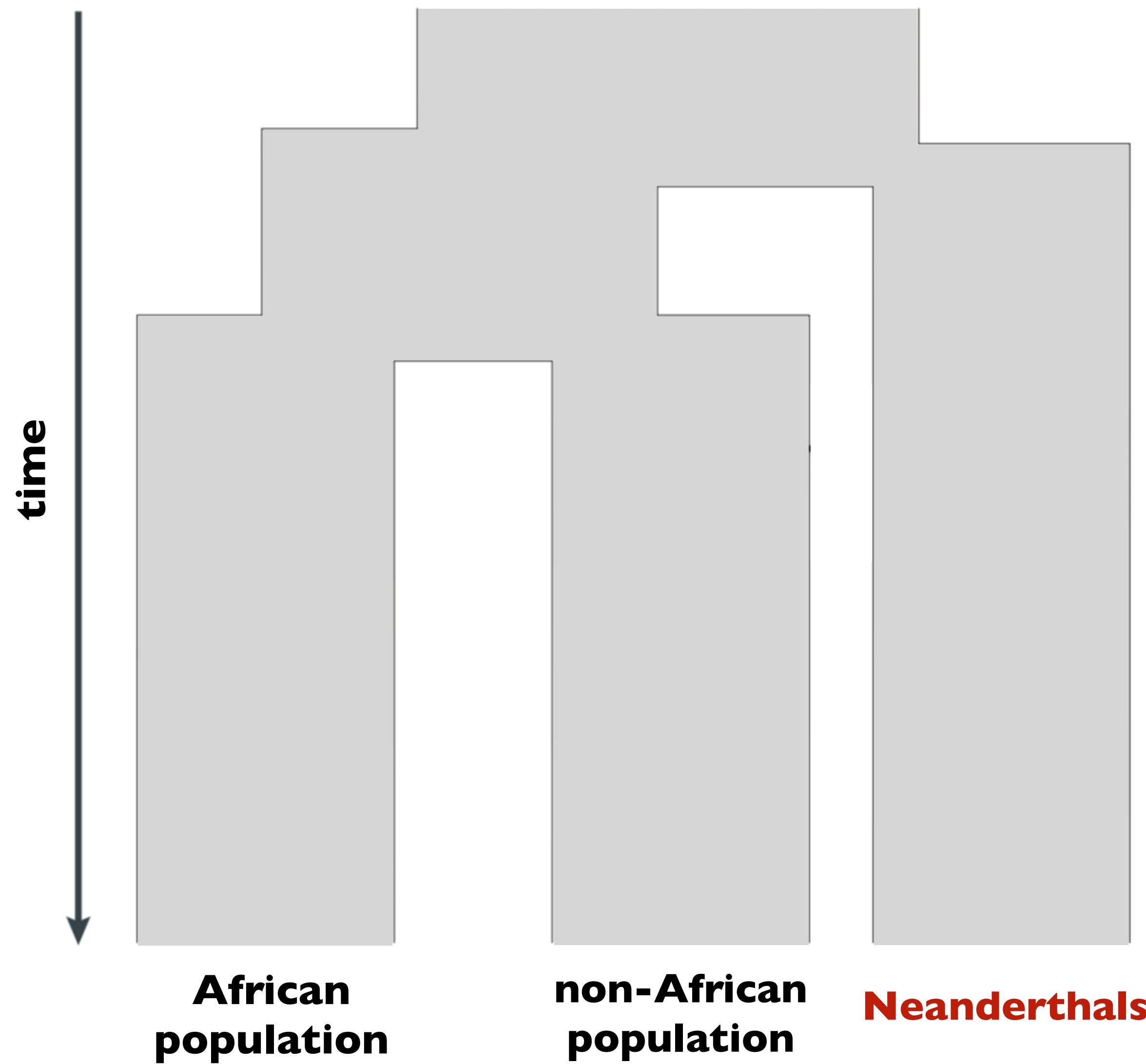
# Genomic maps of Neanderthal DNA today



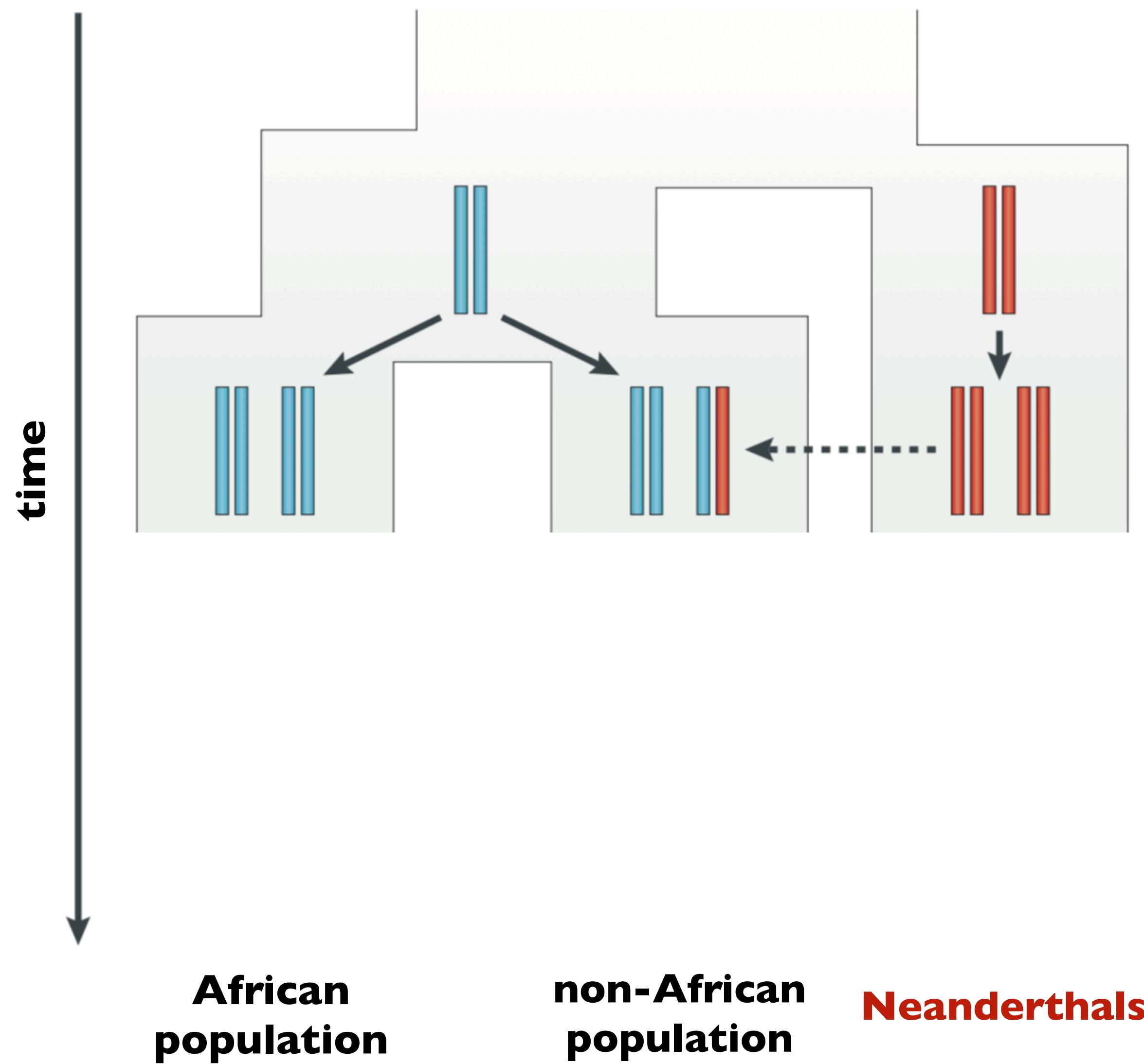
**Map reconstructed from genomes of 700 people of **Asian** and **European** ancestry.**

**We may each have only 2% of Neanderthal DNA, but together we carry around 40% of a Neanderthal genome!**

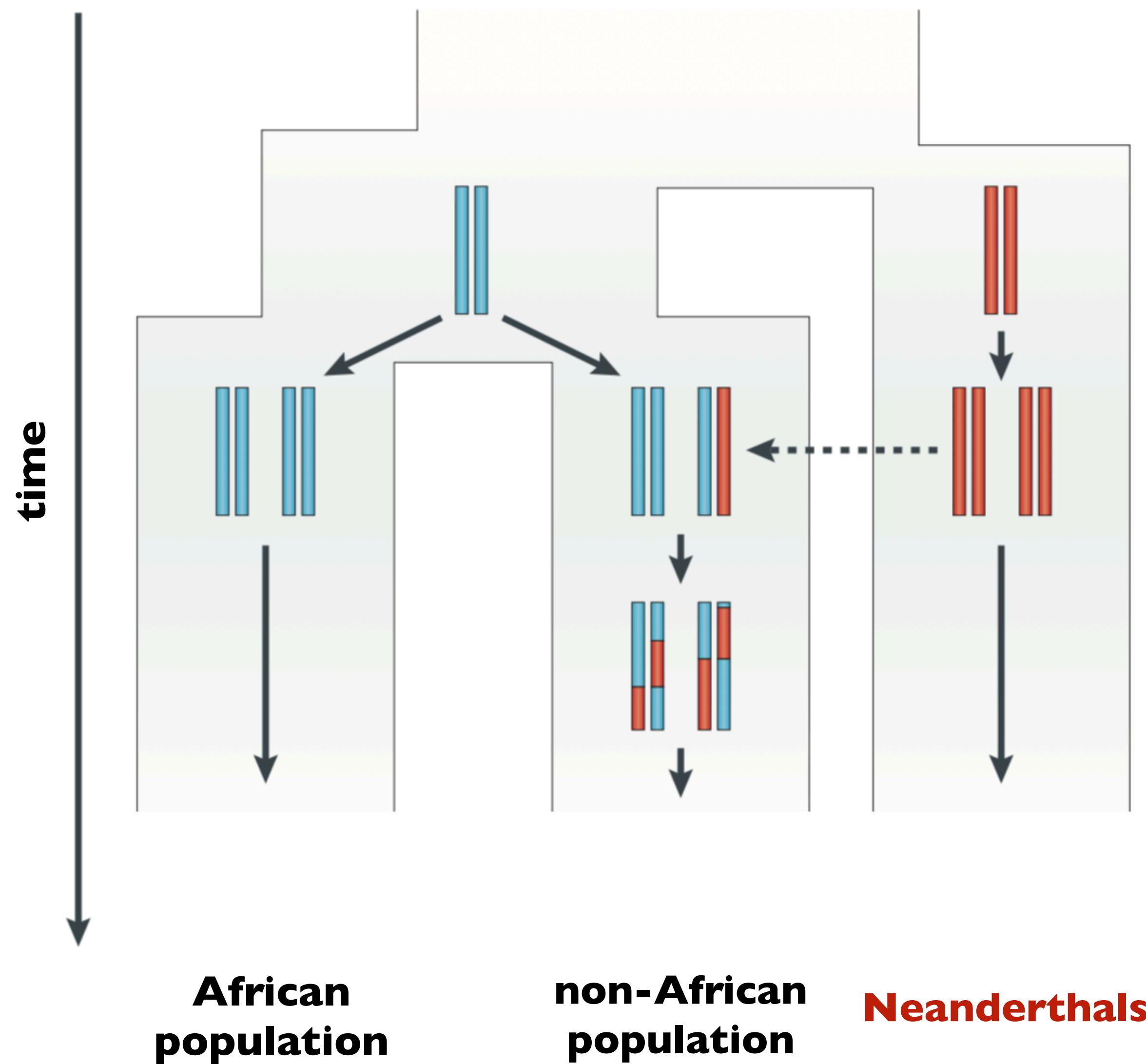
# When did introgression happen?



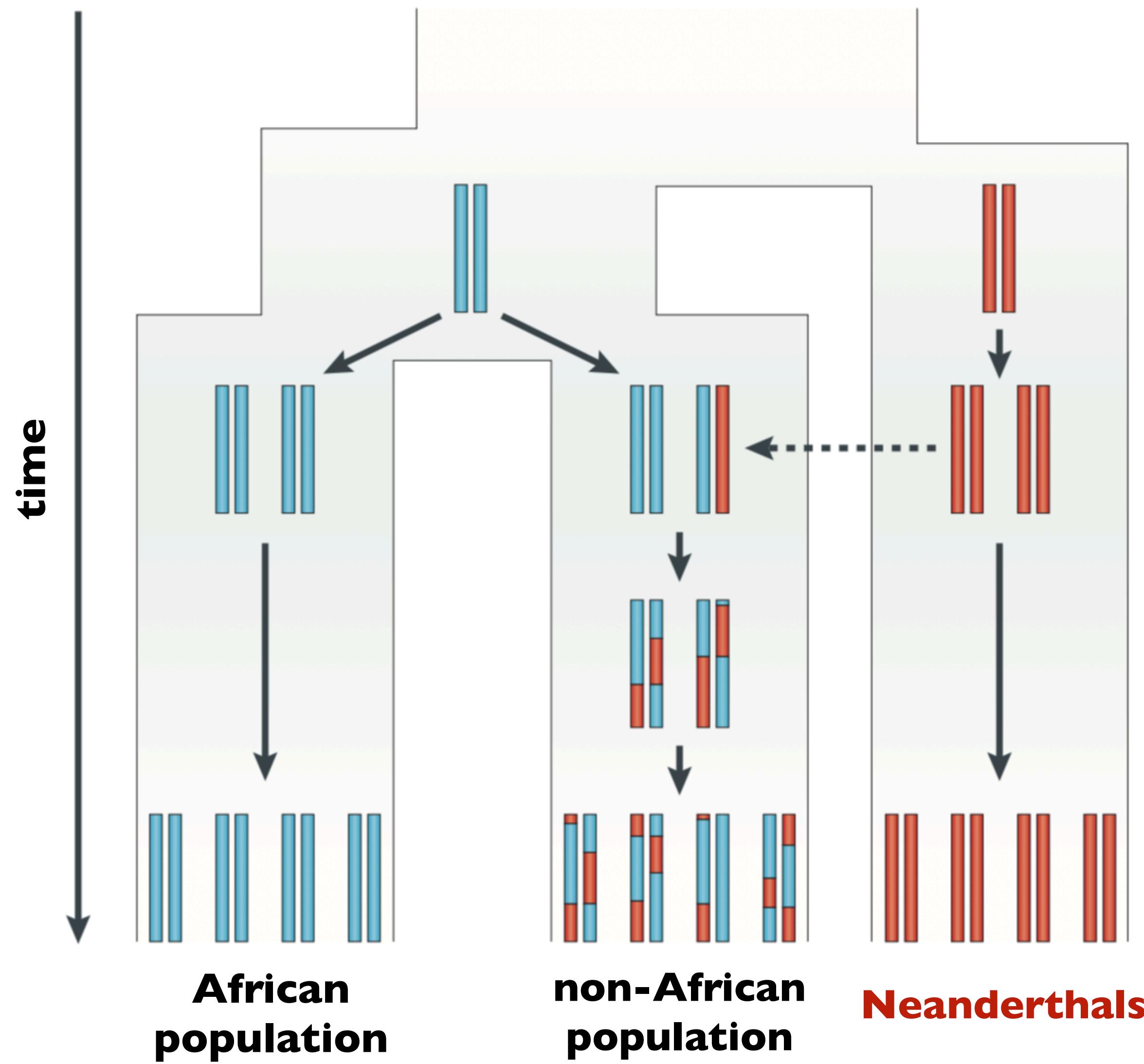
# When did introgression happen?



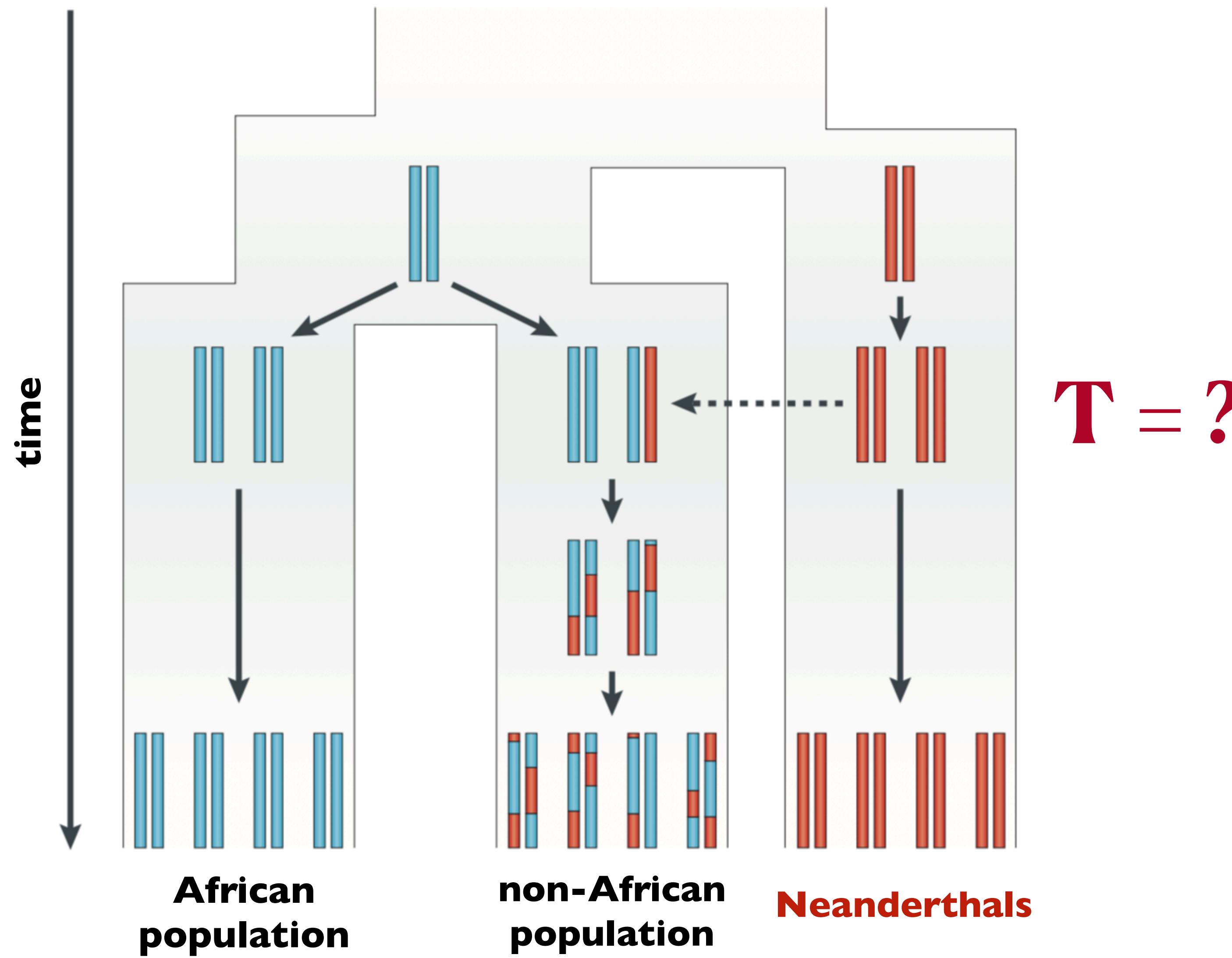
# When did introgression happen?



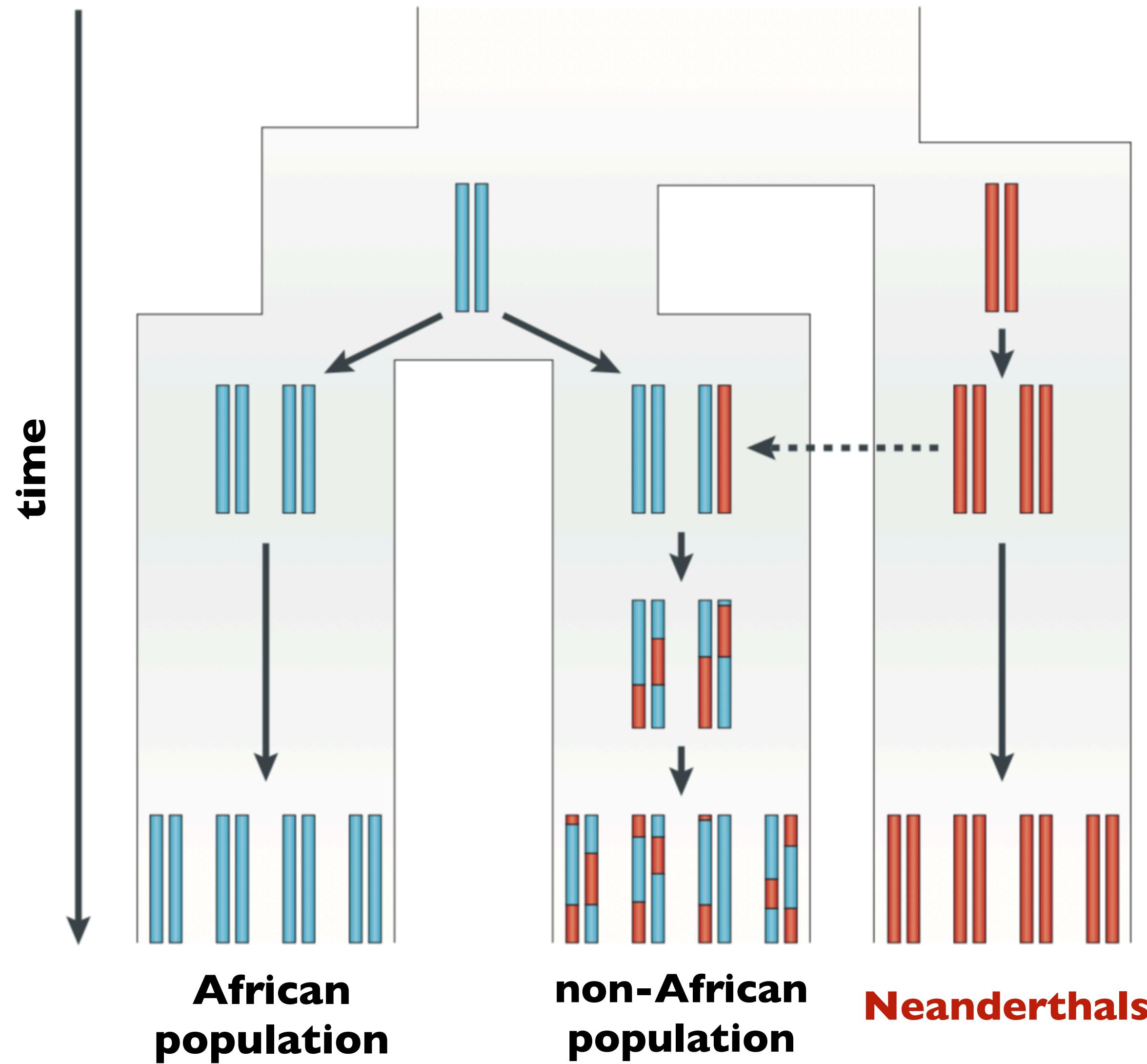
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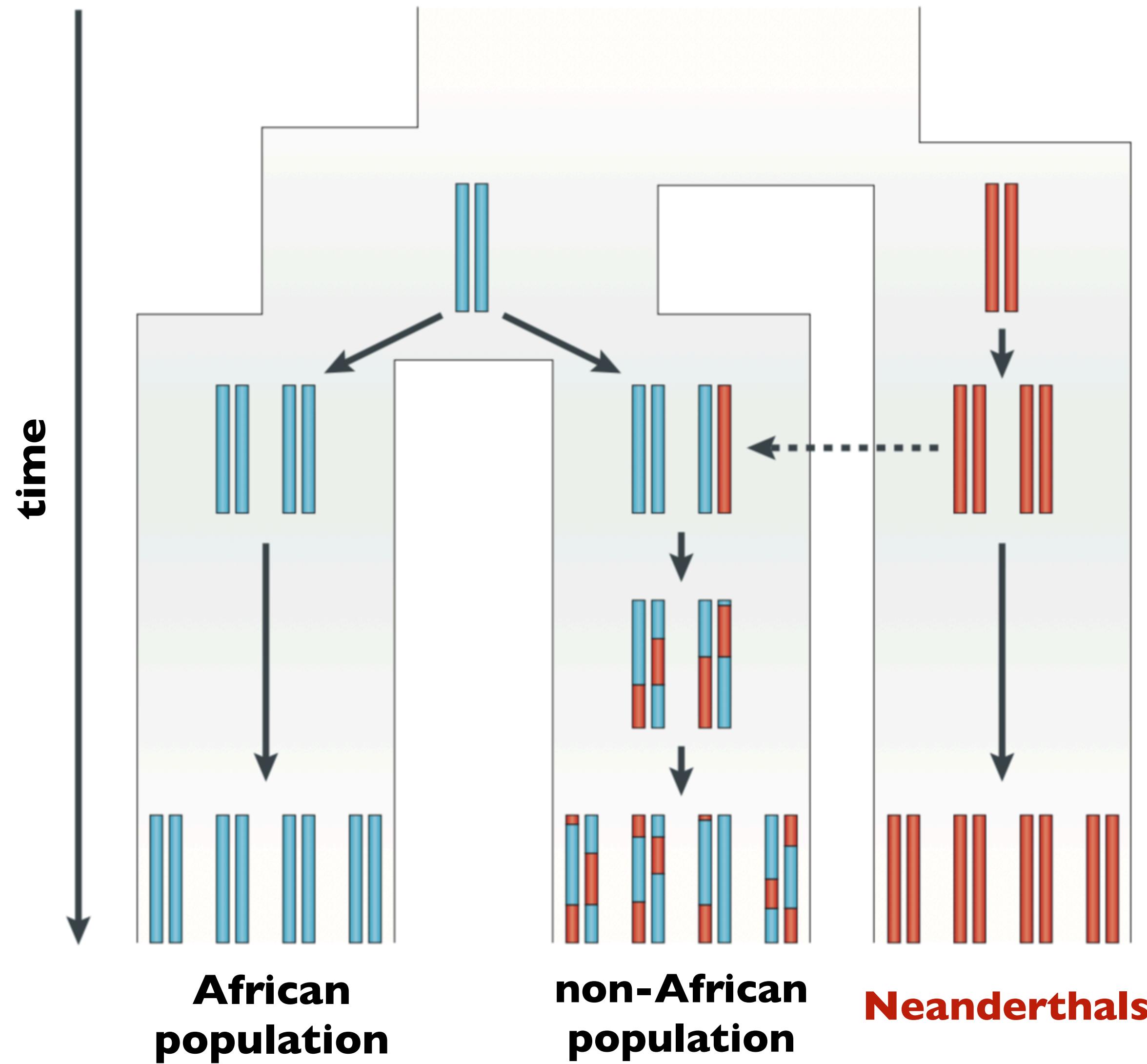
# When did introgression happen?



Haplotypes carrying Neanderthal alleles get shorter over time due to recombination (statistically “regularly”).

T = ?

# When did introgression happen?

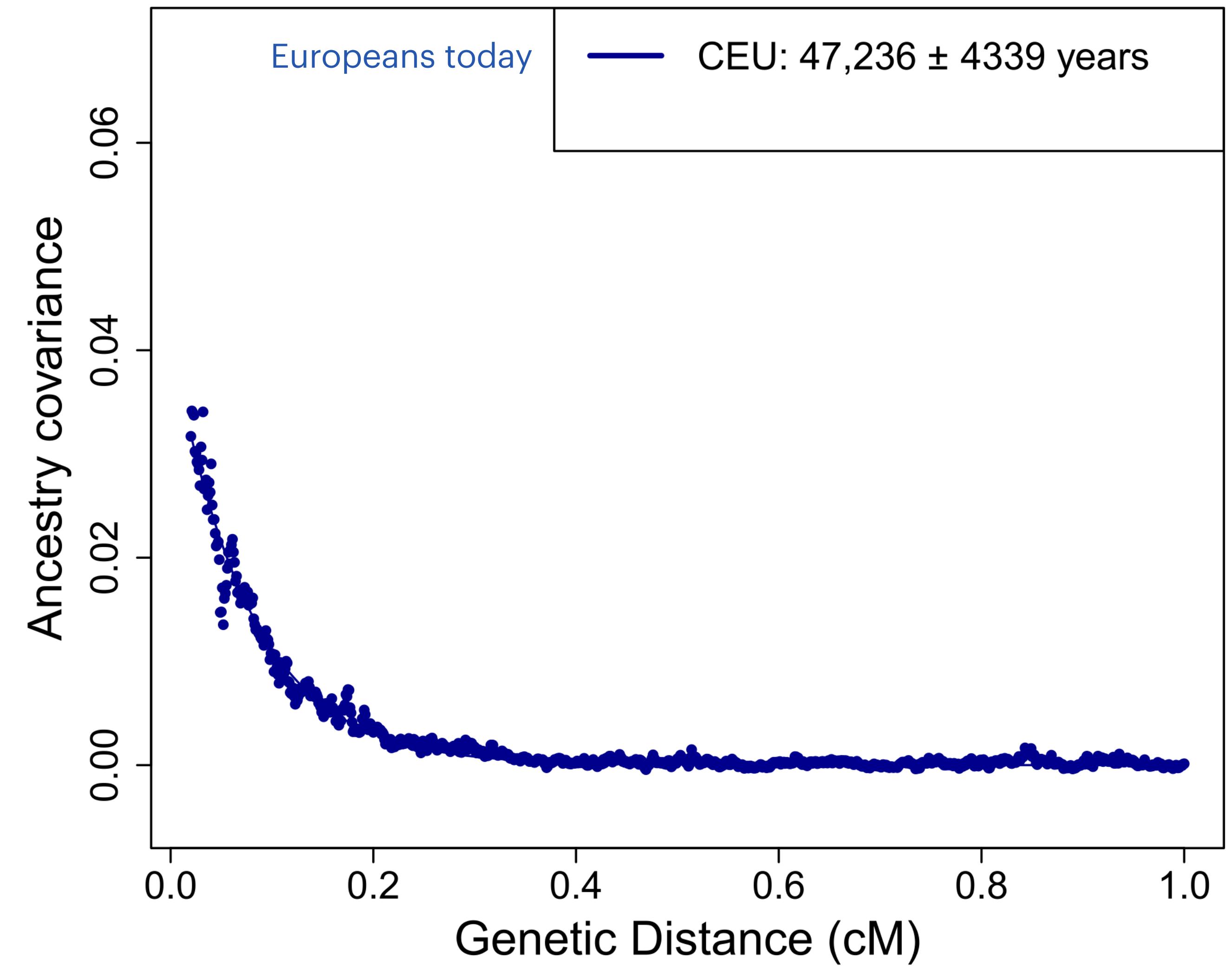
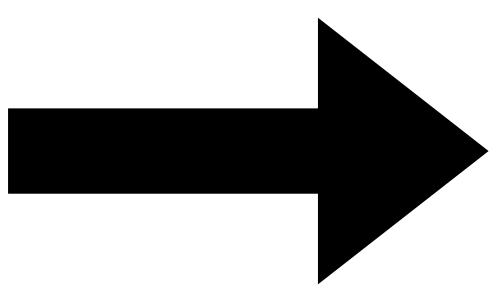
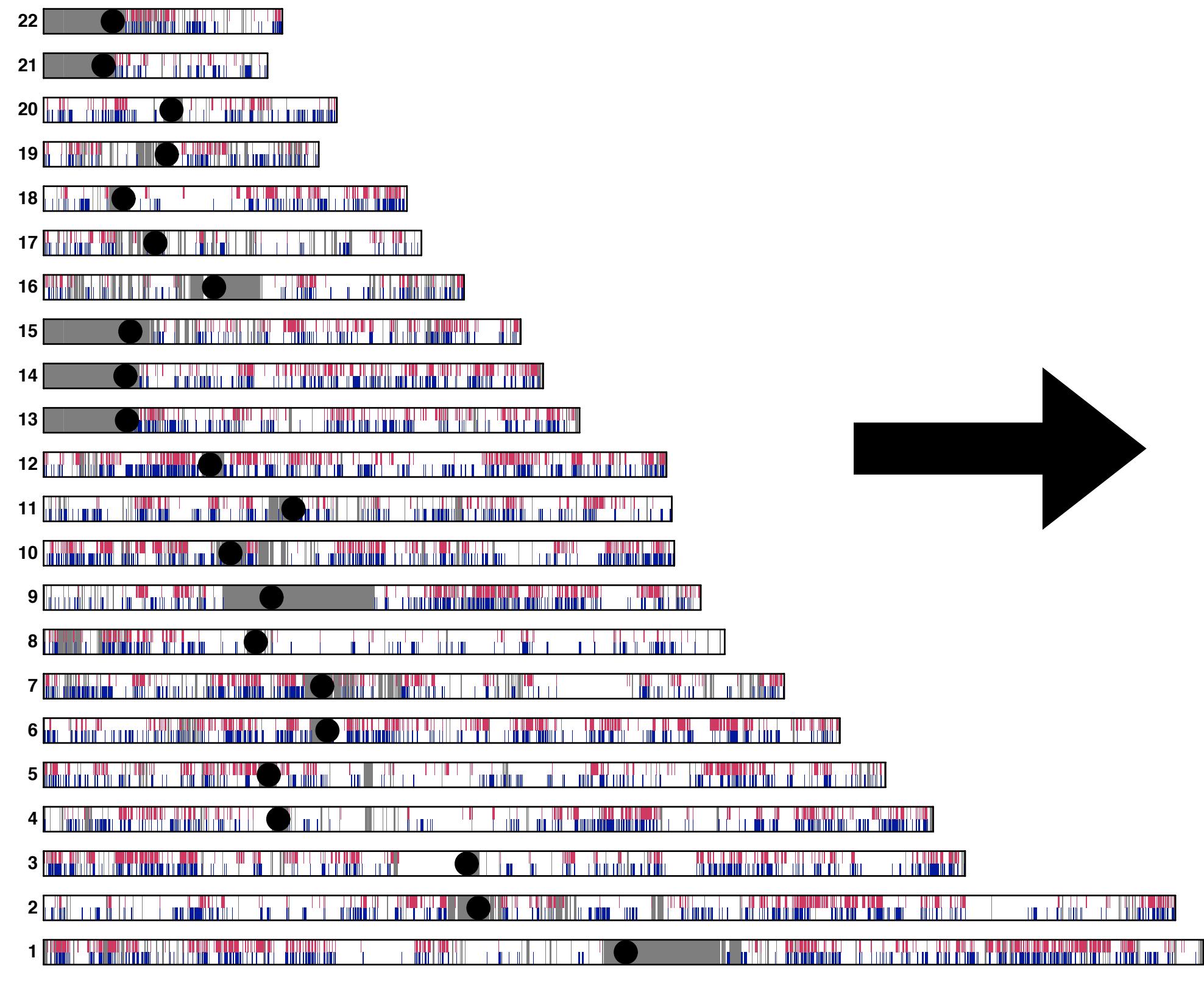


Haplotypes carrying Neanderthal alleles get shorter over time due to recombination (statistically “regularly”).

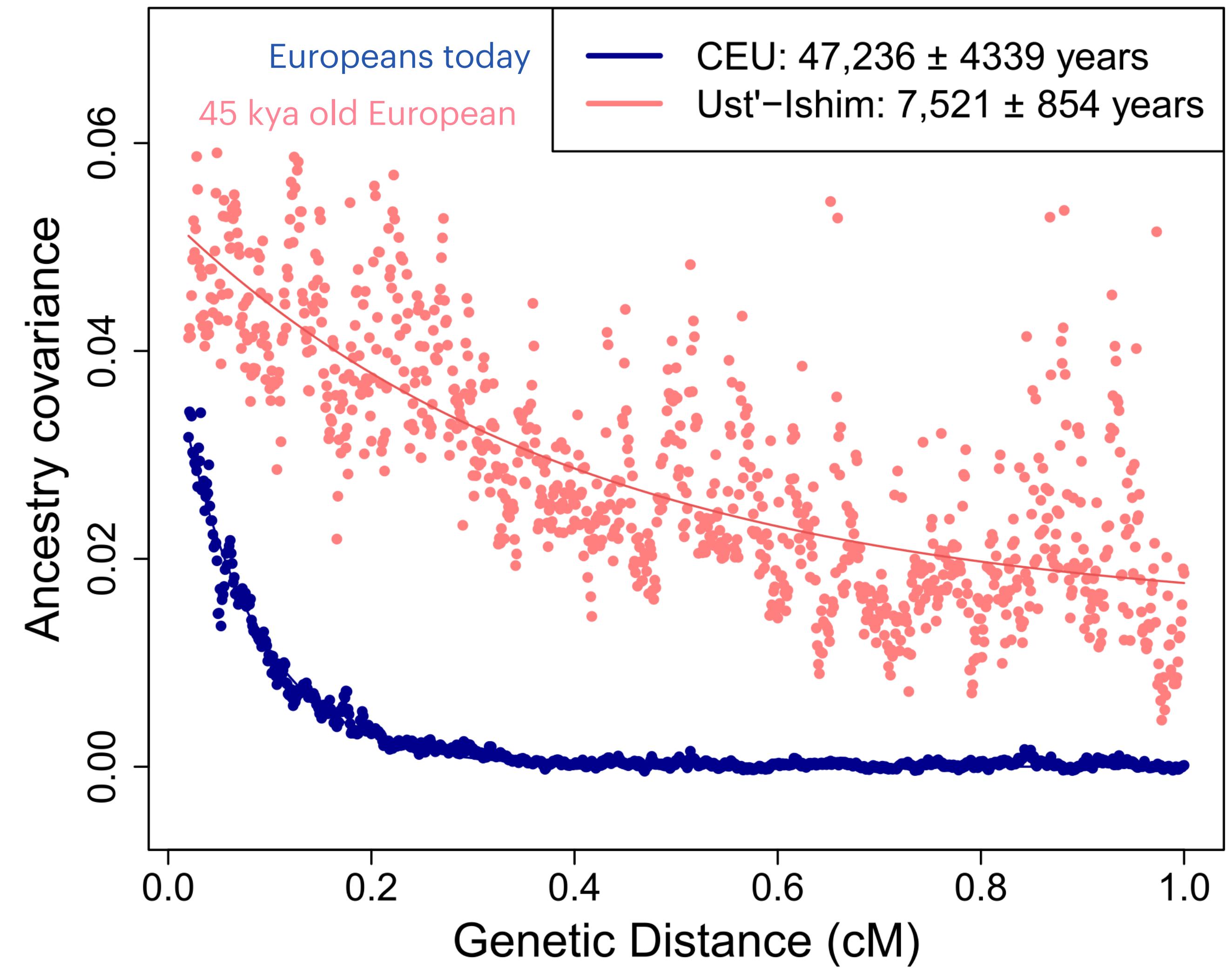
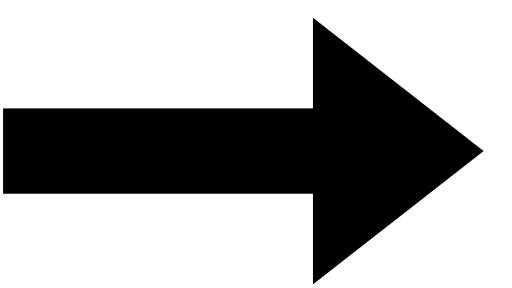
$T = ?$

Expected length of these haplotypes follows the principle of exponential decay.

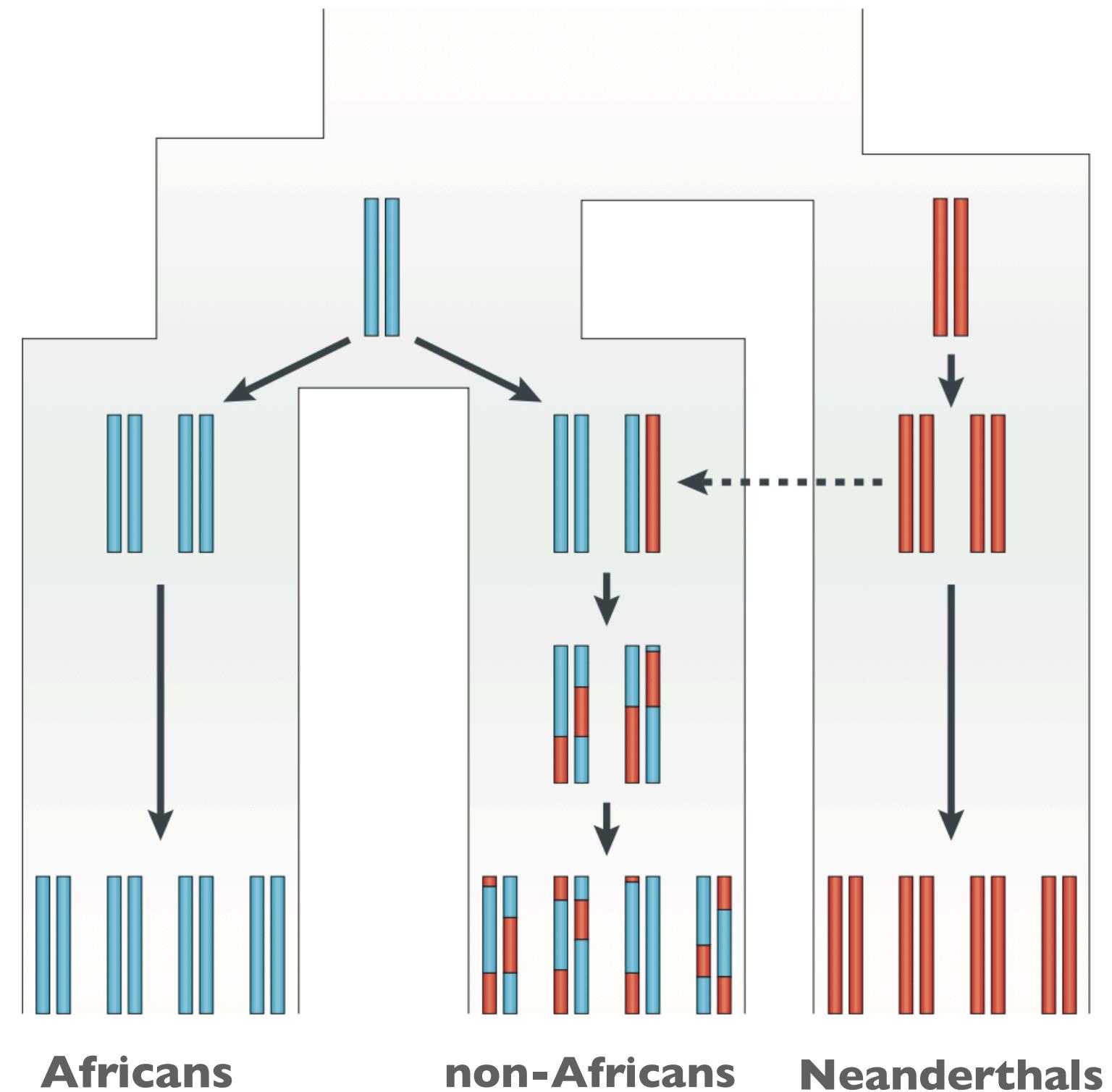
# Introgression happened around 50 thousand years ago



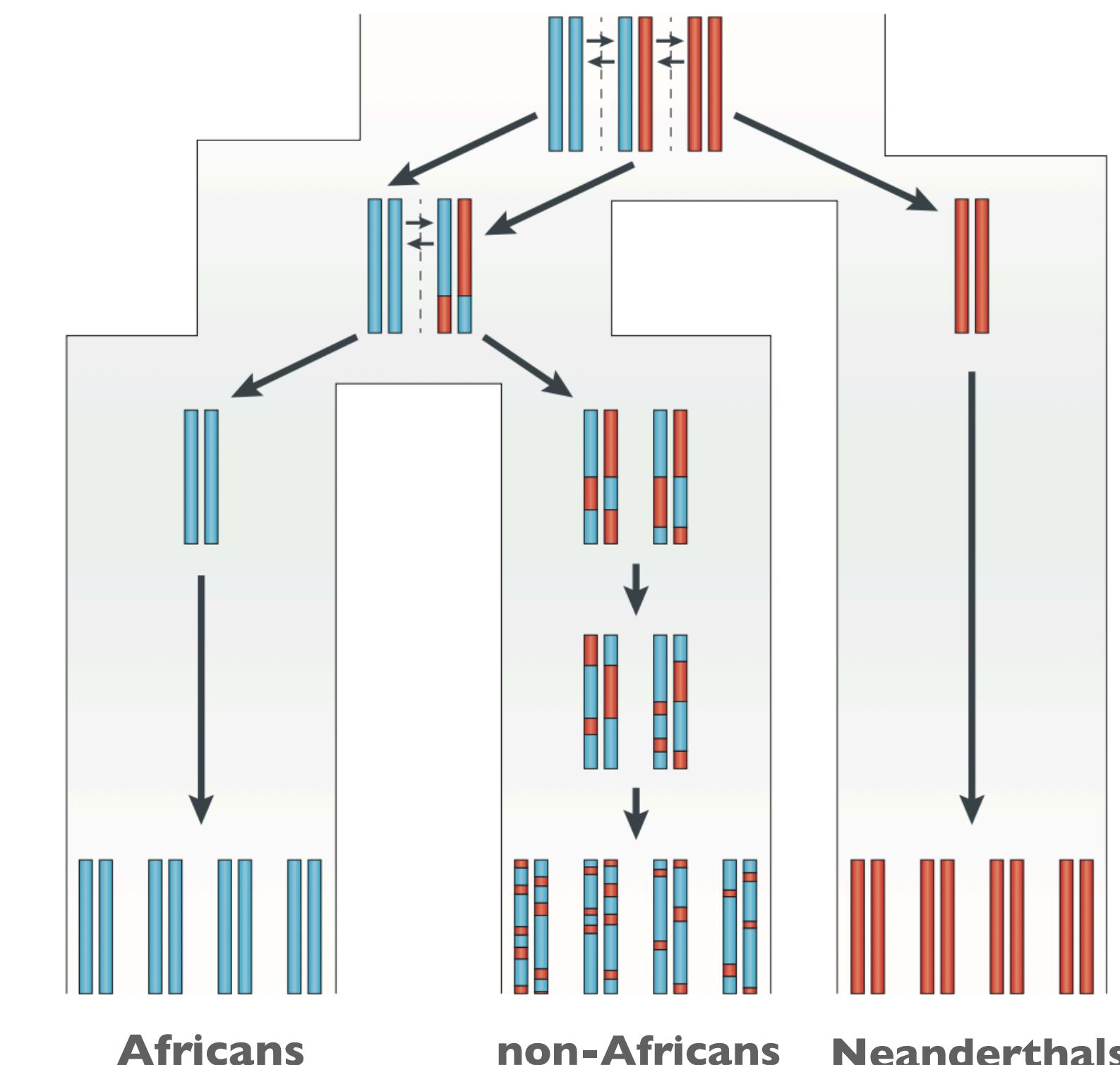
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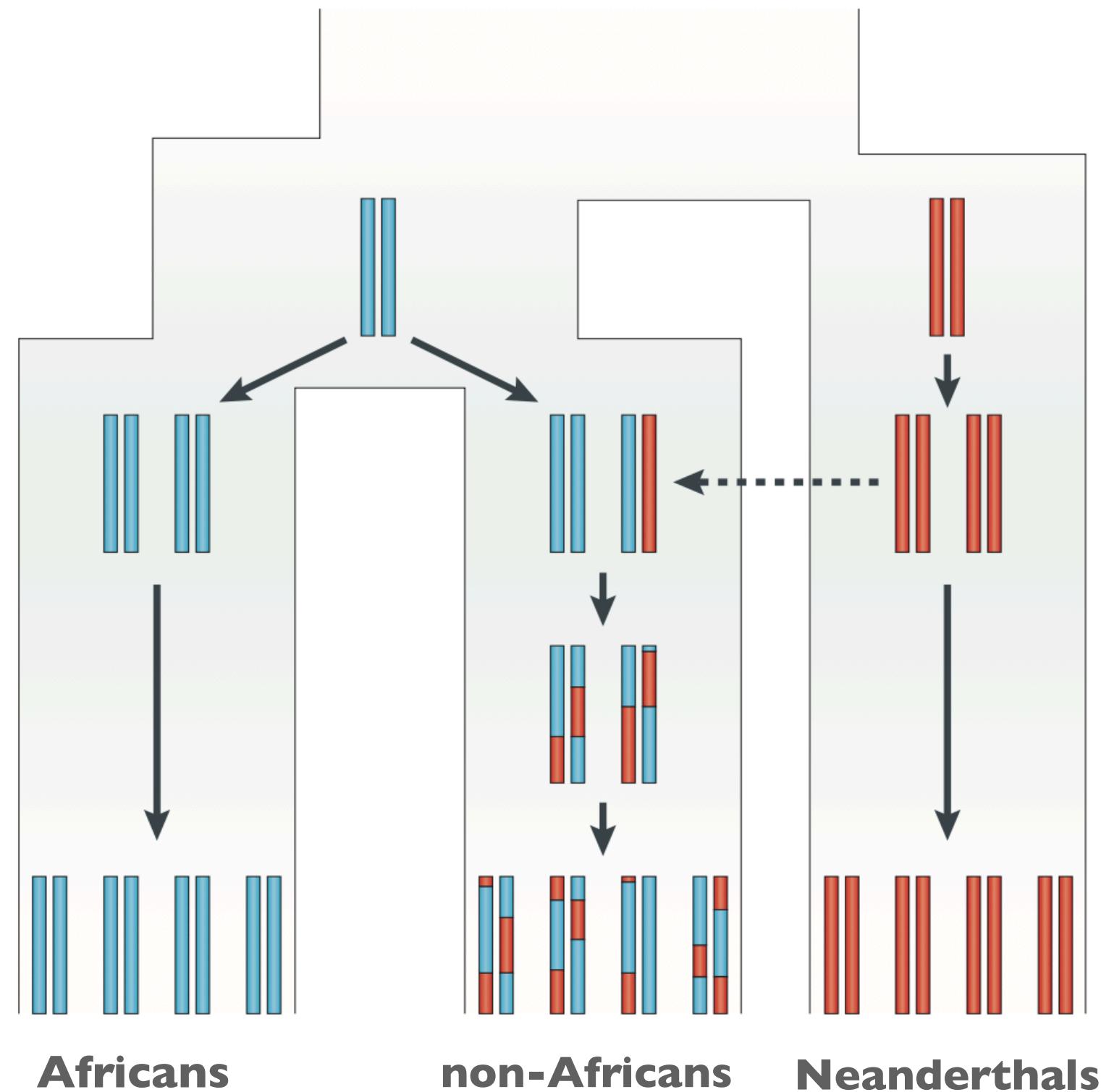
# Introgression?



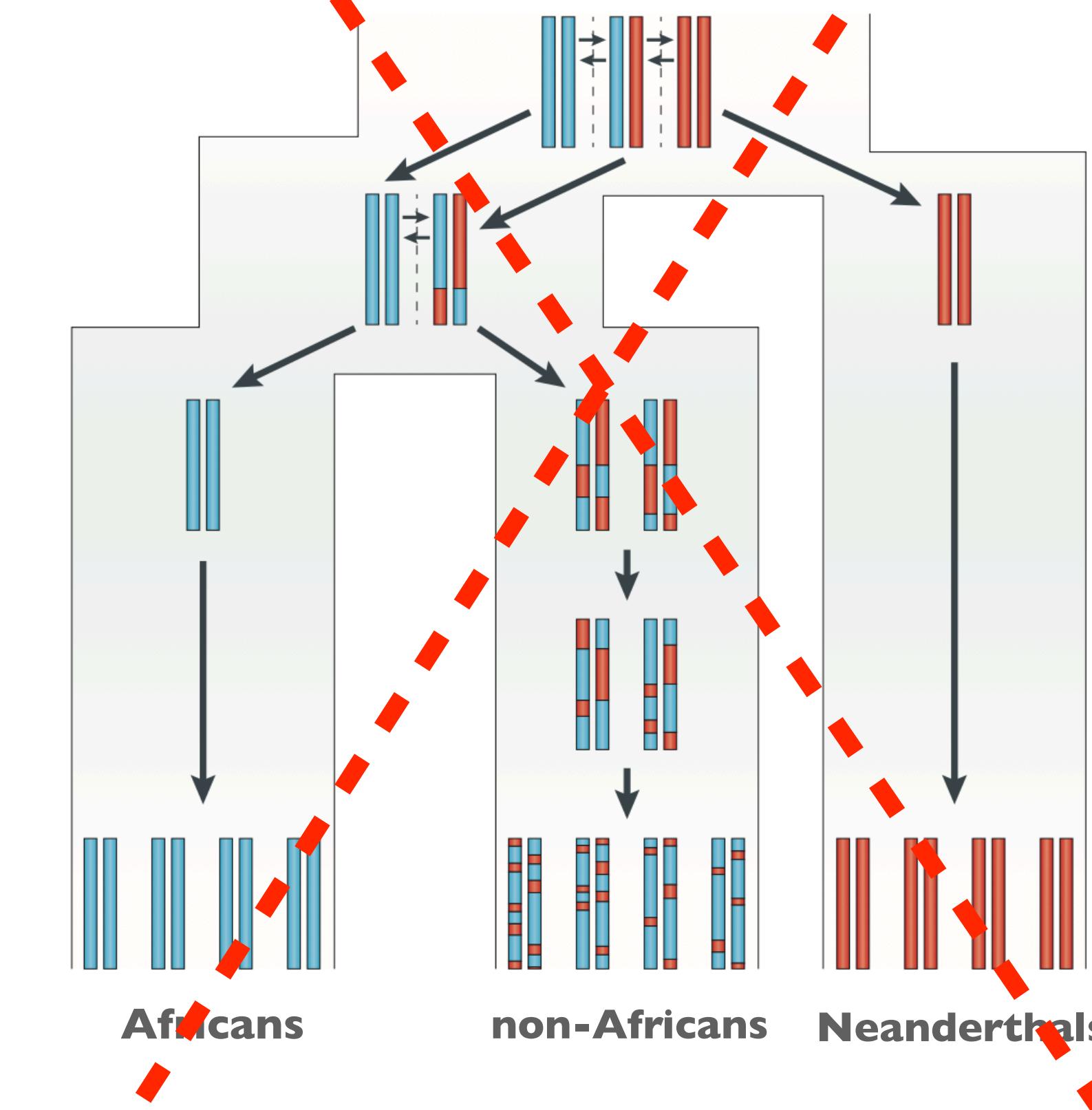
# Structure?



# Introgression?



# Structure?

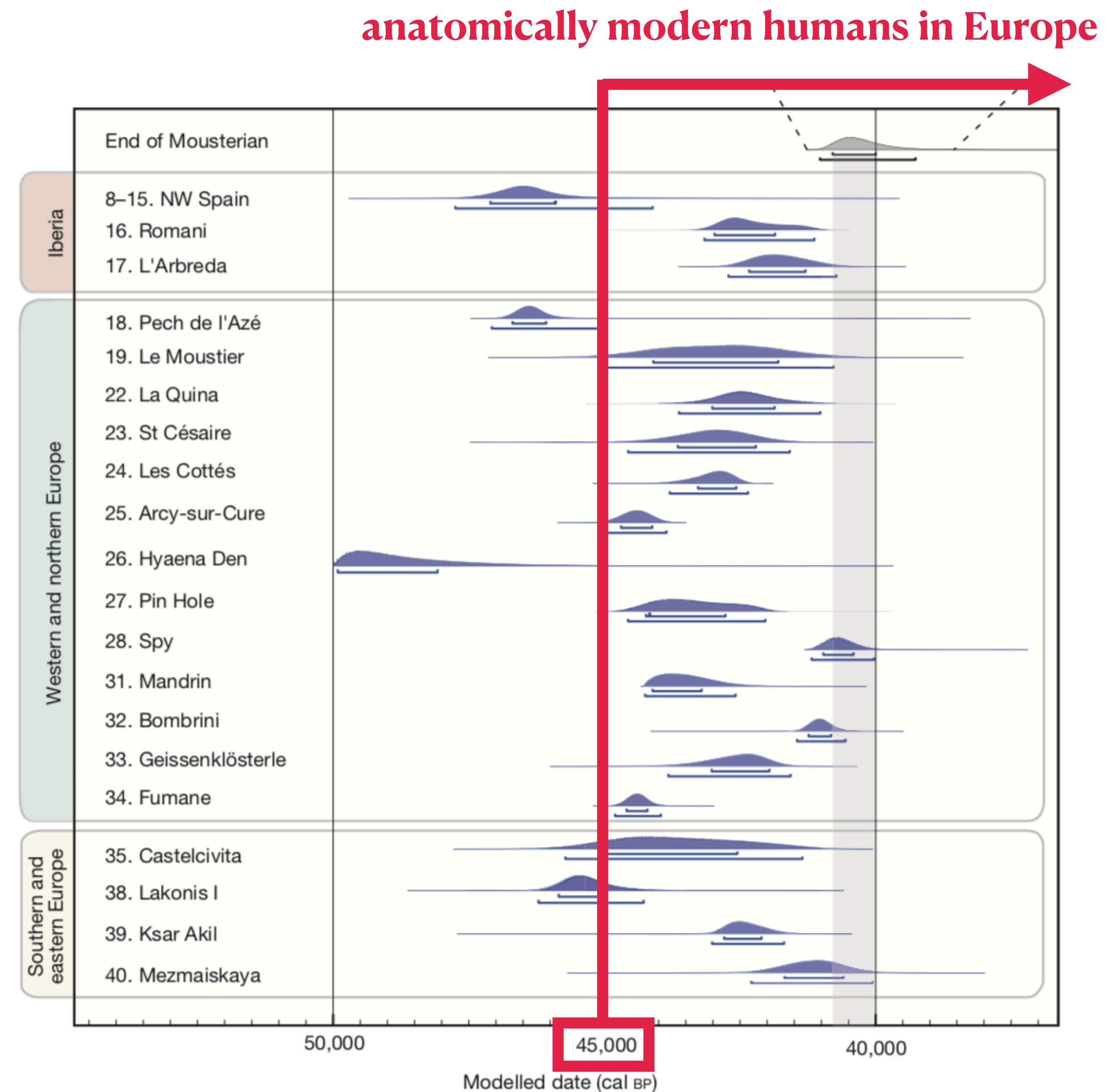
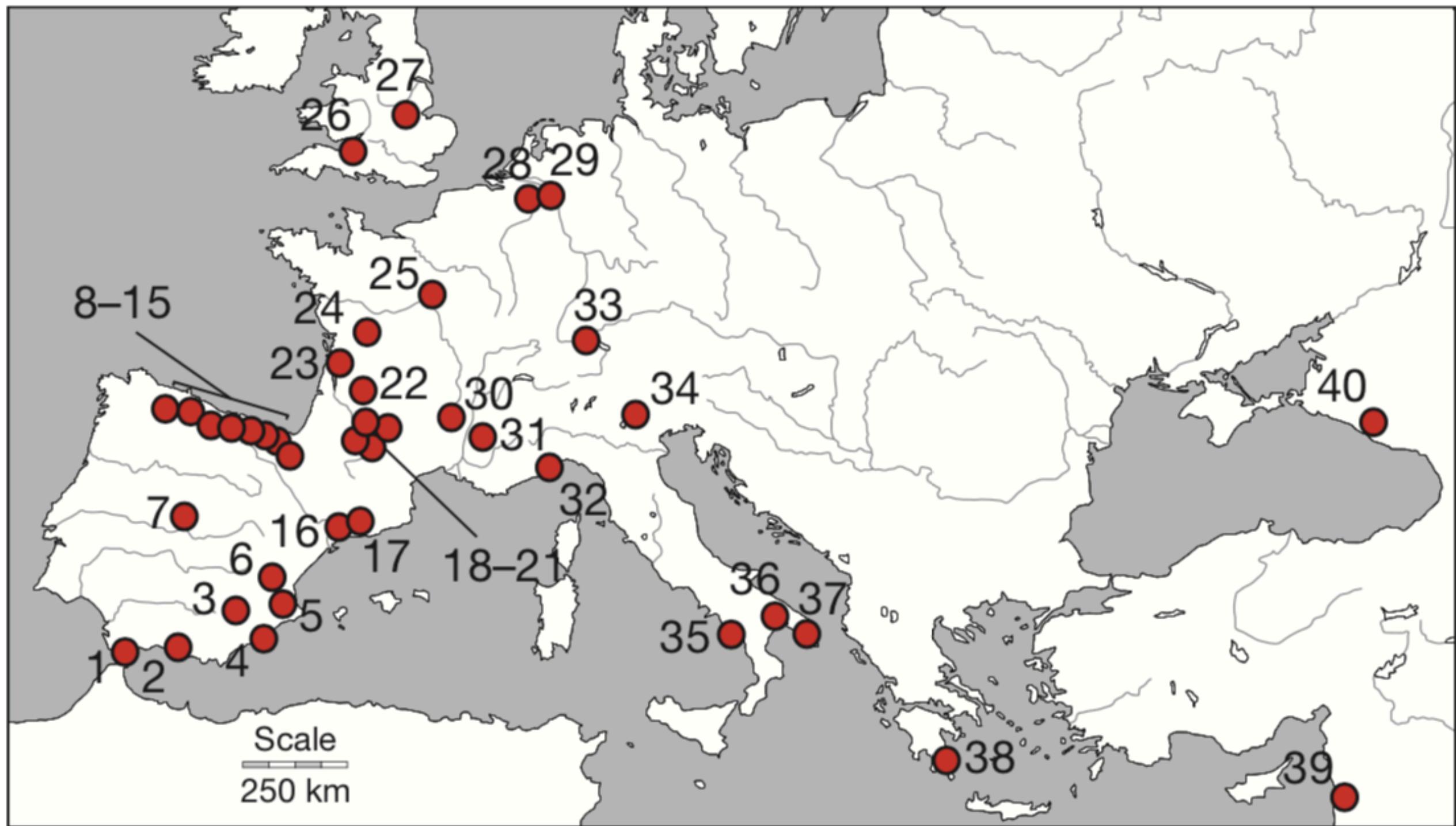


Under structure, “Neanderthal-looking”  
haplotypes will be much shorter!



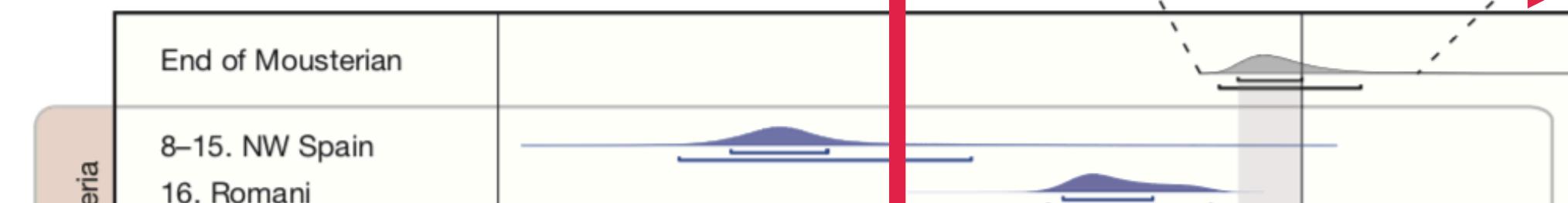
# ABBA/BABA EXERCISES

[github.com/bodkan/ku-introgression2025](https://github.com/bodkan/ku-introgression2025)

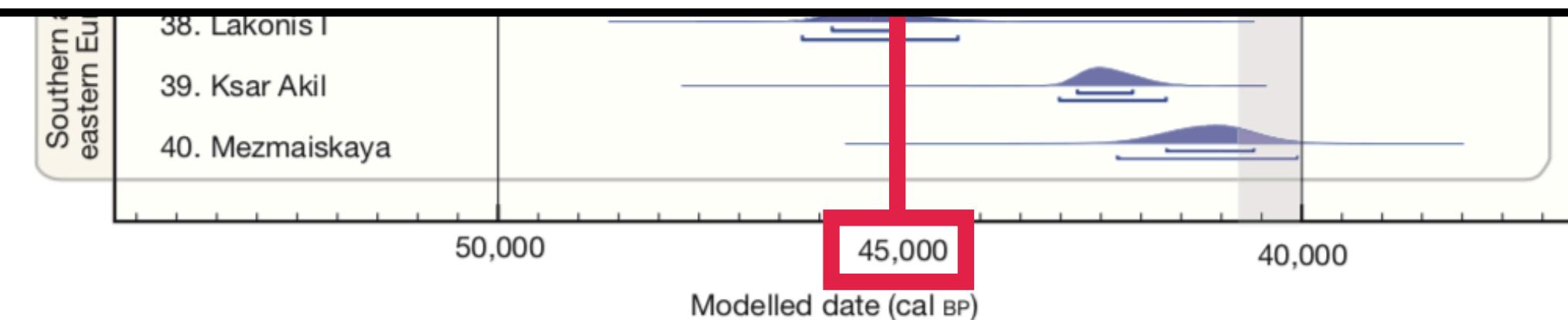


Higham et al. (Nature, 2014)

anatomically modern humans in Europe



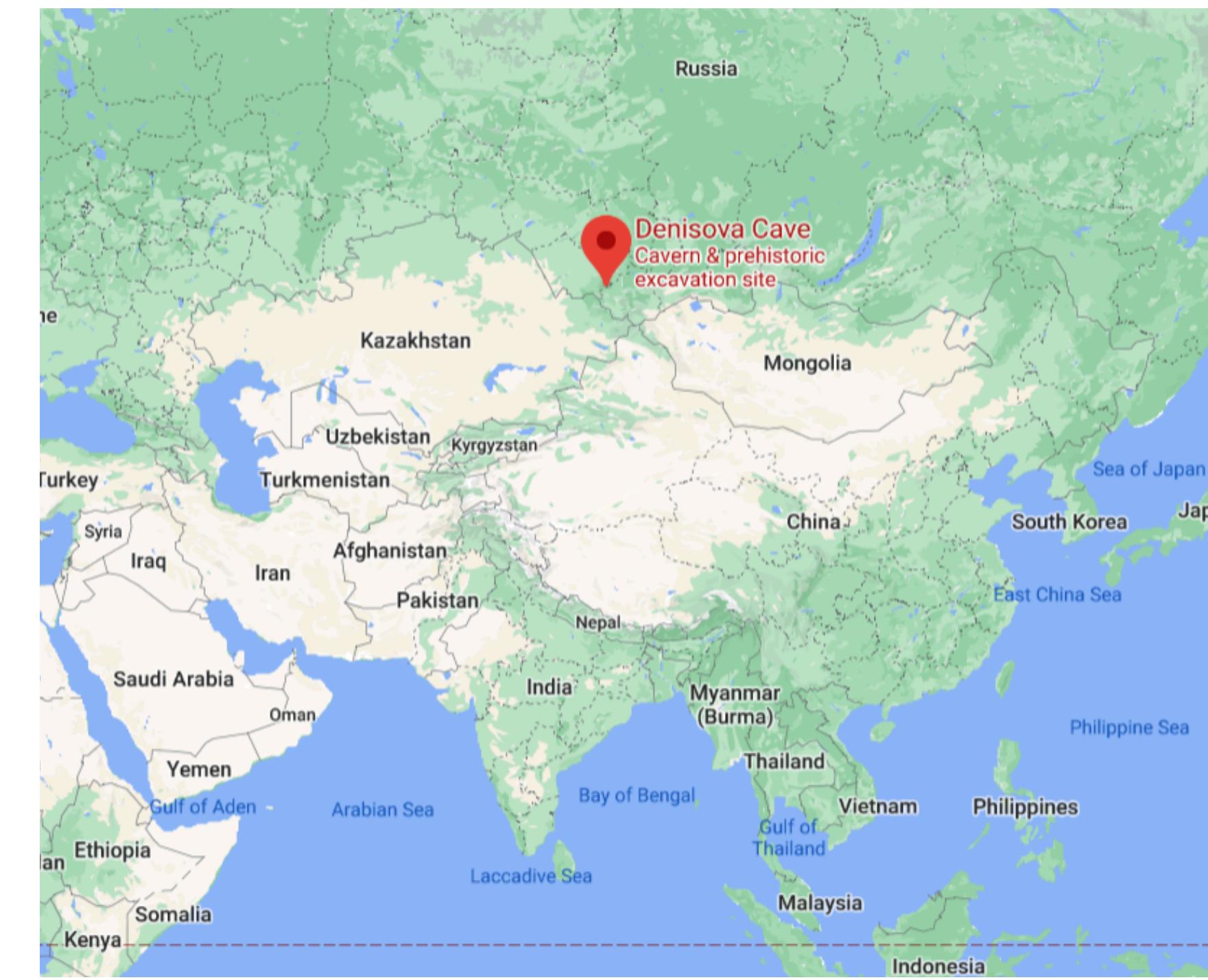
# Neanderthals were not the only archaics around at the time

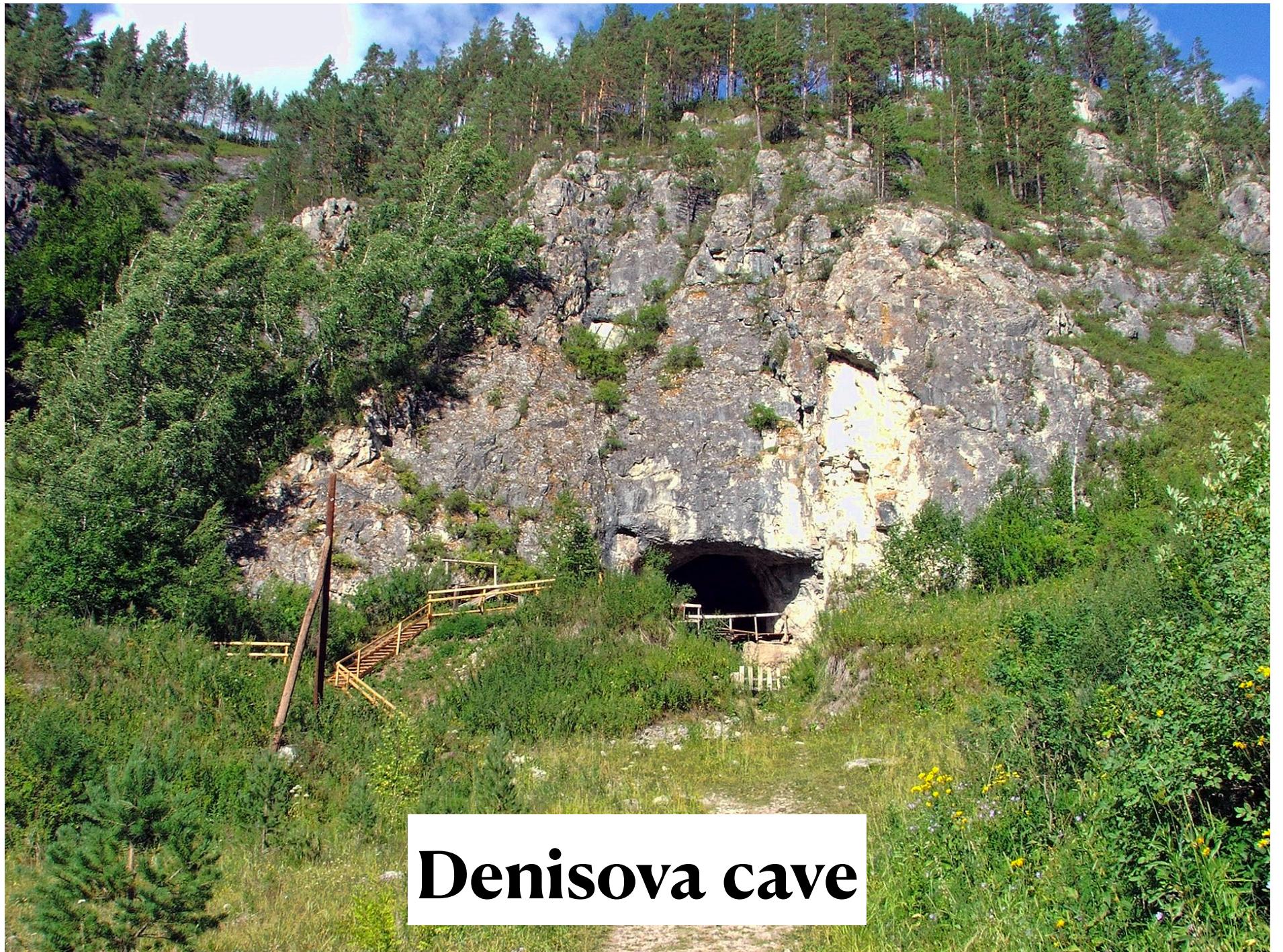


Higham et al. (Nature, 2014)

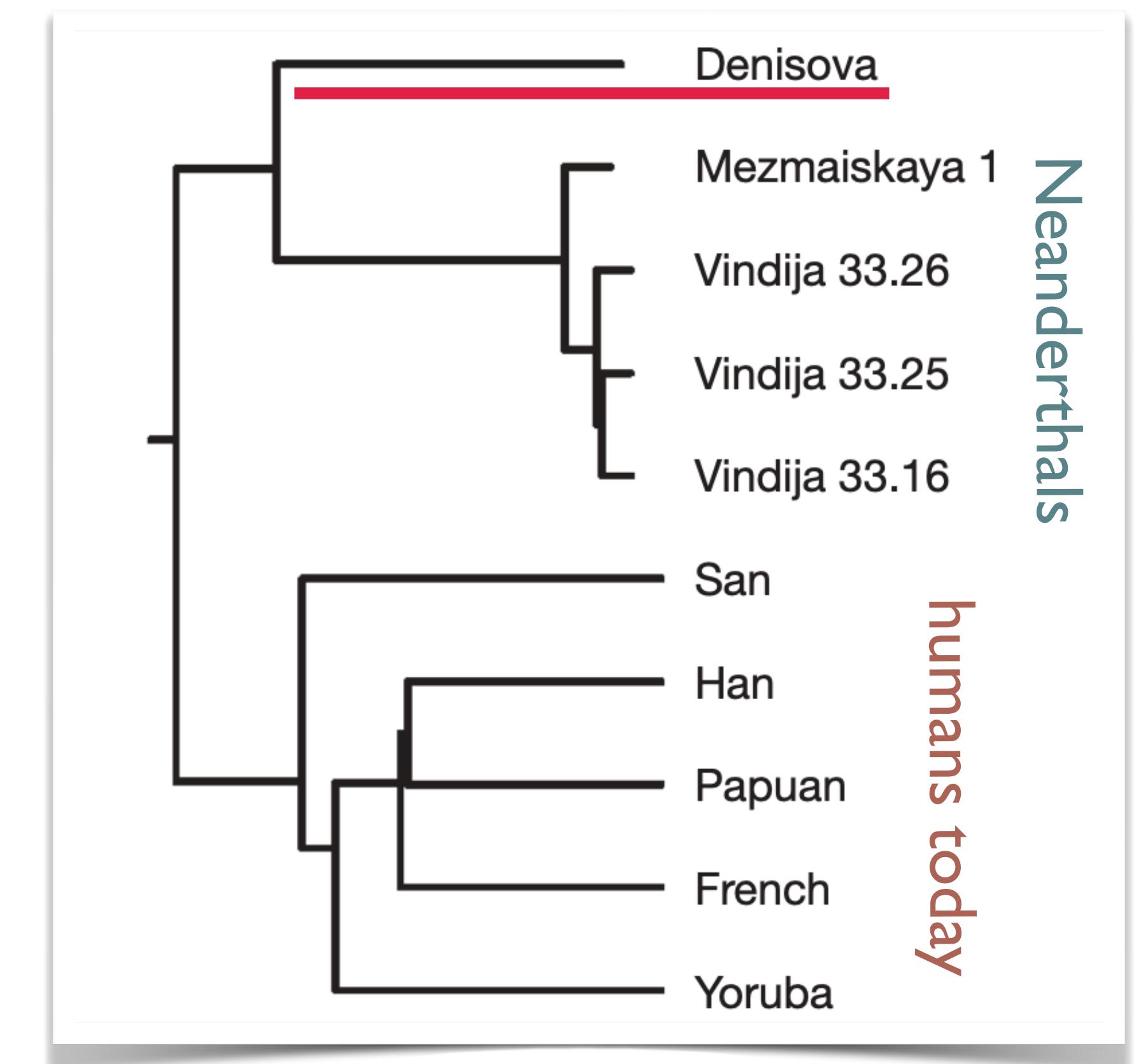


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**nature**

Open Access | Published: 22 December 2010

## Genetic history of an archaic hominin group from Denisova Cave in Siberia

David Reich , Richard E. Green, Martin Kircher, Johannes Krause, Nick Patterson, Eric Y. Durand, Bence Viola , Adrian W. Briggs, Udo Stenzel, Philip L. F. Johnson, Tomislav Maricic, Jeffrey M. Good, Tomas Marques-Bonet, Can Alkan, Qiaomei Fu, Swapan Mallick, Heng Li, Matthias Meyer, Evan E. Eichler, Mark Stoneking, Michael Richards, Sahra Talamo, Michael V. Shunkov, Anatoli P. Derevianko, Jean-Jacques Hublin, Janet Kelso, Montgomery Slatkin & Svante Pääbo 

— Show fewer authors

*Nature* 468, 1053–1060 (2010) | [Cite this article](#)

# Traces of Denisovans in genomes of present-day humans

$f4(\text{human 1}, \text{human 2}; \text{Denisovan}, \text{Chimp})$

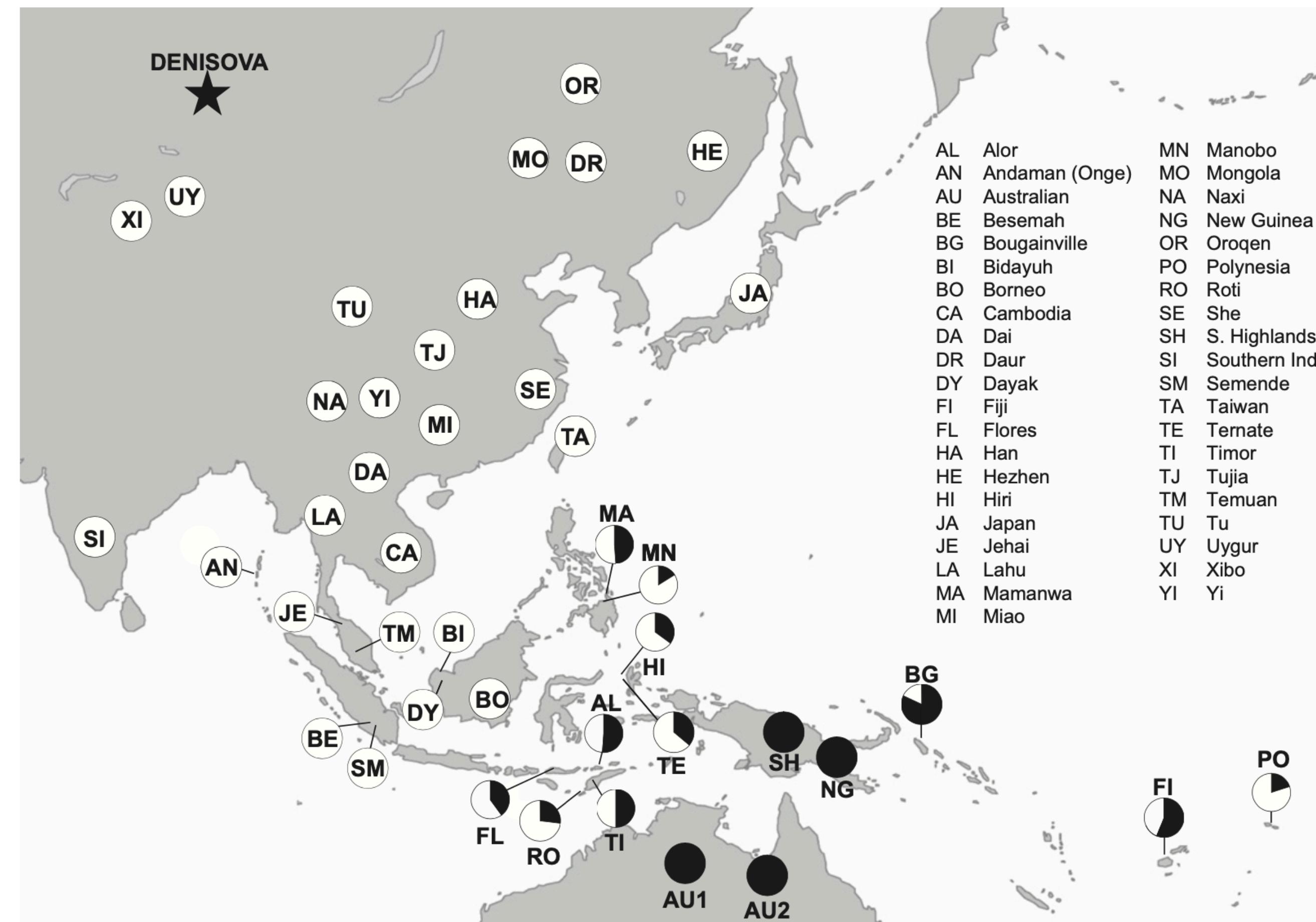


Figure 1. Denisovan Genetic Material as a Fraction of that in New Guineans

Reich et al., 2011

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$f4(\text{human 1}, \text{human 2}; \text{Denisovan}, \text{Chimp})$

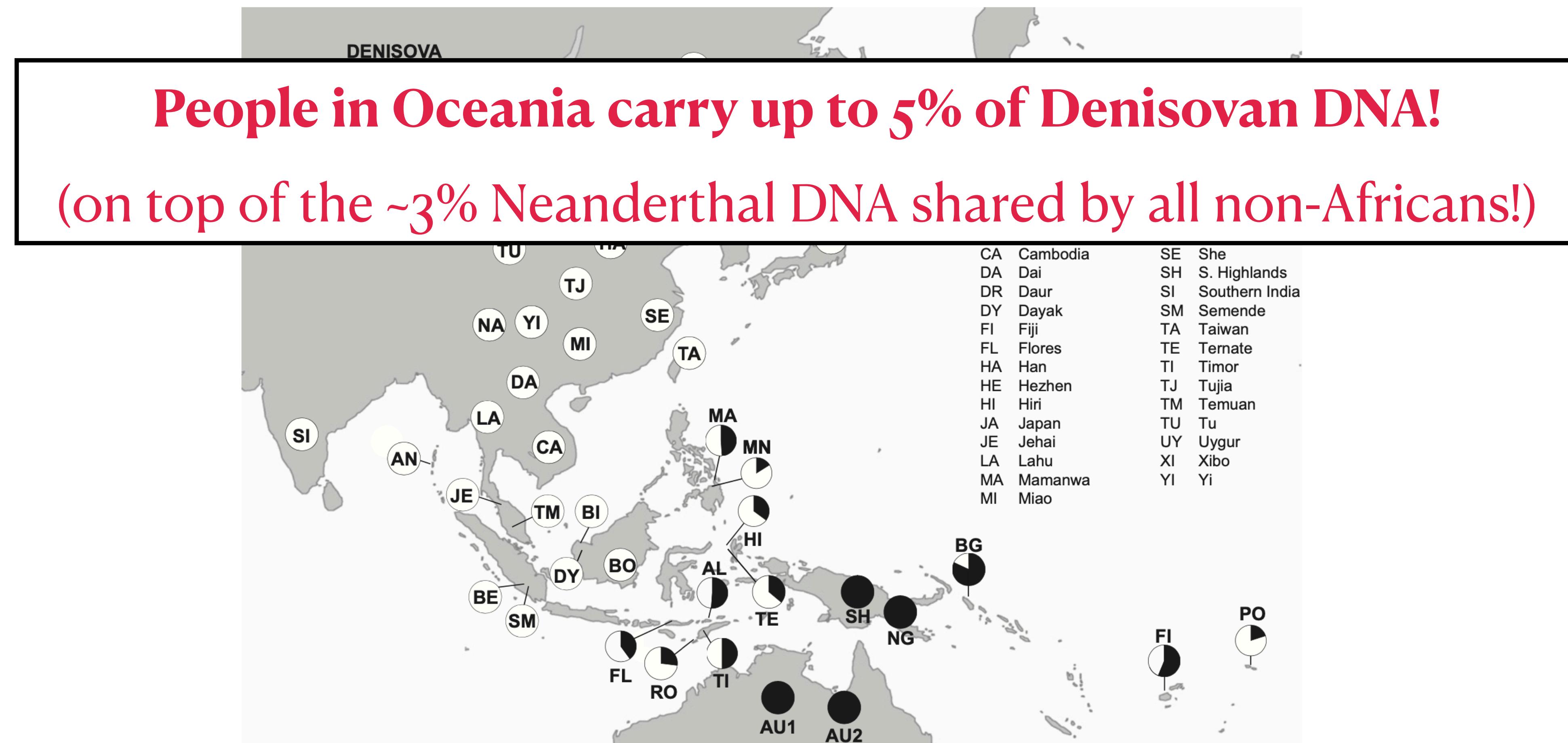
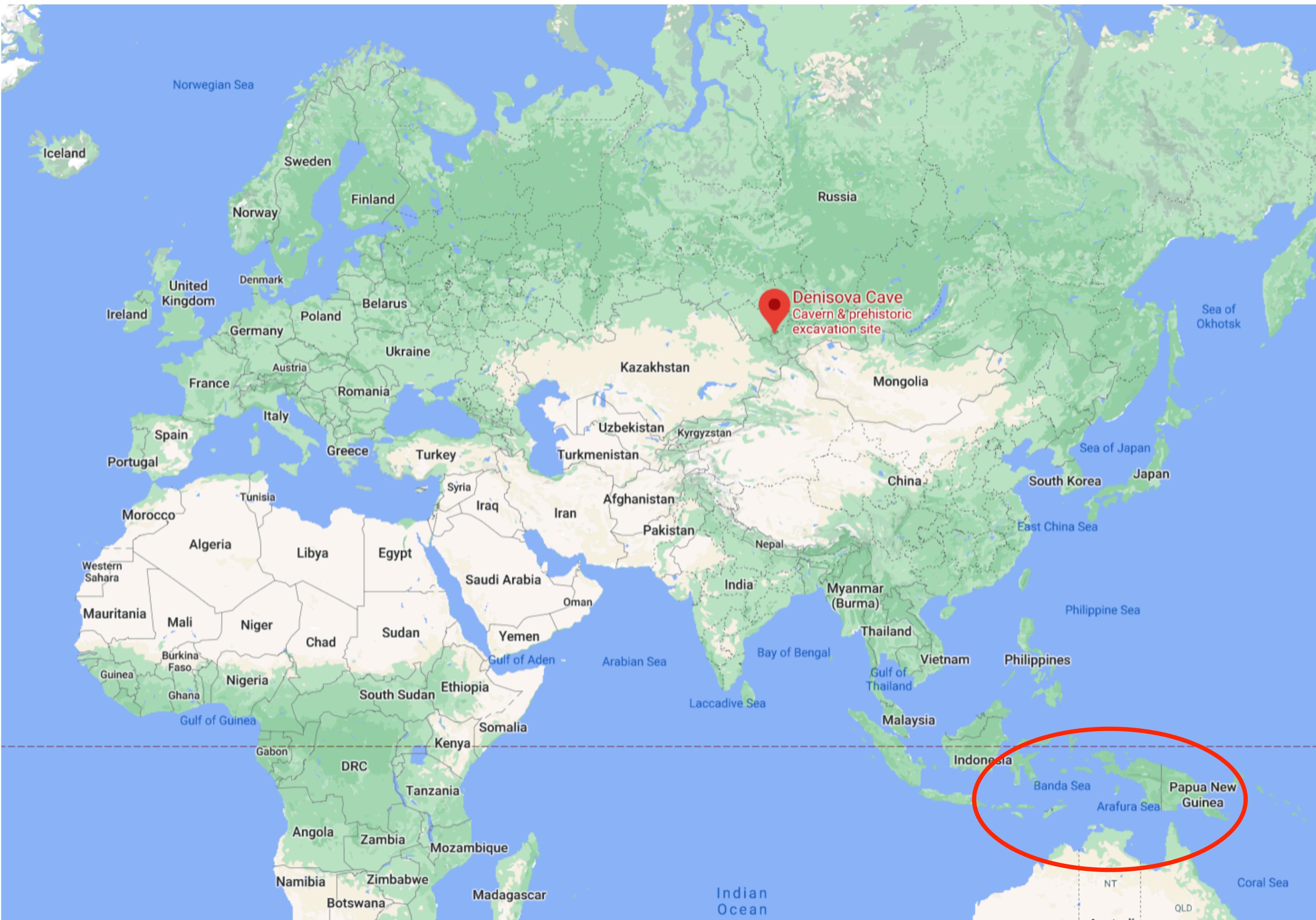


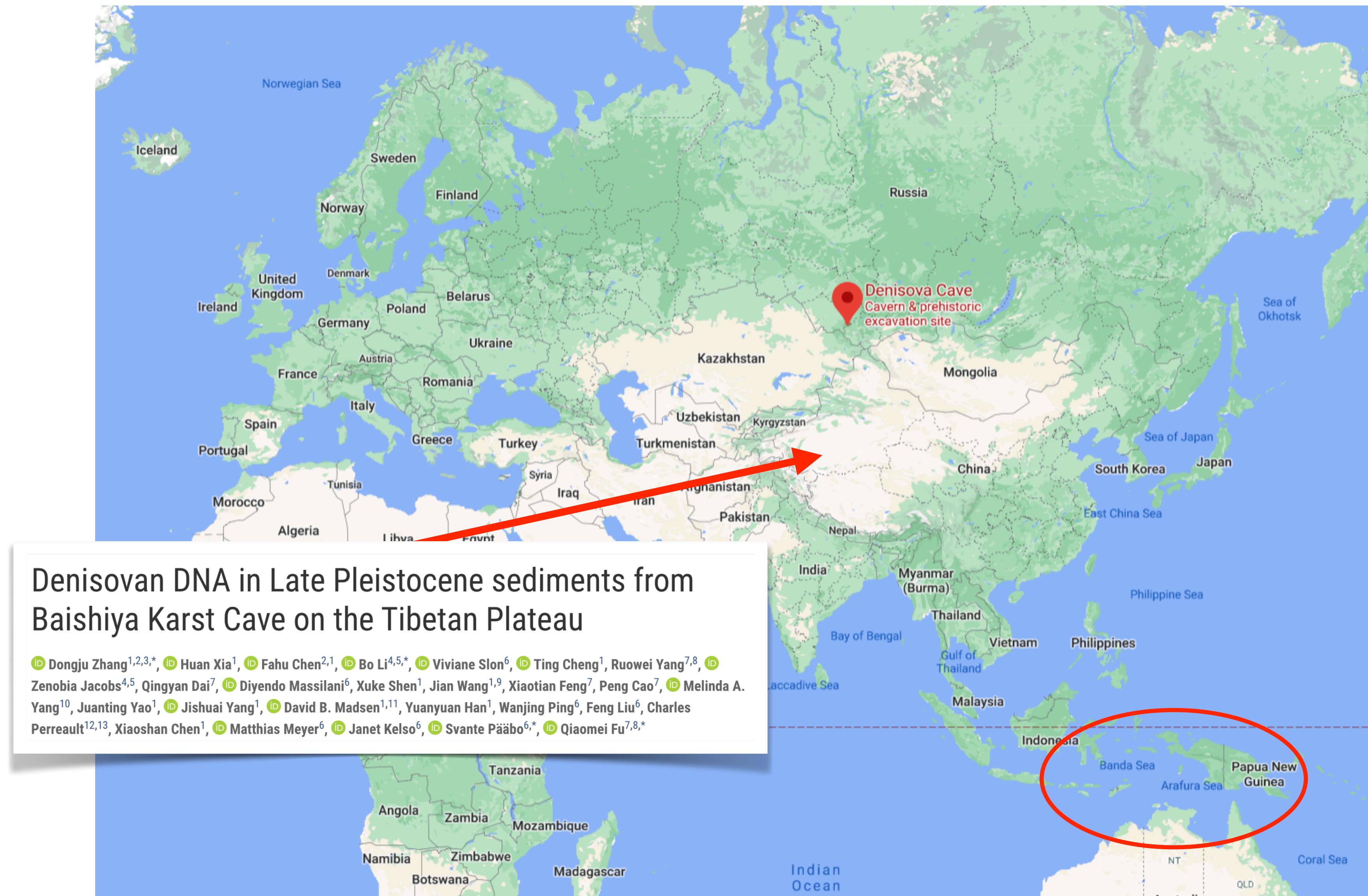
Figure 1. Denisovan Genetic Material as a Fraction of that in New Guineans

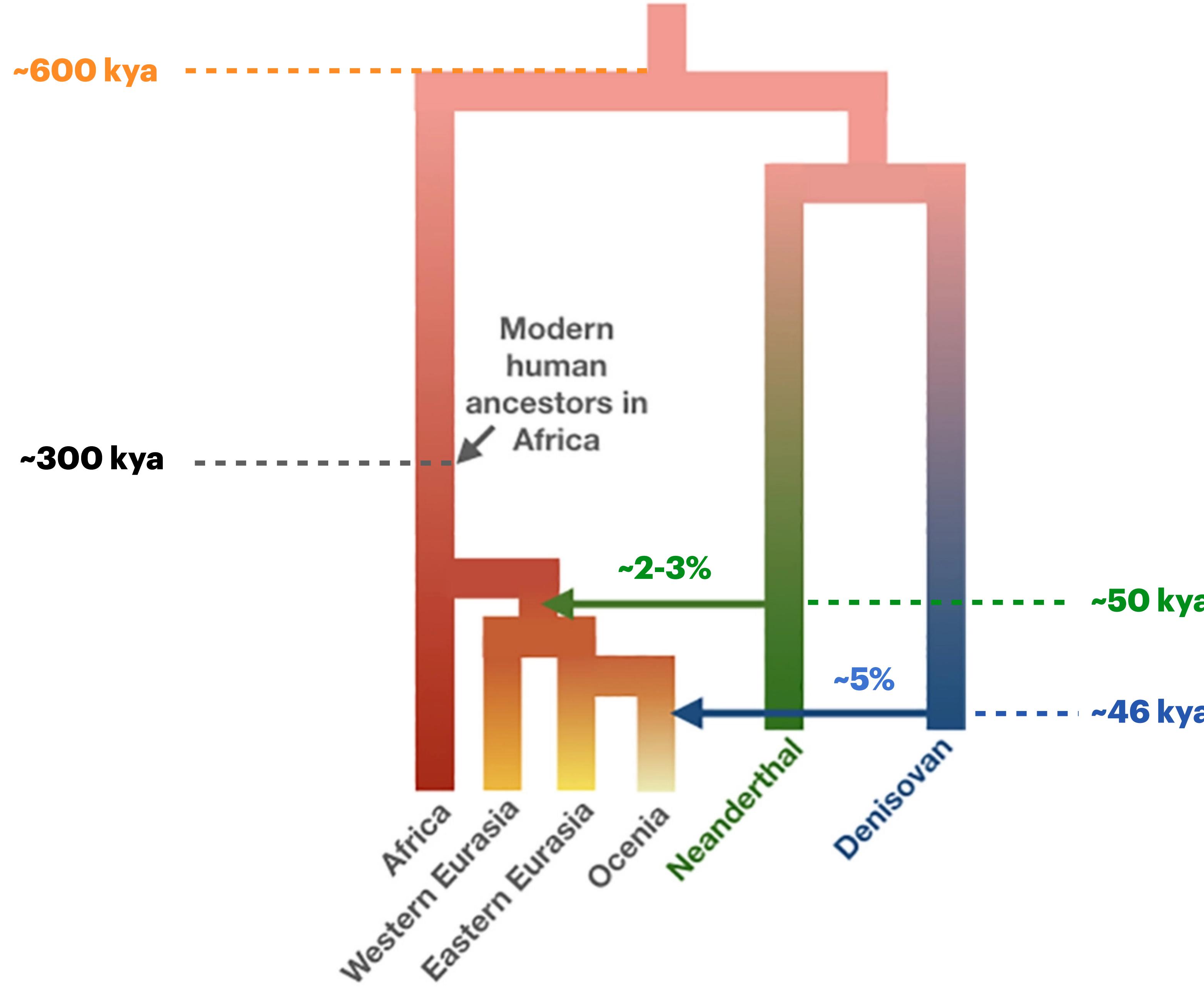
Reich et al., 2011

# Geographic range of Denisovans?



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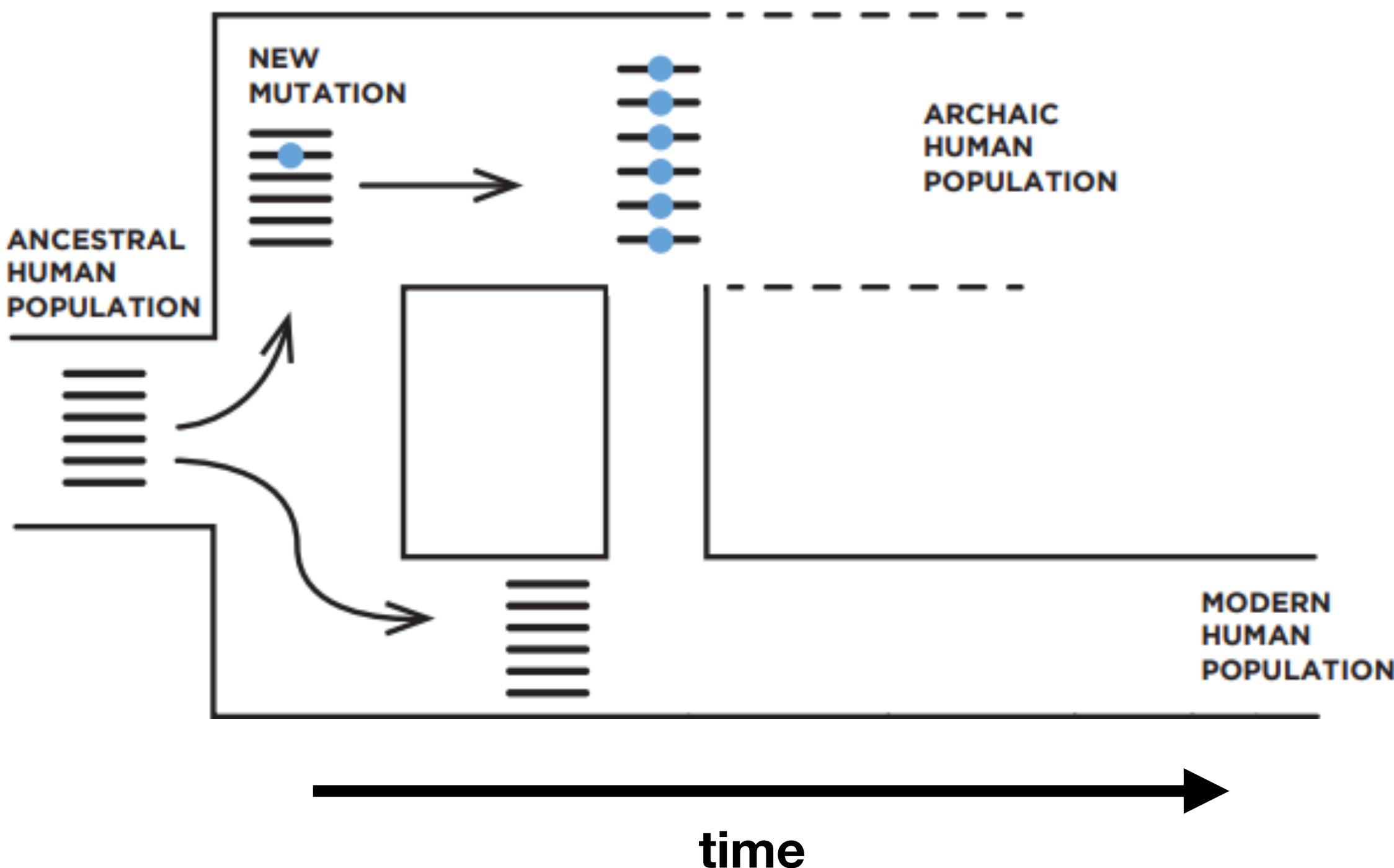




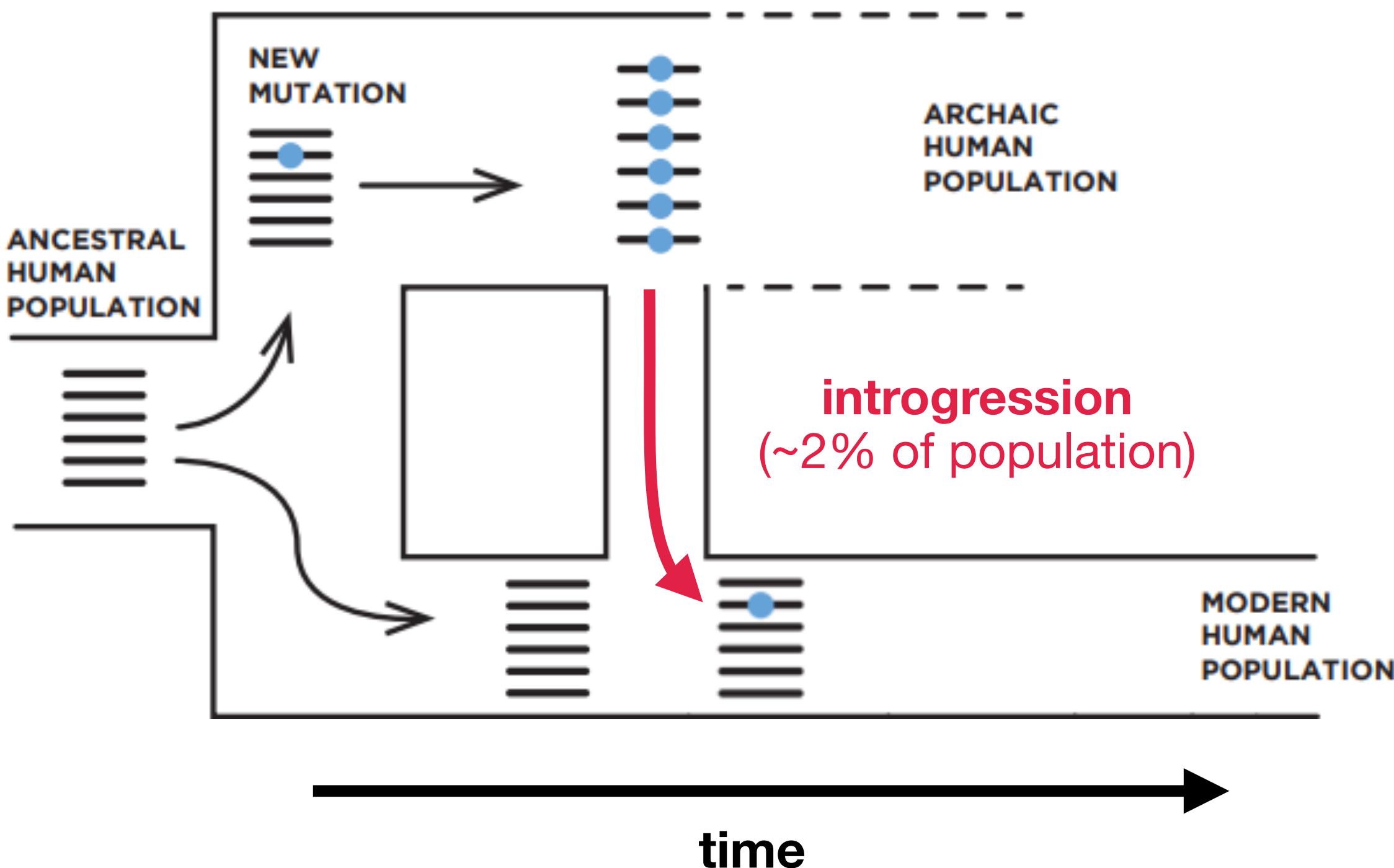
adapted from the Yearbook of Physical Anthropology (2019) by Gokcumen

# Consequences of introgression on human functional biology?

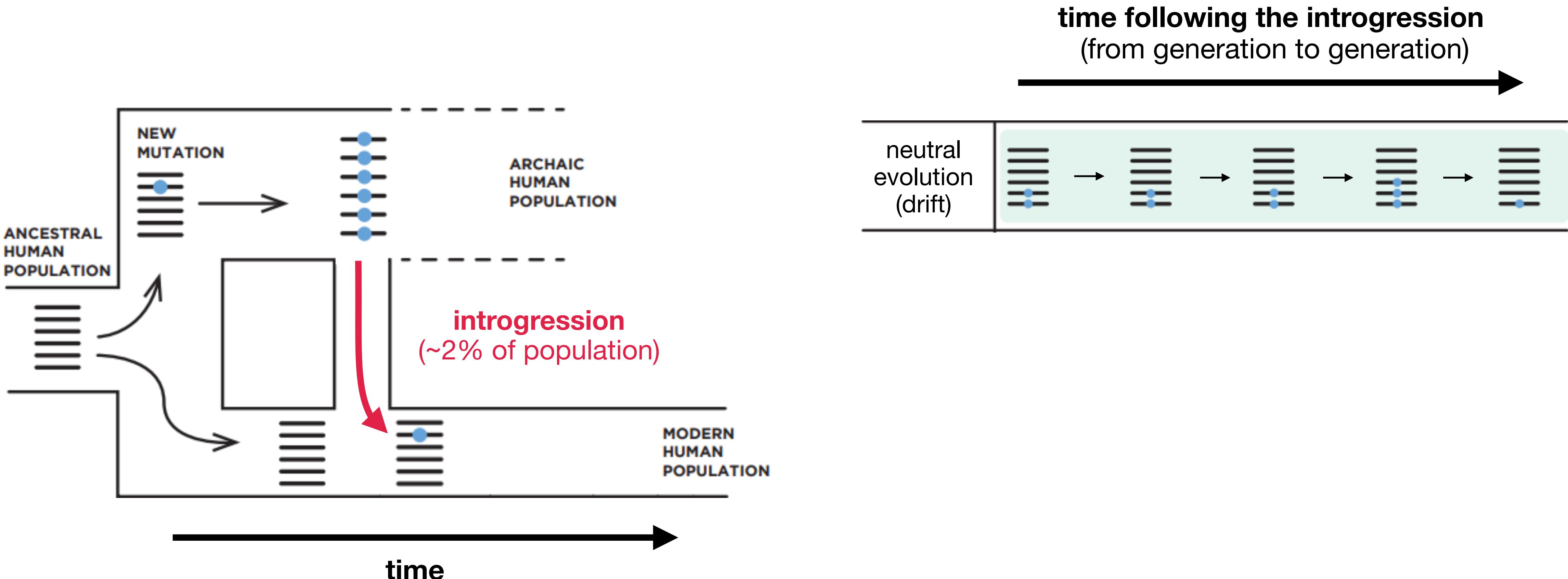
# What are the possible fates of introgressed DNA?



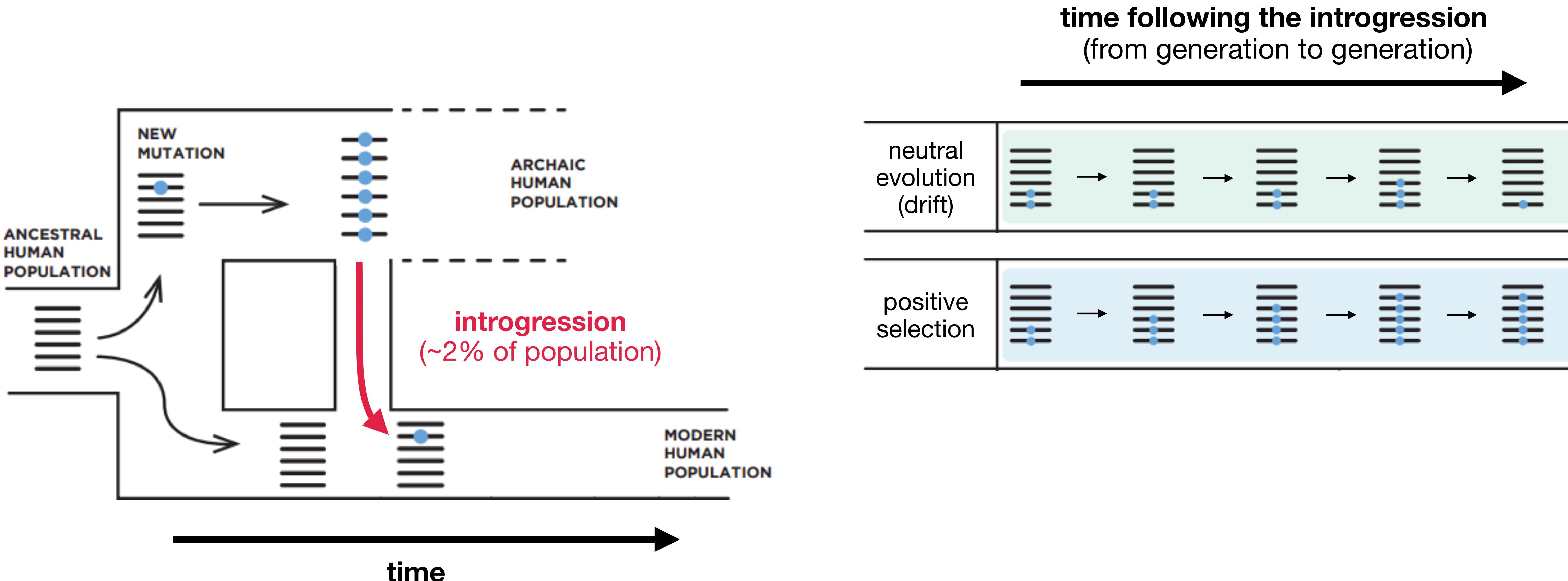
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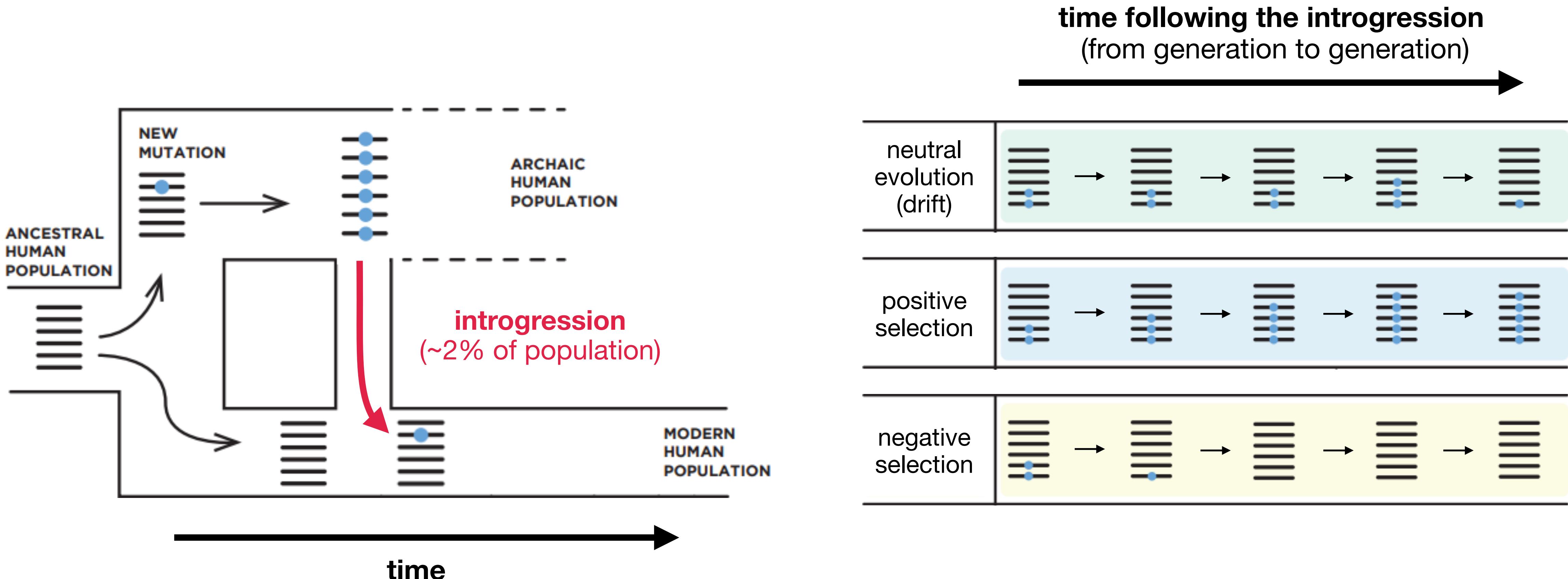
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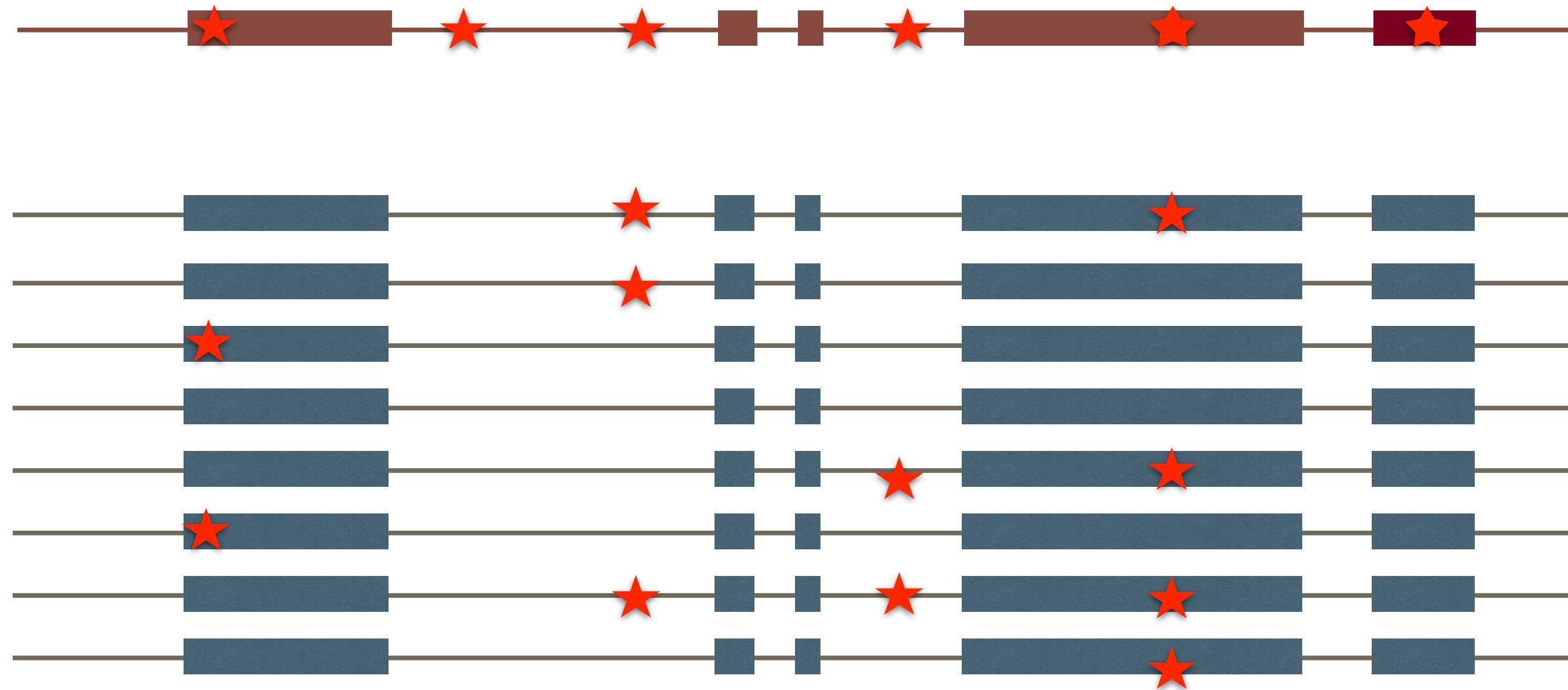


# What are the possible fates of introgressed DNA?



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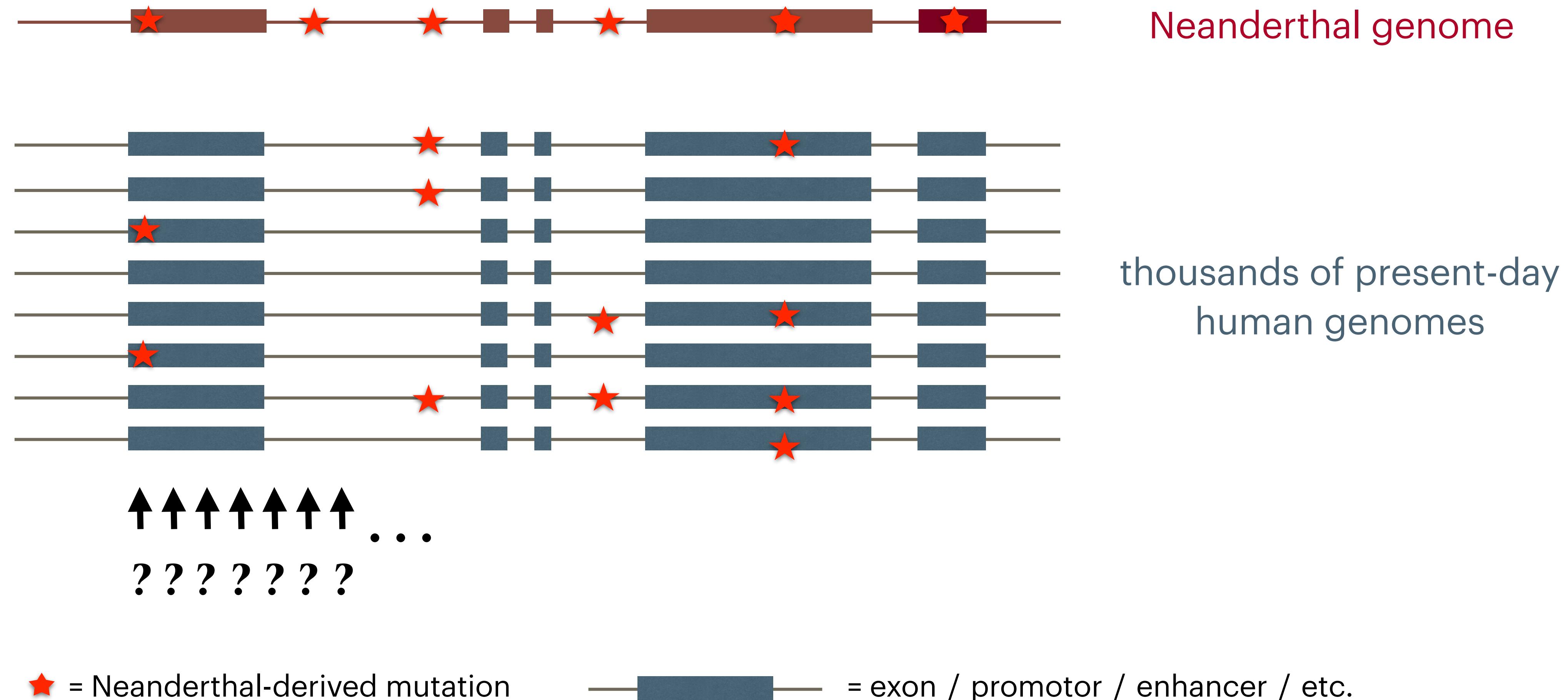
Neanderthal genome

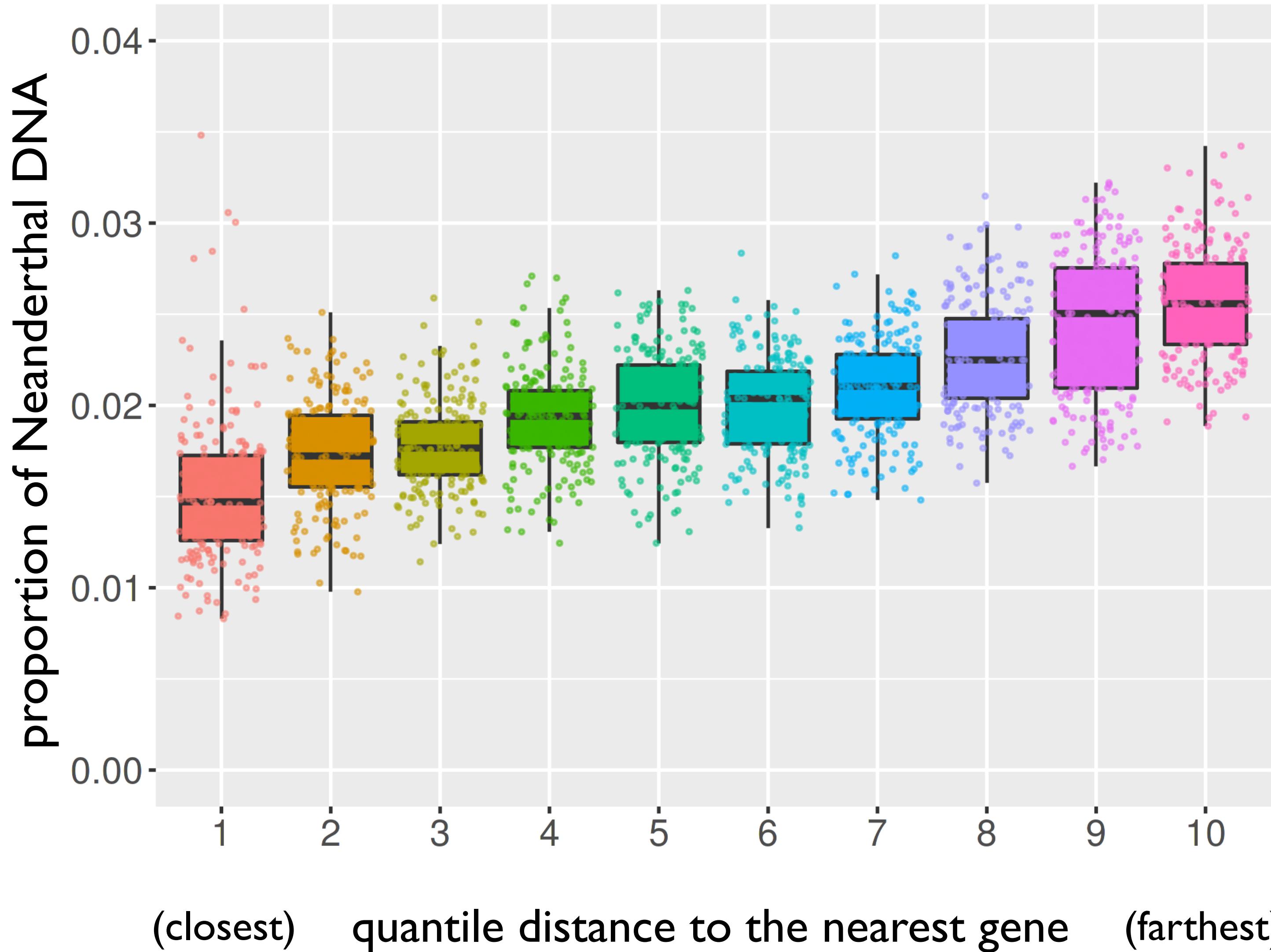
thousands of present-day  
human genomes

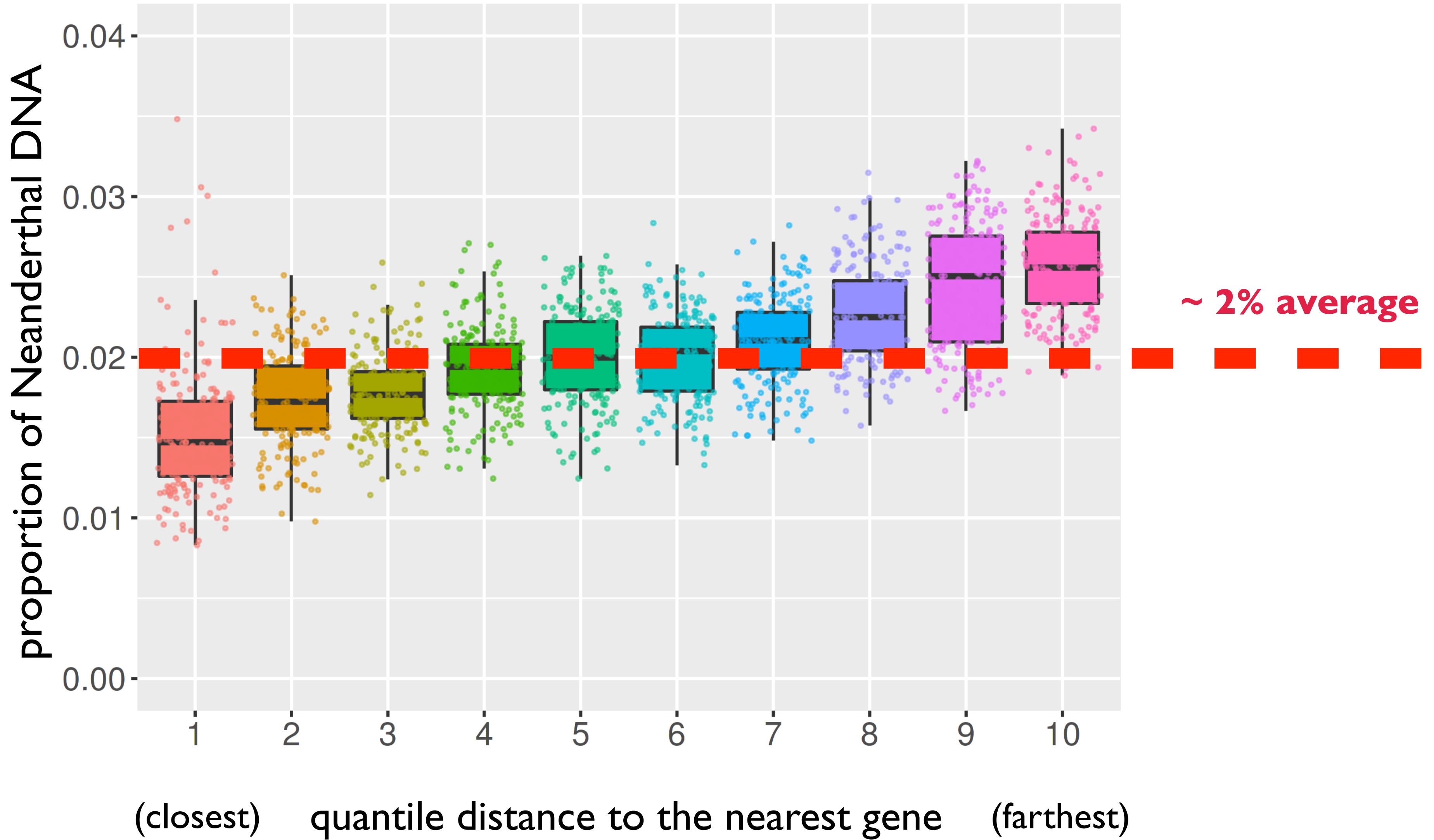
★ = Neanderthal-derived mutation

—■— = exon / promotor / enhancer / etc.

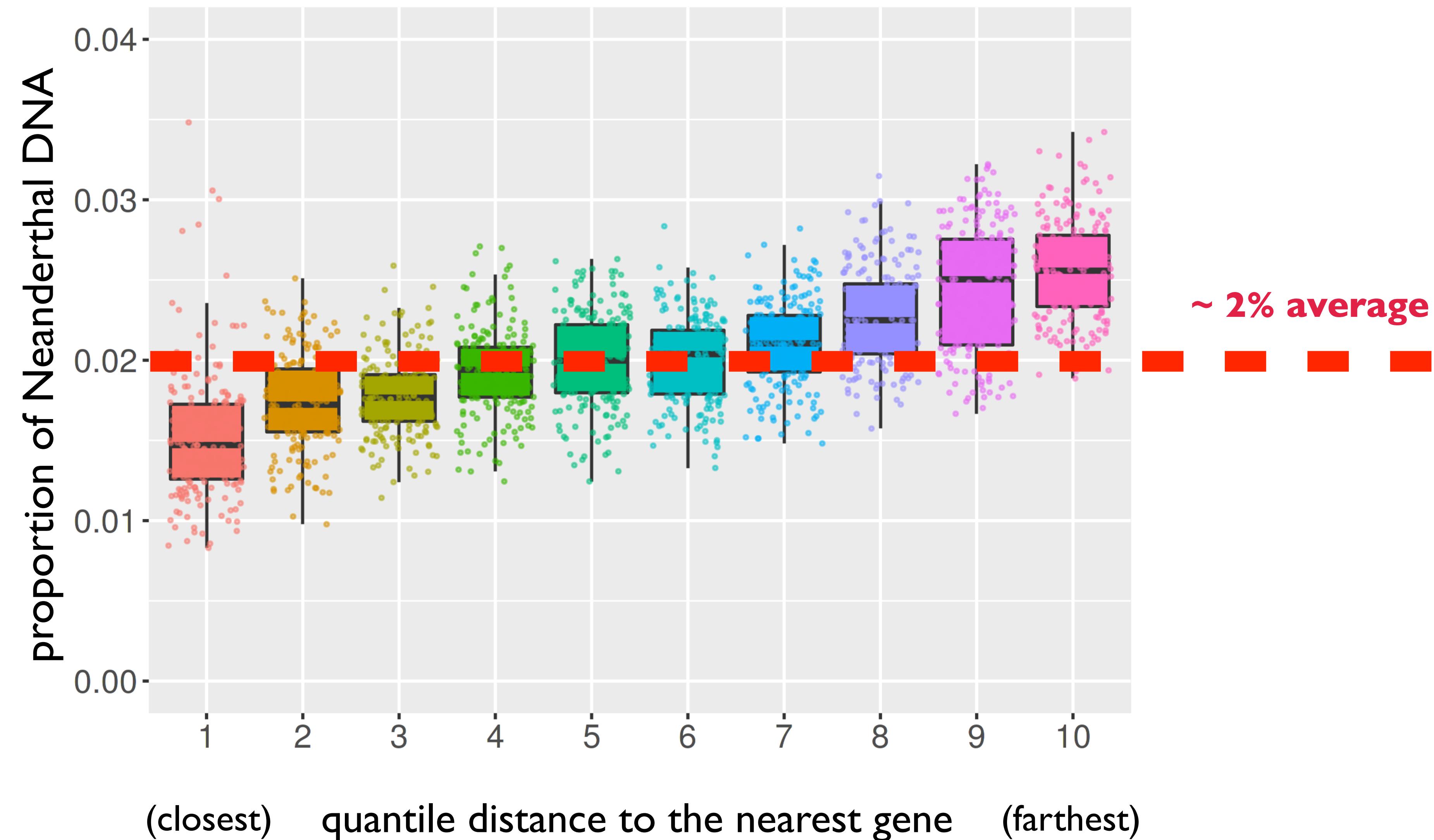
# Is there a relationship between the presence of a Neanderthal allele and its distance to the nearest important gene?



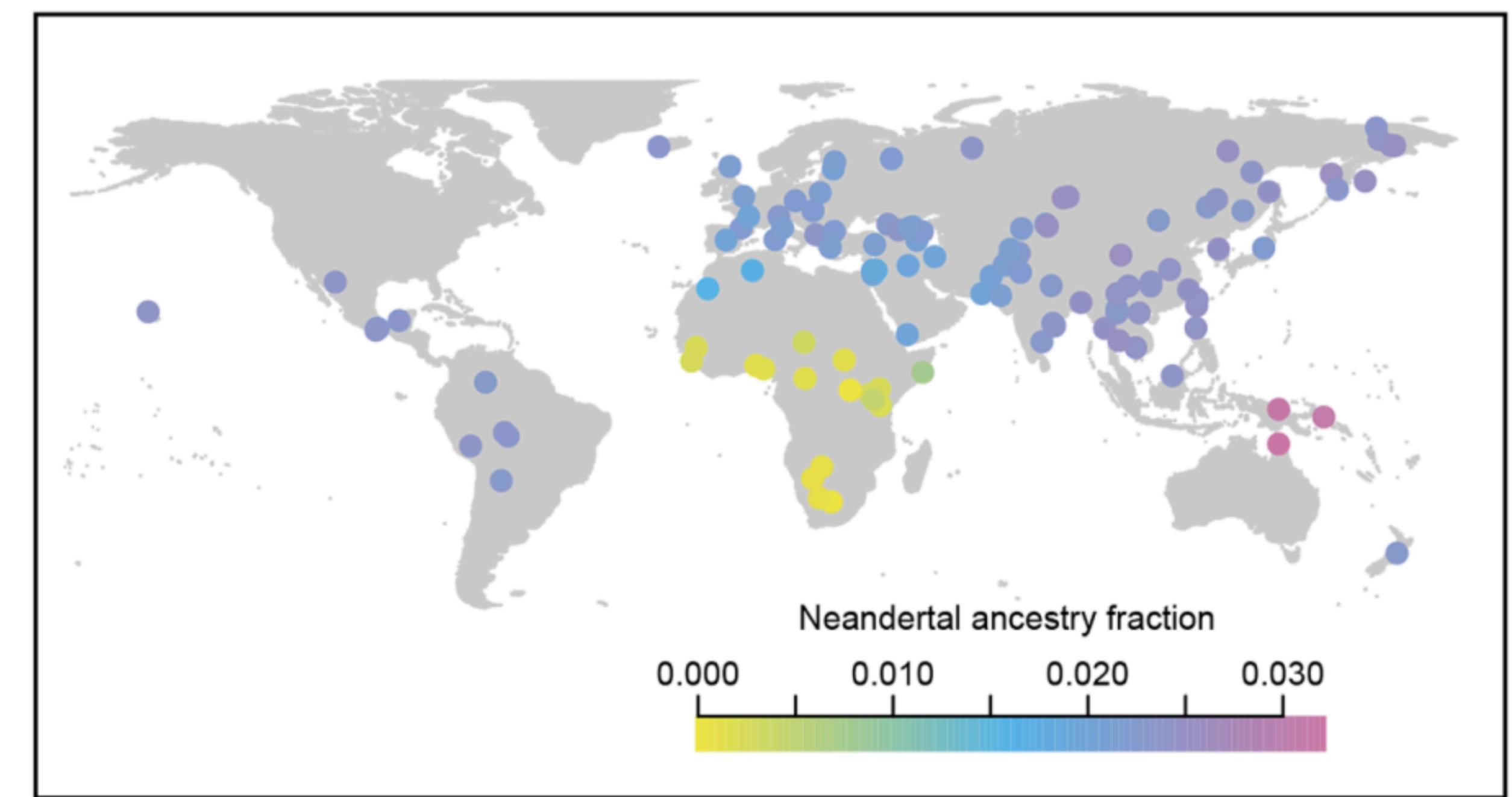
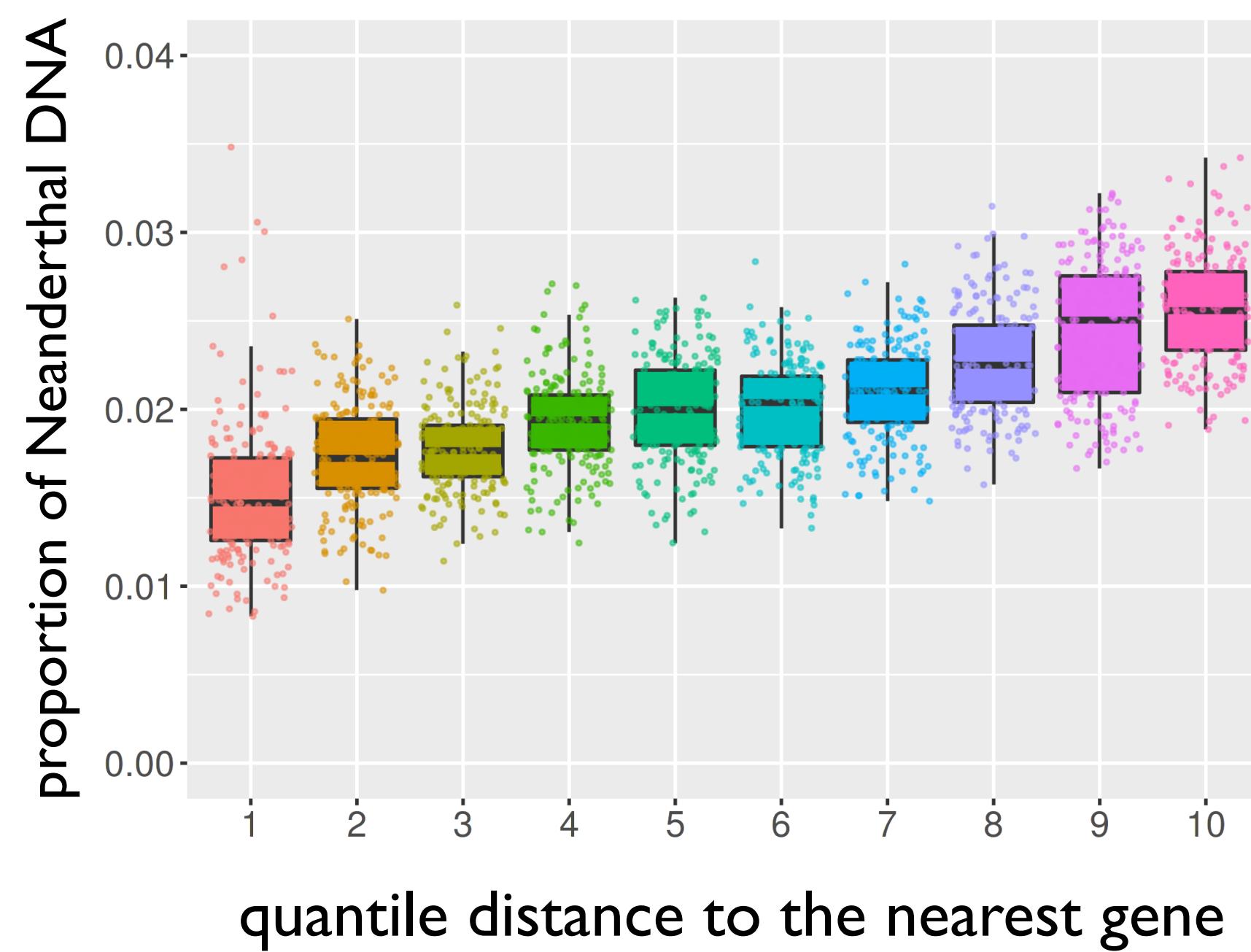




# Genome-wide selection *against* Neanderthal DNA!

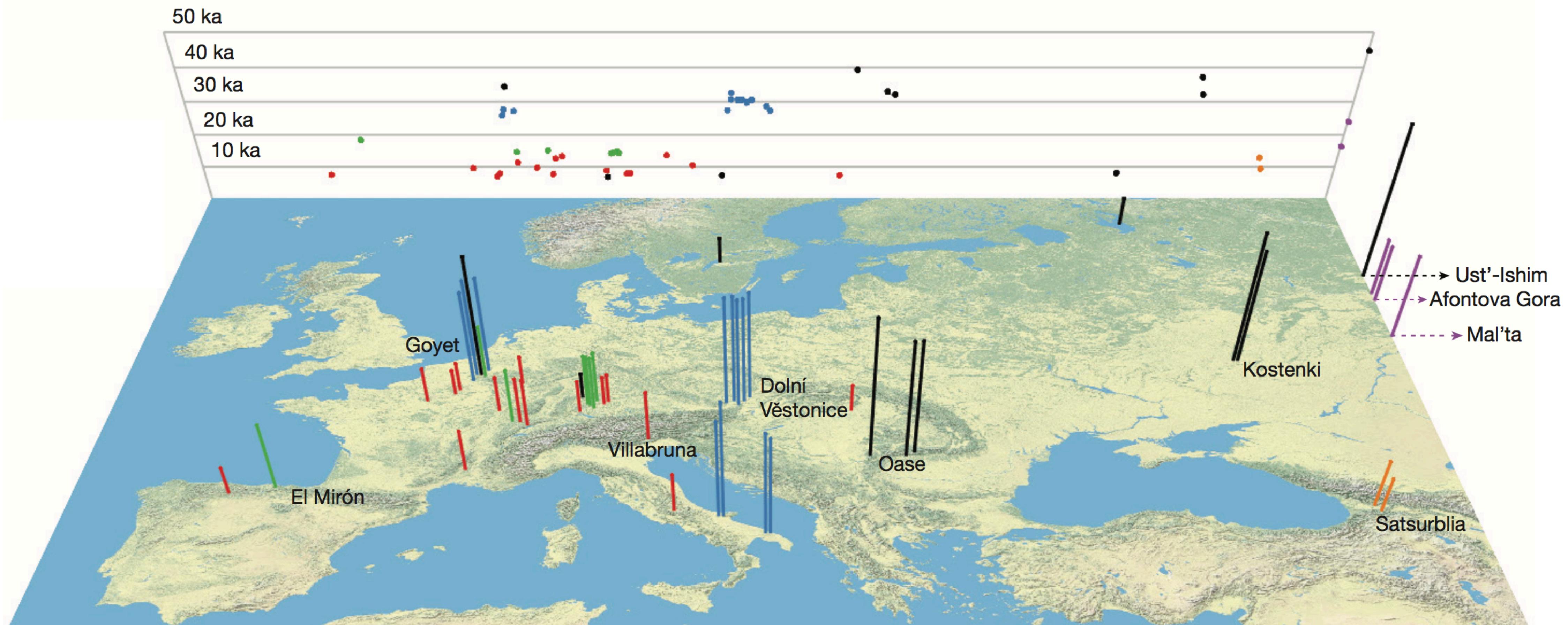


# On what time scale did this happen?

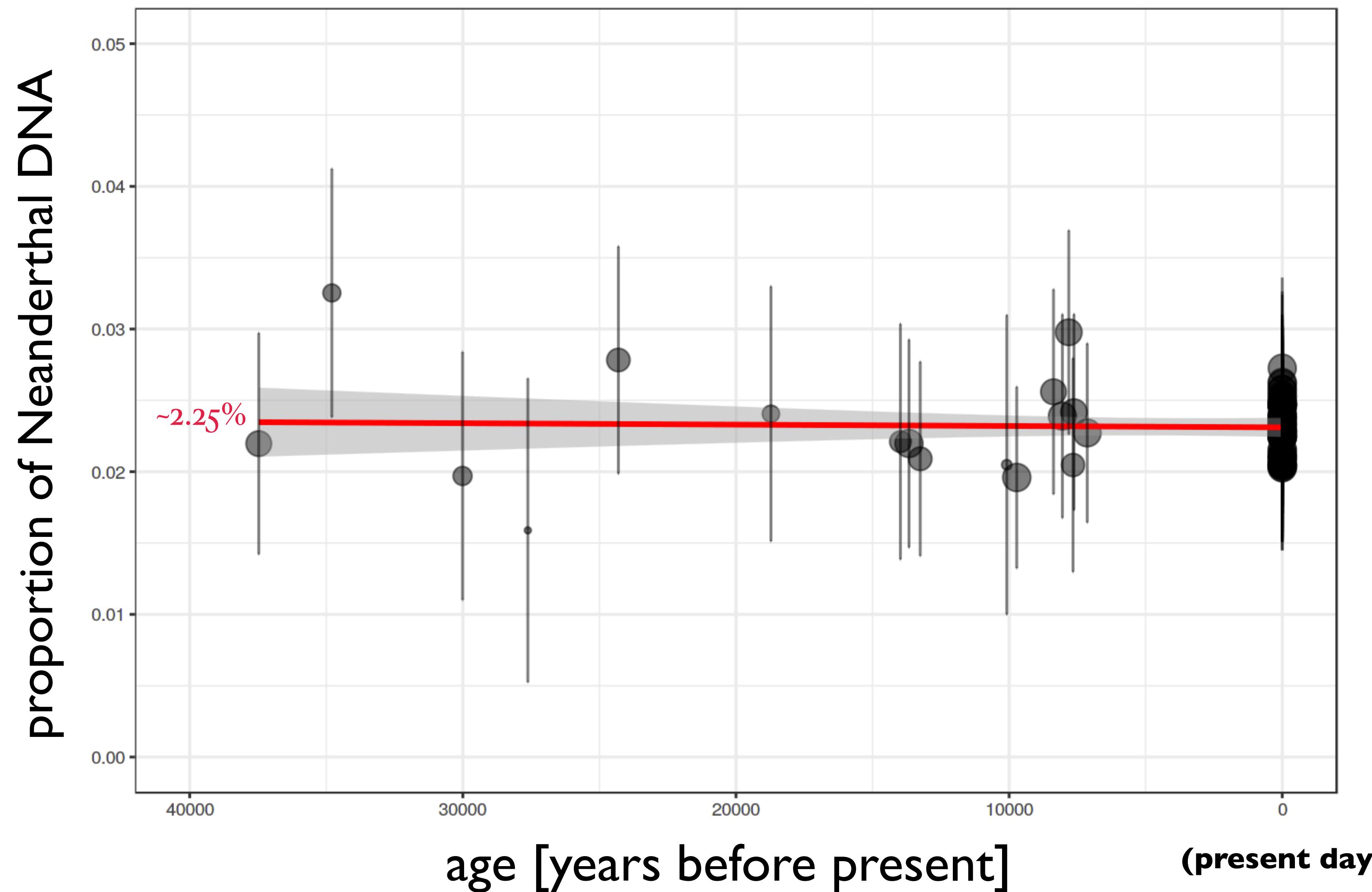


Prufer et al. (Science 2017)

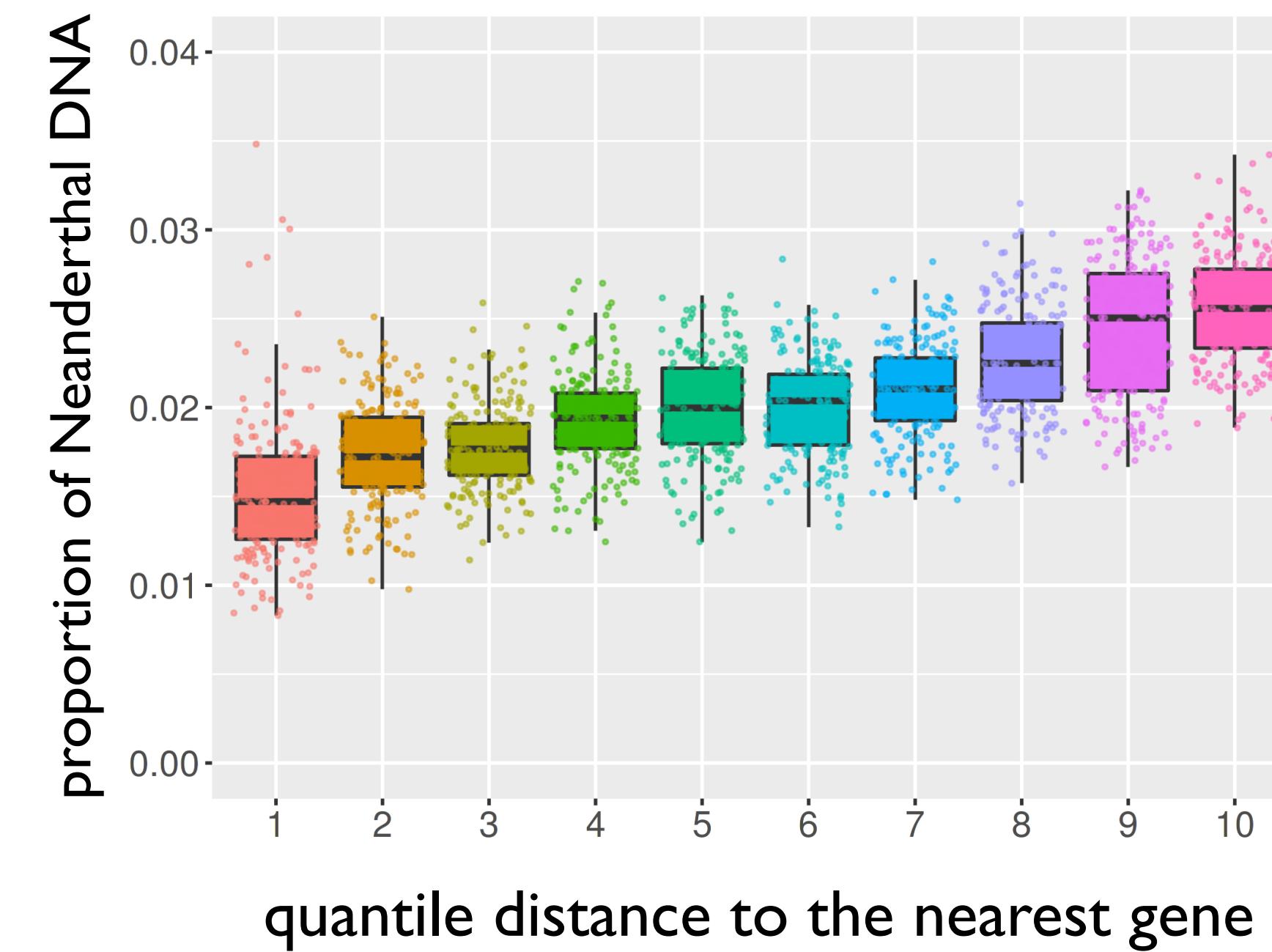
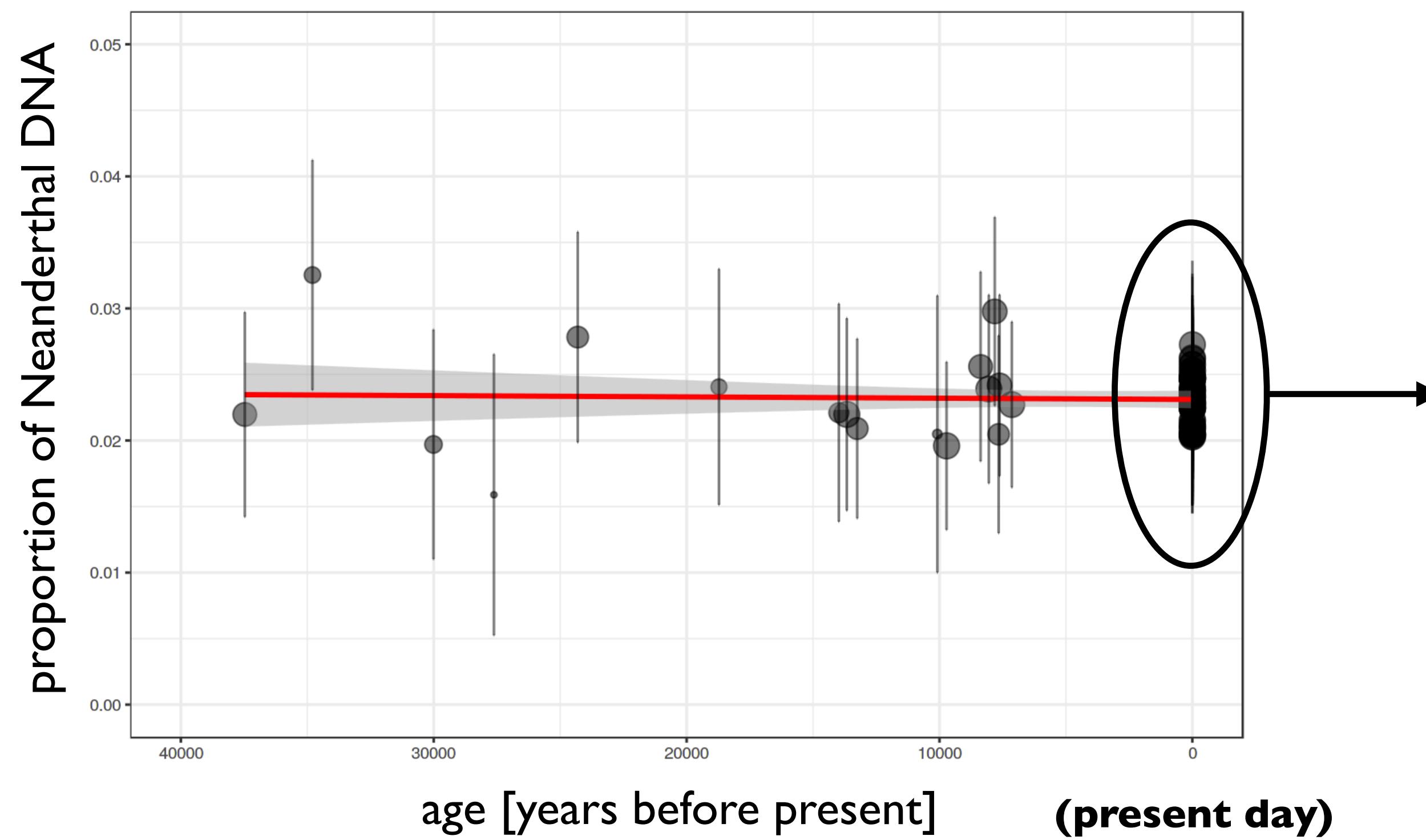
# aDNA of “early-modern humans” from Europe (45-10 kya BP)



# Proportion of Neanderthal ancestry in modern humans remained constant for tens of thousands of years

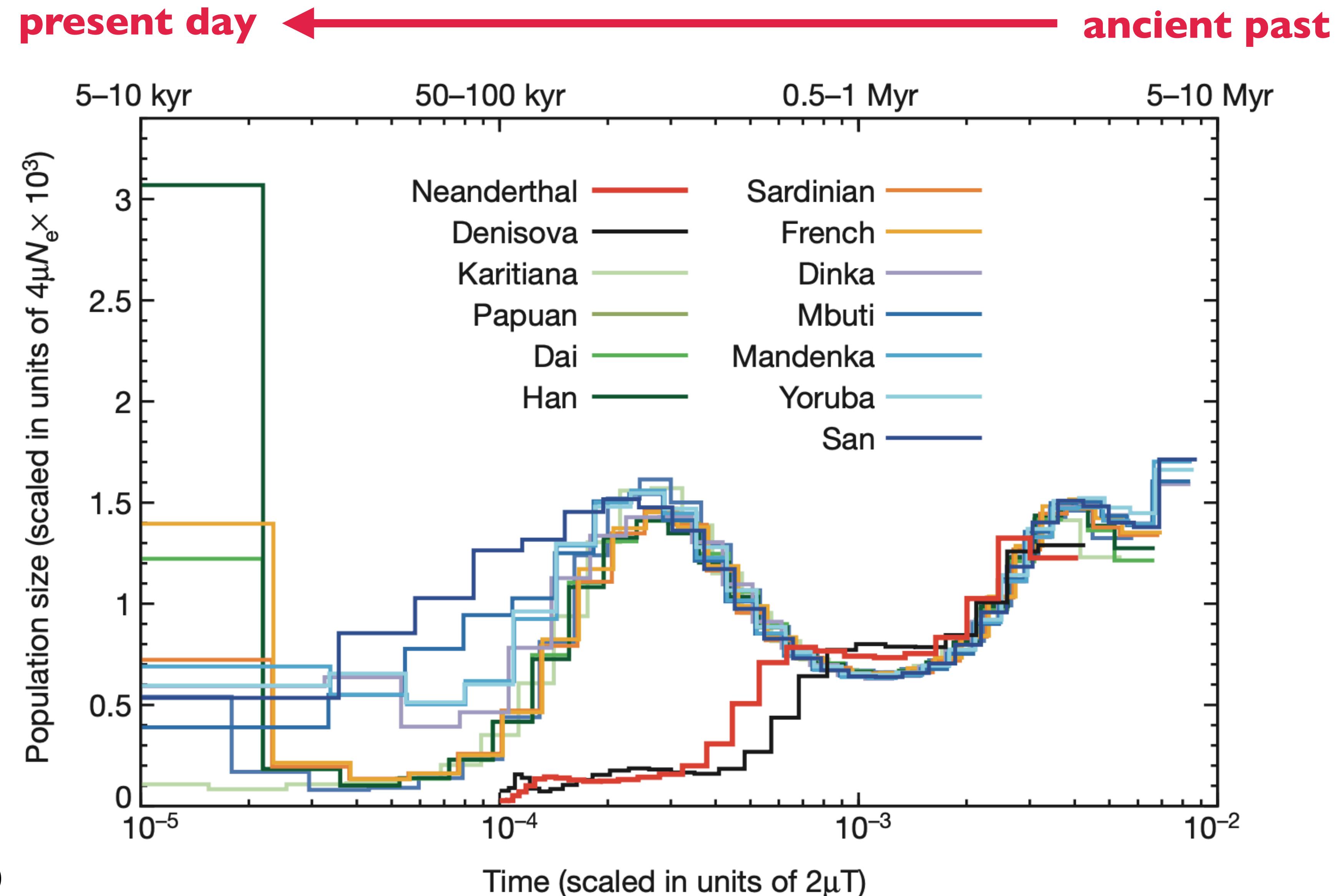


# Empirical trajectory of Neanderthal ancestry contradicts the signal of negative selection?



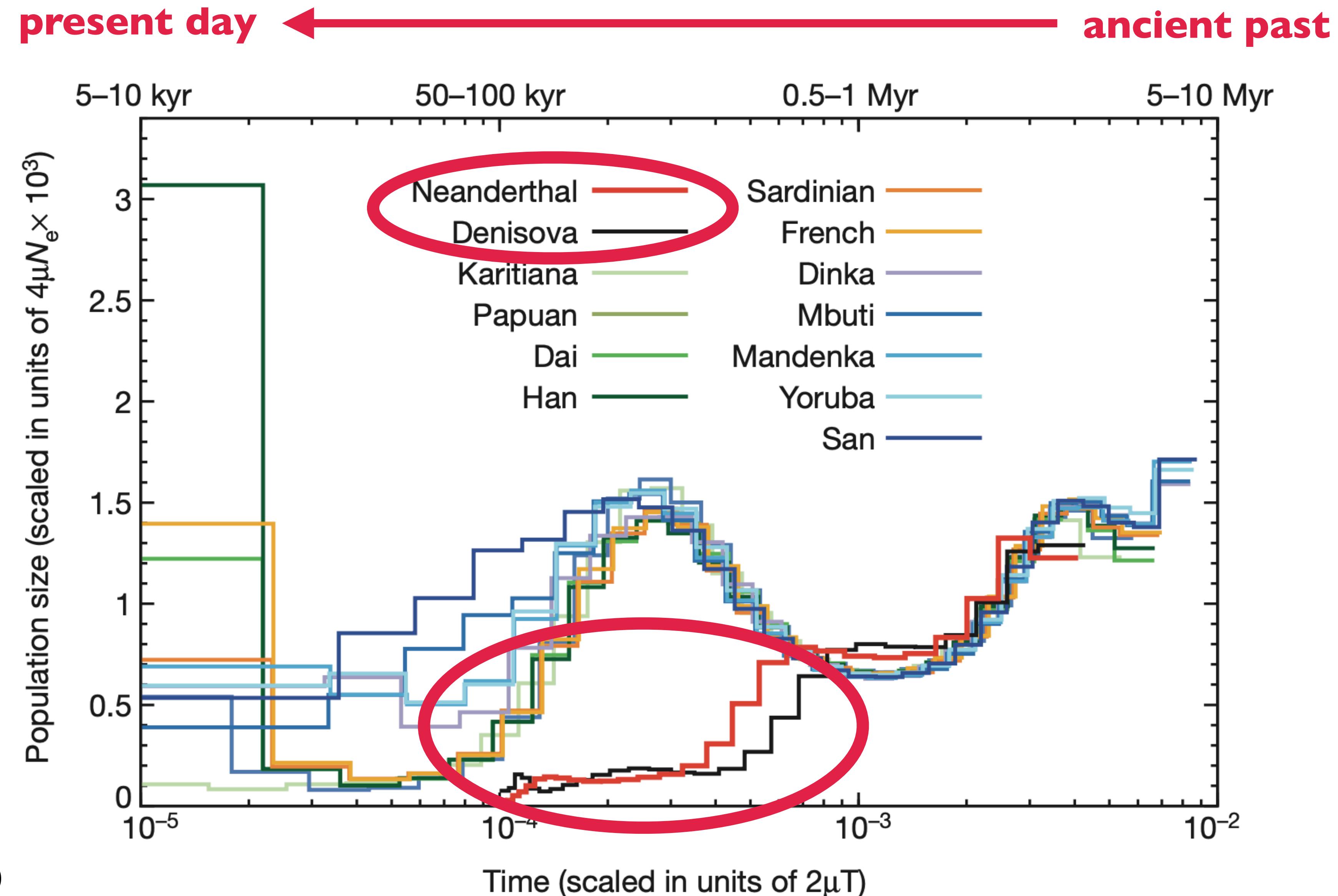
# Demographic collapse of archaic human populations

Pairwise Sequentially  
Markovian Coalescent  
(PSMC) model



# Demographic collapse of archaic human populations

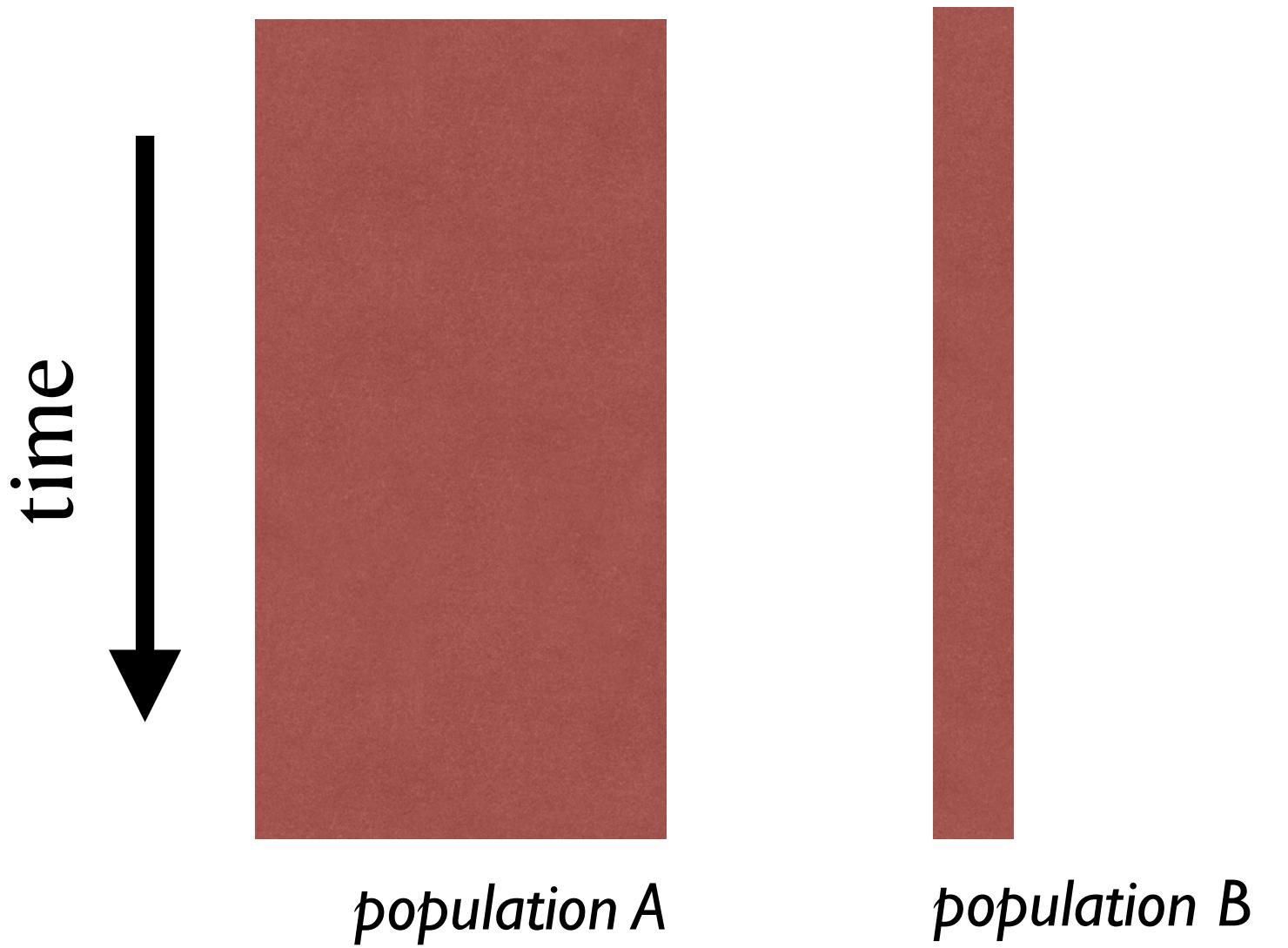
Pairwise Sequentially  
Markovian Coalescent  
(PSMC) model



**What was the impact of this on  
accumulation of deleterious mutations?**

# Nearly-neutral theory of molecular evolution

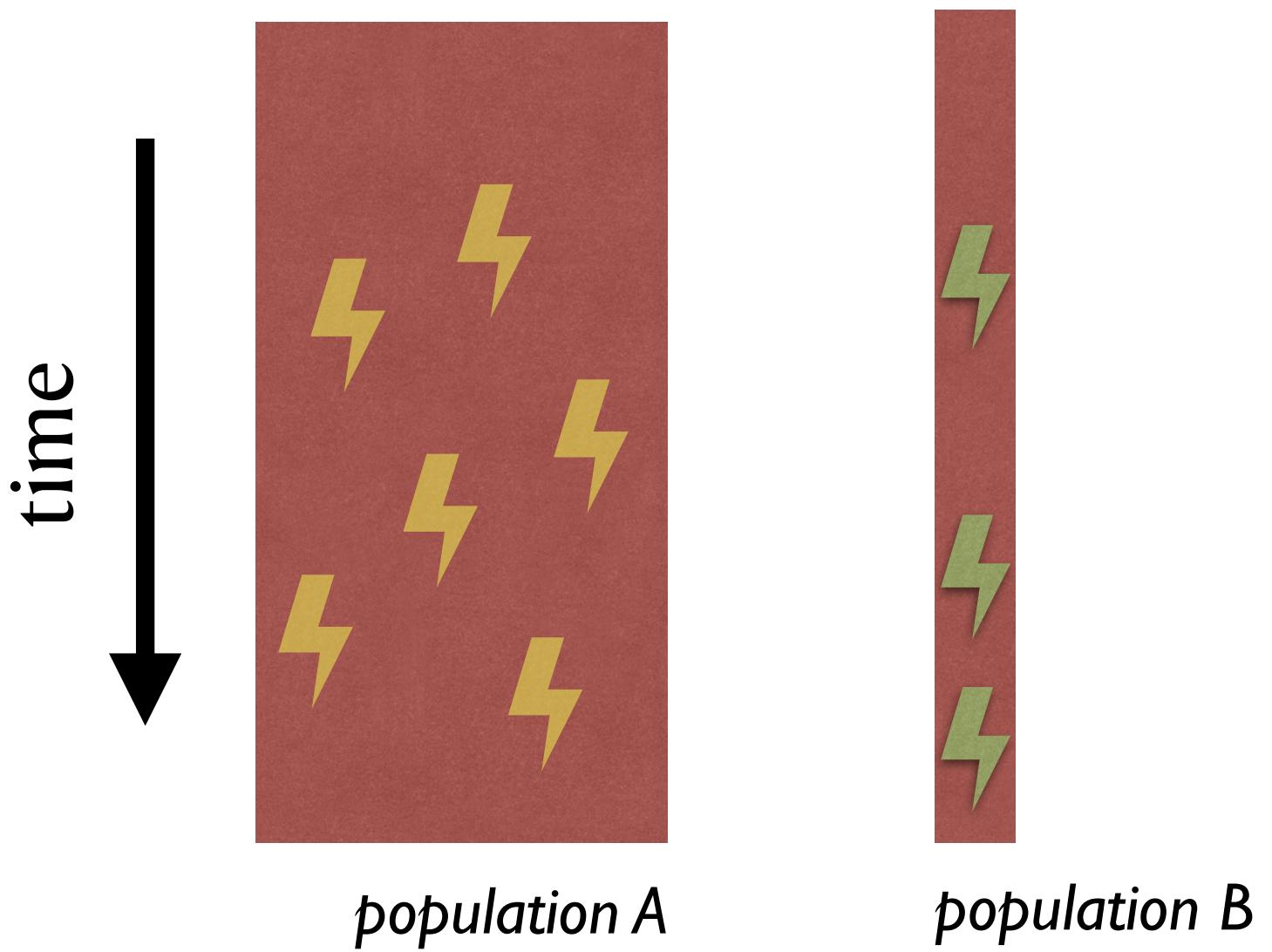
**Tomoko  
Ohta**



<https://womentyoushouldknow.net/population-genetics-tomoko-ohta/>

# Nearly-neutral theory of molecular evolution

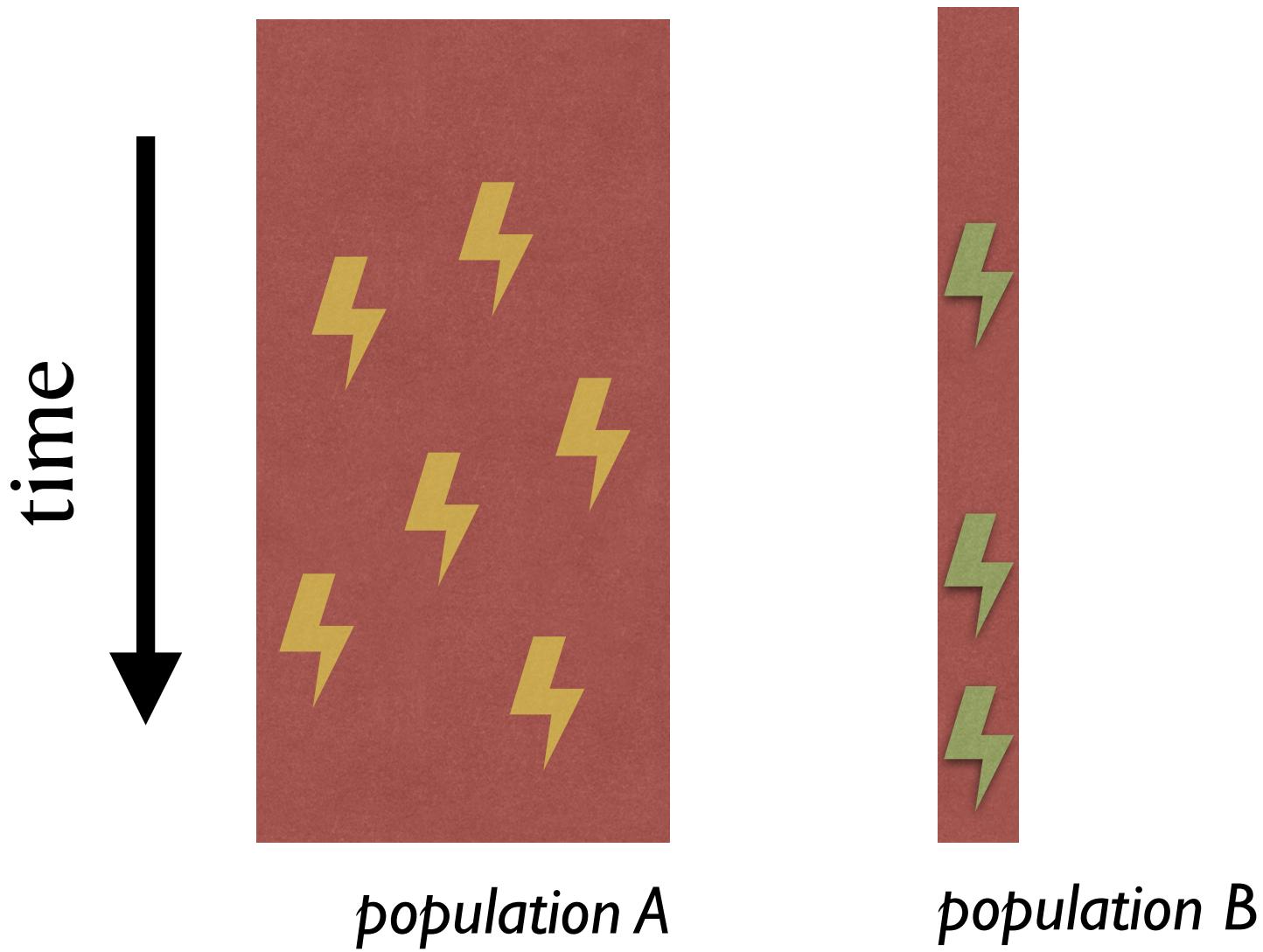
**Tomoko  
Ohta**



We know that genomes accumulate mutations

# Nearly-neutral theory of molecular evolution

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**We know that genomes accumulate mutations**

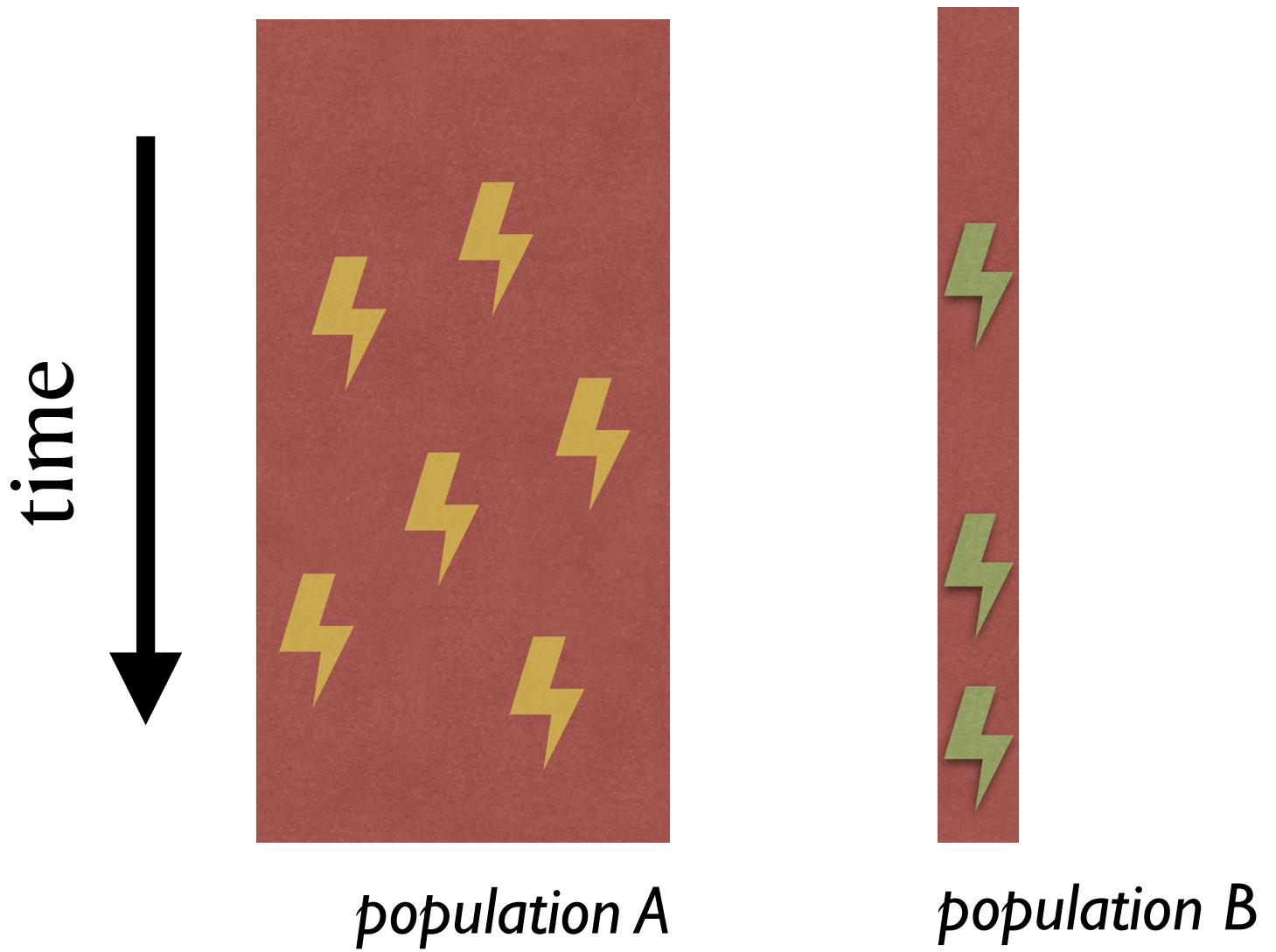
- a tiny number are extremely negative (**lethal**)
- a tiny number are positive (**adaptive**)
- a large number does nothing (**neutral**)
- many are “mildly deleterious” (**nearly neutral**)

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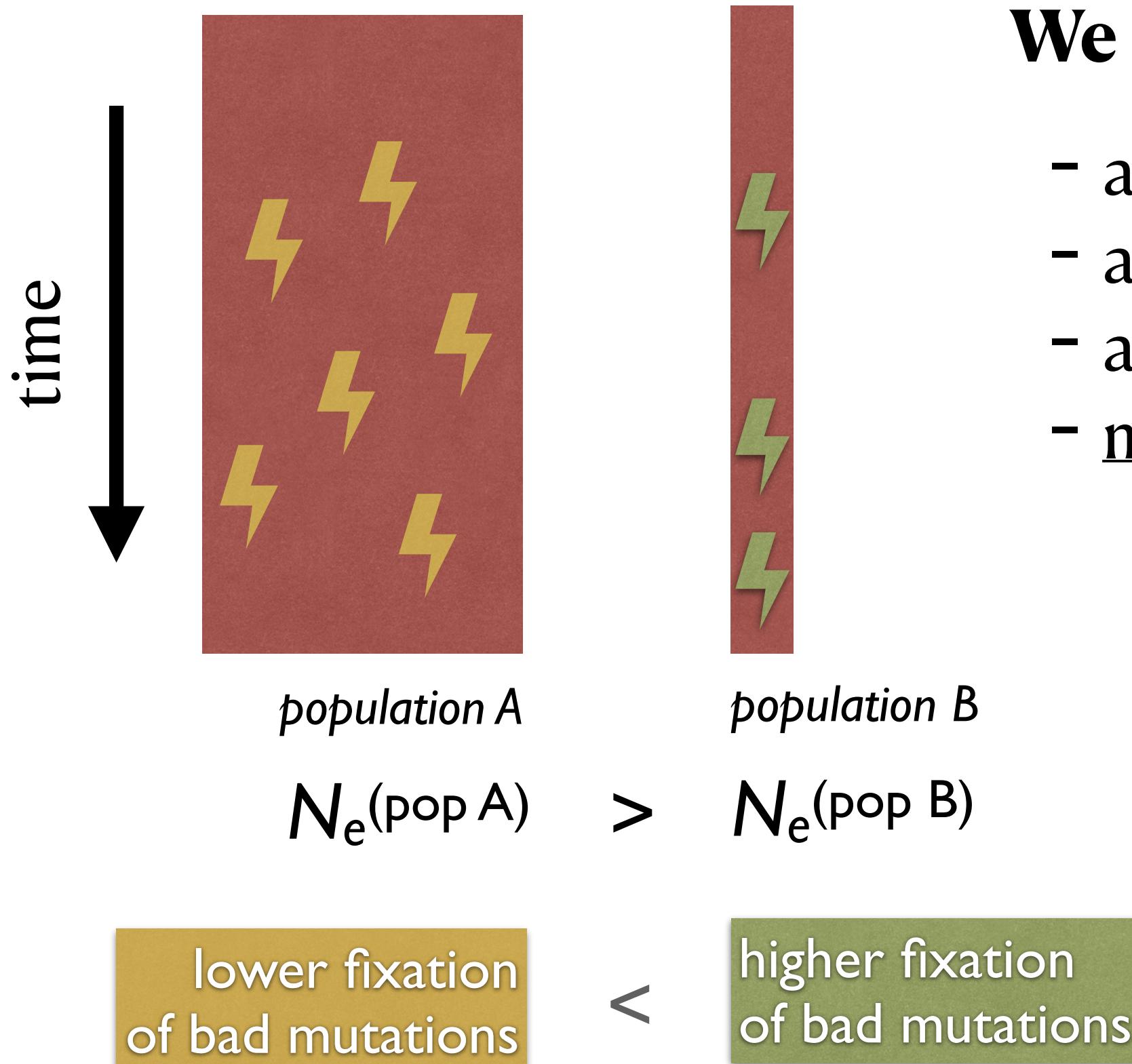
**Efficacy of negative selection  
depends on the effective  
population size ( $N_e$ ).**

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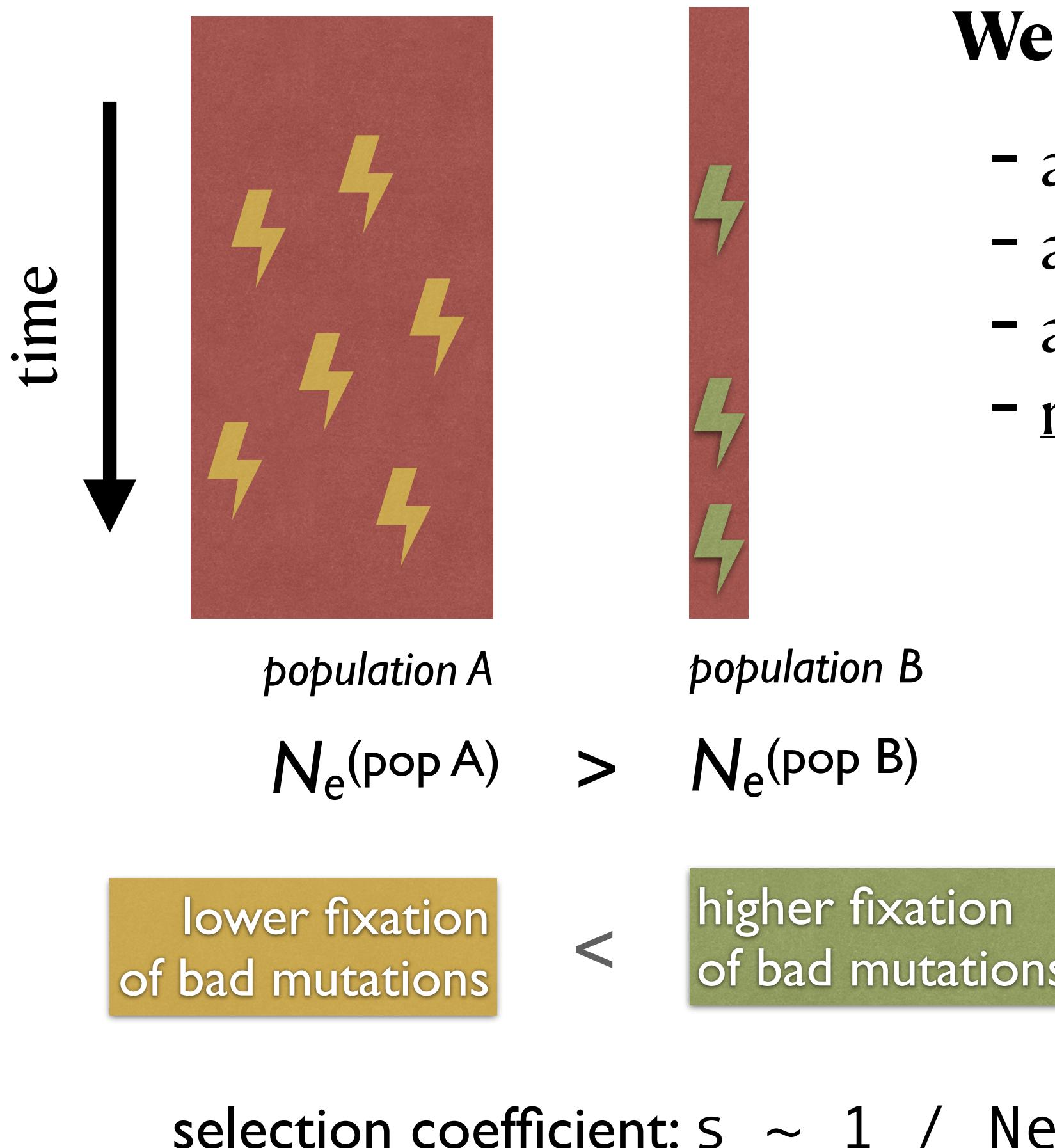
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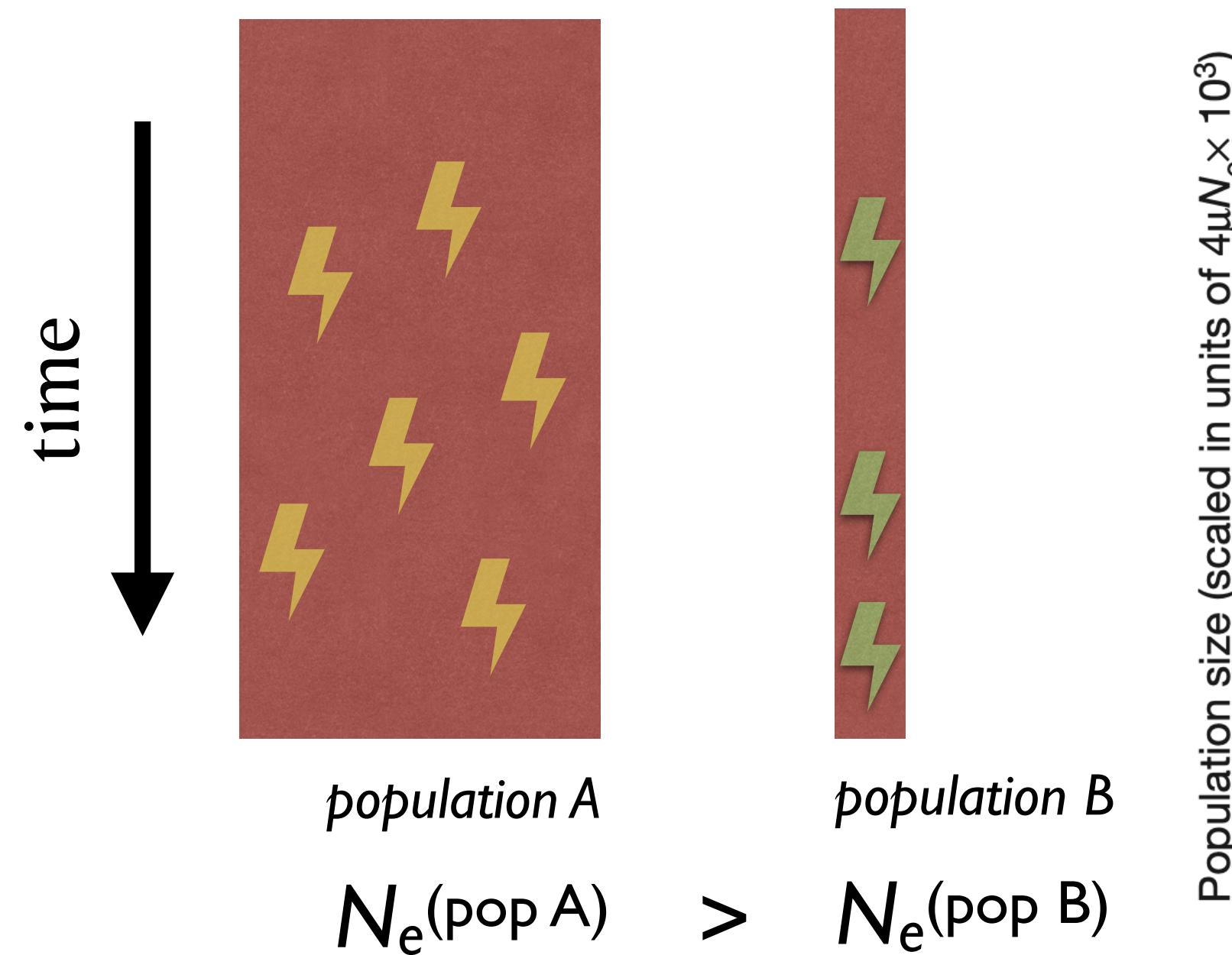
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**Tomoko  
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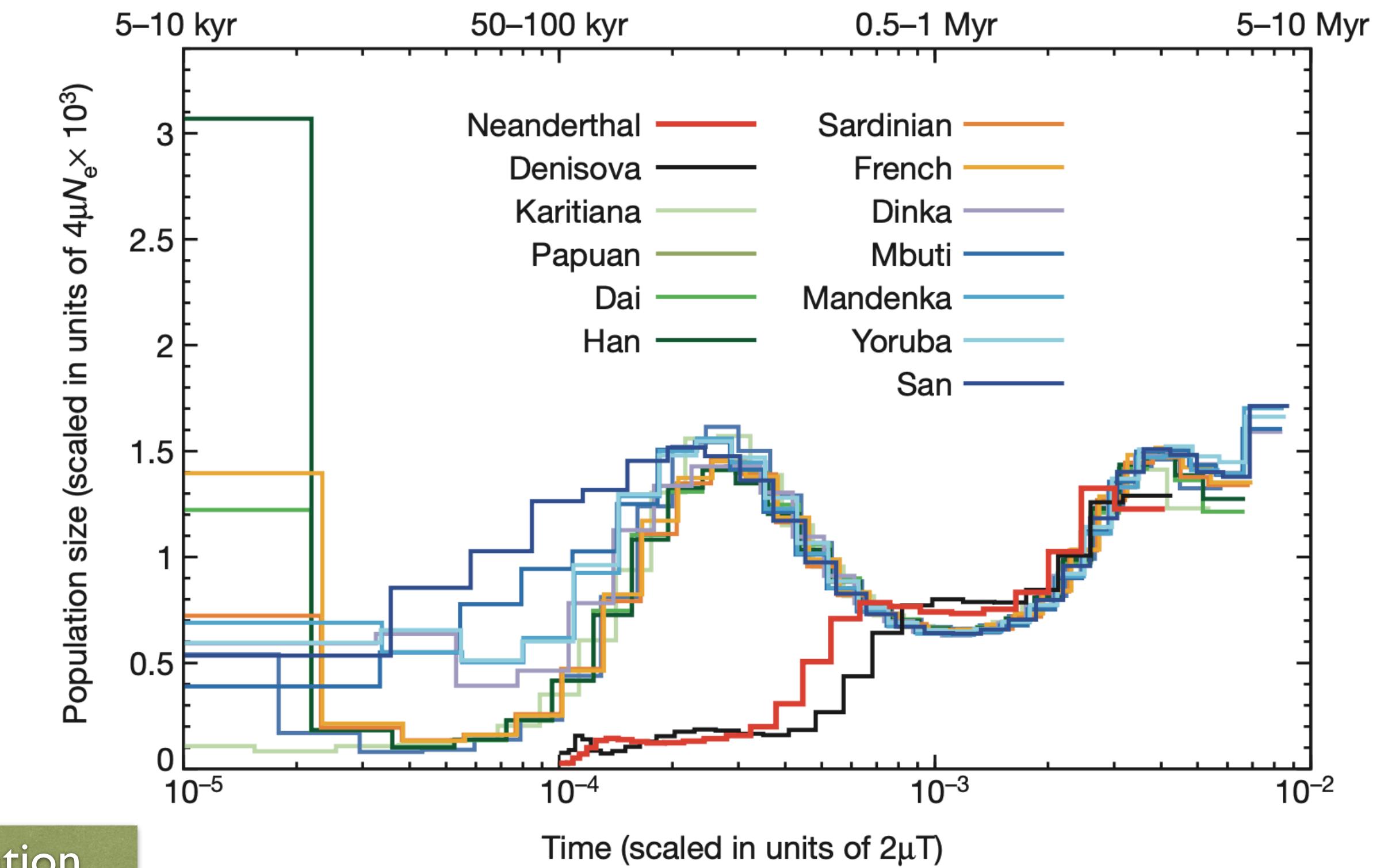


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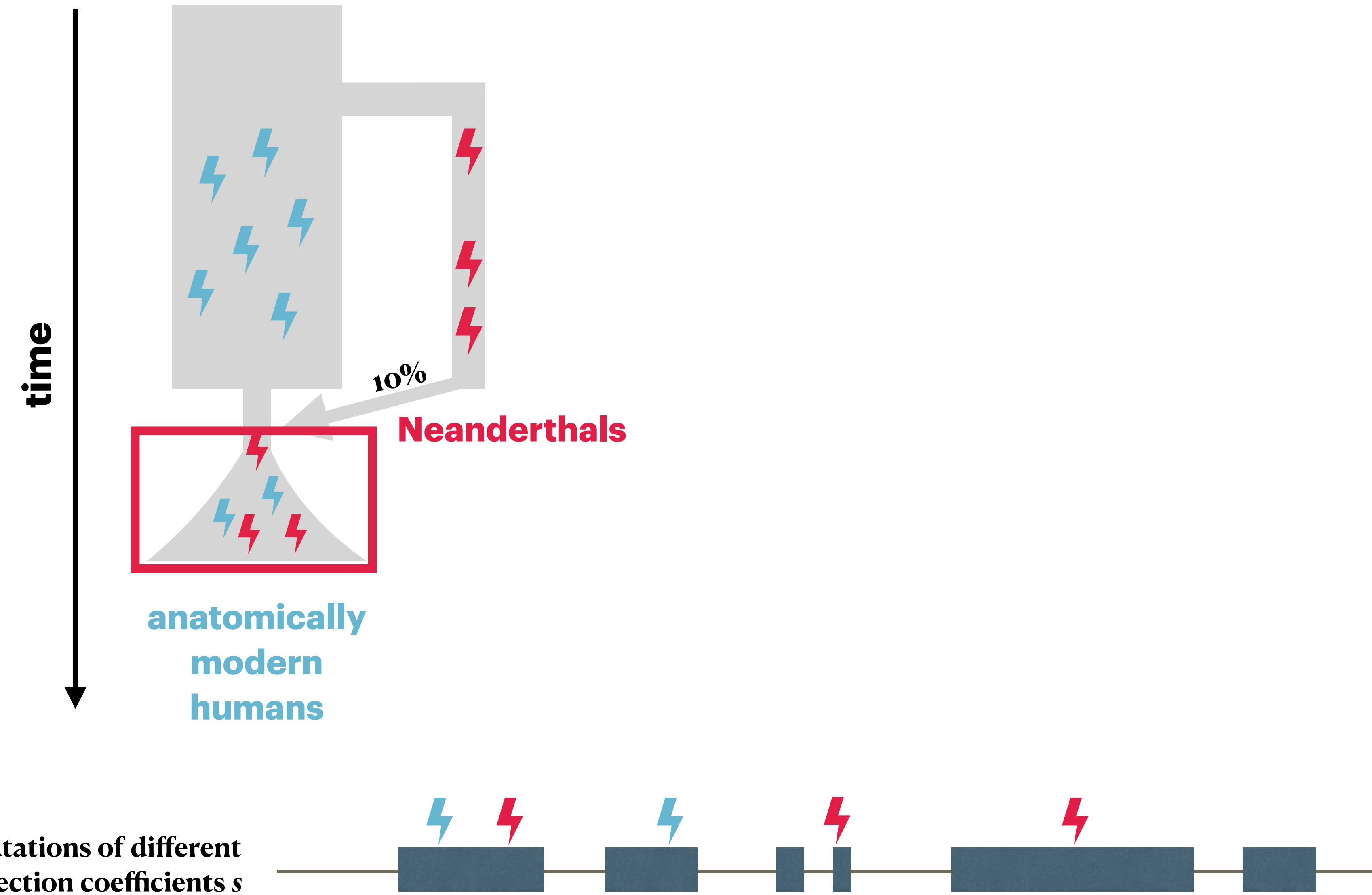
"anatomically  
modern humans"

"Neanderthals"

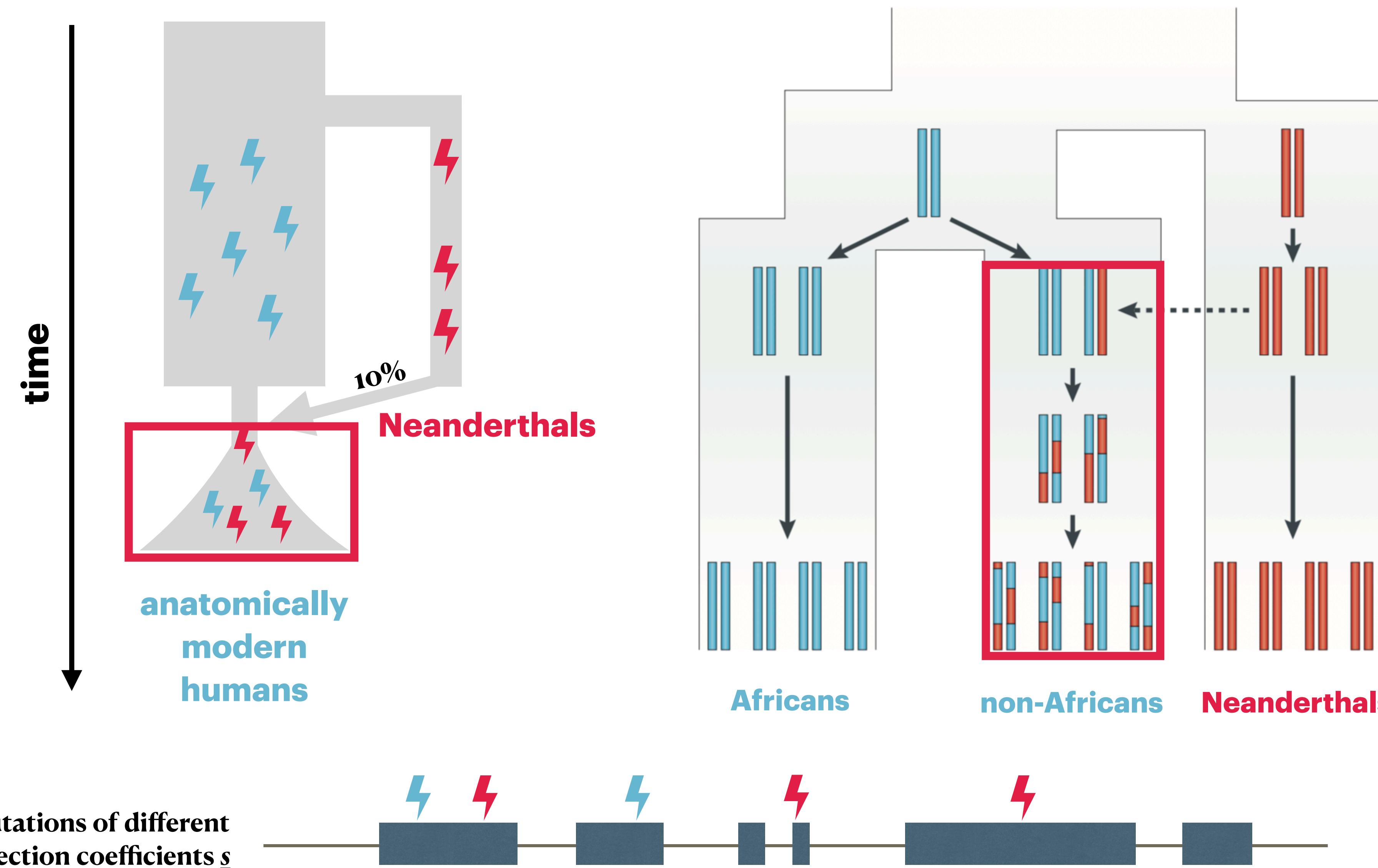


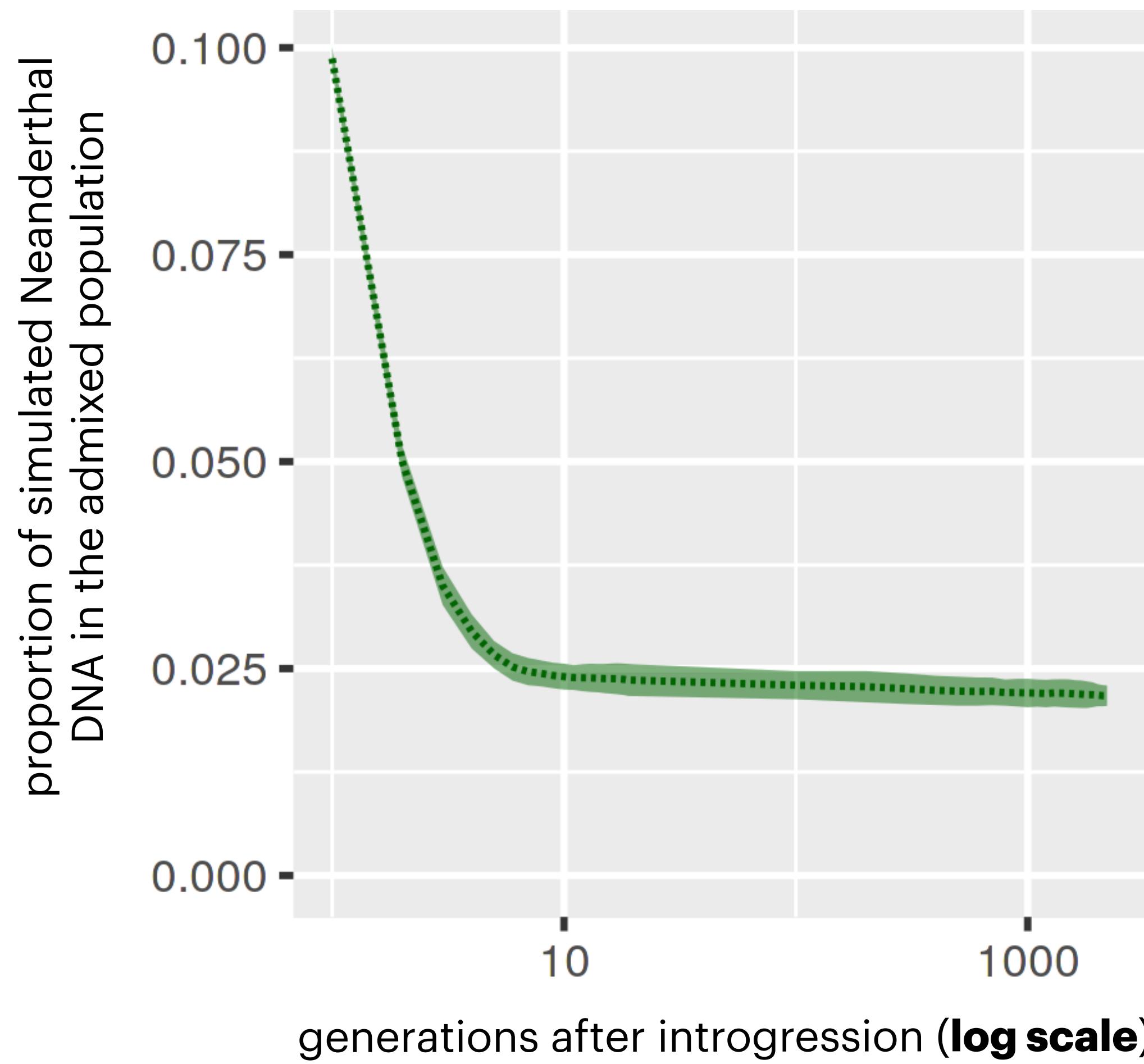
Ohta (Nature, 1973)

# Simulations: tracing the trajectory of introgressed DNA over time

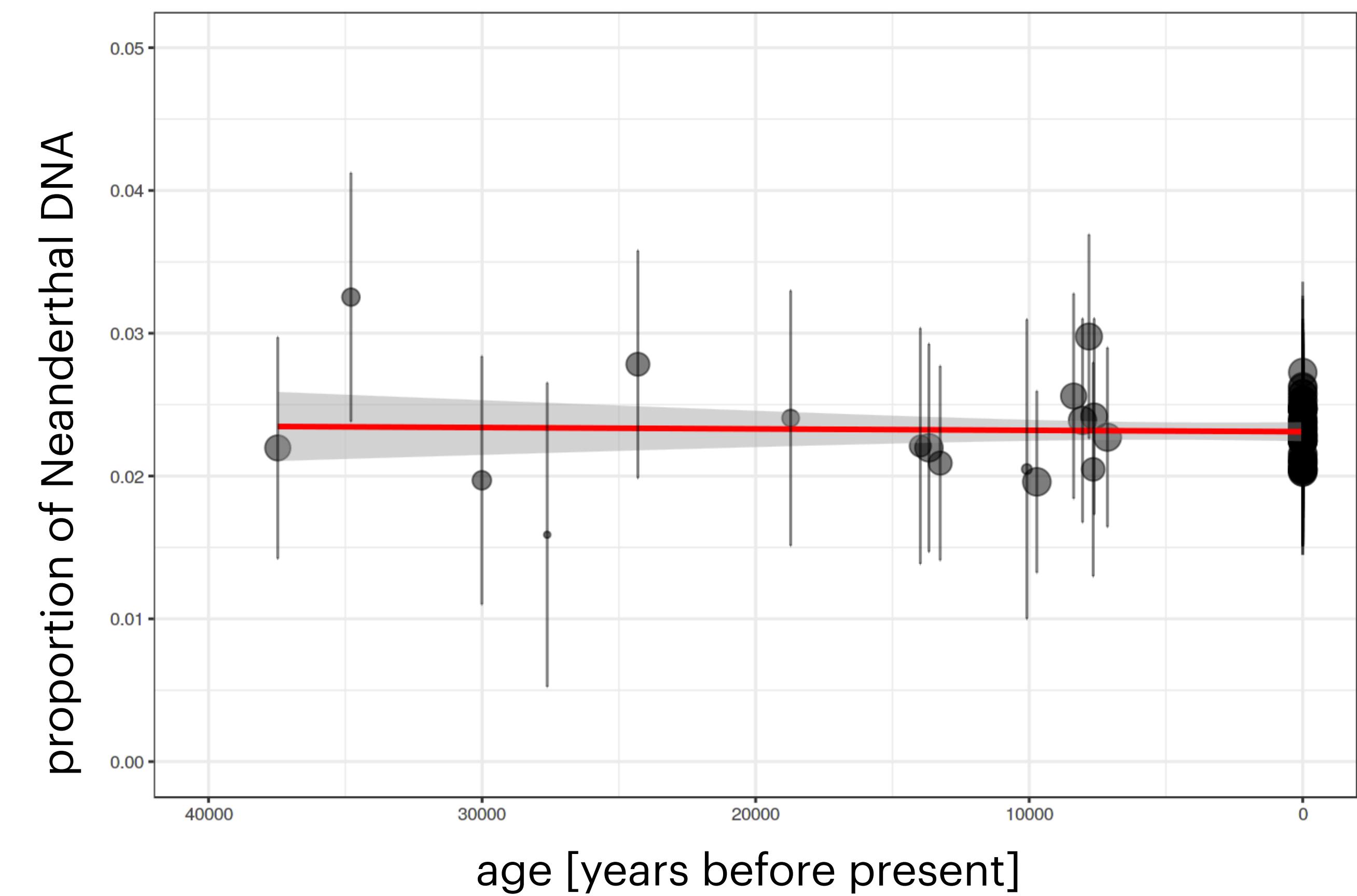
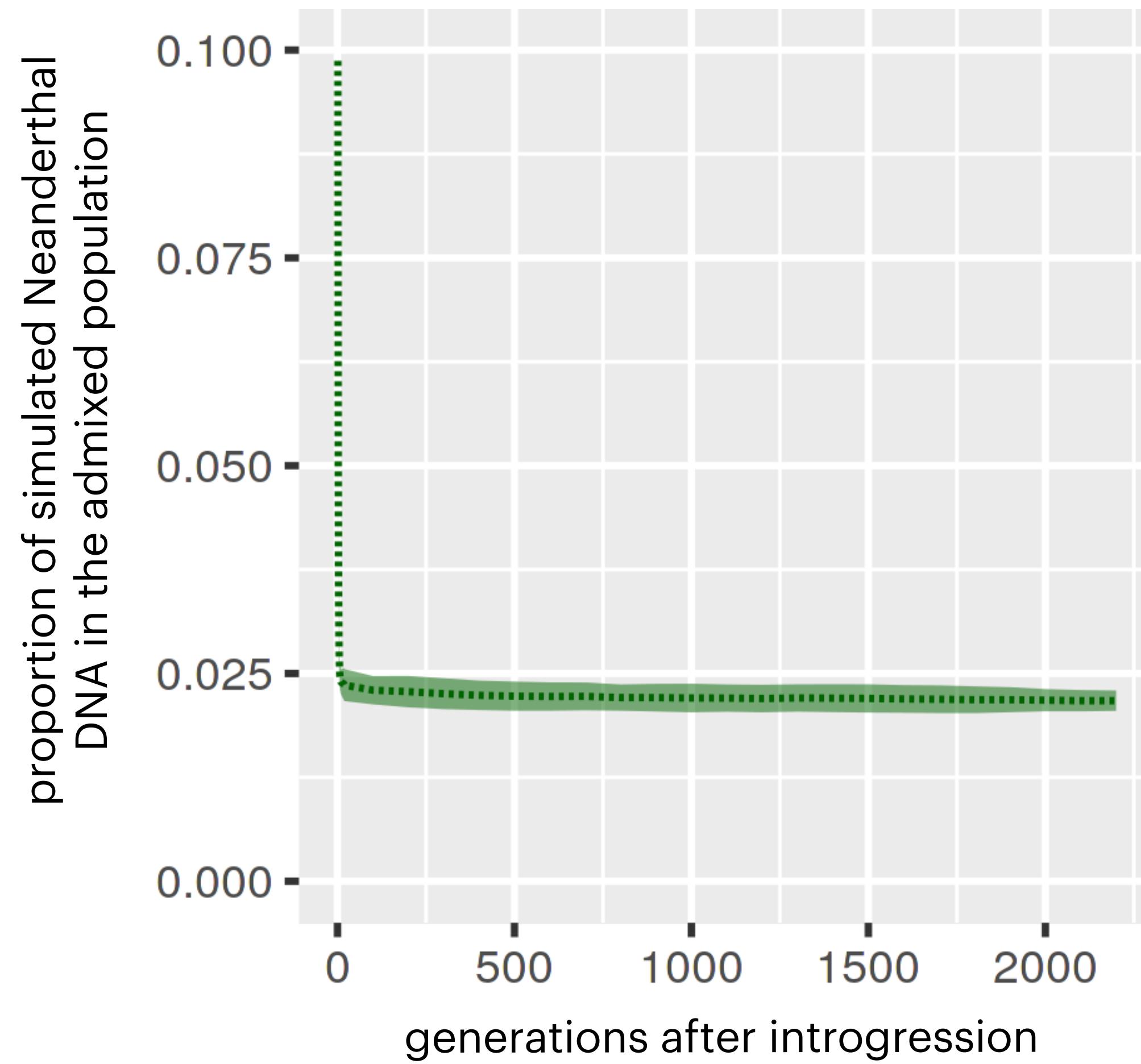


# Simulations: tracing the trajectory of introgressed DNA over time



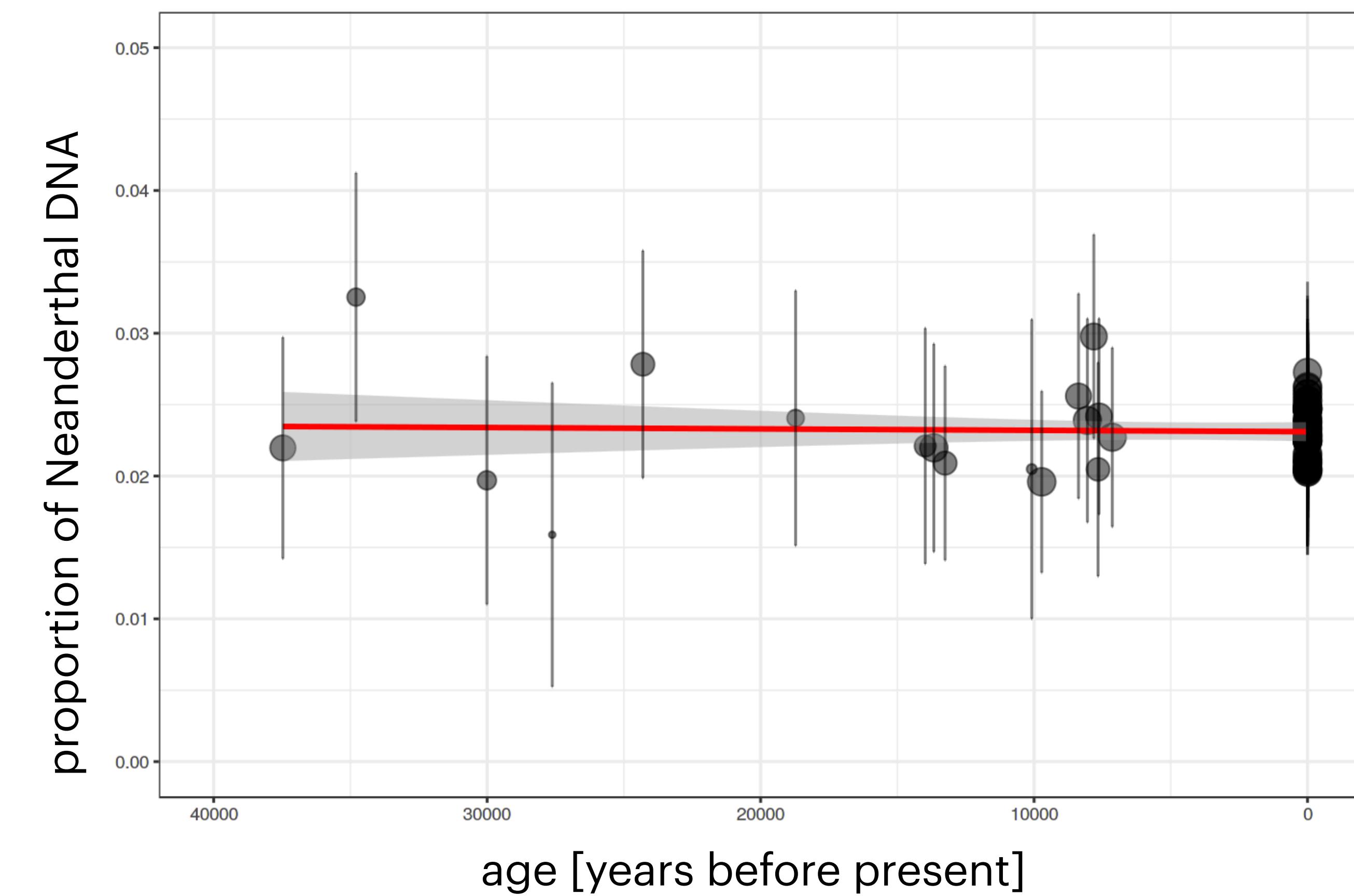
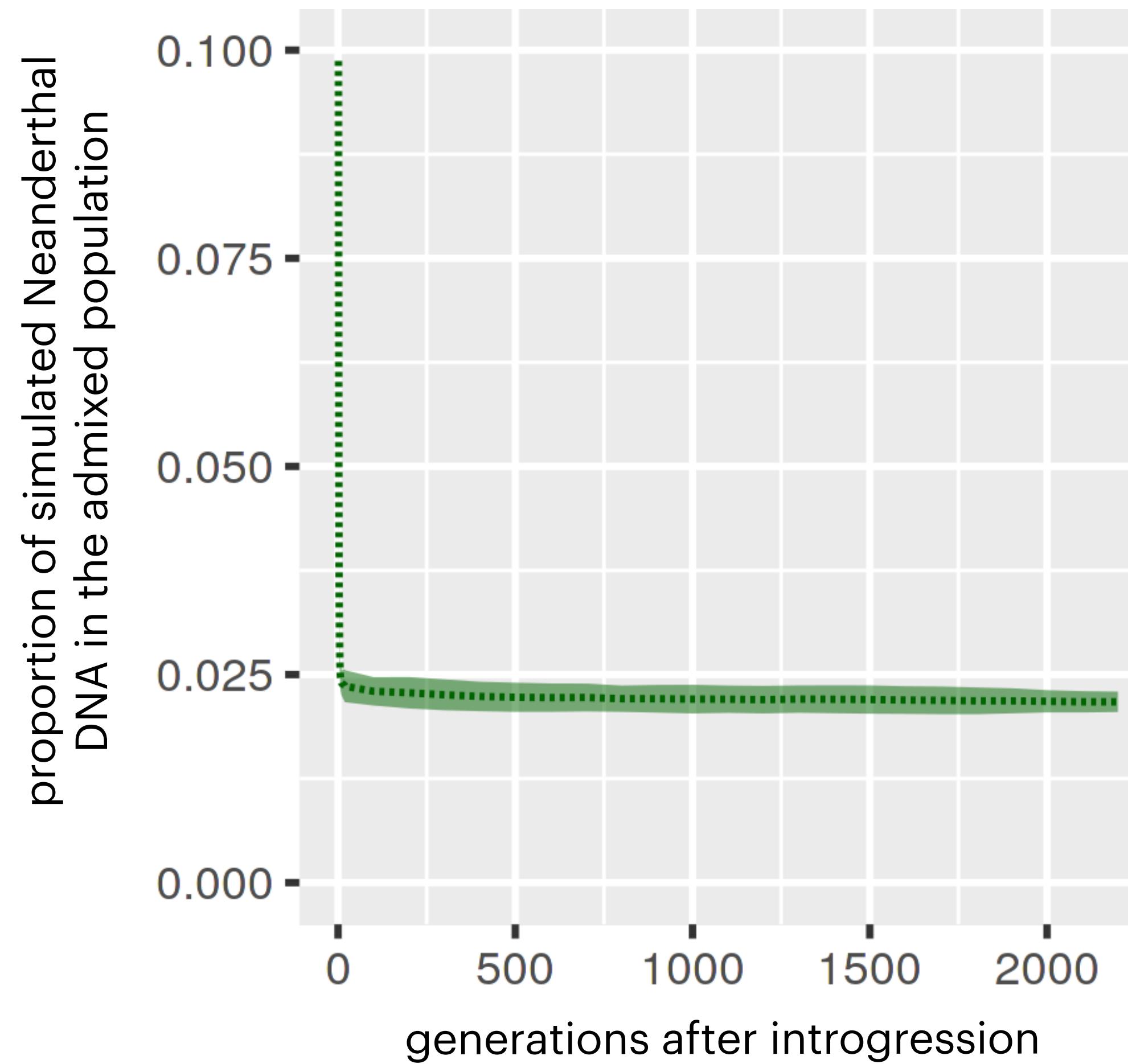


Harris et al. (2016); Juric et al. (2016); Petr et al. (2019)



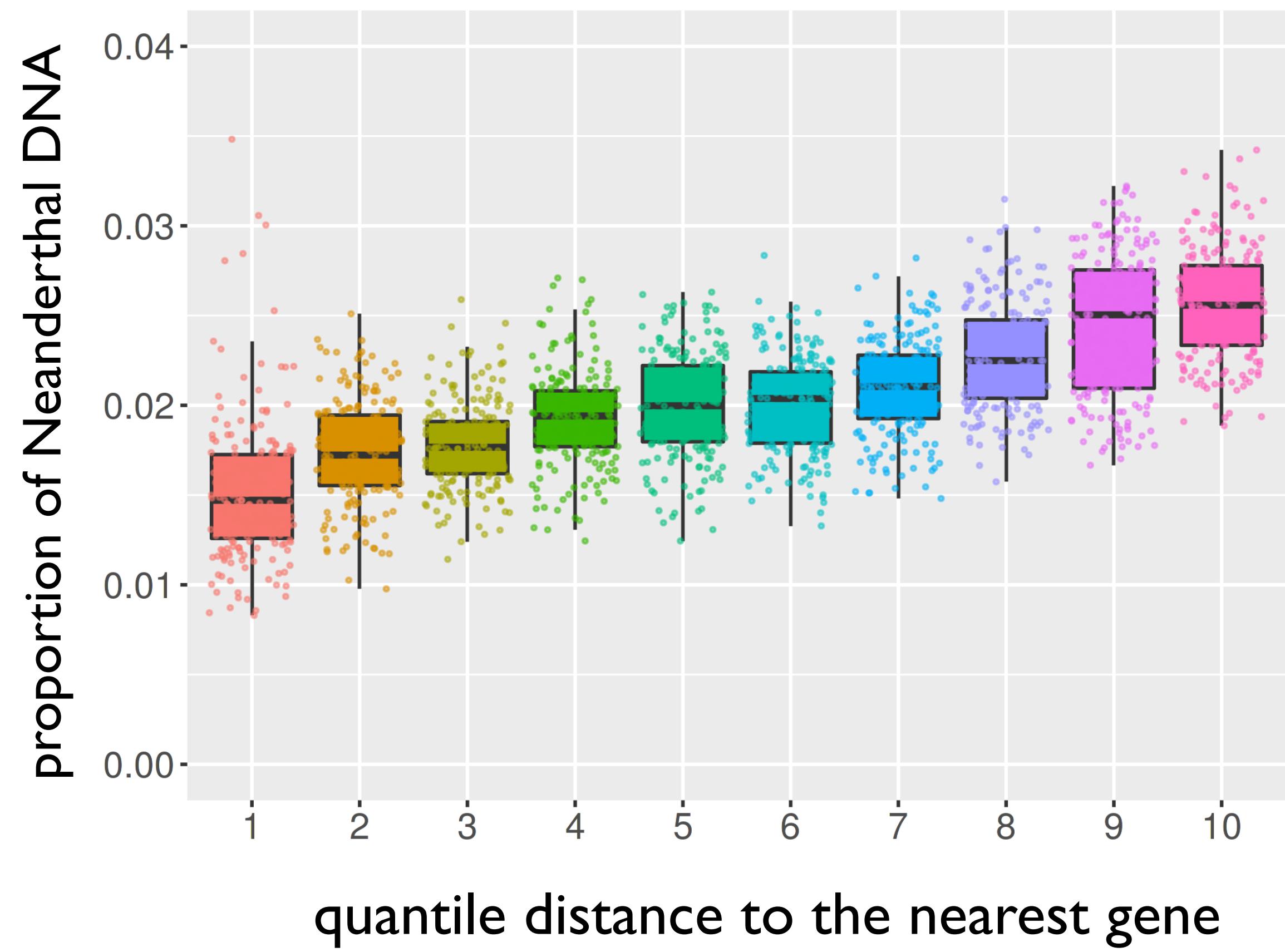
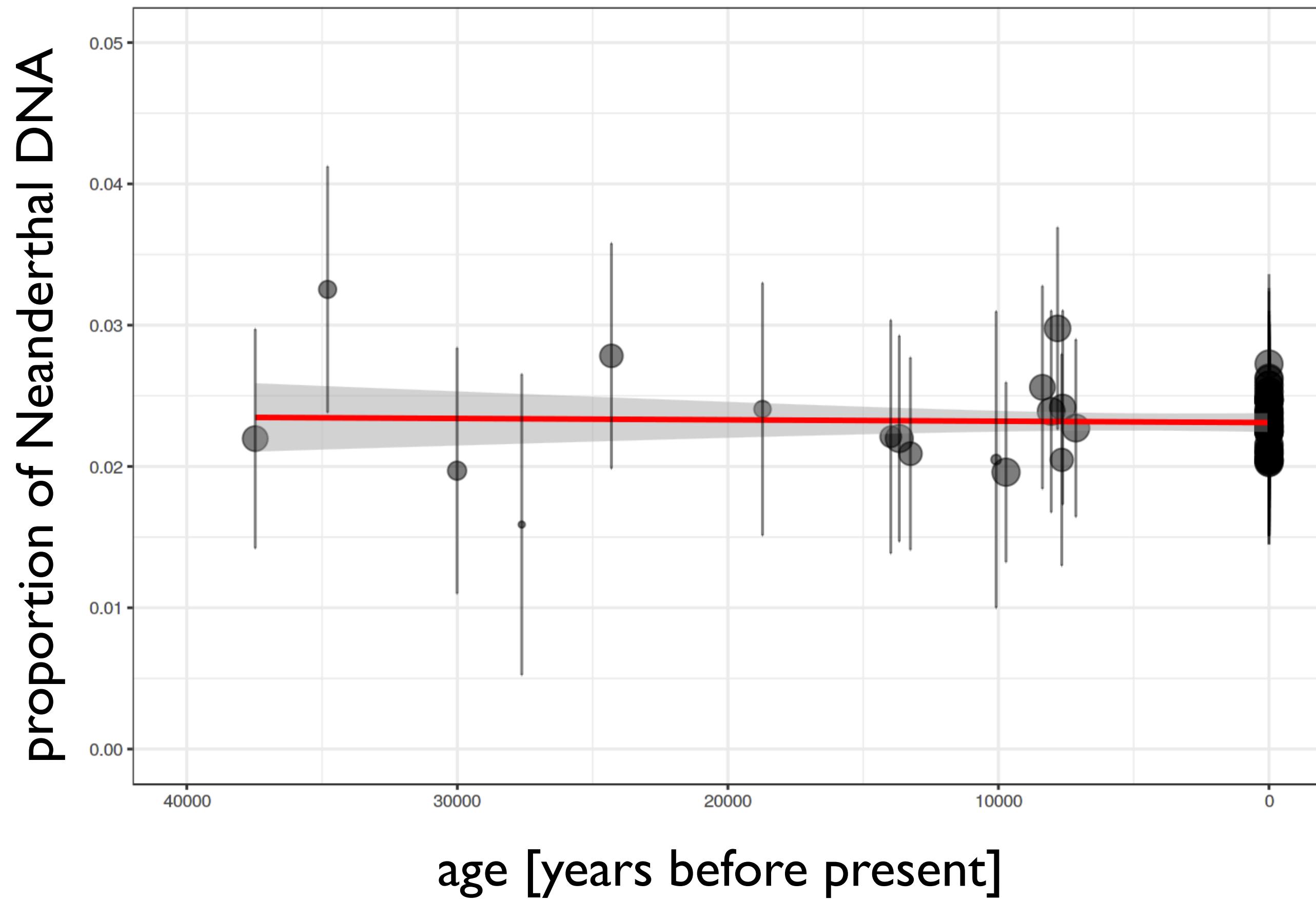
Harris et al. (2016); Juric et al. (2016); Petr et al. (2019)

# Neanderthal ancestry trajectory matches simulations...

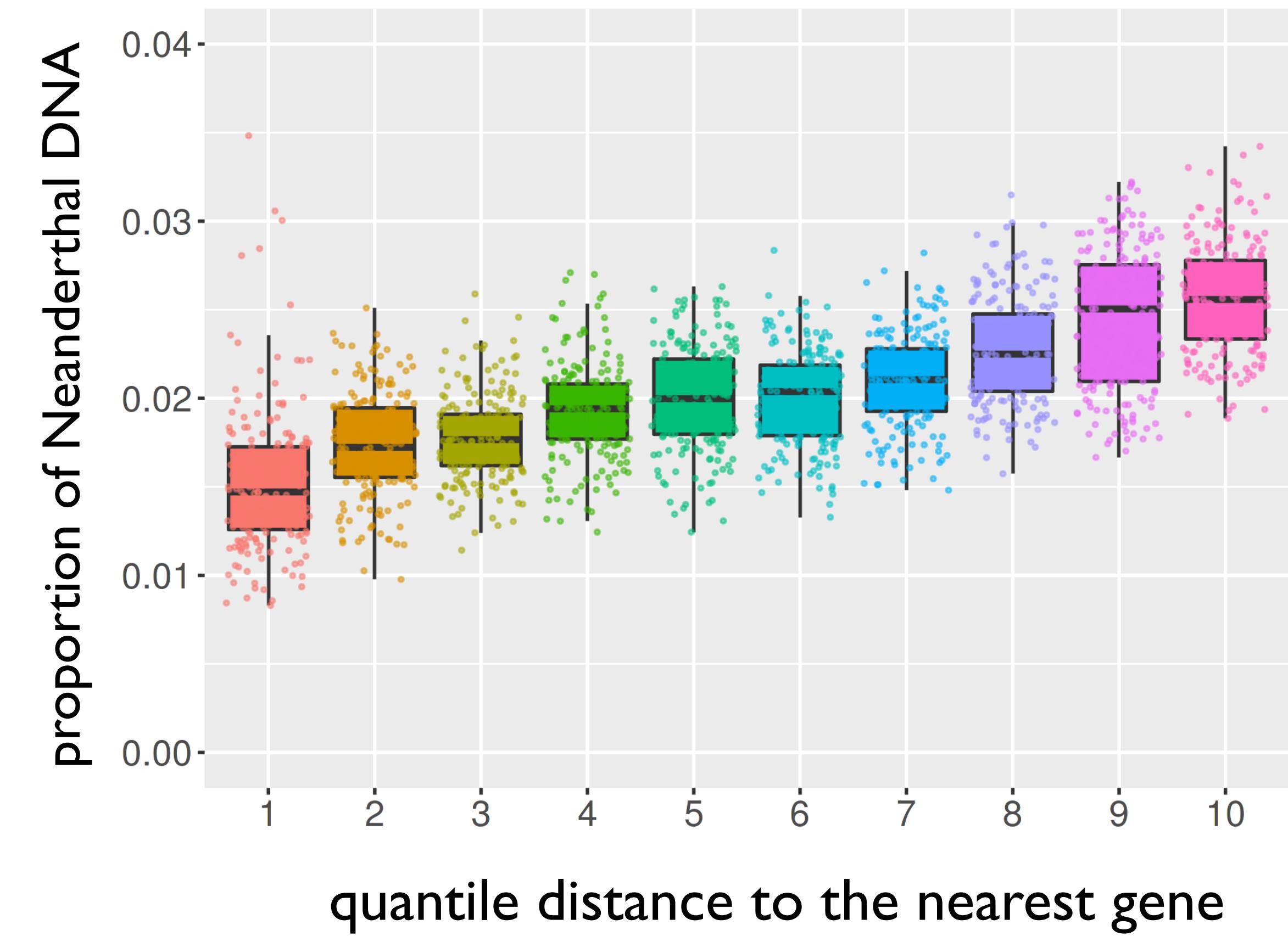
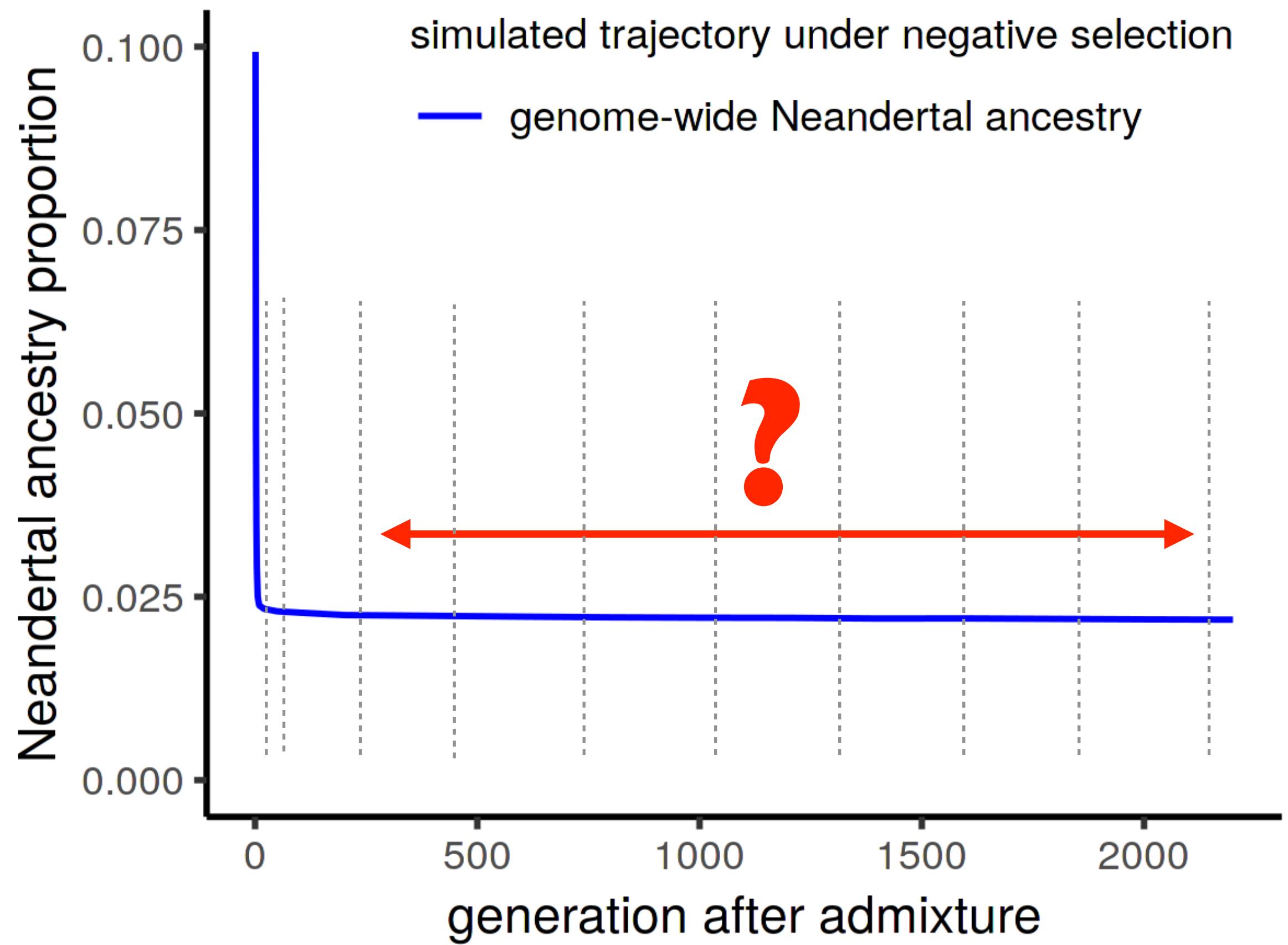


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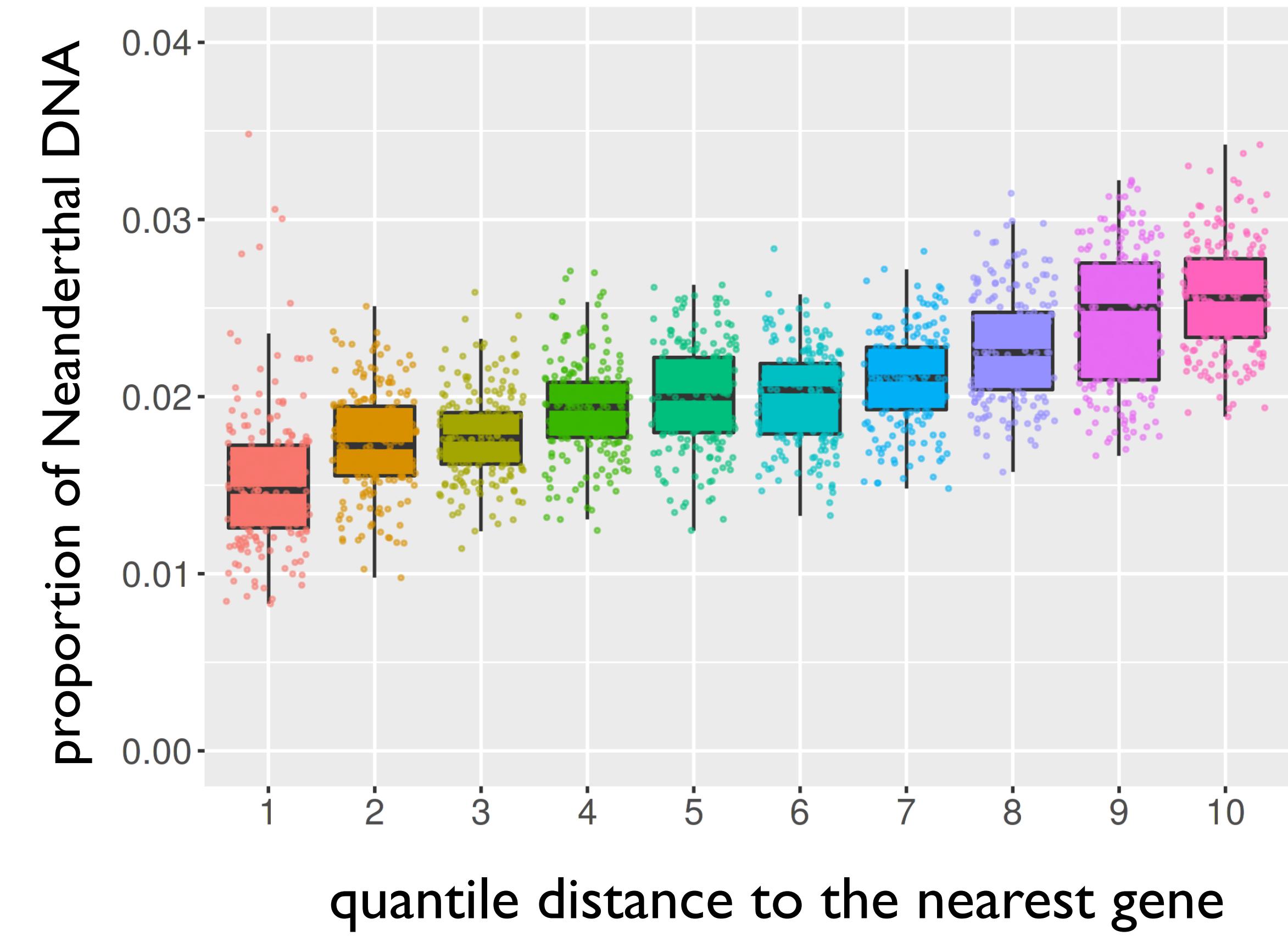
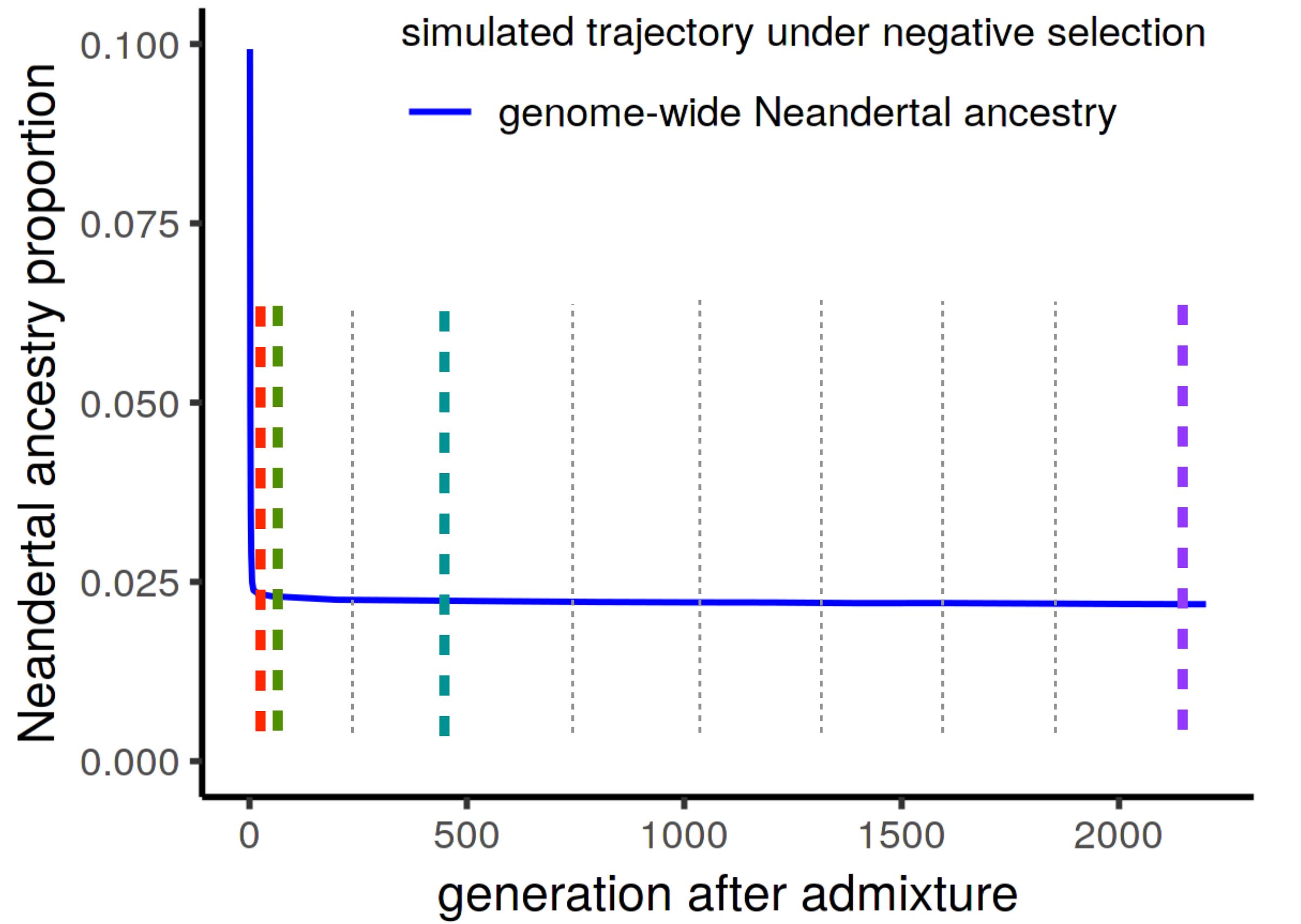
# ... what about the whole-genome negative selection signal?



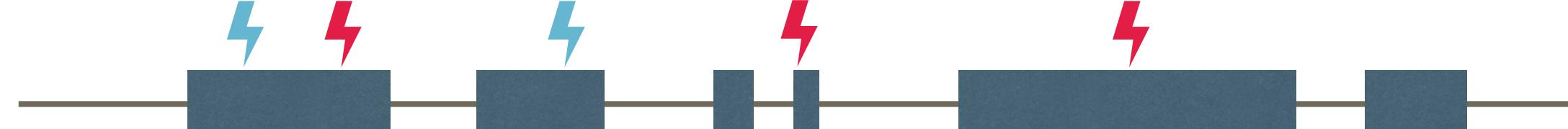
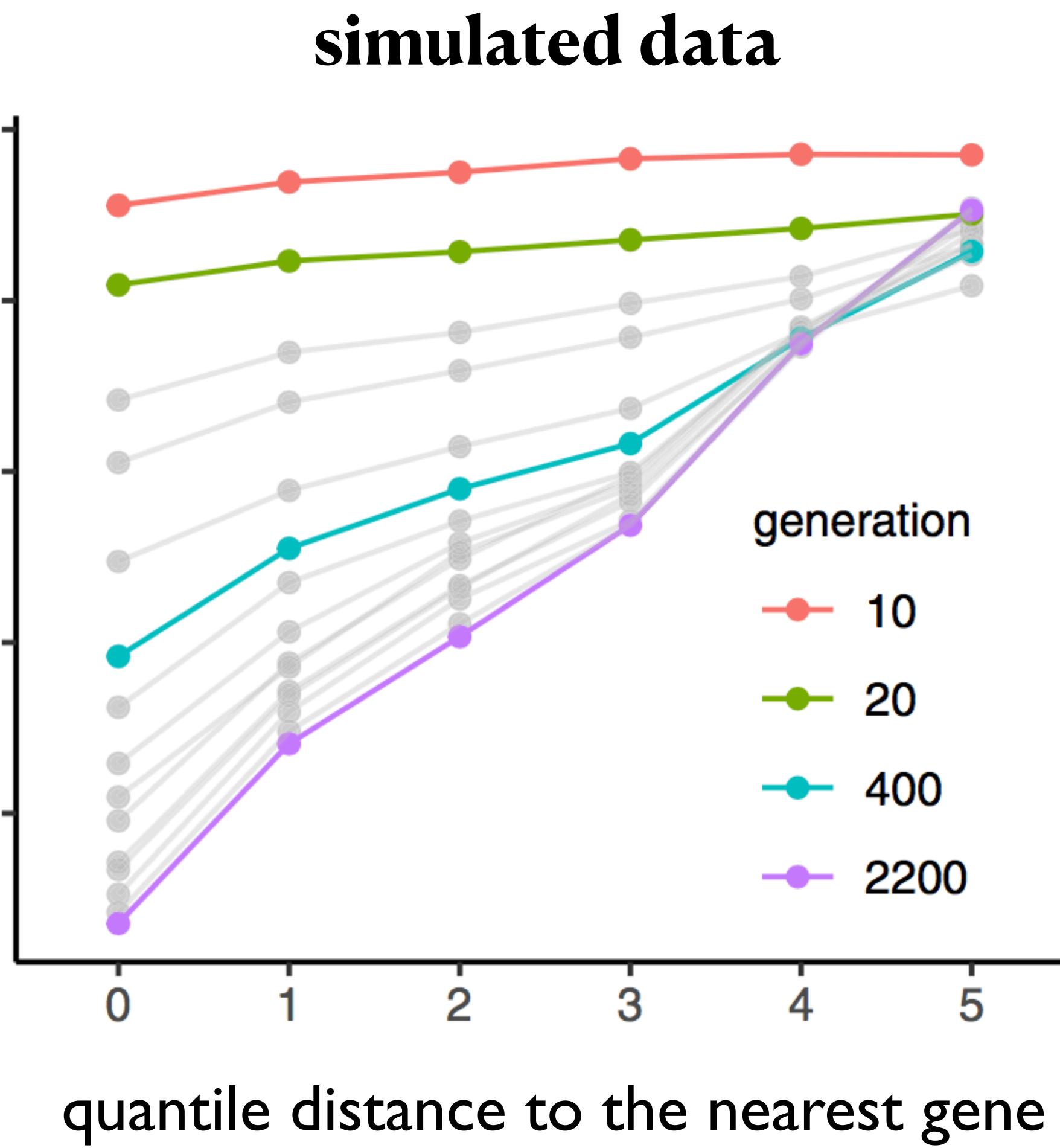
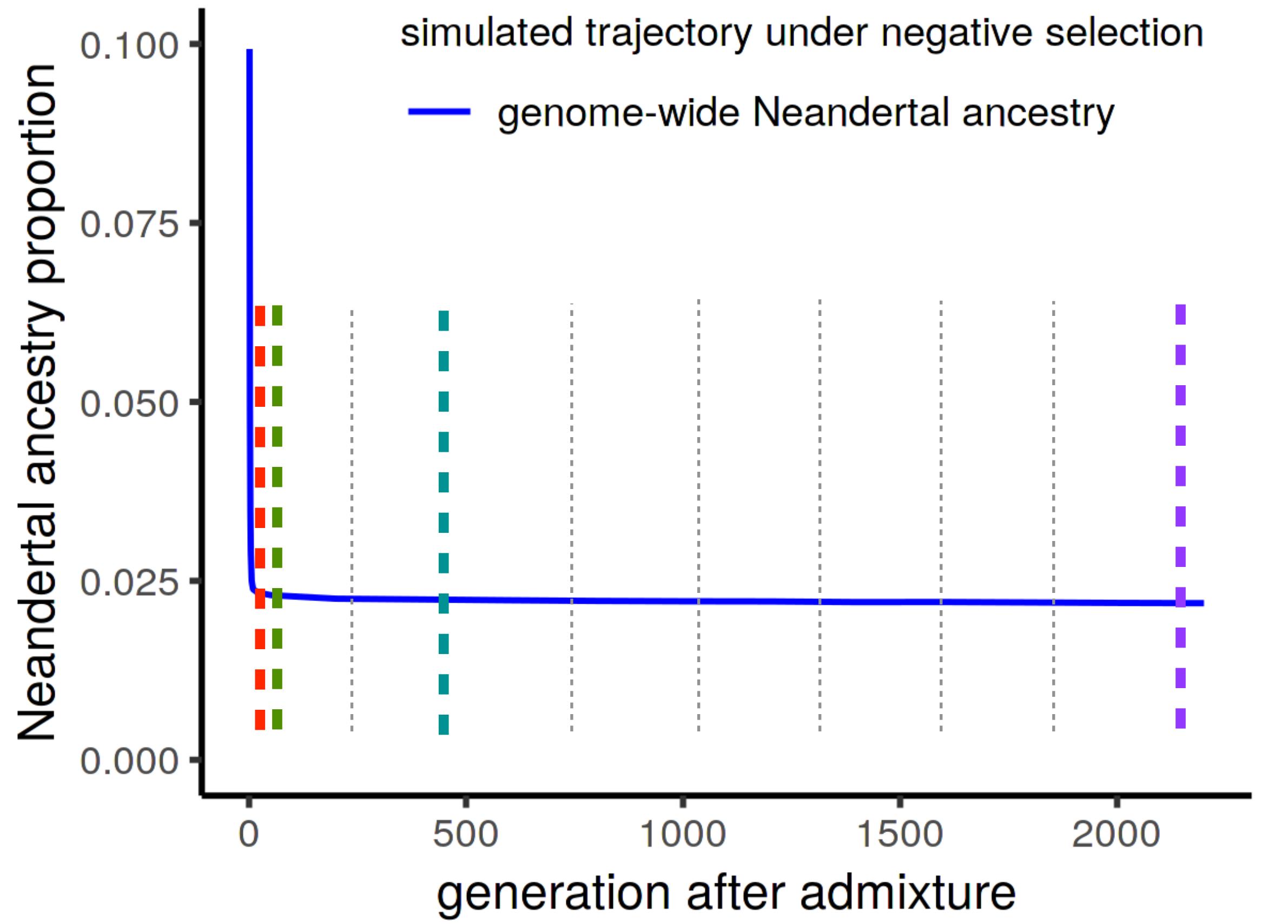
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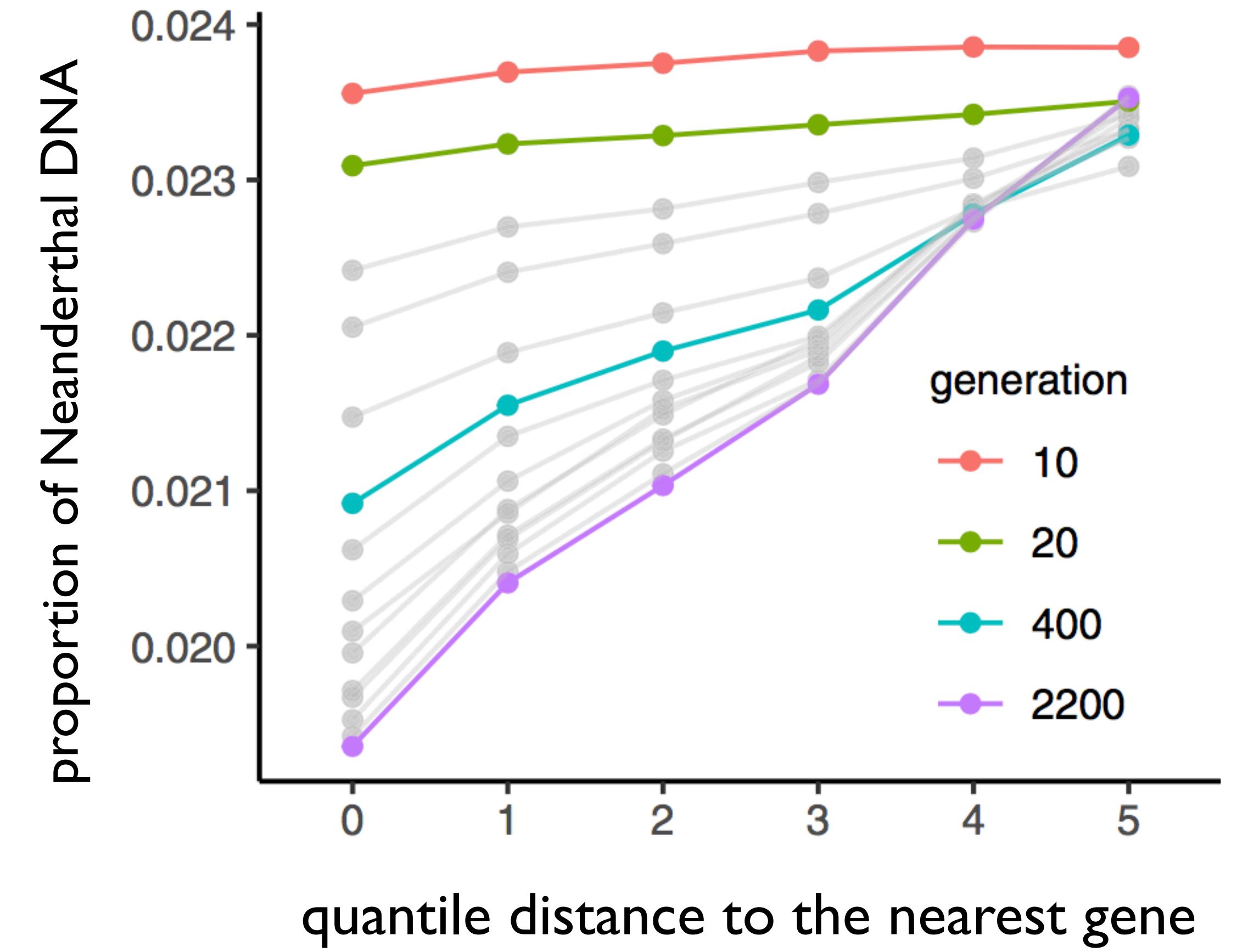
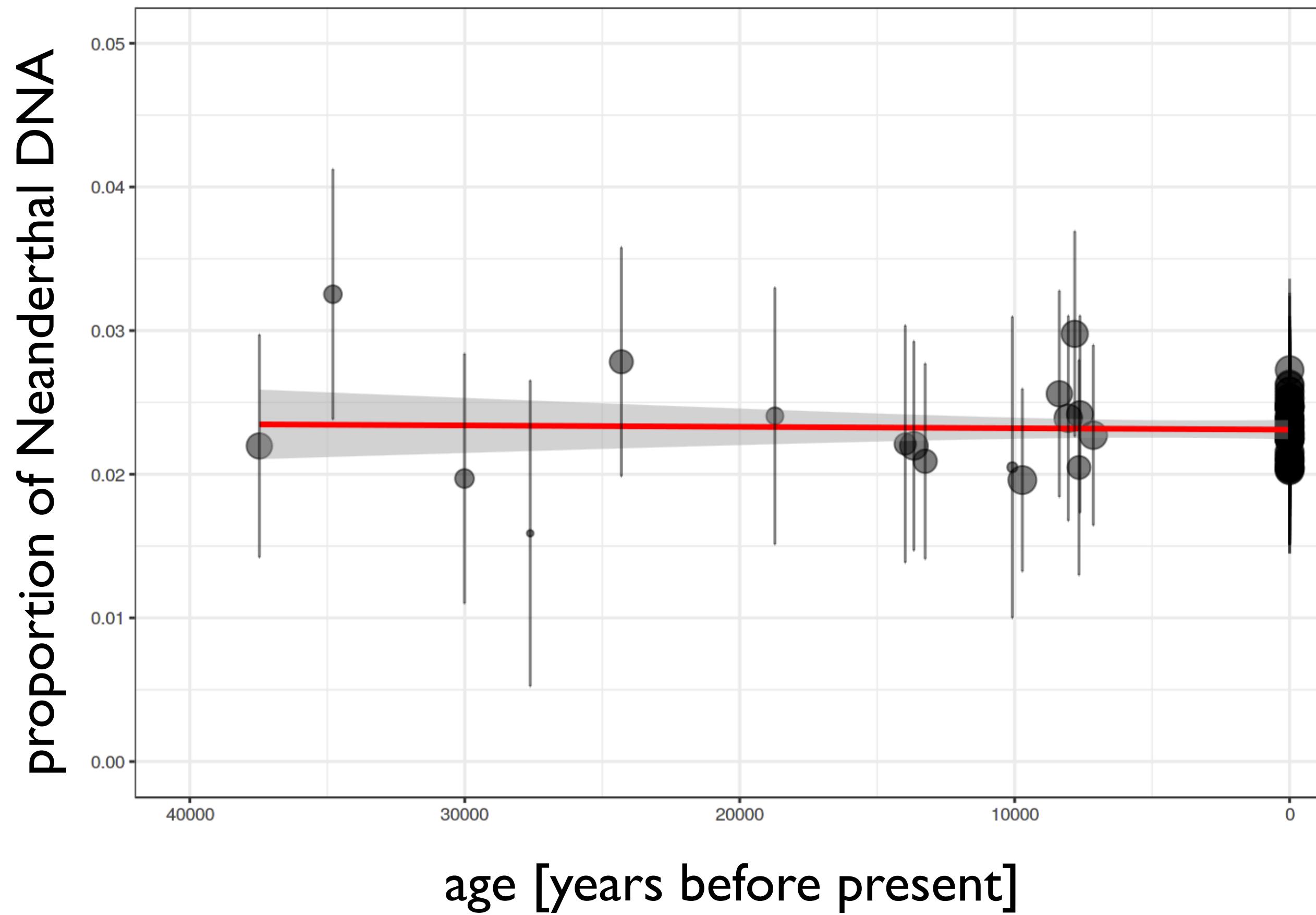
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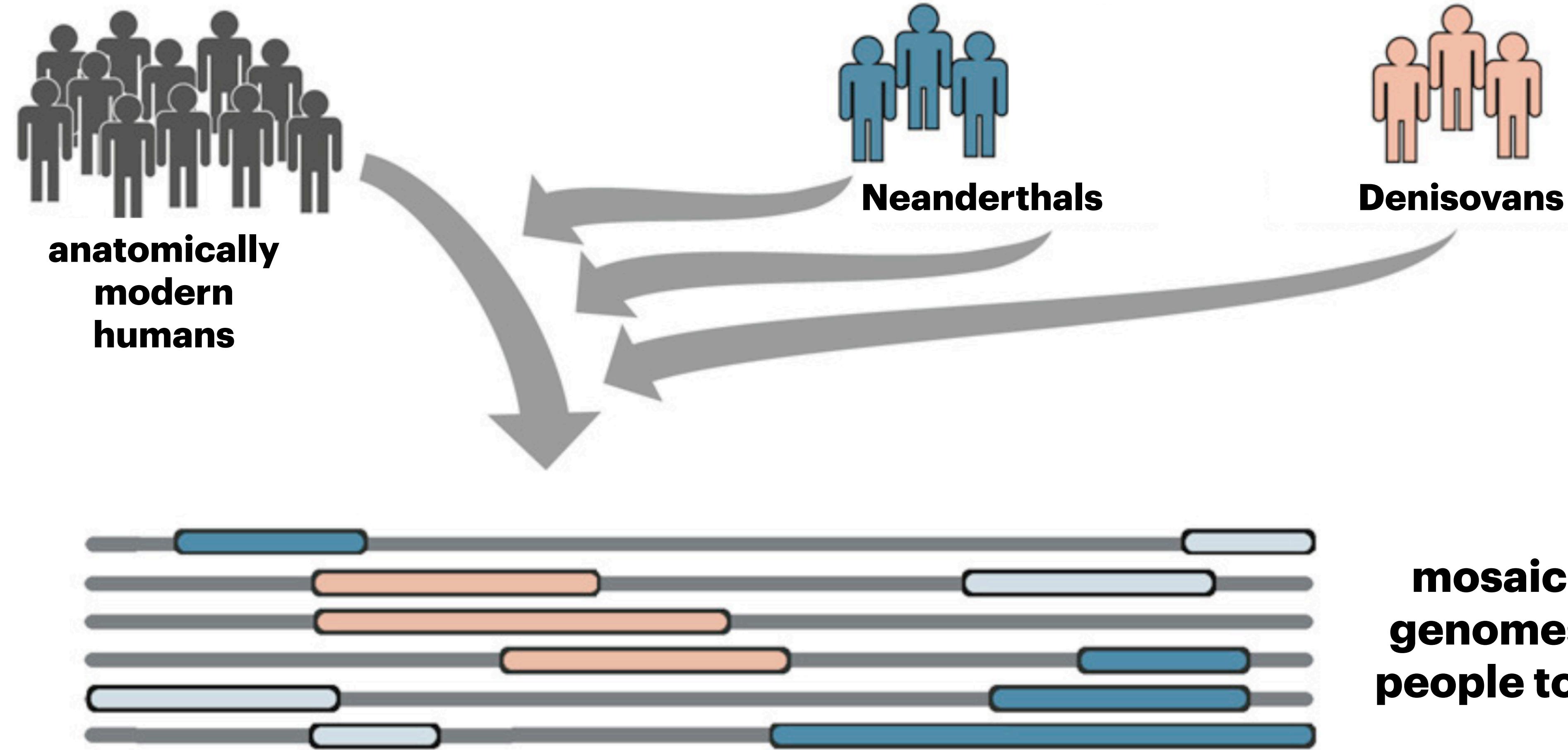


# ... what about the whole-genome negative selection signal?

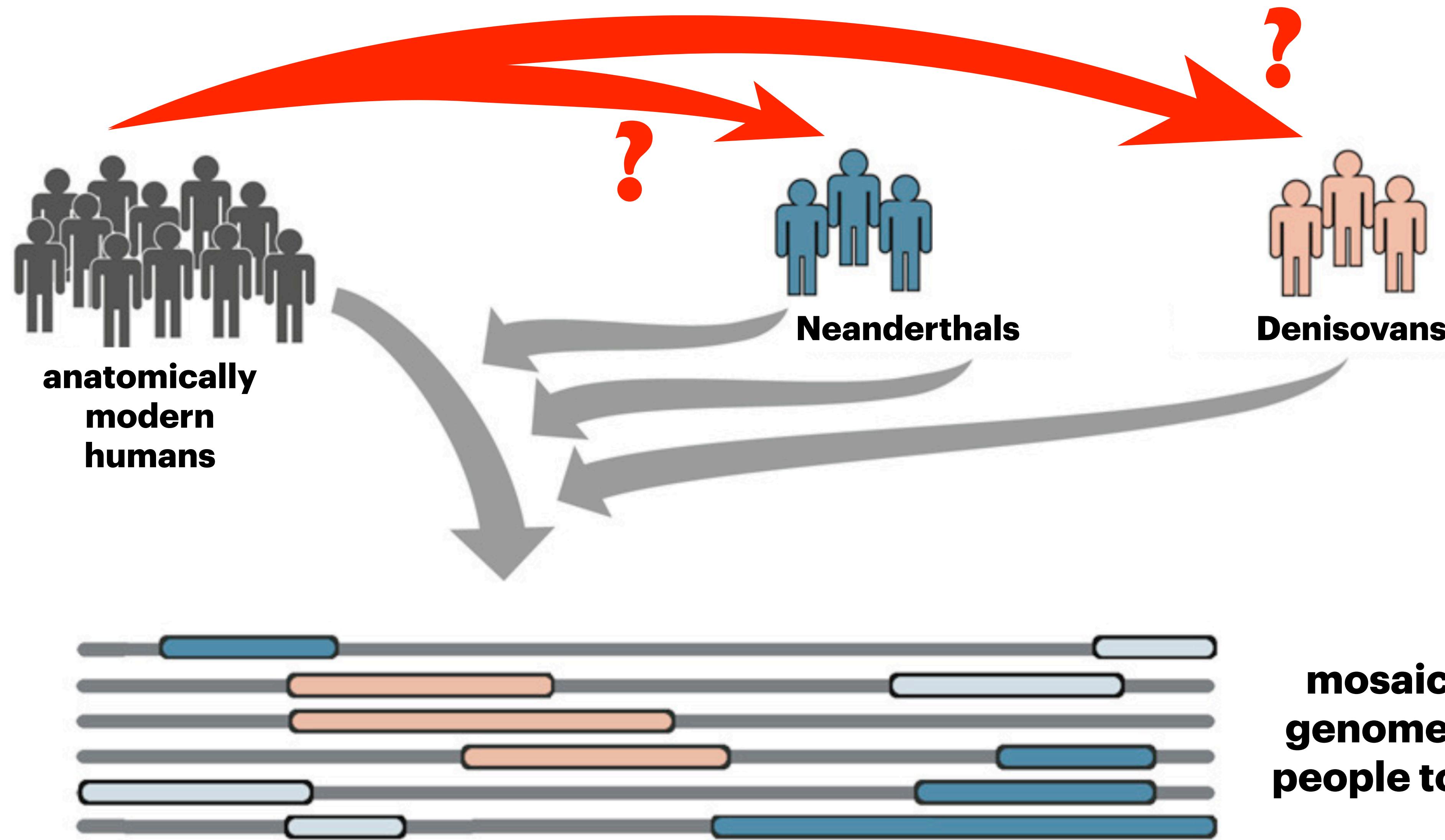


# Both empirical results match population genetic theory!



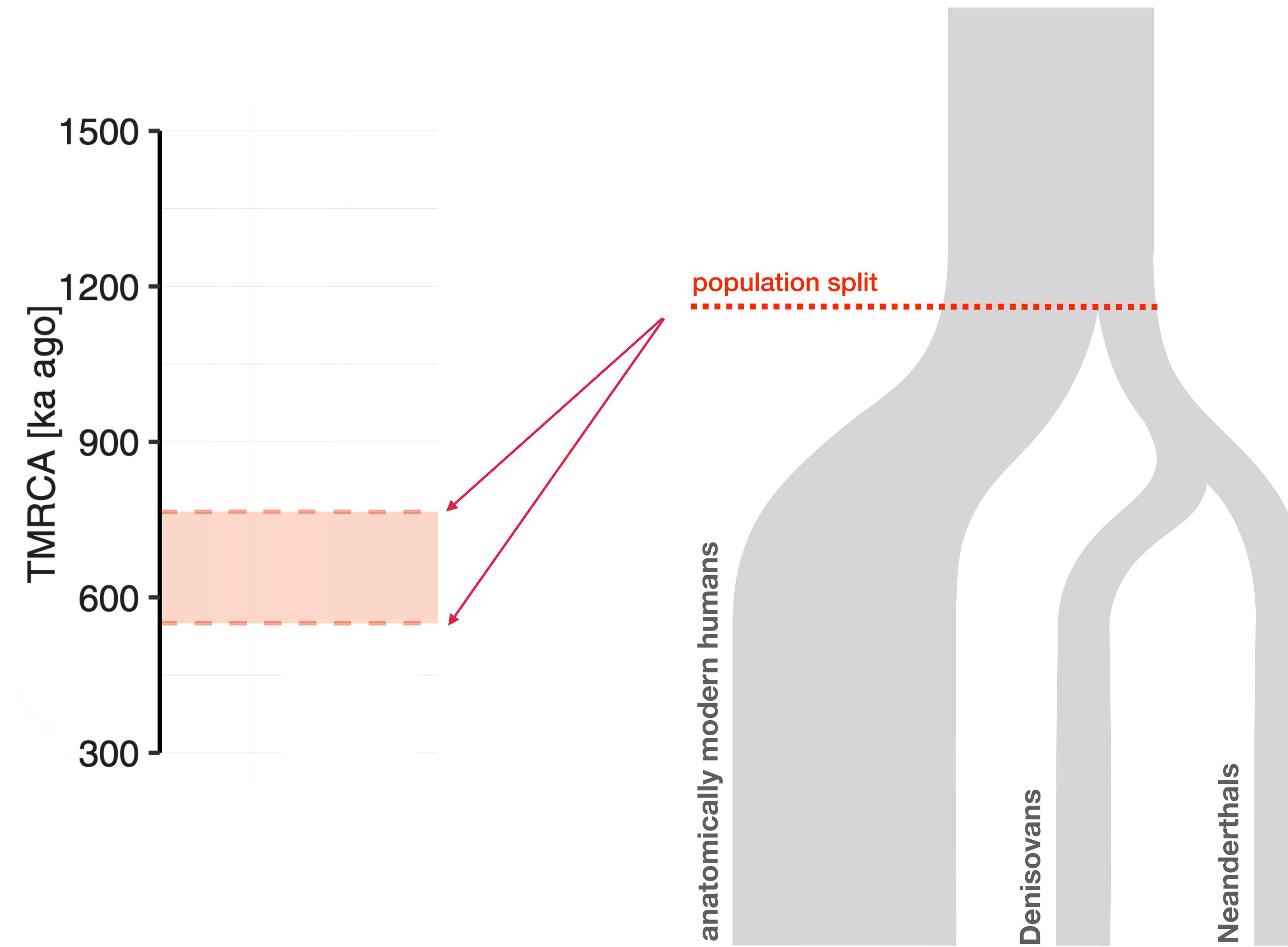


adapted from Browning et al., Cell, 2018

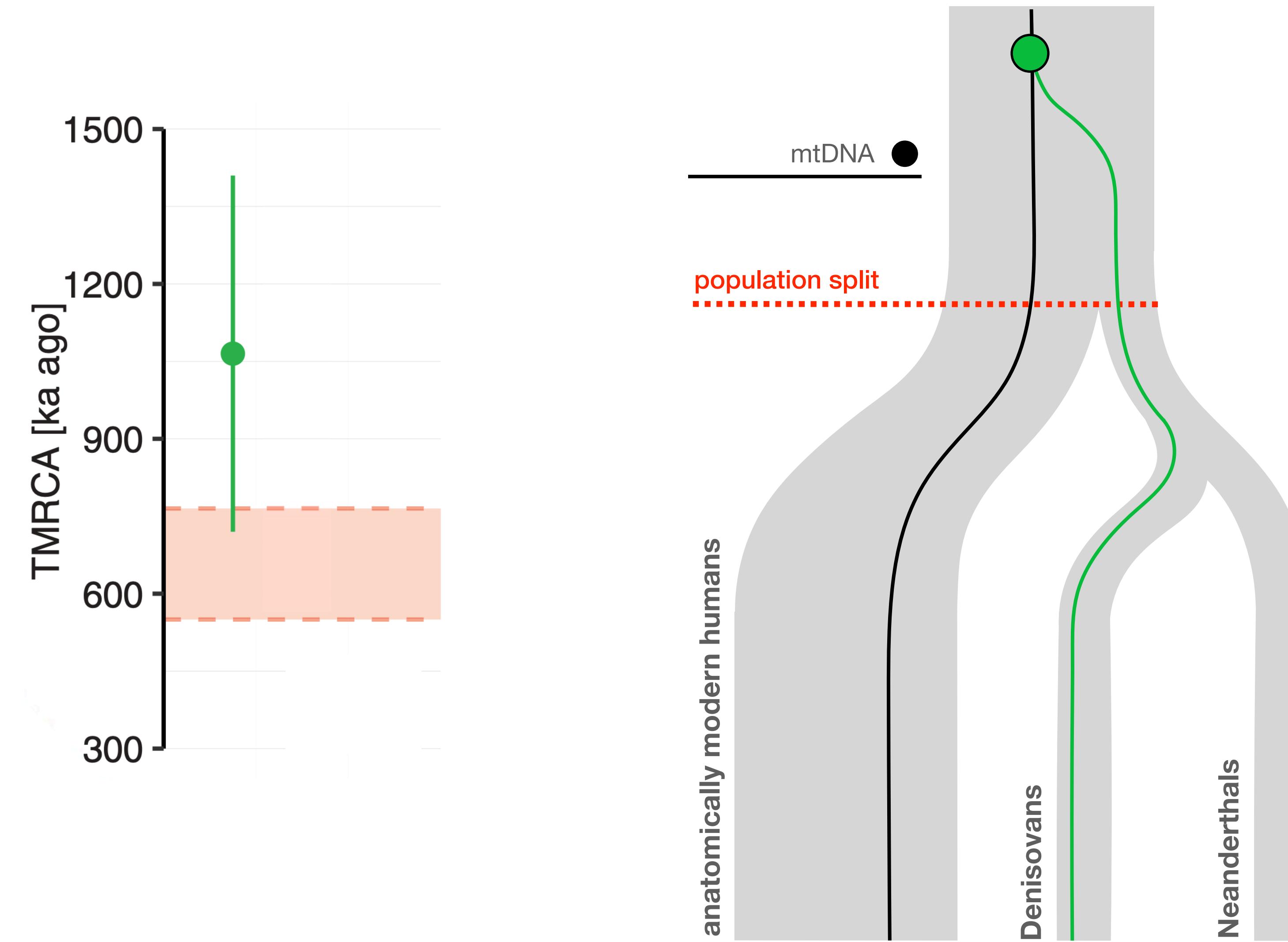


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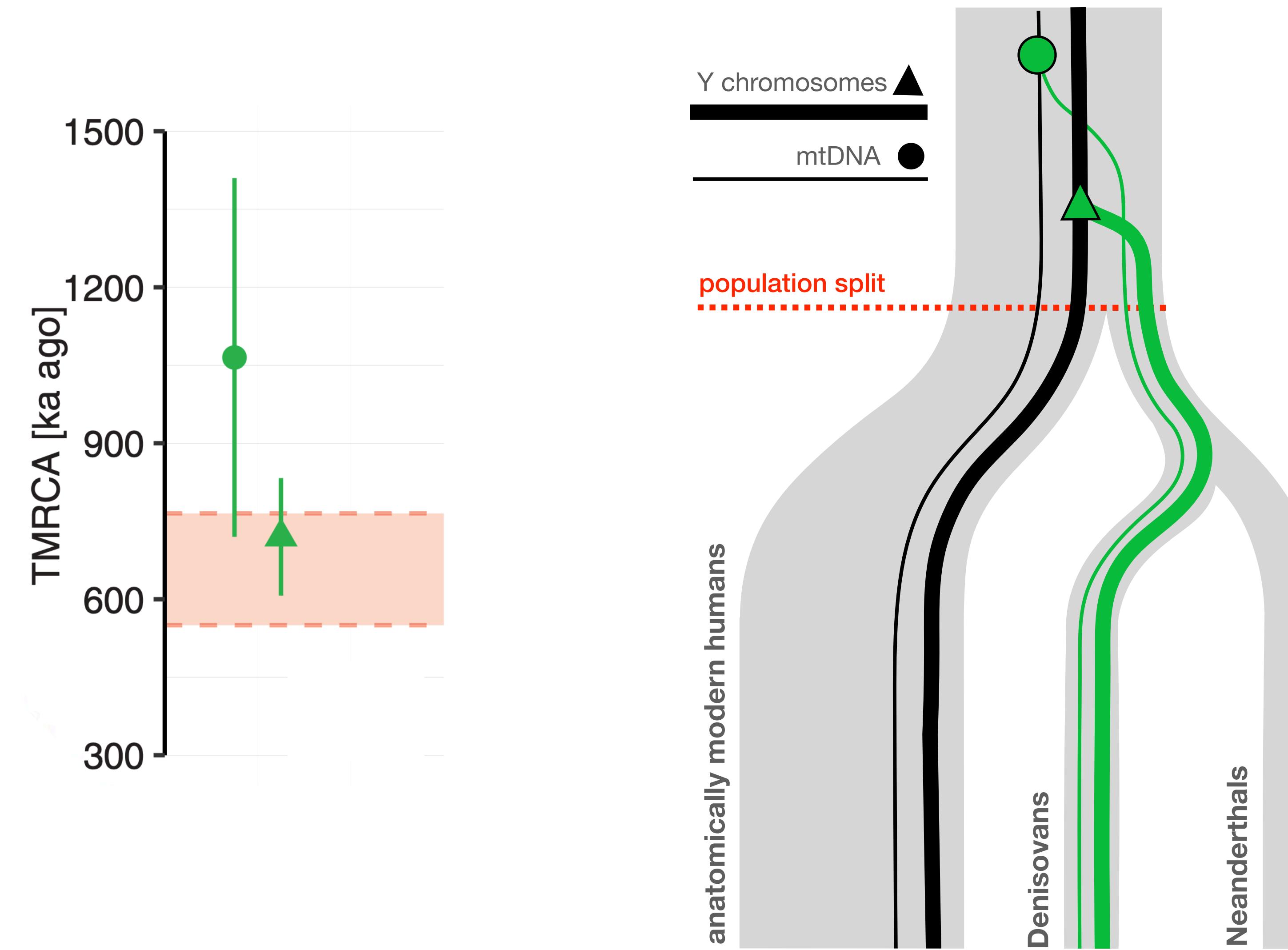
# Population history on a nuclear DNA level



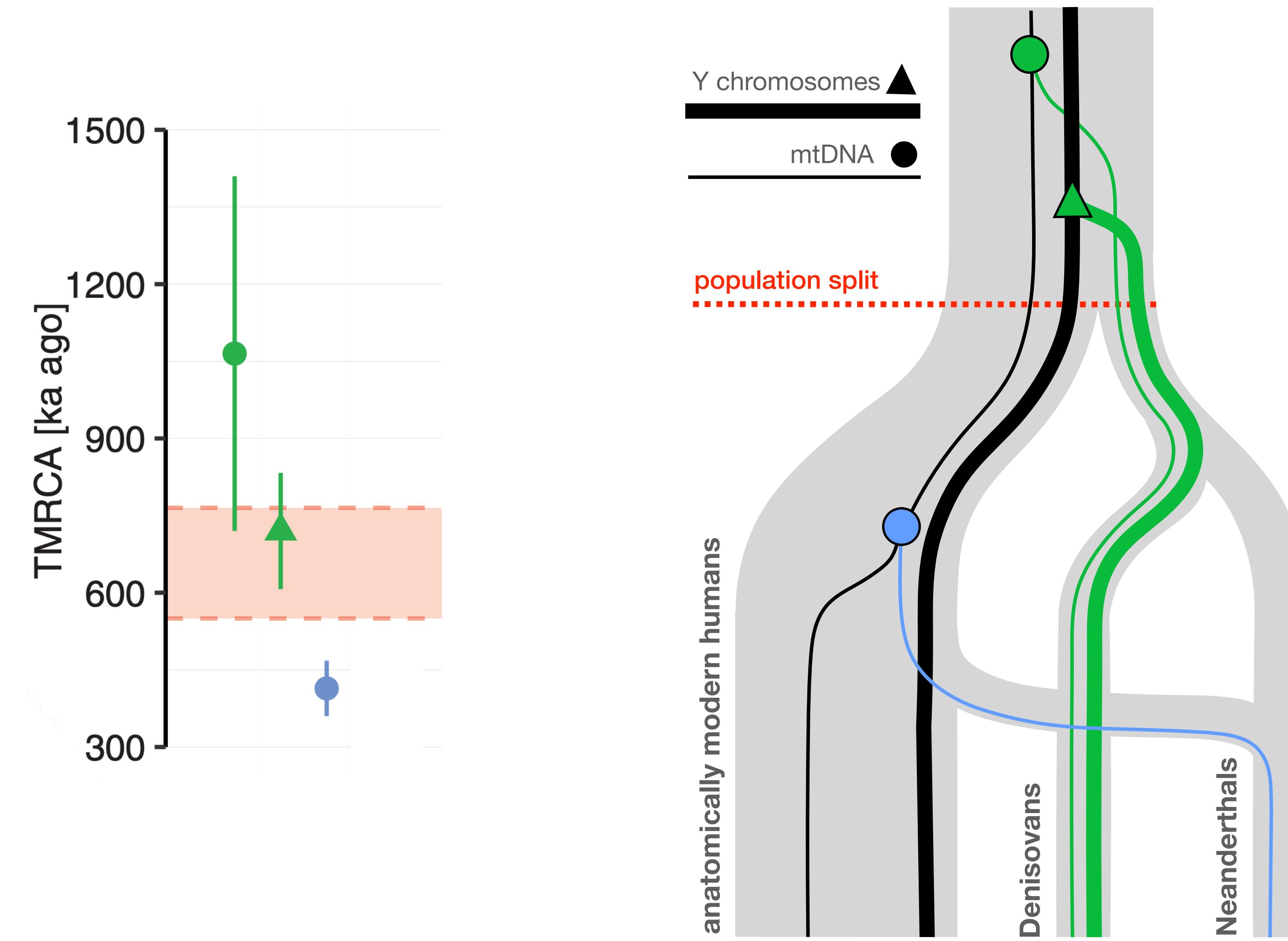
# Denisovan mt and Y DNA follow known population history



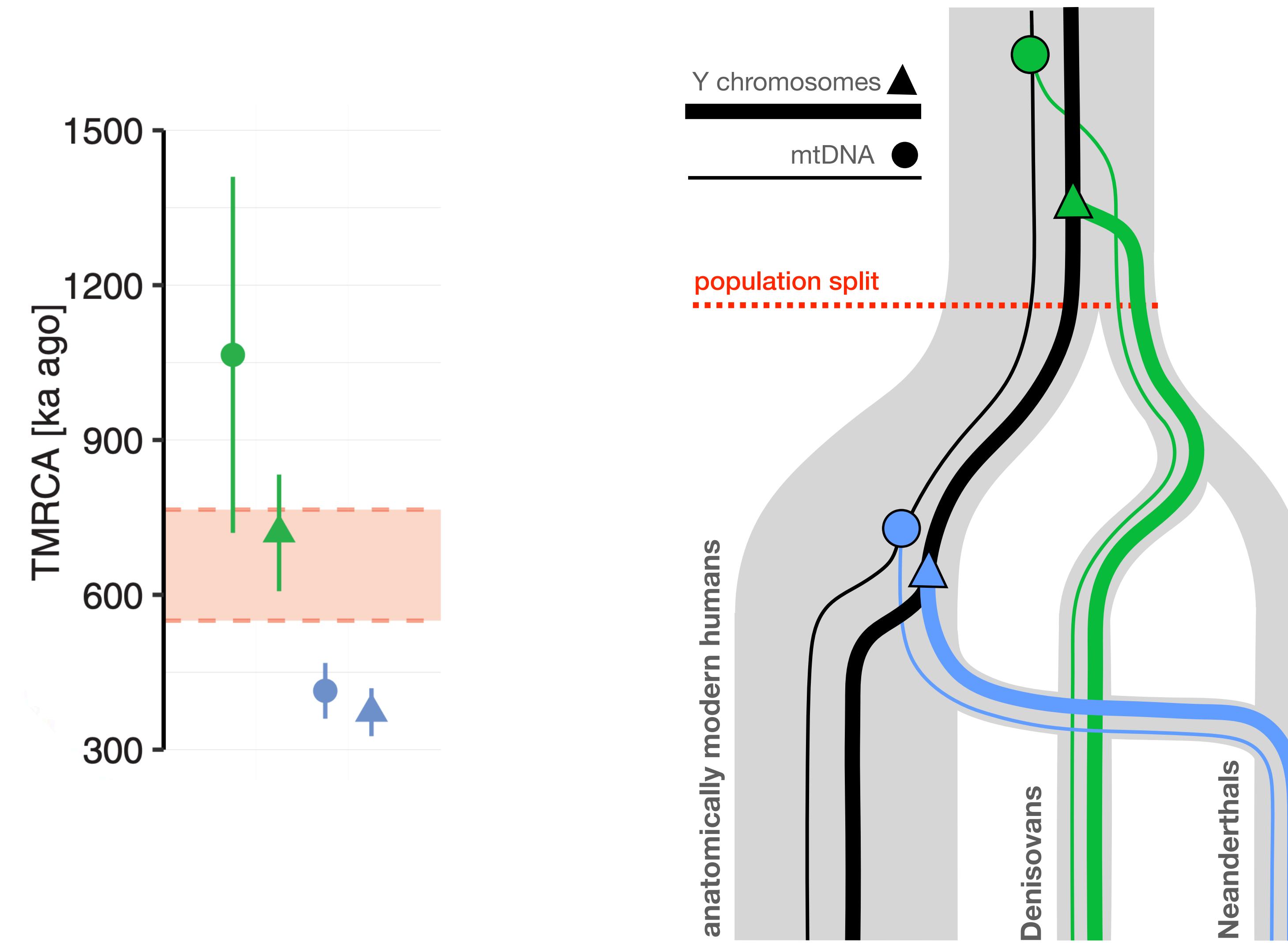
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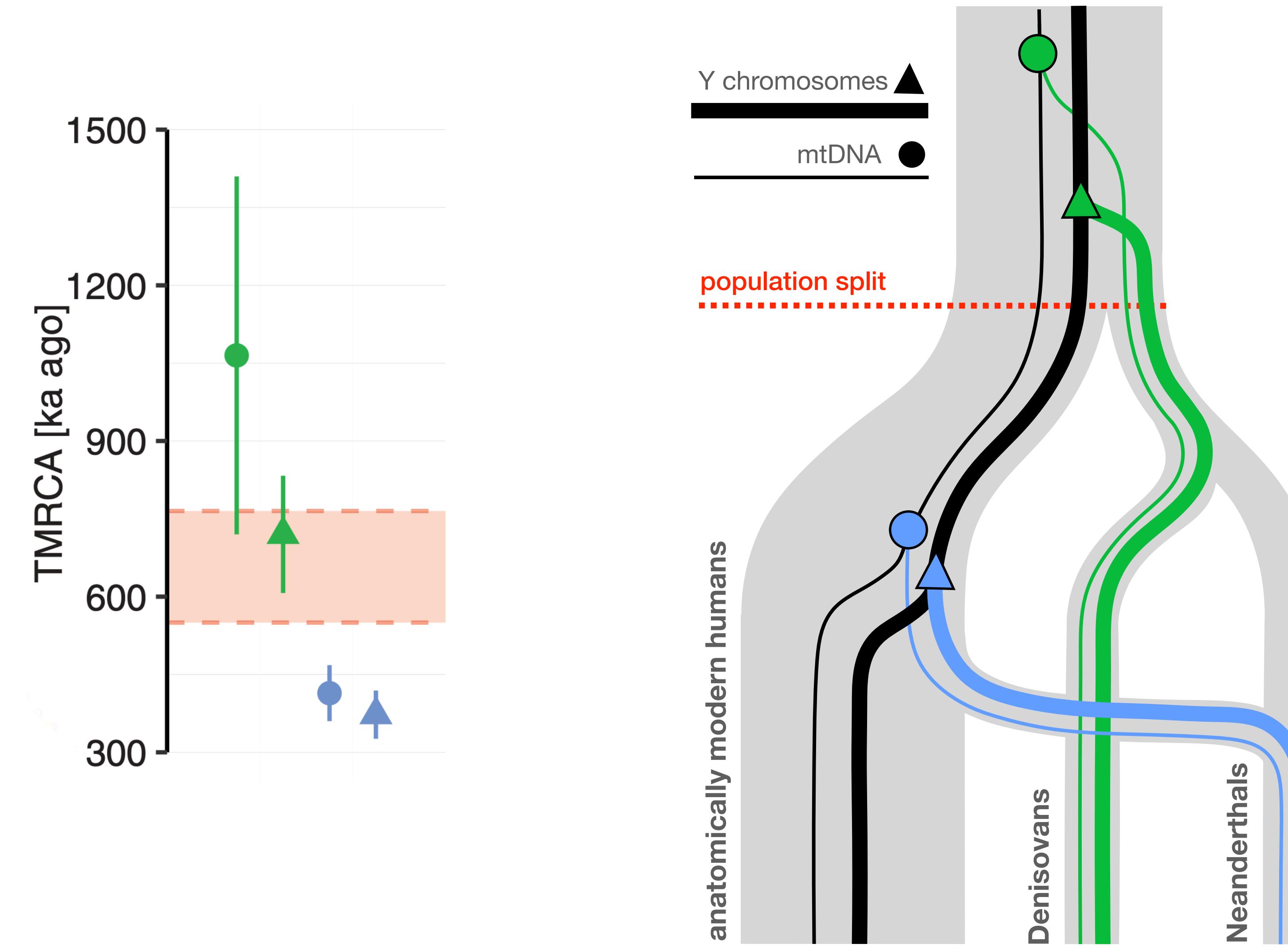
# Neanderthal mitochondrial DNAs contradict this!



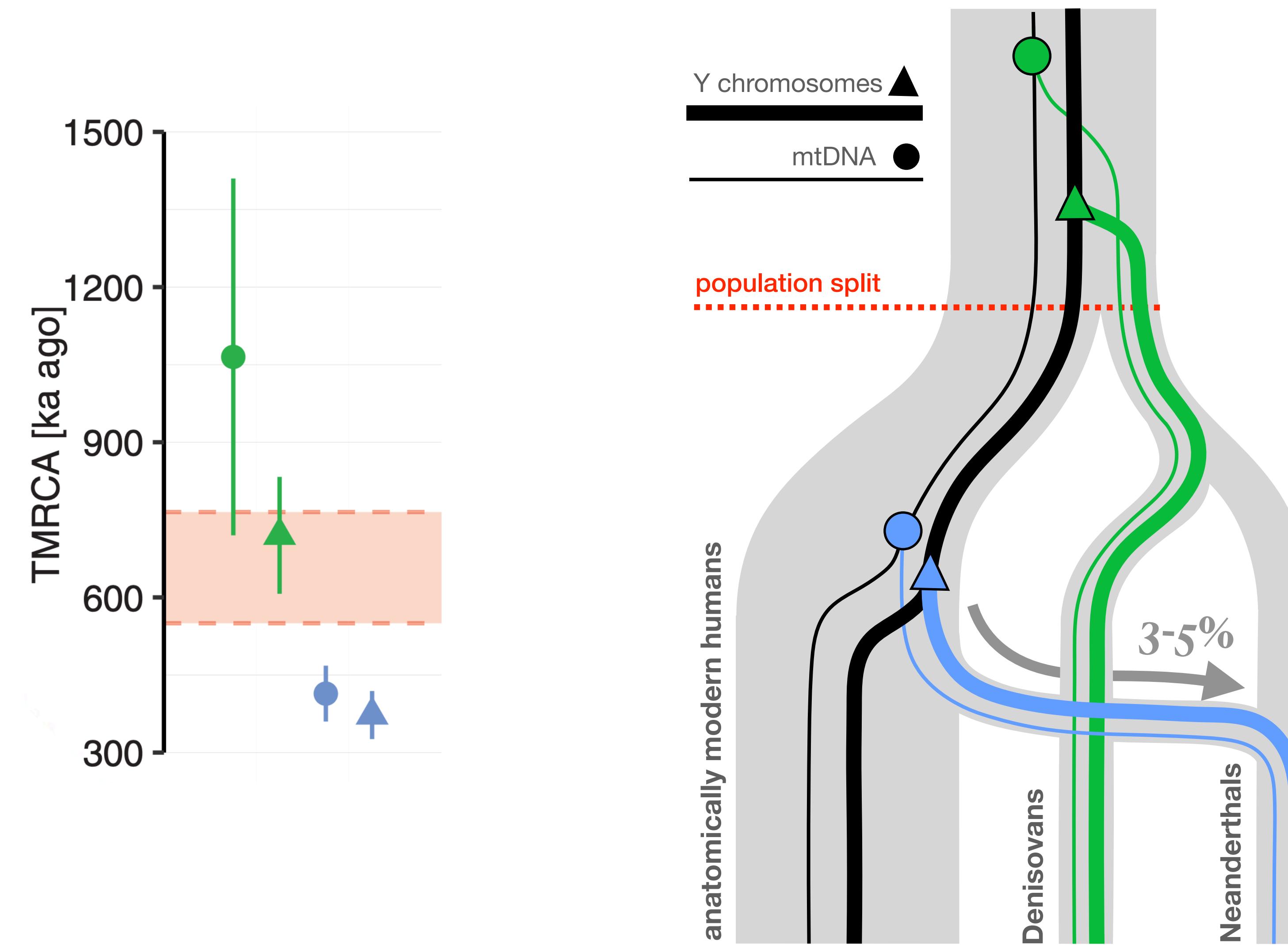
# Neanderthal Y chromosomes also contradict this!



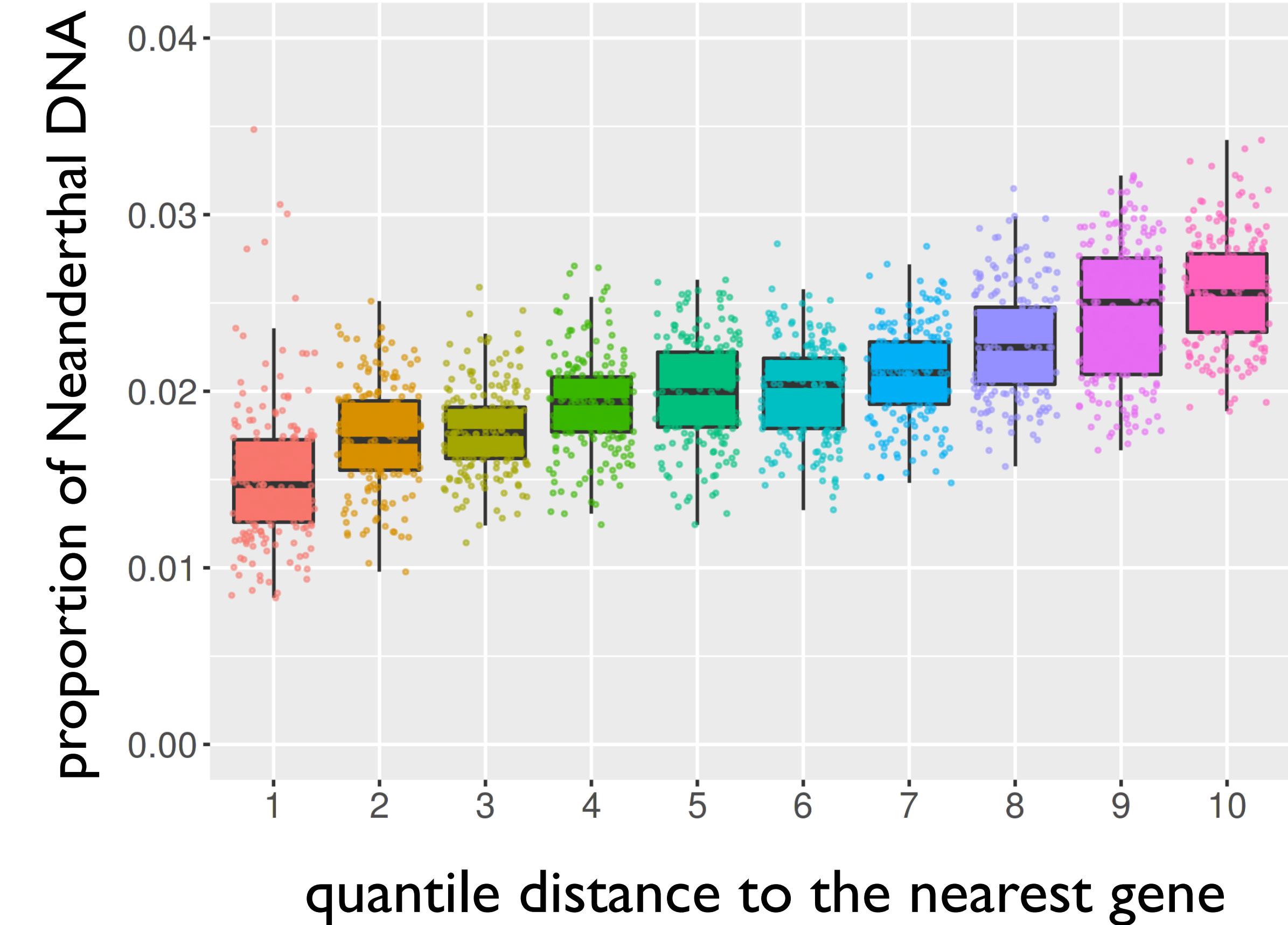
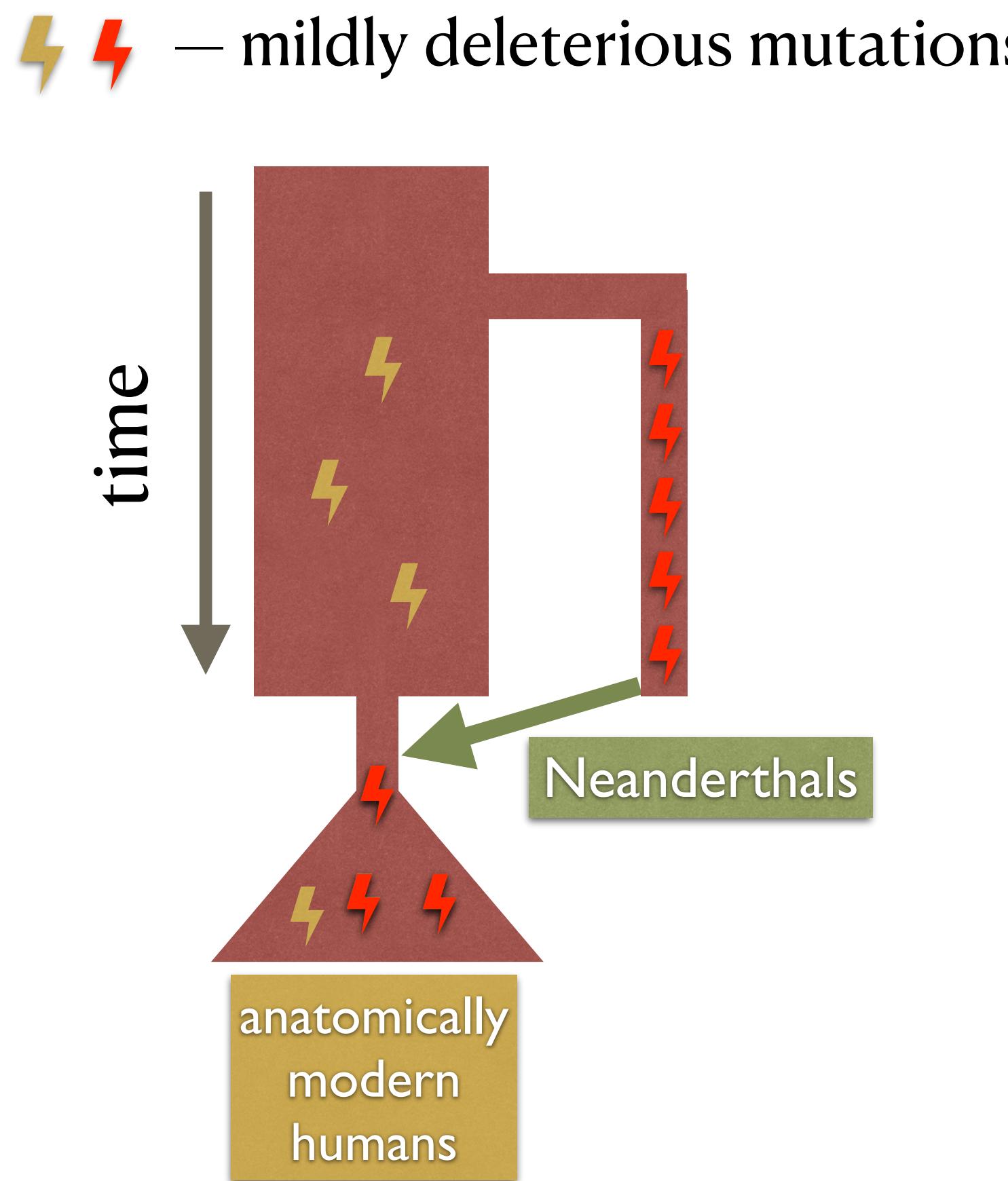
# Original Neanderthal mtDNA/Y experienced replacement



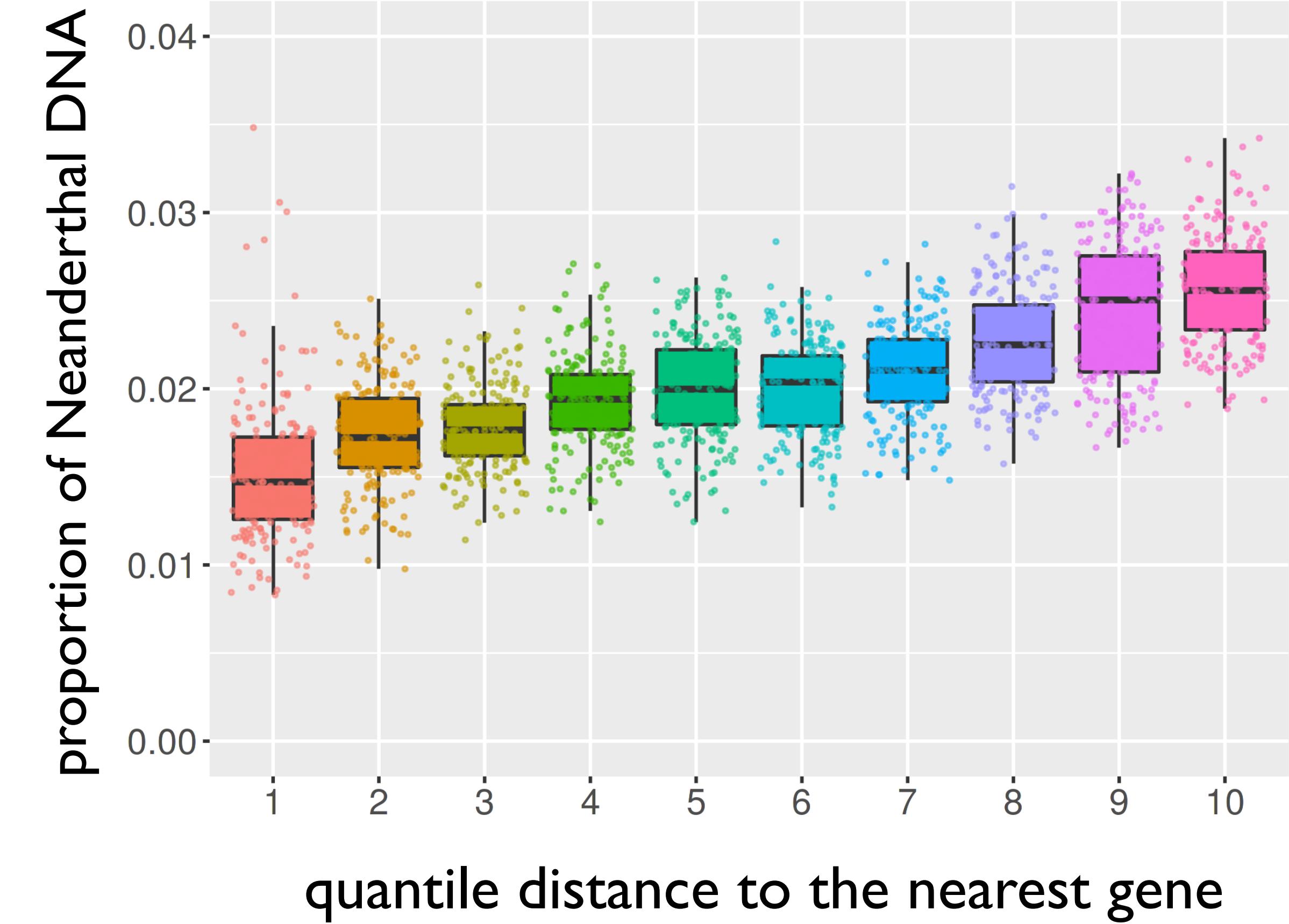
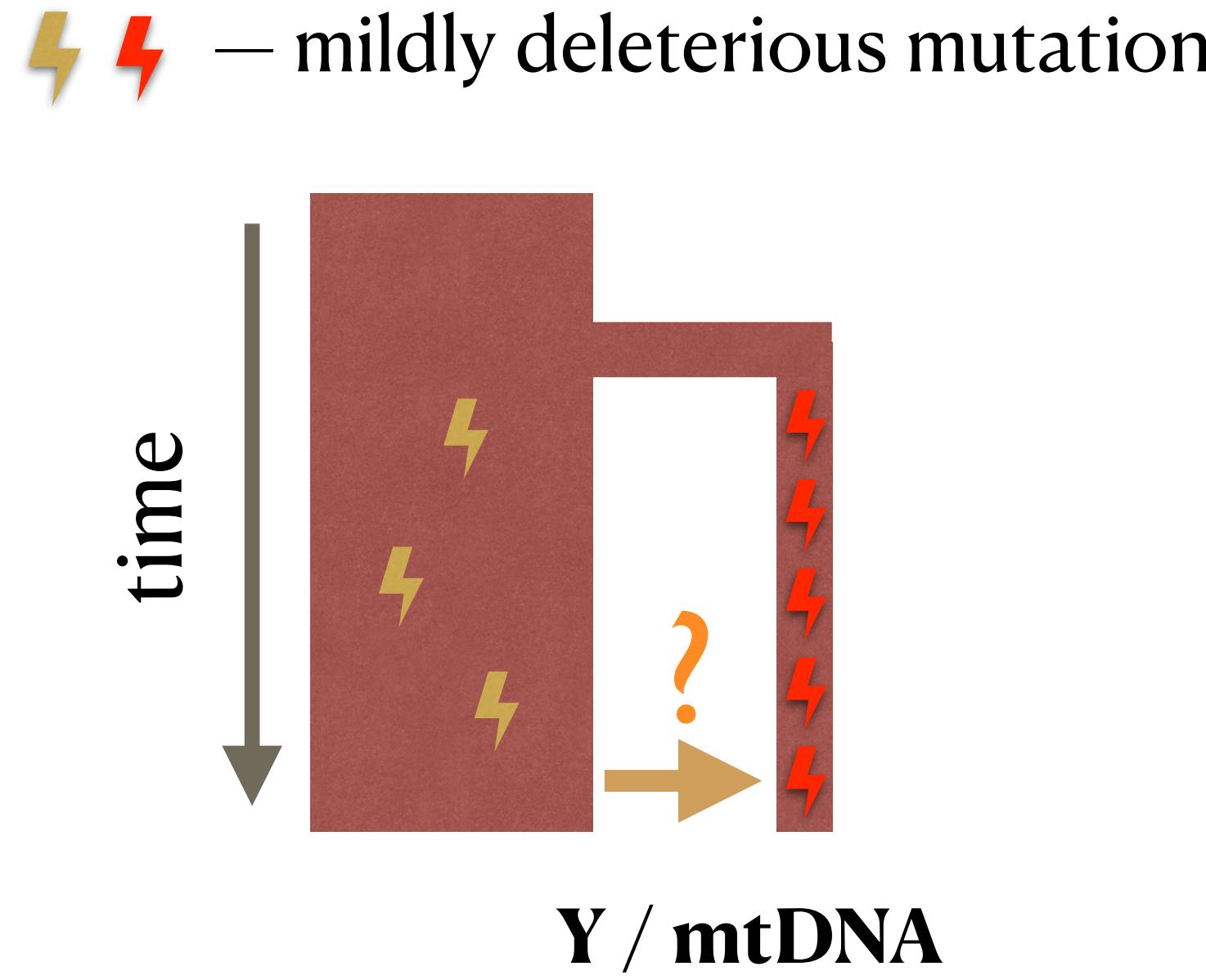
# Original Neanderthal mtDNA/Y experienced replacement (very unlikely under neutrality!)



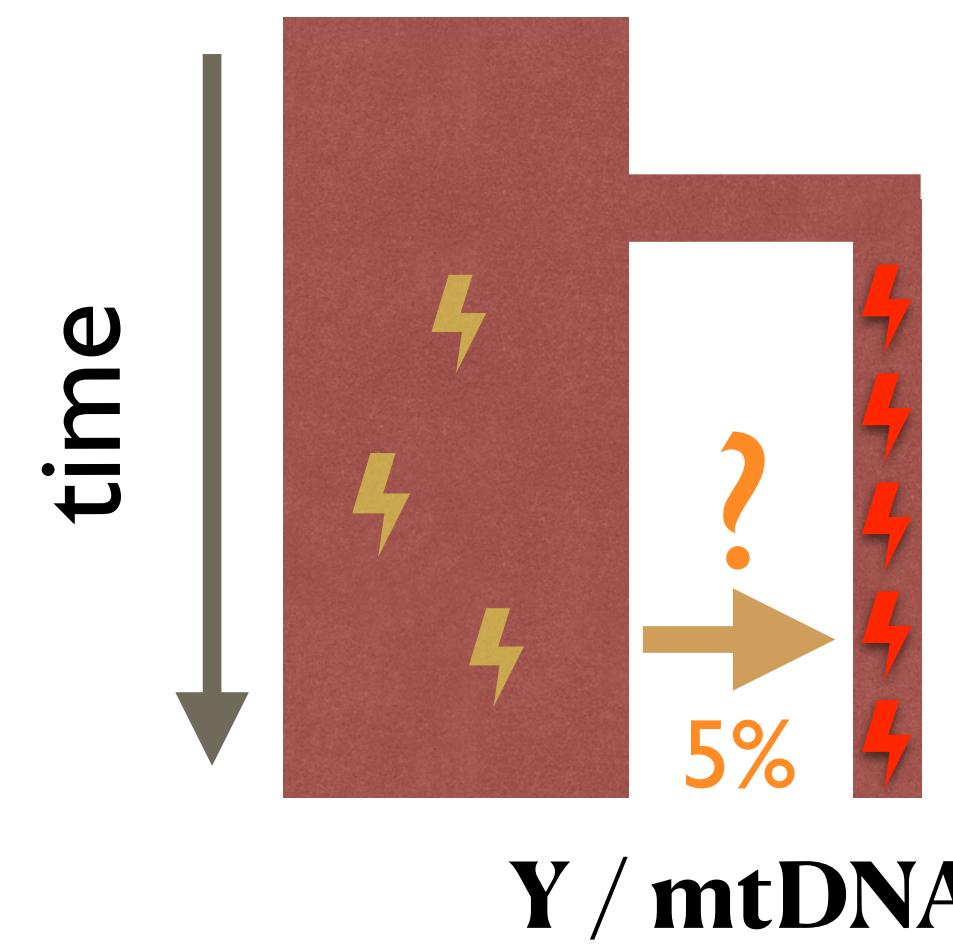
# ...but we know introgression was not neutral!



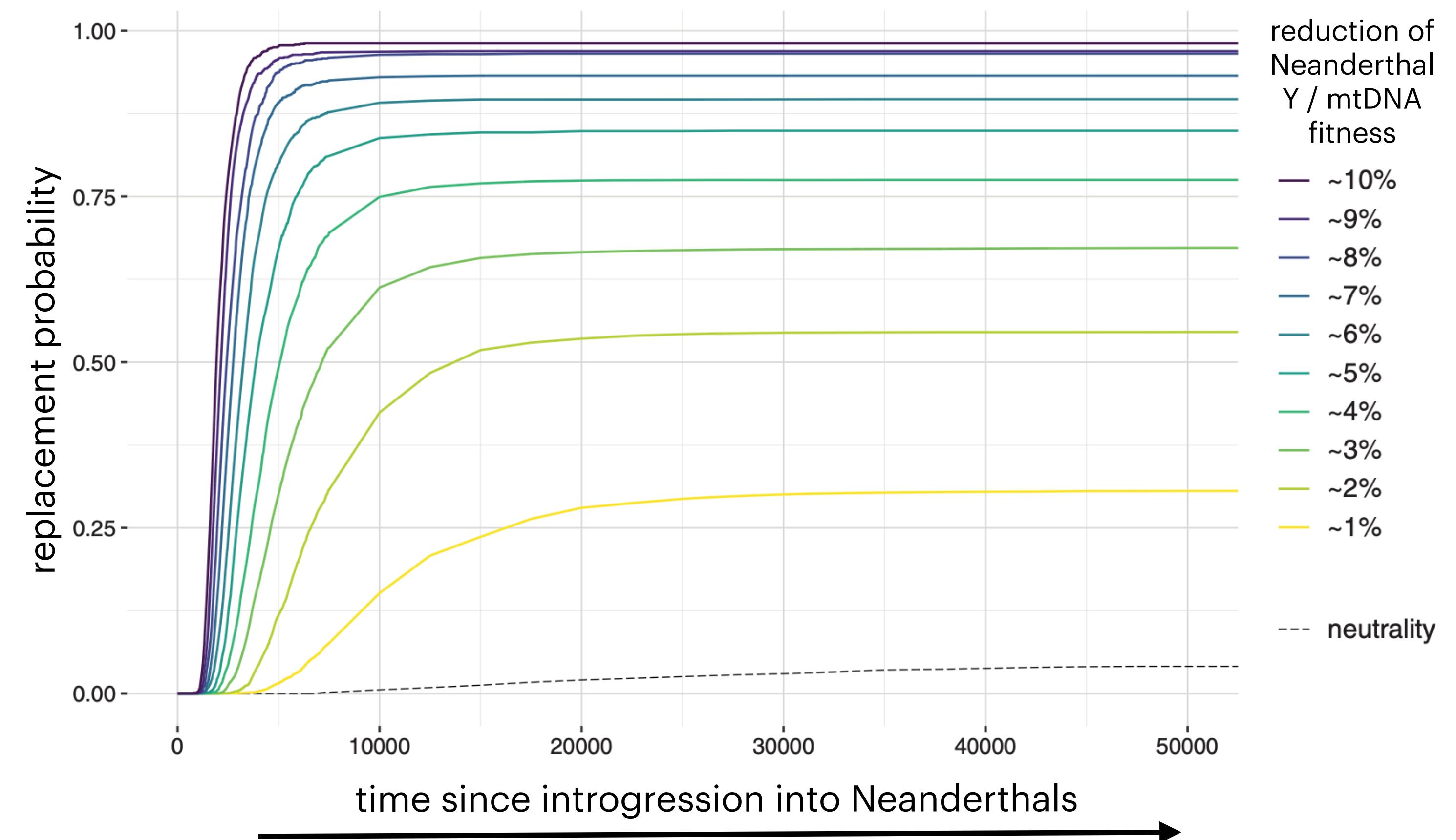
# What is the expected scenario for Y / mtDNA introgression?



# Natural selection in Neanderthals favors modern human Y / mtDNA



**Simulation of 5% gene flow from modern humans**

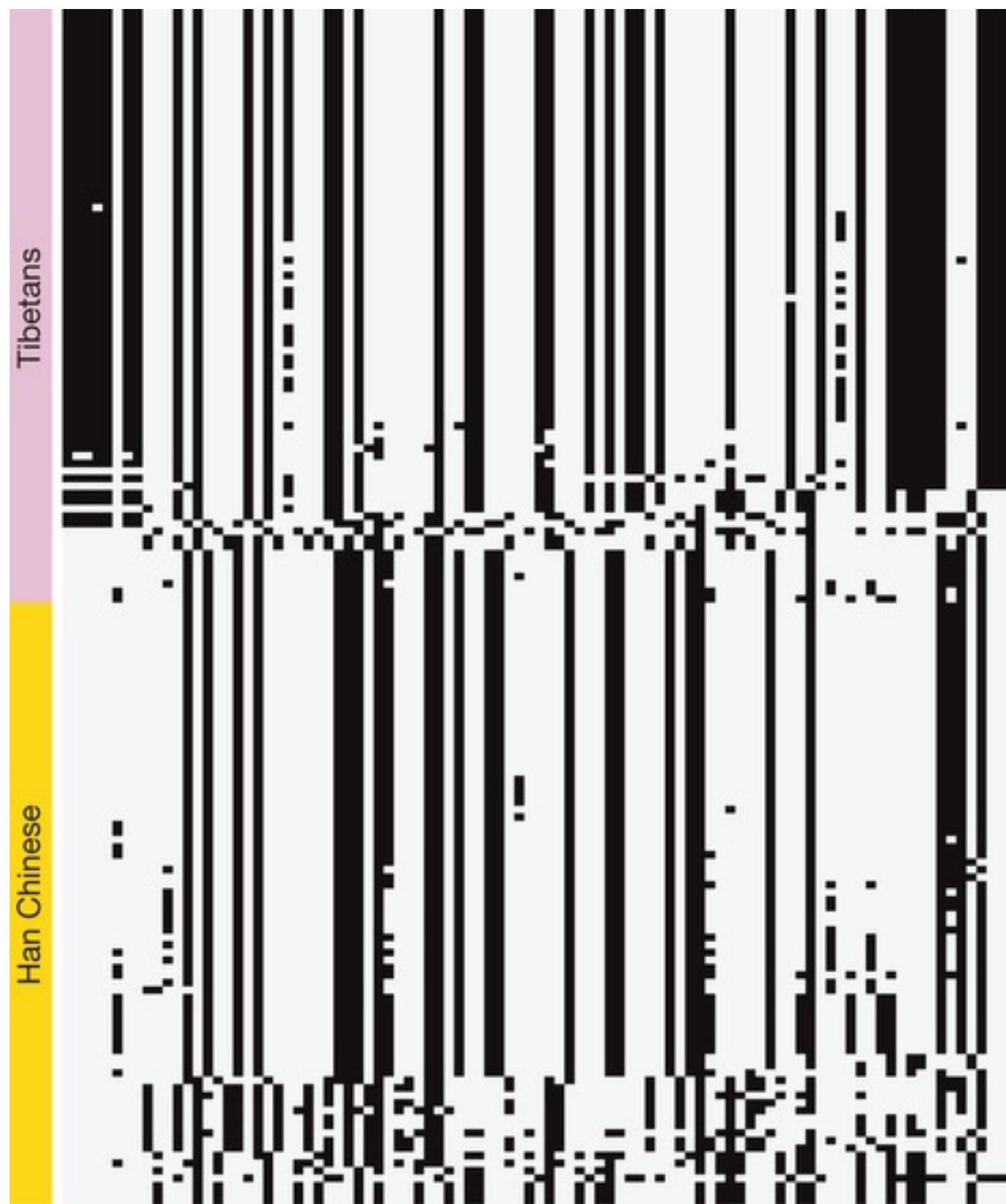


**It wasn't all bad though**

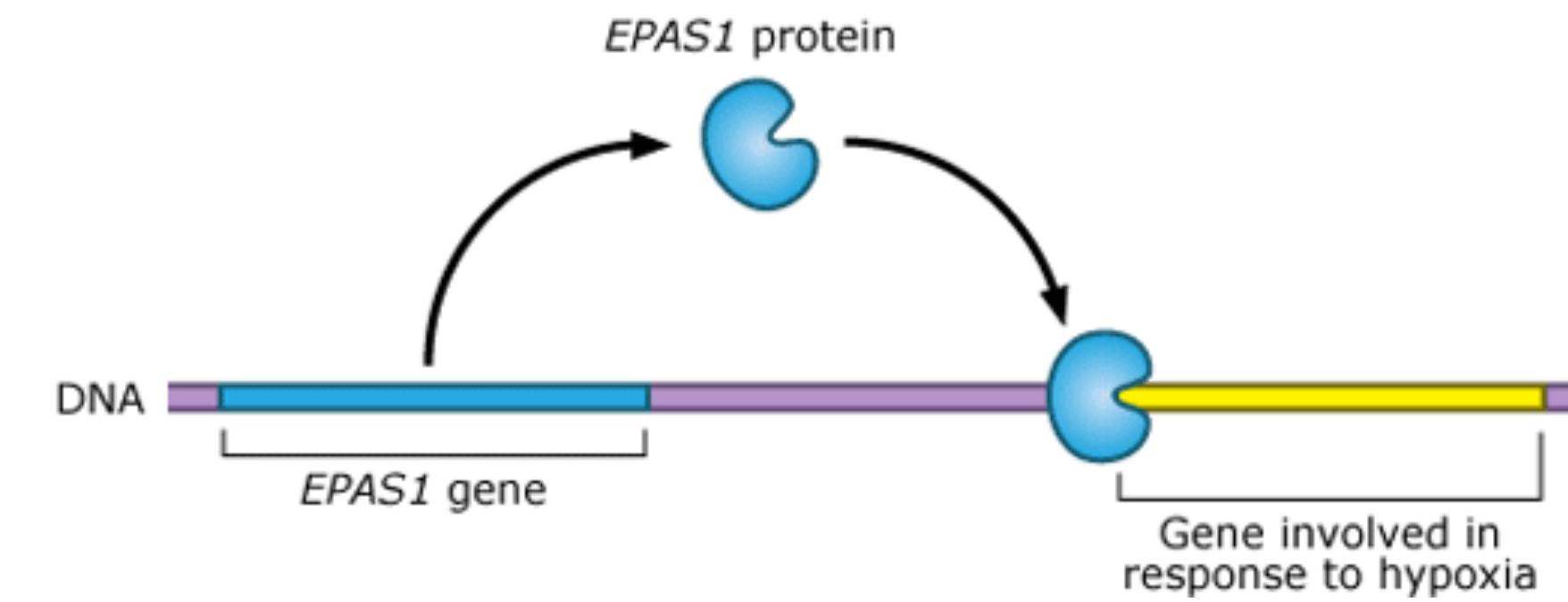
**positive selection / adaptive introgression**

# High altitude adaptation in Tibetans

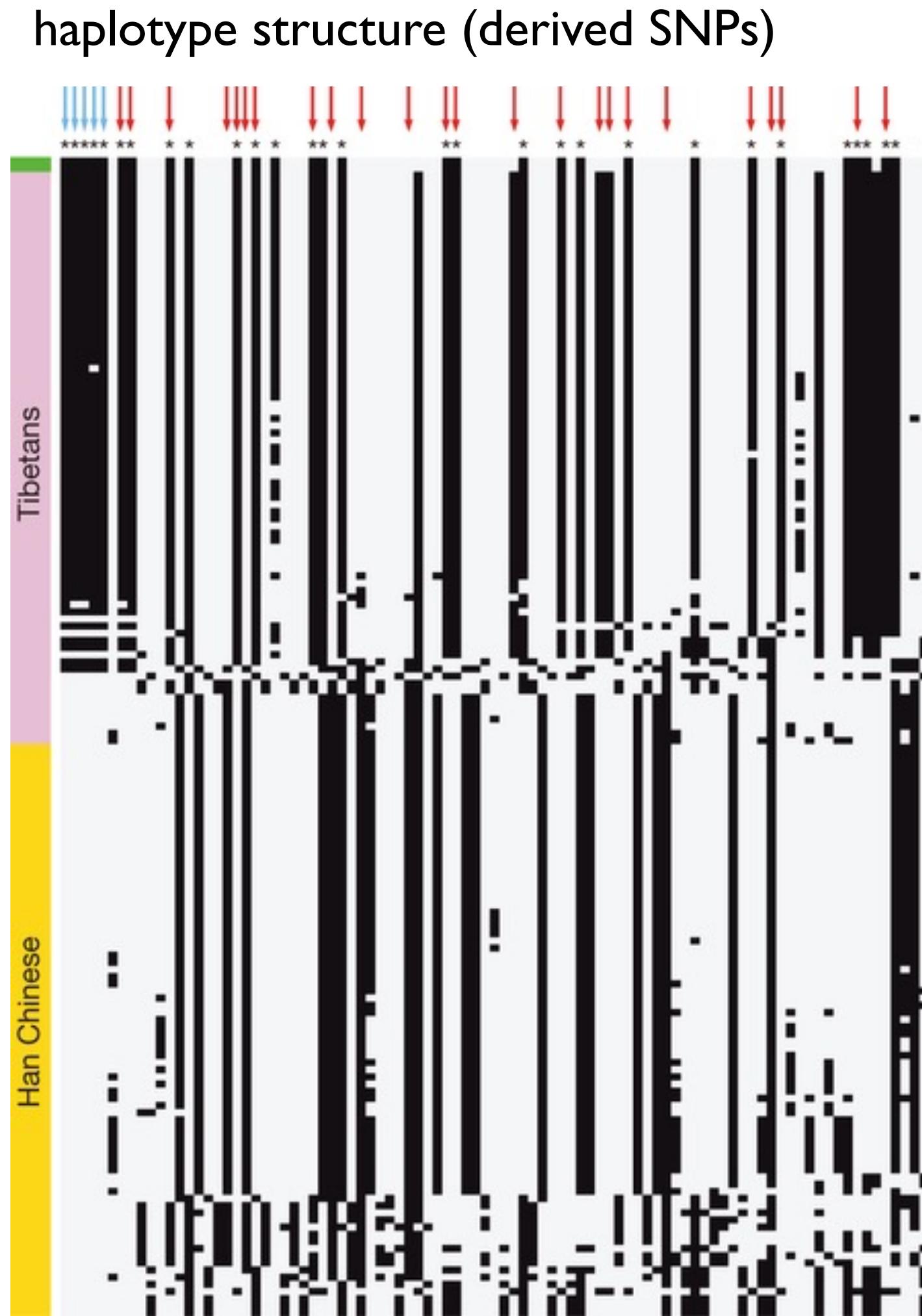
haplotype structure (derived SNPs)



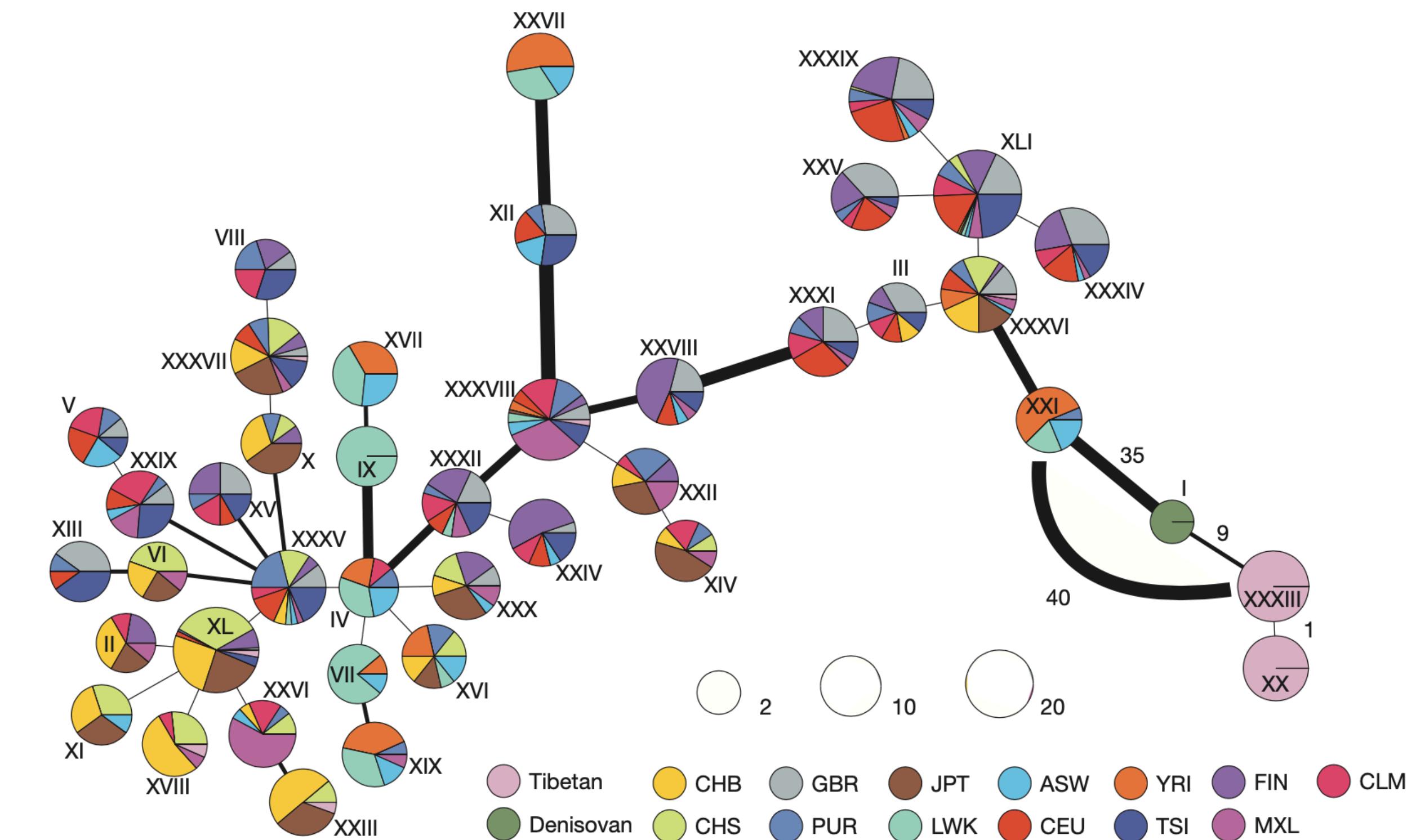
Schematic of *EPAS1* function



# High altitude adaptation via Denisovan introgression!



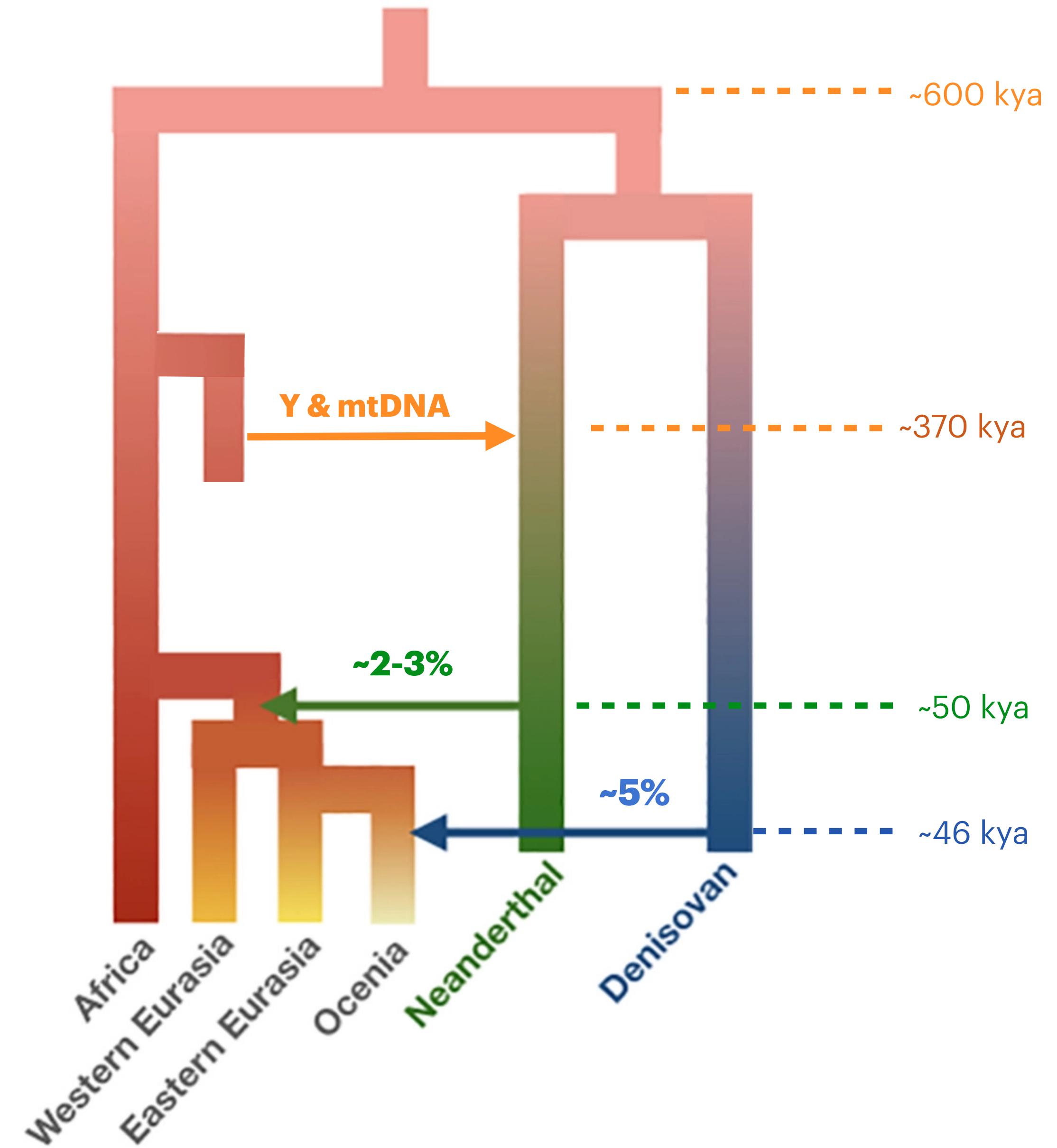
haplotype network based on pairwise-differences



**Introgression has been a very frequent occurrence throughout human history.**

**Introgressed DNA can have a strong impact on the biology of “recipient populations” (not just negative!).**

**Population genetic simulations critical for testing evolutionary hypotheses.**



adapted from the Yearbook of Physical Anthropology (2019) by Gokcumen



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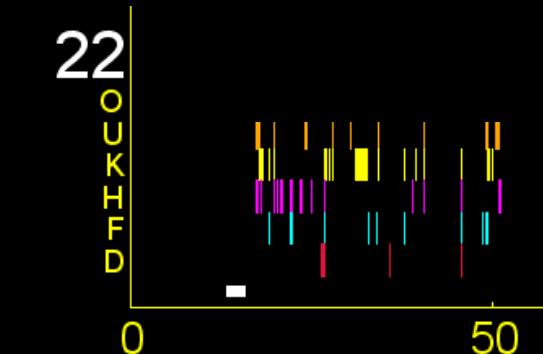
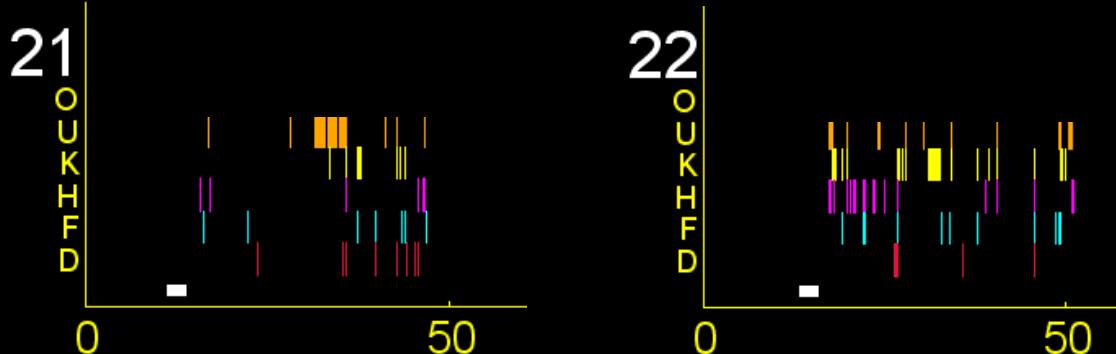
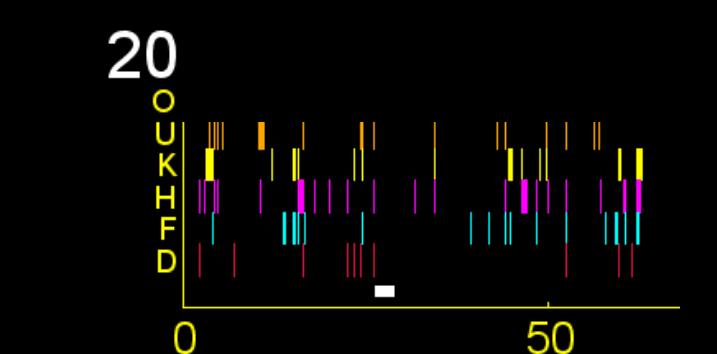
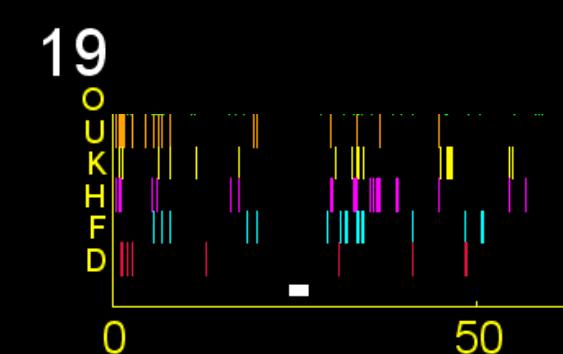
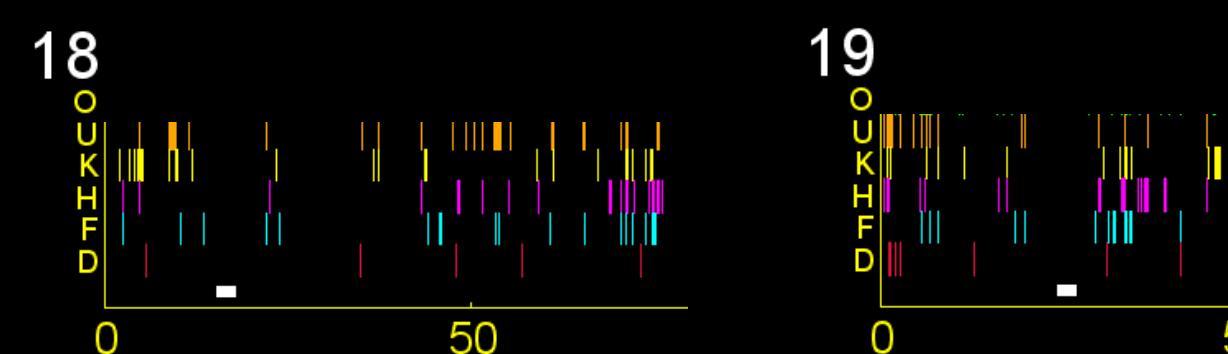
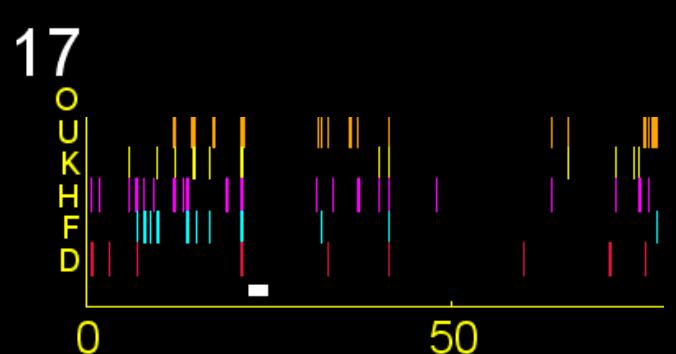
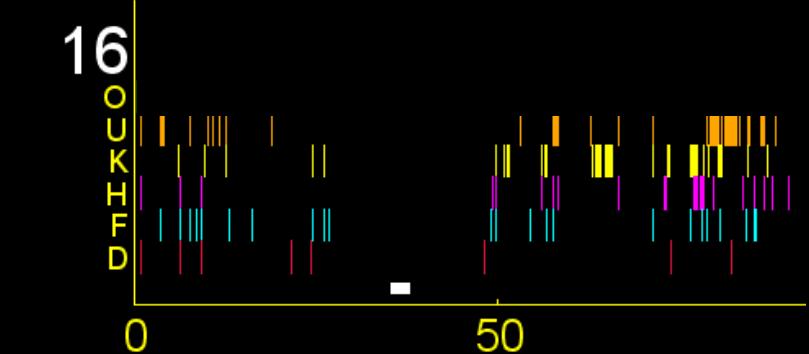
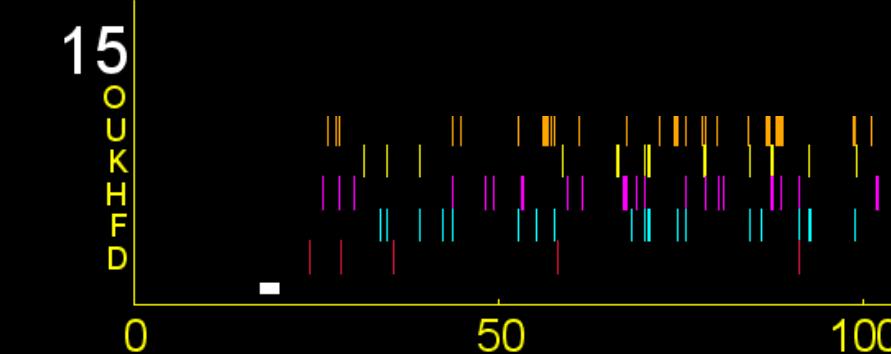
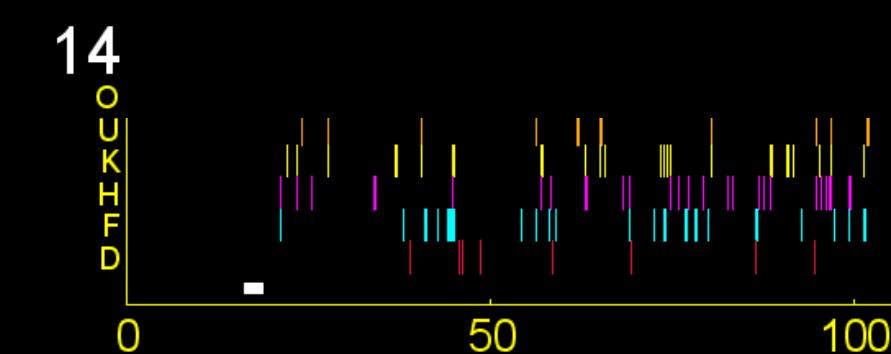
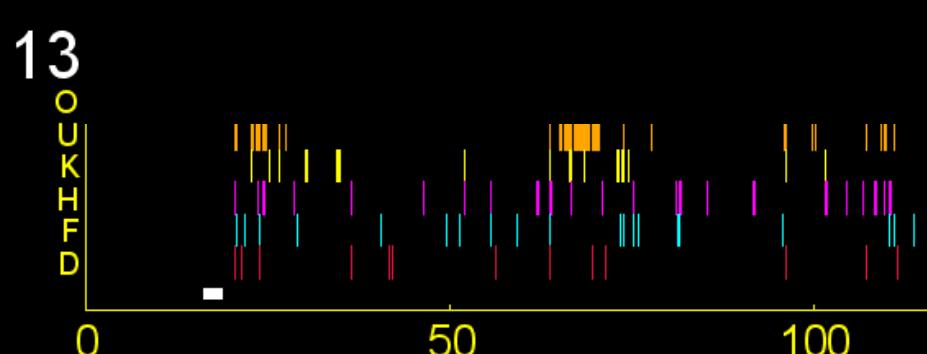
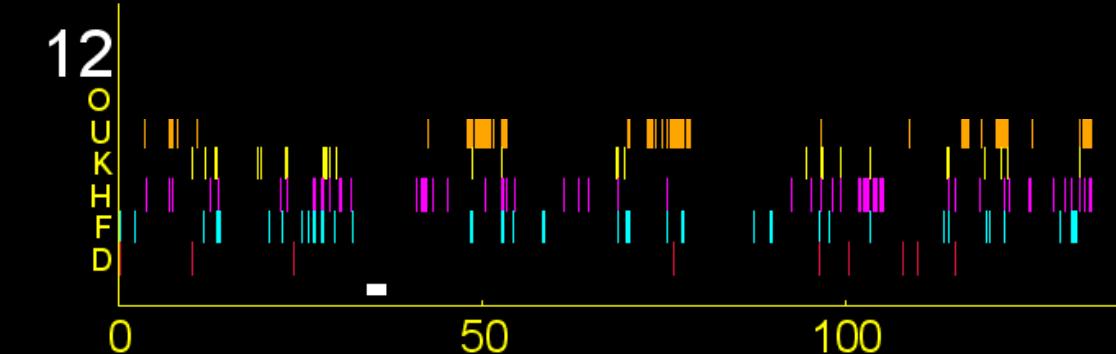
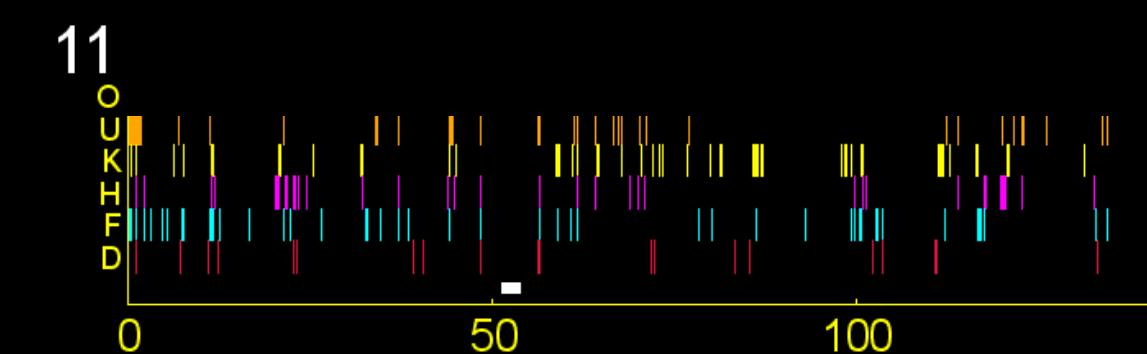
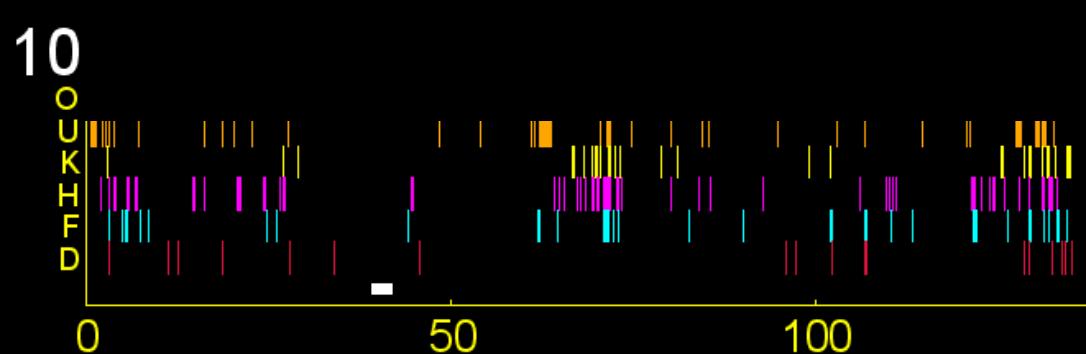
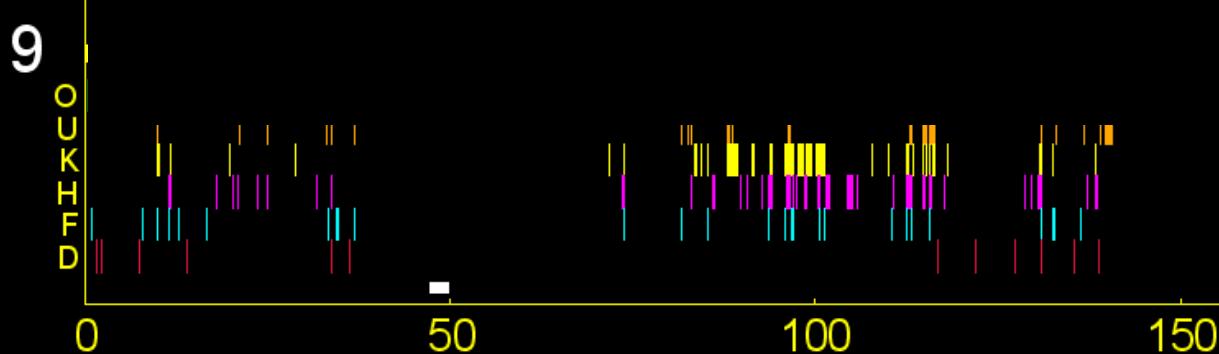
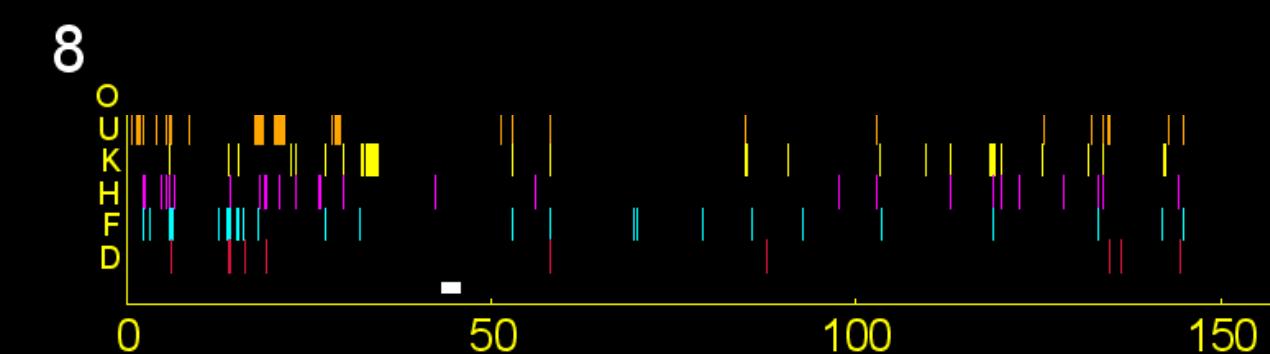
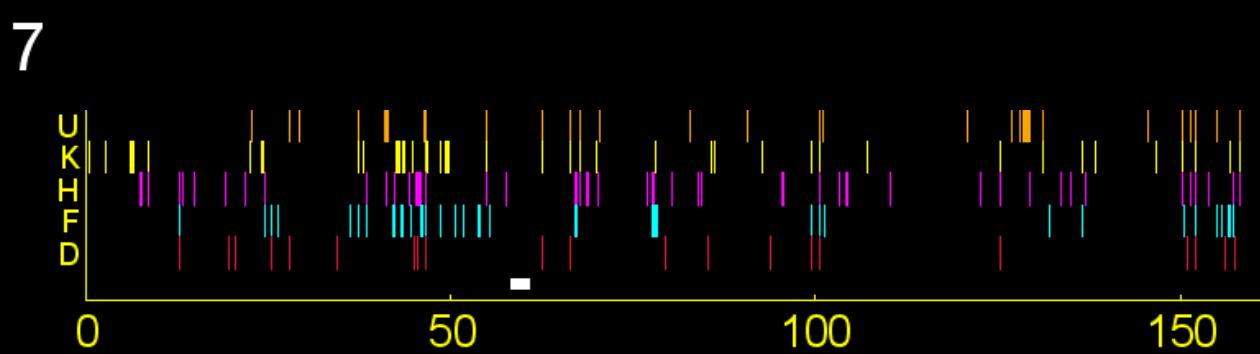
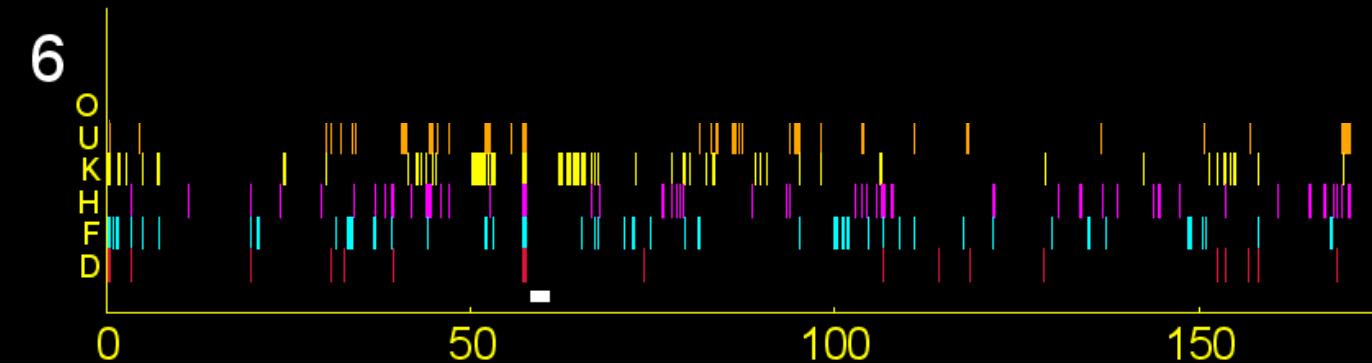
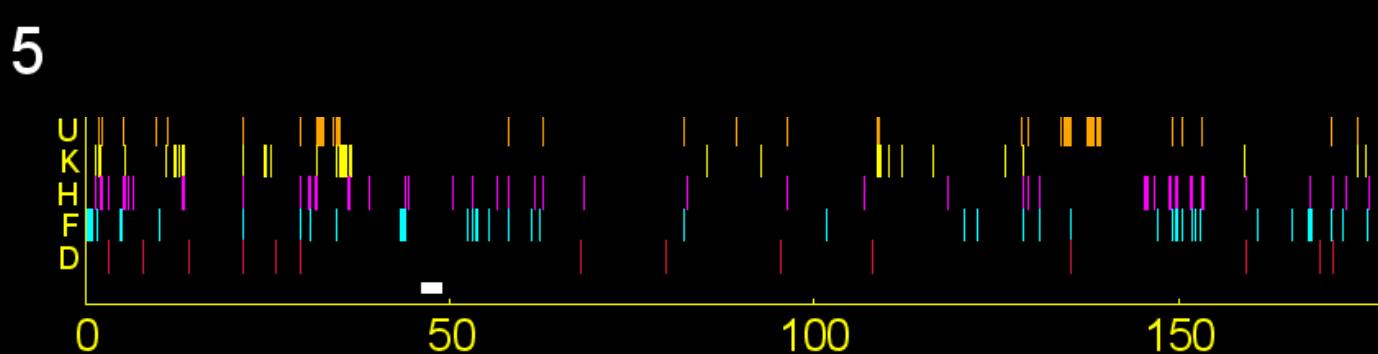
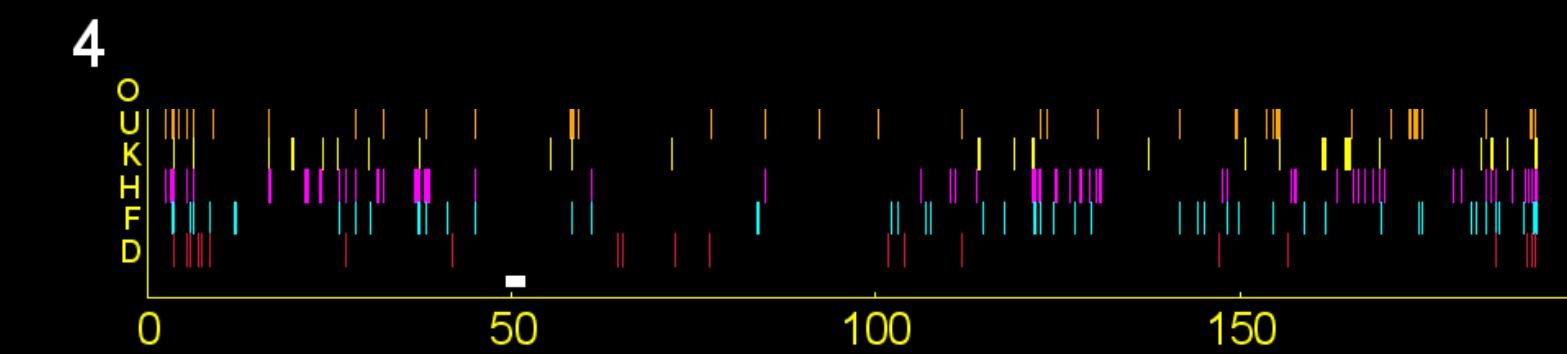
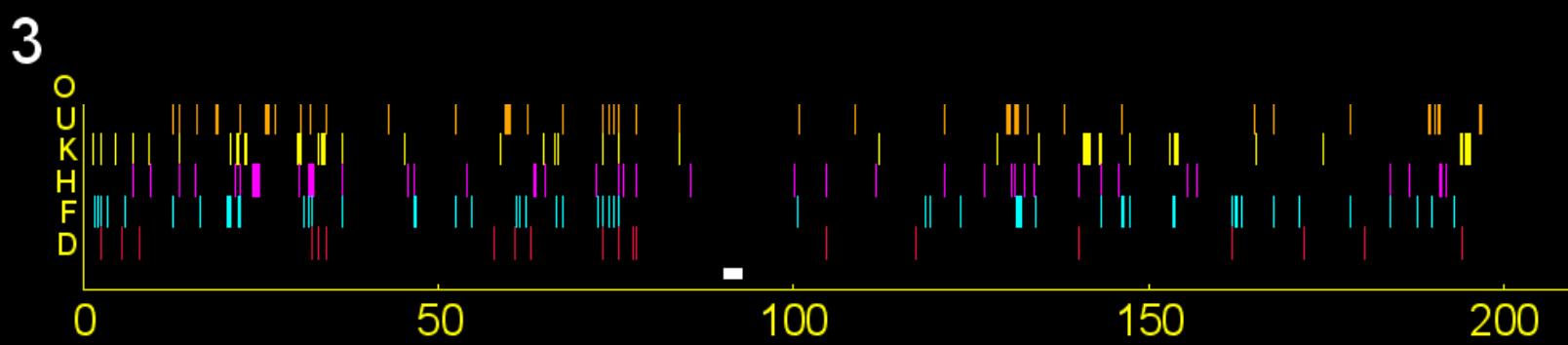
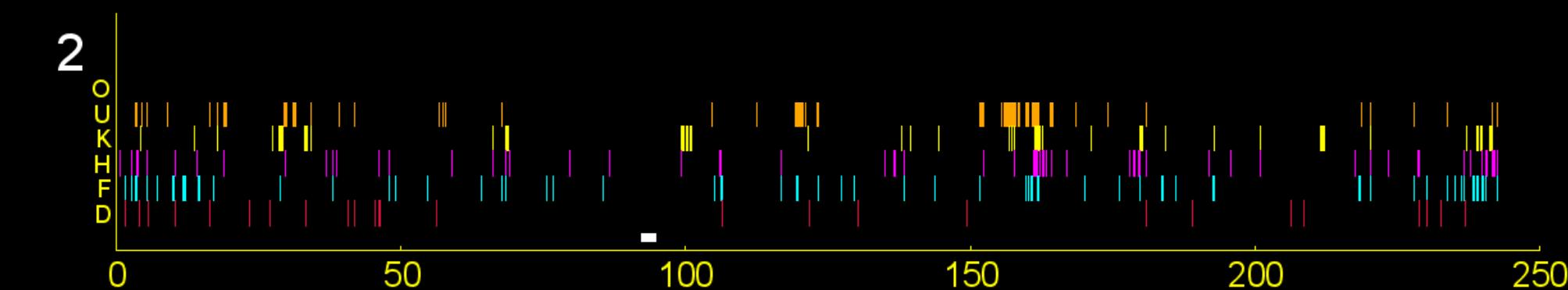
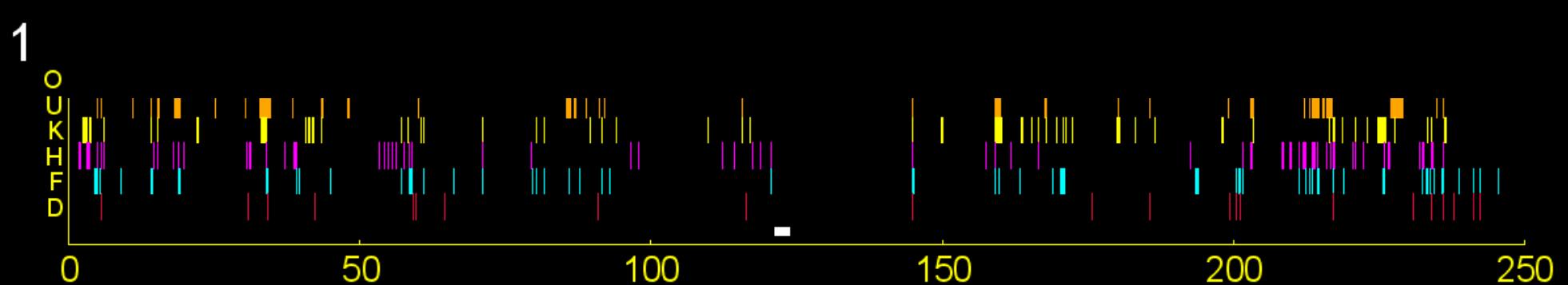


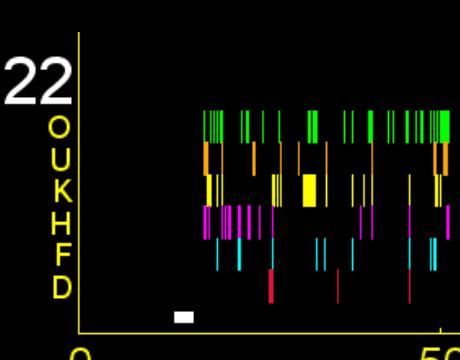
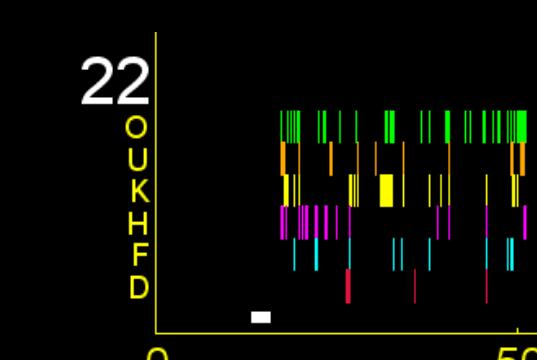
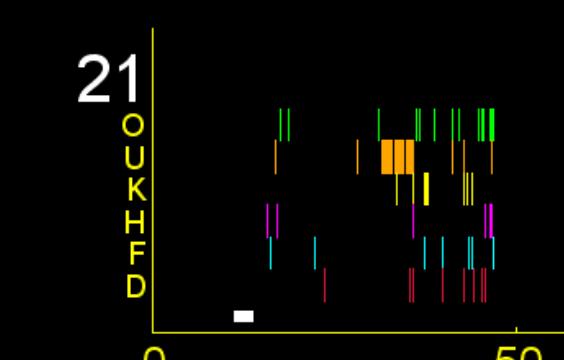
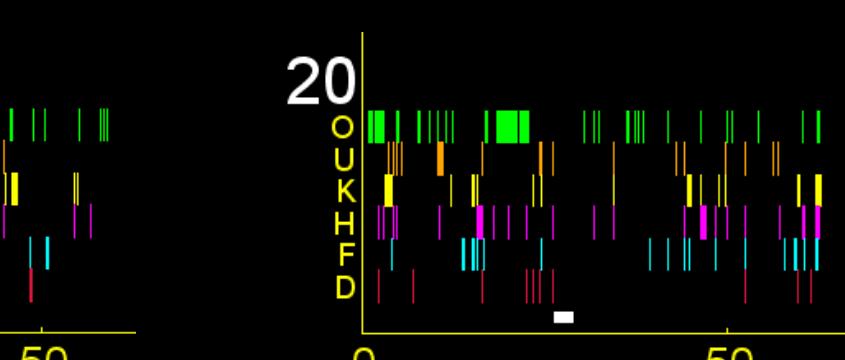
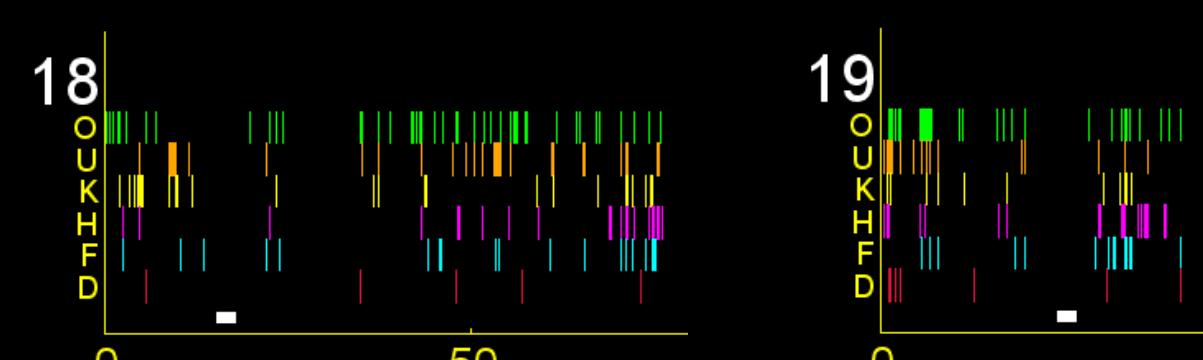
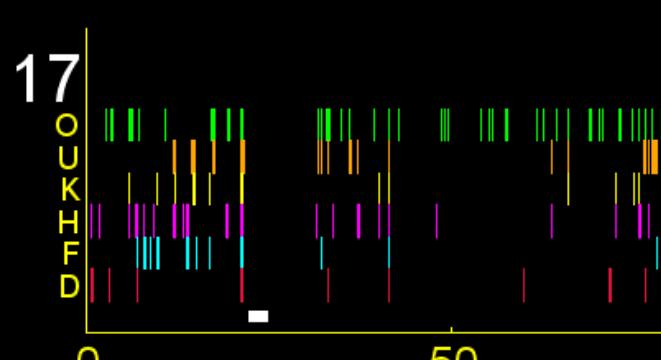
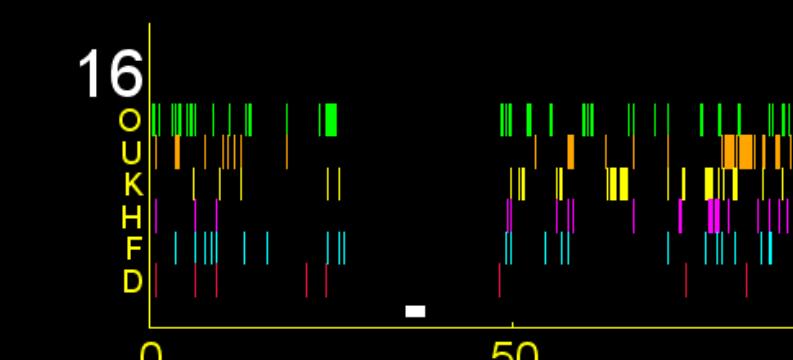
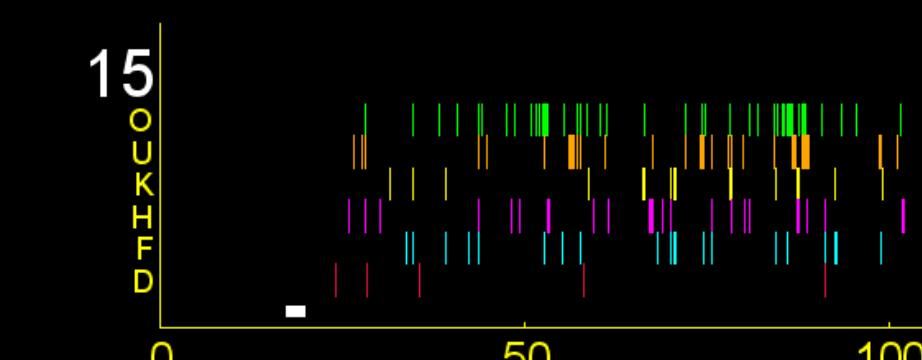
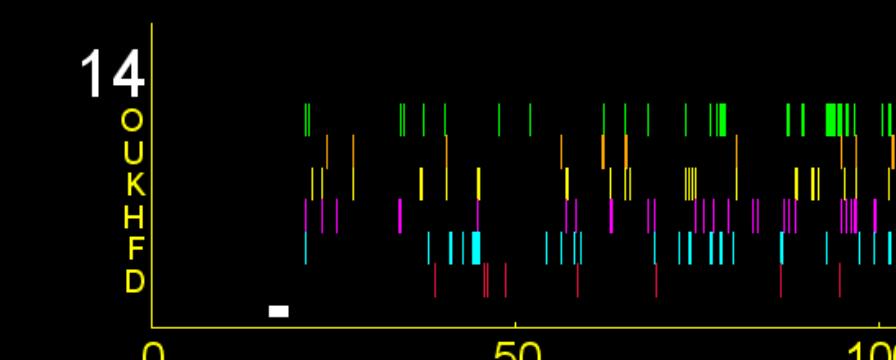
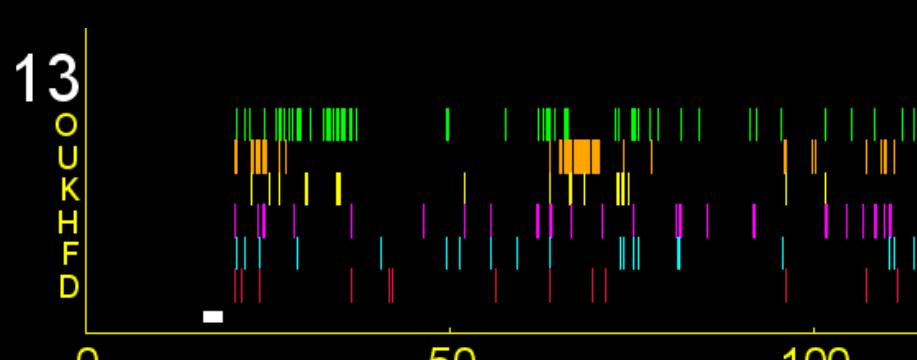
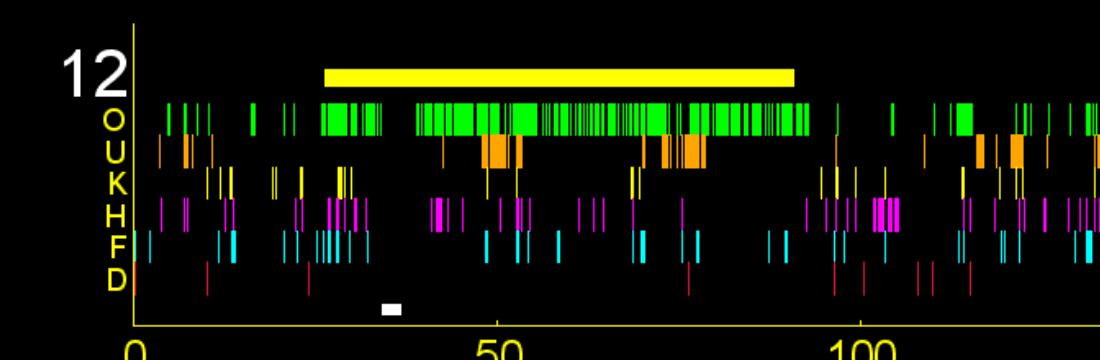
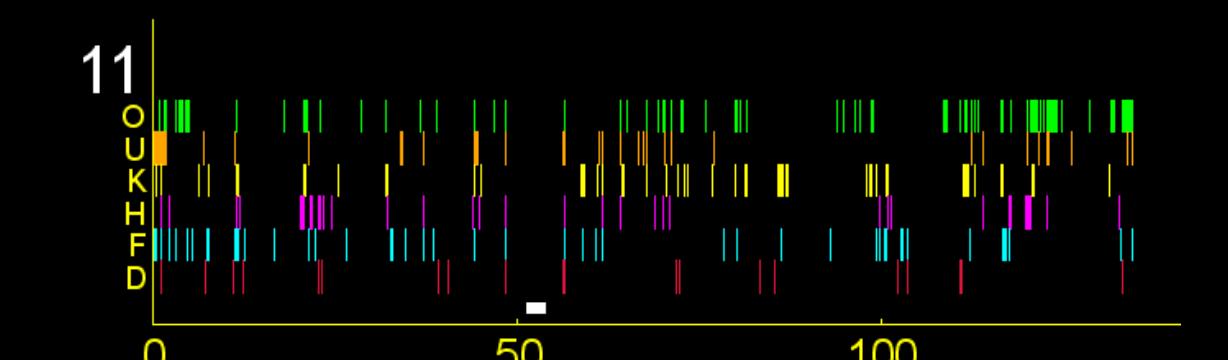
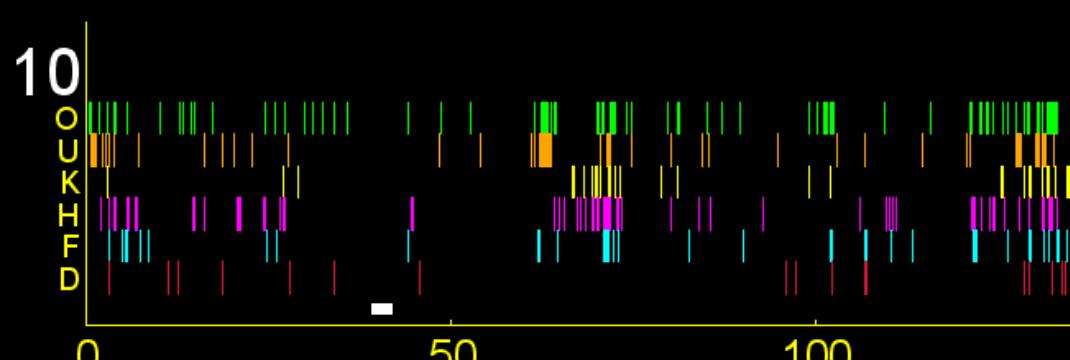
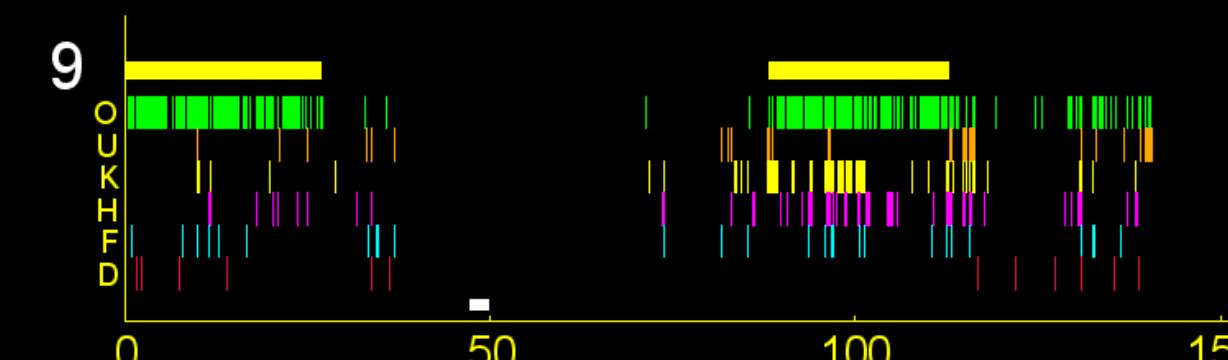
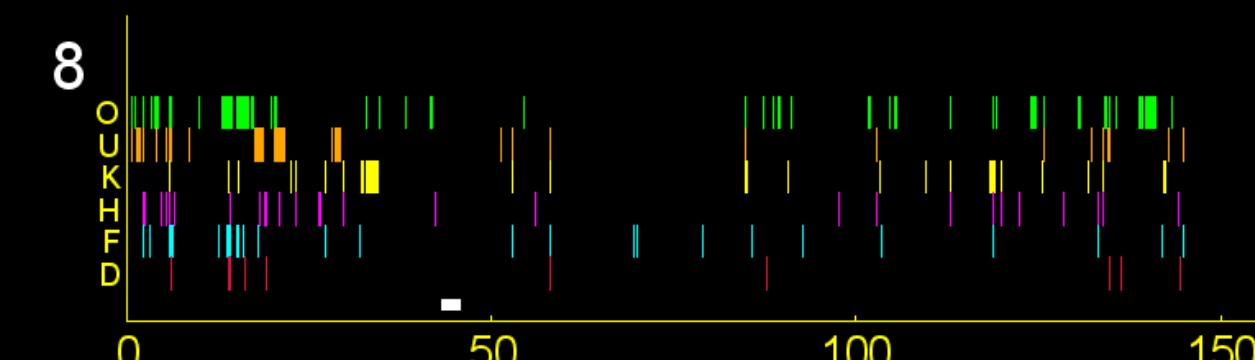
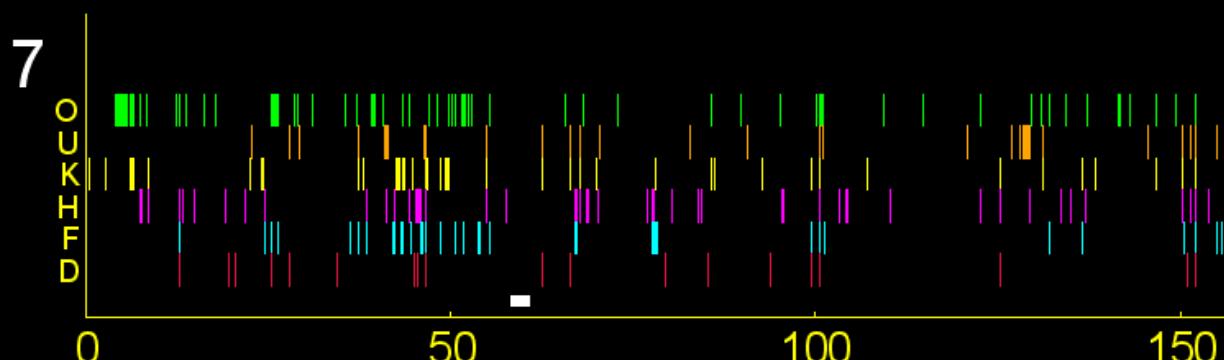
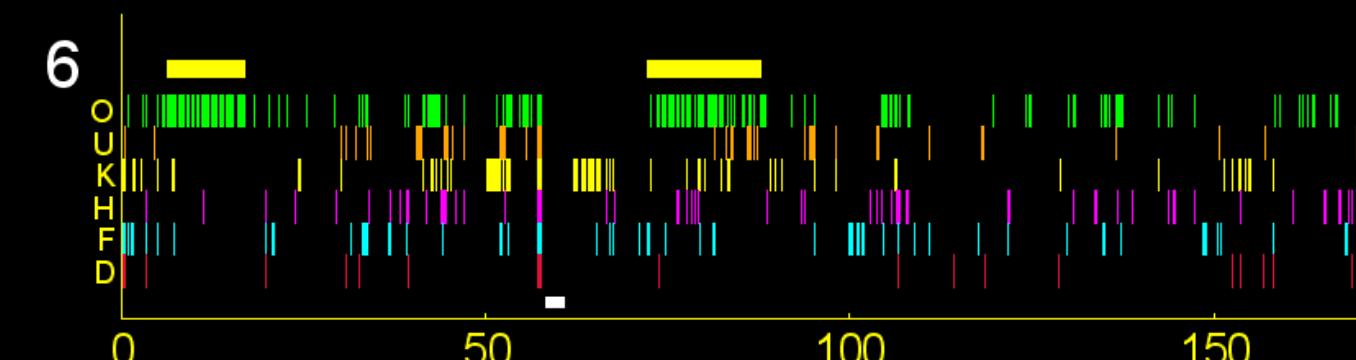
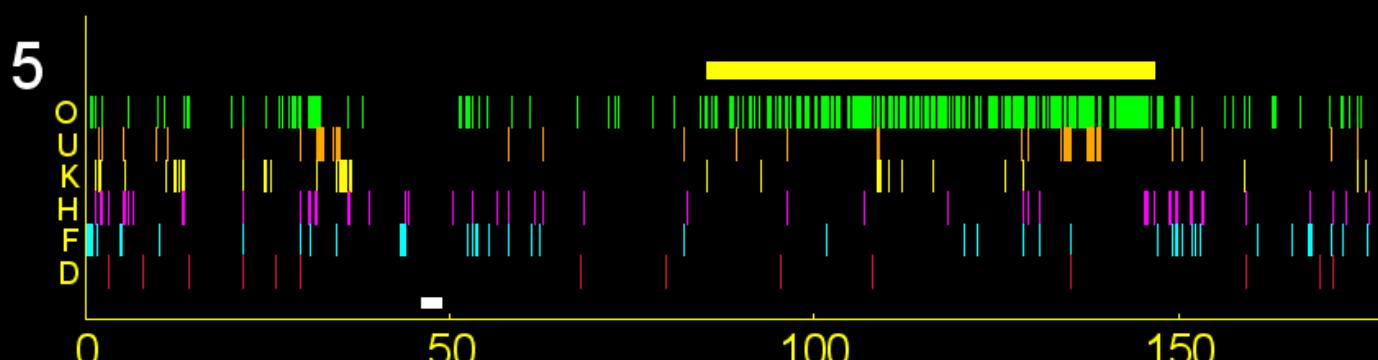
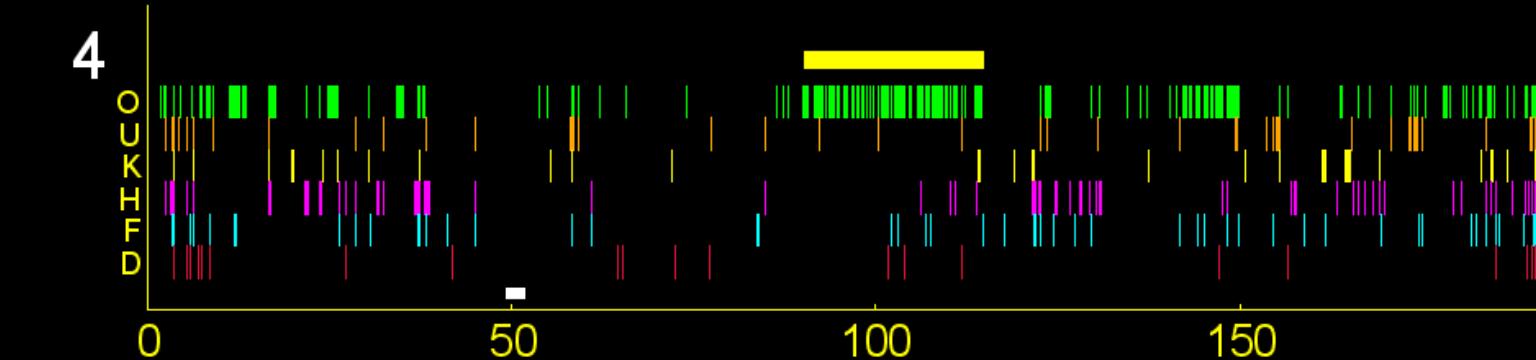
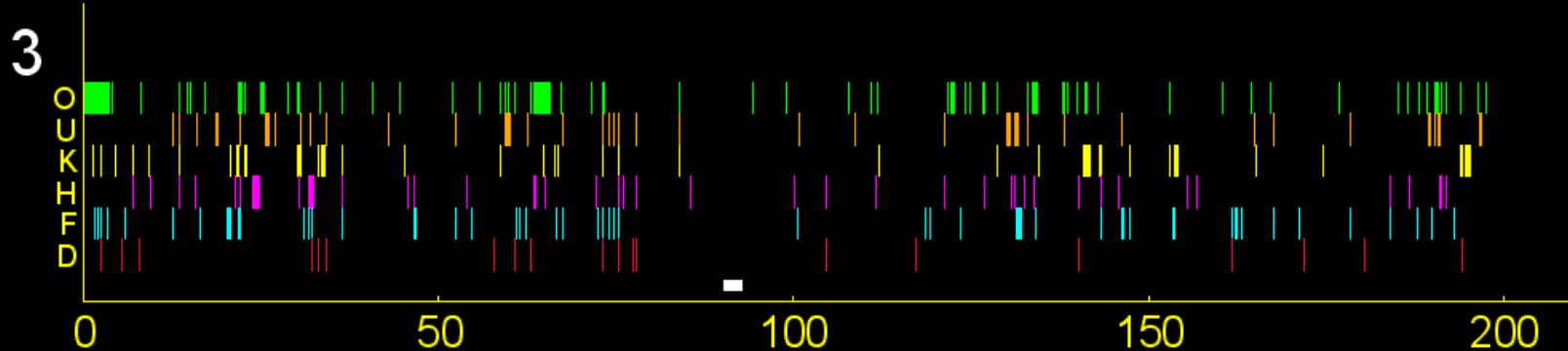
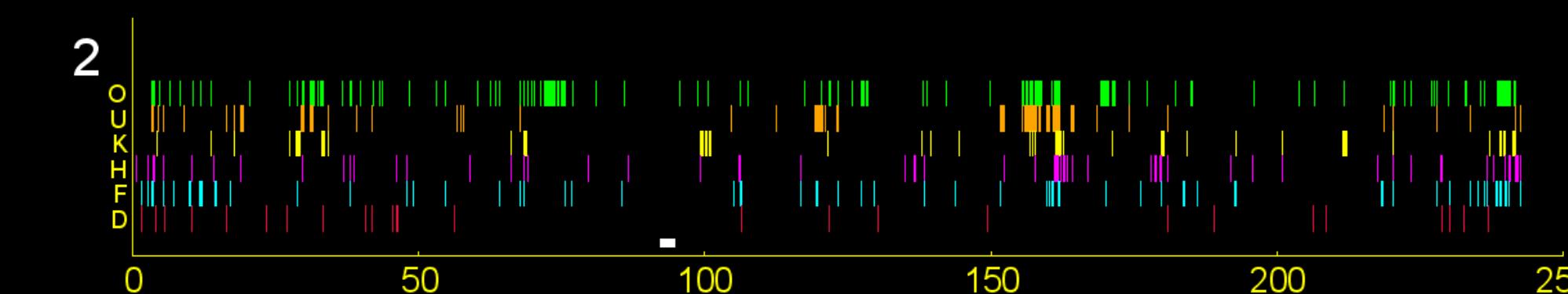
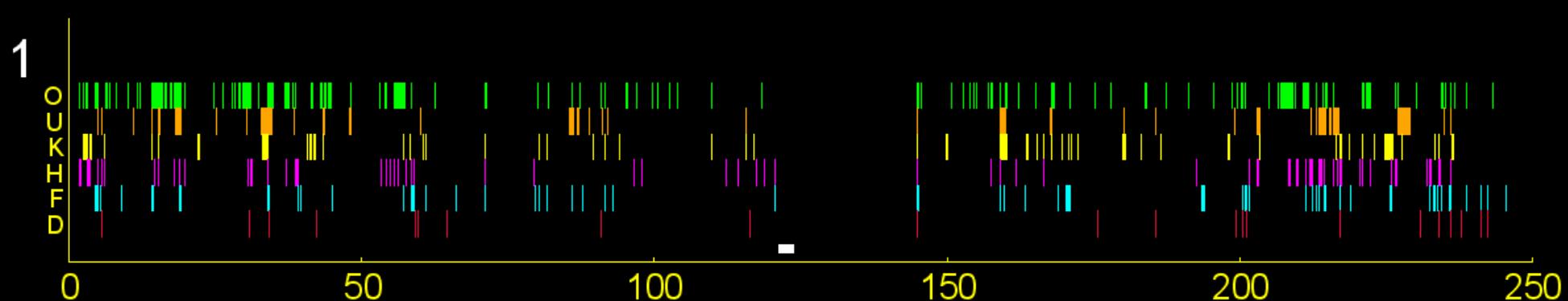
# Morphological evidence?



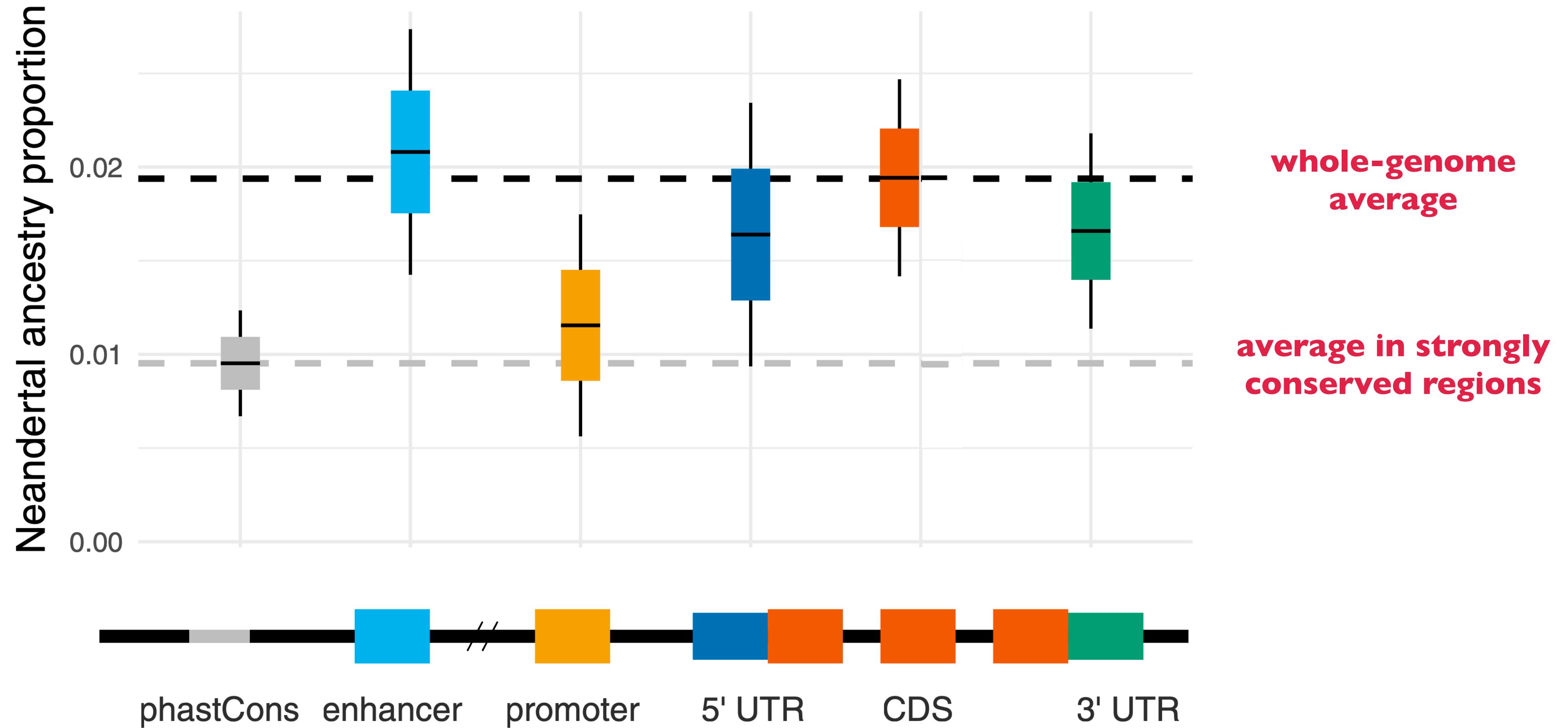
**~40 thousand years old  
remains of a modern human  
Peștera cu Oase, Romania**

Trinkaus et al. PNAS, 2003

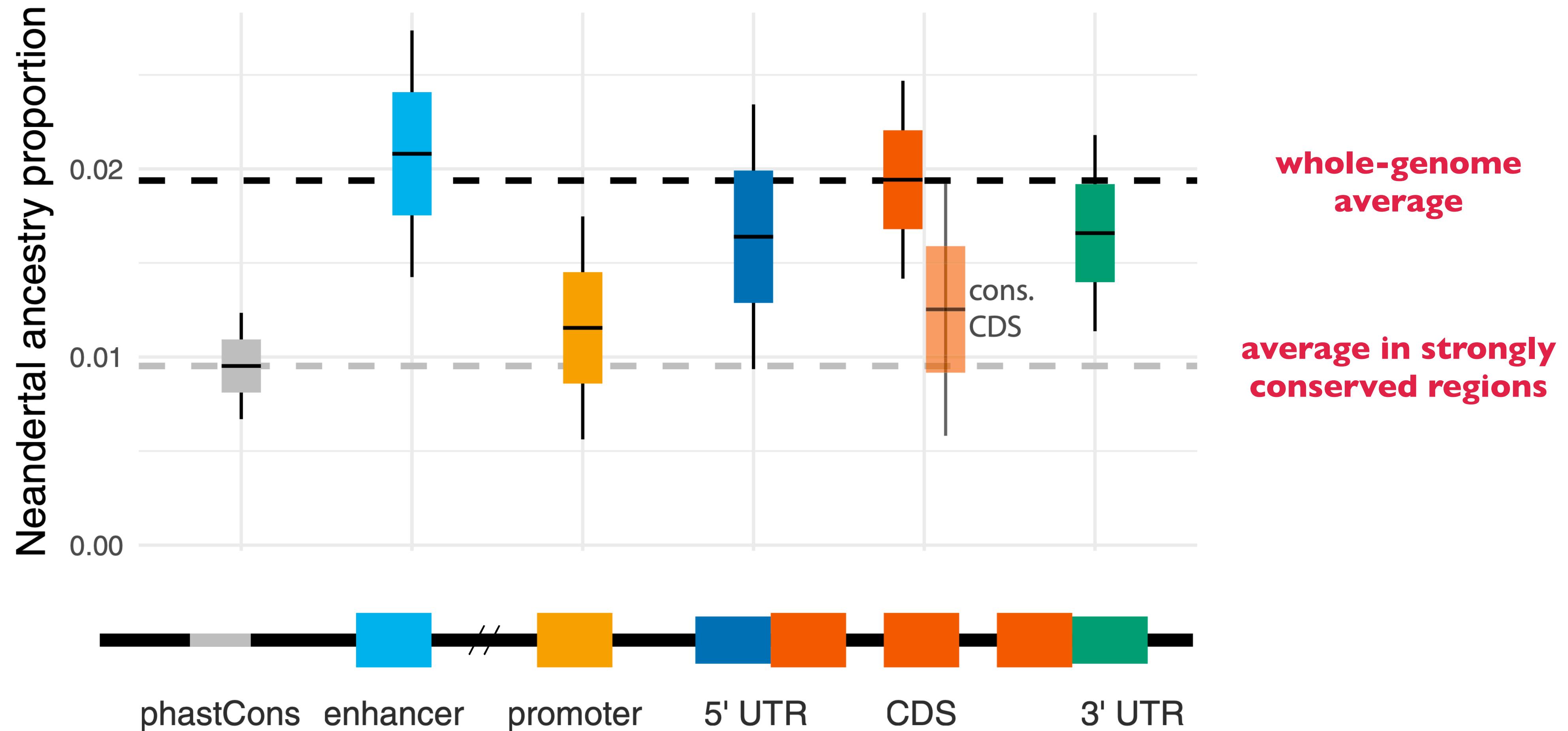




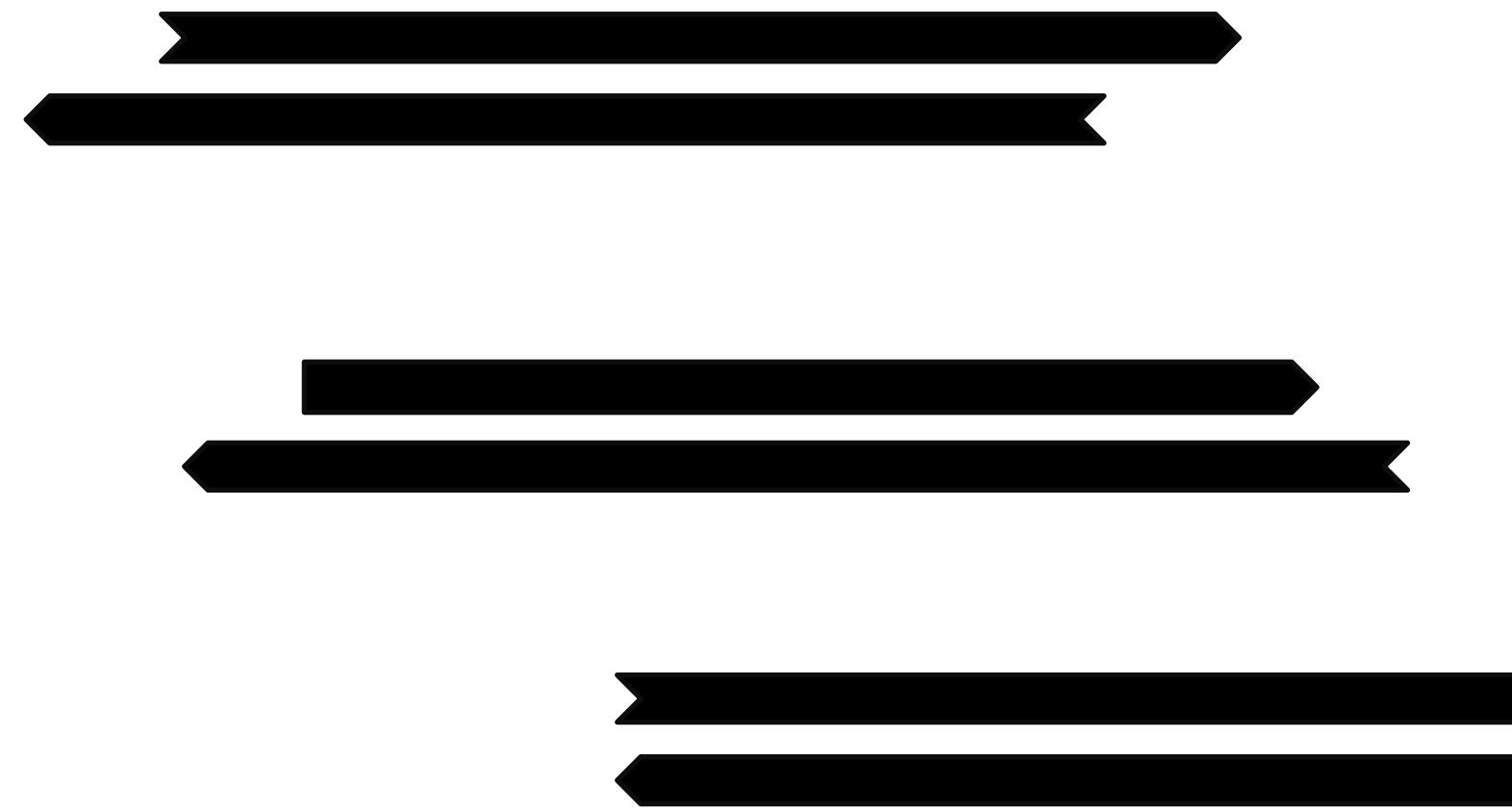
# The story is much more complicated if we zoom in...



# The story is much more complicated if we zoom in...



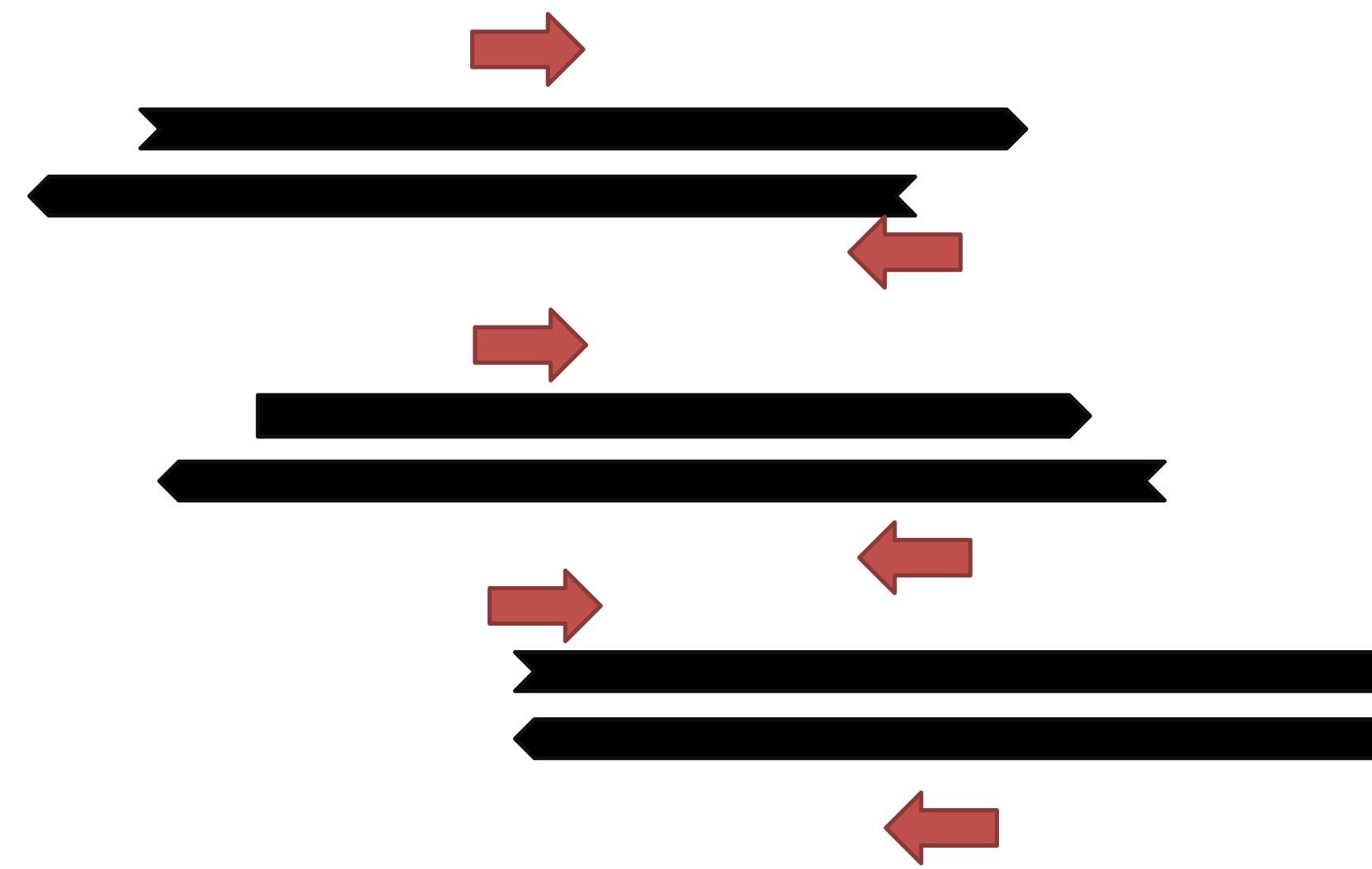
**PCR**



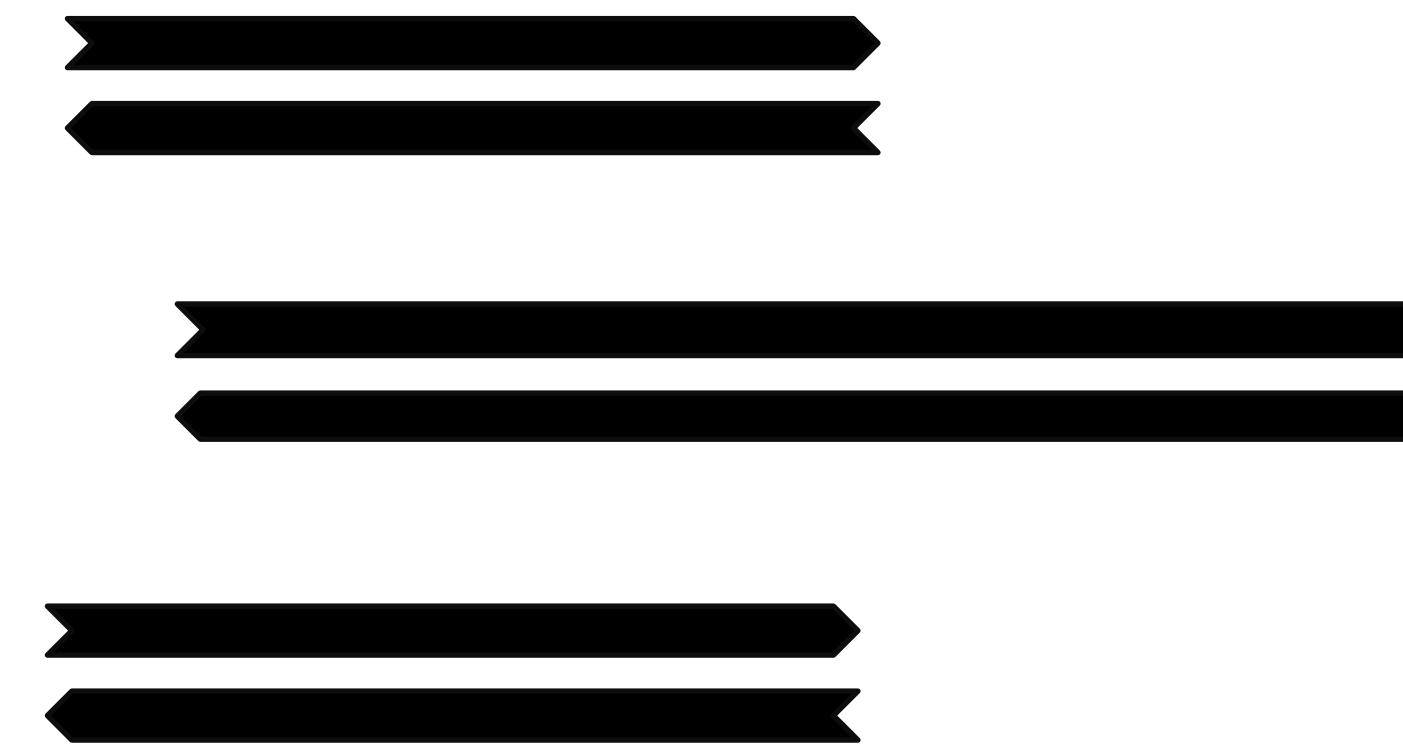
**Library preparation**



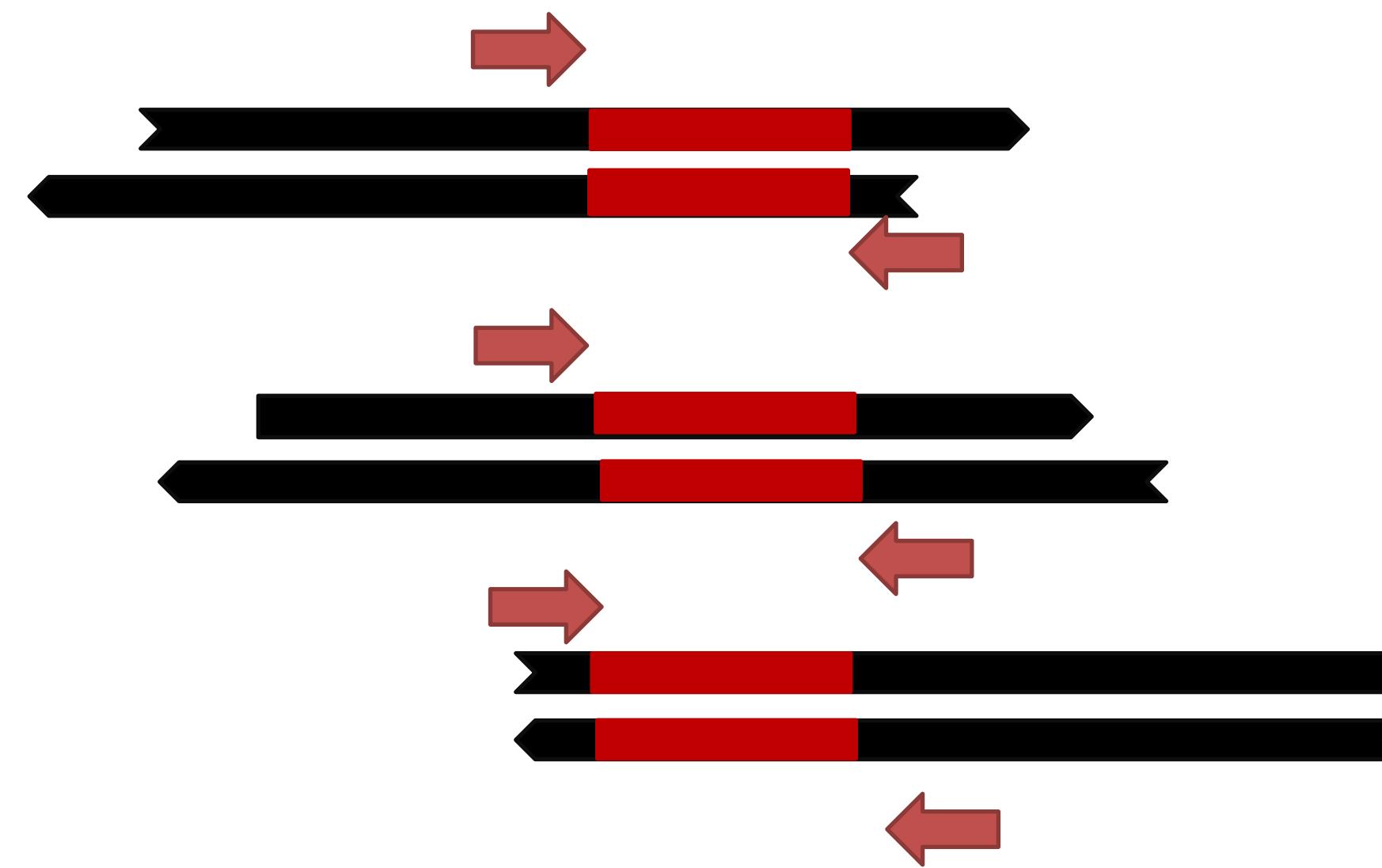
**PCR**



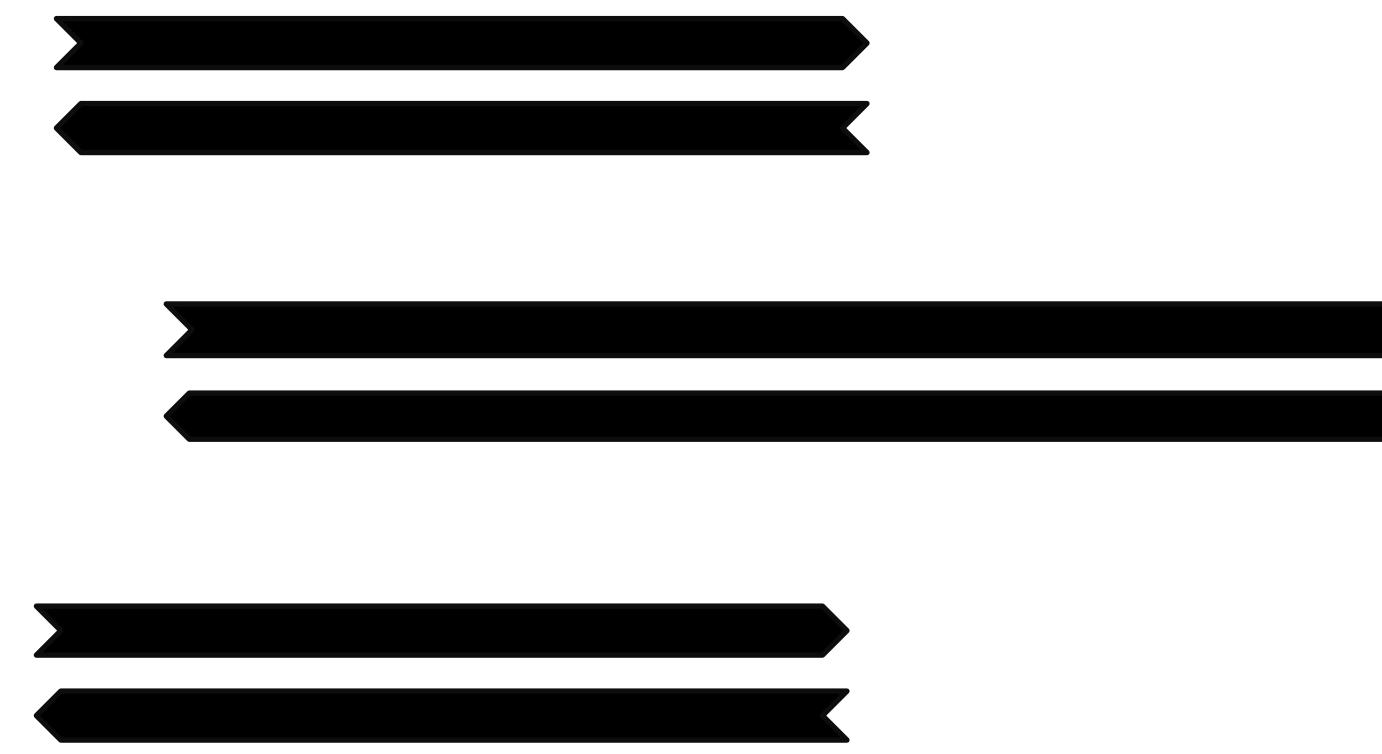
**Library preparation**



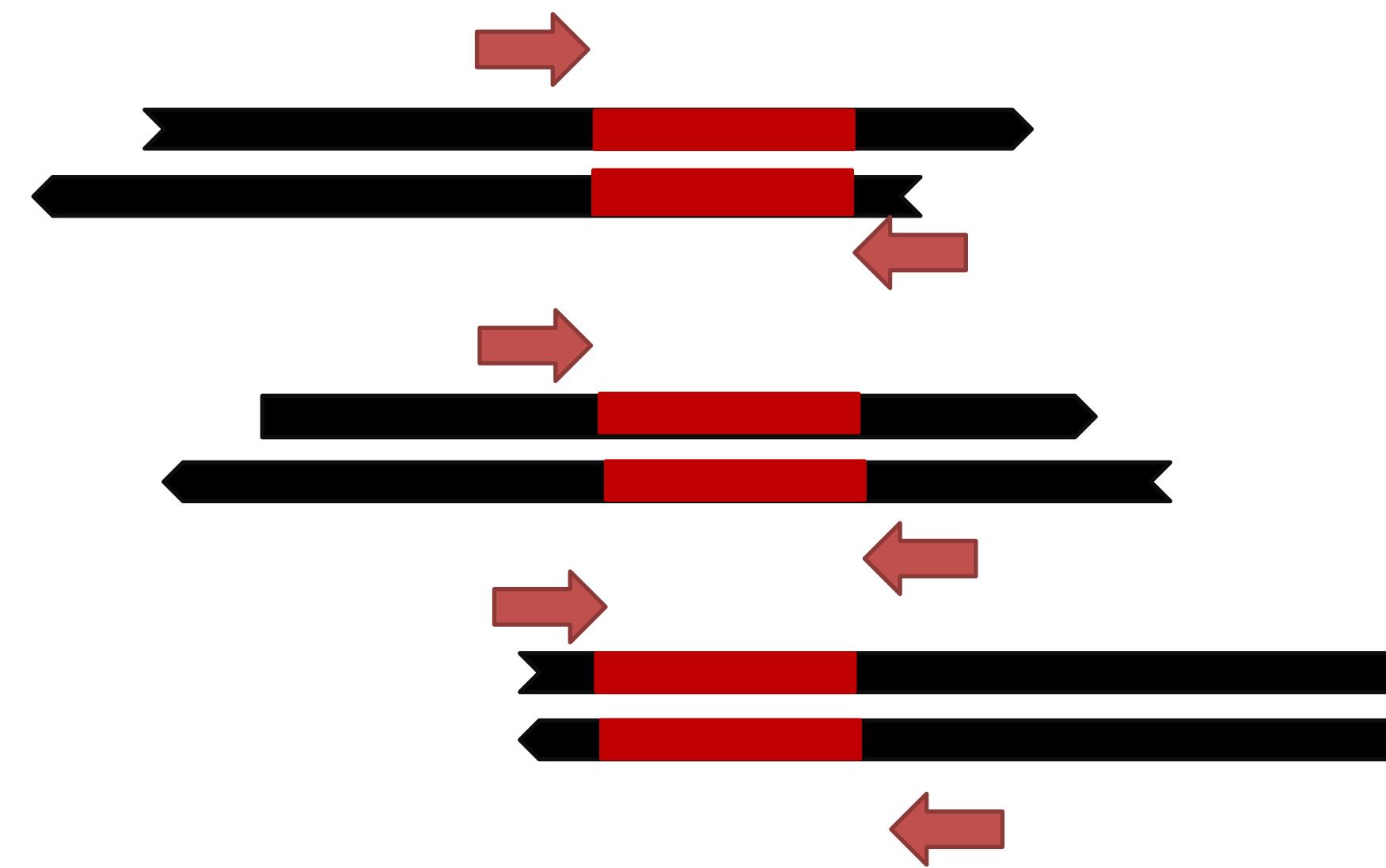
**PCR**



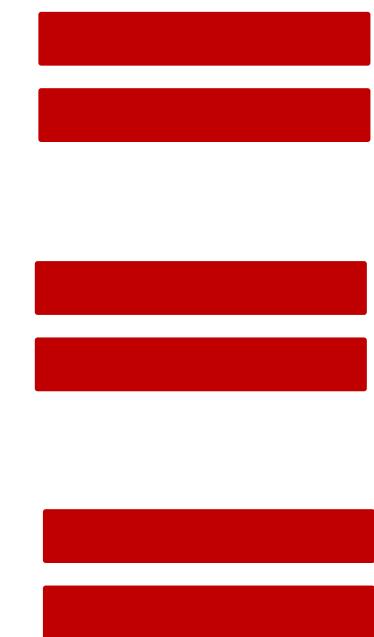
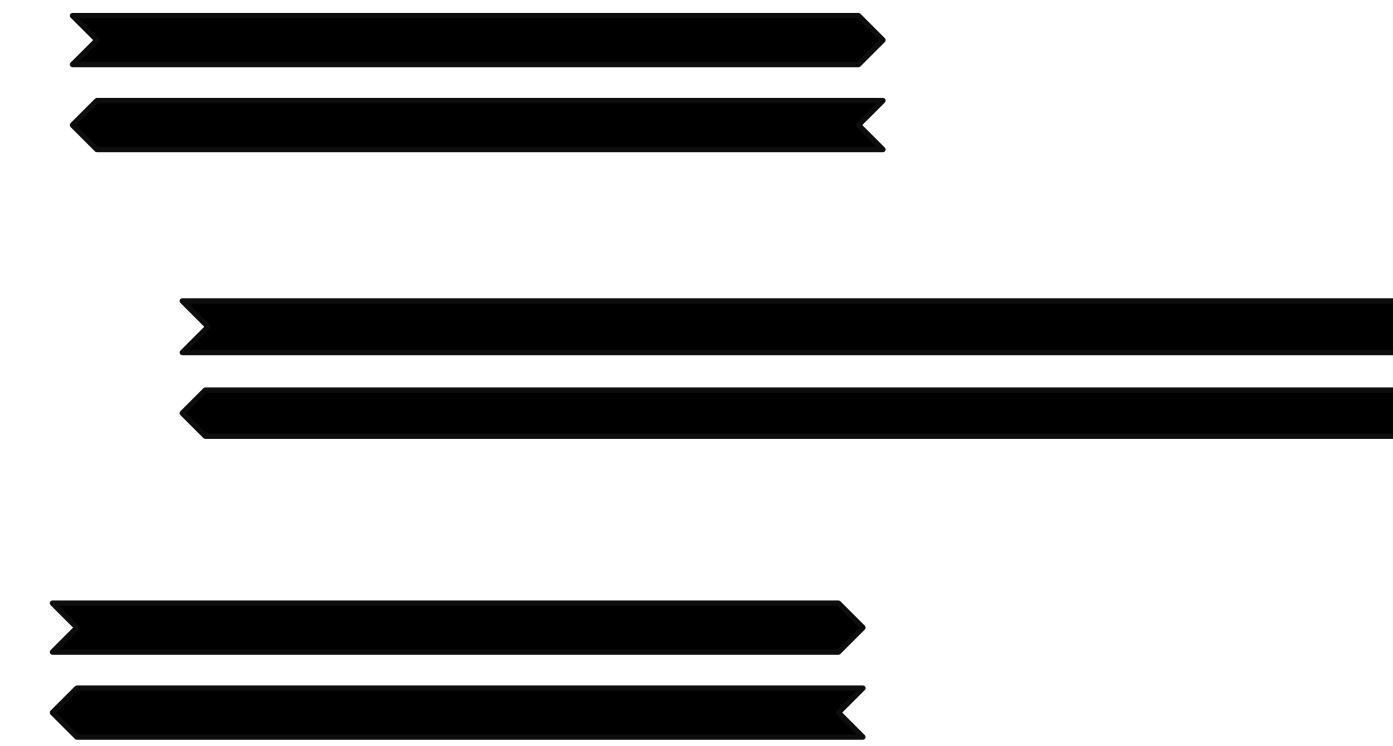
**Library preparation**



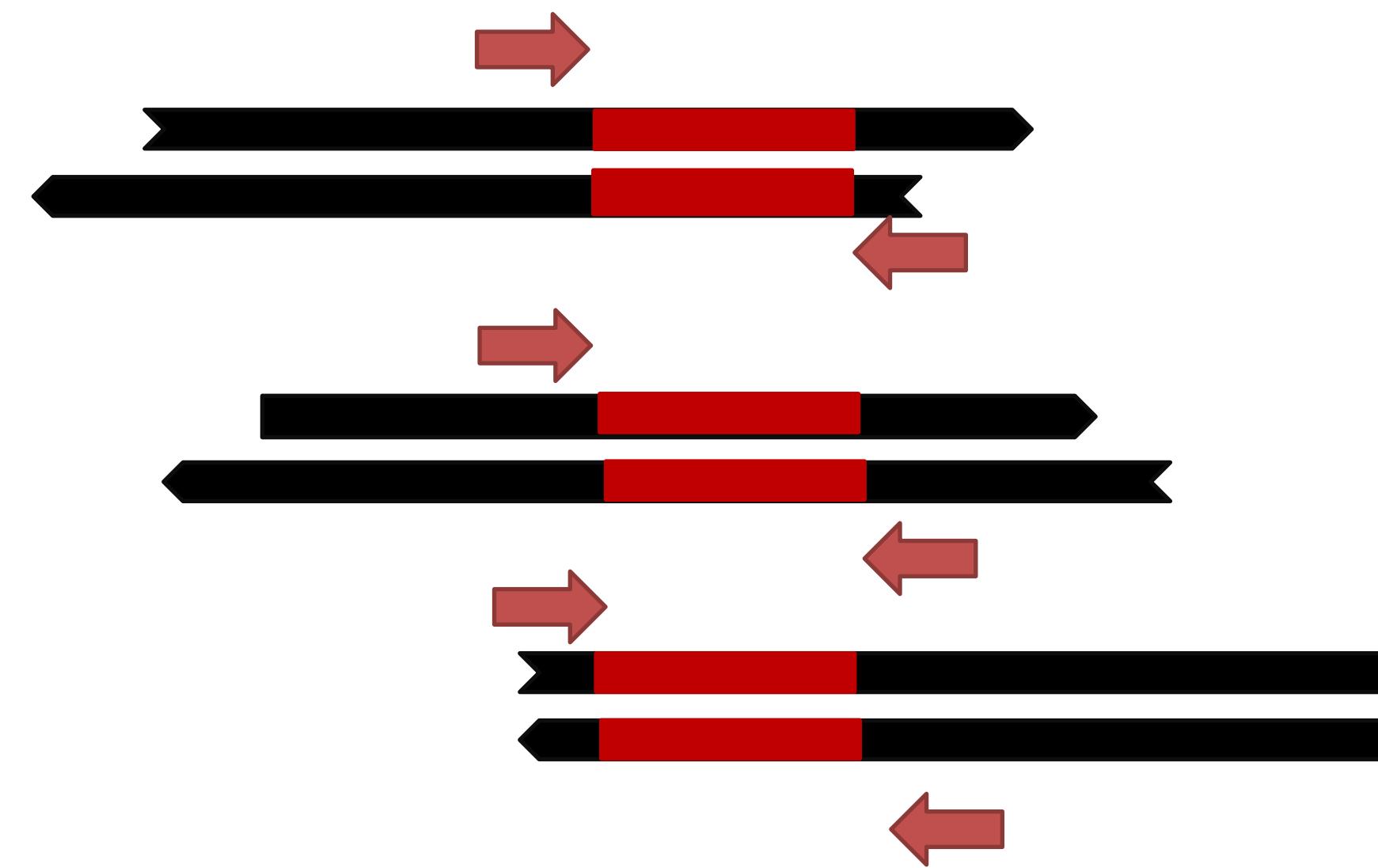
## PCR



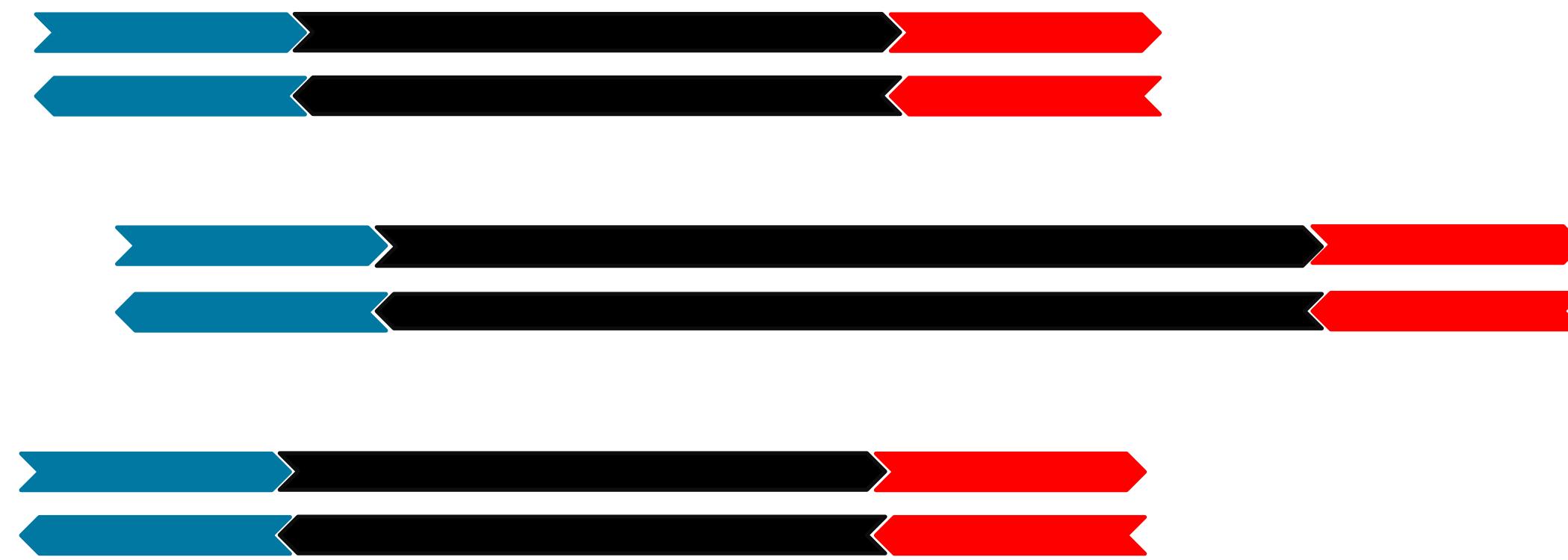
## Library preparation



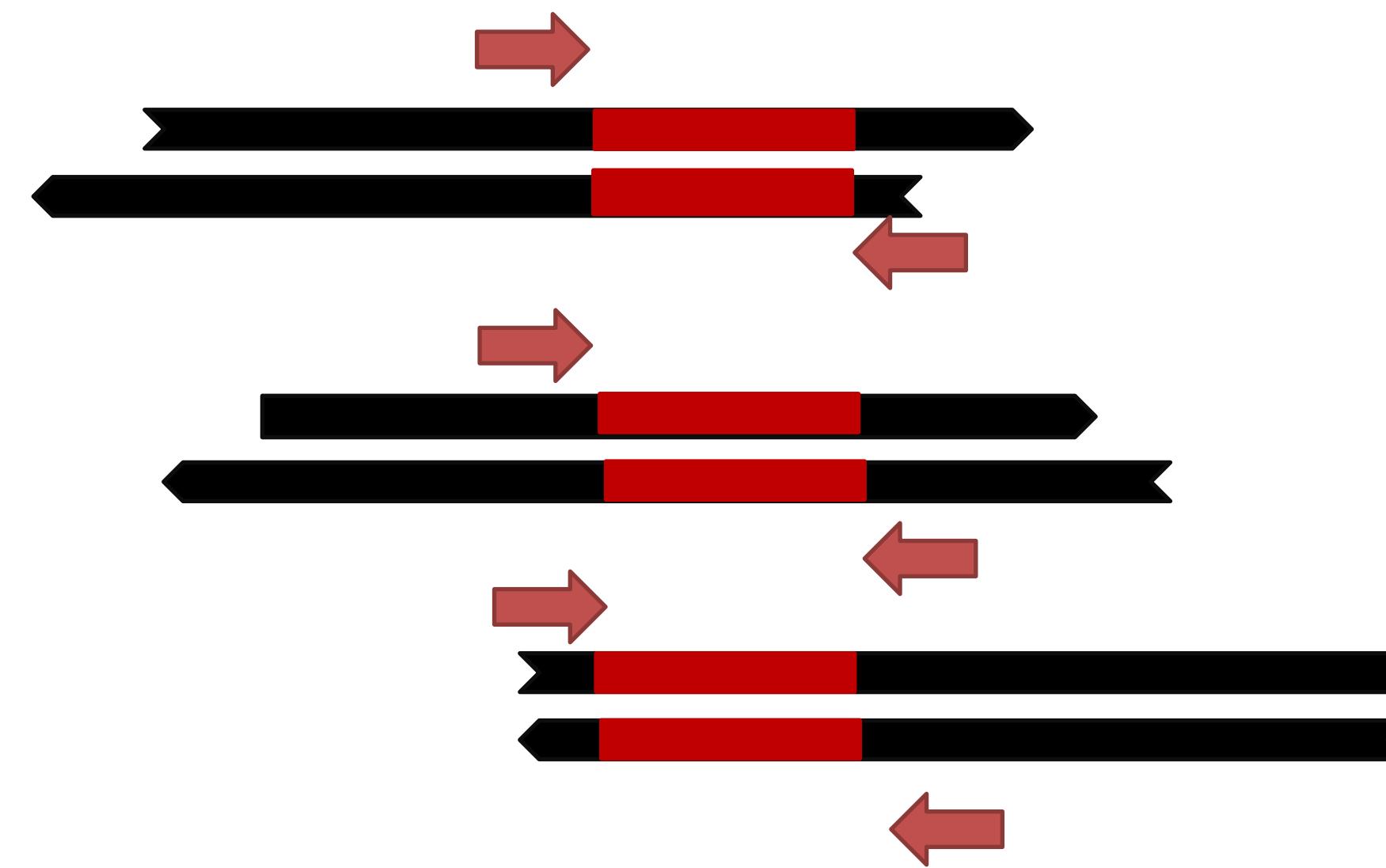
## PCR



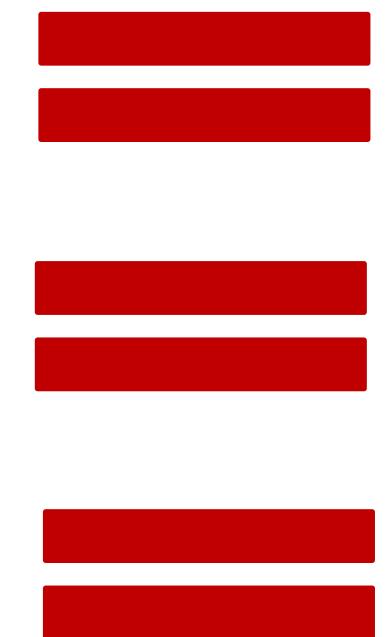
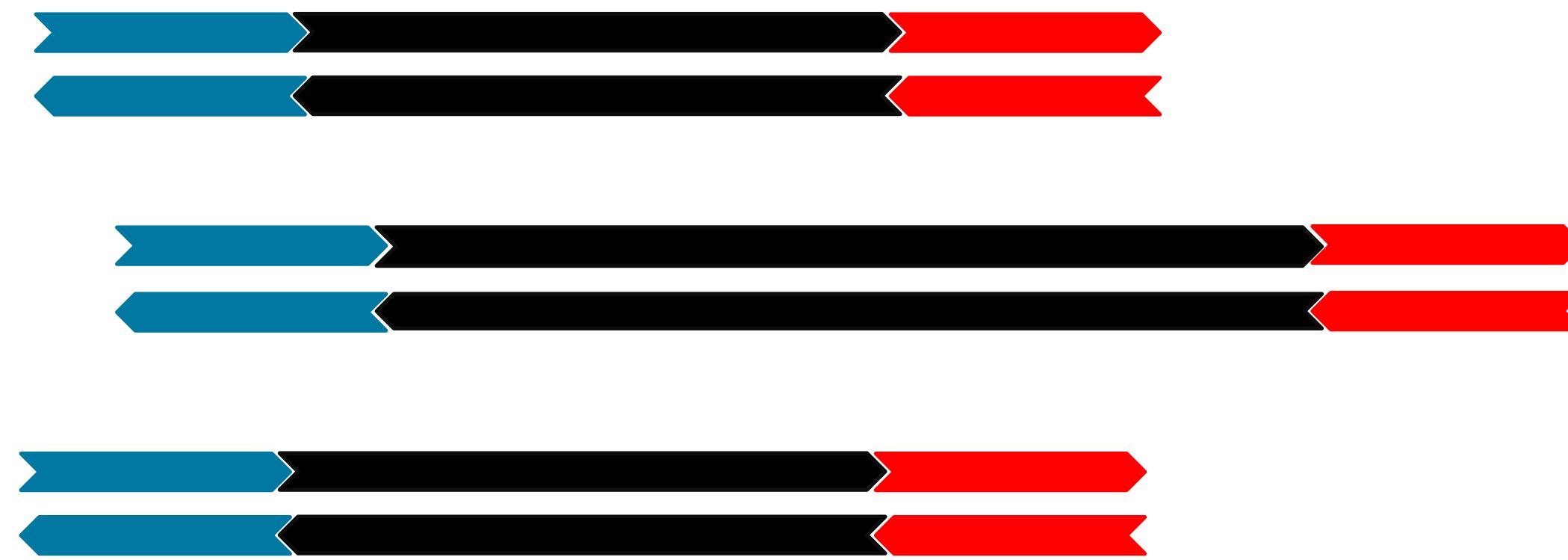
## Library preparation

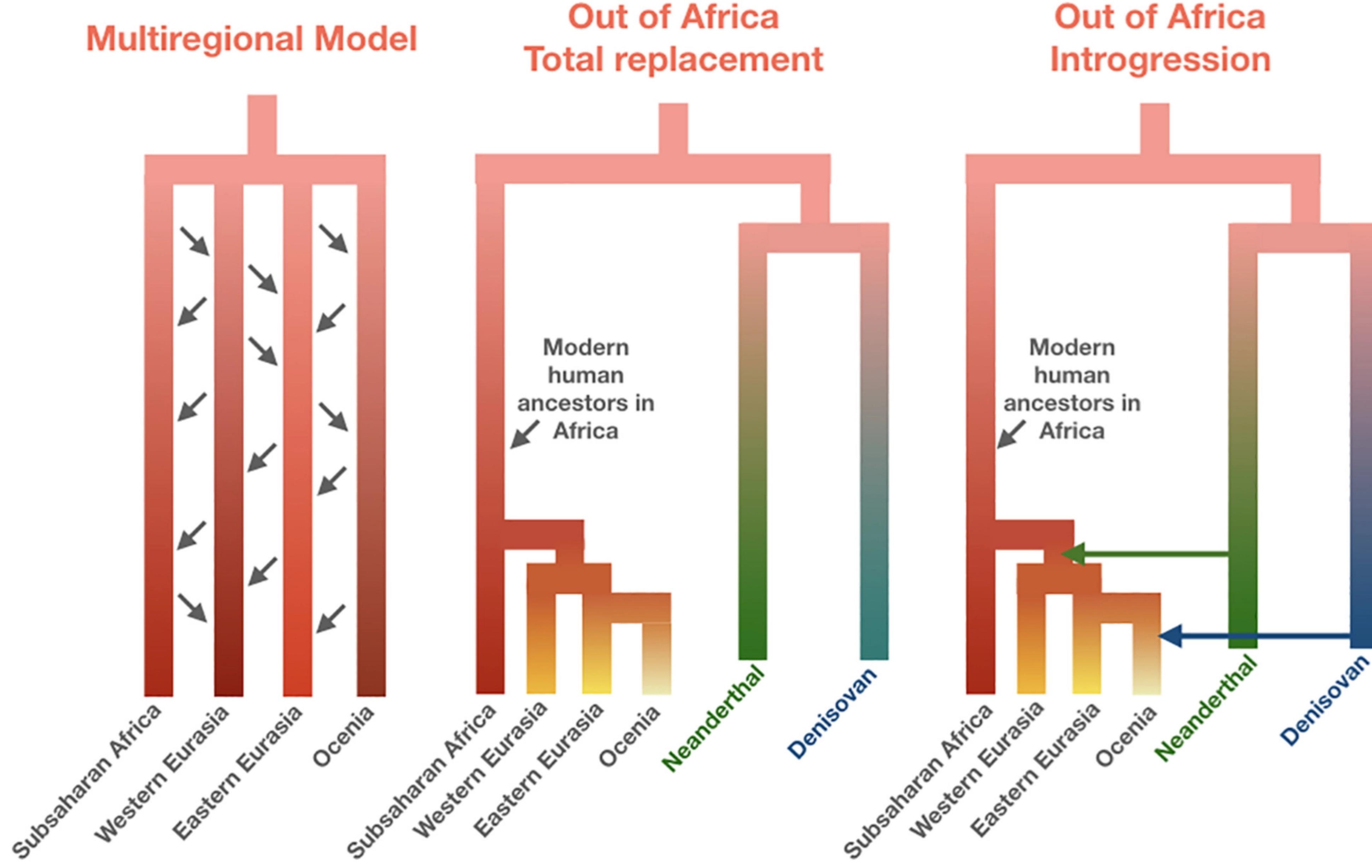


## PCR



## Library preparation





# Genomics in practice...

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##reference=1000Genomes-NCBI37
##FORMAT=<ID=GT,Number=1>Type=String,Description="Genotype">
##FORMAT=<ID=AP,Number=2>Type=Float,Description="Allelic Probability, P(Allele=1|Haplotype)">
#CHROM POS ID REF ALT QUAL FILTER INFO FORMAT HG00096 HG00097 HG00099 HG00100 HG00101 HG00102
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12 60252 . A G 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.300 0|1:0.010,0.590
12 60317 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 60344 . C A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.020,0.025 0|0:0.005,0.000
12 60383 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 60405 . T C 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 60474 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|1:0.015,0.705 0|1:0.020,0.775
12 60614 . C A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.005 0|0:0.000,0.015
12 60628 . T C 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.070 0|0:0.000,0.000
12 60654 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61021 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61107 . G T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.015 0|0:0.000,0.000
12 61172 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61220 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.005,0.265 0|1:0.020,0.665
12 61258 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.005,0.465 0|1:0.020,0.895
12 61272 . T C 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61329 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61341 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|1:0.010,0.560 0|1:0.020,0.855
12 61368 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|1:0.020,0.630 0|1:0.020,0.955
12 61392 . T A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61405 . G C 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61411 . C A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.015
12 61416 . G A 100 PASS . GT:AP 0|0:0.000,0.025 0|0:0.000,0.010 0|0:0.015,0.075
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12 61510 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61516 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.005 0|0:0.000,0.000
12 61552 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61604 . T G 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61687 . G A 100 PASS . GT:AP 1|0:1.000,0.000 0|1:0.015,0.625 0|1:0.020,0.960
12 61700 . C T 100 PASS . GT:AP 0|0:0.005,0.000 0|0:0.000,0.035 0|0:0.025,0.060
```

# Genomics in practice...

```

##fileformat=VCFv4.0
##source=BCM:SNPTools:hapfuse
##reference=1000Genomes-NCBI37
##FORMAT=<ID=GT,Number=1>Type=String,Description="Genotype">
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#CHROM POS ID REF ALT QUAL FILTER INFO FORMAT HG00096 HG00097 HG00099 HG00100 HG00101 HG00102
12 60076 . A C 100 PASS . GT:AP 1|0:1.000,0.000 0|0:0.000,0.005 0|0:0.000,0.005
12 60252 . A G 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.300 0|1:0.010,0.590
12 60317 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 60344 . C A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.020,0.025 0|0:0.005,0.000
12 60383 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 60405 . T C 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 60474 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|1:0.015,0.705 0|1:0.020,0.775
12 60614 . C A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.005 0|0:0.000,0.015
12 60628 . T C 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.070 0|0:0.000,0.000
12 60654 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61021 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61107 . G T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.015 0|0:0.000,0.000
12 61172 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61220 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.005,0.265 0|1:0.020,0.665
12 61258 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.005,0.465 0|1:0.020,0.895
12 61272 . T C 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61329 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61341 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|1:0.010,0.560 0|1:0.020,0.855
12 61368 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|1:0.020,0.630 0|1:0.020,0.955
12 61392 . T A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61405 . G C 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61411 . C A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.015
12 61416 . G A 100 PASS . GT:AP 0|0:0.000,0.025 0|0:0.000,0.010 0|0:0.015,0.075
12 61422 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.105 0|0:0.005,0.010
12 61476 . C G 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.005,0.000
12 61510 . G A 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61516 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.005 0|0:0.000,0.000
12 61552 . C T 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61604 . T G 100 PASS . GT:AP 0|0:0.000,0.000 0|0:0.000,0.000 0|0:0.000,0.000
12 61687 . G A 100 PASS . GT:AP 1|0:1.000,0.000 0|1:0.015,0.625 0|1:0.020,0.960
12 61700 . C T 100 PASS . GT:AP 0|0:0.005,0.000 0|0:0.000,0.035 0|0:0.025,0.060

```

chromosome position

# Genomics in practice...

#fileformat=VCFv4.0 ##source=BCM:SNPTools:hapfuse ##reference=1000Genomes-NCBI37 ##FORMAT=<ID=GT,Number=1>Type=String,Description="Genotype"> ##FORMAT=<ID=AP,Number=2>Type=Float,Description="Allelic Probability, P(Allele=1 Haplotype)">														
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12	60252	.	A	G	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.300	0 1:0.010,0.590			
12	60317	.	C	T	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	60344	.	C	A	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.020,0.025	0 0:0.005,0.000			
12	60383	.	G	A	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	60405	.	T	C	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	60474	.	G	A	100	PASS	.	GT:AP	0 0:0.000,0.000	0 1:0.015,0.705	0 1:0.020,0.775			
12	60614	.	C	A	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.005	0 0:0.000,0.015			
12	60628	.	T	C	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.070	0 0:0.000,0.000			
12	60654	.	G	A	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	61021	.	C	T	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	61107	.	G	T	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.015	0 0:0.000,0.000			
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12	61220	.	G	A	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.005,0.265	0 1:0.020,0.665			
12	61258	.	C	T	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.005,0.465	0 1:0.020,0.895			
12	61272	.	T	C	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	61329	.	C	T	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	61341	.	G	A	100	PASS	.	GT:AP	0 0:0.000,0.000	0 1:0.010,0.560	0 1:0.020,0.855			
12	61368	.	C	T	100	PASS	.	GT:AP	0 0:0.000,0.000	0 1:0.020,0.630	0 1:0.020,0.955			
12	61392	.	T	A	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	61405	.	G	C	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	61411	.	C	A	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.015			
12	61416	.	G	A	100	PASS	.	GT:AP	0 0:0.000,0.025	0 0:0.000,0.010	0 0:0.015,0.075			
12	61422	.	C	T	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.105	0 0:0.005,0.010			
12	61476	.	C	G	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.005,0.000			
12	61510	.	G	A	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	61516	.	C	T	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.005	0 0:0.000,0.000			
12	61552	.	C	T	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	61604	.	T	G	100	PASS	.	GT:AP	0 0:0.000,0.000	0 0:0.000,0.000	0 0:0.000,0.000			
12	61687	.	G	A	100	PASS	.	GT:AP	1 0:1.000,0.000	0 1:0.015,0.625	0 1:0.020,0.960			
12	61700	.	C	T	100	PASS	.	GT:AP	0 0:0.005,0.000	0 0:0.000,0.035	0 0:0.025,0.060			

chromosome position

SNP

# Genomics in practice...

#fileformat=VCFv4.0 ##source=BCM:SNPTools:hapfuse ##reference=1000Genomes-NCBI37 ##FORMAT=<ID=GT,Number=1>Type=String,Description="Genotype"> ##FORMAT=<ID=AP,Number=2>Type=Float,Description="Allelic Probability, P(A Allele=1 Haplotype)">														
#CHROM	POS	ID	REF	ALT	QUAL	FILTER	INFO	FORMAT	HG00096	HG00097	HG00099	HG00100	HG00101	HG00102
12	60076	.	A	C	100	PASS	.	GT:AP	1 0	1.000,0.000	0 0	0.000,0.005	0 0	0.000,0.005
12	60252	.	A	G	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.300	0 1	0.010,0.590
12	60317	.	C	T	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	60344	.	C	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.020,0.025	0 0	0.005,0.000
12	60383	.	G	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	60405	.	T	C	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	60474	.	G	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 1	0.015,0.705	0 1	0.020,0.775
12	60614	.	C	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.005	0 0	0.000,0.015
12	60628	.	T	C	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.070	0 0	0.000,0.000
12	60654	.	G	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	61021	.	C	T	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	61107	.	G	T	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.015	0 0	0.000,0.000
12	61172	.	G	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	61220	.	G	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.005,0.265	0 1	0.020,0.665
12	61258	.	C	T	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.005,0.465	0 1	0.020,0.895
12	61272	.	T	C	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	61329	.	C	T	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	61341	.	G	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 1	0.010,0.560	0 1	0.020,0.855
12	61368	.	C	T	100	PASS	.	GT:AP	0 0	0.000,0.000	0 1	0.020,0.630	0 1	0.020,0.955
12	61392	.	T	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	61405	.	G	C	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	61411	.	C	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.015
12	61416	.	G	A	100	PASS	.	GT:AP	0 0	0.000,0.025	0 0	0.000,0.010	0 0	0.015,0.075
12	61422	.	C	T	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.105	0 0	0.005,0.010
12	61476	.	C	G	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.005,0.000
12	61510	.	G	A	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	61516	.	C	T	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.005	0 0	0.000,0.000
12	61552	.	C	T	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	61604	.	T	G	100	PASS	.	GT:AP	0 0	0.000,0.000	0 0	0.000,0.000	0 0	0.000,0.000
12	61687	.	G	A	100	PASS	.	GT:AP	1 0	1.000,0.000	0 1	0.015,0.625	0 1	0.020,0.960
12	61700	.	C	T	100	PASS	.	GT:AP	0 0	0.005,0.000	0 0	0.000,0.035	0 0	0.025,0.060

chromosome position

SNP

genotype ind. 1 genotype ind. 2 genotype ind. 3 ...