
NEANDERTHAL ANCESTRY IN MODERN HUMAN GENOMES



MAX-PLANCK-GESELLSCHAFT

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Max Planck Institute for Evolutionary Anthropology
Leipzig, Germany

1856 — DISCOVERY OF A ‘NEW MAN’



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



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

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Neander's valley

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Neander's valley

valley = Thal in German

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

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

Neander’s valley
valley = Thal in German



Neanderthal

AN ANCESTOR: THE MAN OF TWENTY THOUSAND YEARS AGO

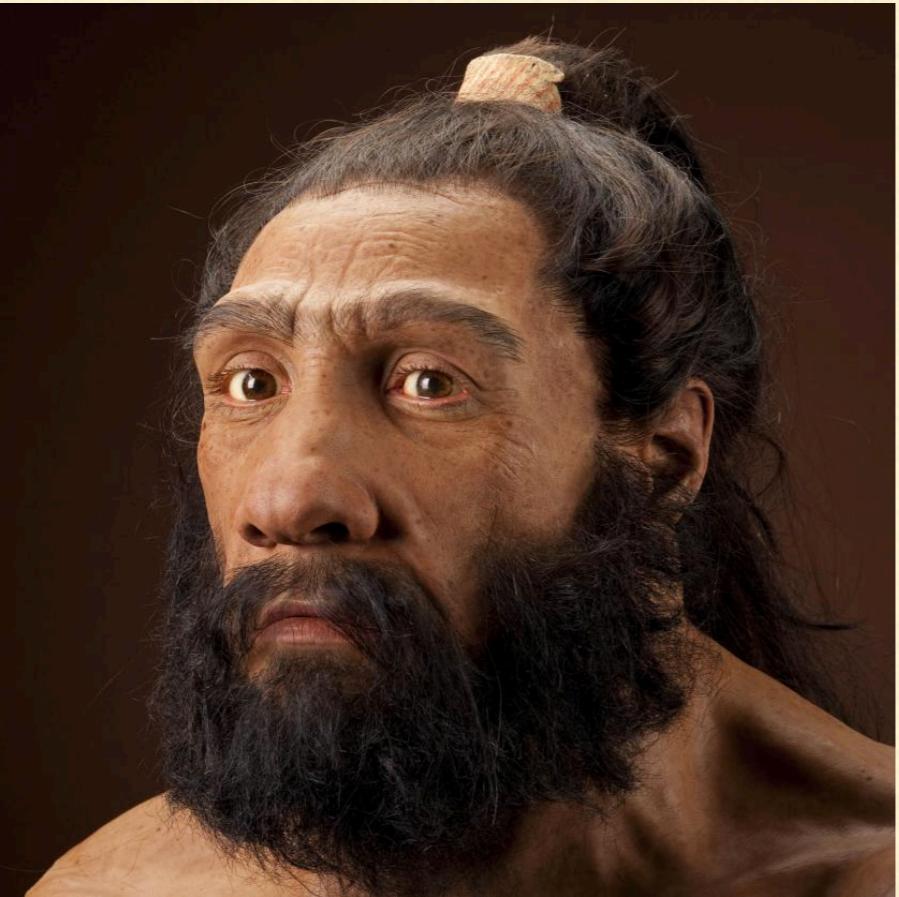


THE MAN OF 20,000 YEARS AGO. AN ILLUSTRATED RECONSTRUCTION OF THE PRIMITIVE CAVE MAN WHOSE SKULL WAS FOUND IN THE DEPARTMENT OF TORRENT.

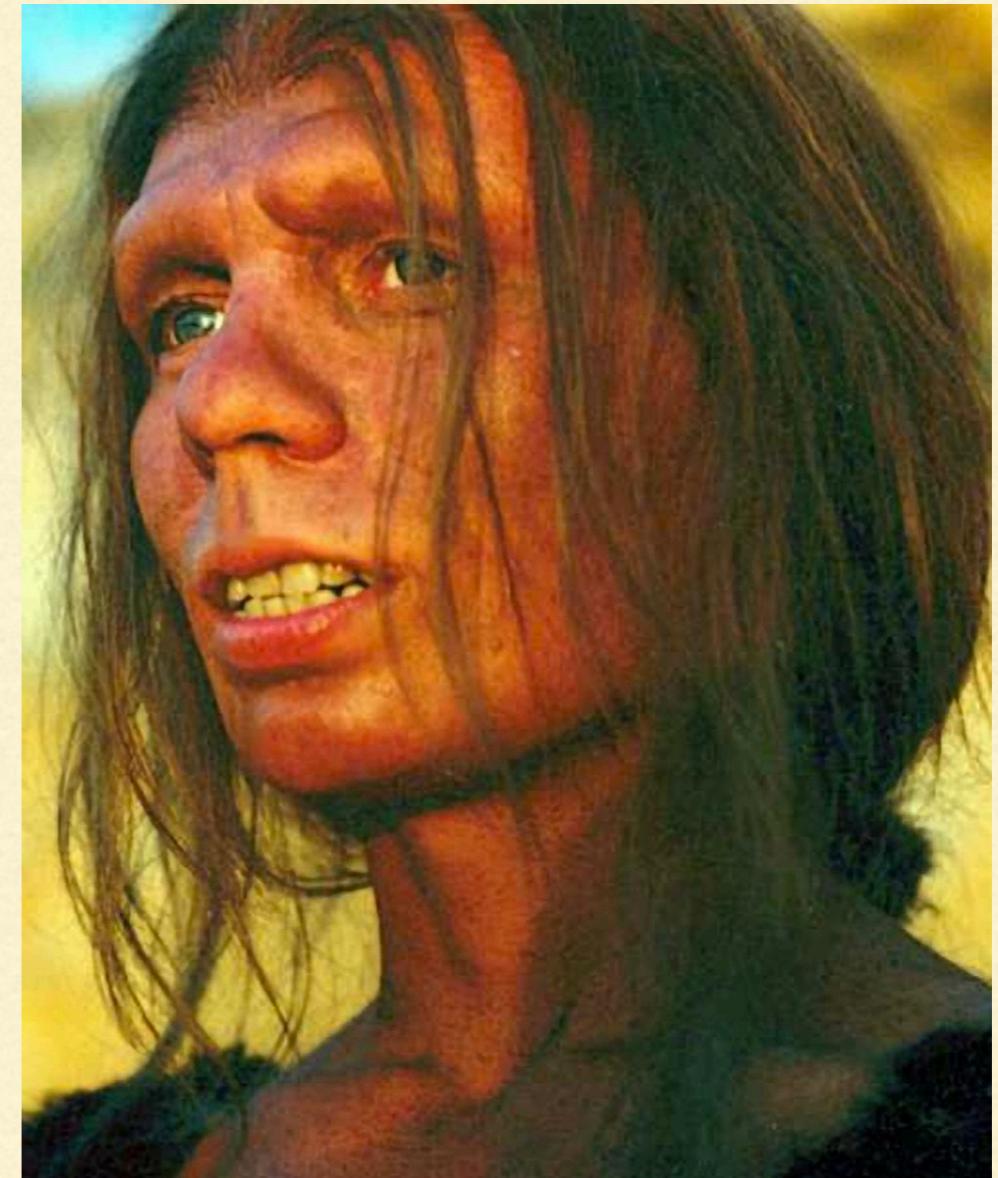
Illustrated London News, 1909



The Neanderthal Man poster, 1953



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

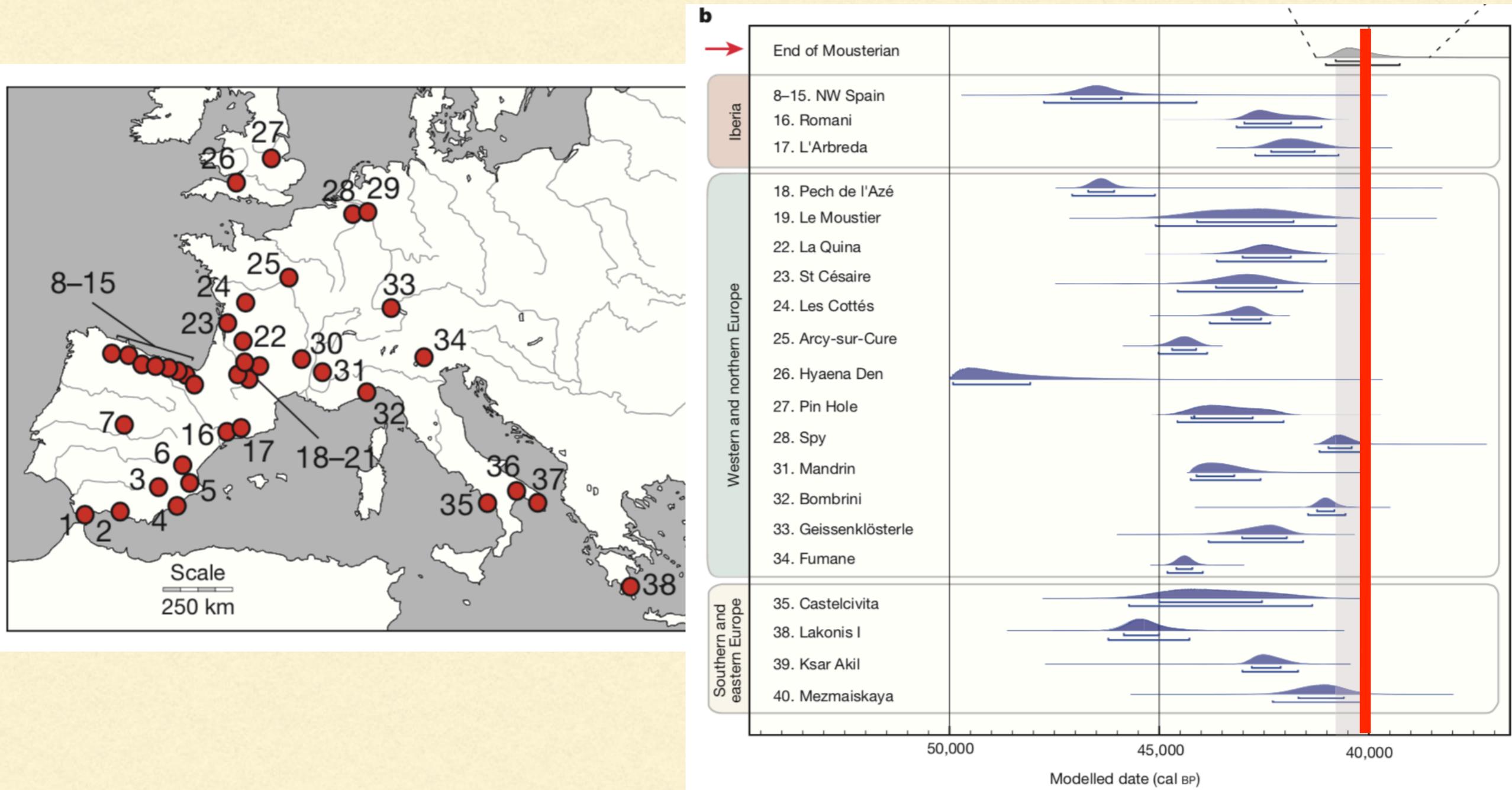


<https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.0020449>

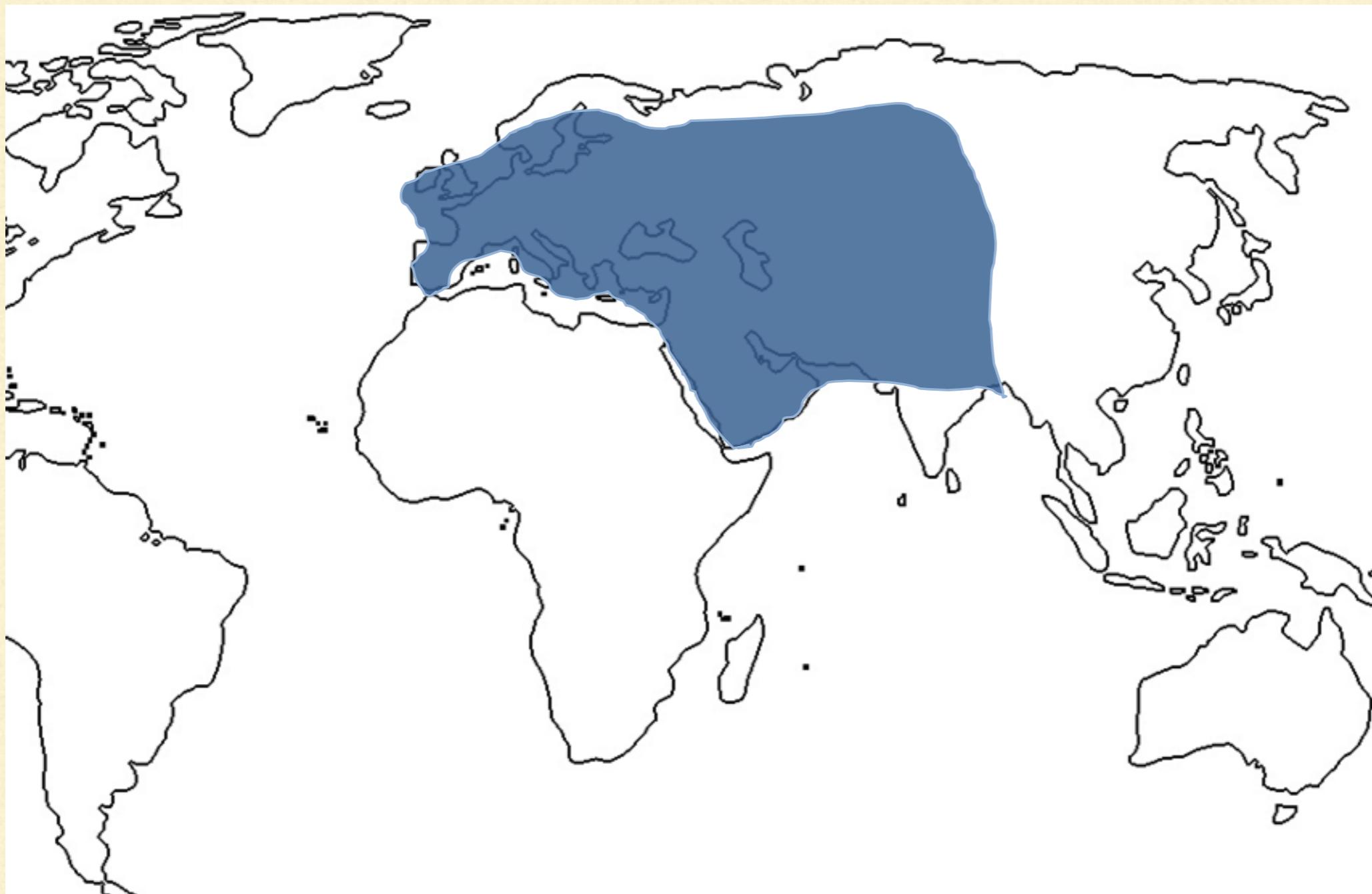


<https://www.neanderthal.de>

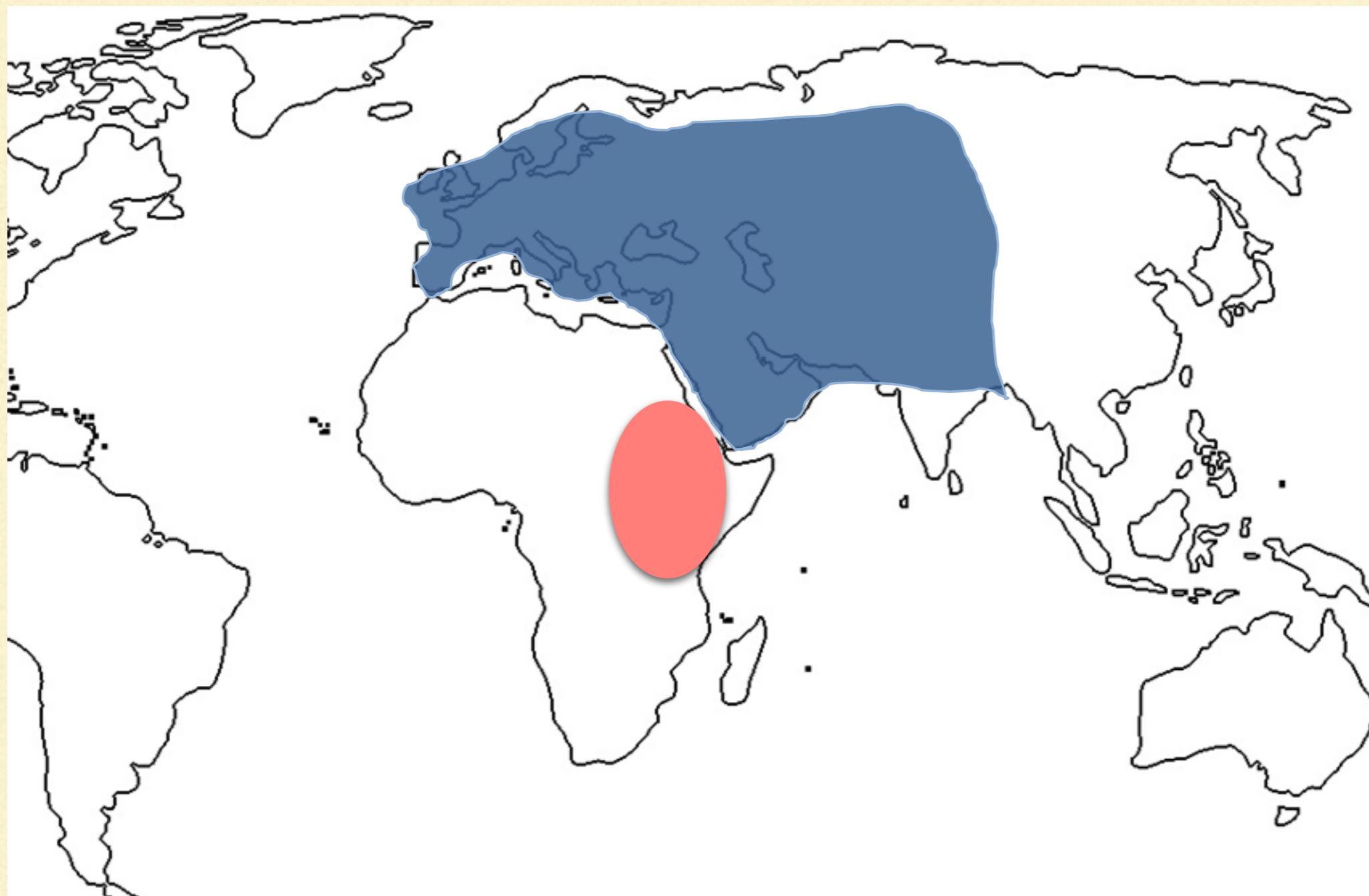
NEANDERTHALS GONE ~40K YEARS AGO



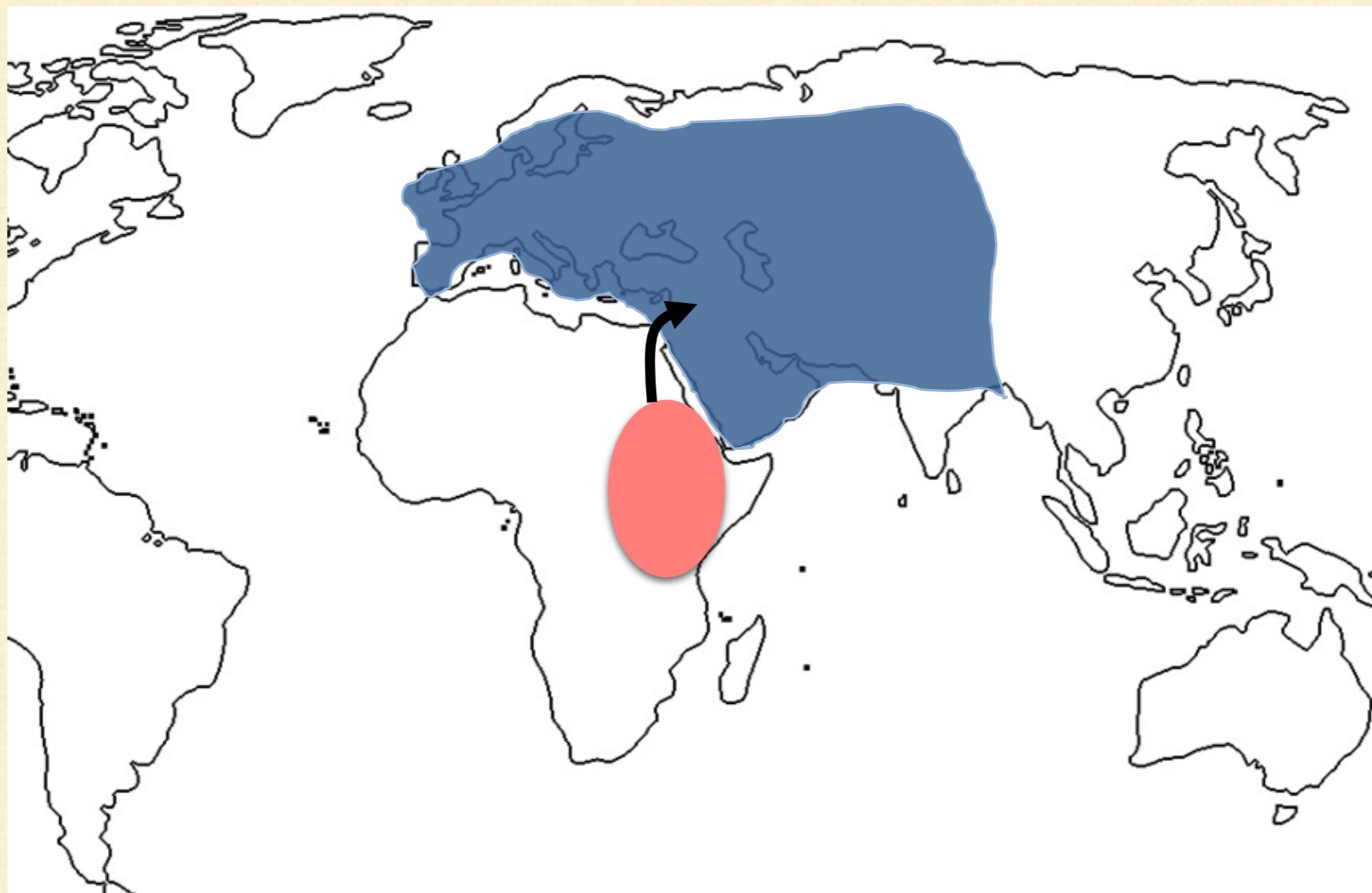
Neanderthals in Eurasia ~400 thousand years ago



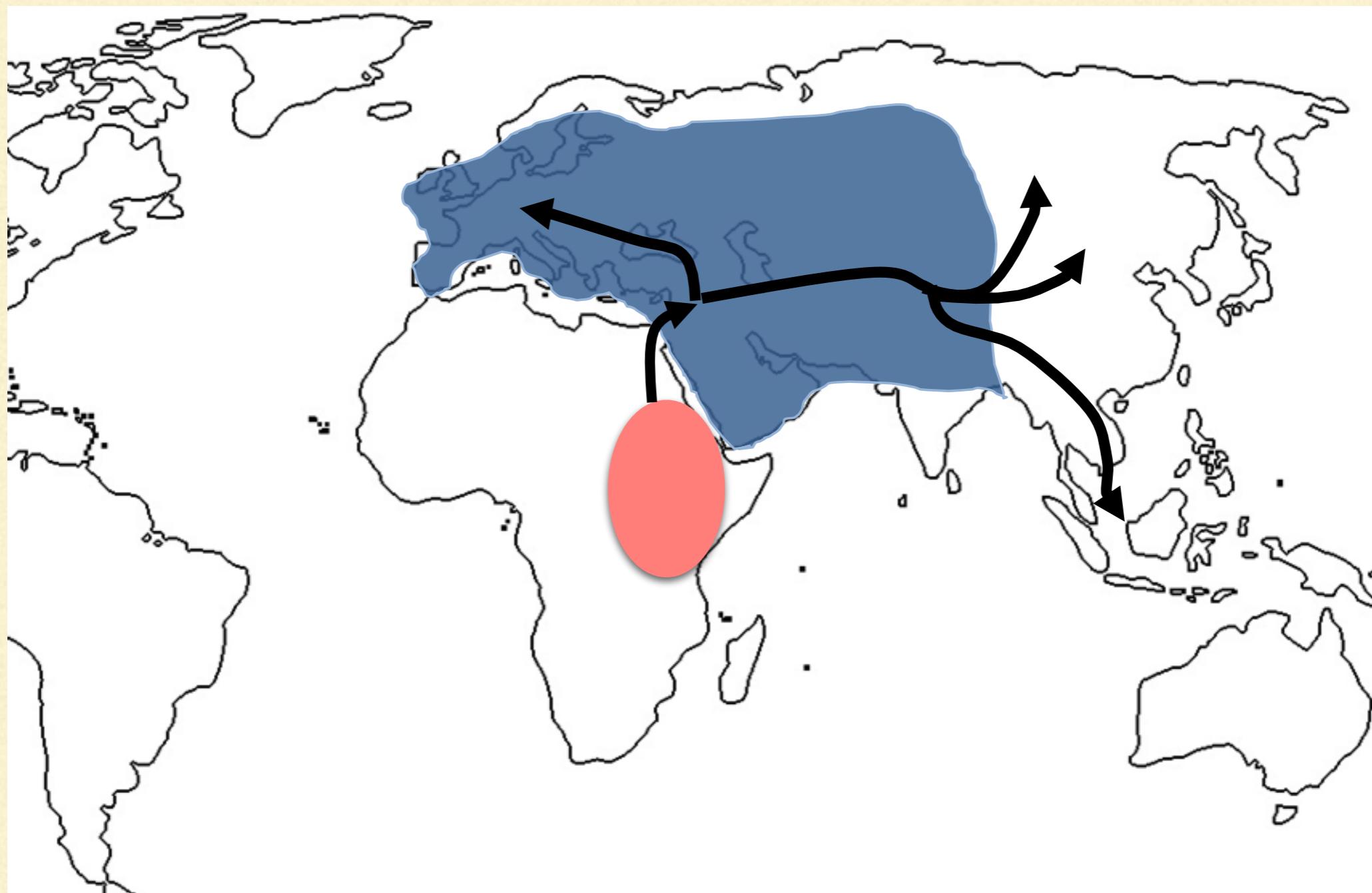
Anatomically modern humans (AMH) in East Africa ~300 thousand years ago



**AMH migrated out of Africa
~80-60 thousand years ago...**



**... and reached different corners of
Europe and Asia ~45 thousand years ago**



**AMH and Neanderthals overlapped
in Eurasia for several thousands of years!**



DID NEANDERTHALS INTERBREED WITH MODERN HUMANS?



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

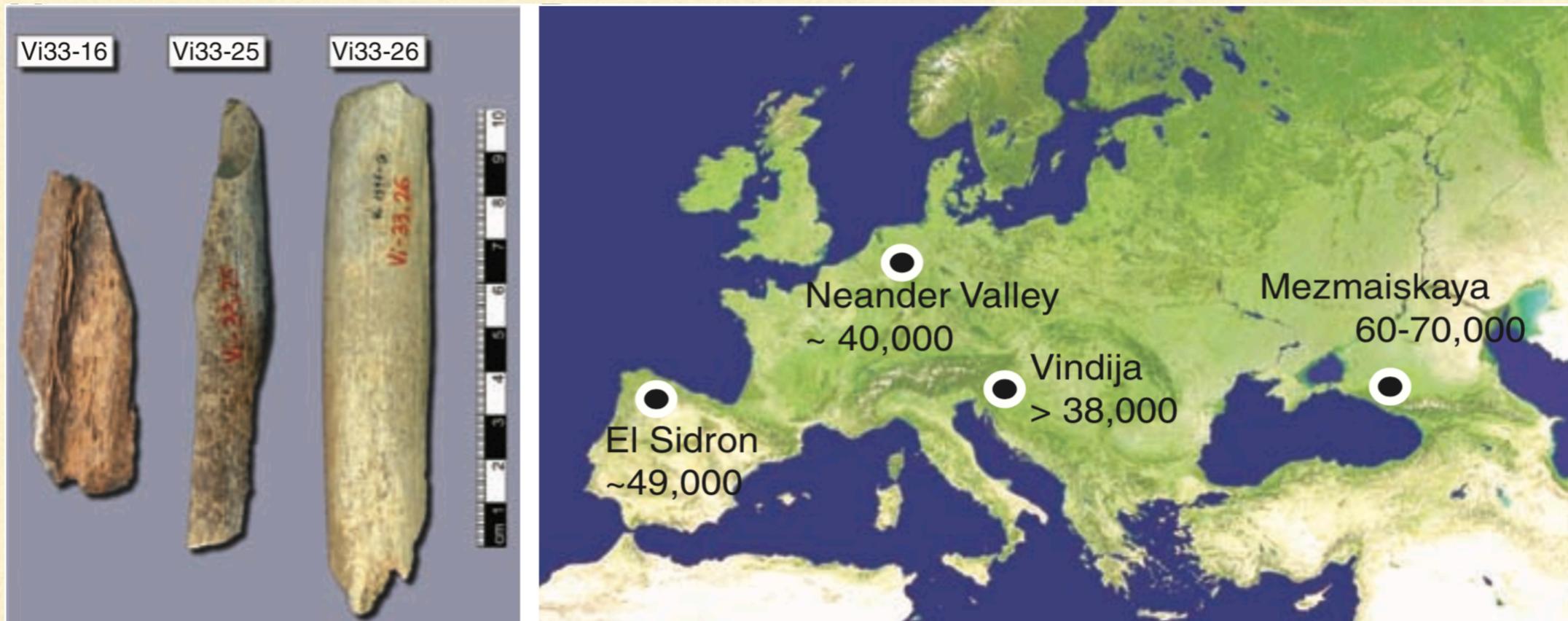
(INTERBREEDING = INTROGRESSION = ADMIXTURE)

MORPHOLOGICAL EVIDENCE?

mandible from Peștera cu Oase (Romania)



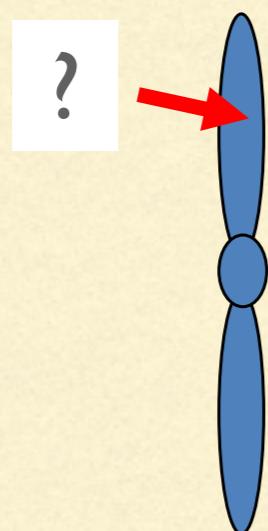
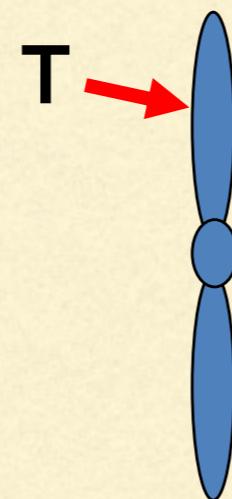
2010: NEANDERTHAL “DRAFT” GENOME



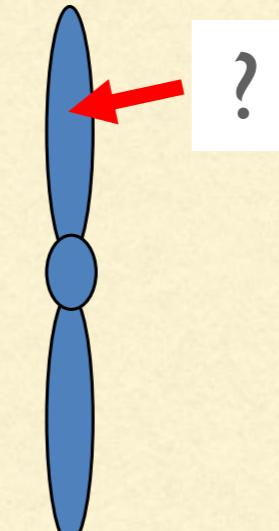
- DNA extracted from bone powder drilled from several bones
- ~1.3X coverage of the whole DNA sequence (later at 30-40X)
- **Culmination of two decades of research in Leipzig**

DETECTING ADMIXTURE

Neanderthal



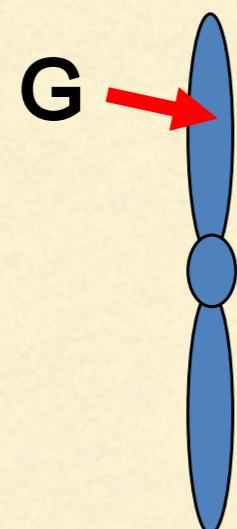
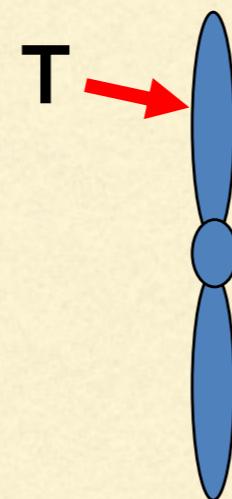
Africans



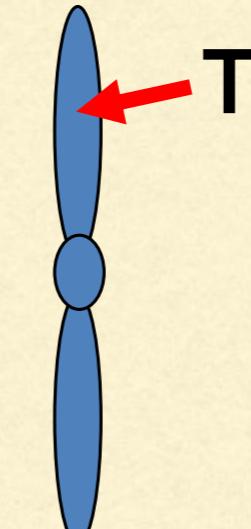
European or Asian

DETECTING ADMIXTURE

Neanderthal

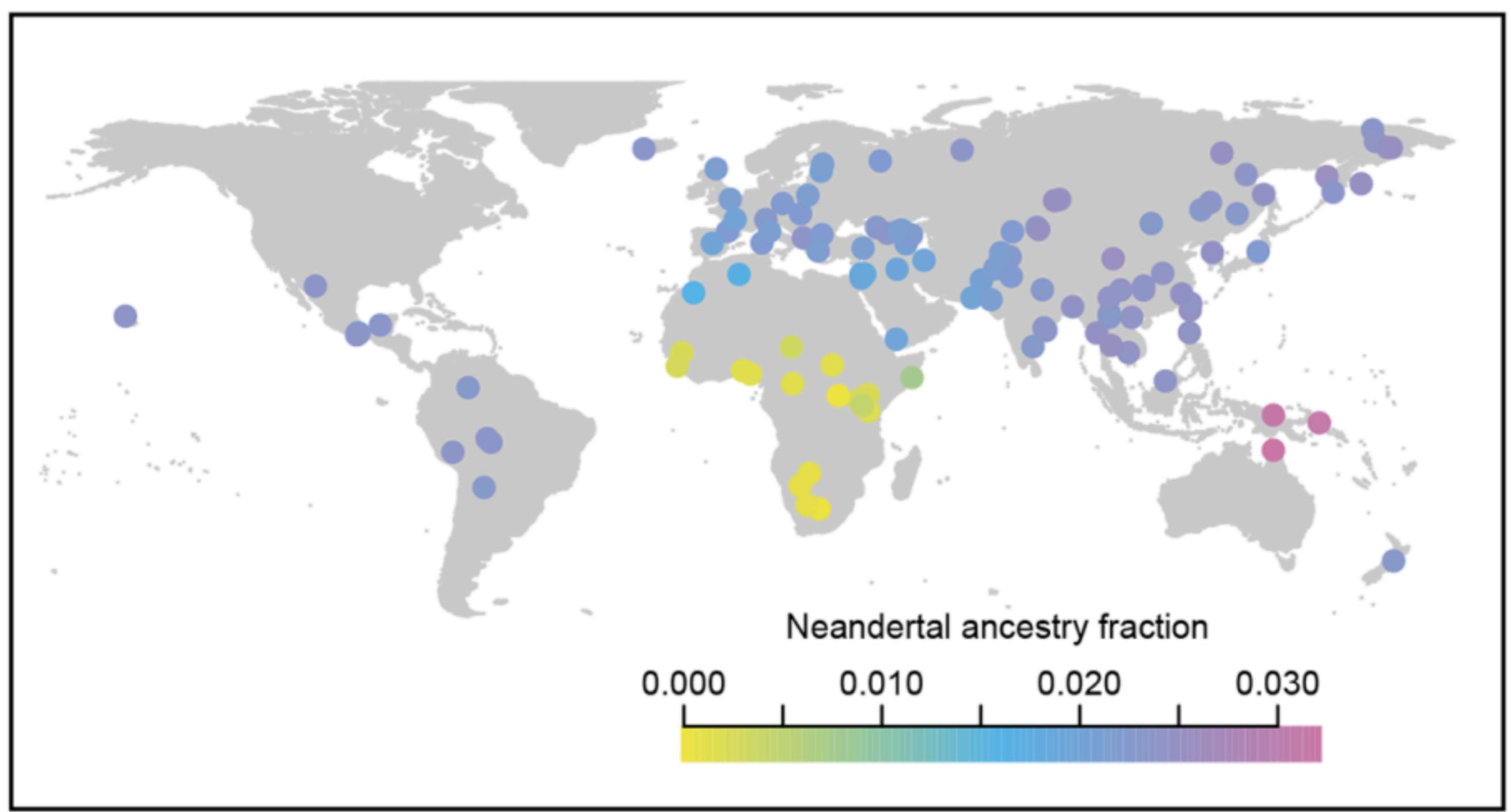


Africans

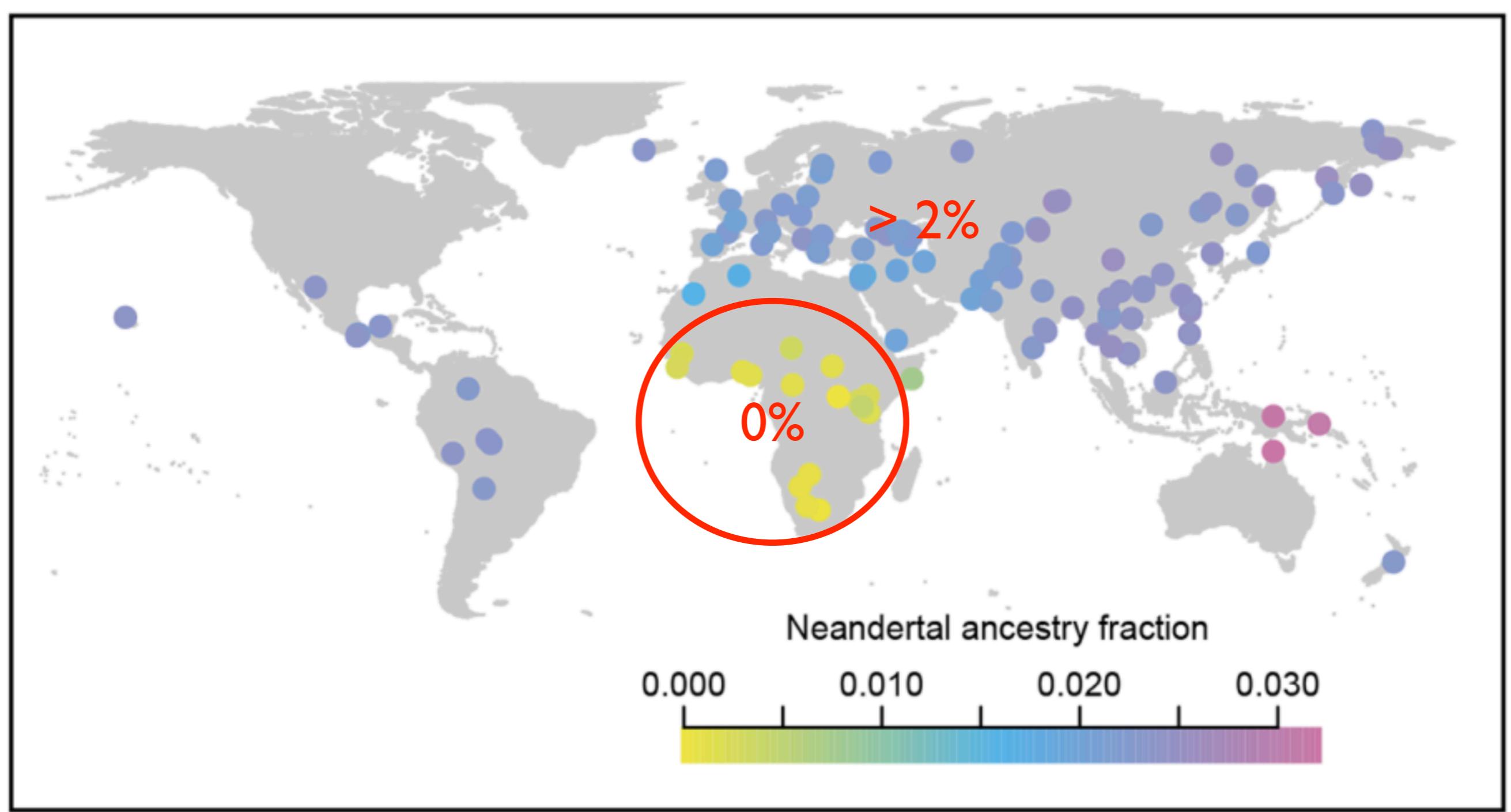


European or Asian

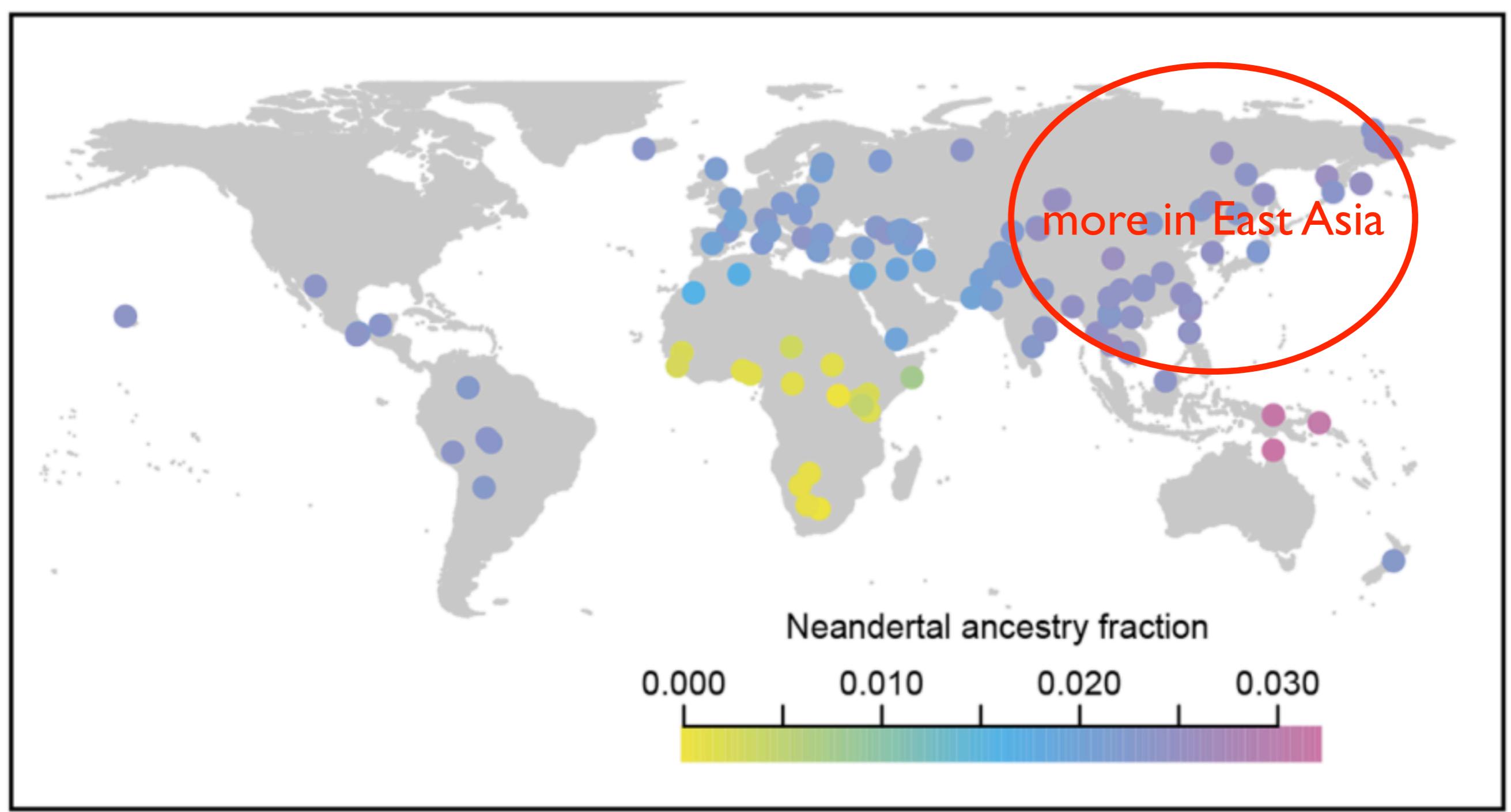
GEOGRAPHIC DISTRIBUTION OF NEANDERTHAL ANCESTRY IN THE WORLD



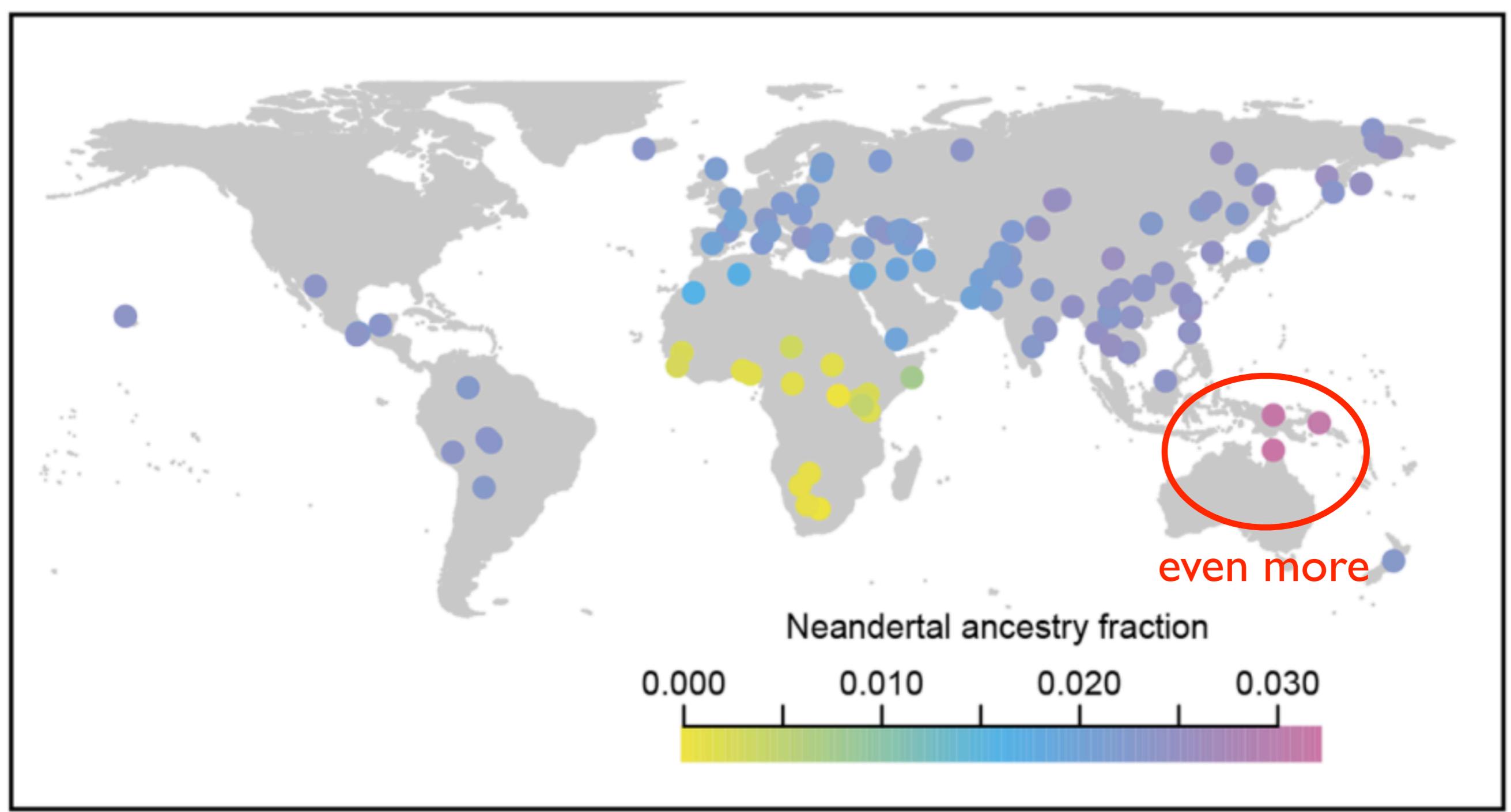
GEOGRAPHIC DISTRIBUTION OF NEANDERTHAL ANCESTRY IN THE WORLD

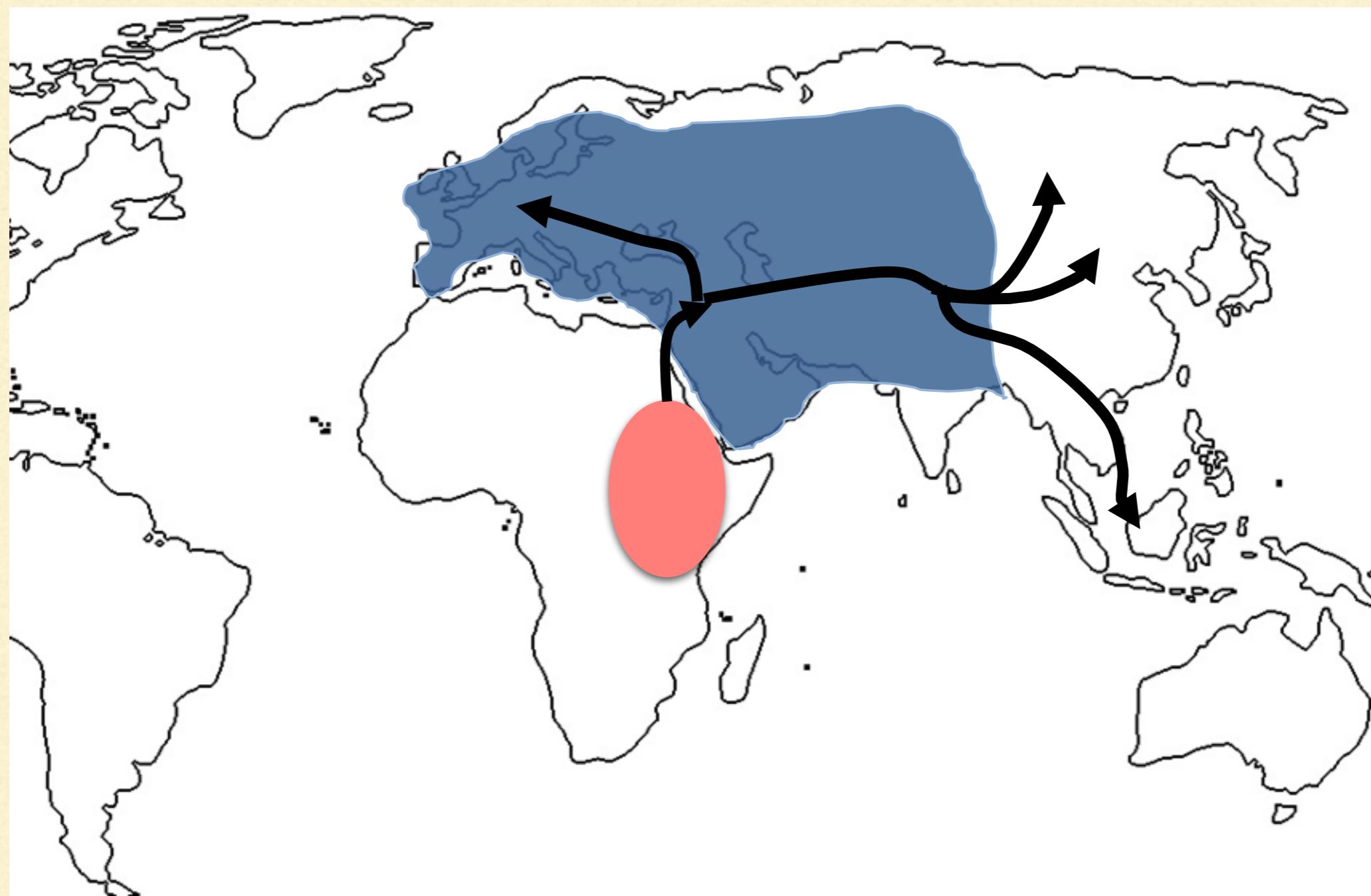


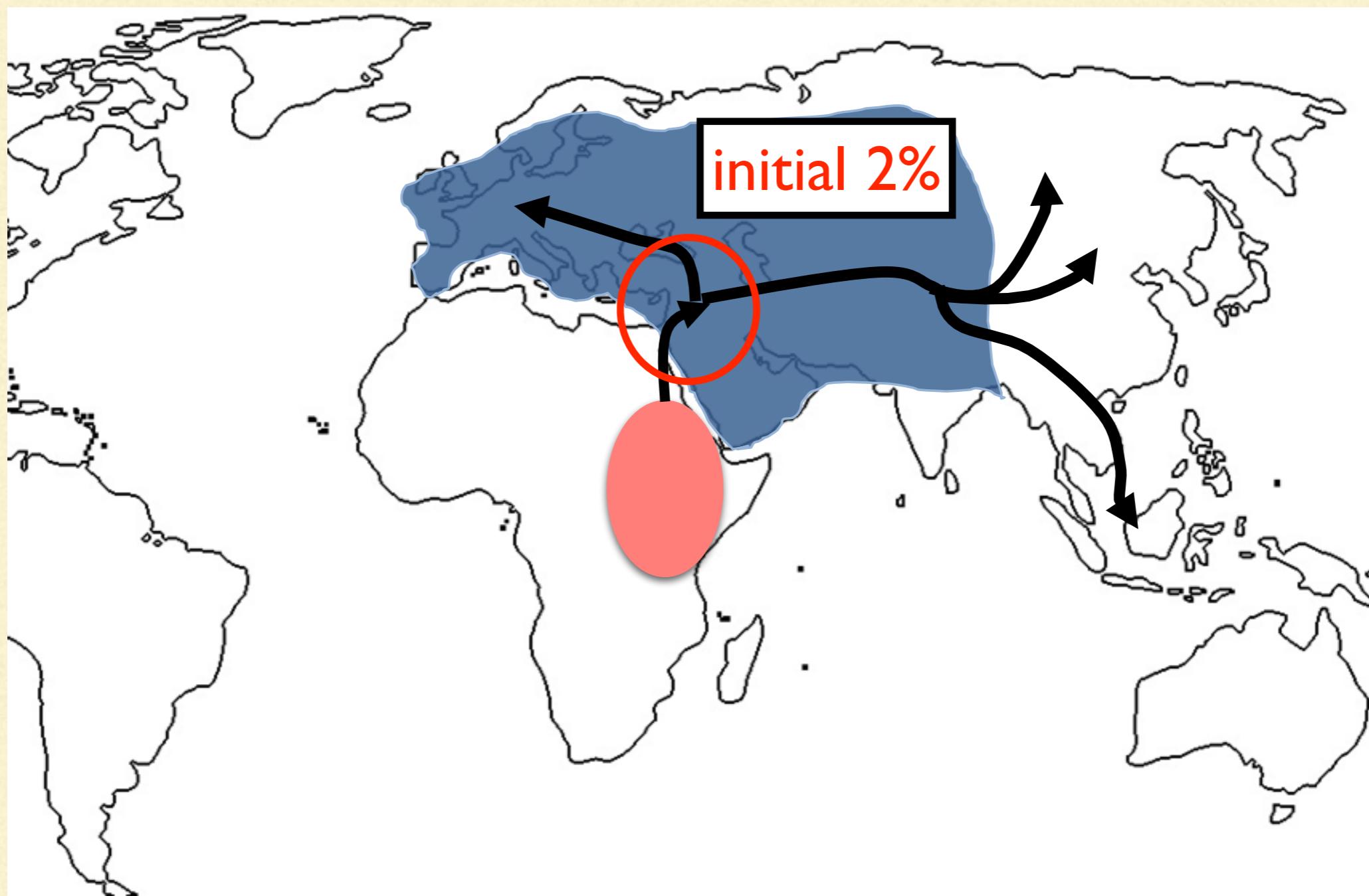
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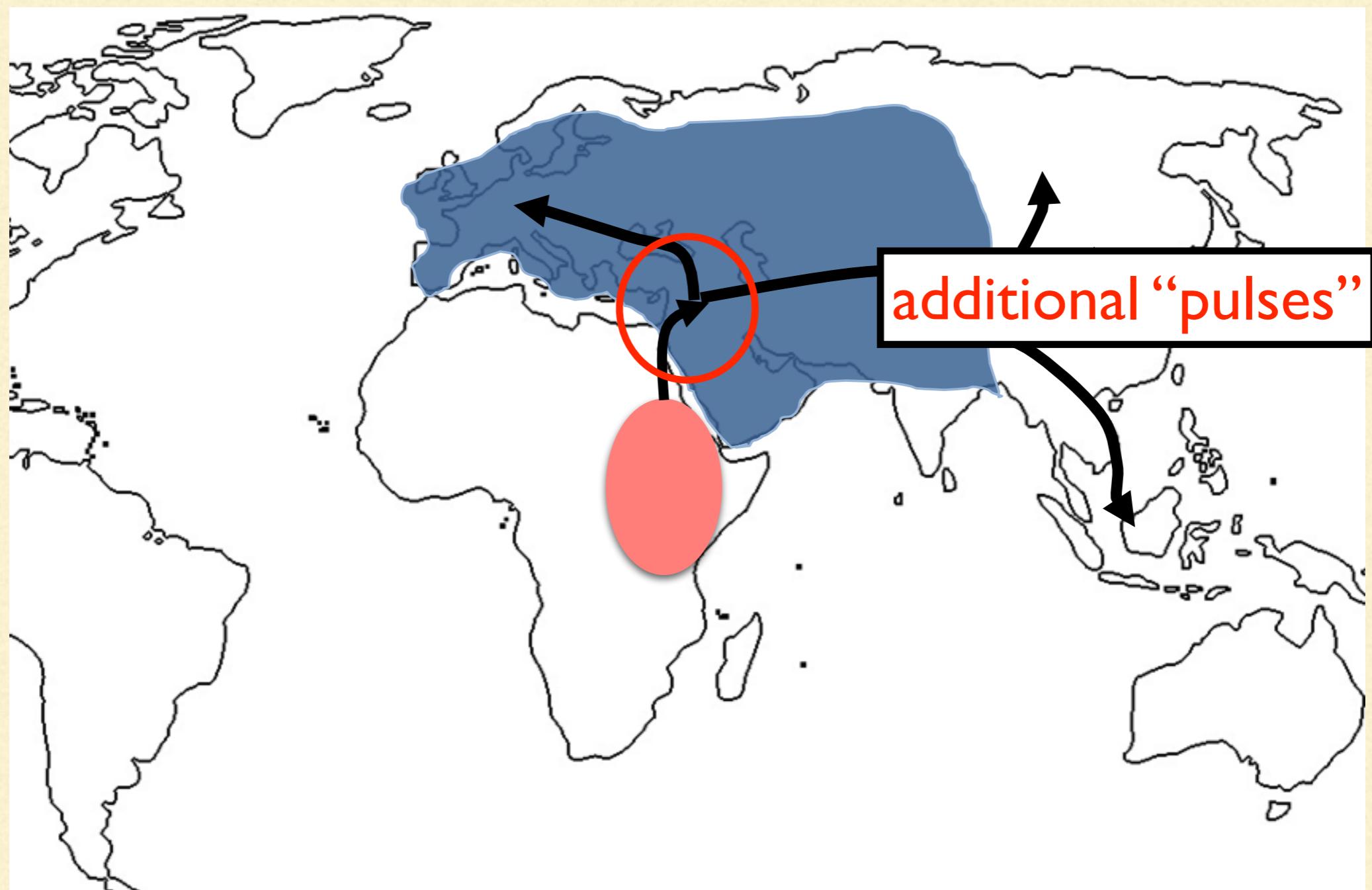


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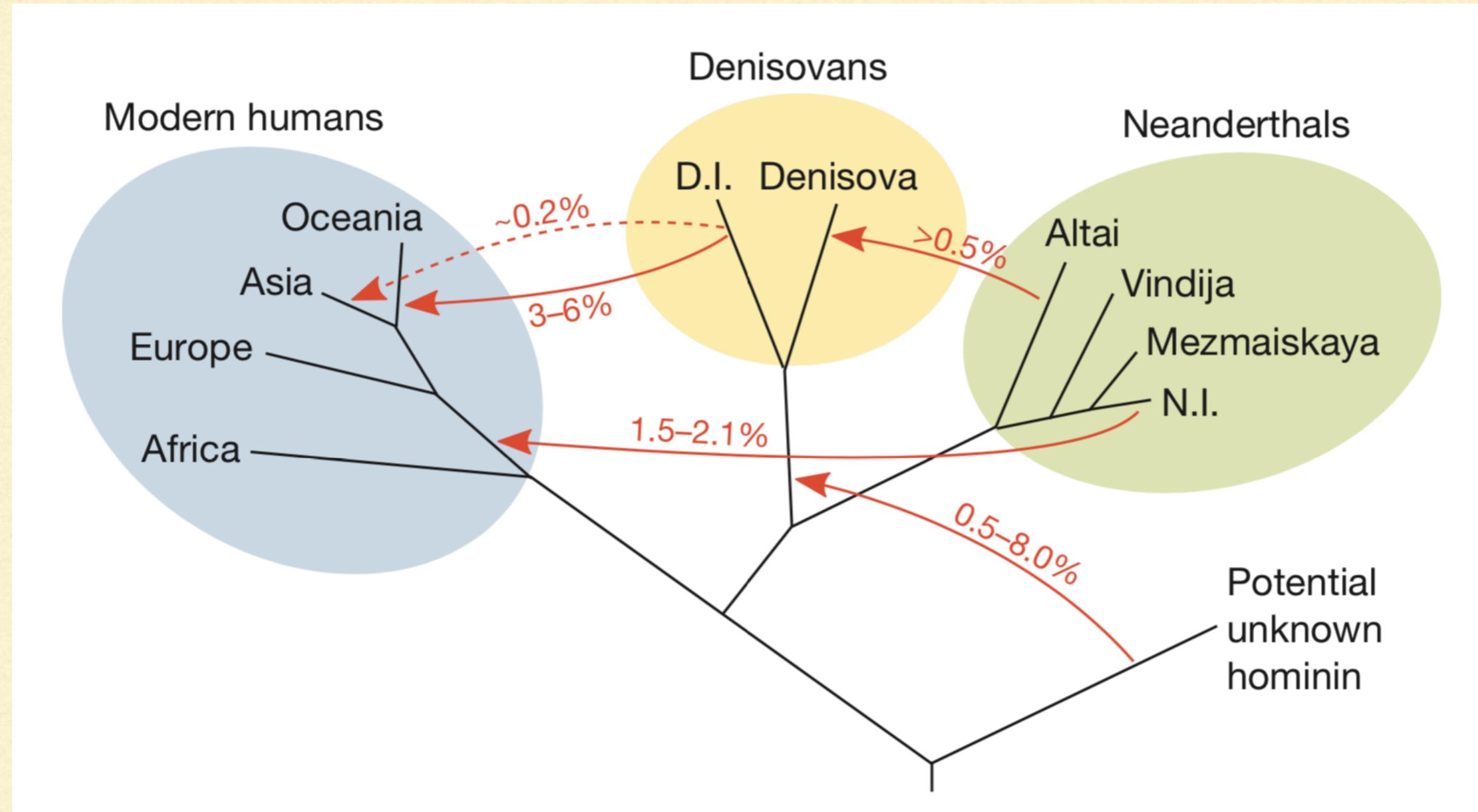


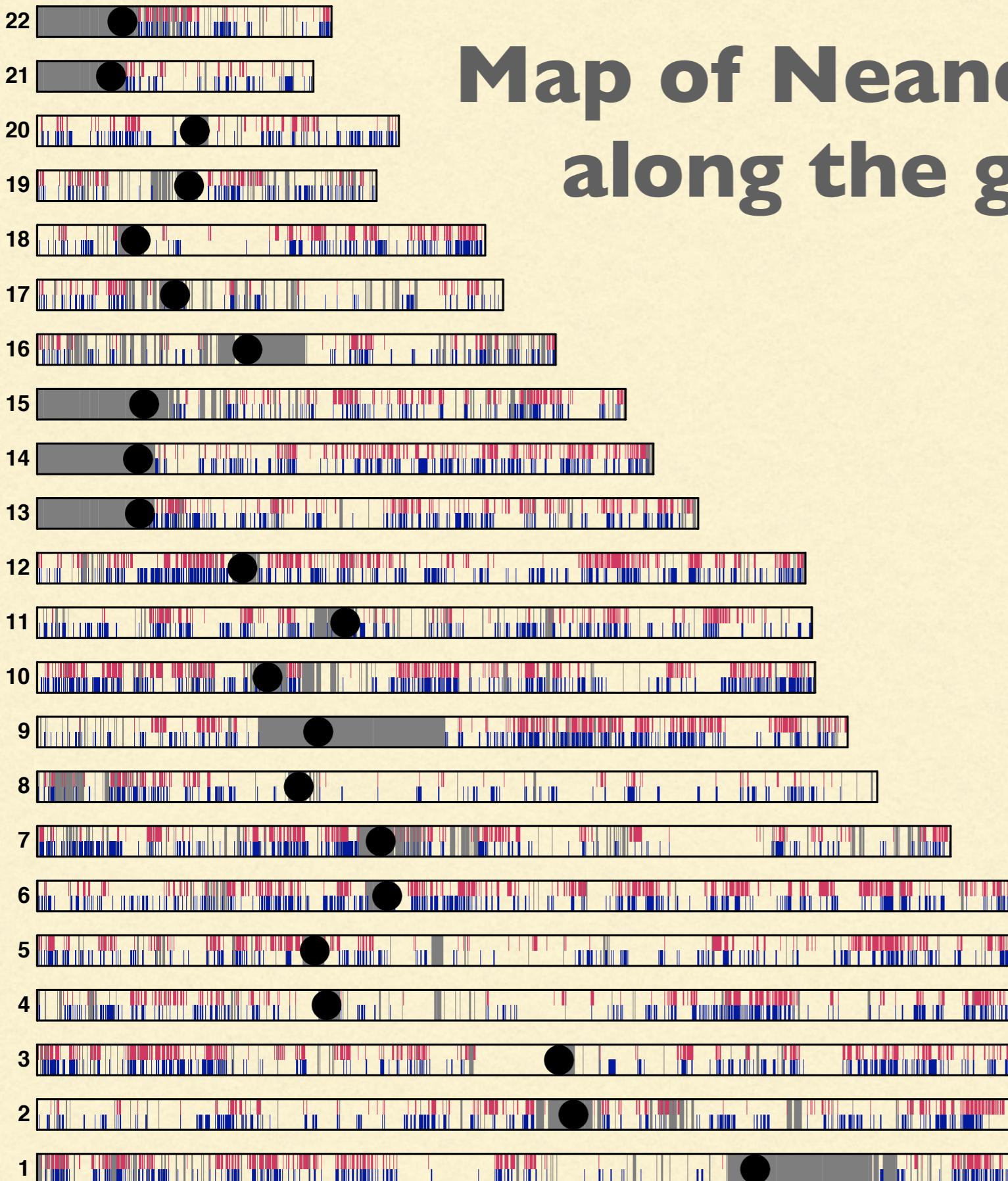






ADMIXTURE WAS COMMON!



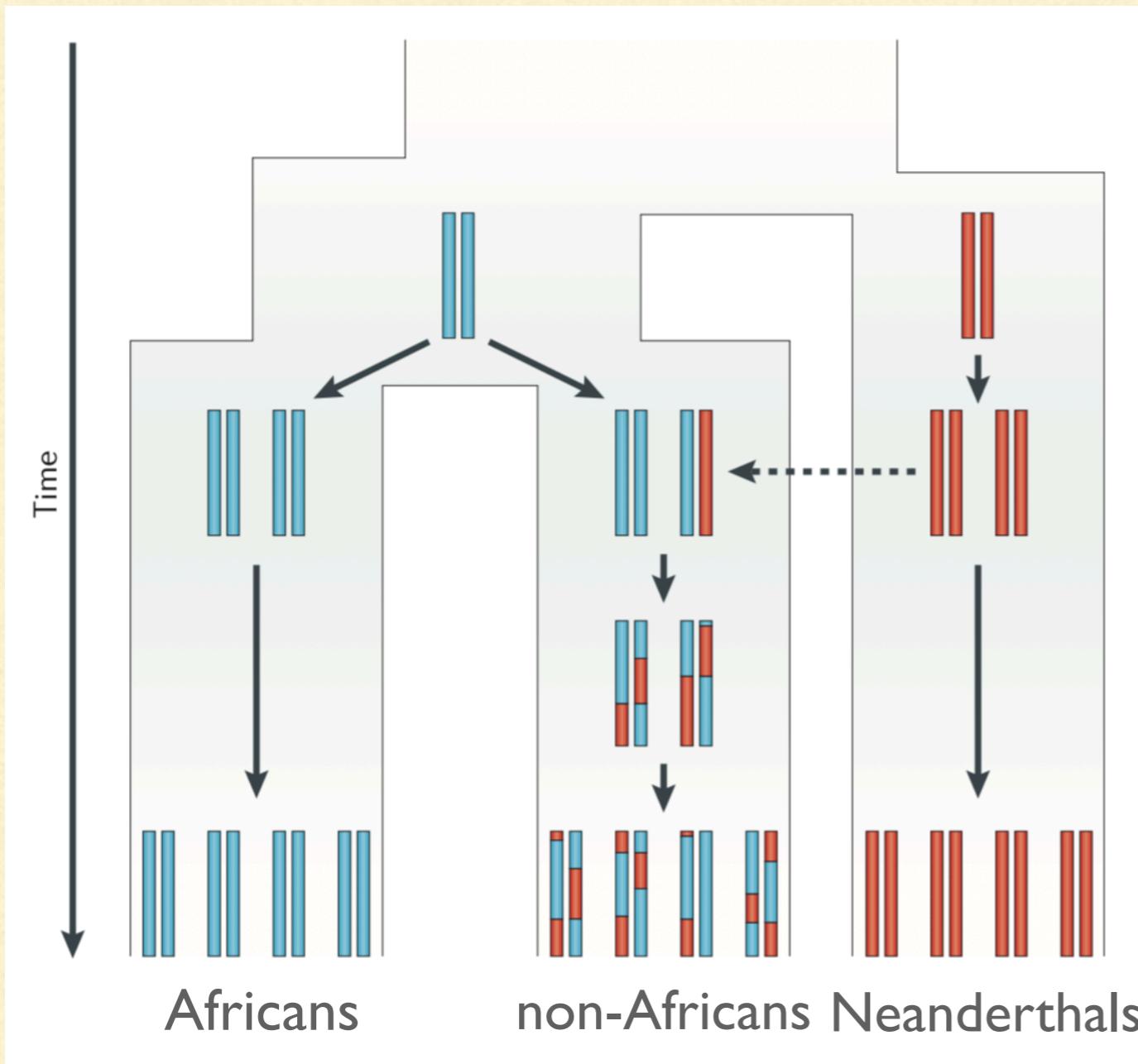


Map of Neanderthal ancestry along the genomes of ~700 East Asians and Europeans.

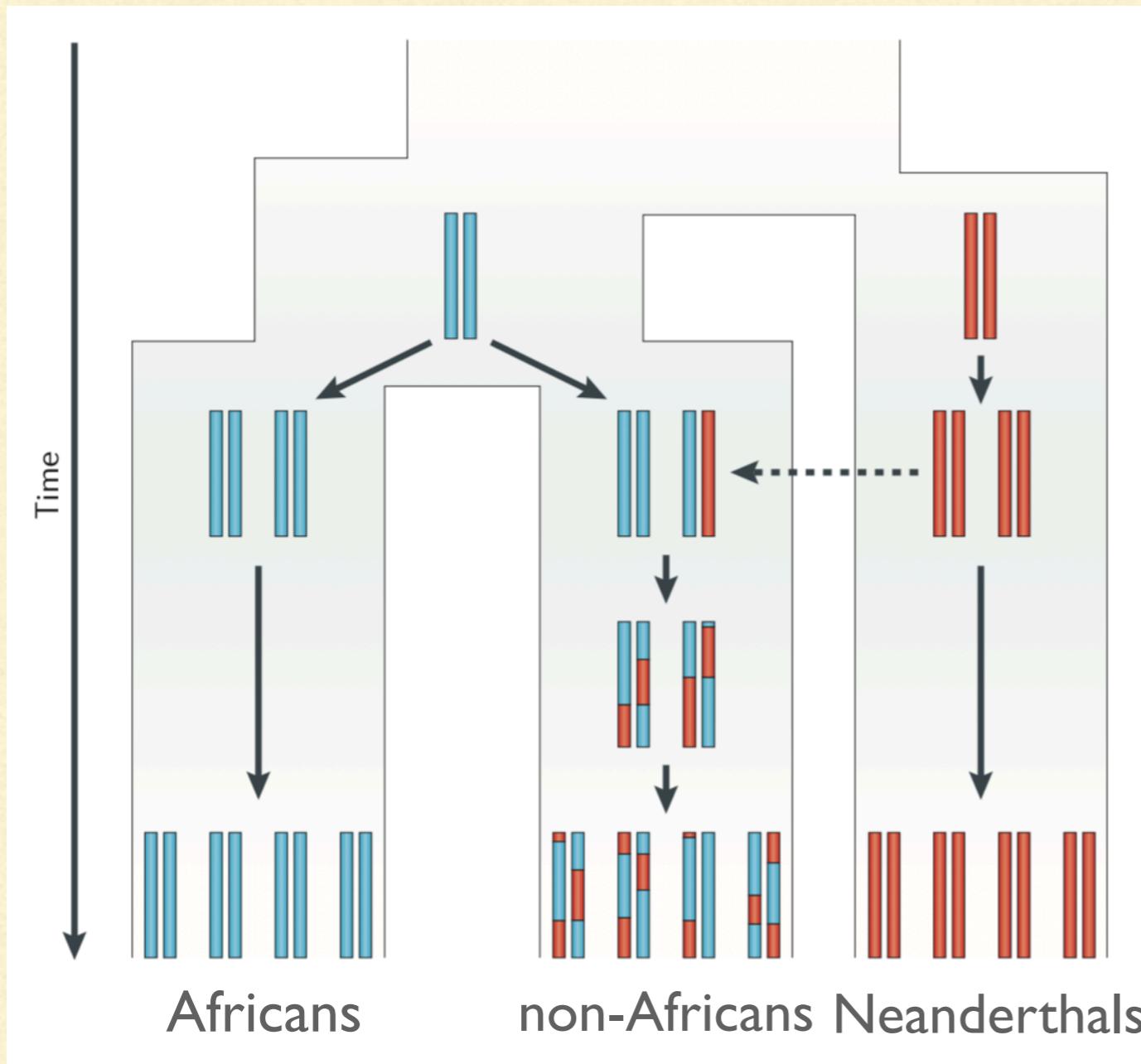
East Asians
Europeans

DATING THE NEANDERTHAL ADMIXTURE

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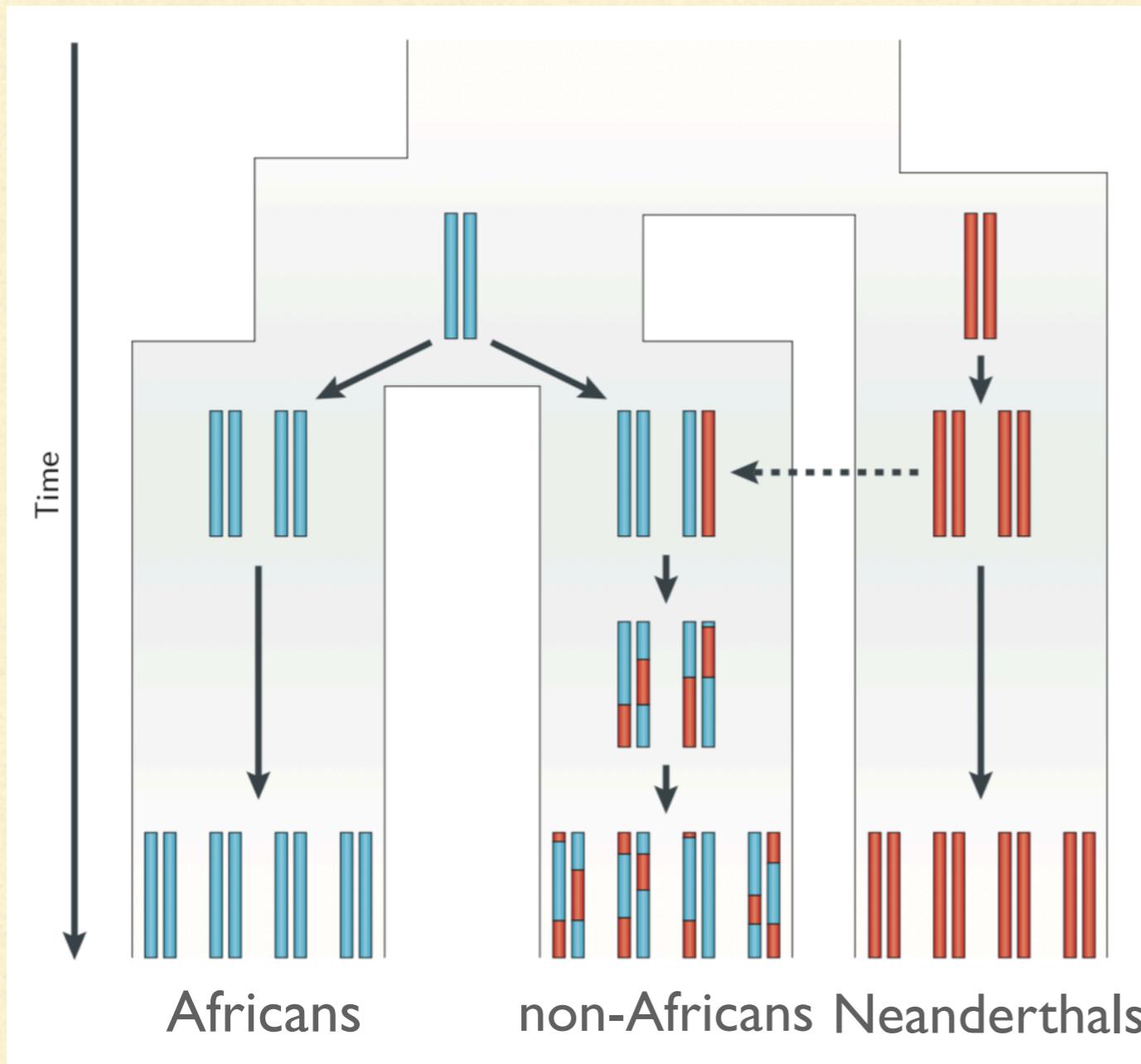


DATING THE NEANDERTHAL ADMIXTURE



Ancestry chunks are getting shorter and shorter

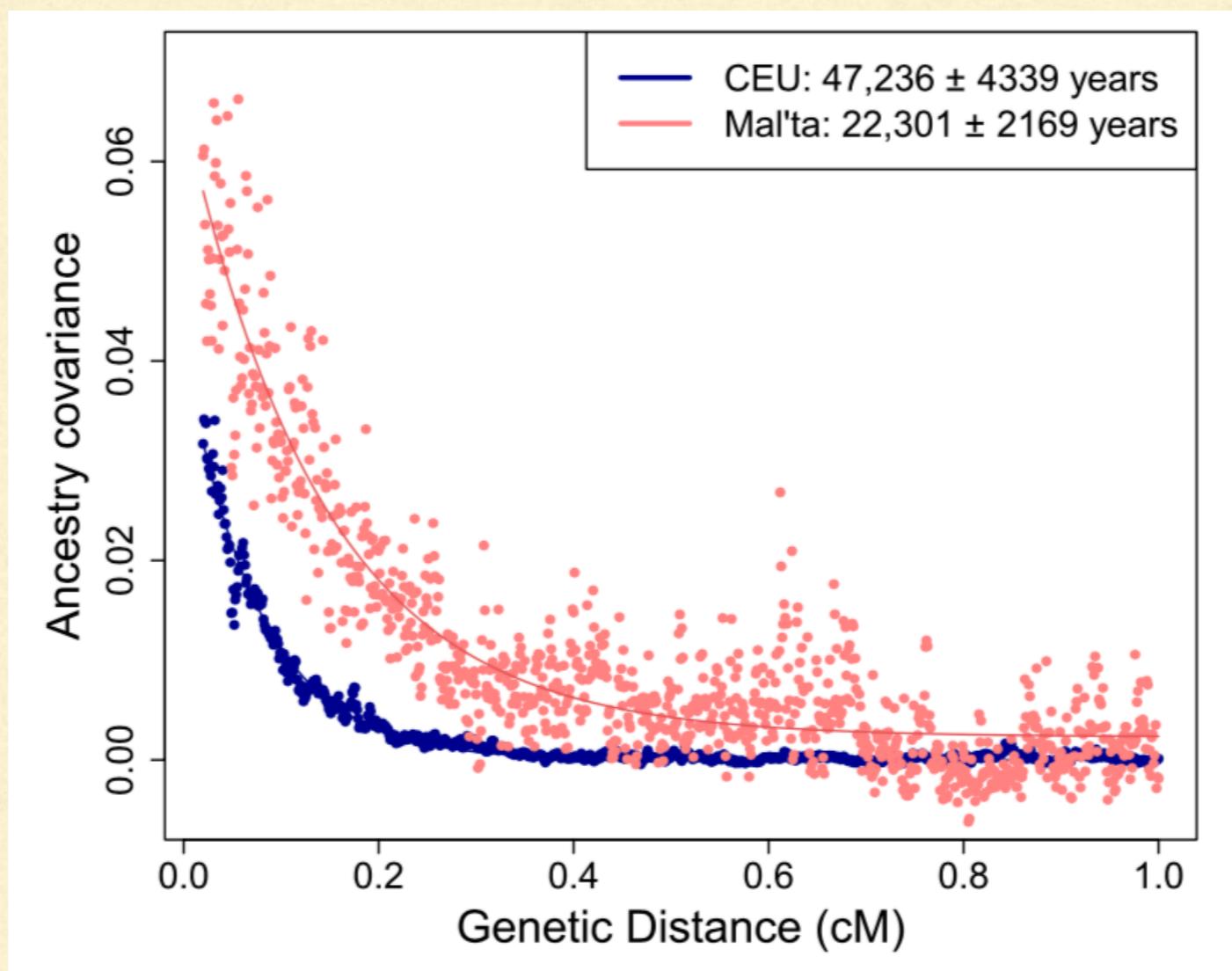
DATING THE NEANDERTHAL ADMIXTURE



Ancestry chunks are getting shorter and shorter

Expected chunk length at each time-point follows exponential decay

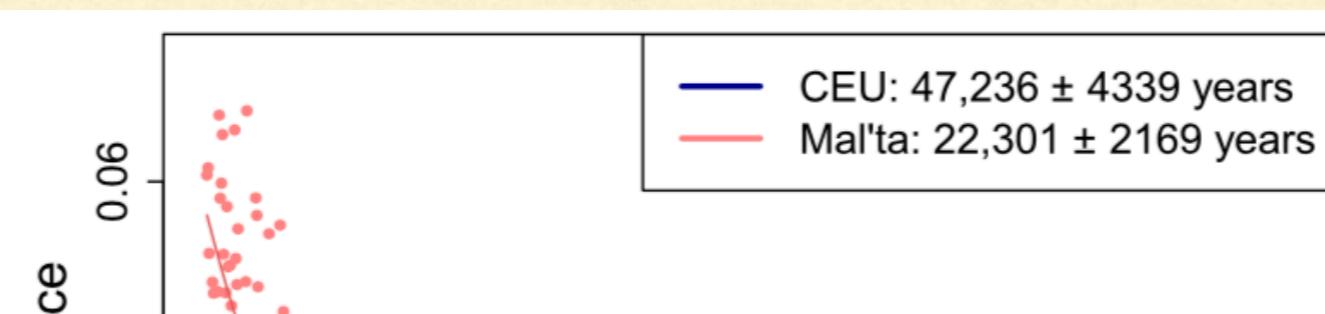
Fitting the exponential decay



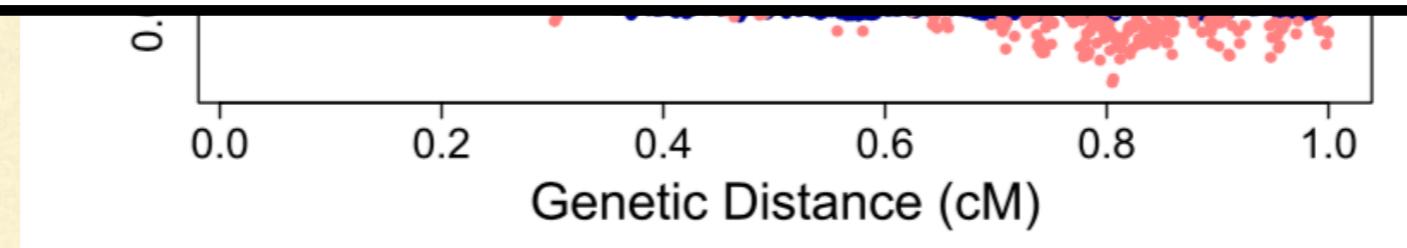
blue — distribution for present-day genomes

red — distribution for an ancient human genome

Fitting the exponential decay



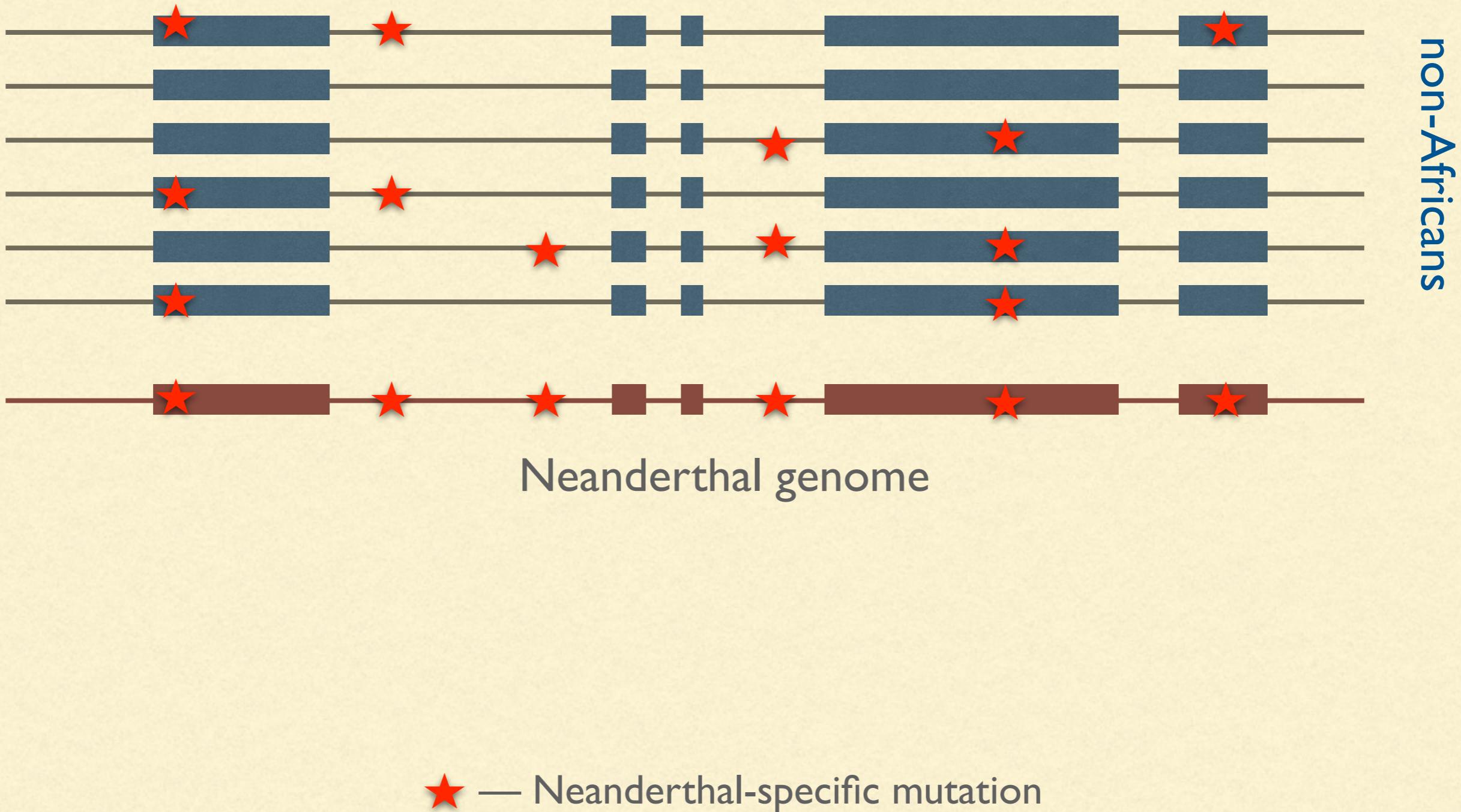
NEANDERTHAL ADMIXTURE ~55 THOUSAND YEARS AGO



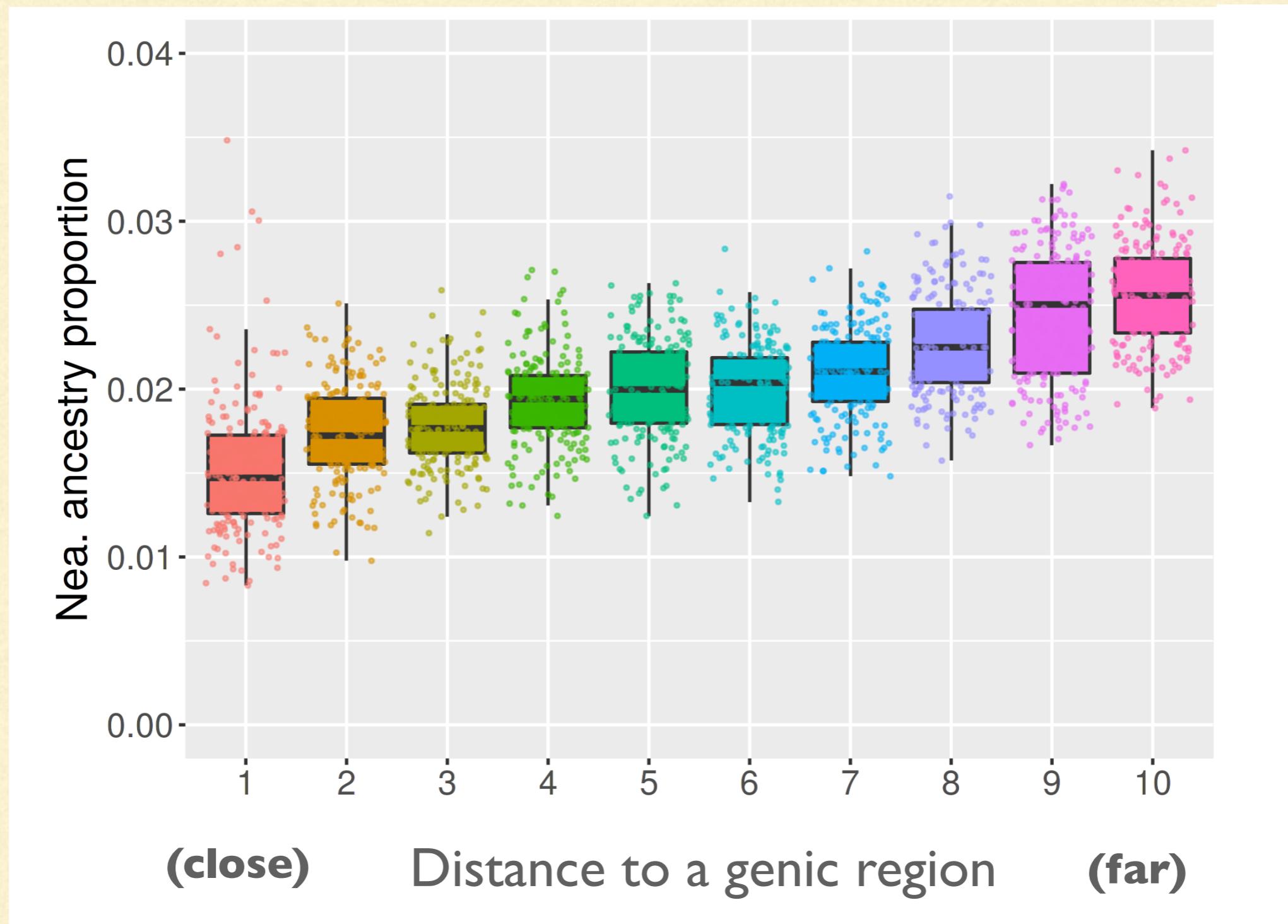
blue — distribution for present-day genomes

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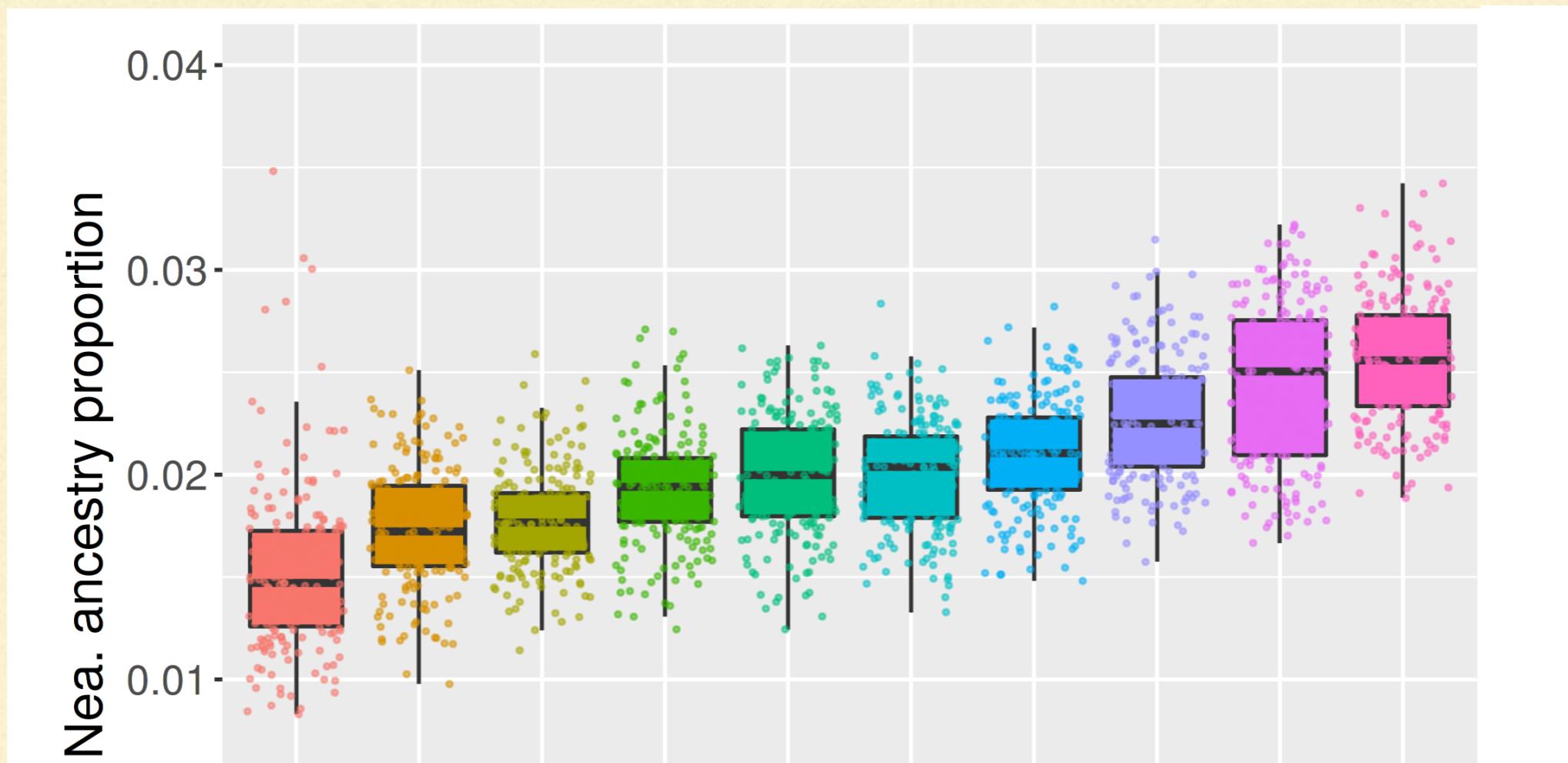
NEAND. ANCESTRY VS DISTANCE TO GENES?



LESS NEANDERTHAL ANCESTRY NEAR GENES



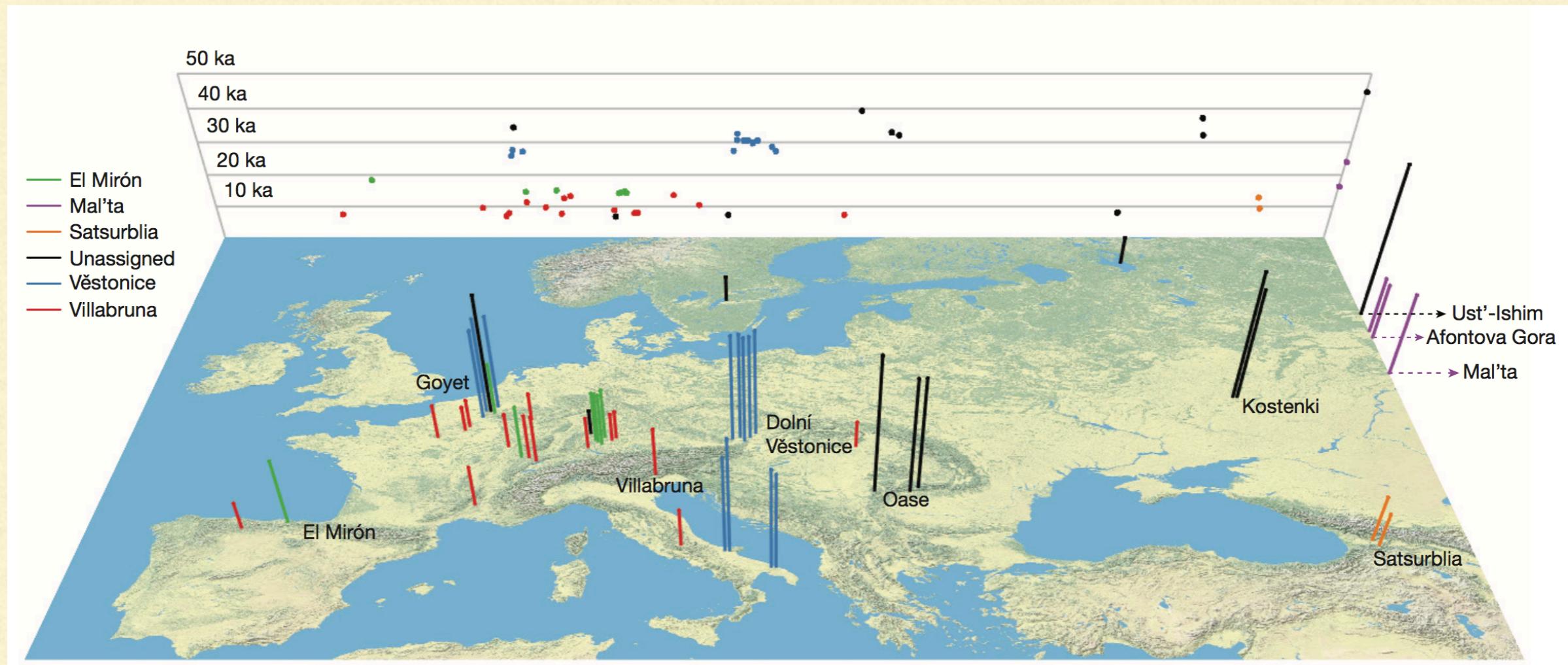
LESS NEANDERTHAL ANCESTRY NEAR GENES



**SIGNAL OF GENOME-WIDE NEGATIVE
SELECTION AGAINST INTROGRESSION!**

**ON WHAT TIME-SCALE
DID THIS HAPPEN?**

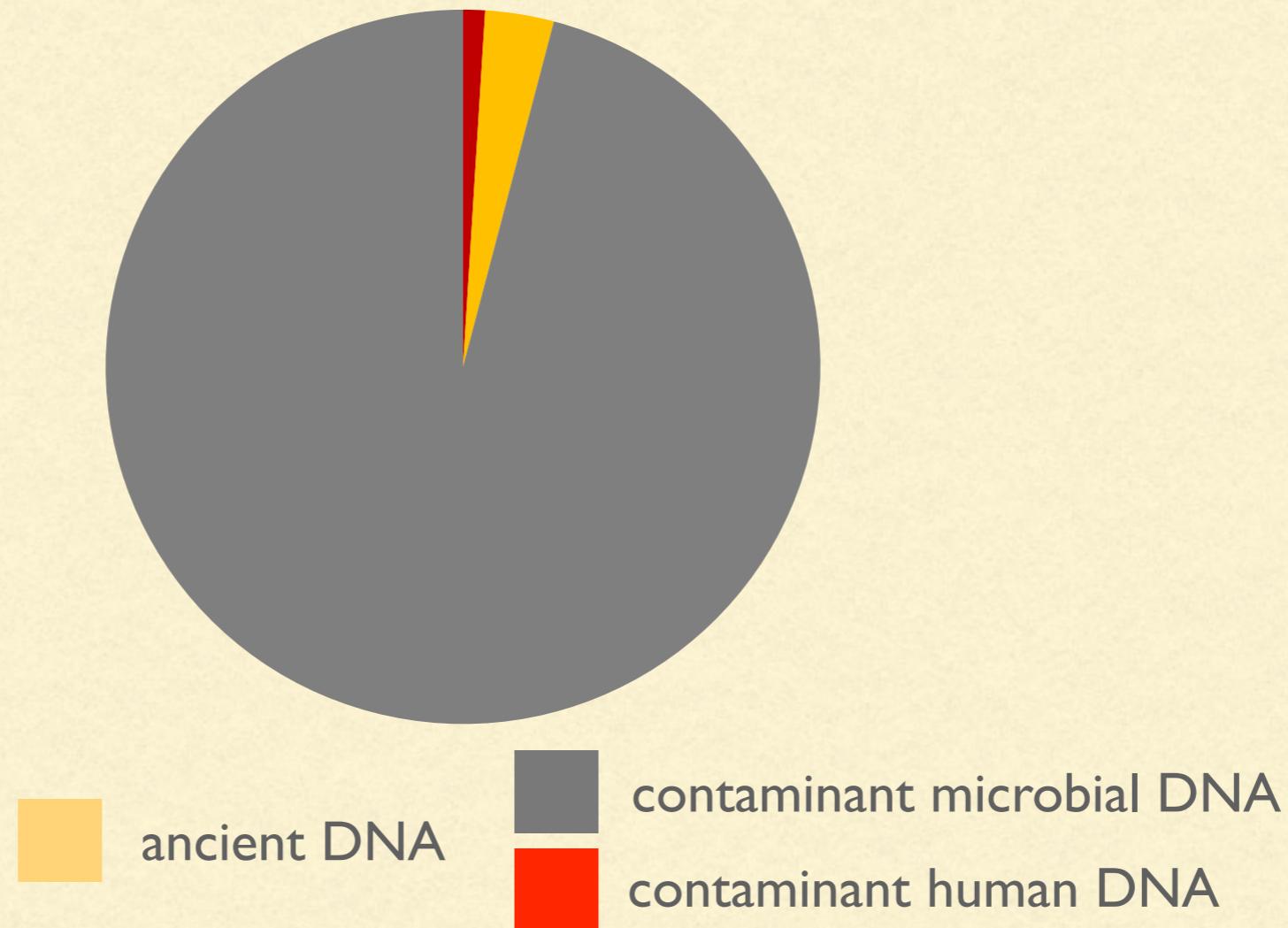
“THE GENETIC HISTORY OF ICE AGE EUROPE”



Bones and teeth of 51 European individuals
(45,000-8,000 years old)

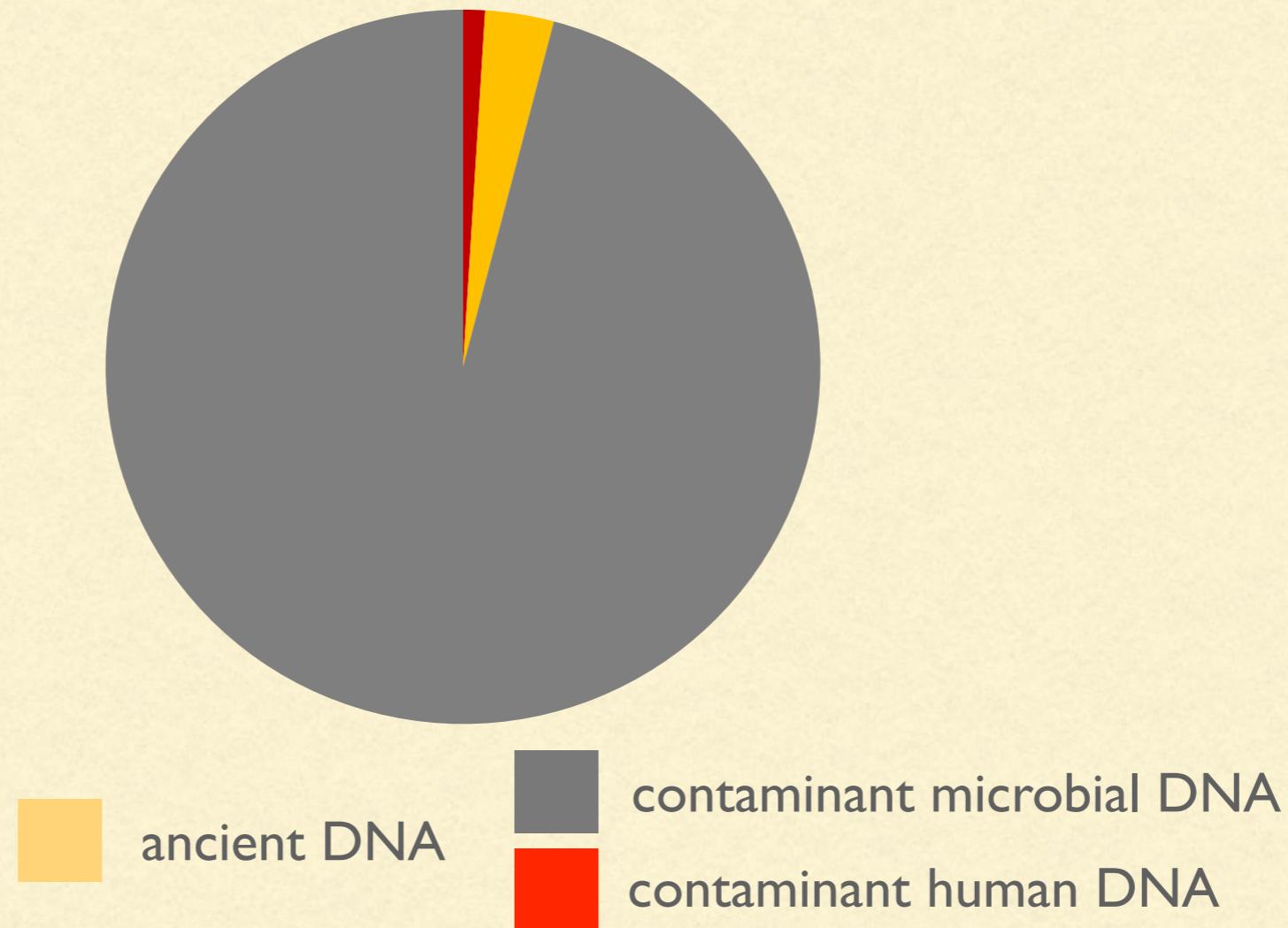
SNP CAPTURE METHOD

- aDNA contaminated by microbes (often < 1% endogenous)



SNP CAPTURE METHOD

- aDNA contaminated by microbes (often < 1% endogenous)
- Majority of the genome the same in every human

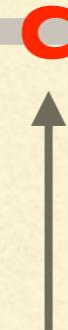


SNP CAPTURE METHOD

- aDNA contaminated by microbes (often < 1% endogenous)
- Majority of the genome the same in every human
- **We can enrich for “interesting” loci (~2 million):**
 - Known to be polymorphic in archaic and modern humans
 - Capture and sequence only those using molecular “baits”

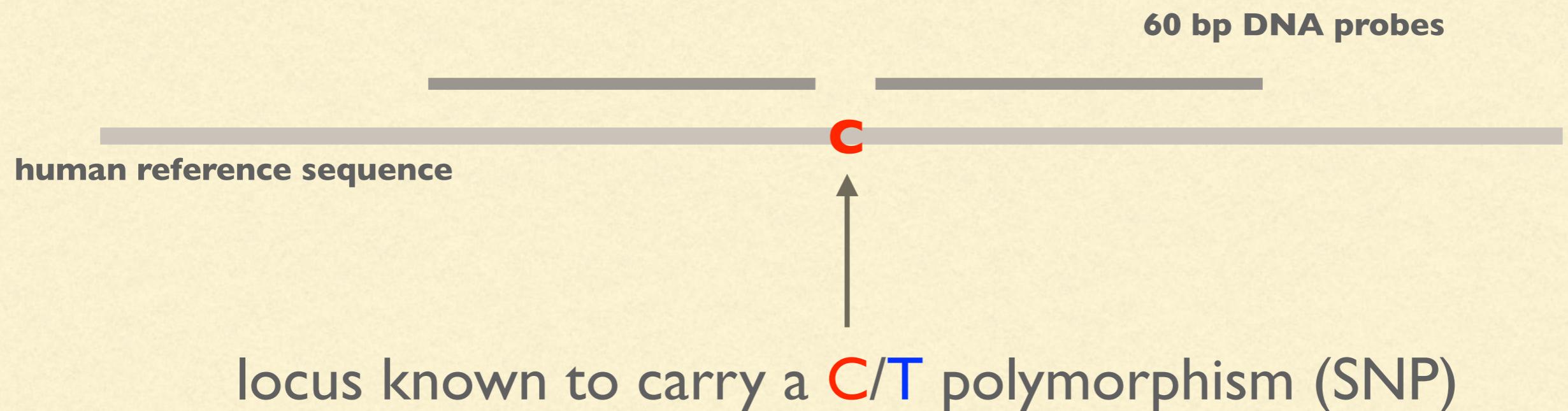
SNP CAPTURE BAITS

human reference sequence

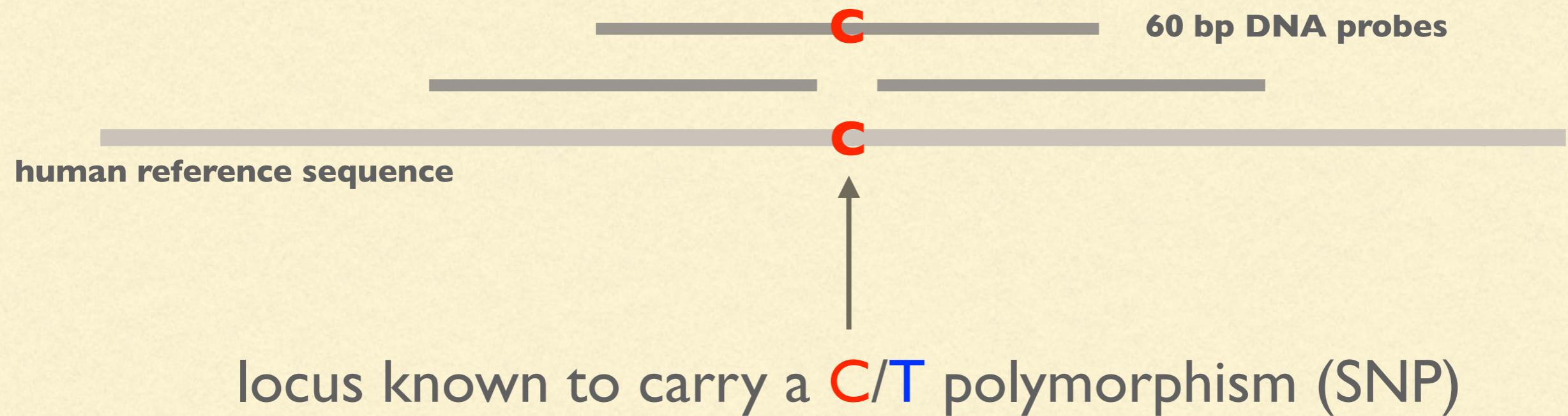


locus known to carry a C/T polymorphism (SNP)

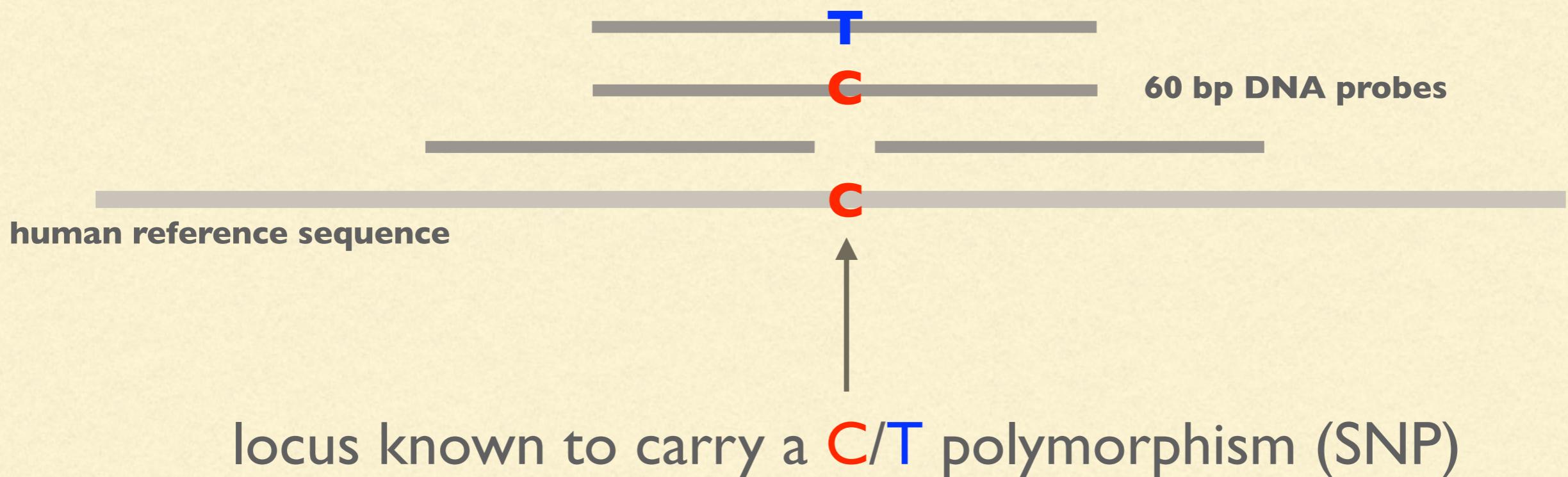
SNP CAPTURE BAITS



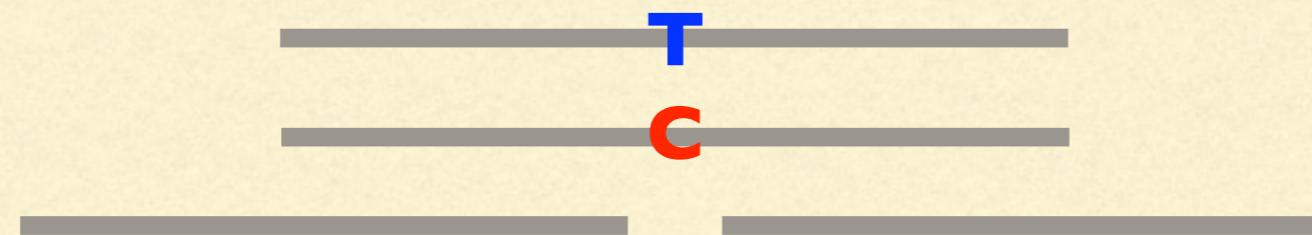
SNP CAPTURE BAITS



SNP CAPTURE BAITS

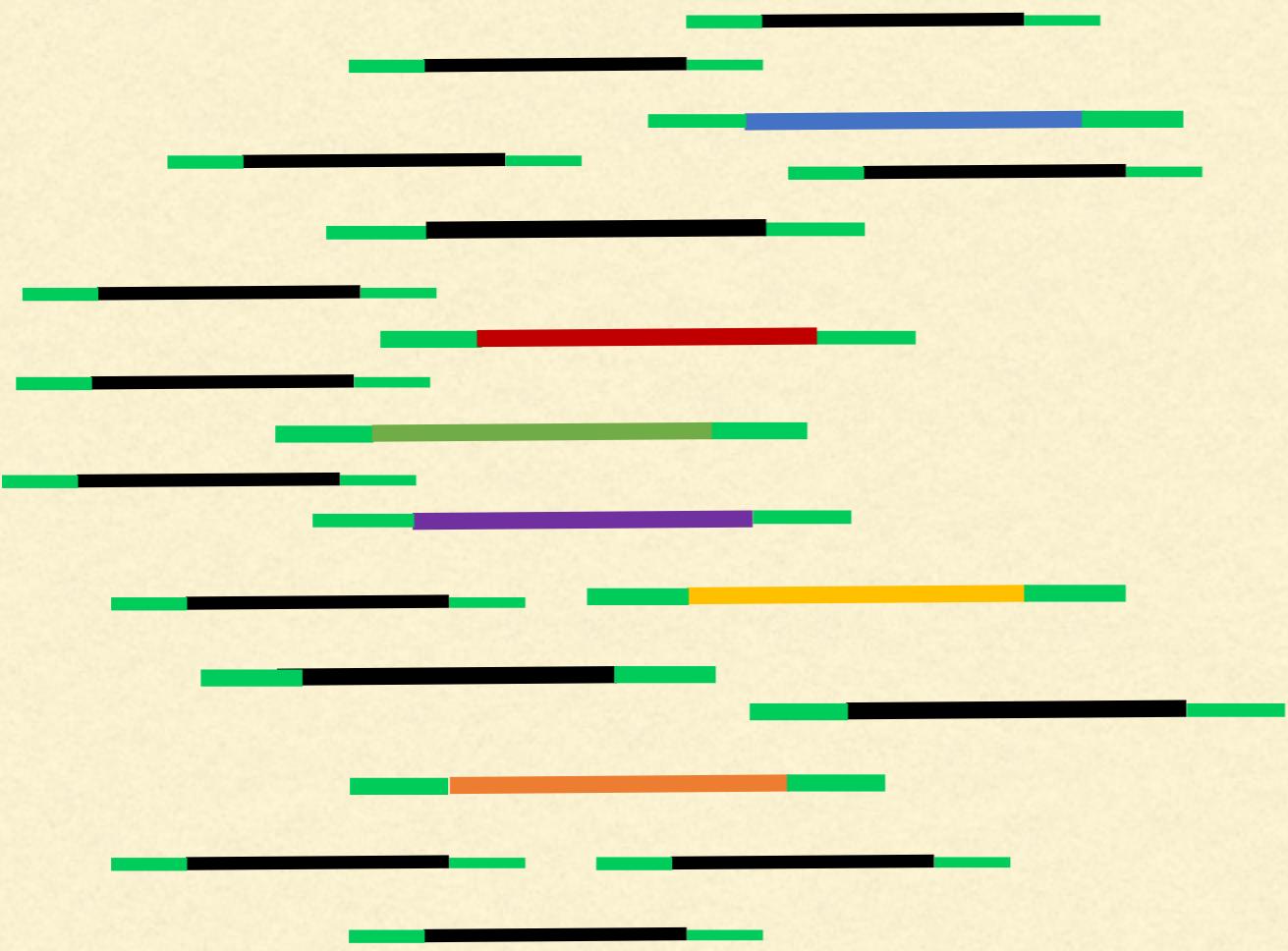


SNP CAPTURE BAITS

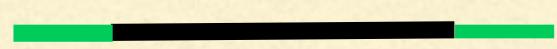
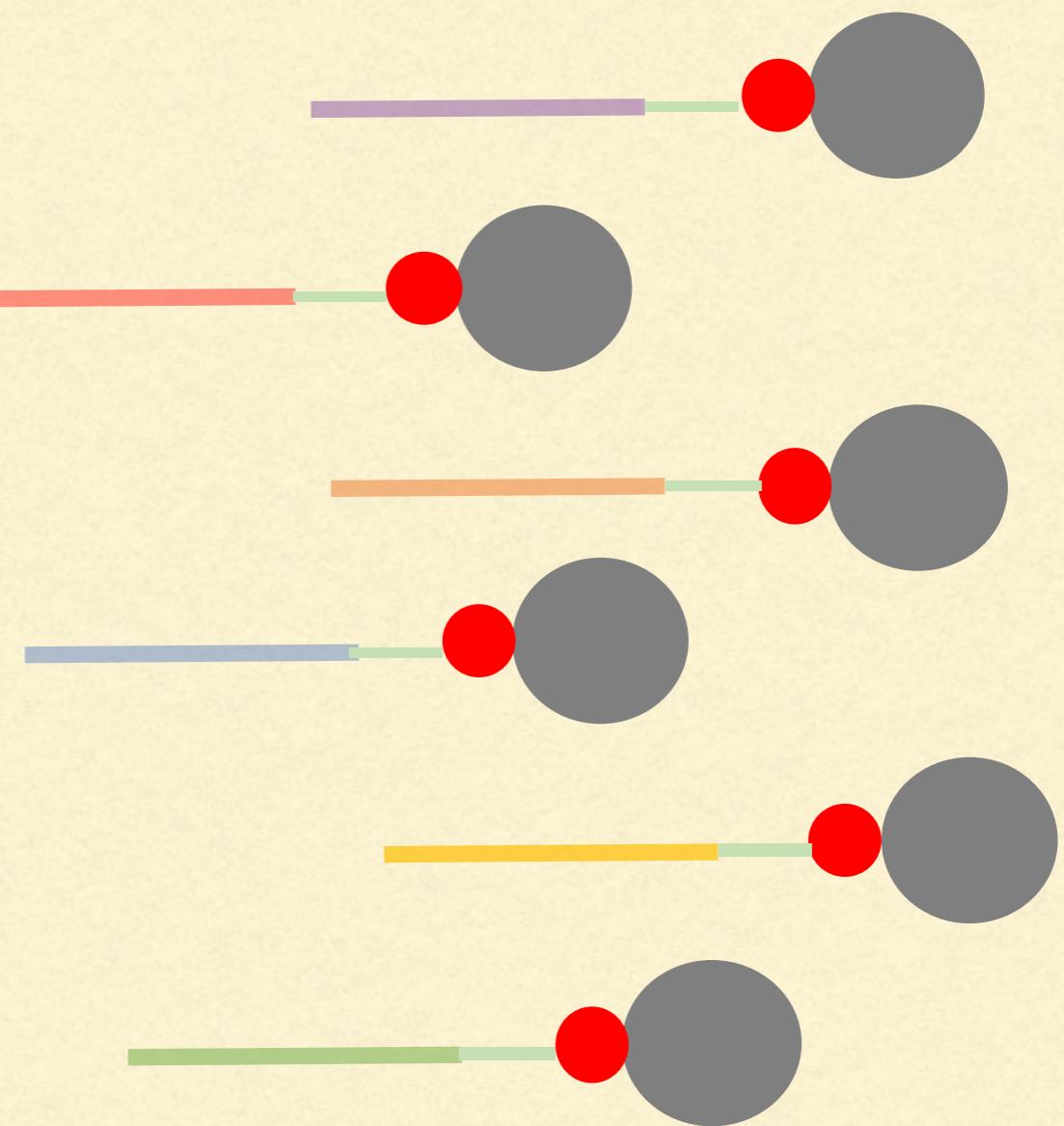


for each SNP we have 4x60 bp synthetic molecular “baits”

DNA mixture from a bone



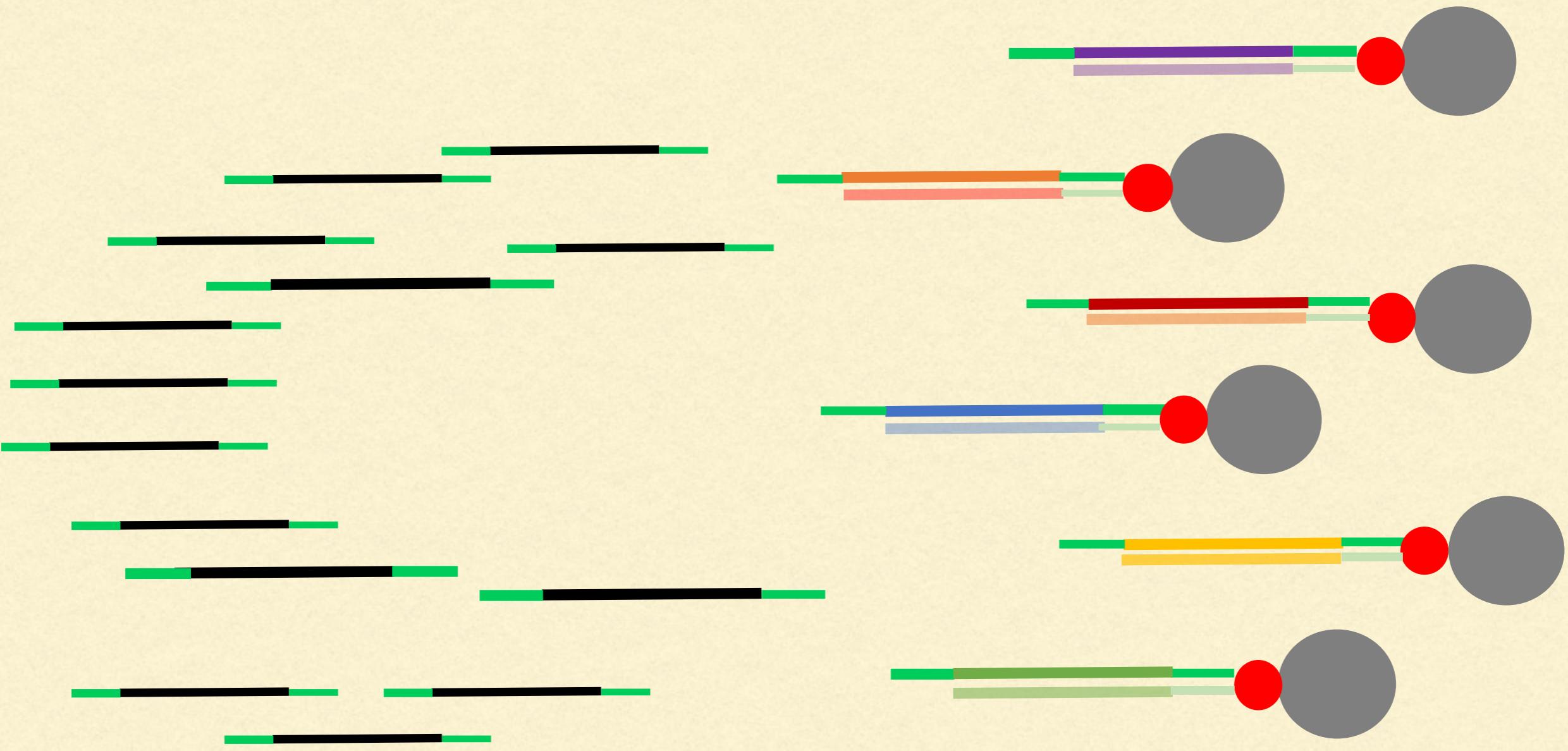
molecular baits



microbial DNA or “uninteresting” human sequence

DNA mixture from a bone

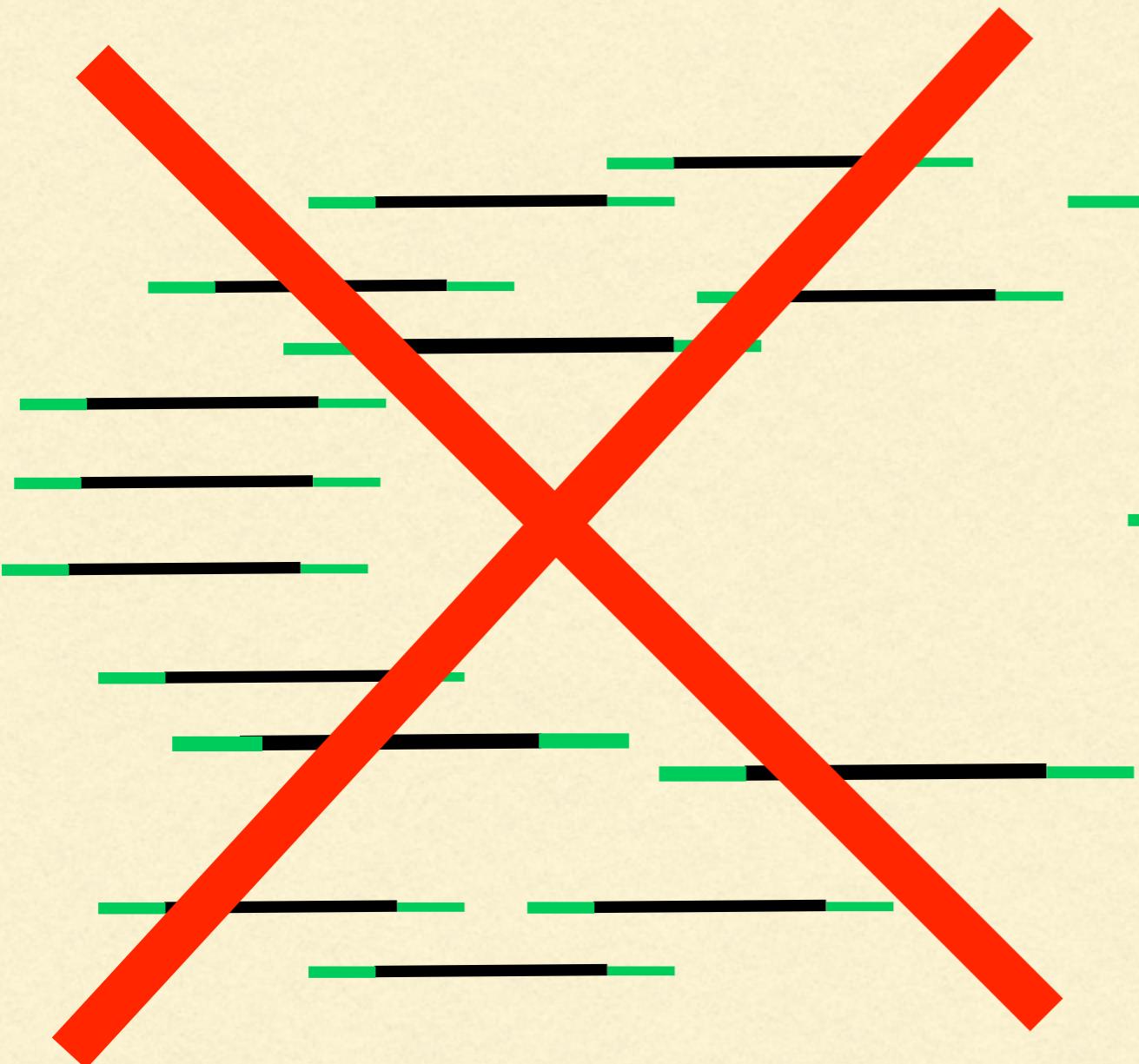
molecular baits



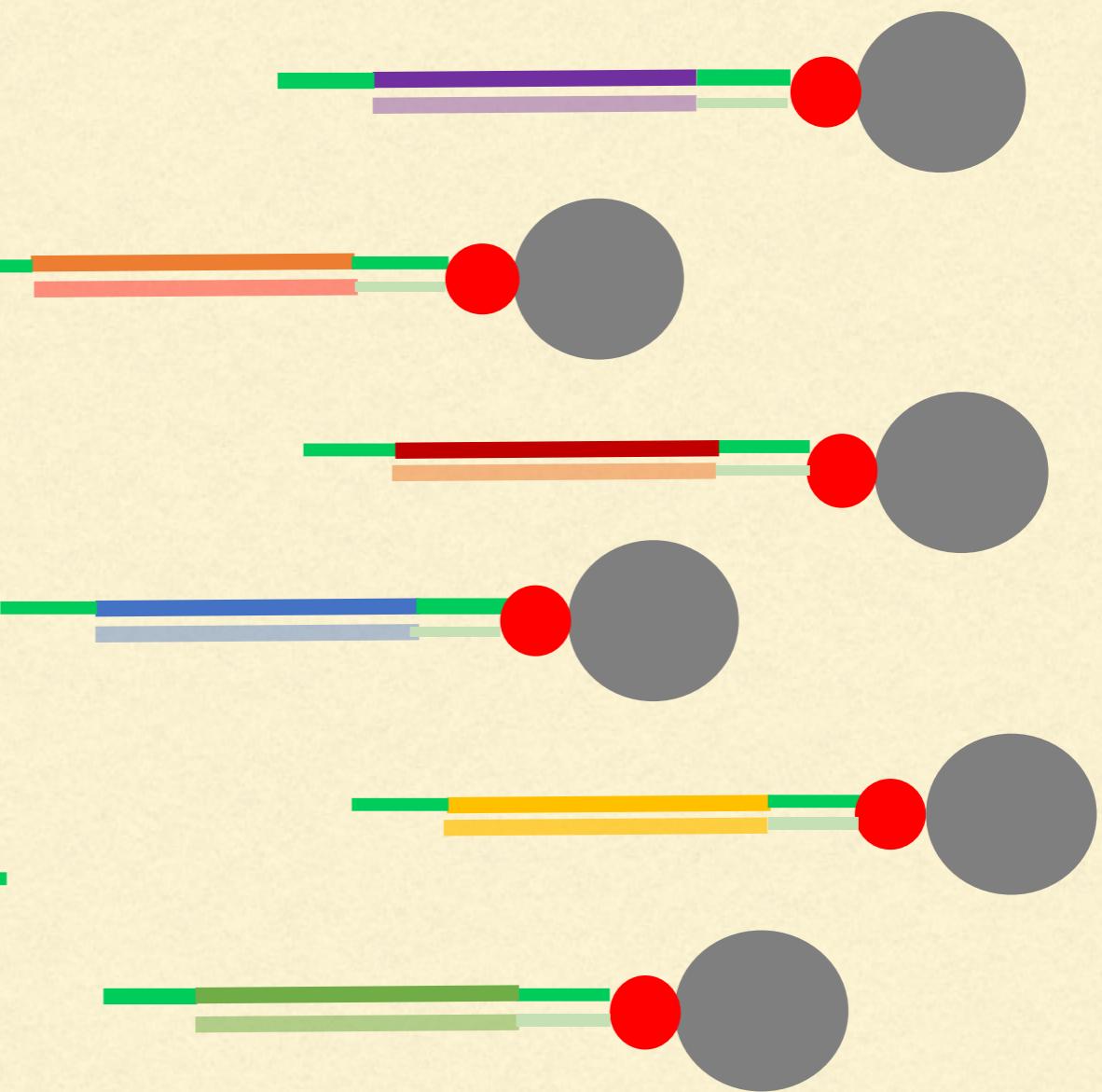
— microbial DNA or “uninteresting” human sequence

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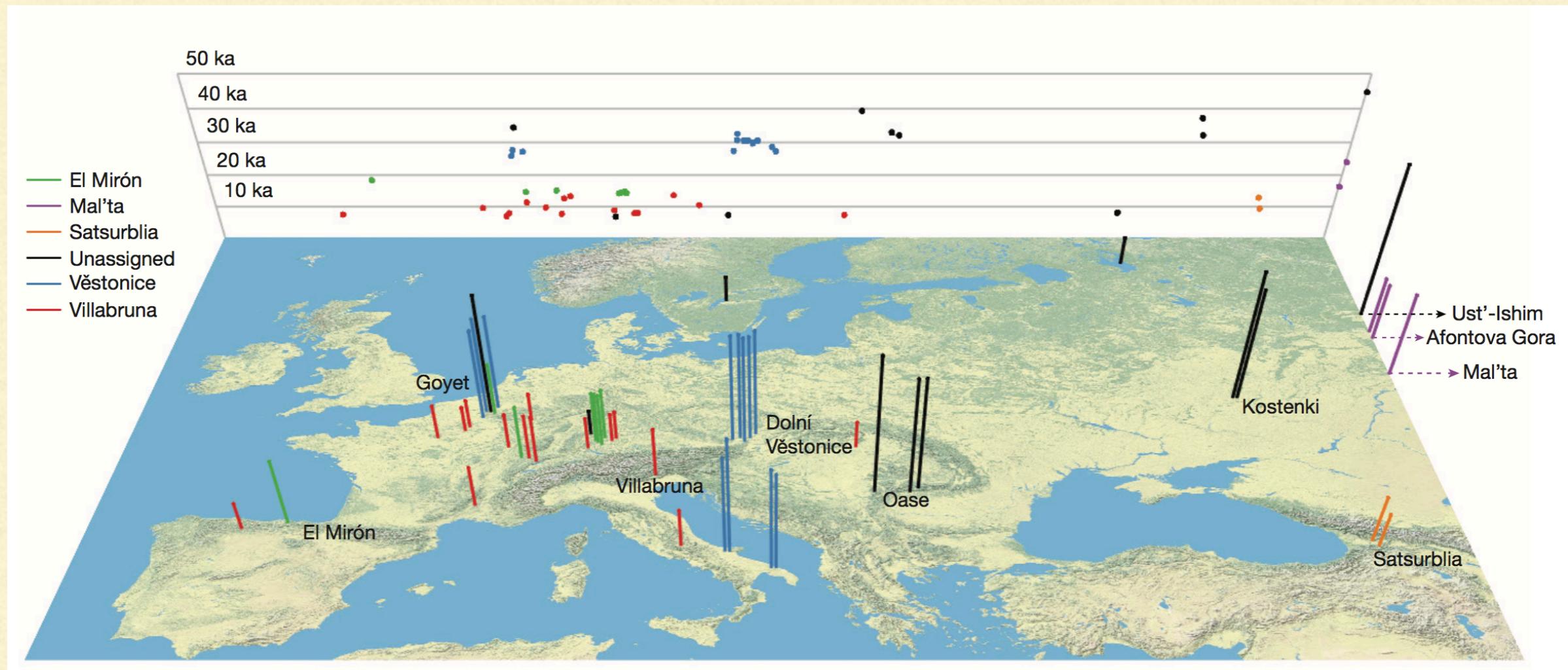


molecular baits



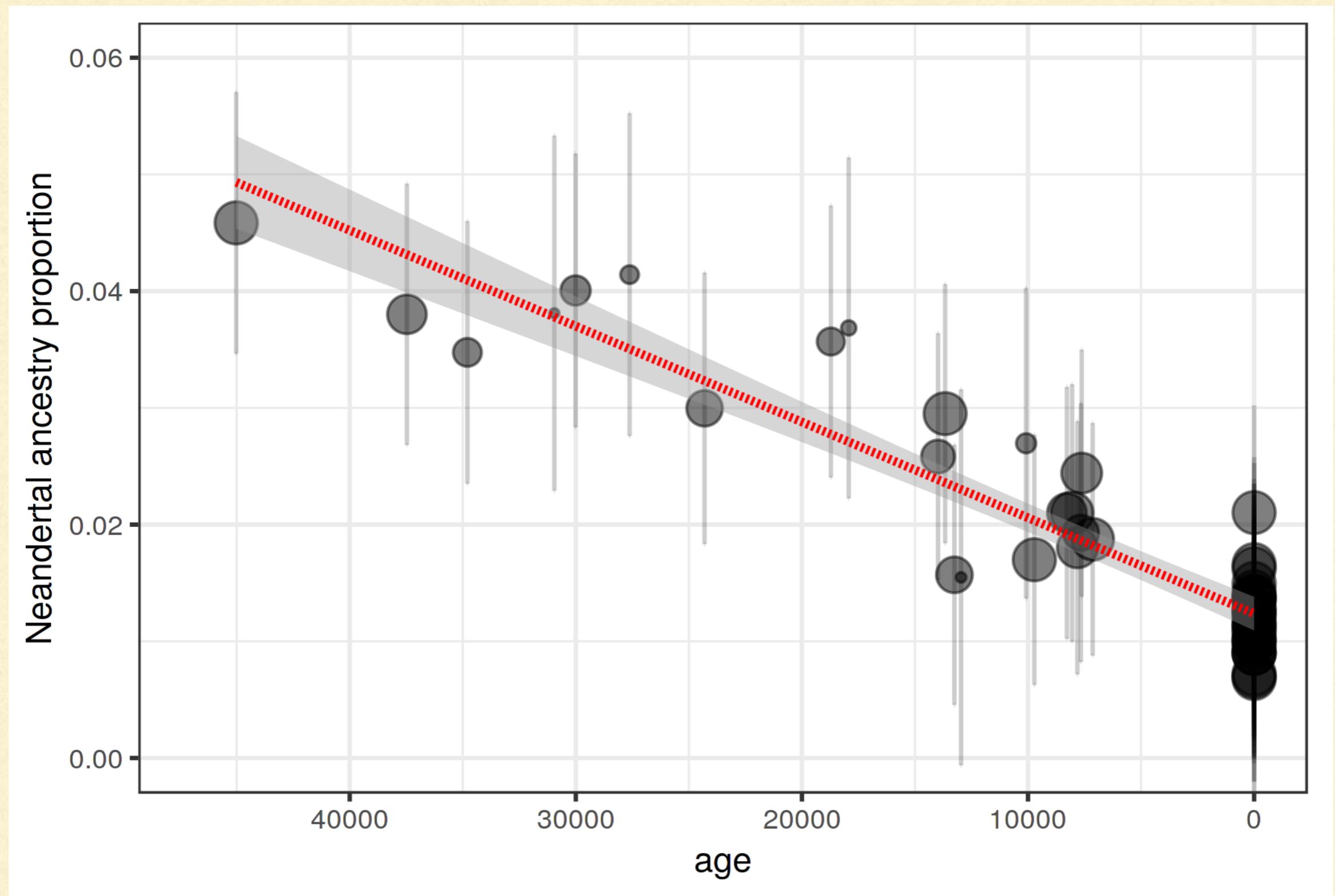
microbial DNA or “uninteresting” human sequence

We have 2 million SNPs from 51 individuals

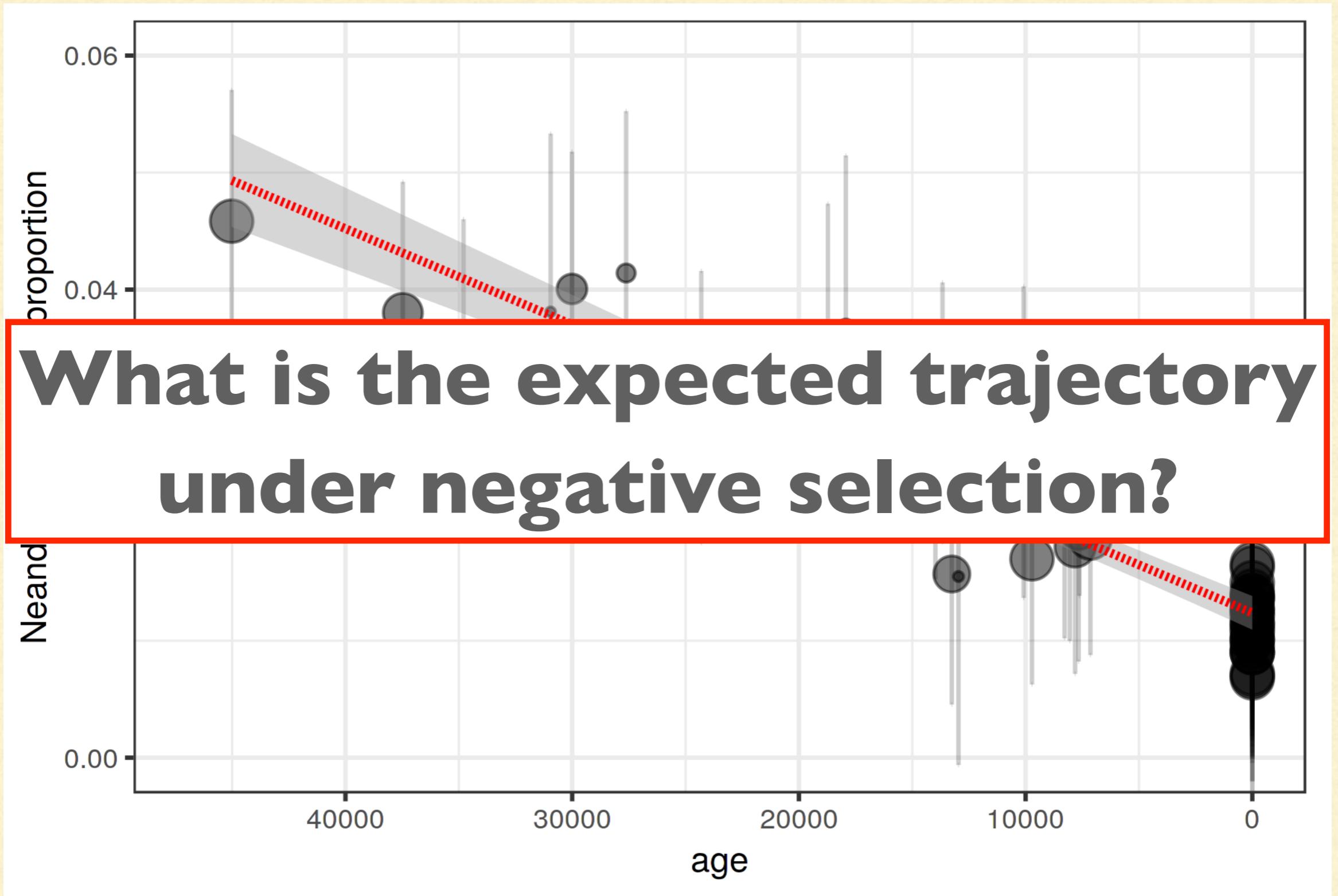


What is trajectory of
Neanderthal ancestry over time?

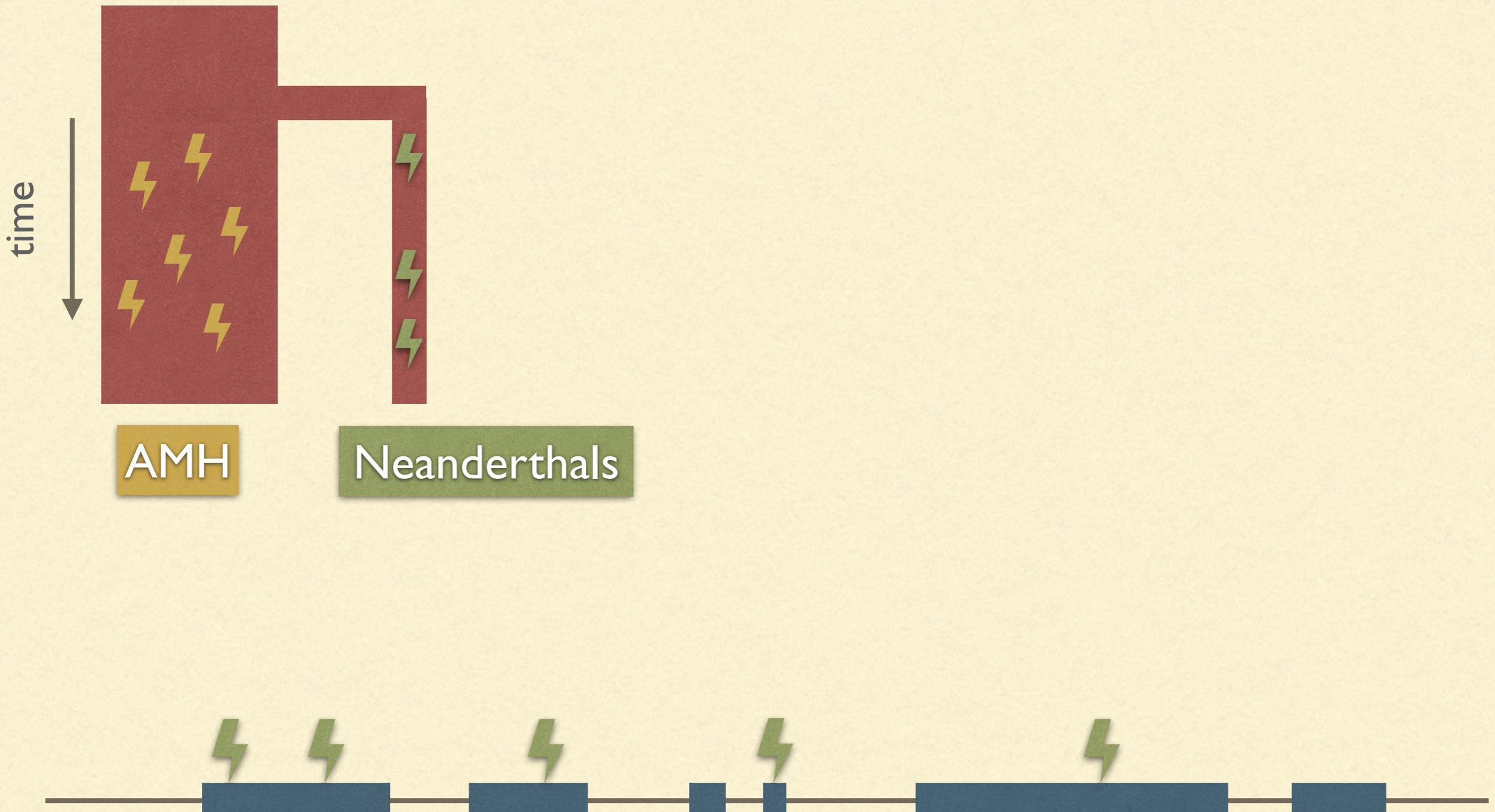
CONTINUOUS DECLINE OVER TIME!



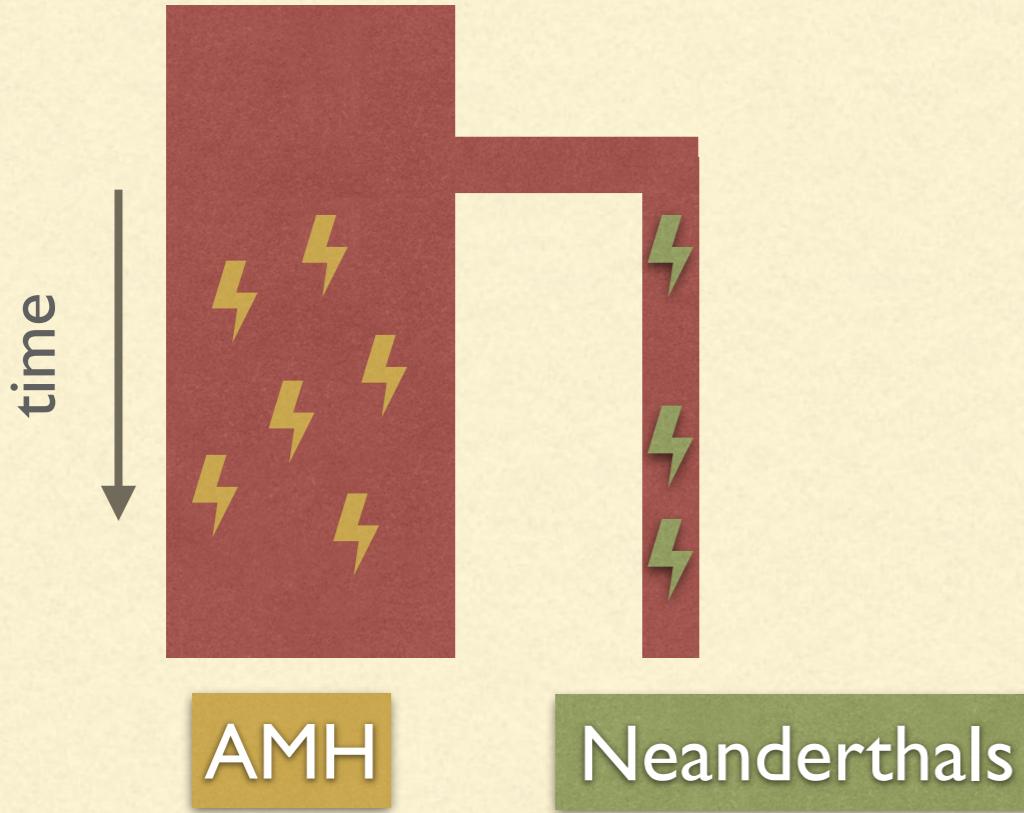
CONTINUOUS DECLINE OVER TIME!



WHOLE-GENOME SIMULATIONS



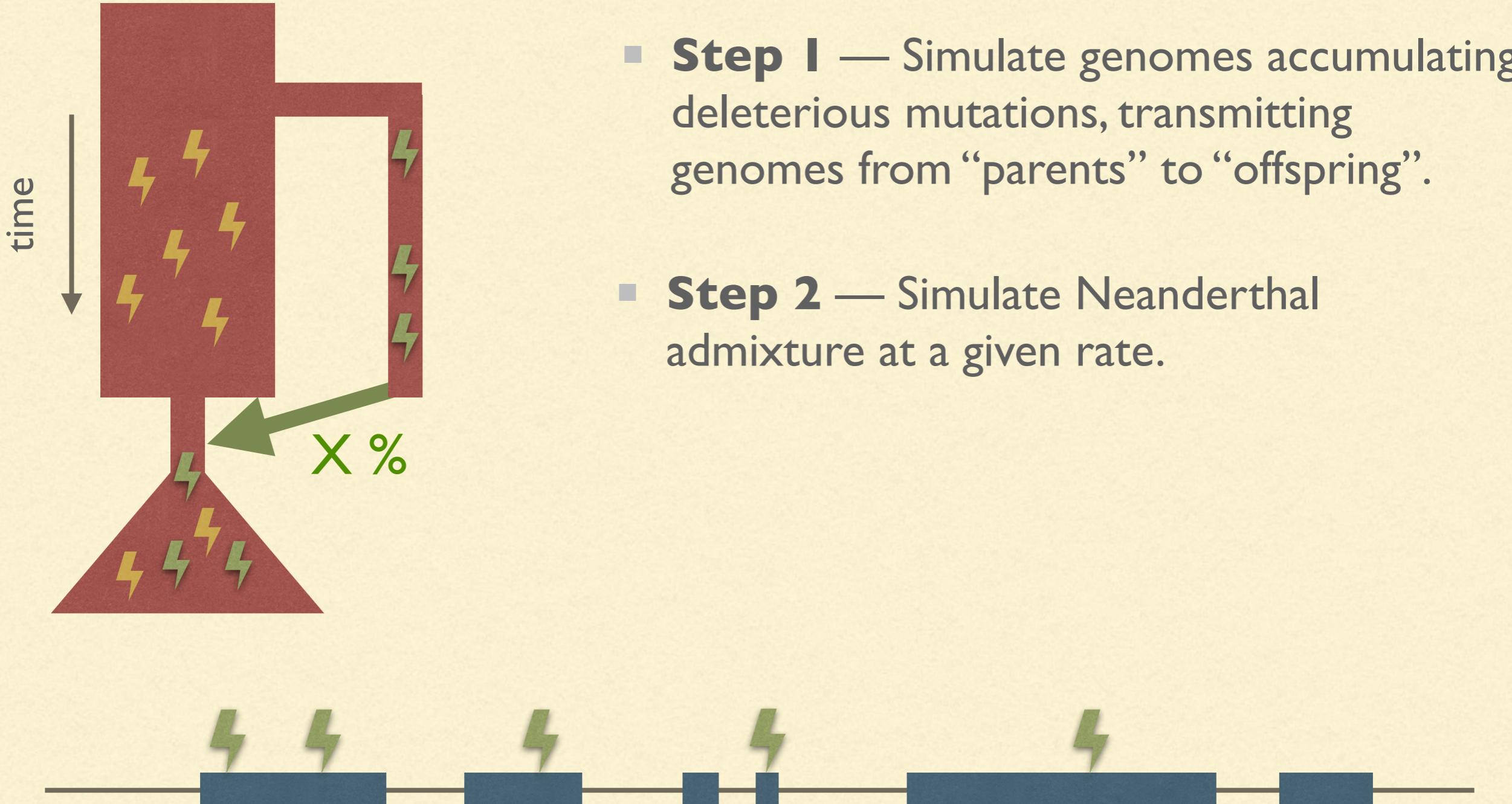
WHOLE-GENOME SIMULATIONS



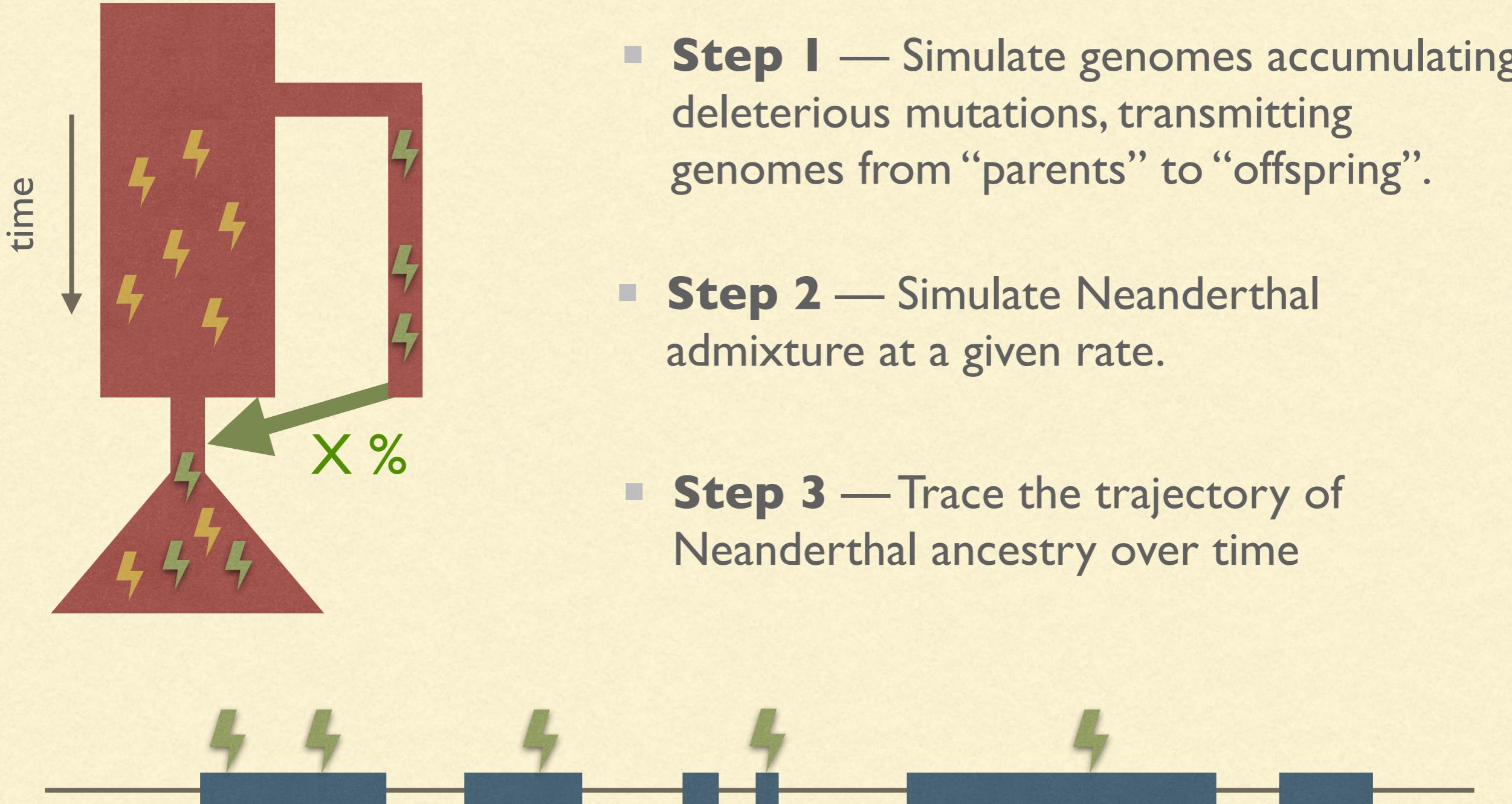
- **Step I** — Simulate genomes accumulating deleterious mutations, transmitting genomes from “parents” to “offspring”.



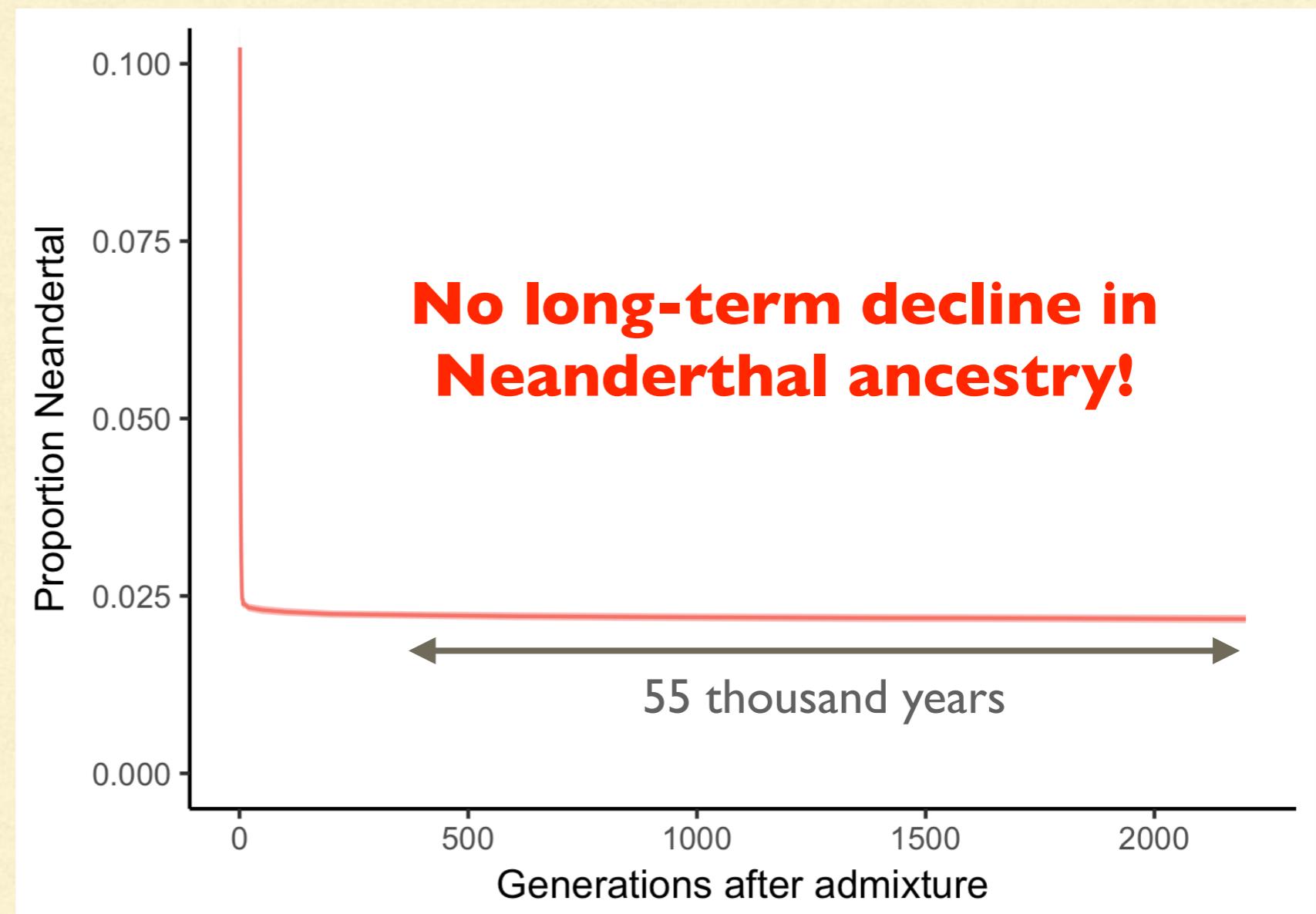
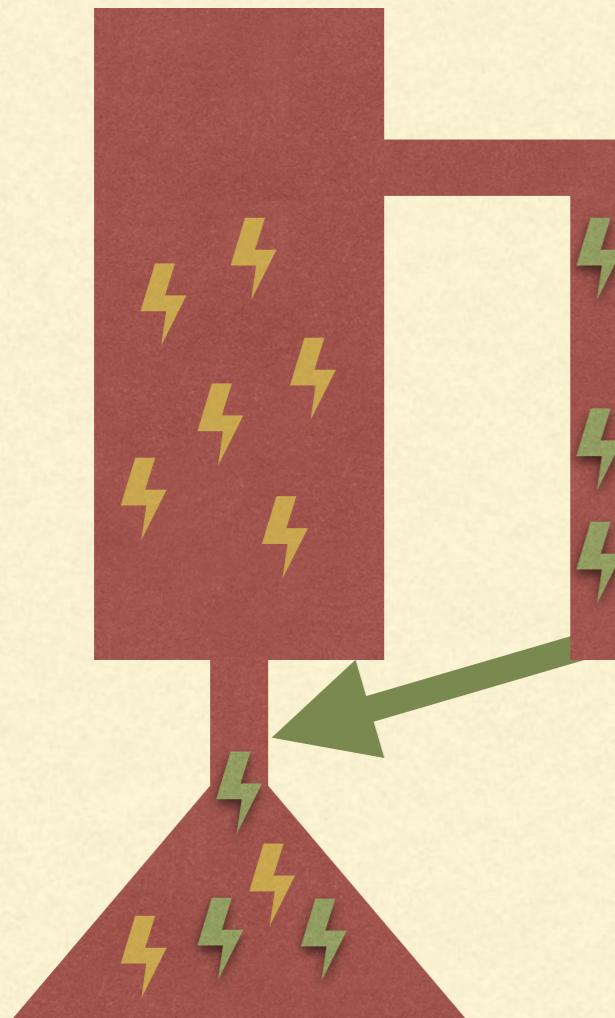
WHOLE-GENOME SIMULATIONS



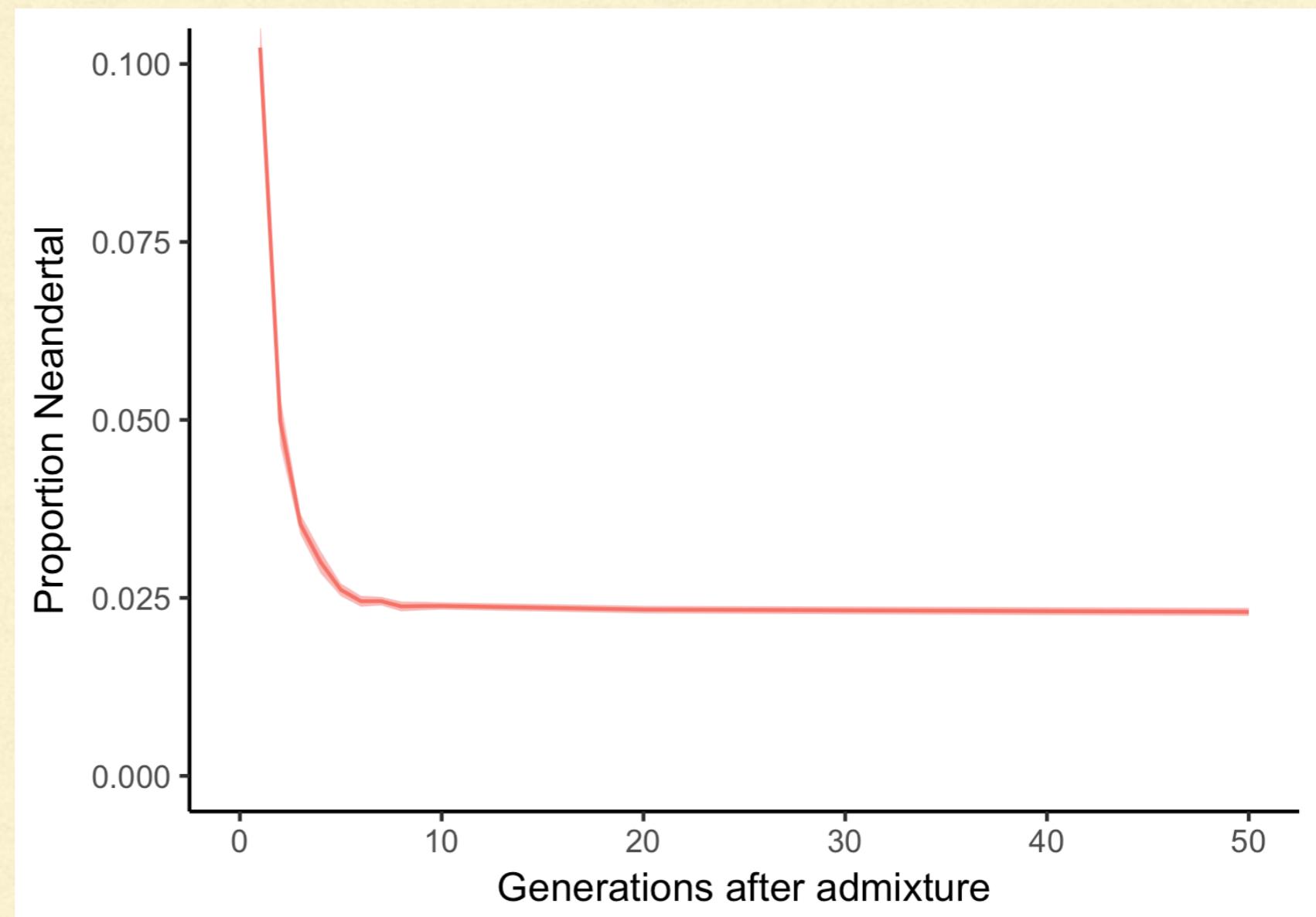
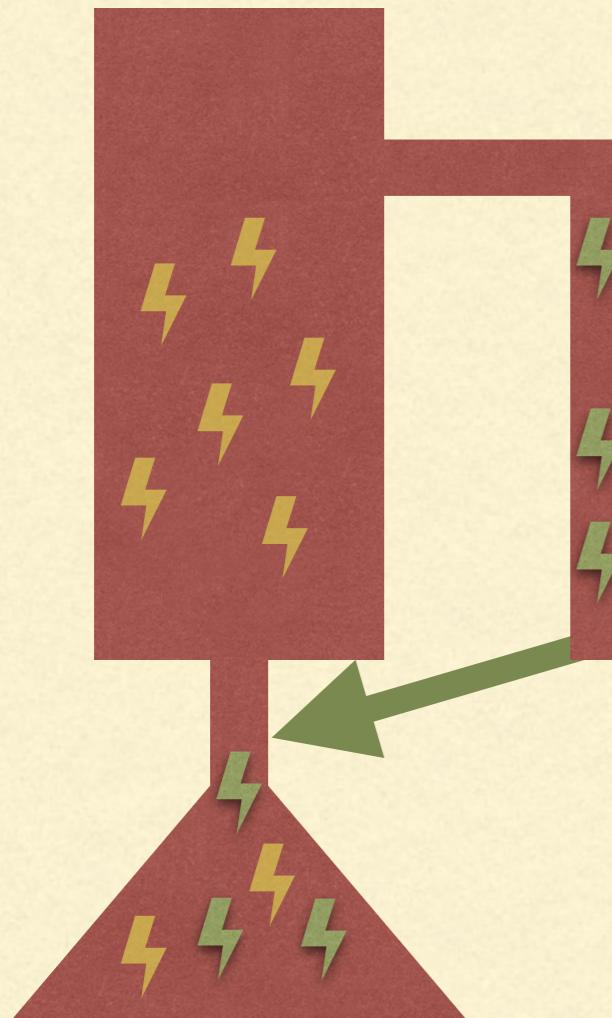
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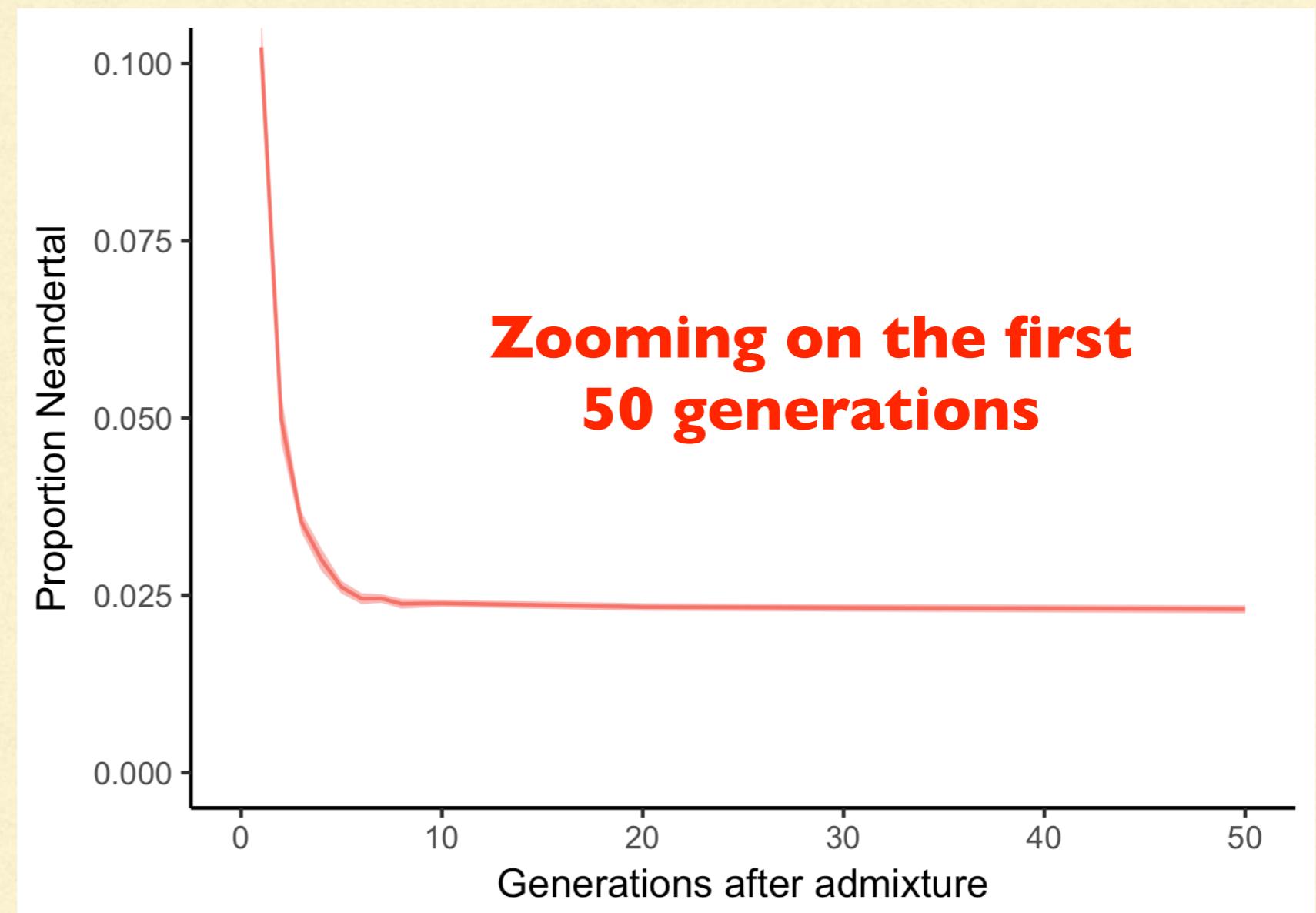
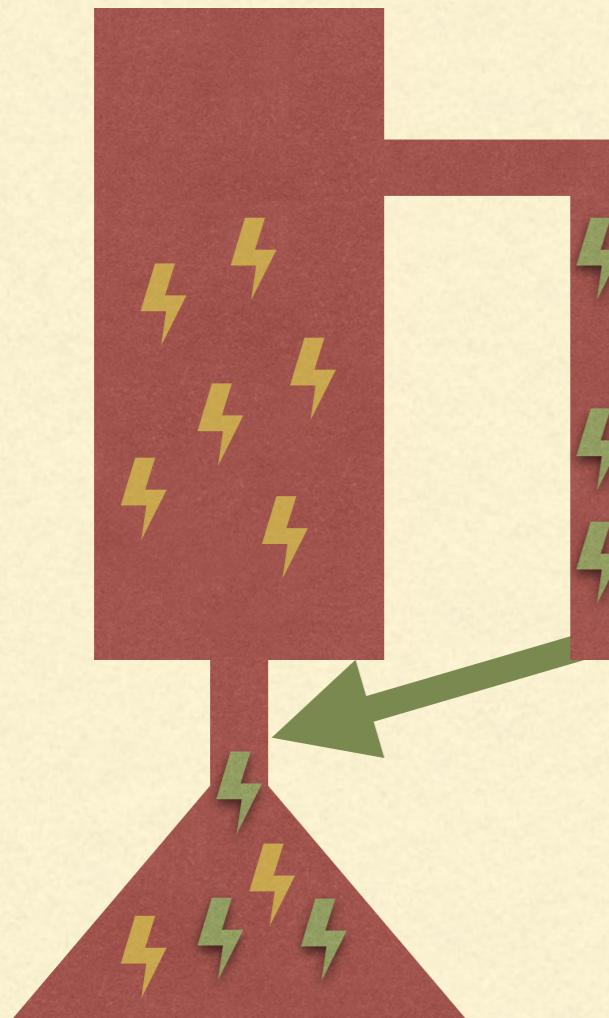
SIMULATION RESULTS



SIMULATION RESULTS

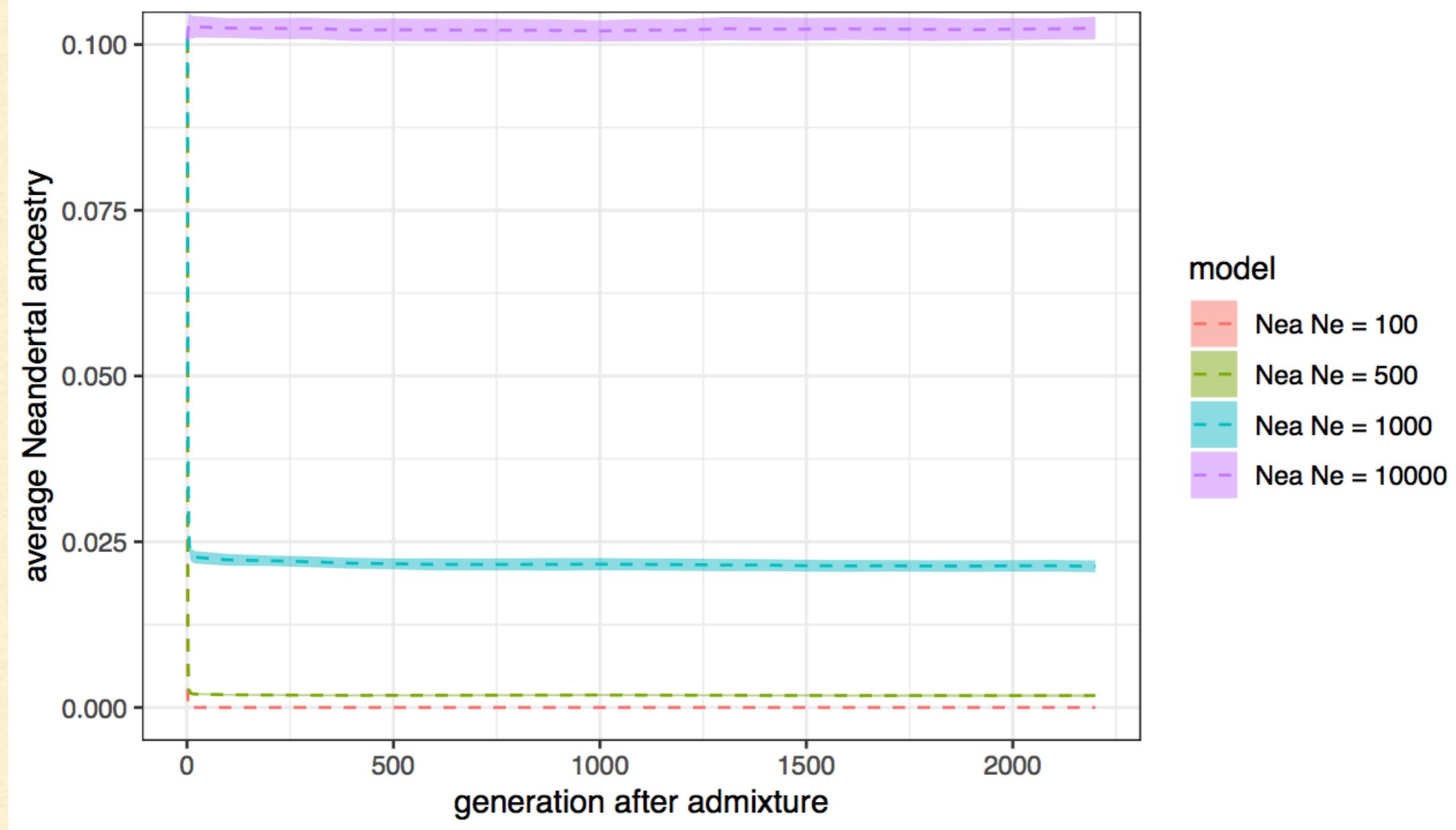


SIMULATION RESULTS

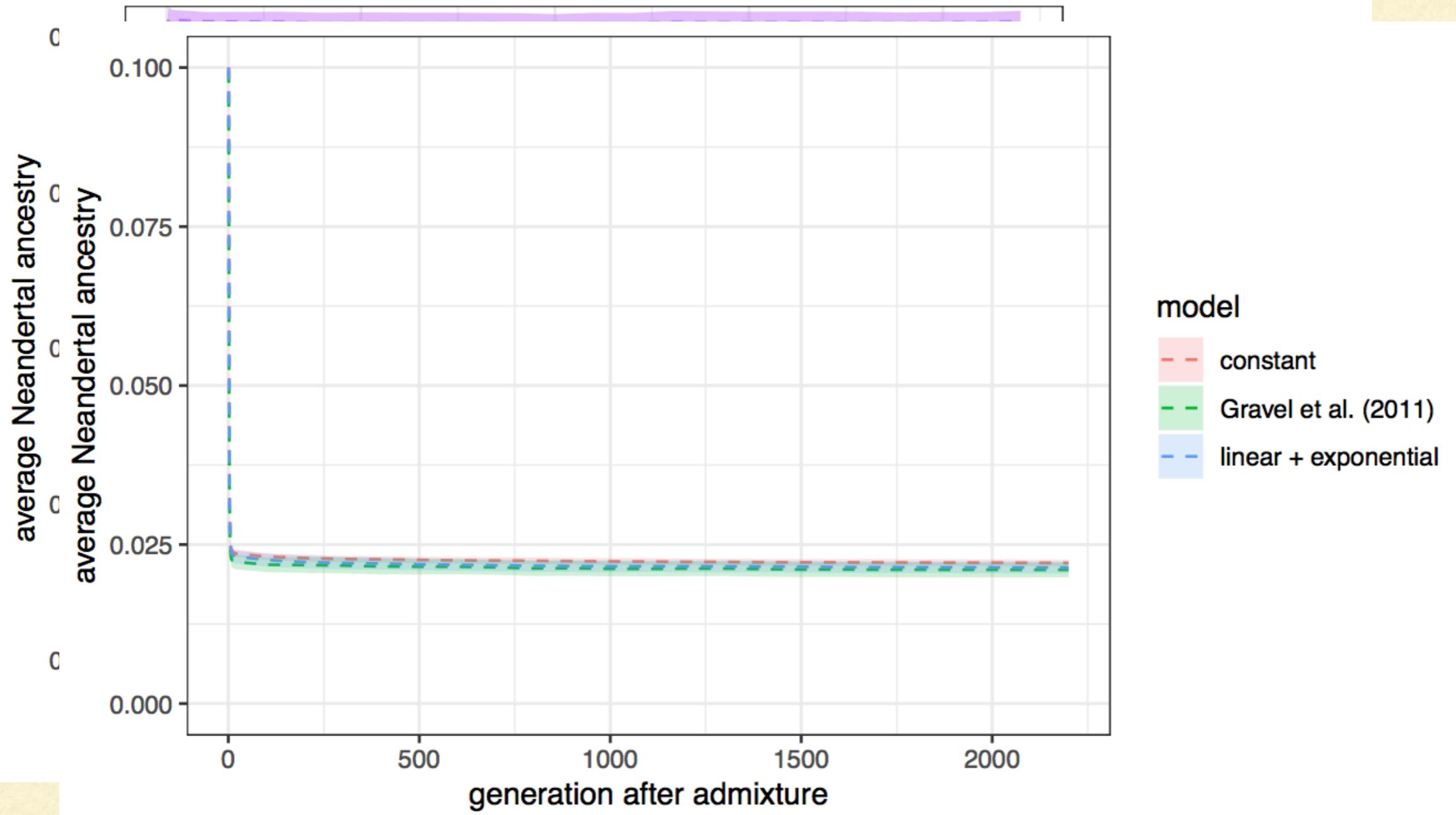


IN ALL SCENARIOS...

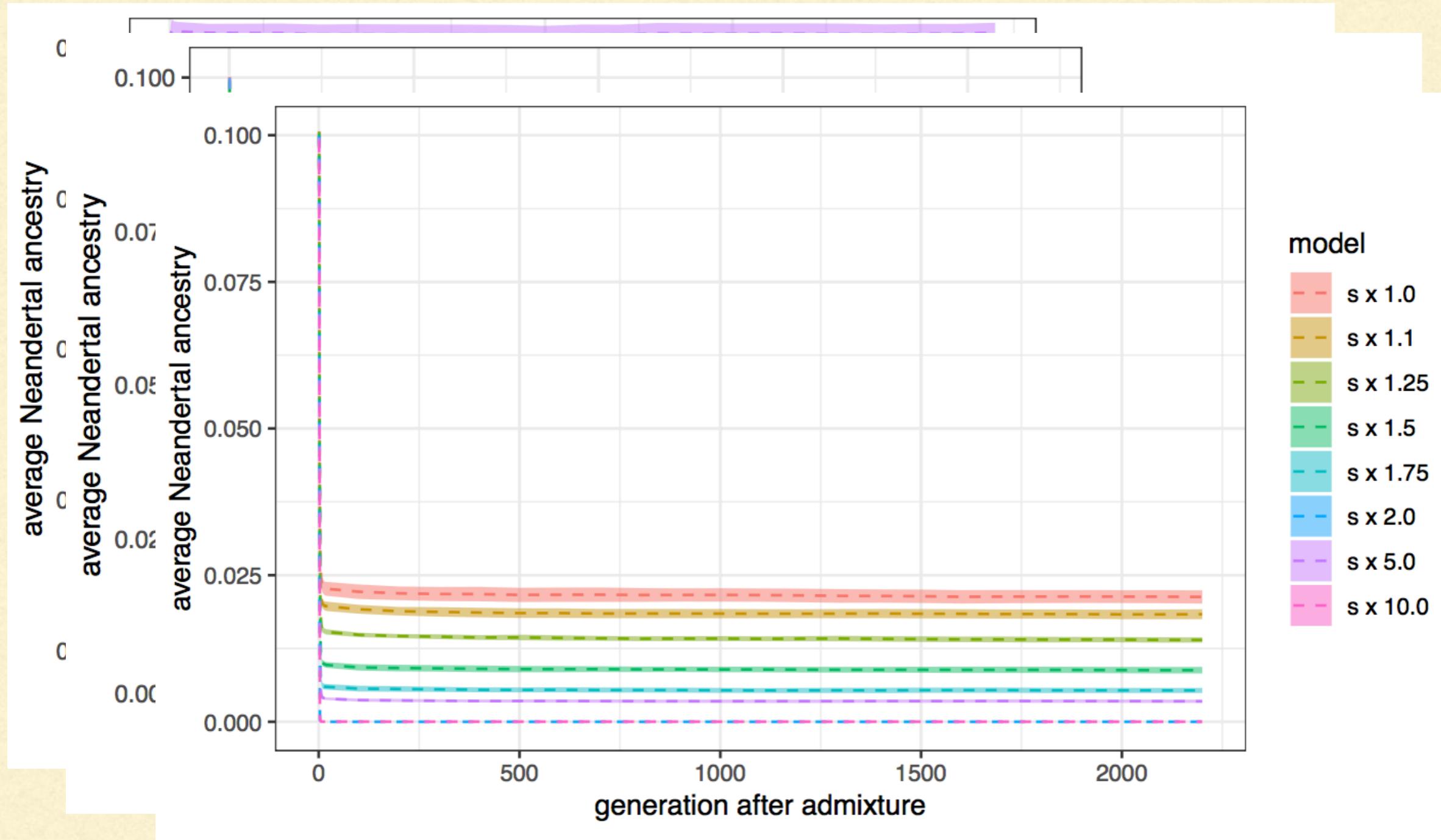
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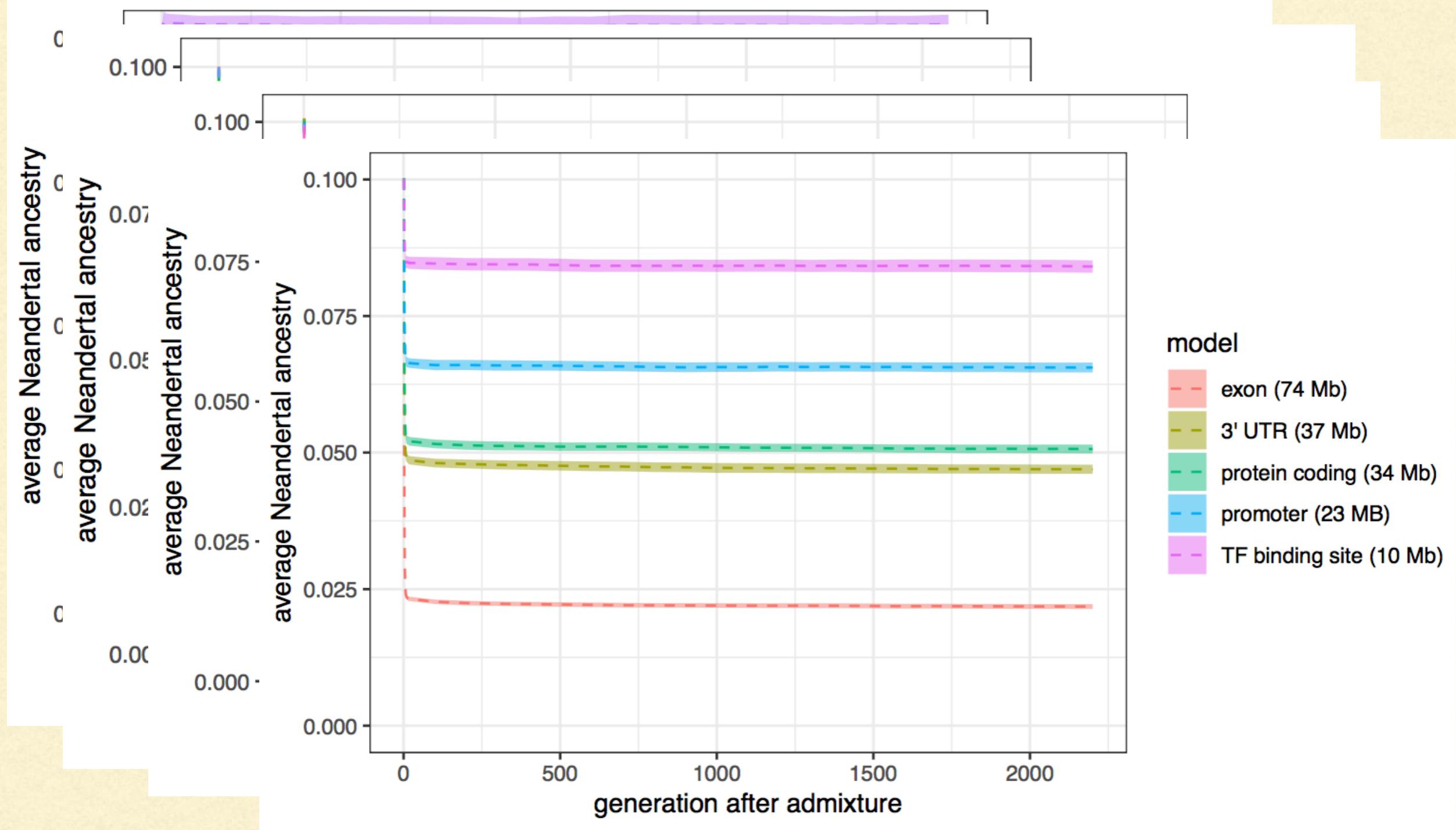
IN ALL SCENARIOS...



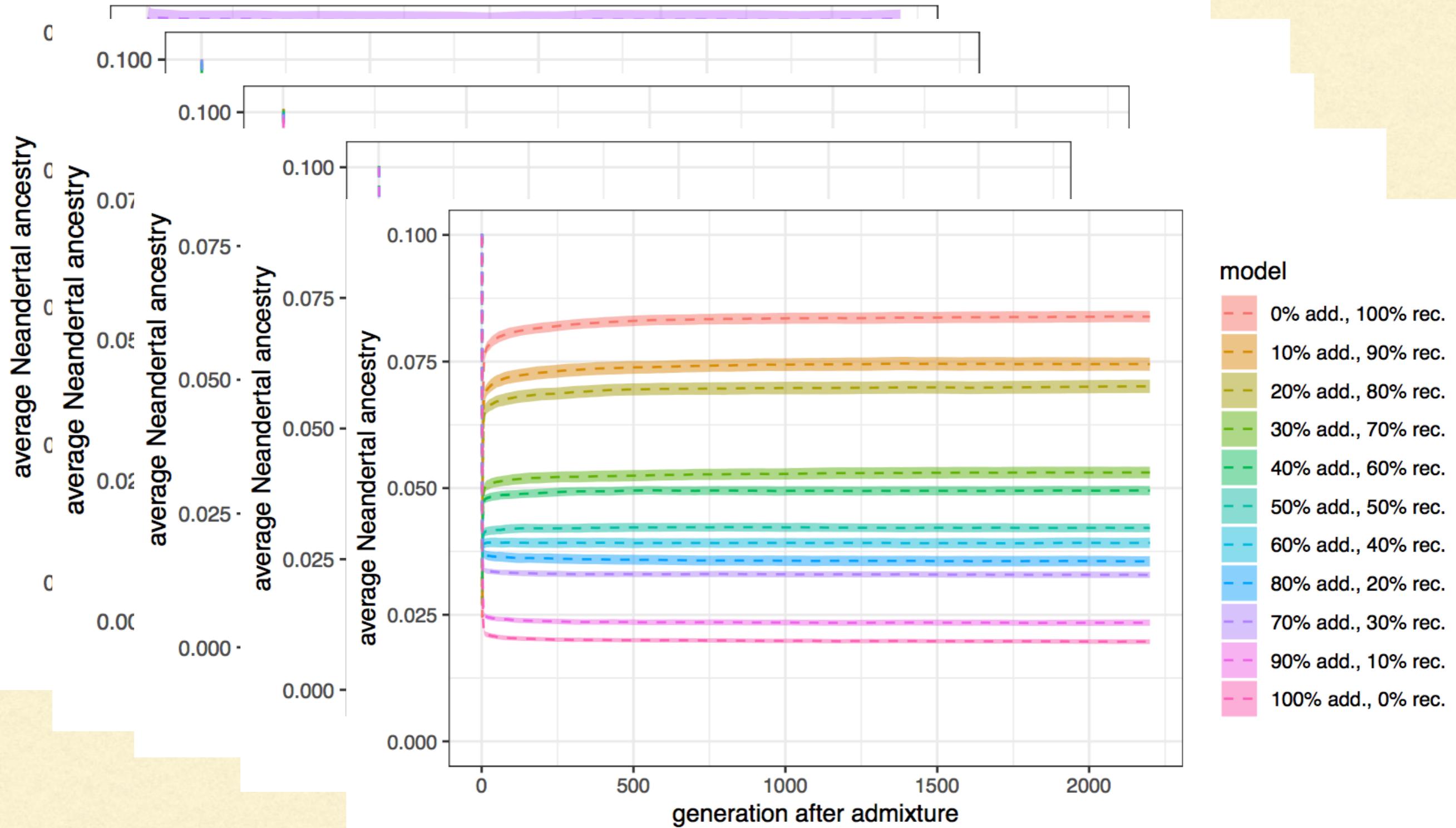
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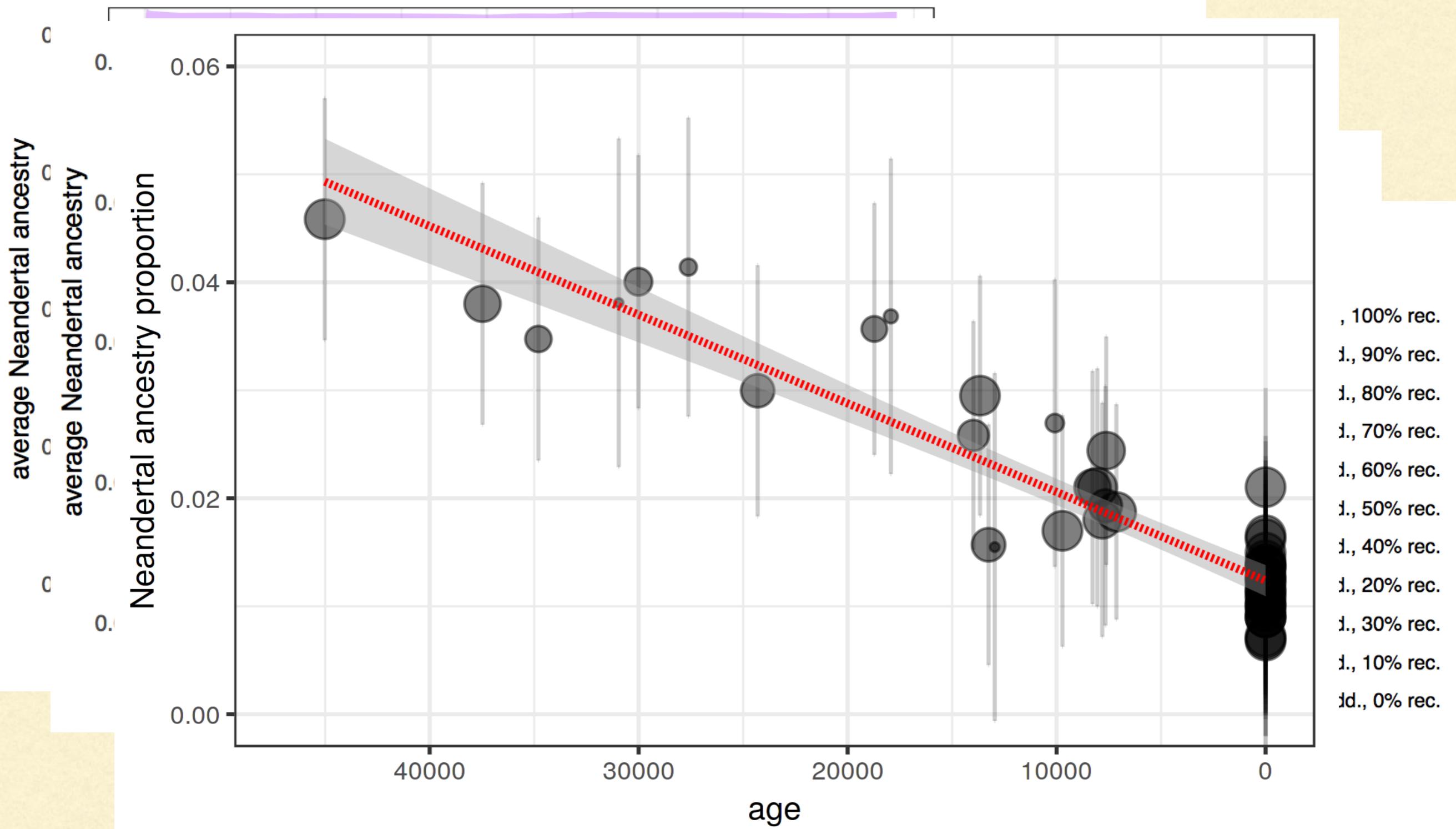
IN ALL SCENARIOS...



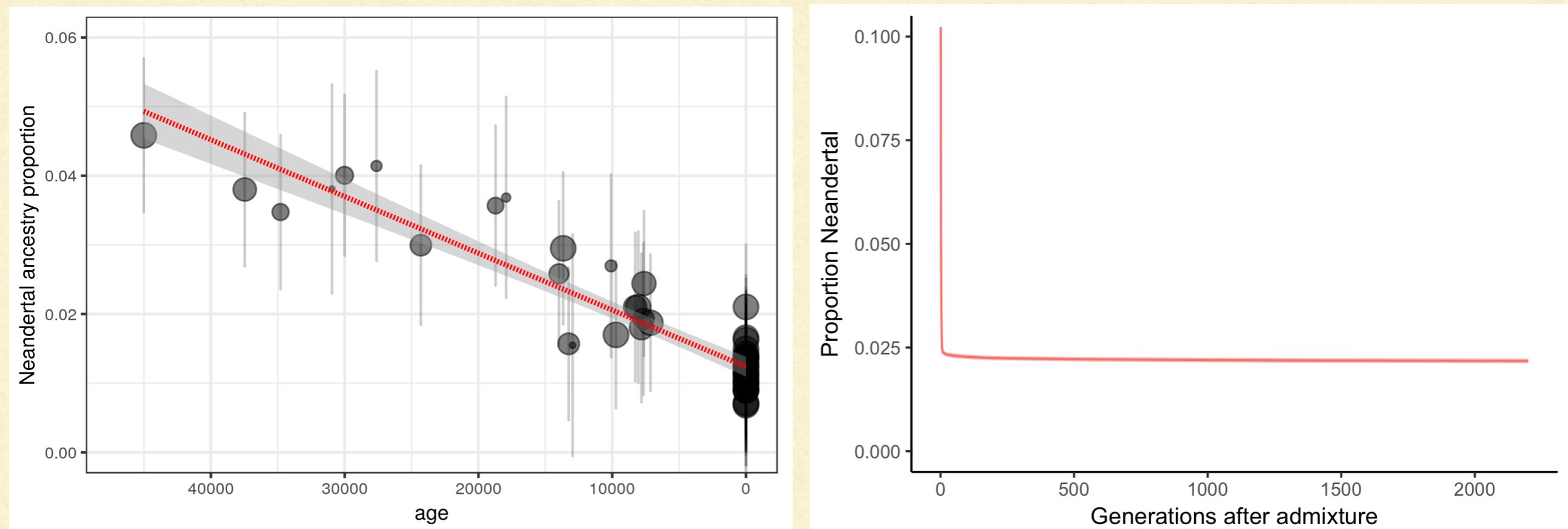
IN ALL SCENARIOS...



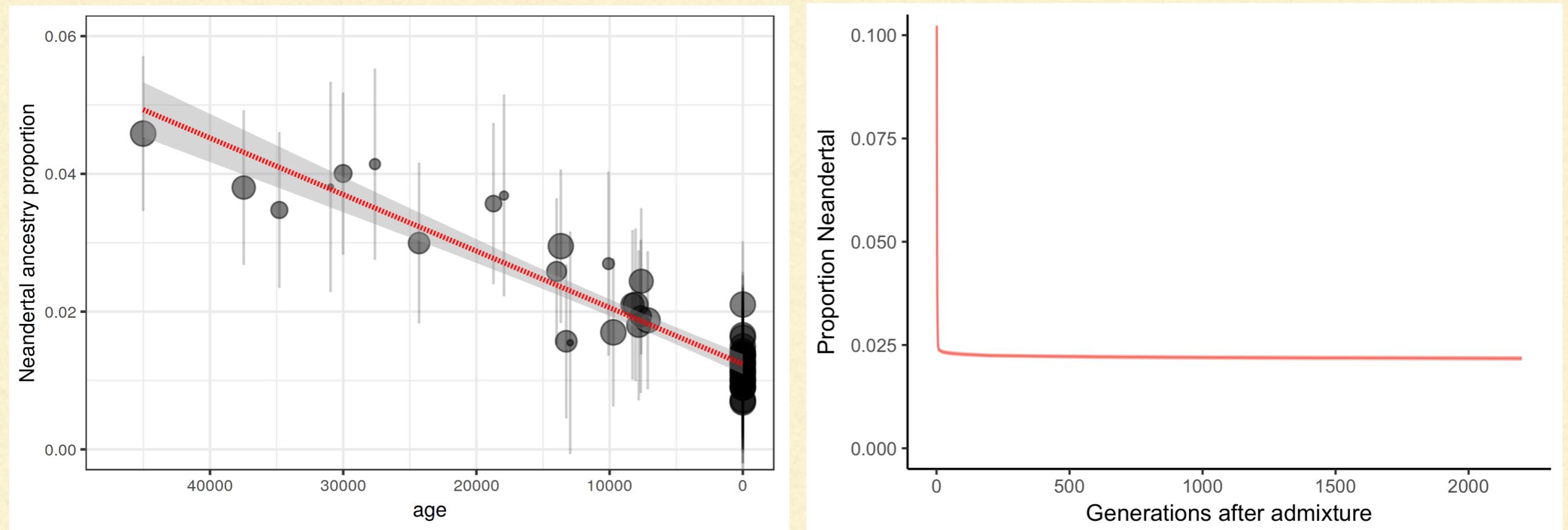
... NO DECLINE IN NEANDERTHAL ANCESTRY



DATA CONTRADICTS THEORY!



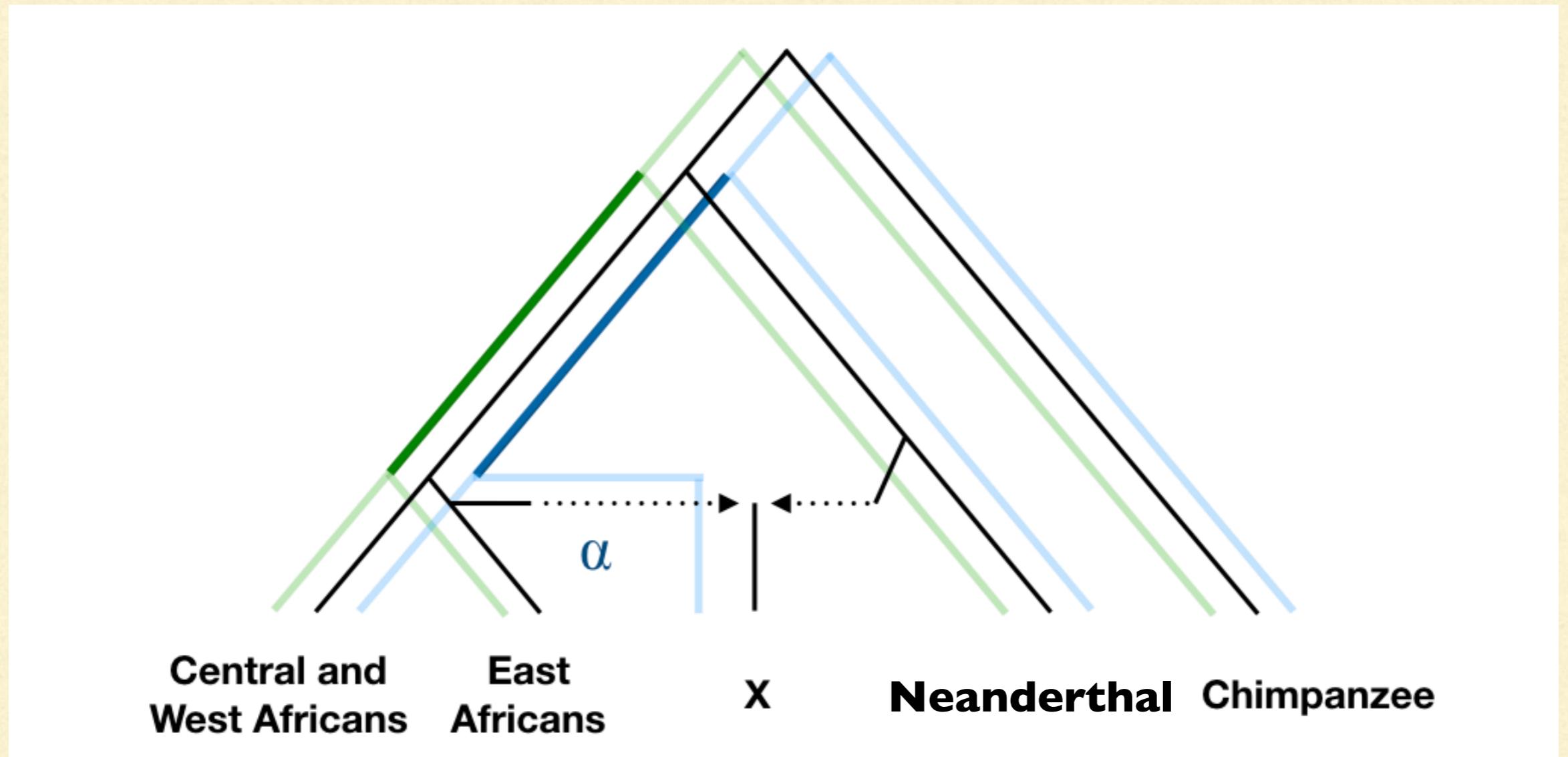
DATA CONTRADICTS THEORY!



Is there a problem with the data?

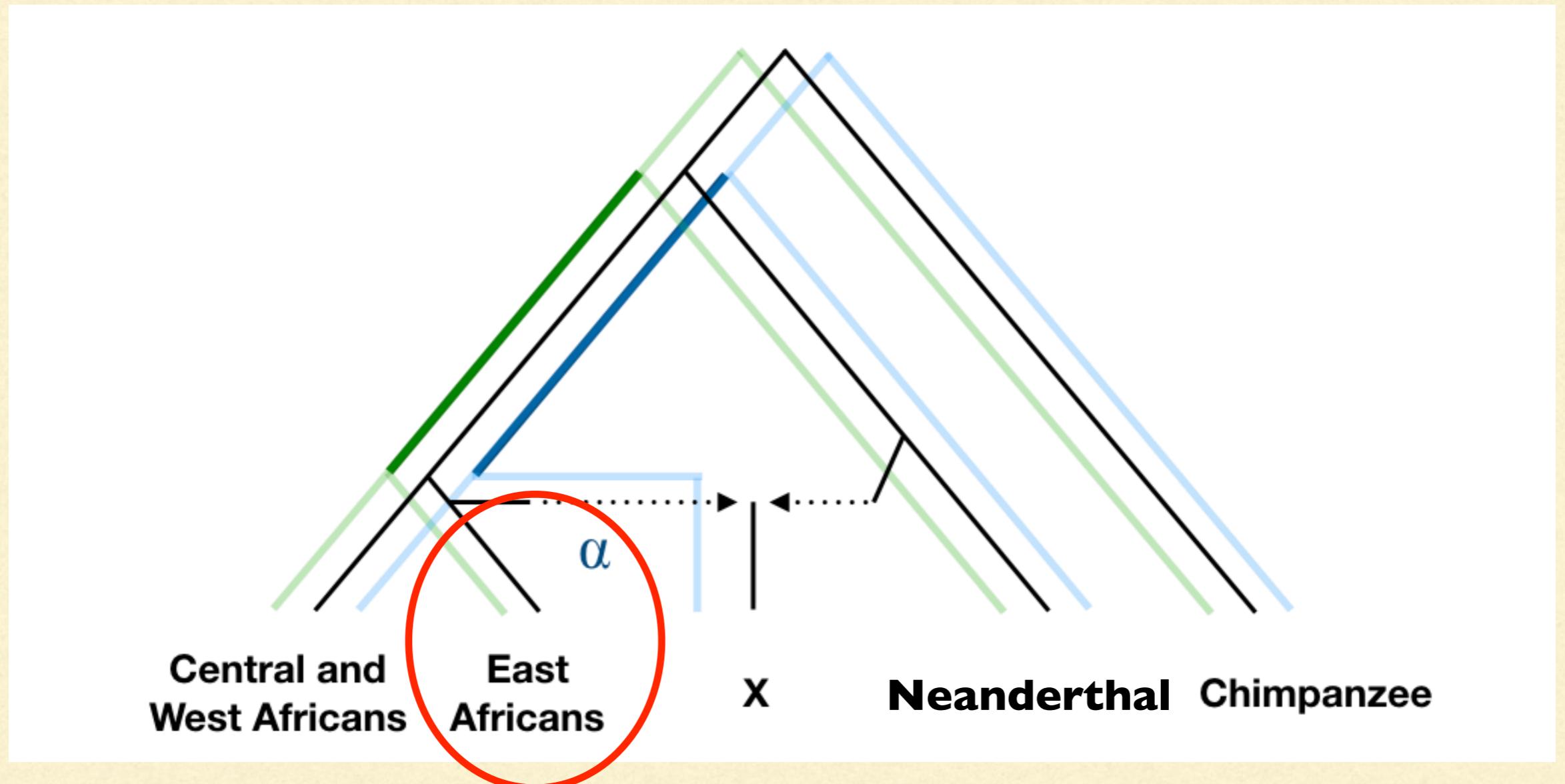
ESTIMATE OF NEANDERTHAL ANCESTRY

— INDIRECT F_4 -RATIO



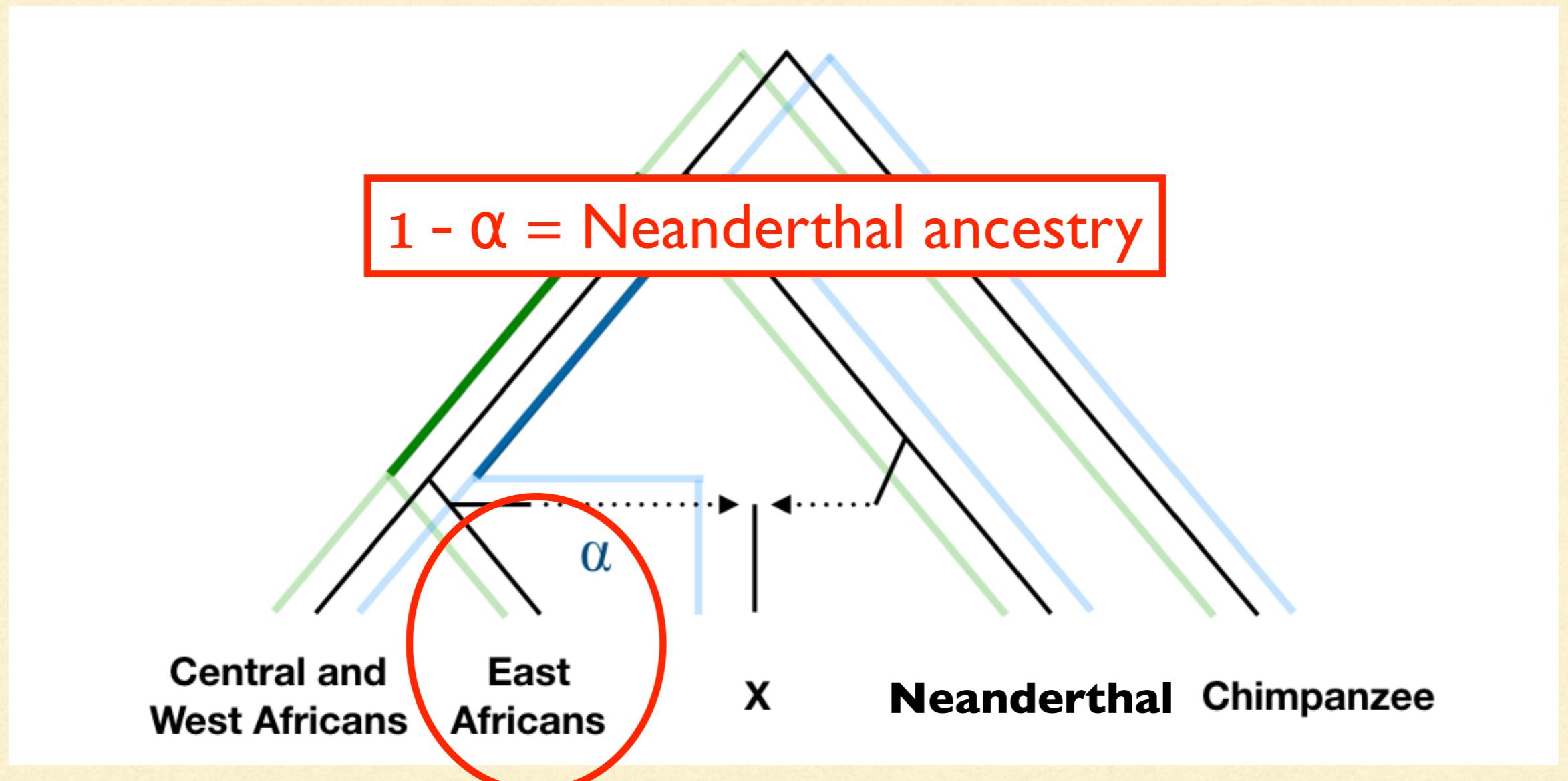
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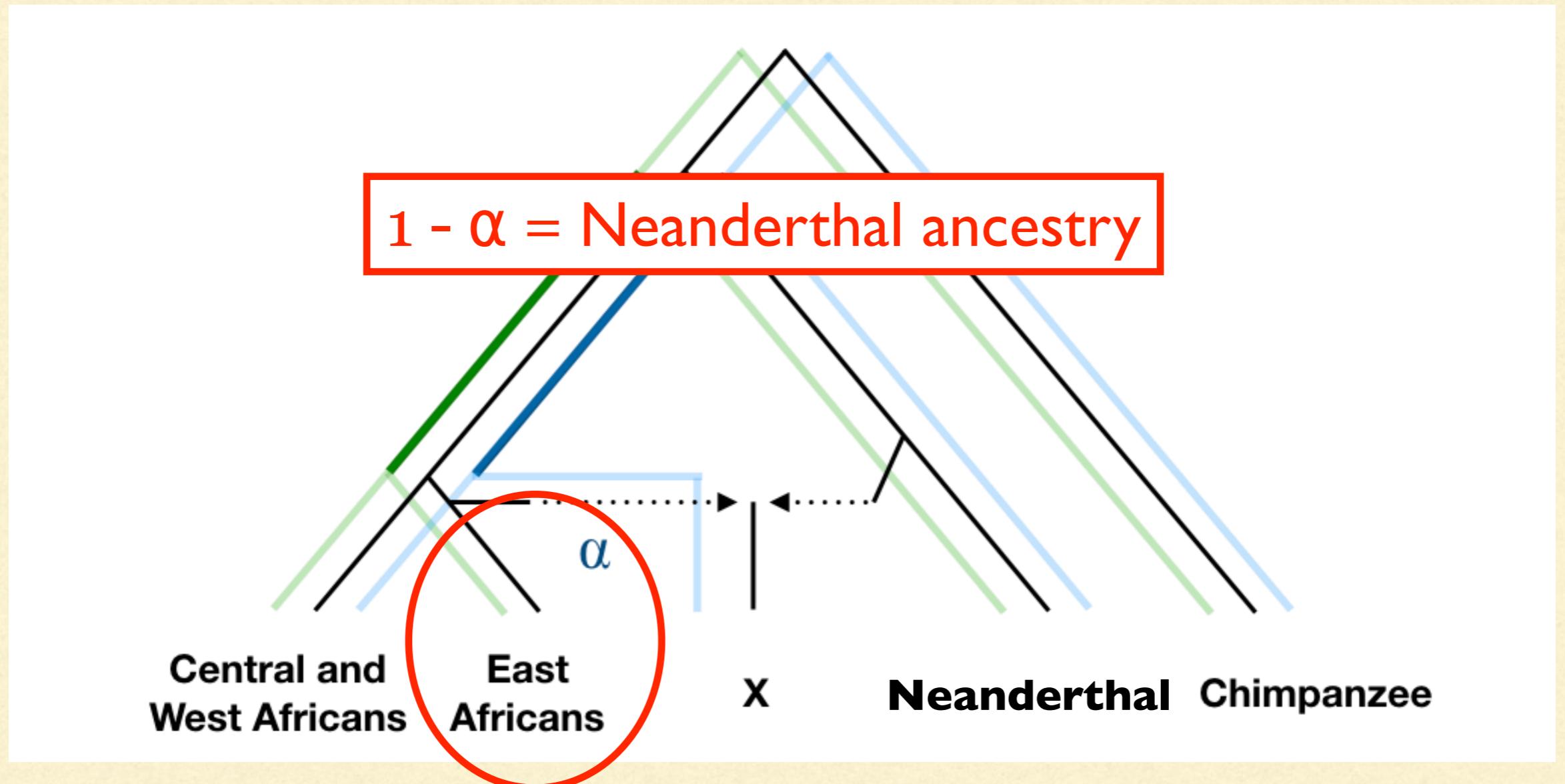
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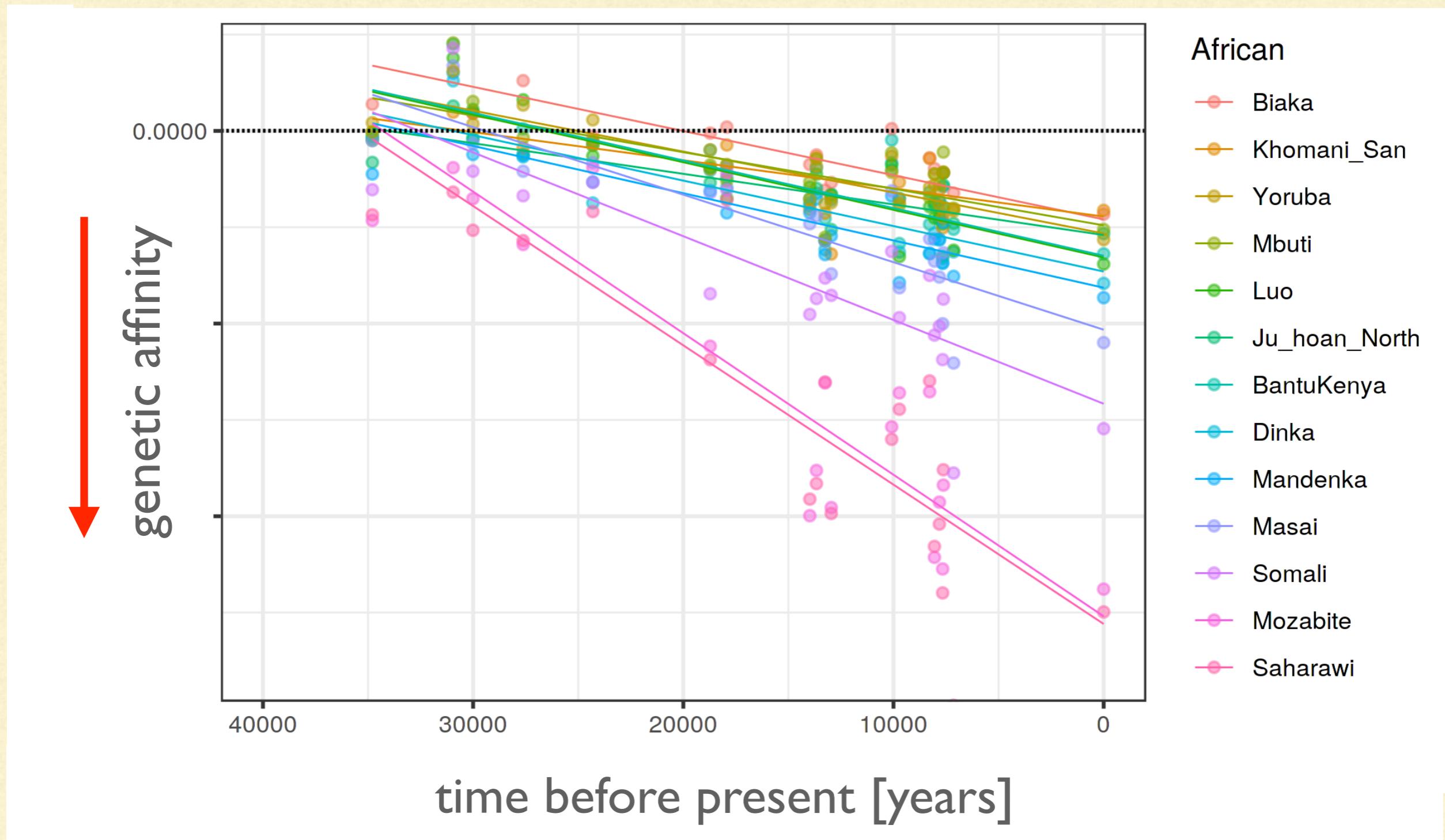
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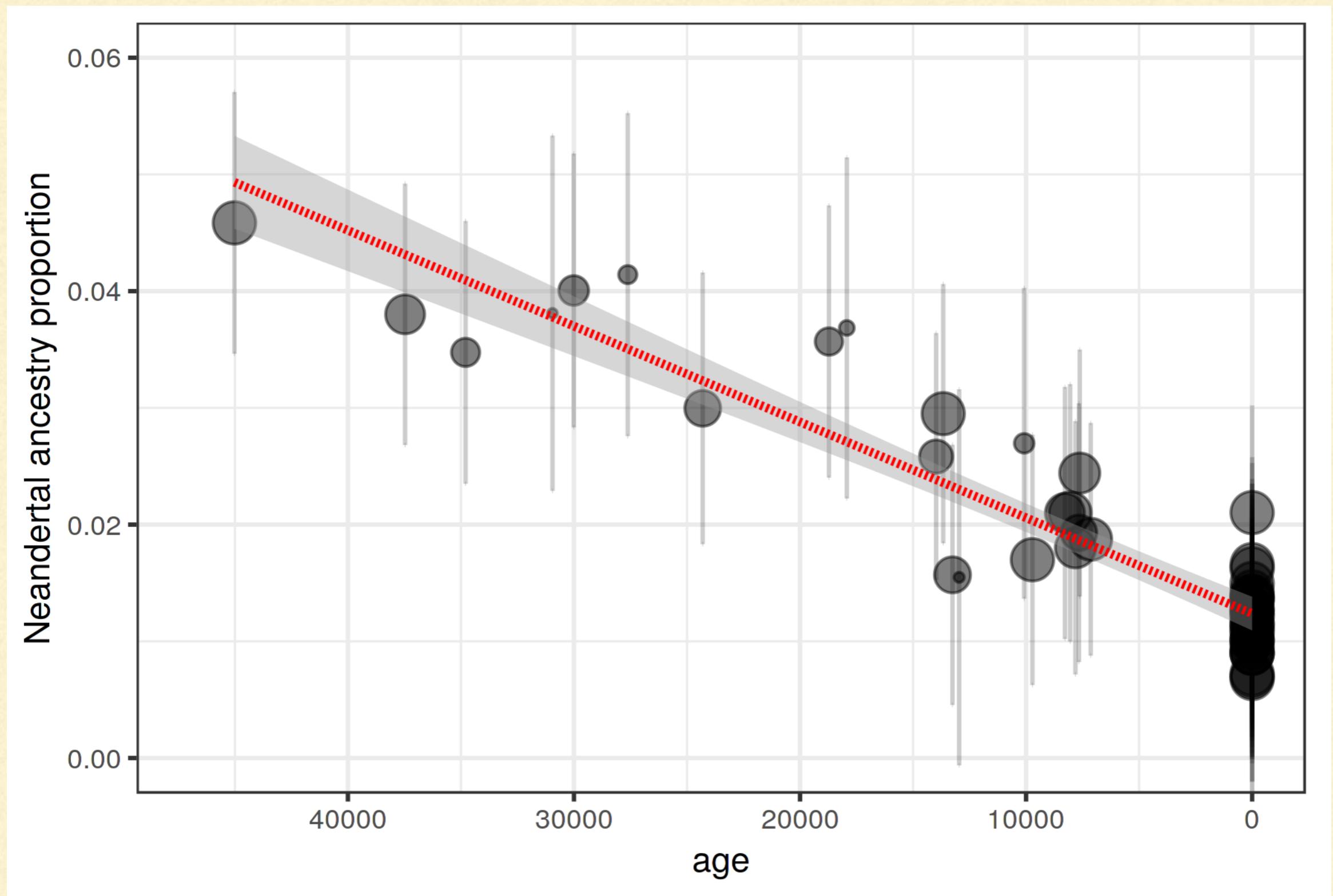


Assumes no changes in EUR-AFR genetic affinity

INCREASING EUR-AFR AFFINITY OVER TIME



“NEANDERTHAL ANCESTRY” OVER TIME



TWO NEANDERTHAL GENOMES

The complete genome sequence of a Neanderthal from the Altai Mountains

Kay Prüfer¹, Fernando Racimo², Nick Patterson³, Flora Jay², Sriram Sankararaman^{3,4}, Susanna Sawyer¹, Anja Heinze¹, Gabriel Renaud¹, Peter H. Sudmant⁵, Cesare de Filippo¹, Heng Li³, Swapan Mallick^{3,4}, Michael Dannemann¹, Qiaomei Fu^{1,6}, Martin Kircher^{1,5}, Martin Kuhlwilm¹, Michael Lachmann¹, Matthias Meyer¹, Matthias Ongyerth¹, Michael Siebauer¹, Christoph Theunert¹, Arti Tandon^{3,4}, Priya Moorjani⁴, Joseph Pickrell⁴, James C. Mullikin⁷, Samuel H. Vohr⁸, Richard E. Green⁸, Ines Hellmann^{9†}, Philip L. F. Johnson¹⁰, Hélène Blanche¹¹, Howard Cann¹¹, Jacob O. Kitzman⁵, Jay Shendure⁵, Evan E. Eichler^{5,12}, Ed S. Lein¹³, Trygve E. Bakken¹³, Liubov V. Golovanova¹⁴, Vladimir B. Doronichev¹⁴, Michael V. Shunkov¹⁵, Anatoli P. Derevianko¹⁵, Bence Viola¹⁶, Montgomery Slatkin², David Reich^{3,4,17}, Janet Kelso¹ & Svante Pääbo¹

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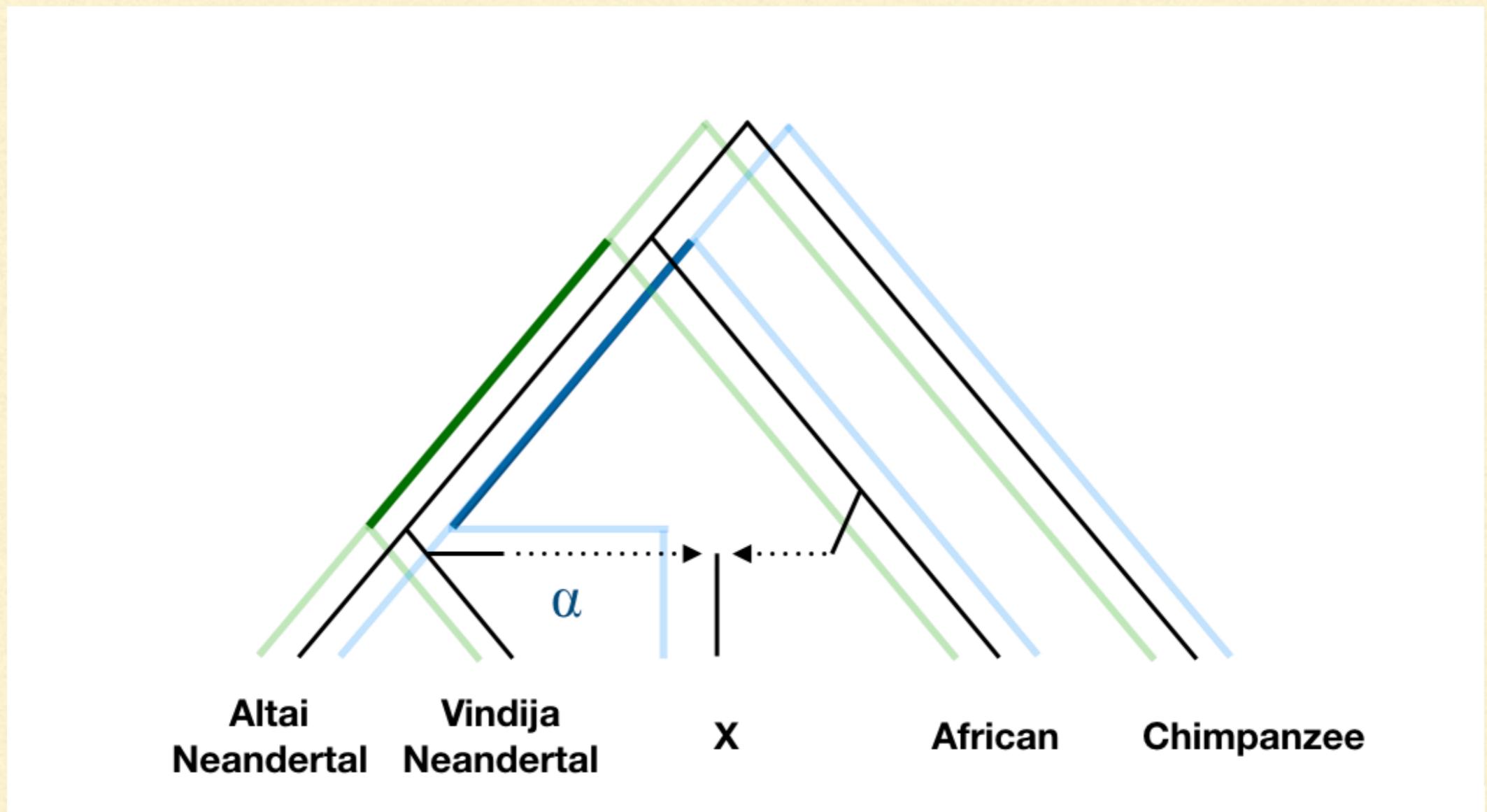
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A high-coverage Neandertal genome from Vindija Cave in Croatia

Kay Prüfer,^{1*} Cesare de Filippo,^{1†} Steffi Grote,^{1†} Fabrizio Mafessoni,^{1†} Petra Korlević,¹ Mateja Hajdinjak,¹ Benjamin Vernot,¹ Laurits Skov,² Pinghsun Hsieh,³ Stéphane Peyrégne,¹ David Reher,¹ Charlotte Hopfe,¹ Sarah Nagel,¹ Tomislav Maricic,¹ Qiaomei Fu,⁴ Christoph Theunert,^{1,8} Rebekah Rogers,⁸ Pontus Skoglund,⁵ Manjusha Chintalapati,¹ Michael Dannemann,¹ Bradley J. Nelson,³ Felix M. Key,¹ Pavao Rudan,⁶ Željko Kućan,⁶ Ivan Gušić,⁶ Liubov V. Golovanova,⁷ Vladimir B. Doronichev,⁷ Nick Patterson,⁵ David Reich,^{5,9,10} Evan E. Eichler,^{3,11} Montgomery Slatkin,⁸ Mikkel H. Schierup,² Aida Andrés,¹ Janet Kelso,¹ Matthias Meyer,¹ Svante Pääbo^{1*}

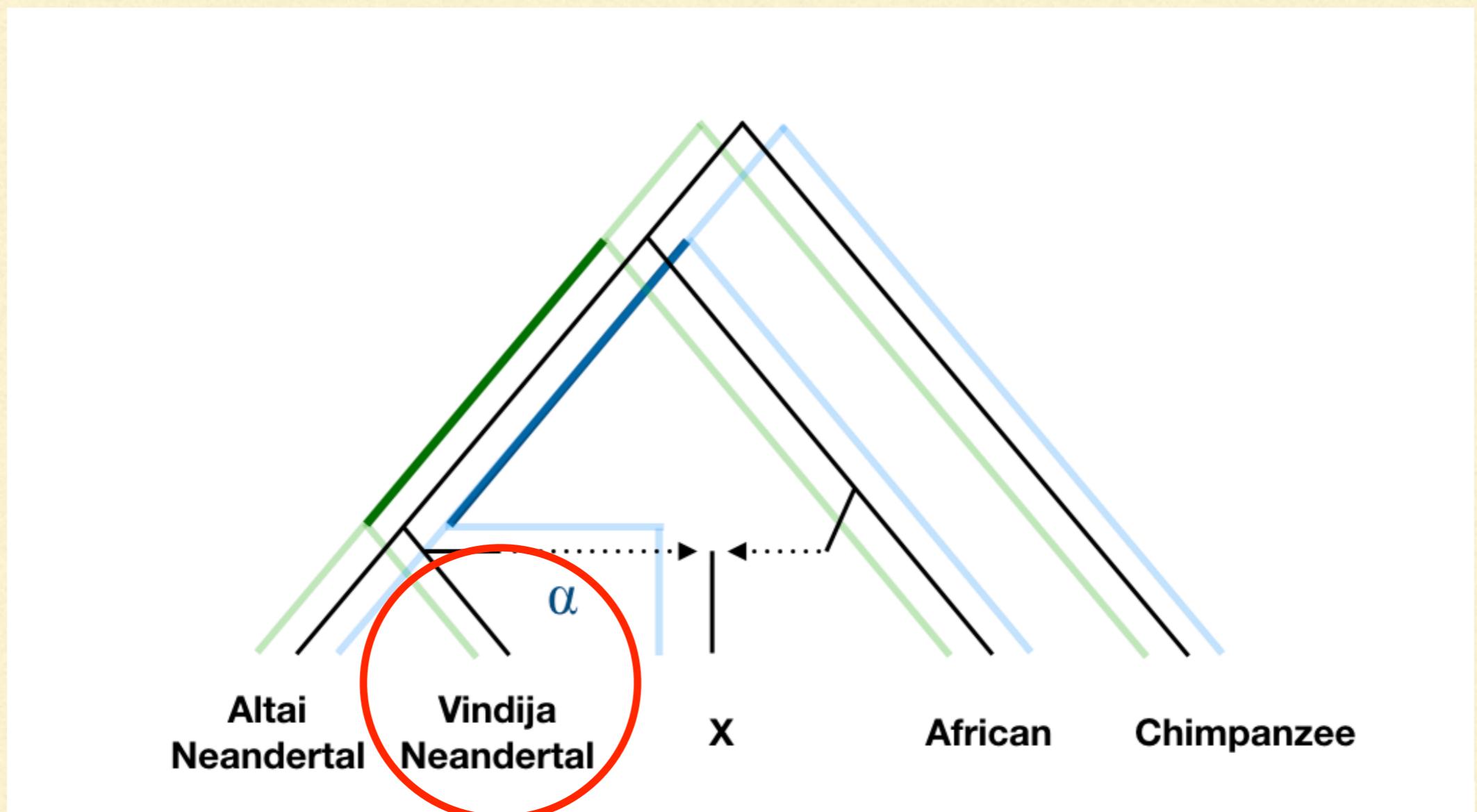
ESTIMATE OF NEANDERTHAL ANCESTRY

— DIRECT F_4 -RATIO

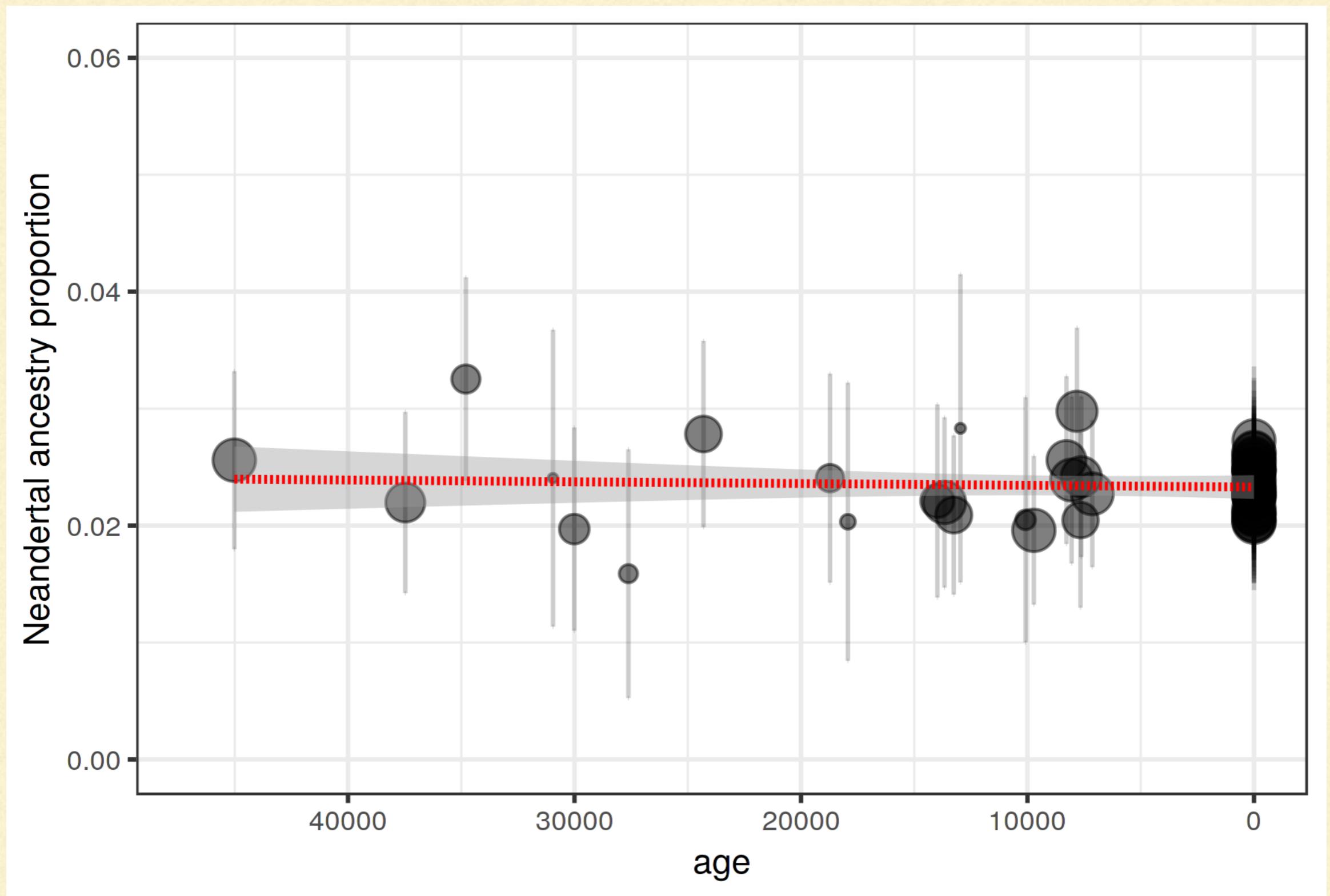


ESTIMATE OF NEANDERTHAL ANCESTRY

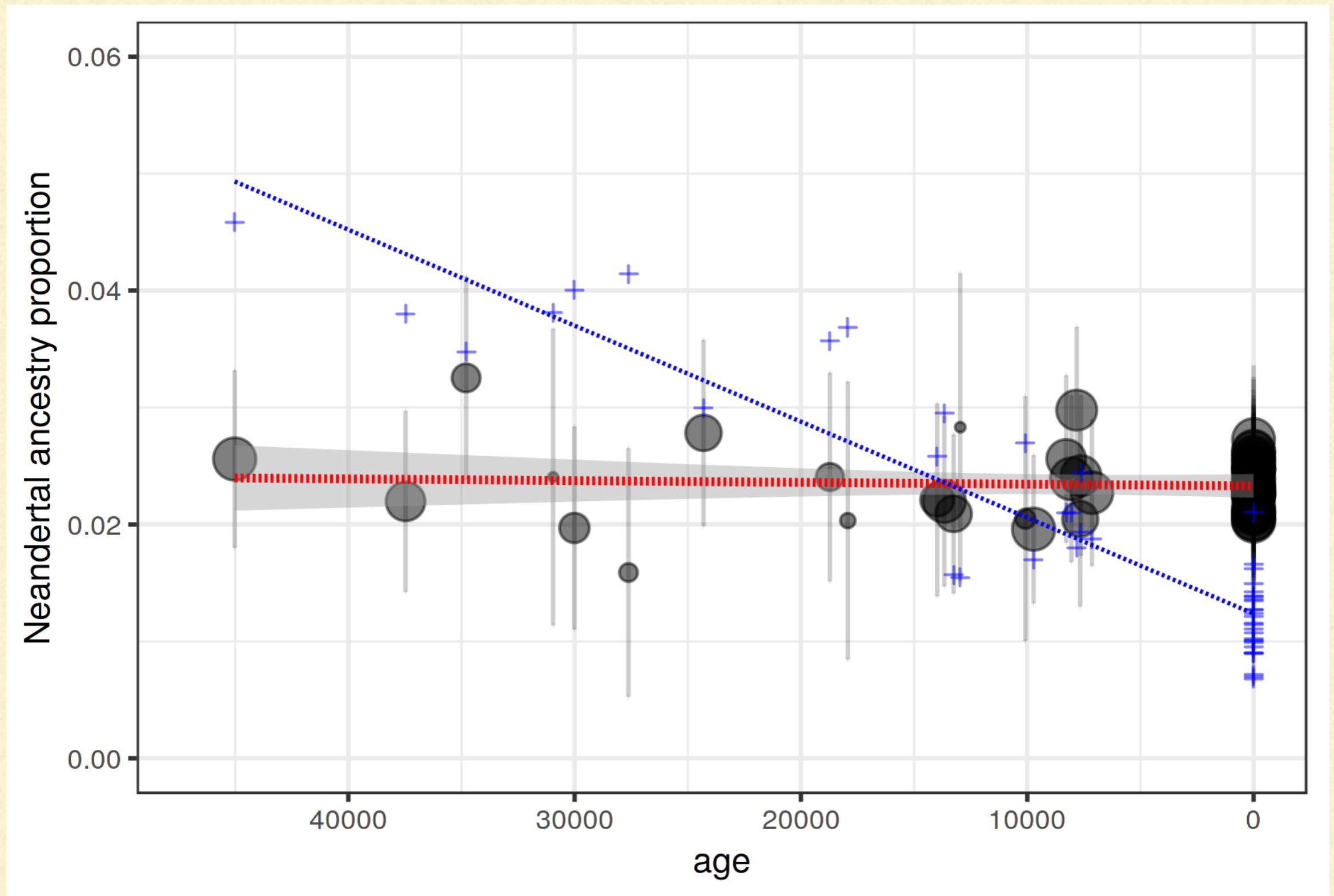
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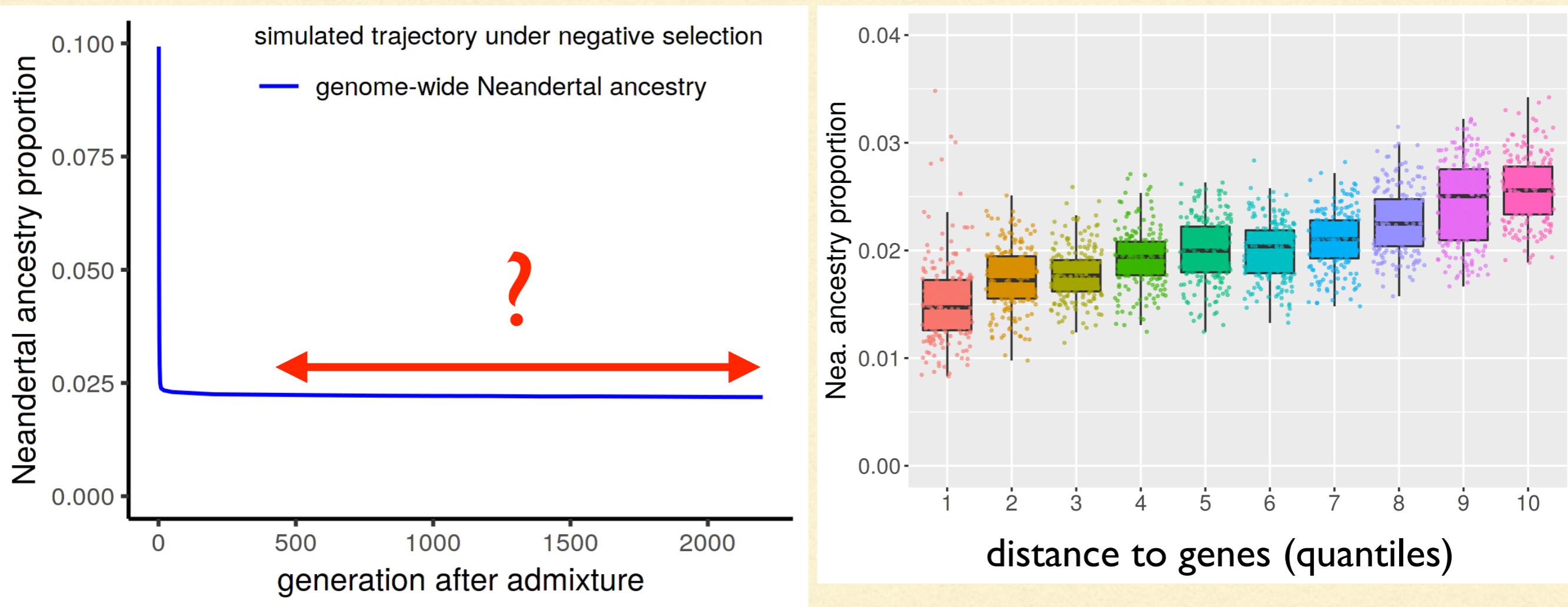
NEW NEANDERTHAL ANCESTRY ESTIMATE



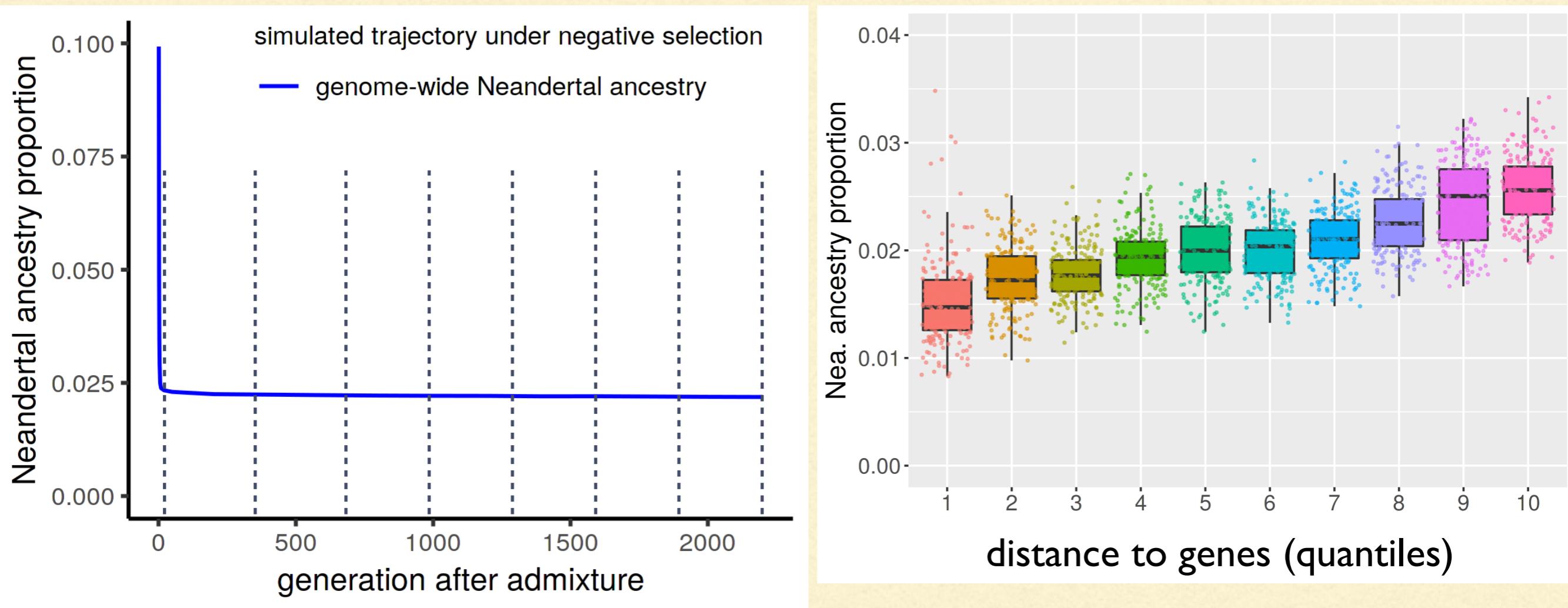
NEW NEANDERTHAL ANCESTRY ESTIMATE



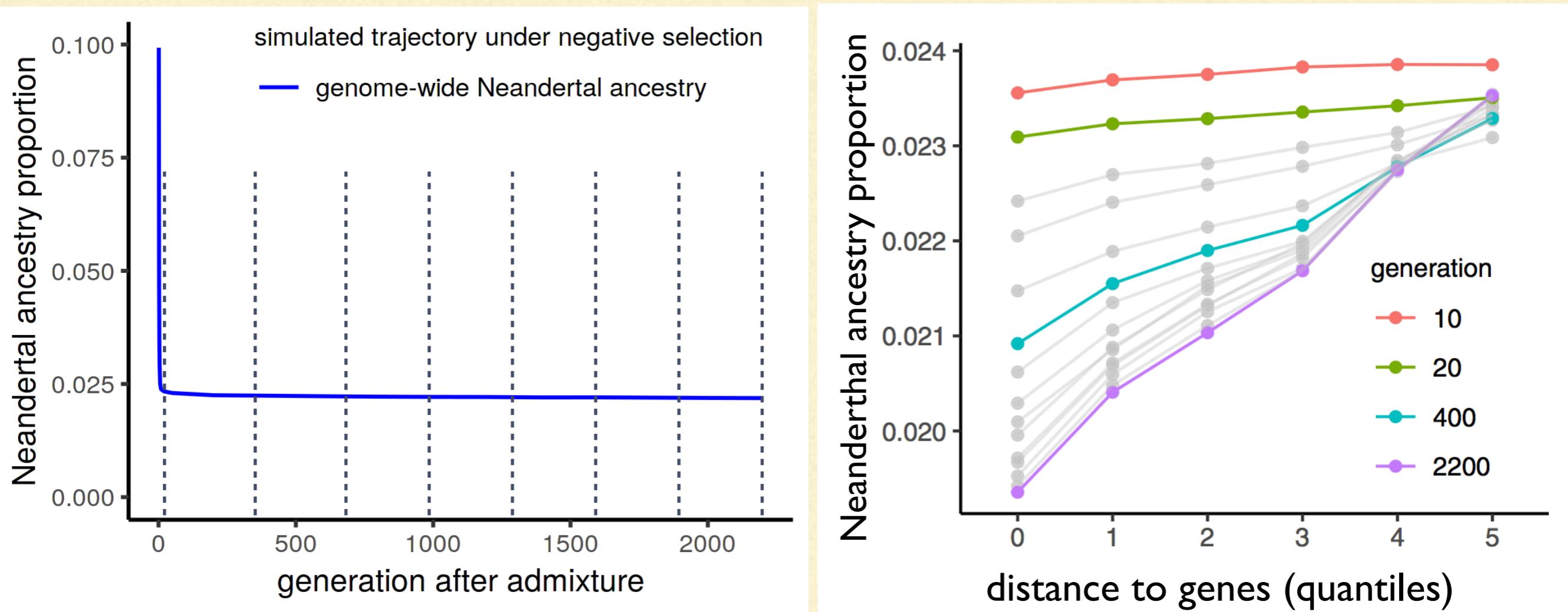
NO NEANDERTHAL ANCESTRY DECLINE —WHAT ABOUT NEGATIVE SELECTION?



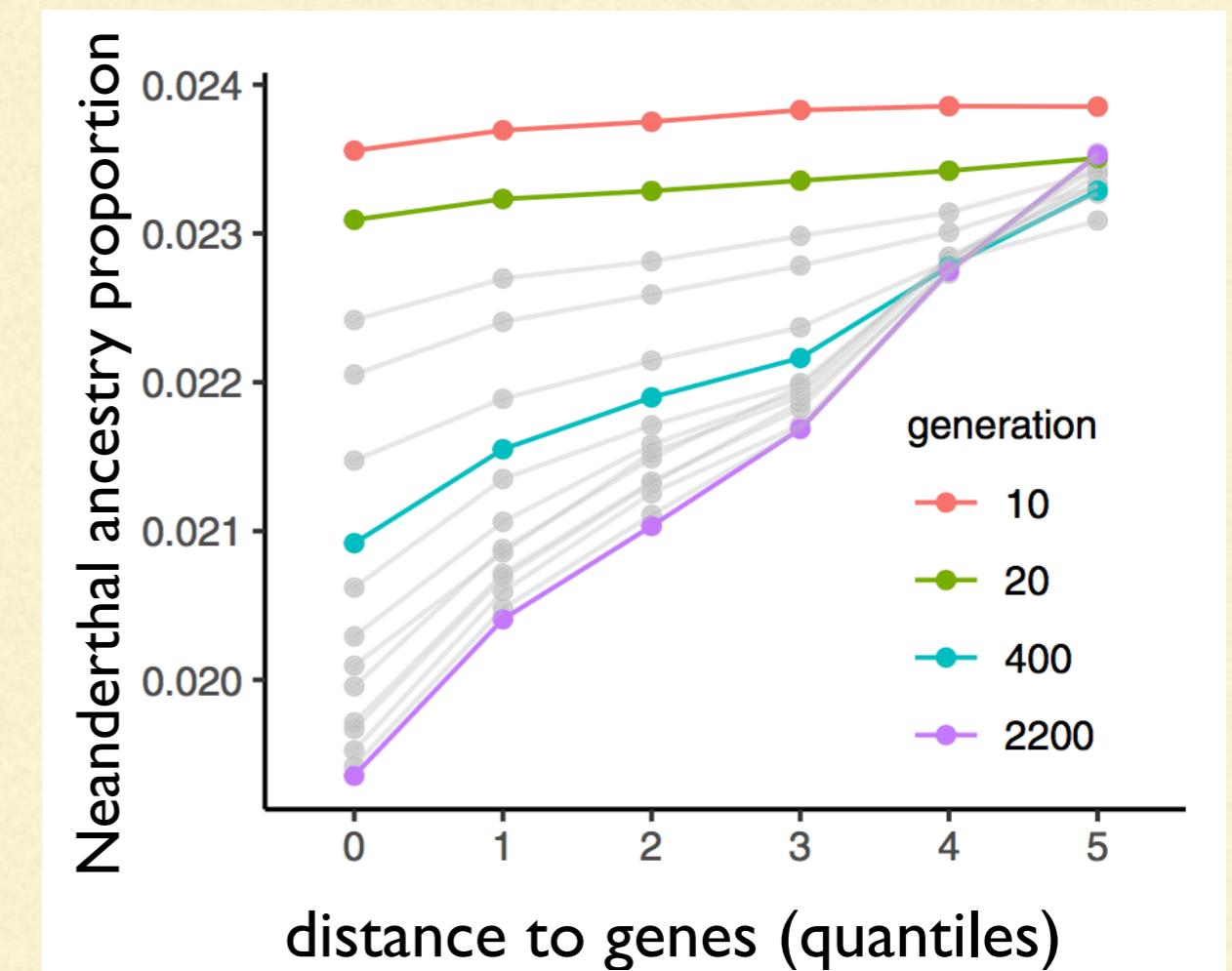
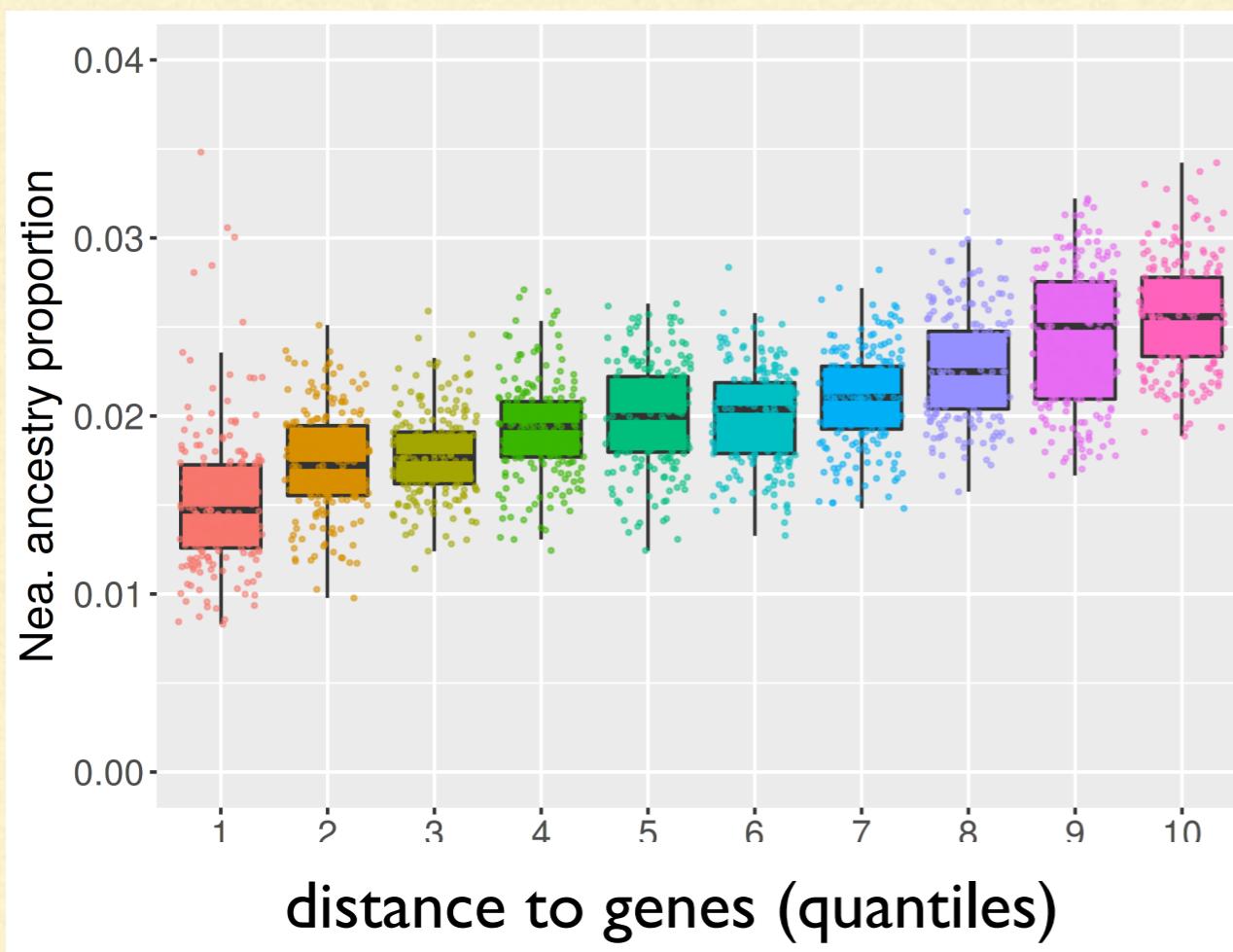
NO NEANDERTHAL ANCESTRY DECLINE —WHAT ABOUT NEGATIVE SELECTION?



NO NEANDERTHAL ANCESTRY DECLINE —WHAT ABOUT NEGATIVE SELECTION?



LONG-TERM NEGATIVE SELECTION STILL OCCURS (ON A LOCAL SCALE)

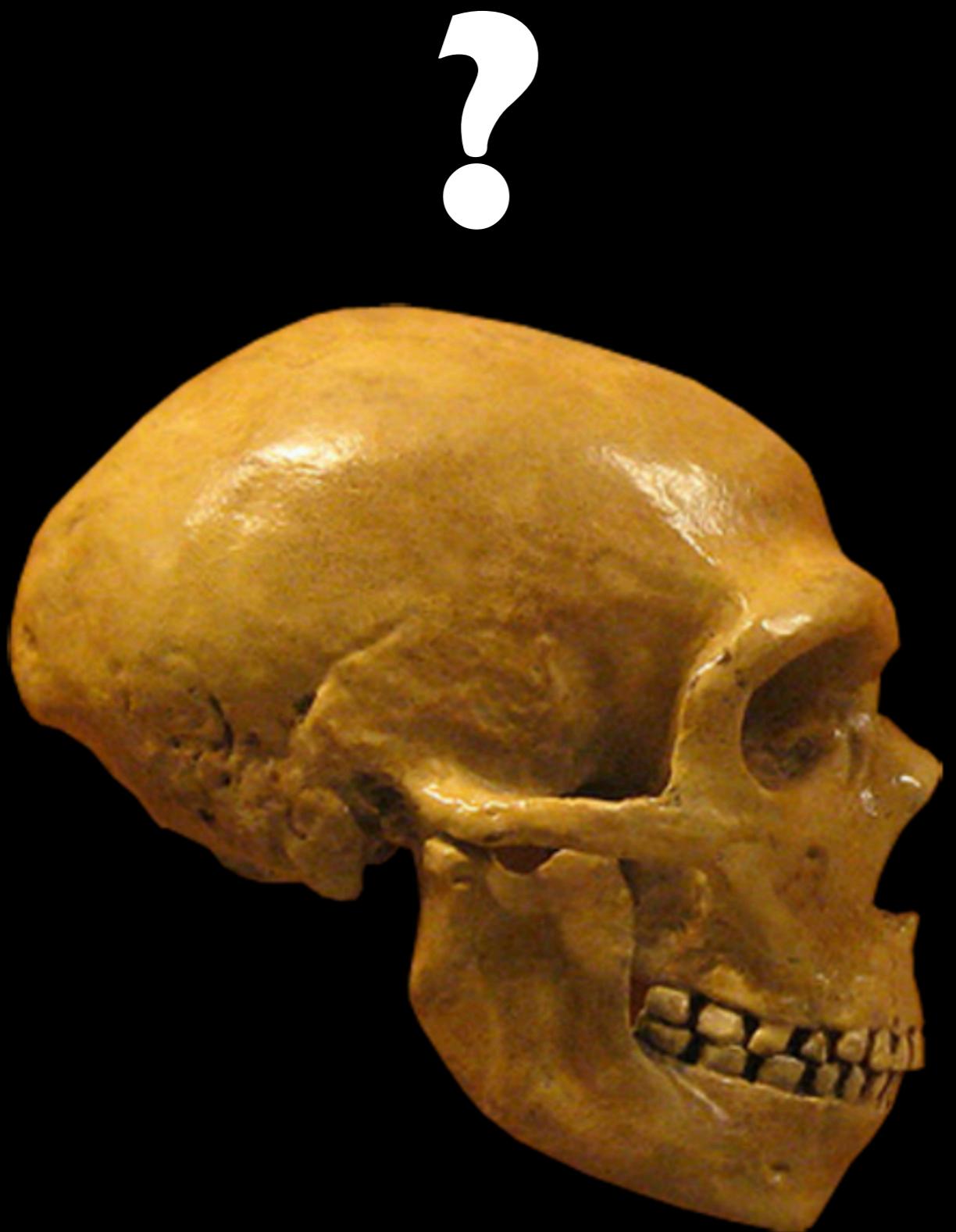


CONCLUSIONS

- Neanderthals disappeared ~40k years ago
- Modern humans...
 - ... migrated out of Africa between 80-60k years ago
 - ... admixed with Neanderthals ~55k years ago
- All non-Africans have ~2% of Neanderthal ancestry
- Neanderthals not truly gone(?)!

CONCLUSIONS

- Neanderthals carried an increased load of bad mutations
- Large part of Neanderthal ancestry removed by selection
- Ancient DNA extremely important for studying selection
- Computer simulations are a powerful tool for fitting (and rejecting!) various evolutionary models



?



?

@fleventy5

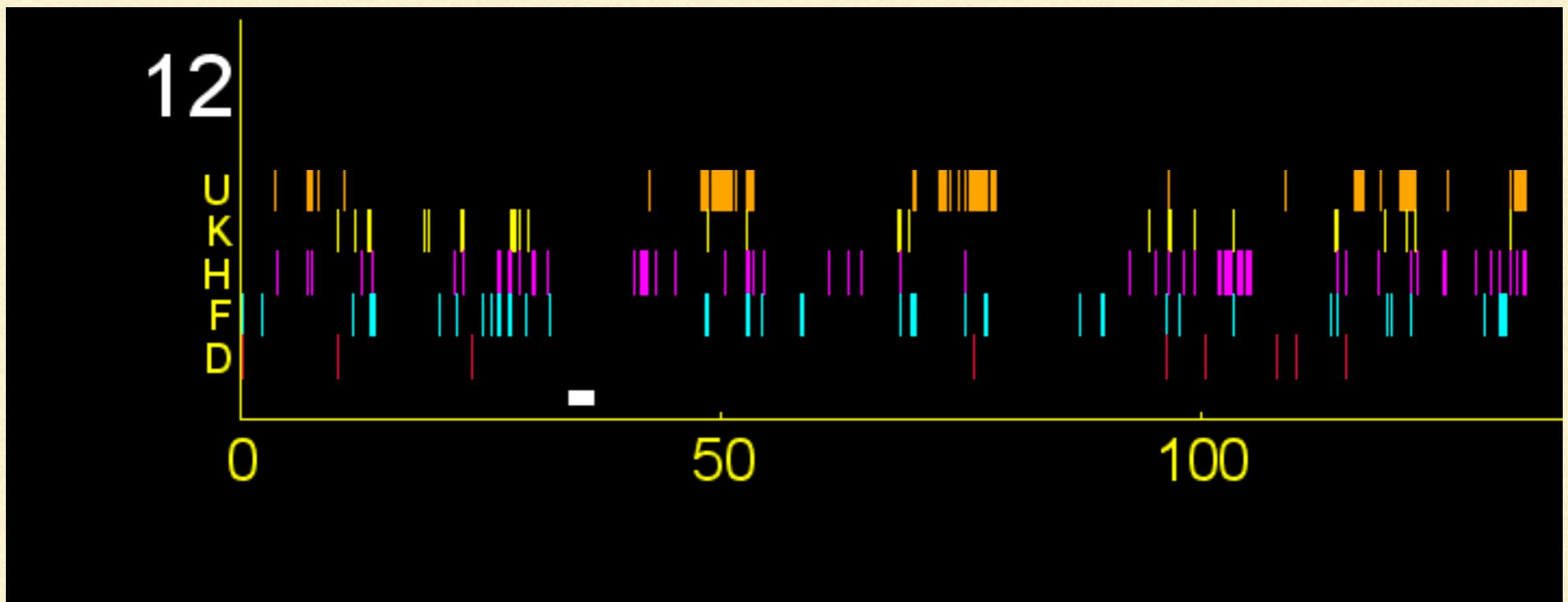
mp@bodkan.net

MORPHOLOGICAL EVIDENCE?

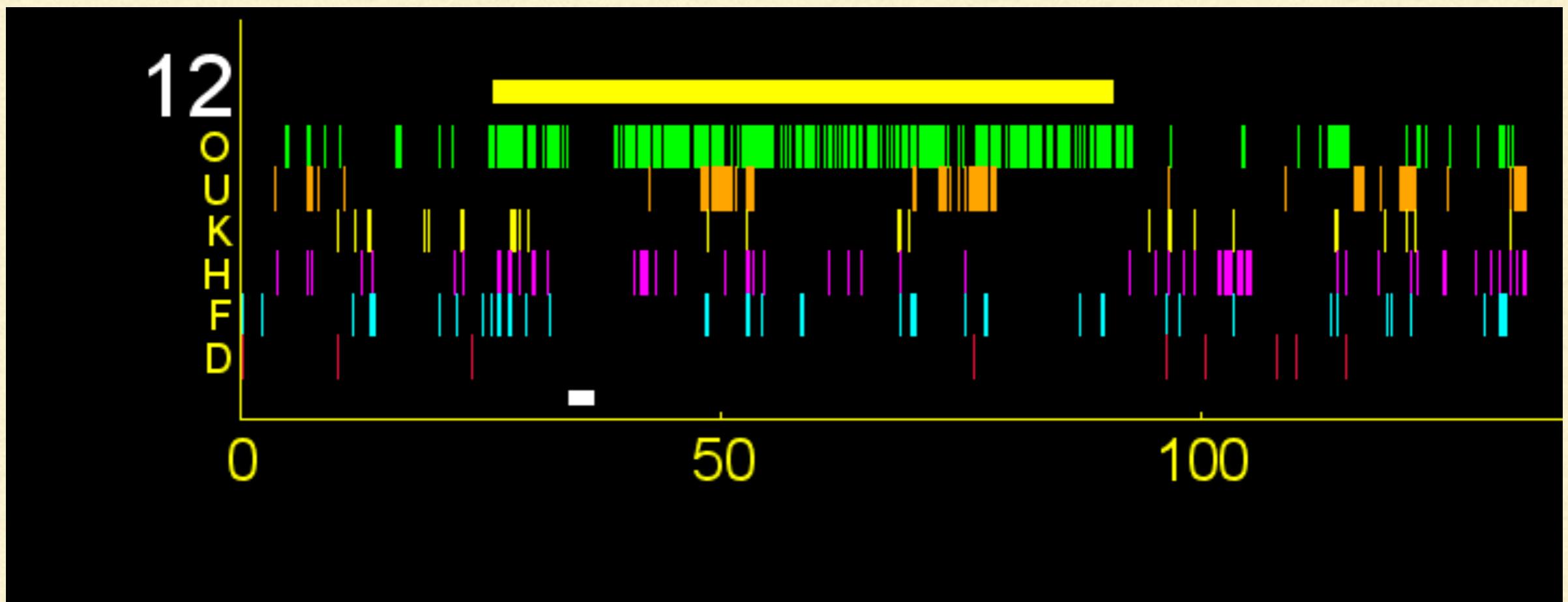
mandible from Peștera cu Oase (Romania)



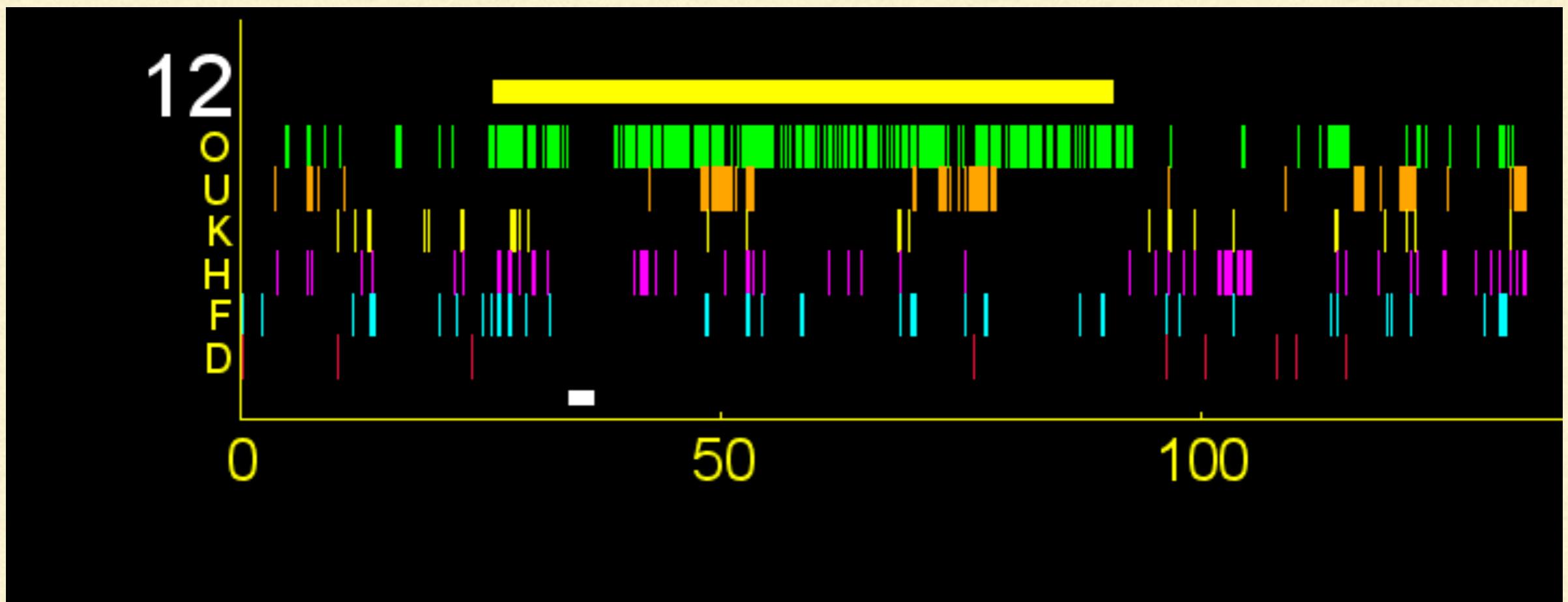
CHROMOSOME 12 OF THE OASE INDIVIDUAL



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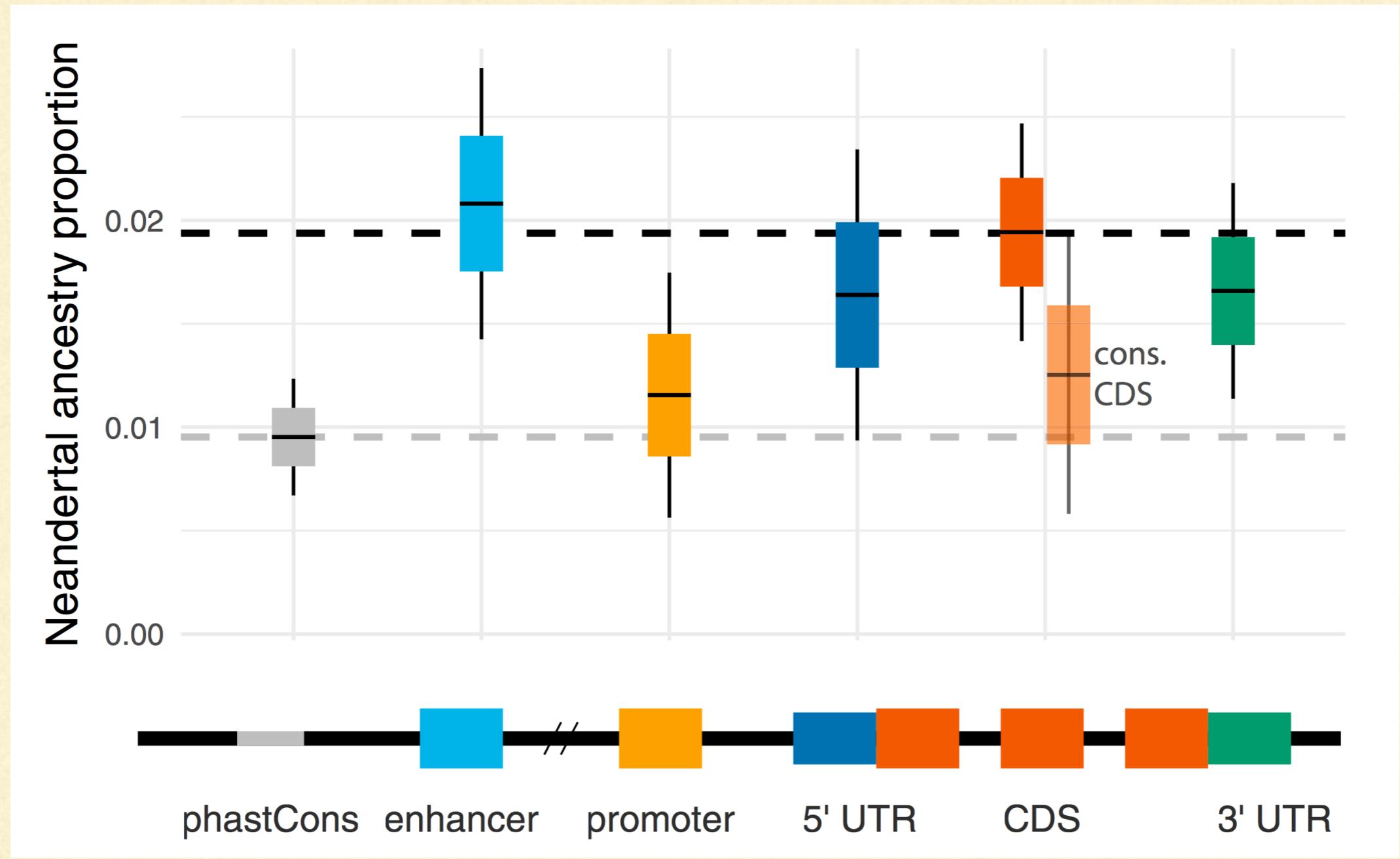


CHROMOSOME 12 OF THE OASE INDIVIDUAL

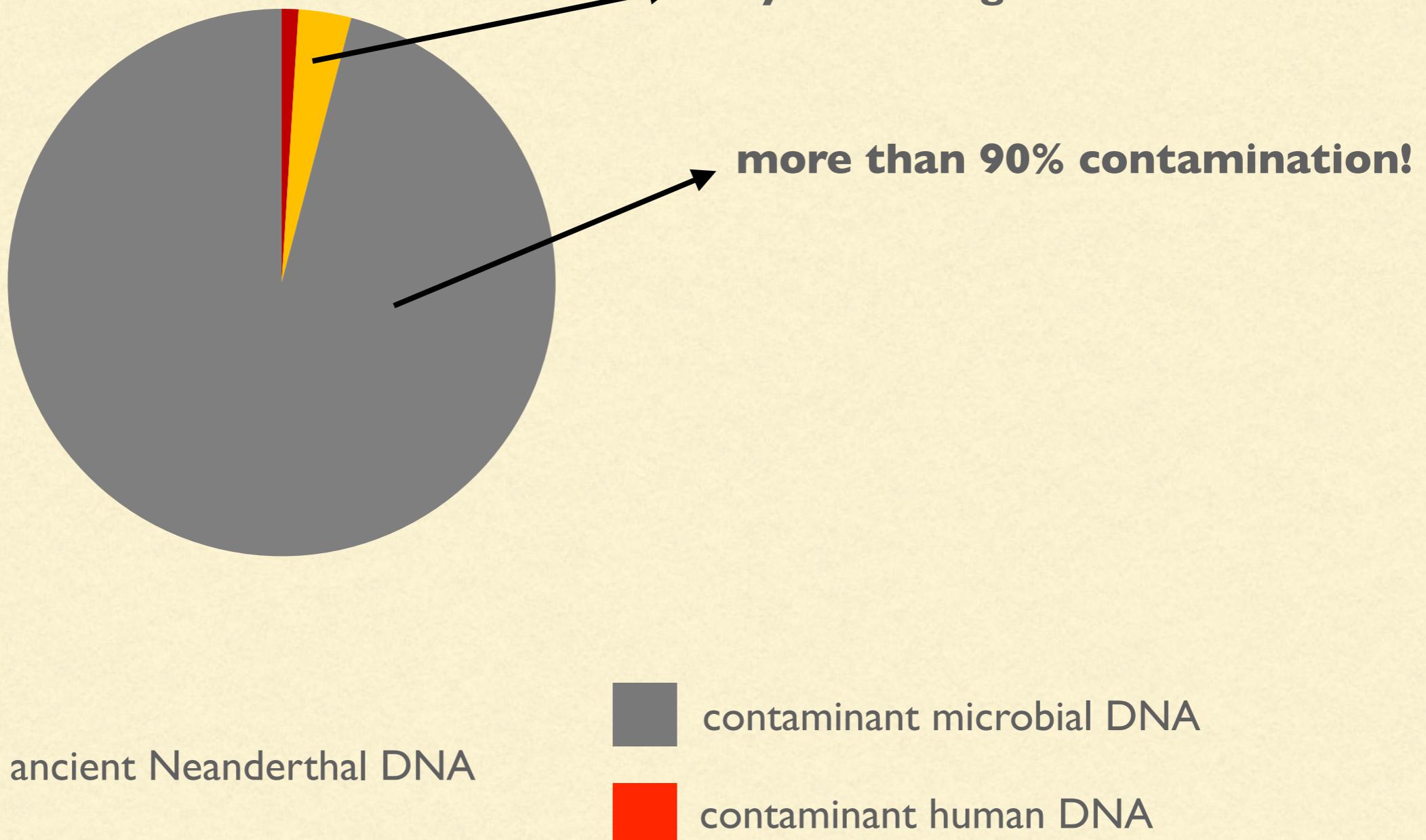


Oase had a direct Neanderthal
ancestor 4-6 generations back!

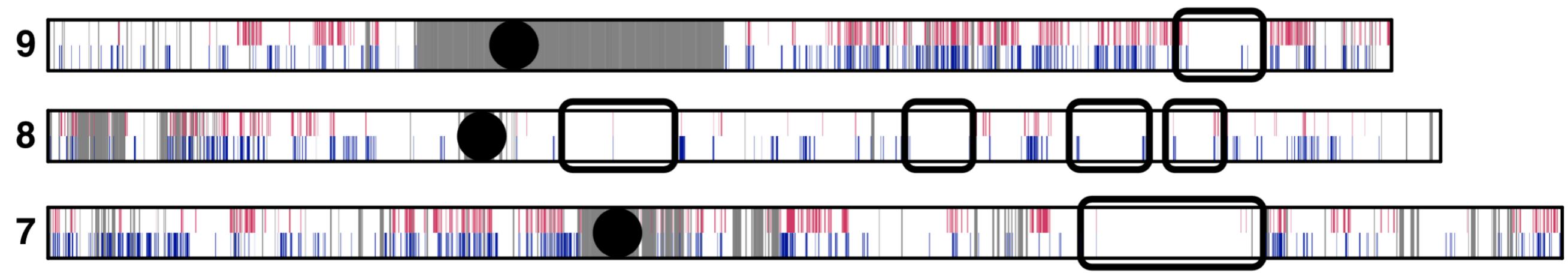
CODING VS REGULATORY REGIONS



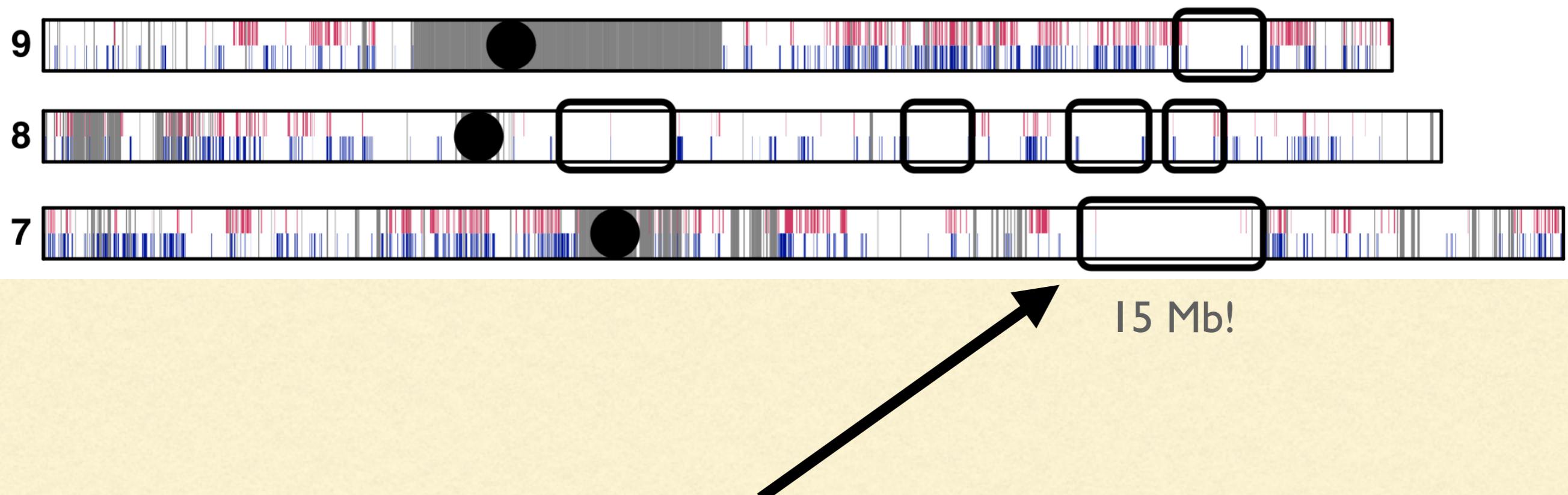
SOURCES OF DNA IN THE BONES



'DESERTS' OF NEANDERTHAL ANCESTRY



'DESERTS' OF NEANDERTHAL ANCESTRY

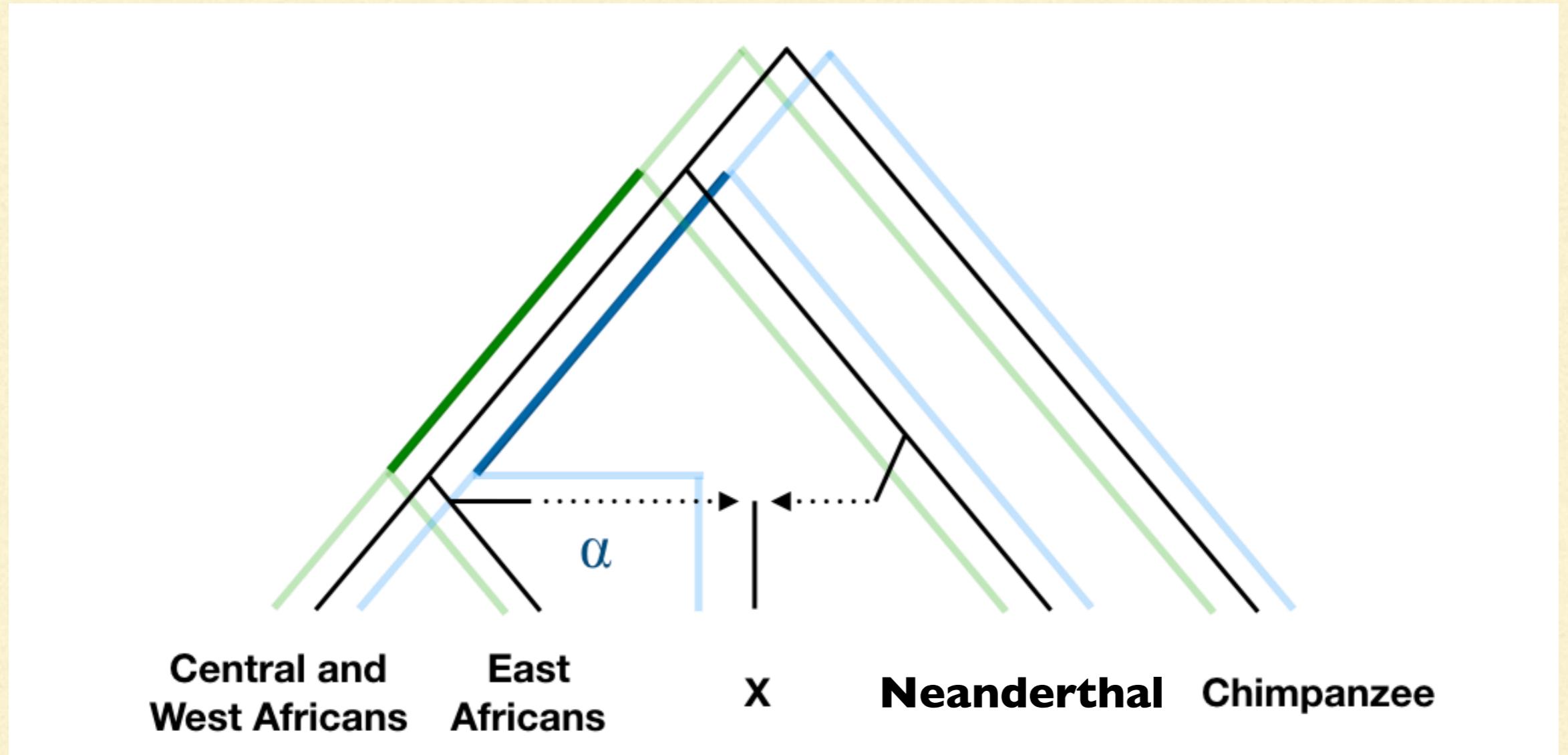


A Recent Evolutionary Change Affects a Regulatory Element in the Human FOXP2 Gene

Tomislav Maricic,^{*1} Viola Günther,² Oleg Georgiev,² Sabine Gehre,¹ Marija Ćurlin,³ Christiane Schreiweis,¹ Ronald Naumann,⁴ Hernán A. Burbano,^{†,1} Matthias Meyer,¹ Carles Lalueza-Fox,⁵ Marco de la Rasilla,⁶ Antonio Rosas,⁷ Srećko Gajović,³ Janet Kelso,¹ Wolfgang Enard,¹ Walter Schaffner,² and Svante Pääbo¹

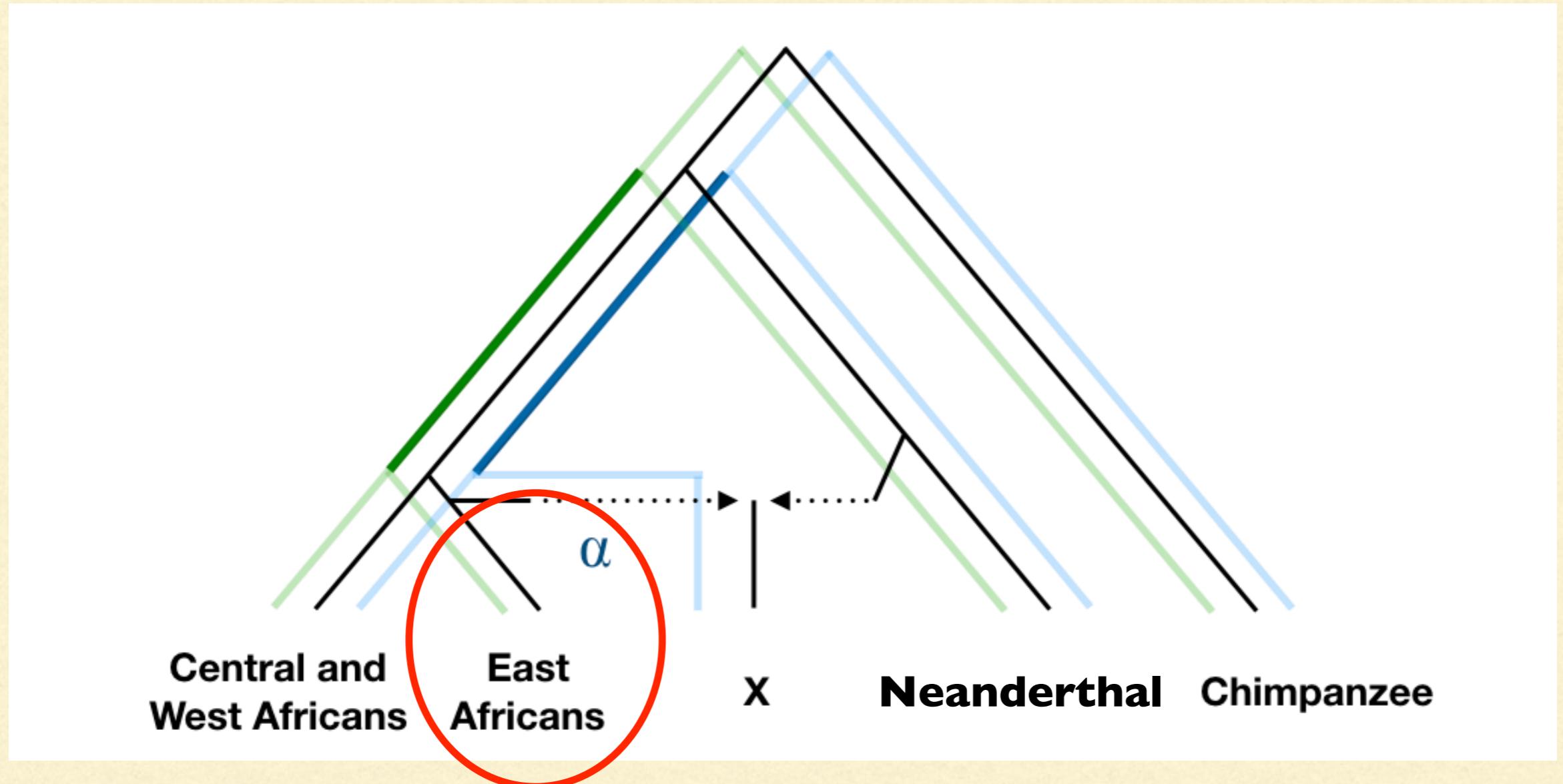
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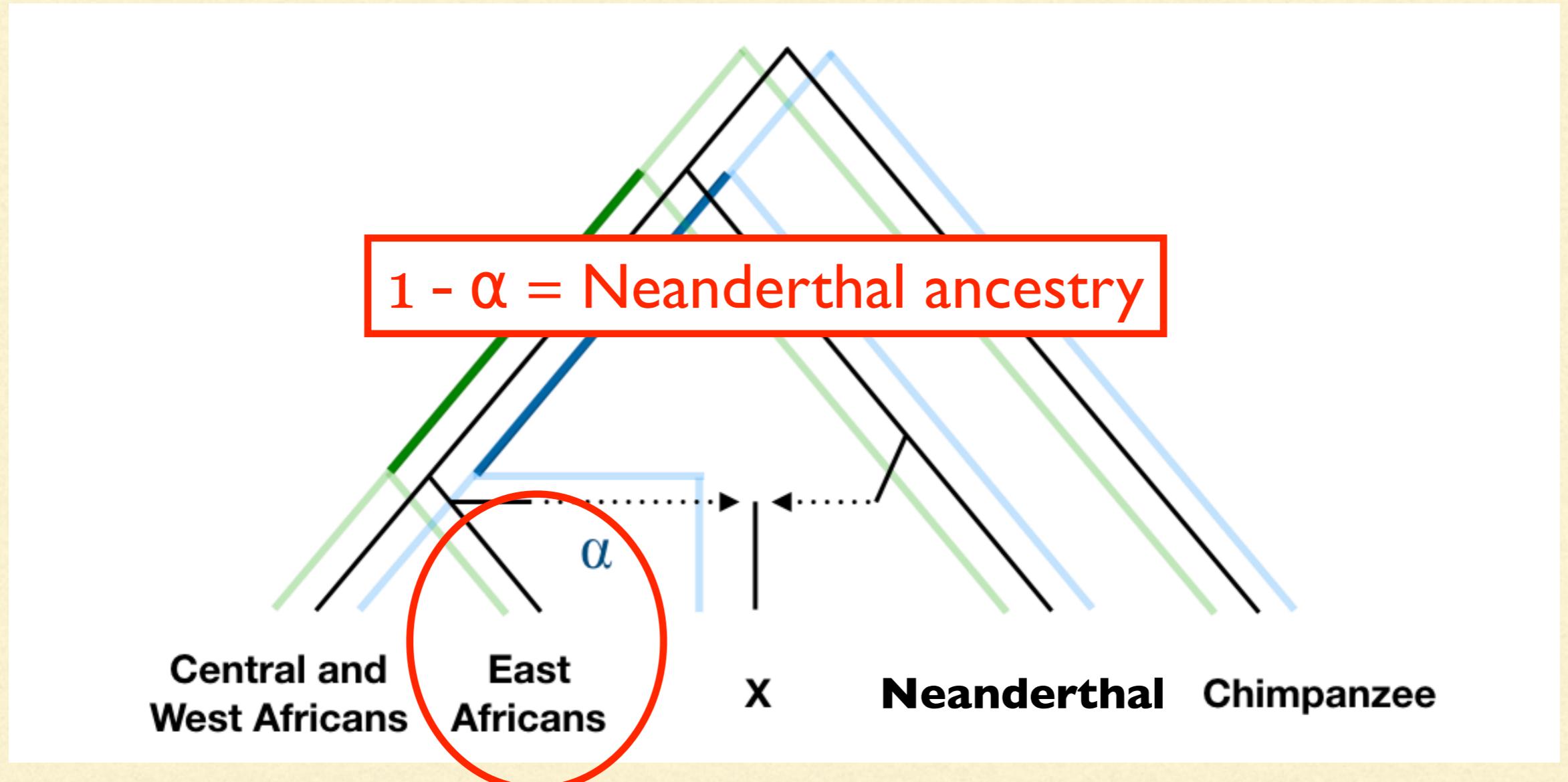
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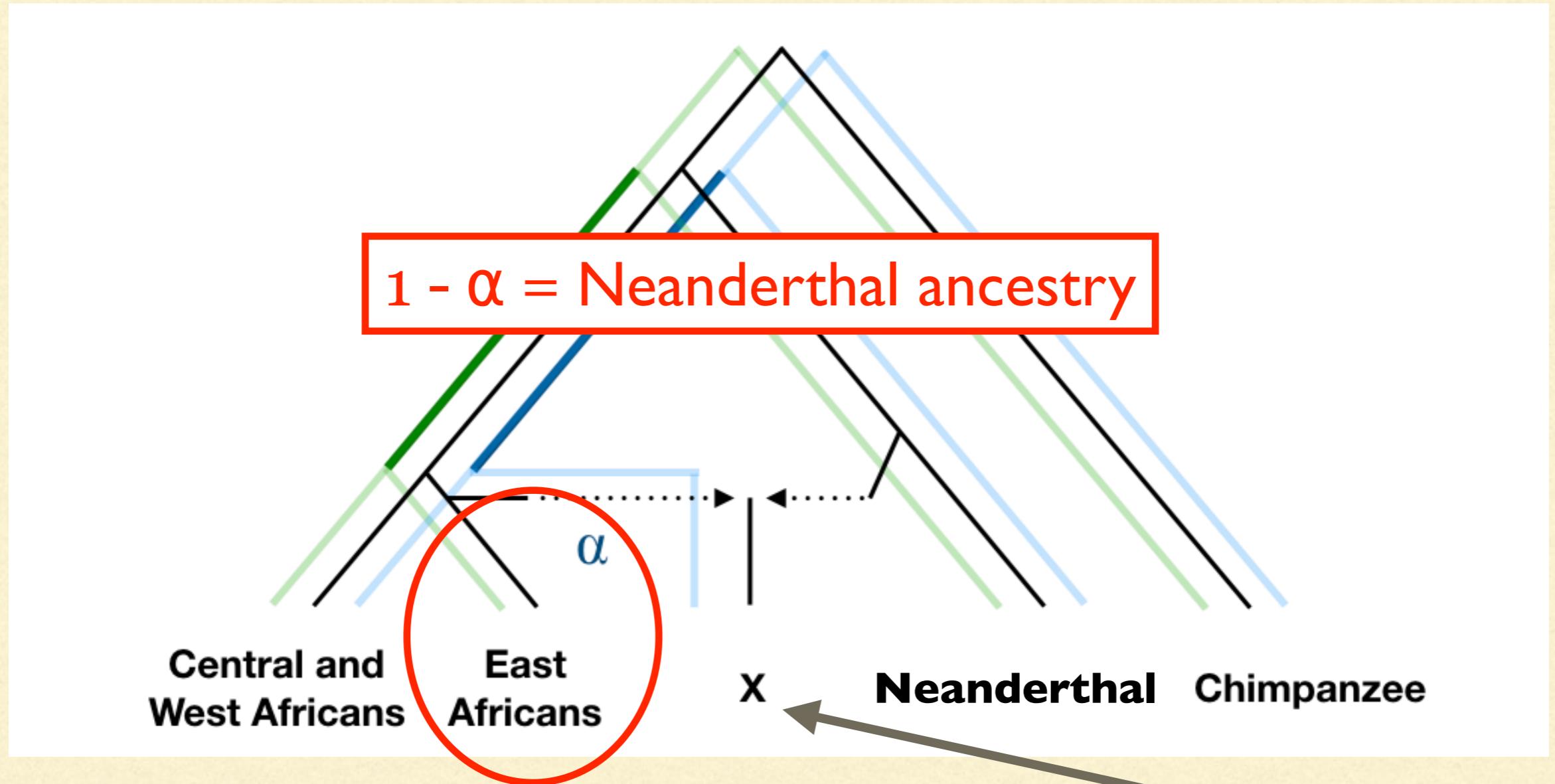
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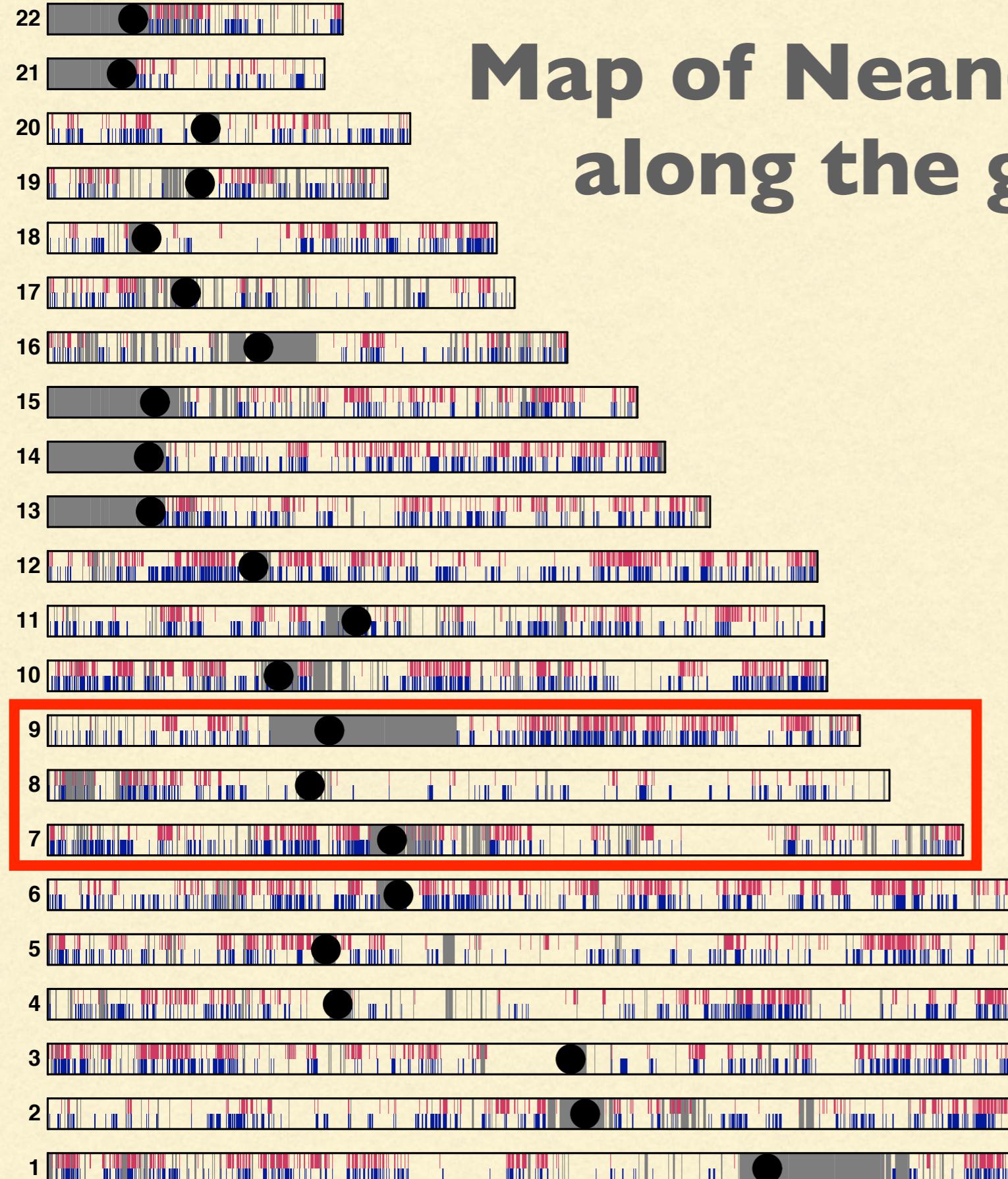


1 - α calculated for each **ancient European X**



Map of Neanderthal ancestry along the genomes of ~700 East Asians and Europeans.

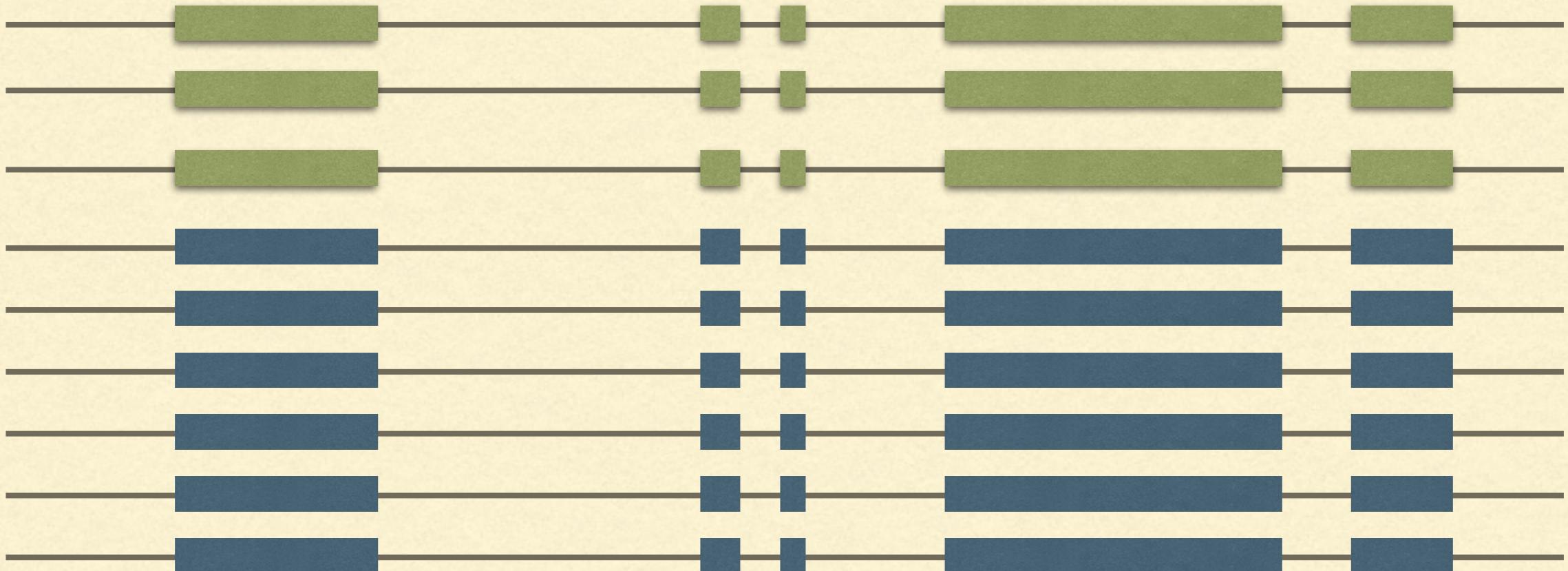
East Asians
Europeans



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East Asians
Europeans

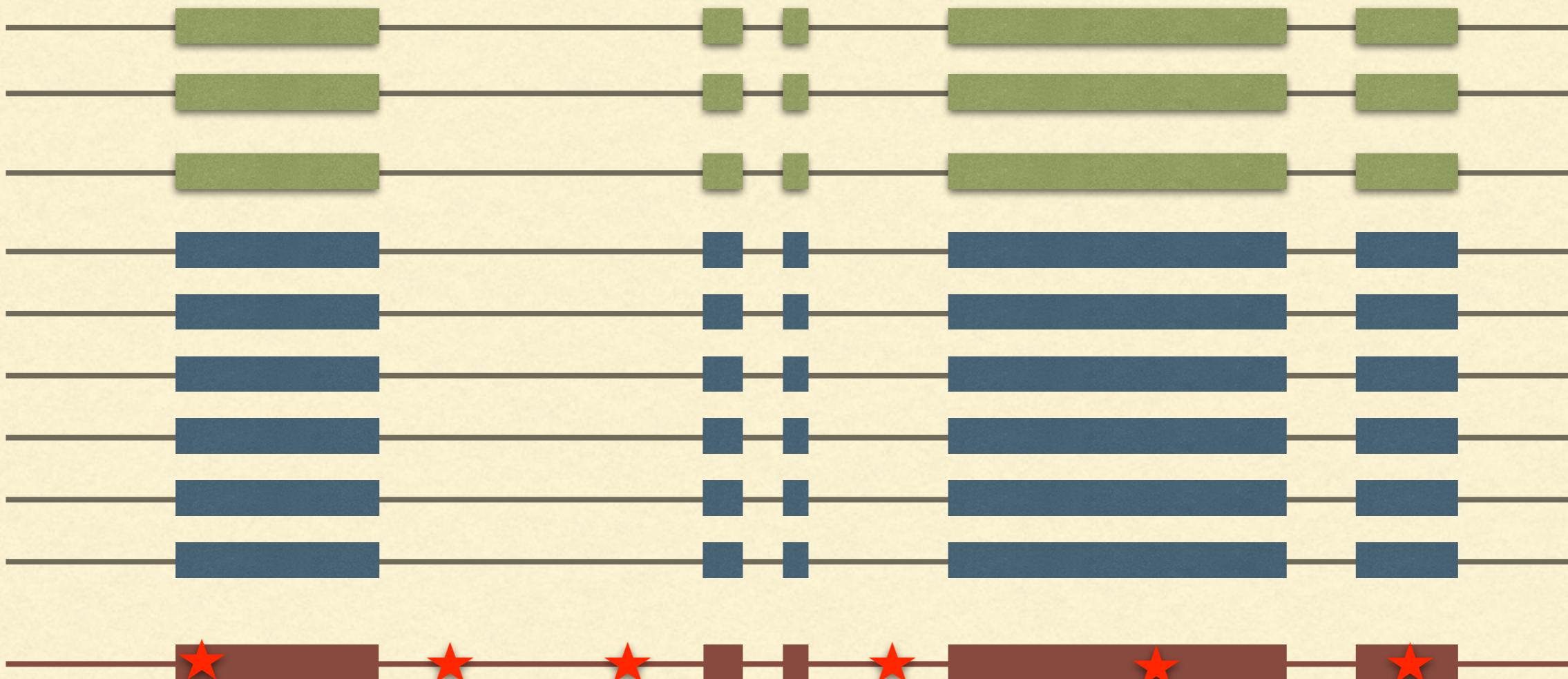
GENOMIC “MAPS” OF NEANDERTHAL ANCESTRY



Africans

non-Africans

GENOMIC “MAPS” OF NEANDERTHAL ANCESTRY



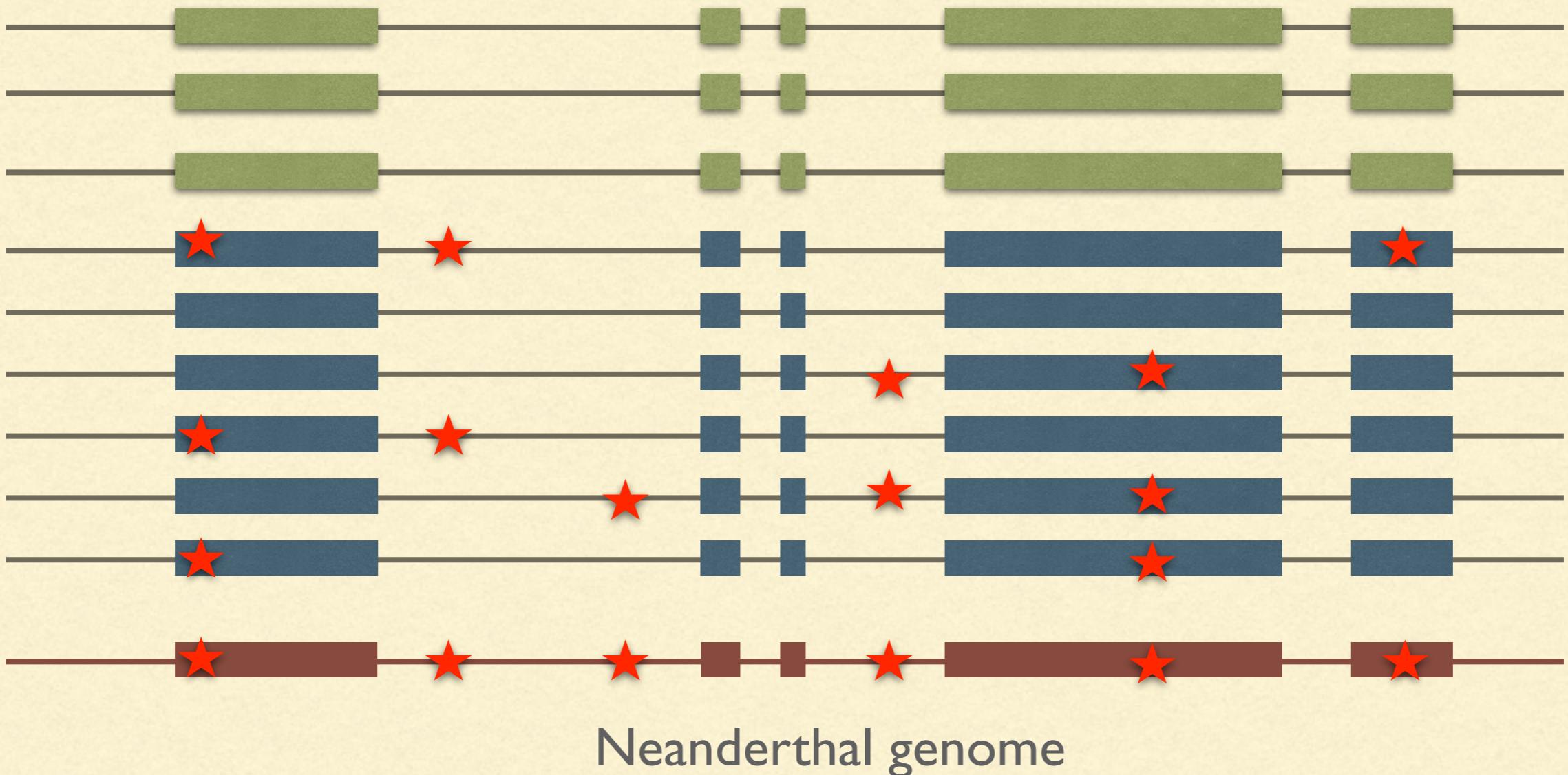
Neanderthal genome

★ — Neanderthal-specific mutation

Africans

non-Africans

GENOMIC “MAPS” OF NEANDERTHAL ANCESTRY



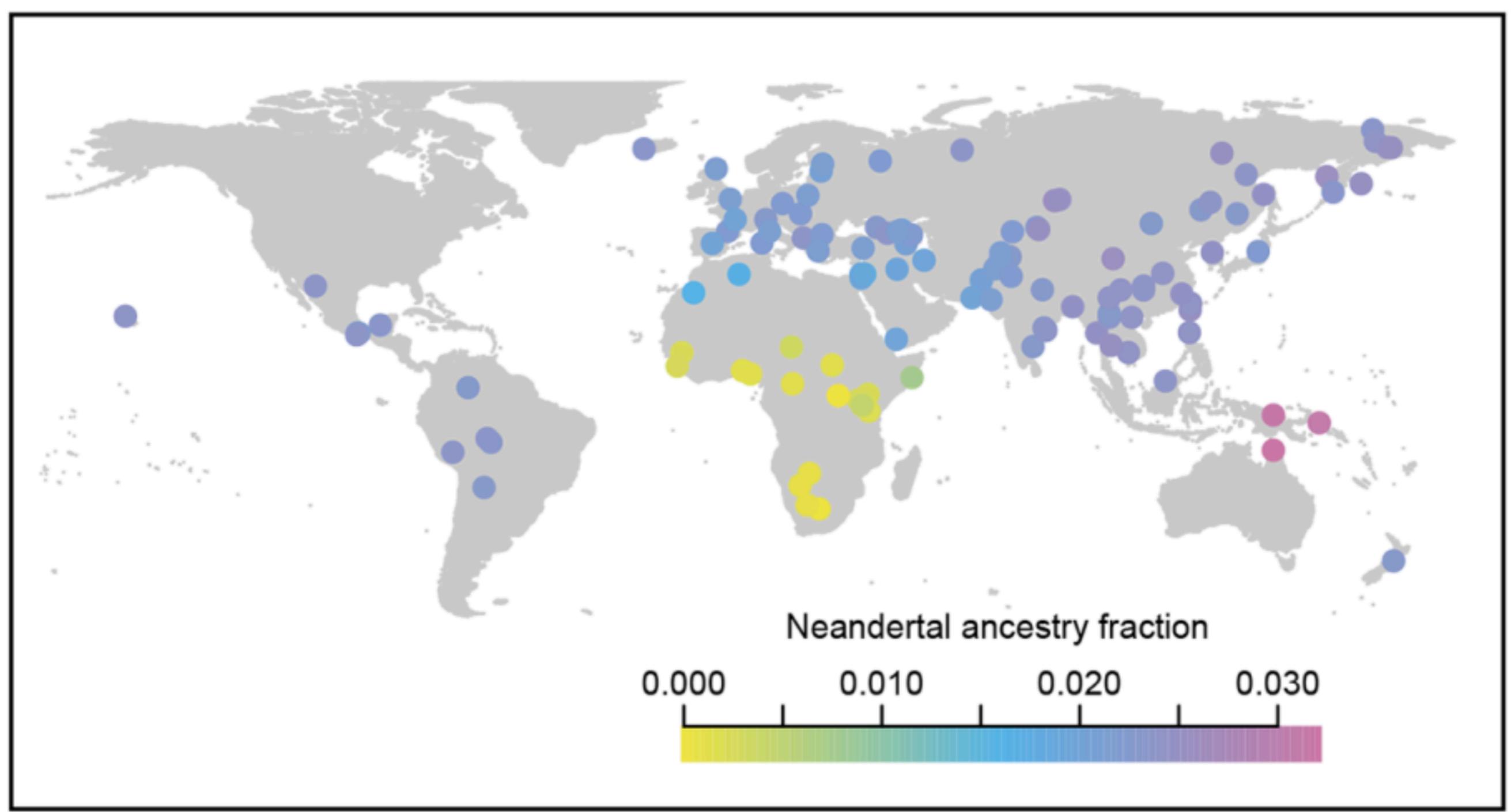
Africans

non-Africans

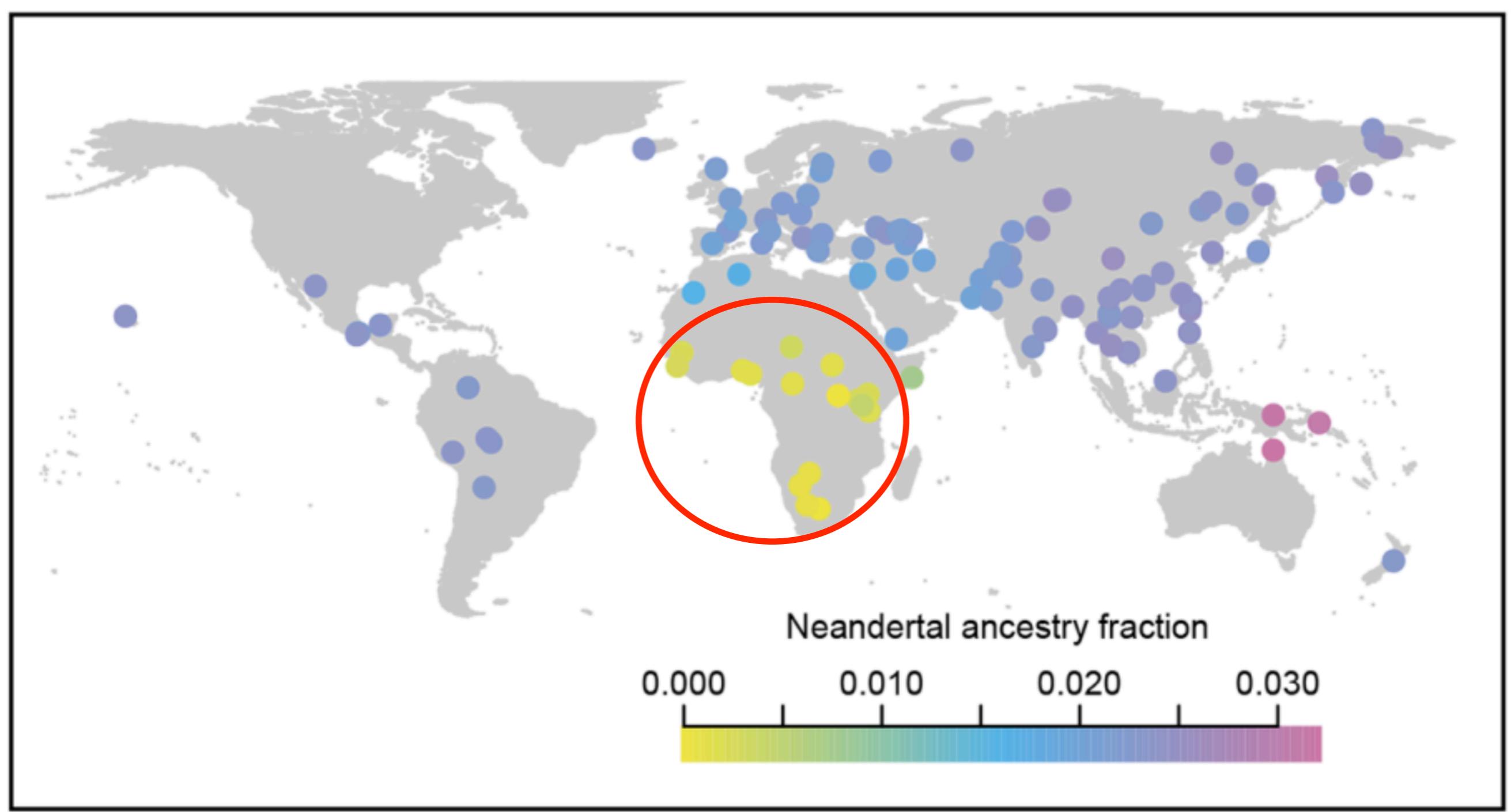
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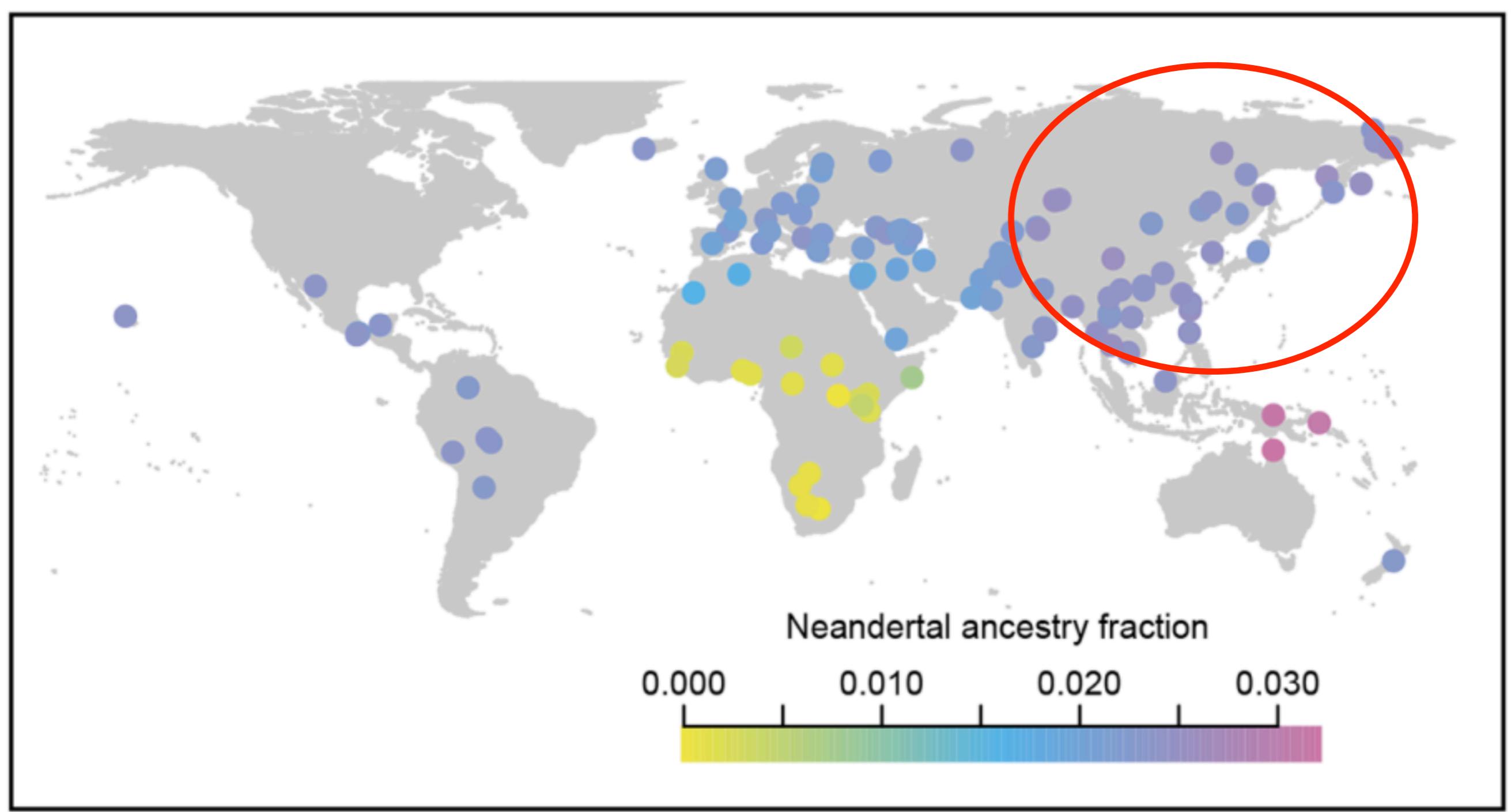
GEOGRAPHIC DISTRIBUTION OF NEANDERTHAL ANCESTRY IN THE WORLD



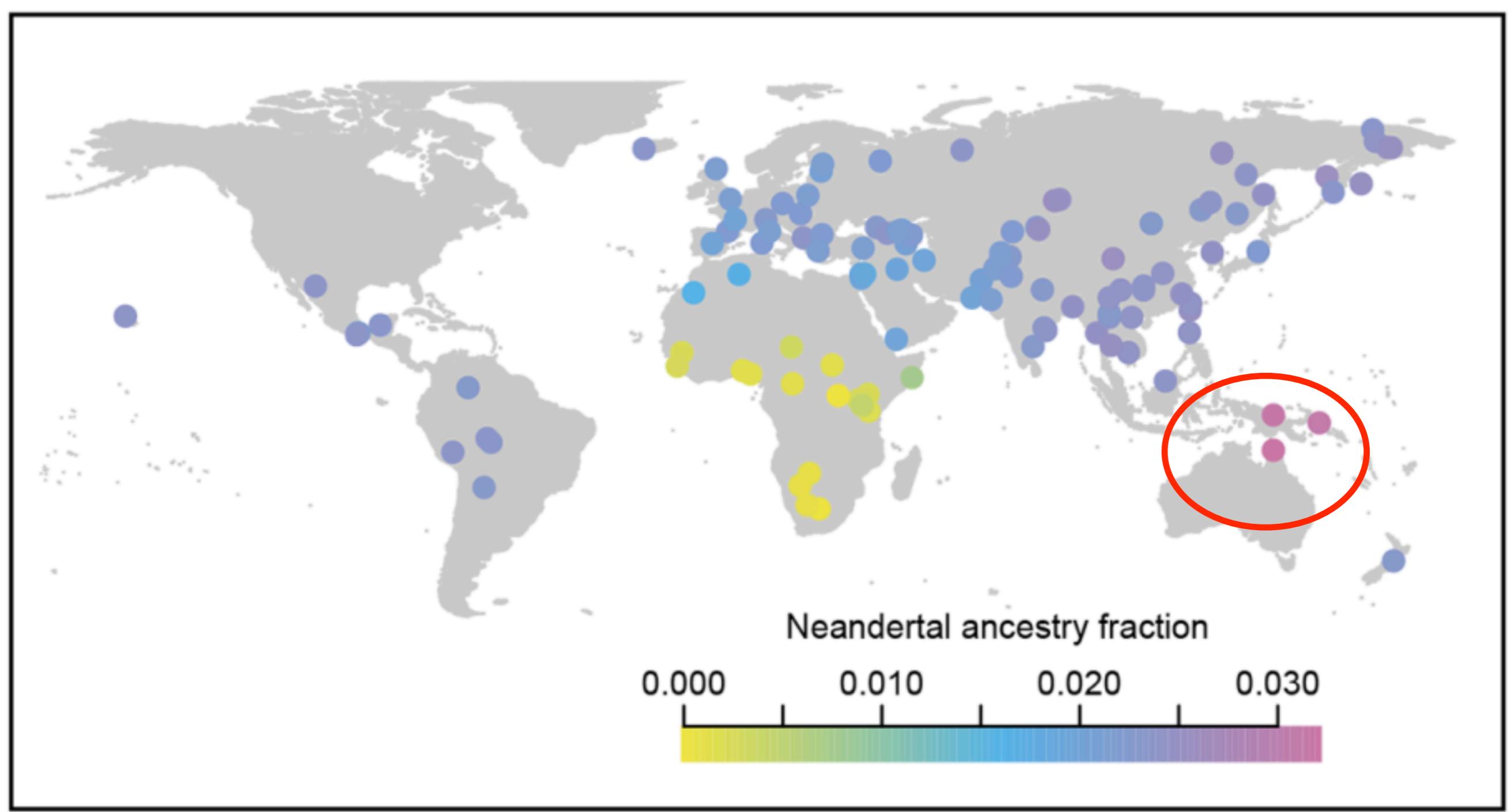
GEOGRAPHIC DISTRIBUTION OF NEANDERTHAL ANCESTRY IN THE WORLD



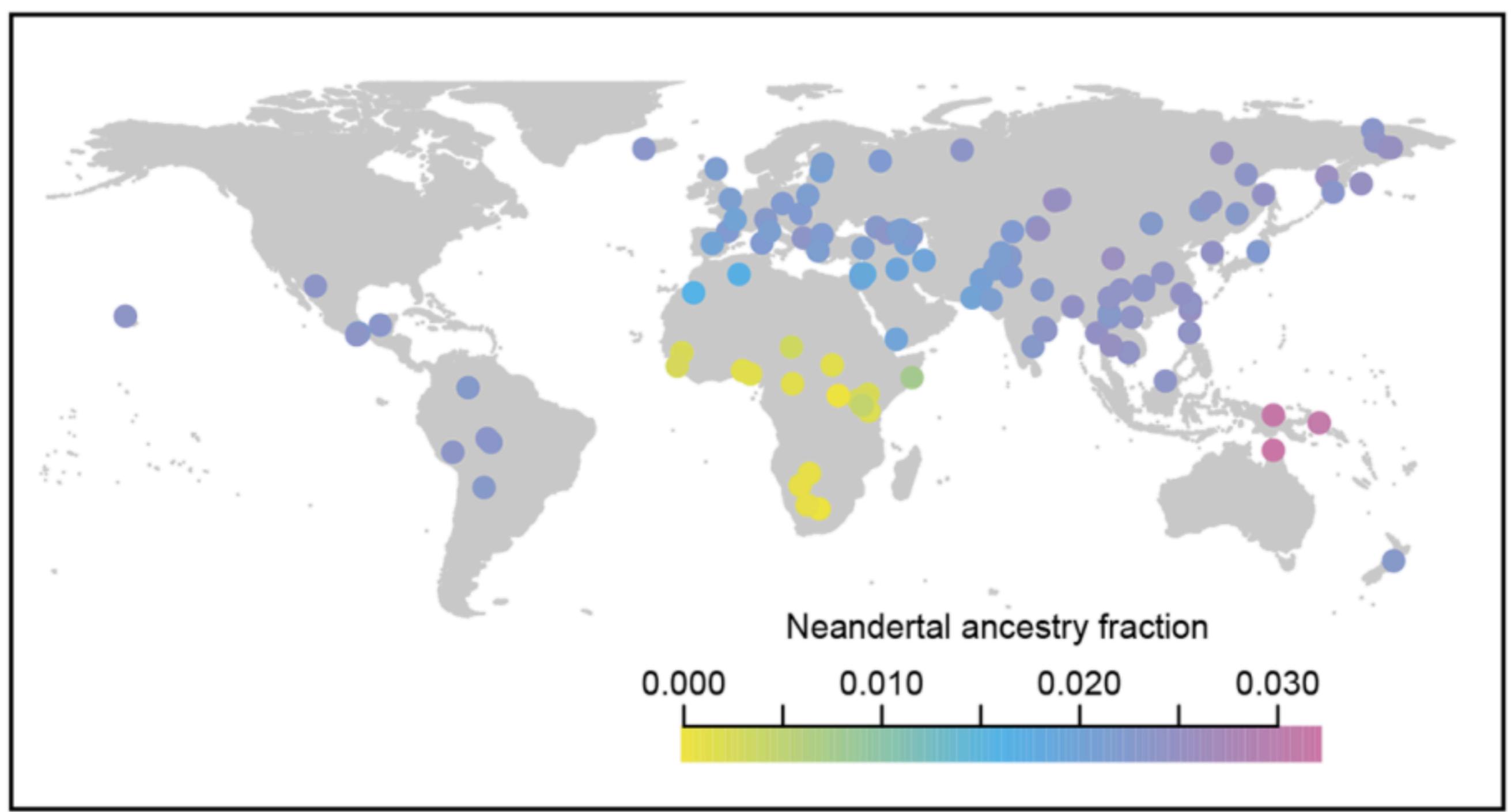
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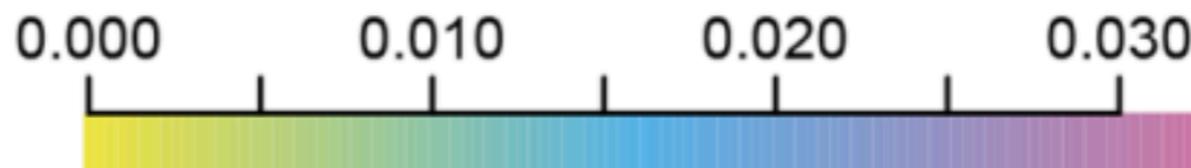
GEOGRAPHIC DISTRIBUTION OF NEANDERTHAL ANCESTRY IN THE WORLD



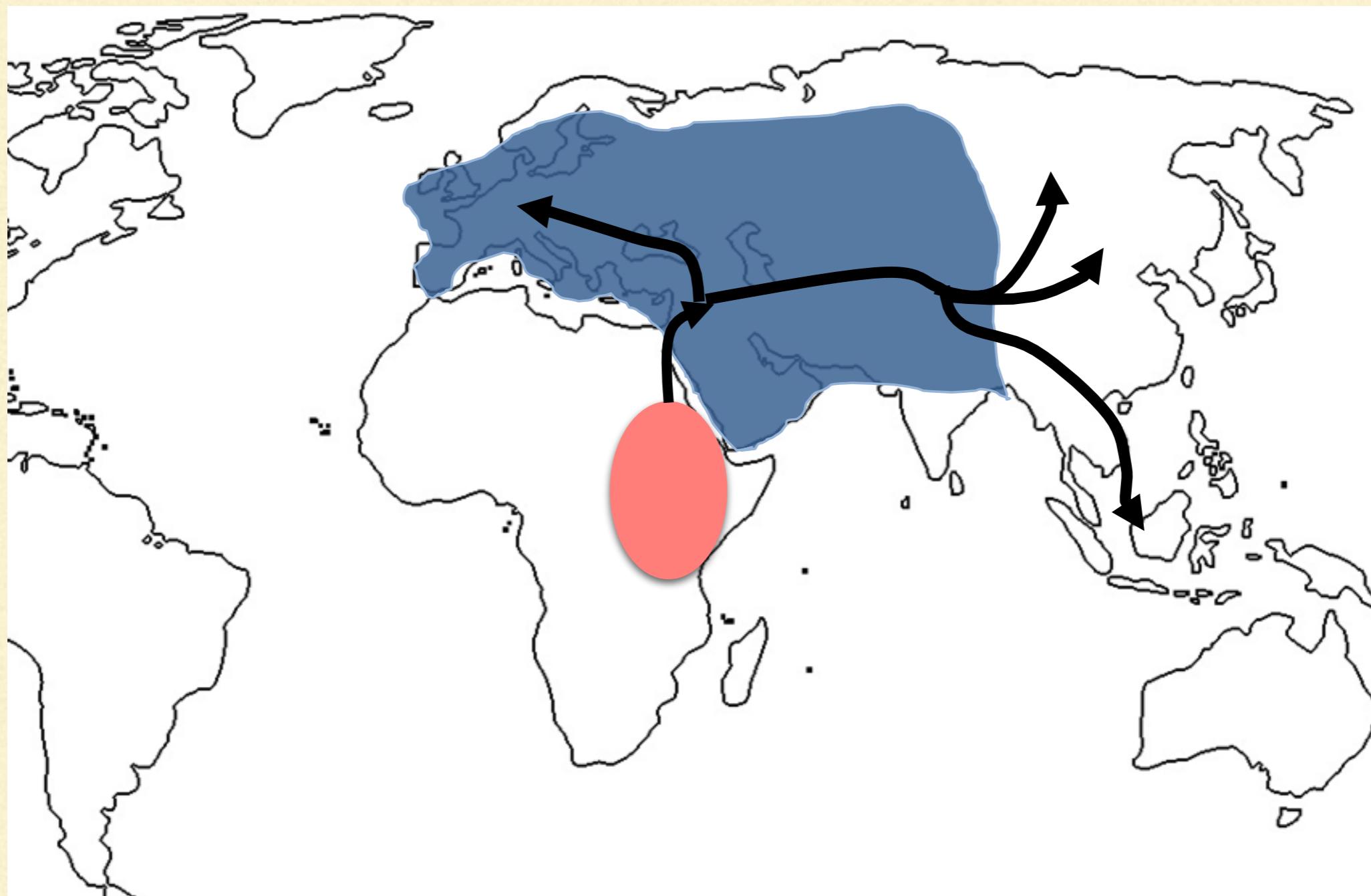
GEOGRAPHIC DISTRIBUTION OF NEANDERTHAL ANCESTRY IN THE WORLD



**ALL NON-AFRICANS HAVE A SHARED
NEANDERTHAL ANCESTRY COMPONENT**
→ **A SINGLE MAJOR ADMIXTURE “PULSE”**

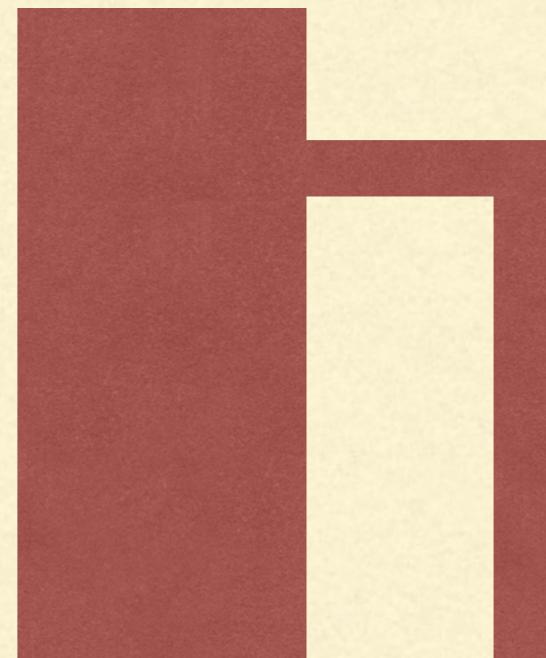


AMH migrated out of Africa
~70-50 thousand years ago



NEARLY NEUTRAL THEORY

TOMOKO OHTA, 1973



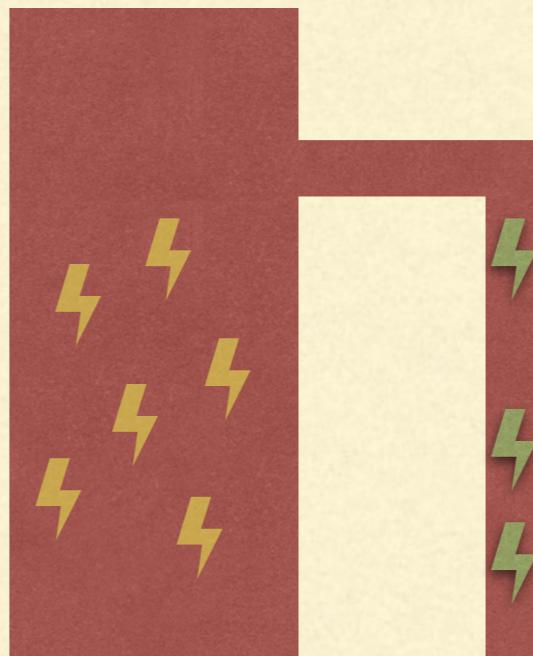
$$N_e(\text{pop A}) > N_e(\text{pop B})$$

N_e = effective population size

Ohta T. Nature. 1973

NEARLY NEUTRAL THEORY

TOMOKO OHTA, 1973



$$N_e(\text{pop A}) > N_e(\text{pop B})$$

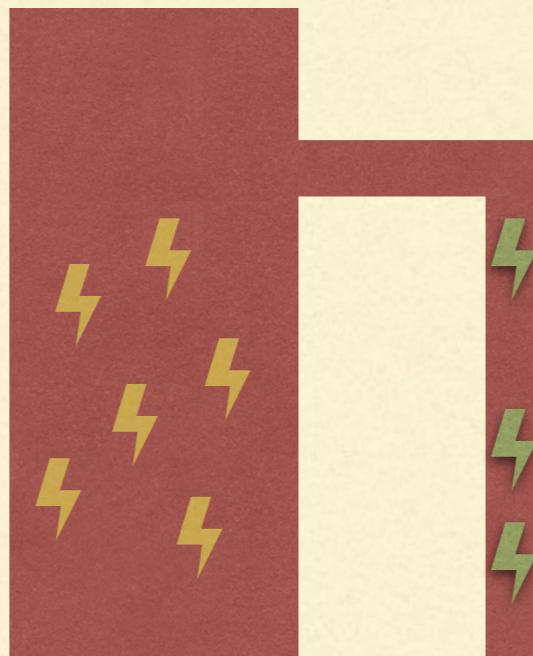
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NEARLY NEUTRAL THEORY

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Efficacy of purifying selection is proportional to N_e

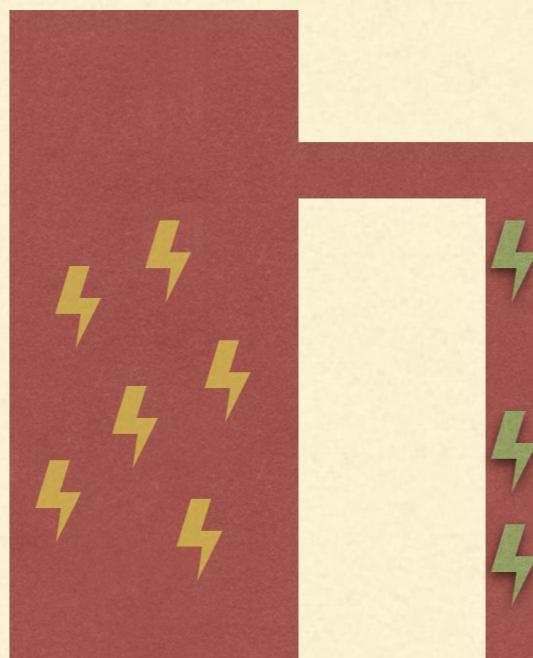


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NEARLY NEUTRAL THEORY

TOMOKO OHTA, 1973

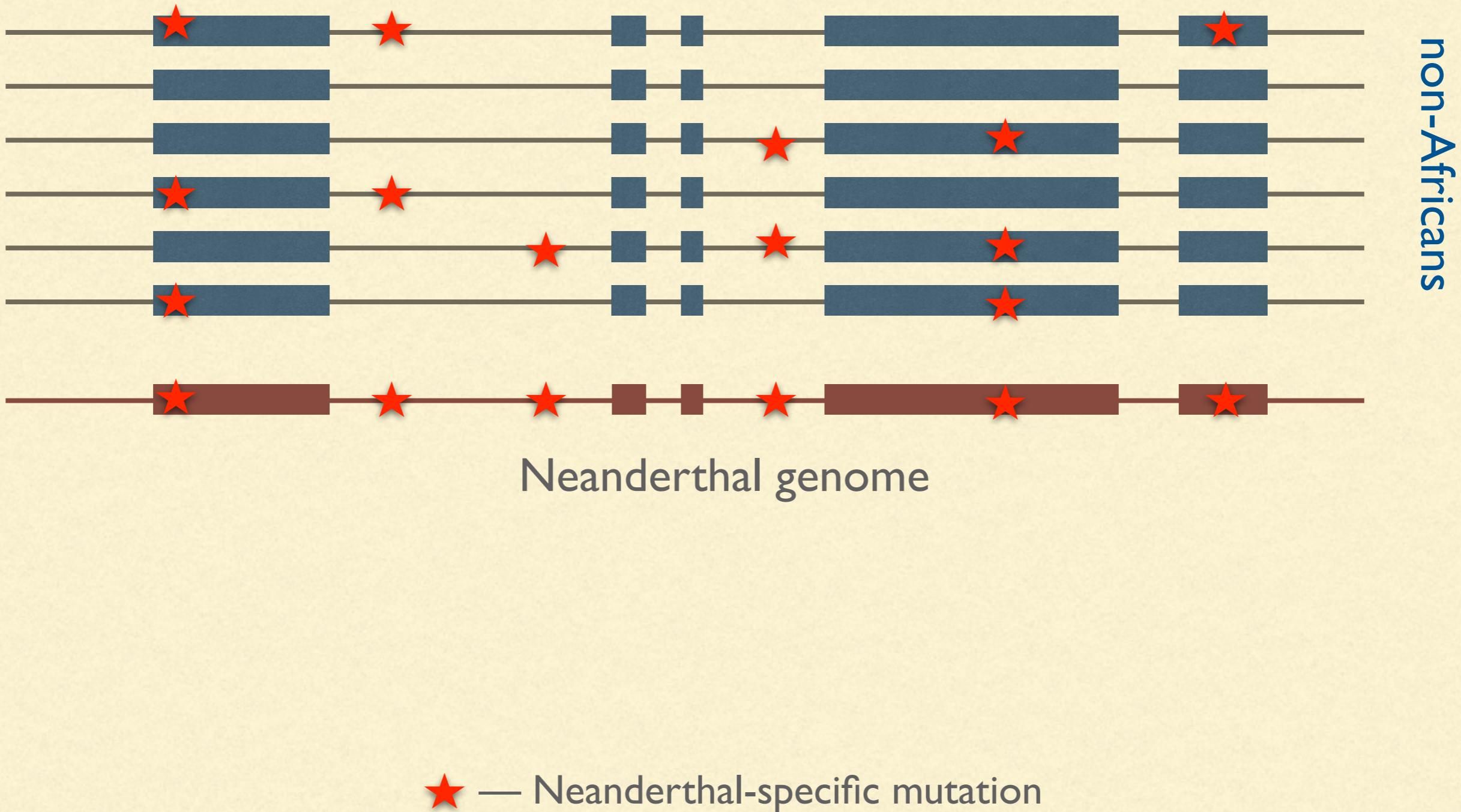
Efficacy of purifying selection is proportional to N_e



$$N_e(\text{pop A}) > N_e(\text{pop B})$$

mutation load < mutation load

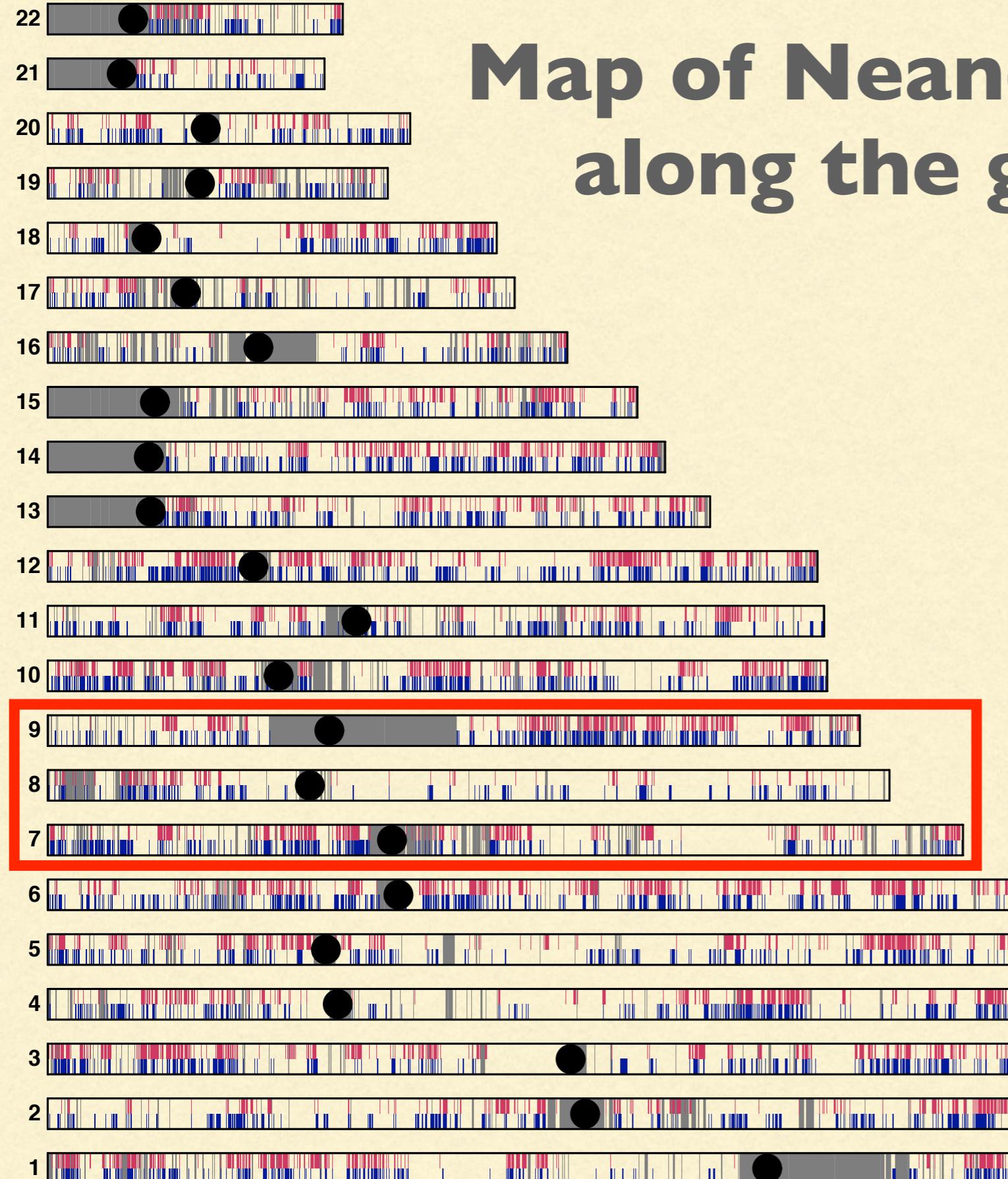
NEAND. ANCESTRY VS DISTANCE TO GENES?





Map of Neanderthal ancestry along the genomes of ~700 East Asians and Europeans.

East Asians
Europeans

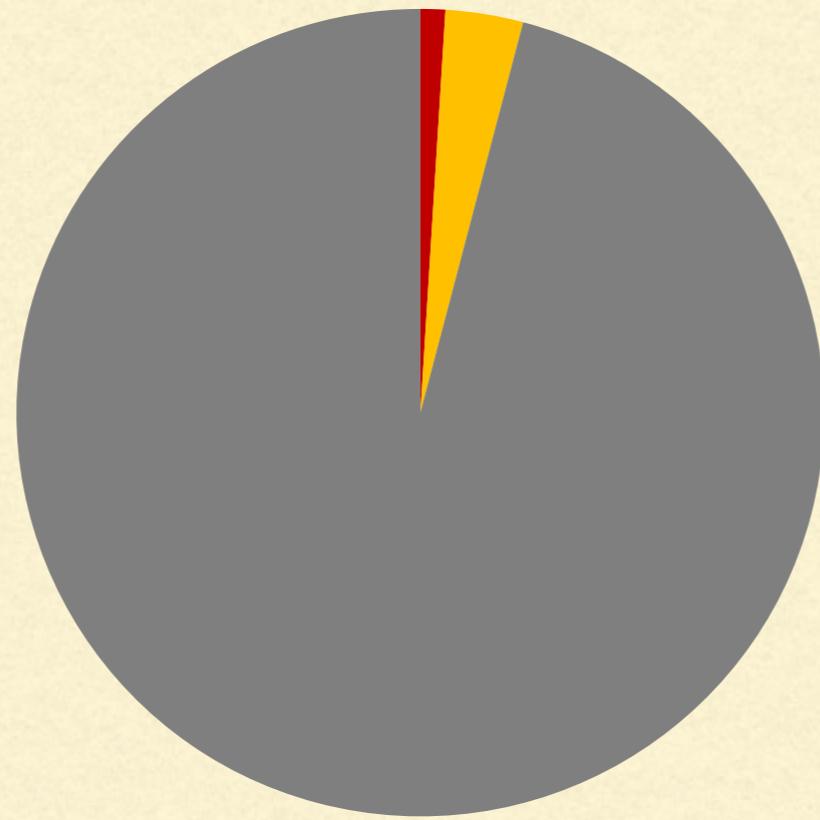


Map of Neanderthal ancestry along the genomes of ~700 East Asians and Europeans.

East Asians
Europeans

SNP CAPTURE METHOD

- aDNA contaminated by microbes (often < 1% endogenous)



ancient Neanderthal DNA



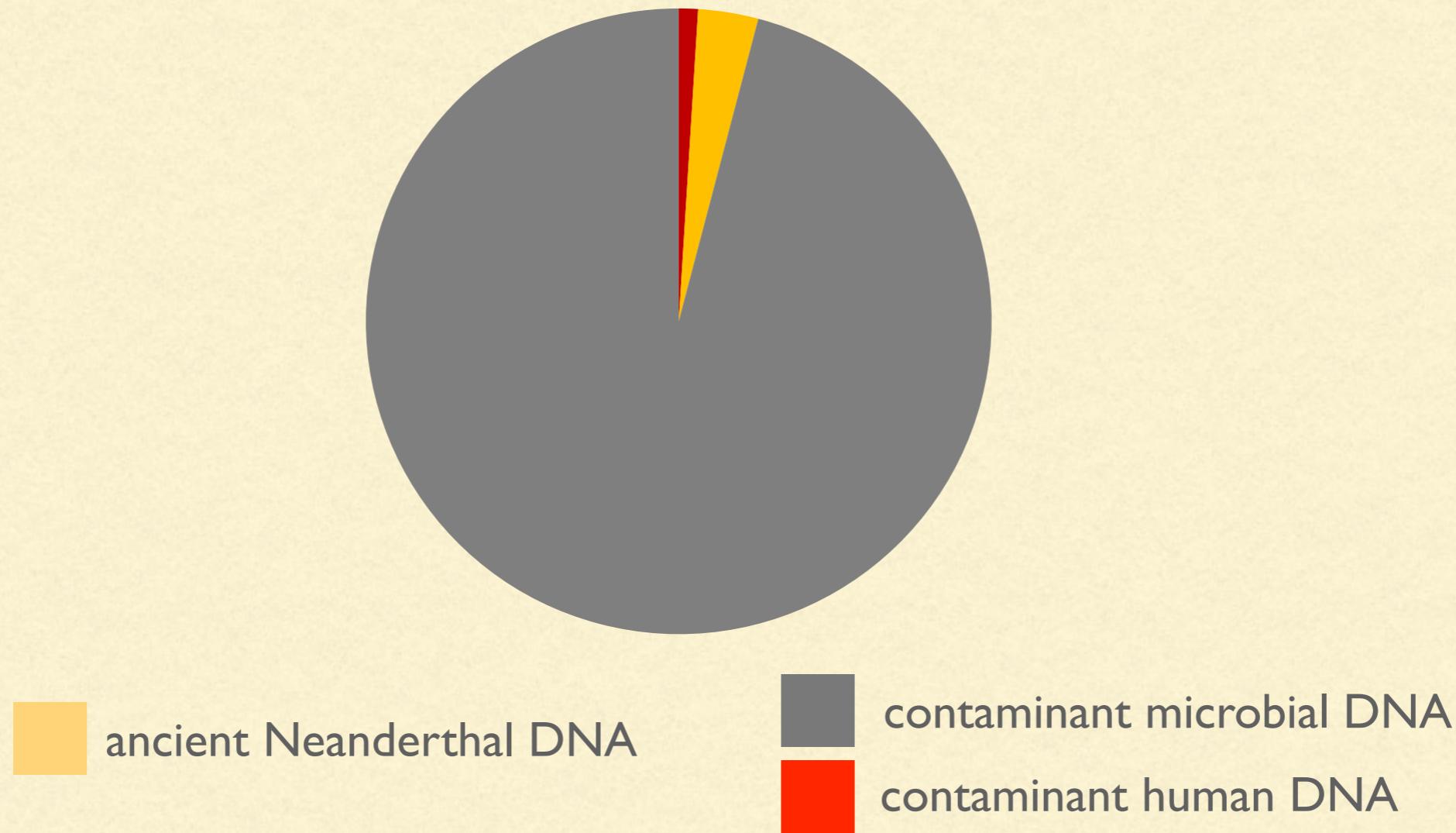
contaminant microbial DNA



contaminant human DNA

SNP CAPTURE METHOD

- aDNA contaminated by microbes (often < 1% endogenous)
- Majority of the genome the same in every human



SNP CAPTURE METHOD

- aDNA contaminated by microbes (often < 1% endogenous)
- Majority of the genome the same in every human
- **We can enrich for “interesting” loci:**
 - Known to be polymorphic in archaic and modern humans
 - Capture and sequence only those using molecular “baits”

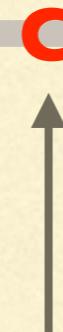
SNP CAPTURE BAIT DESIGN

human reference sequence

C

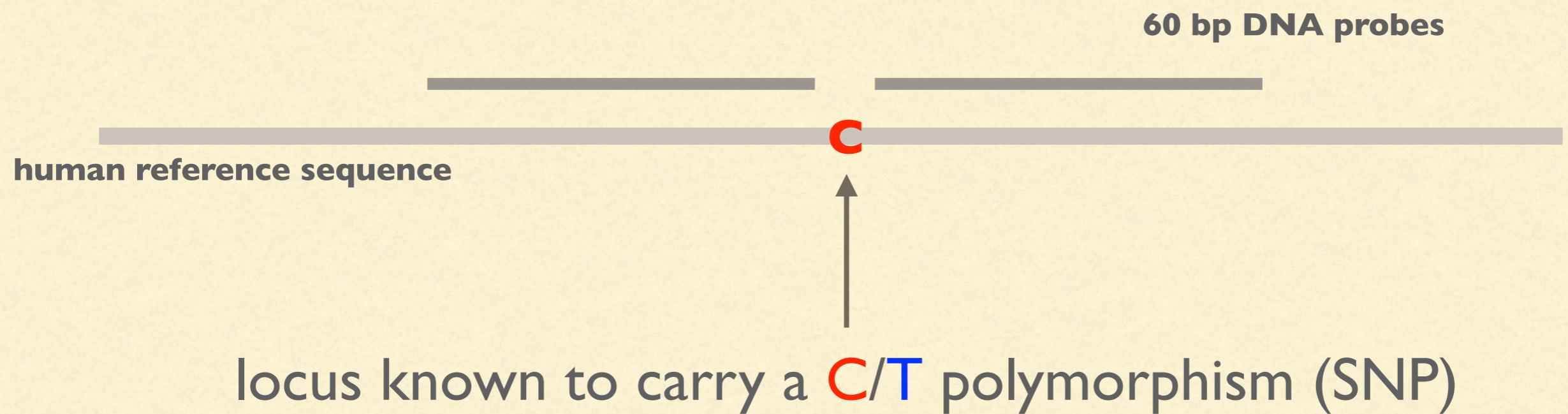
SNP CAPTURE BAIT DESIGN

human reference sequence

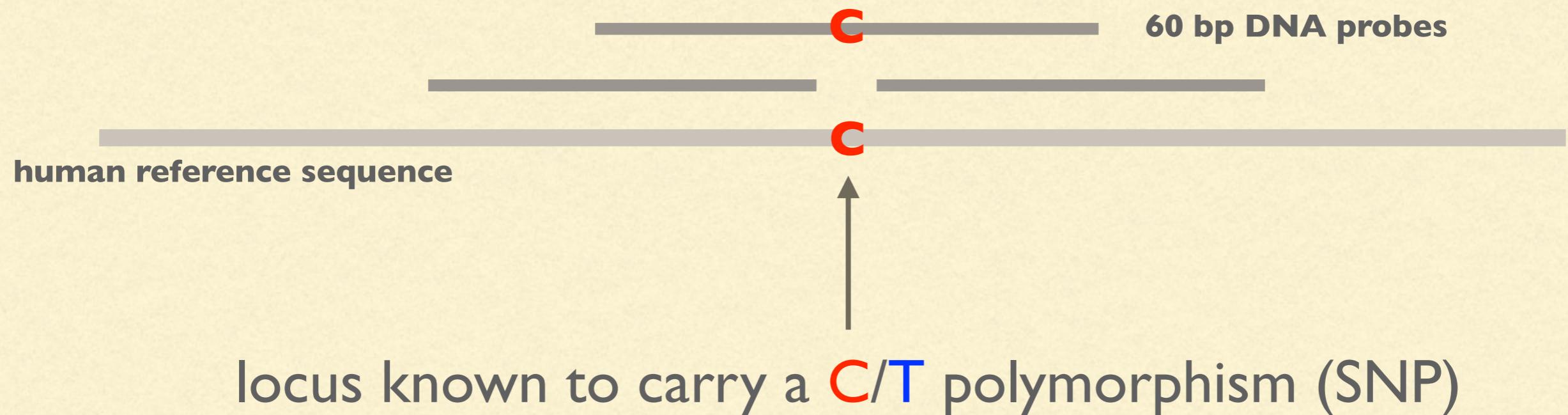


locus known to carry a C/T polymorphism (SNP)

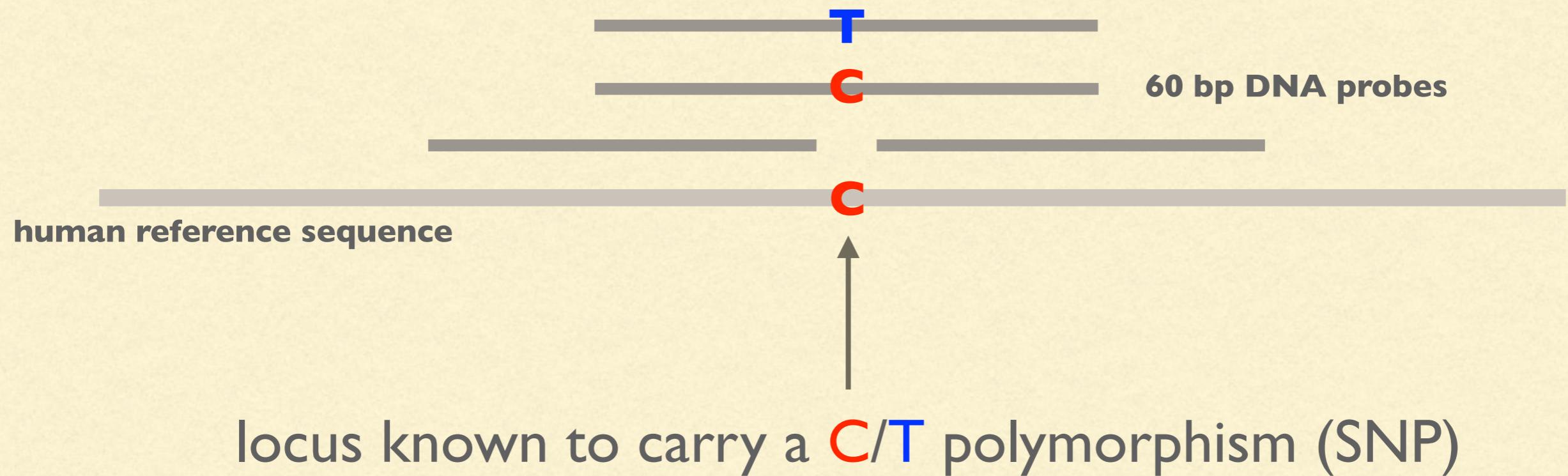
SNP CAPTURE BAIT DESIGN



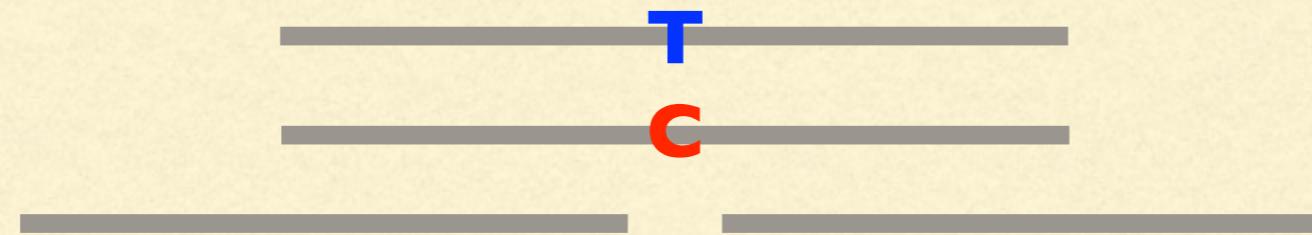
SNP CAPTURE BAIT DESIGN



SNP CAPTURE BAIT DESIGN

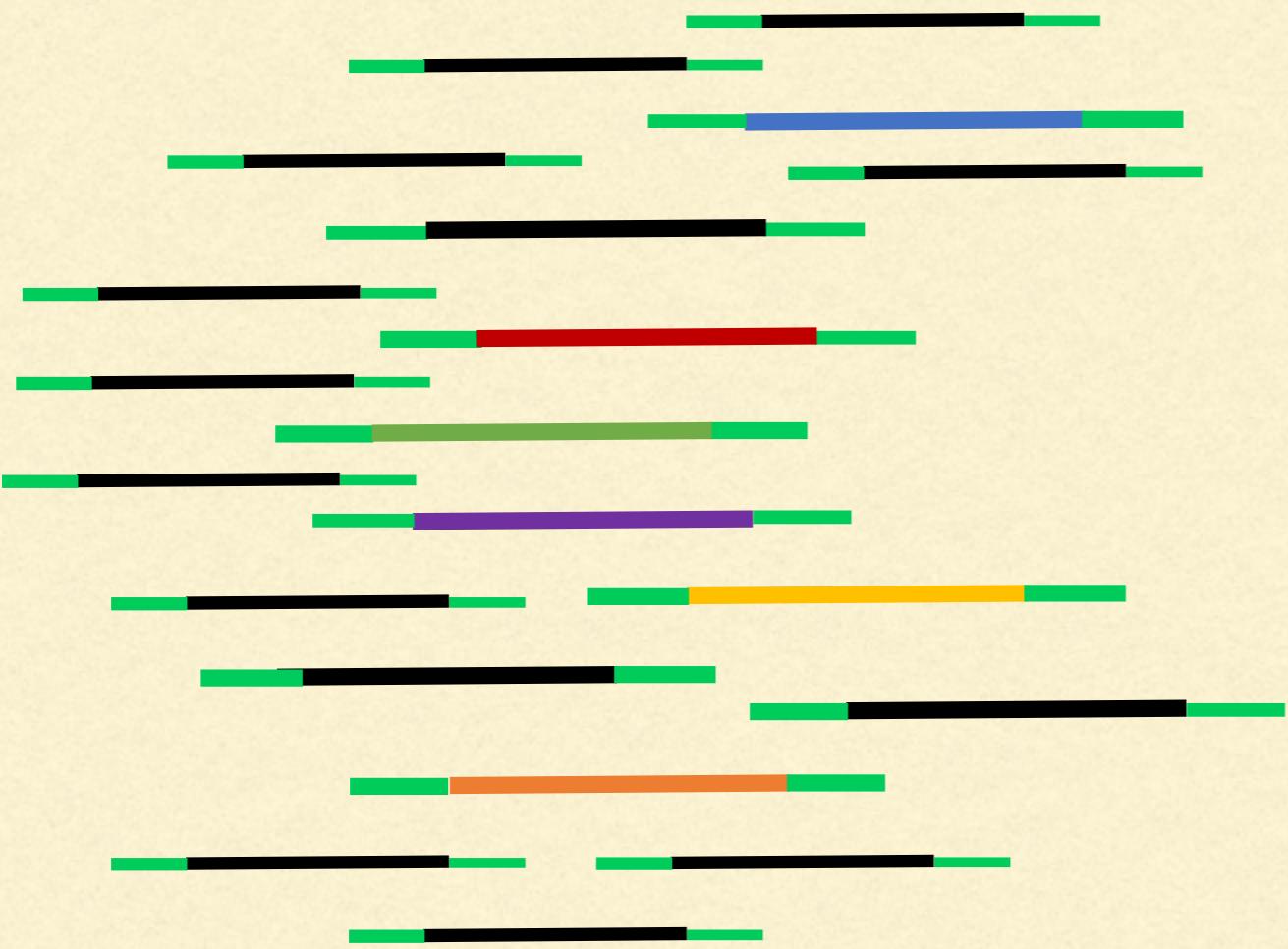


SNP CAPTURE BAIT DESIGN

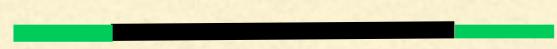
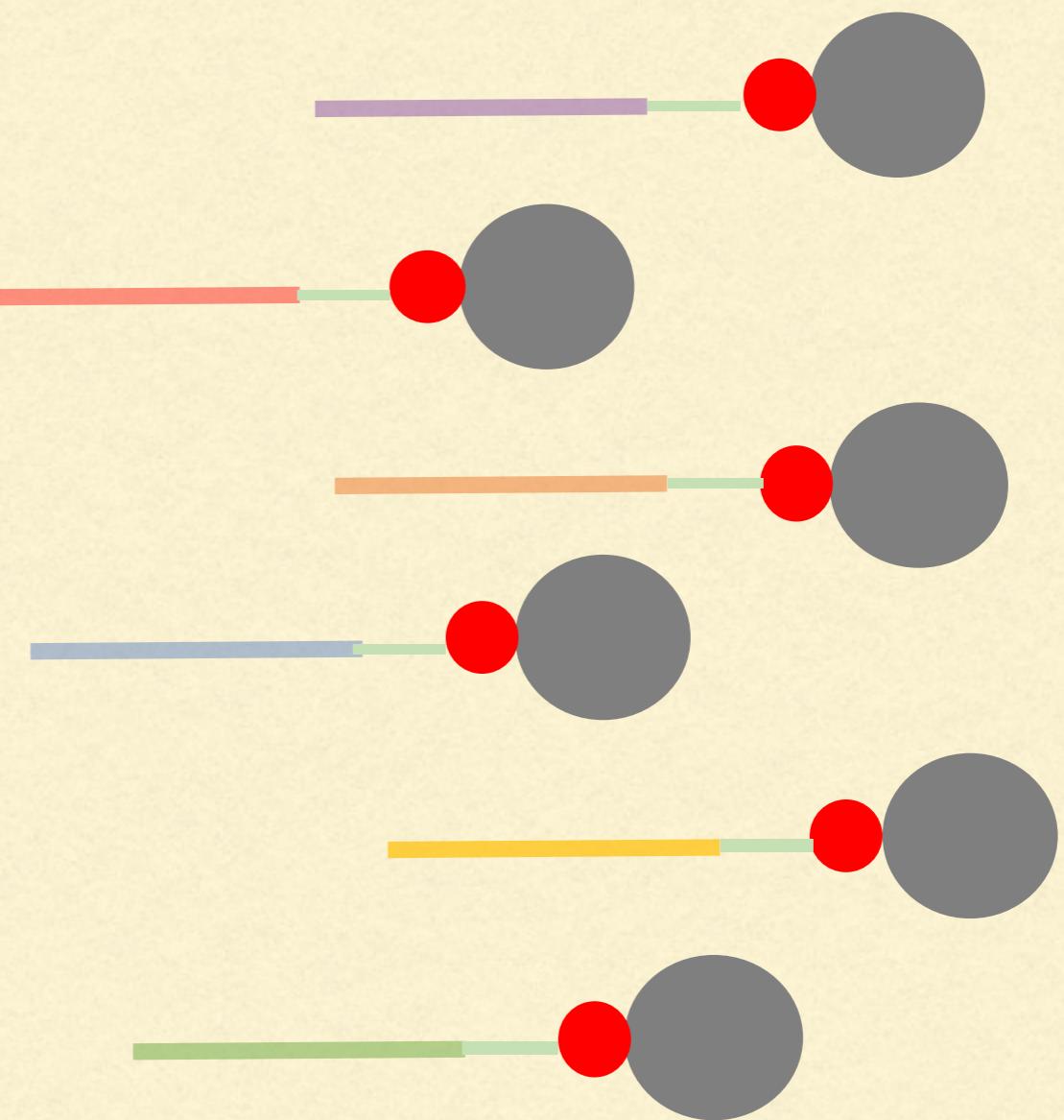


for each SNP we have 4x60 bp synthetic “baits”

DNA mixture from a bone



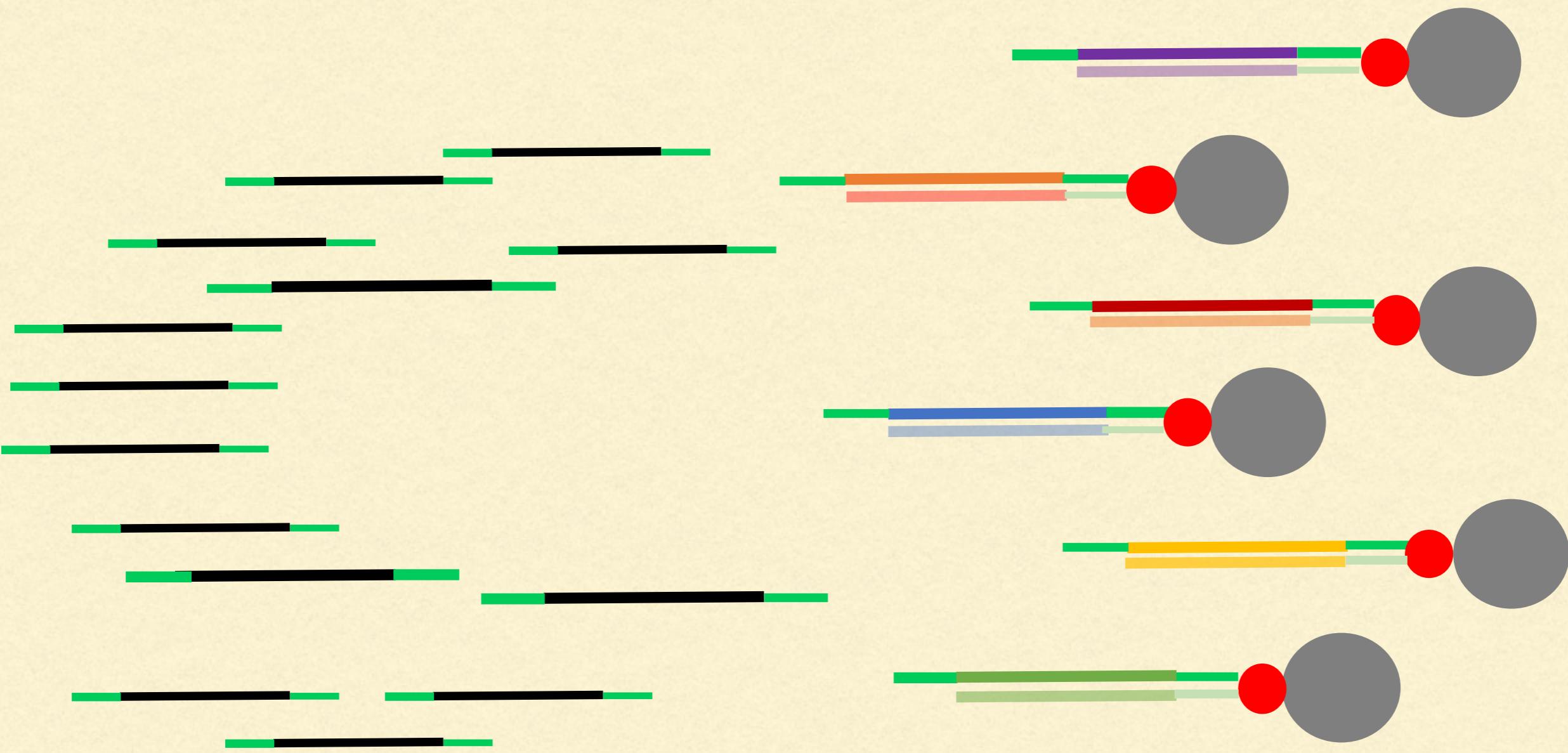
molecular baits



microbial DNA or “uninteresting” human sequence

DNA mixture from a bone

molecular baits

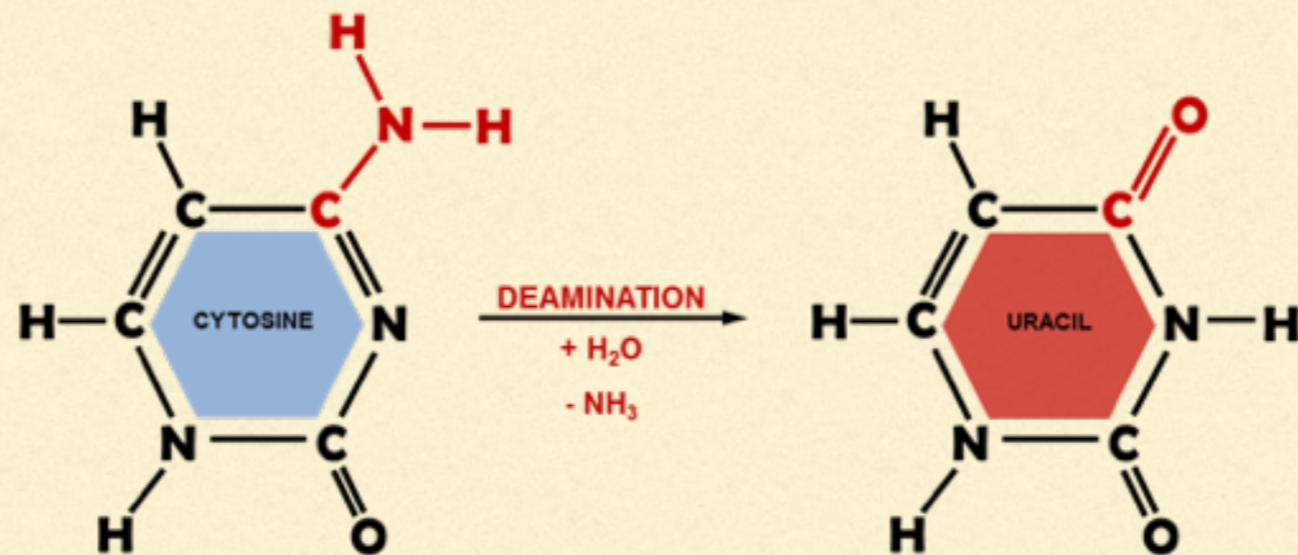


— microbial DNA or “uninteresting” human sequence

— microbial DNA or “uninteresting” human sequence

ANCIENT DNA CHARACTERISTICS

DNA damage



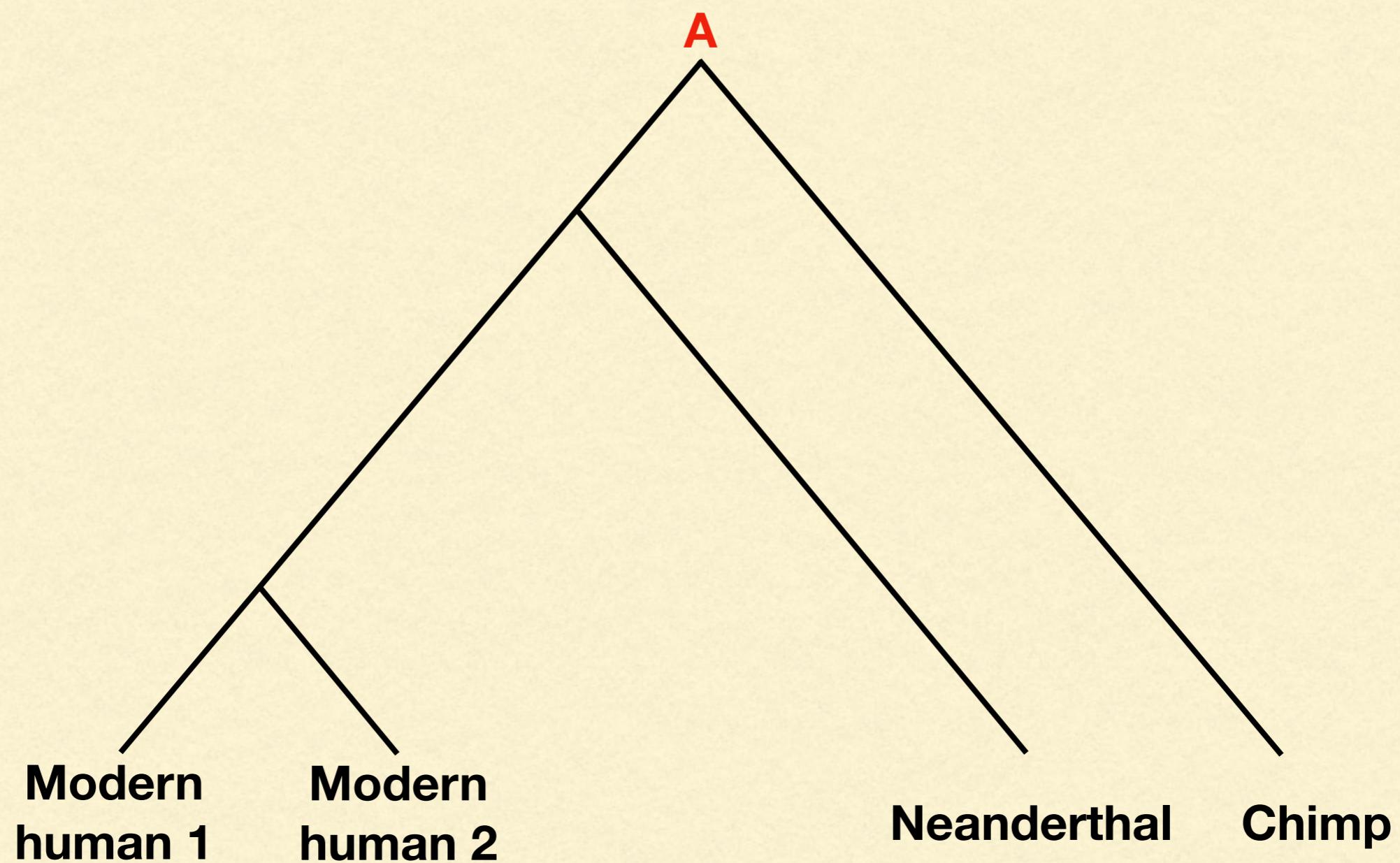
C → U
C → T

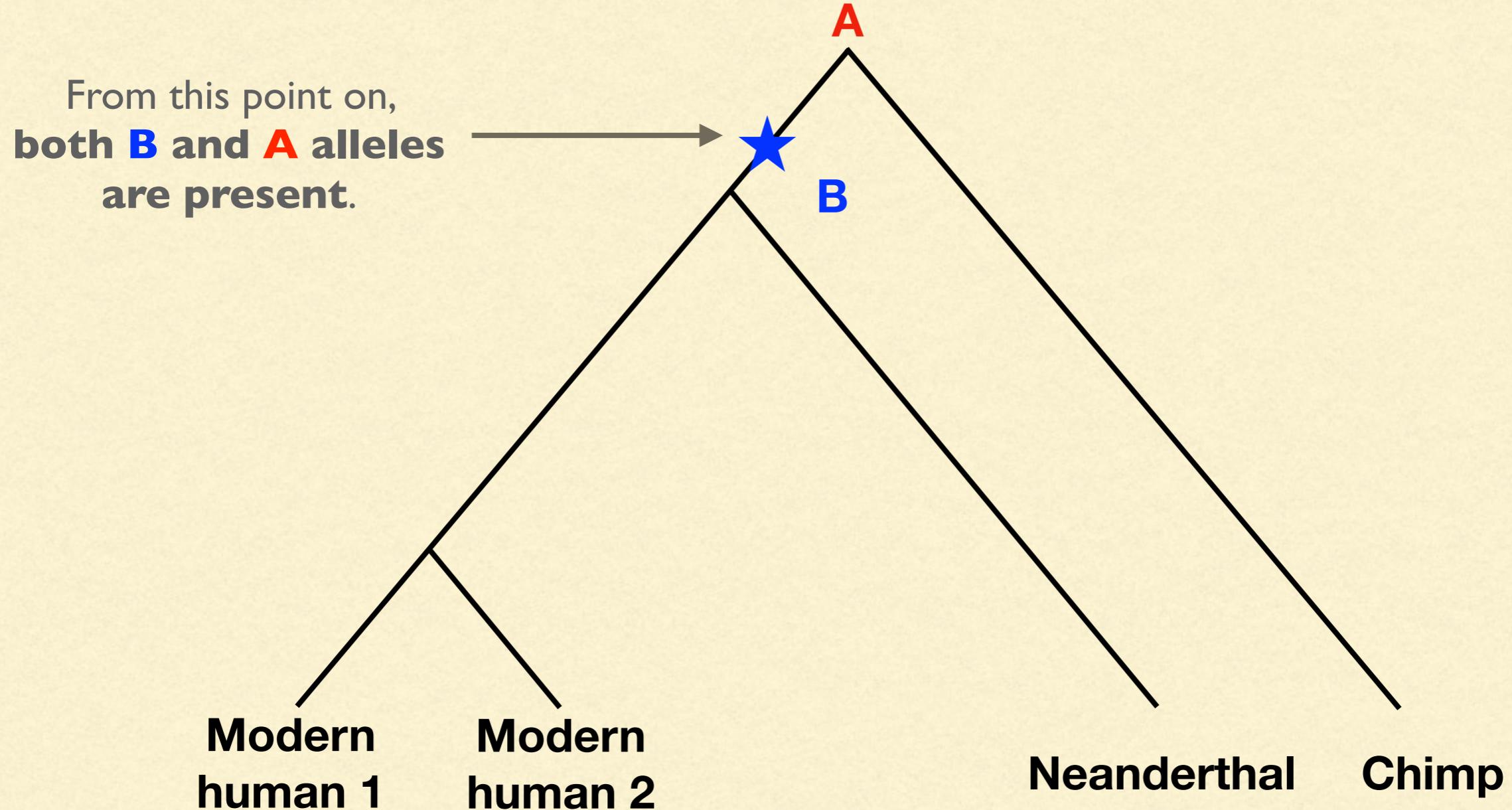
DETECTING NEANDERTHAL ADMIXTURE

—FOUR POPULATION (F4) STATISTIC

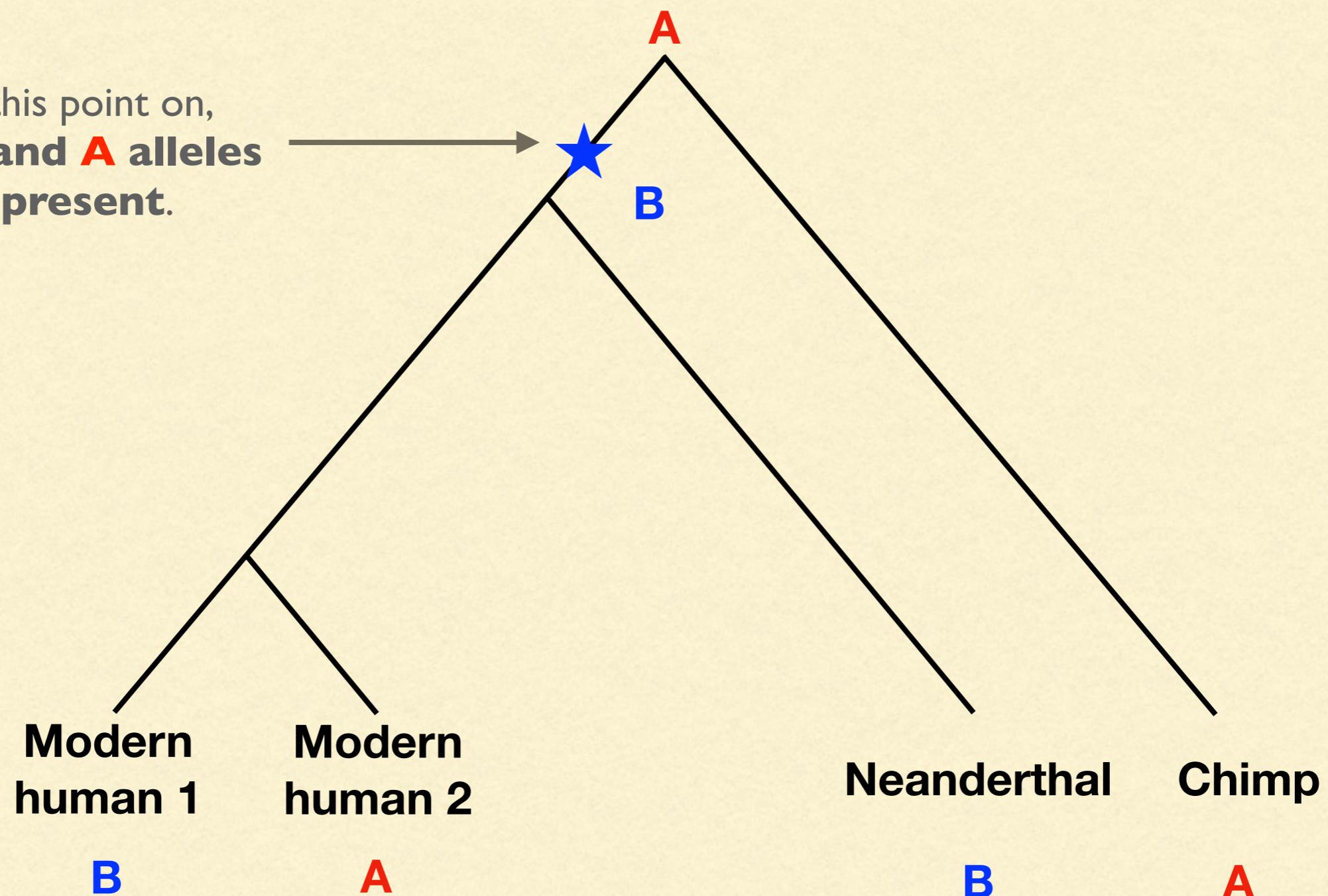


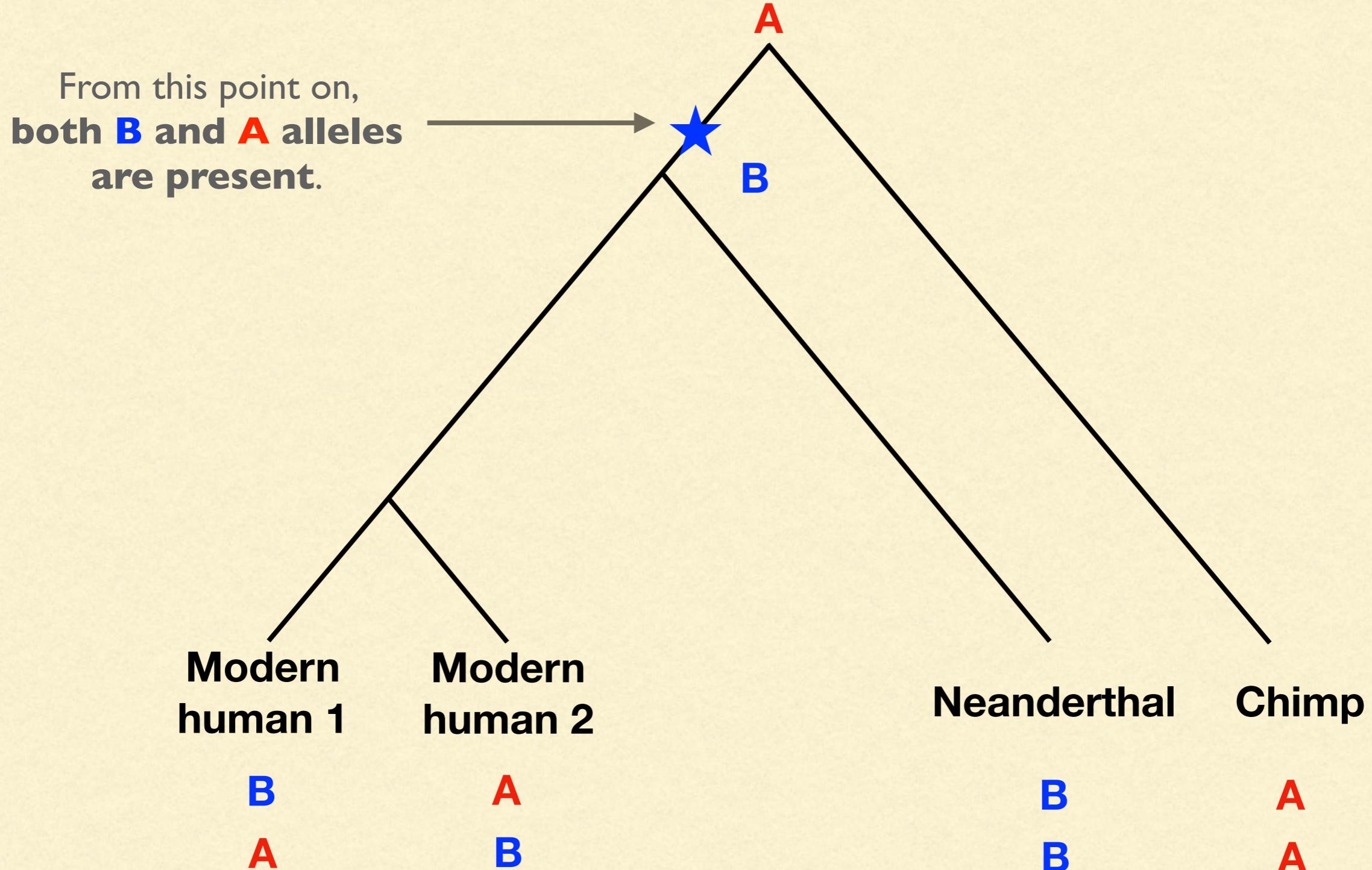
developed by David Reich and Nick Patterson

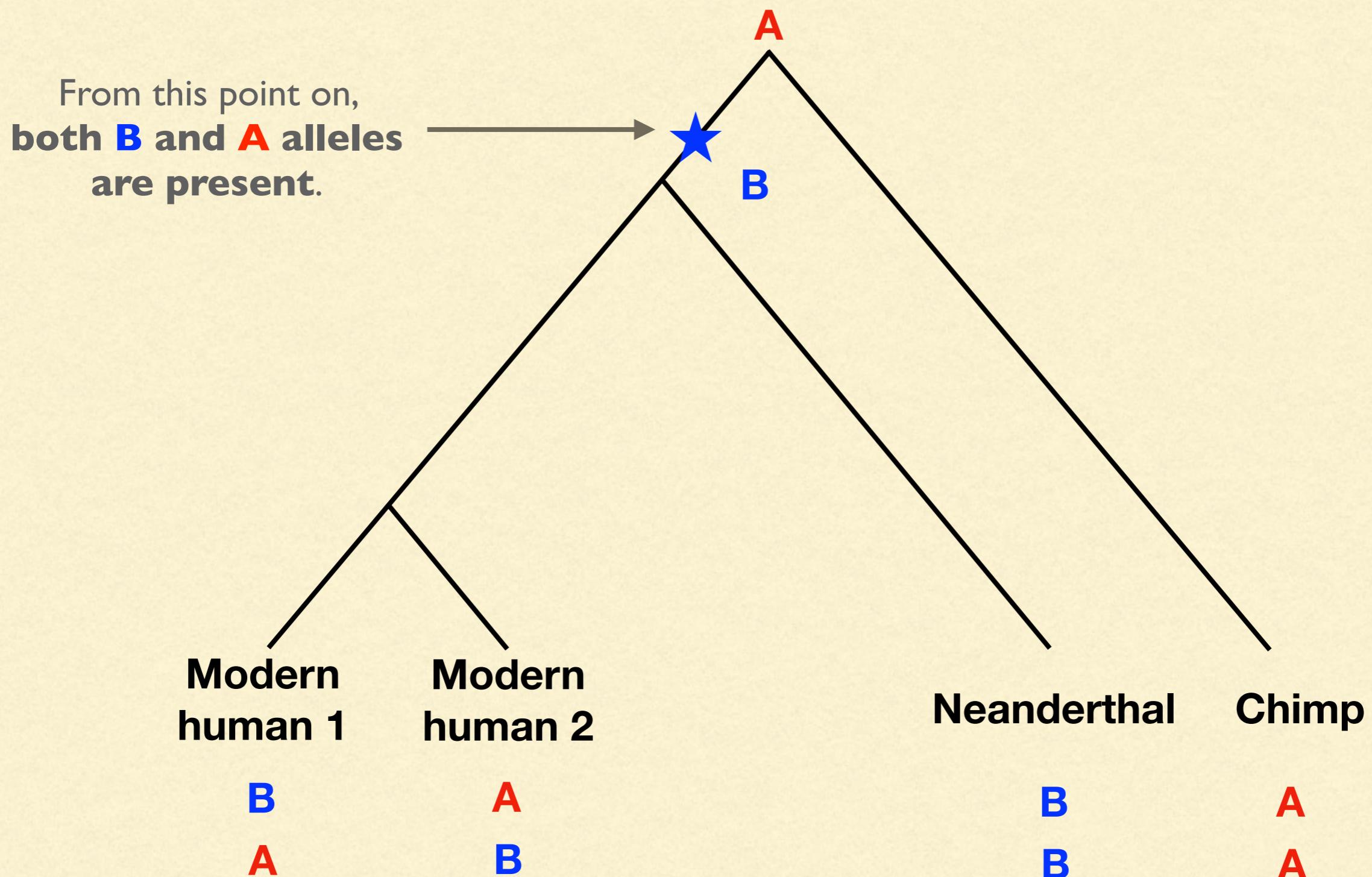




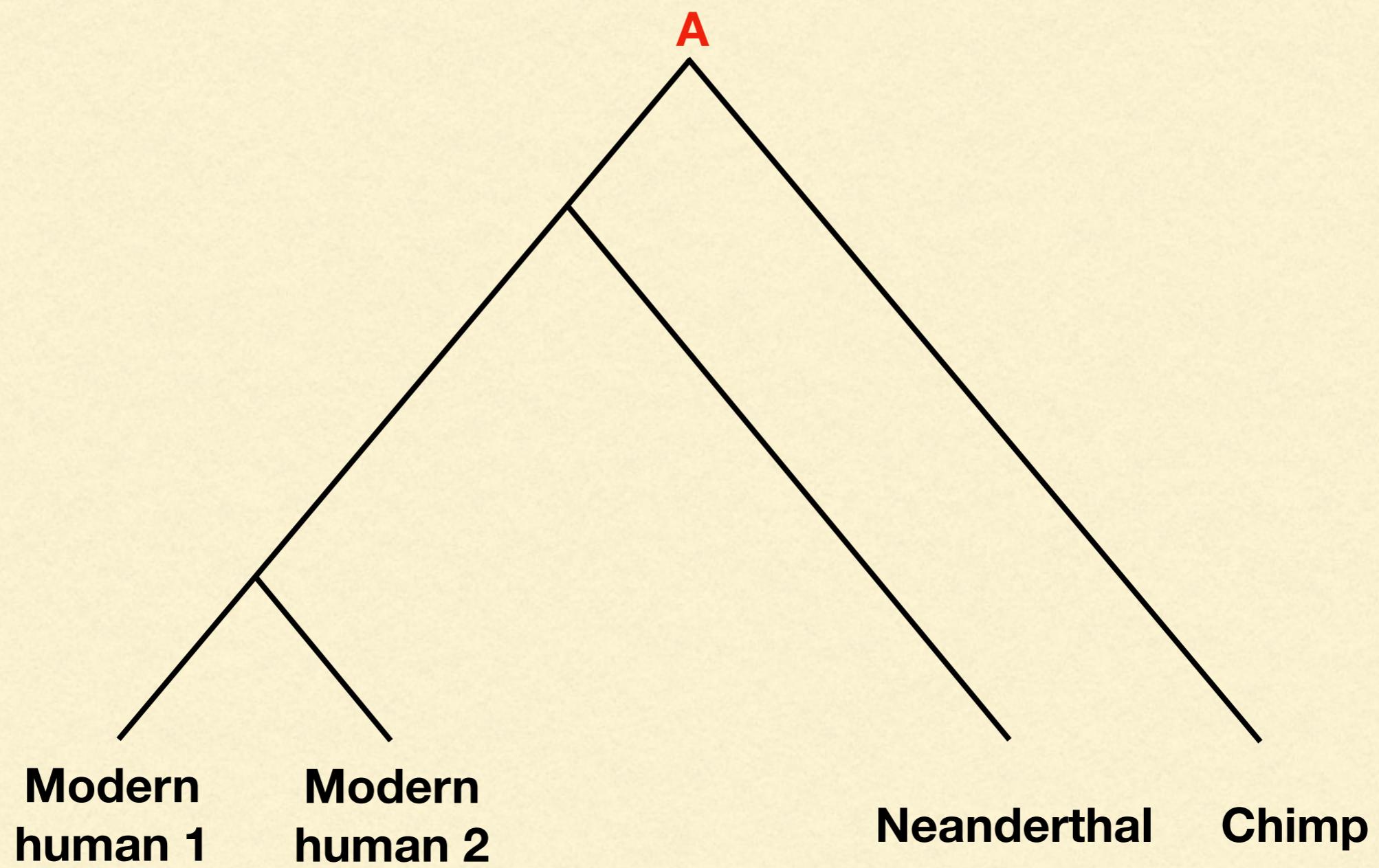
From this point on,
both B and A alleles
are present.

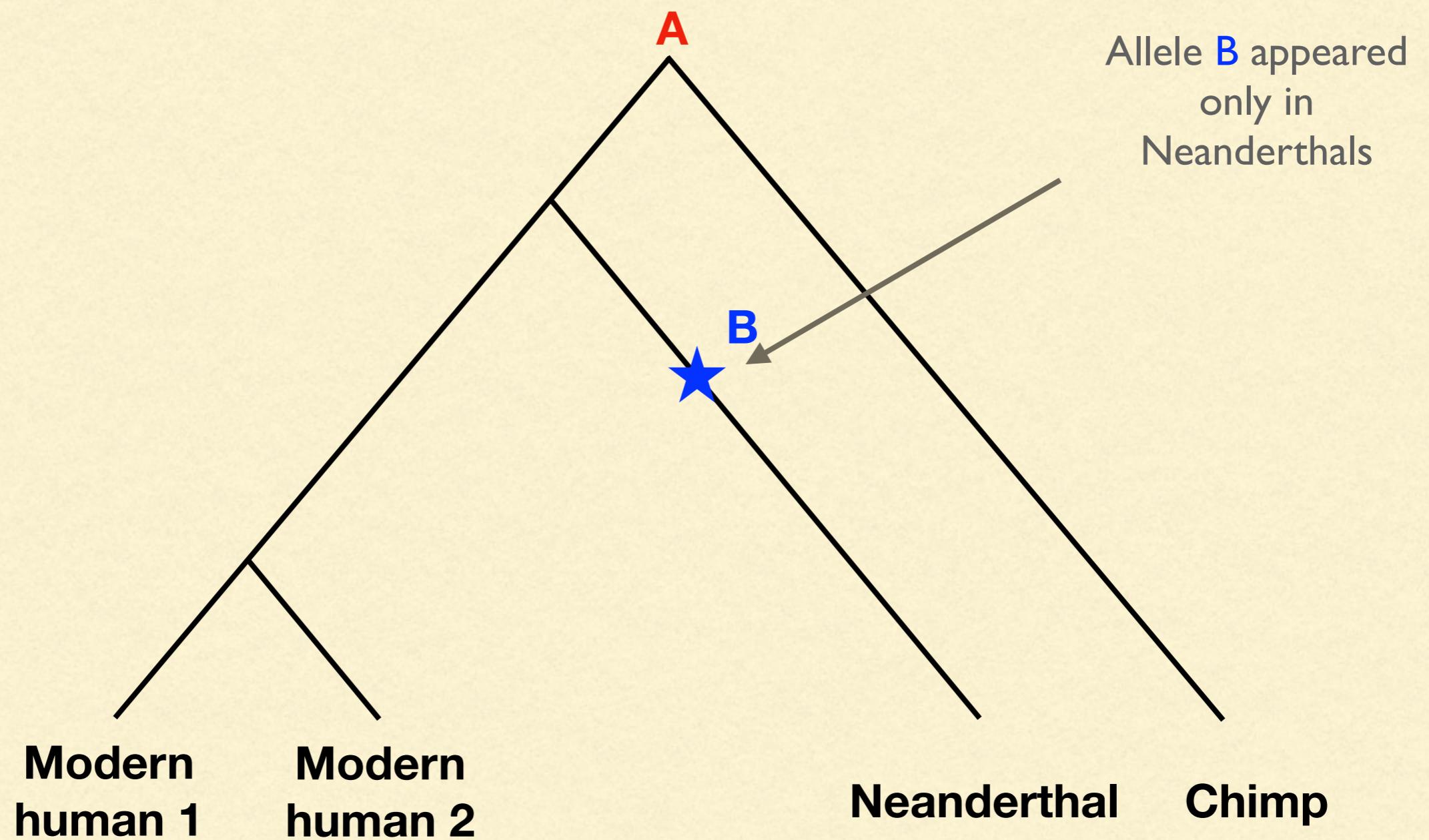


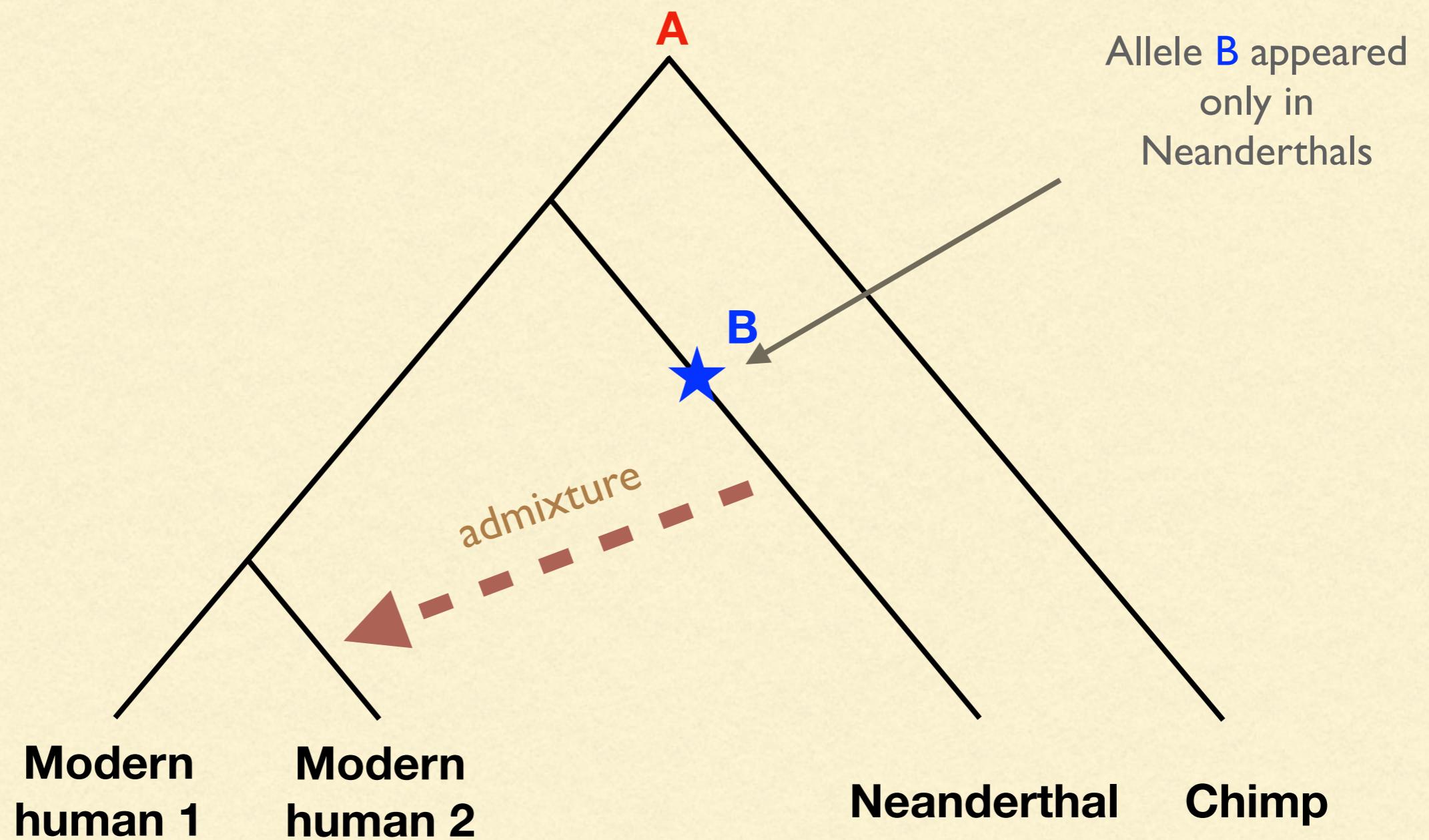


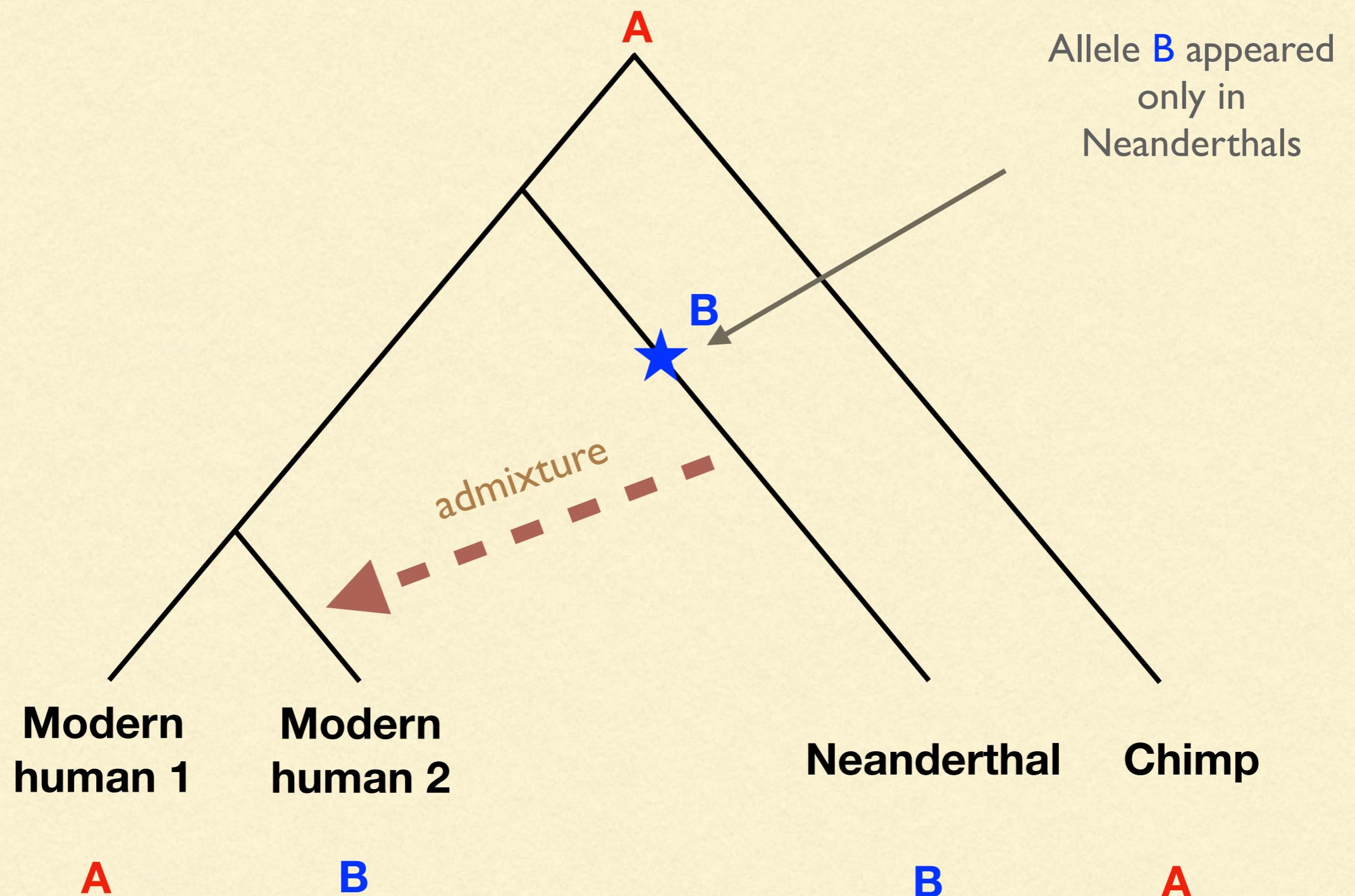


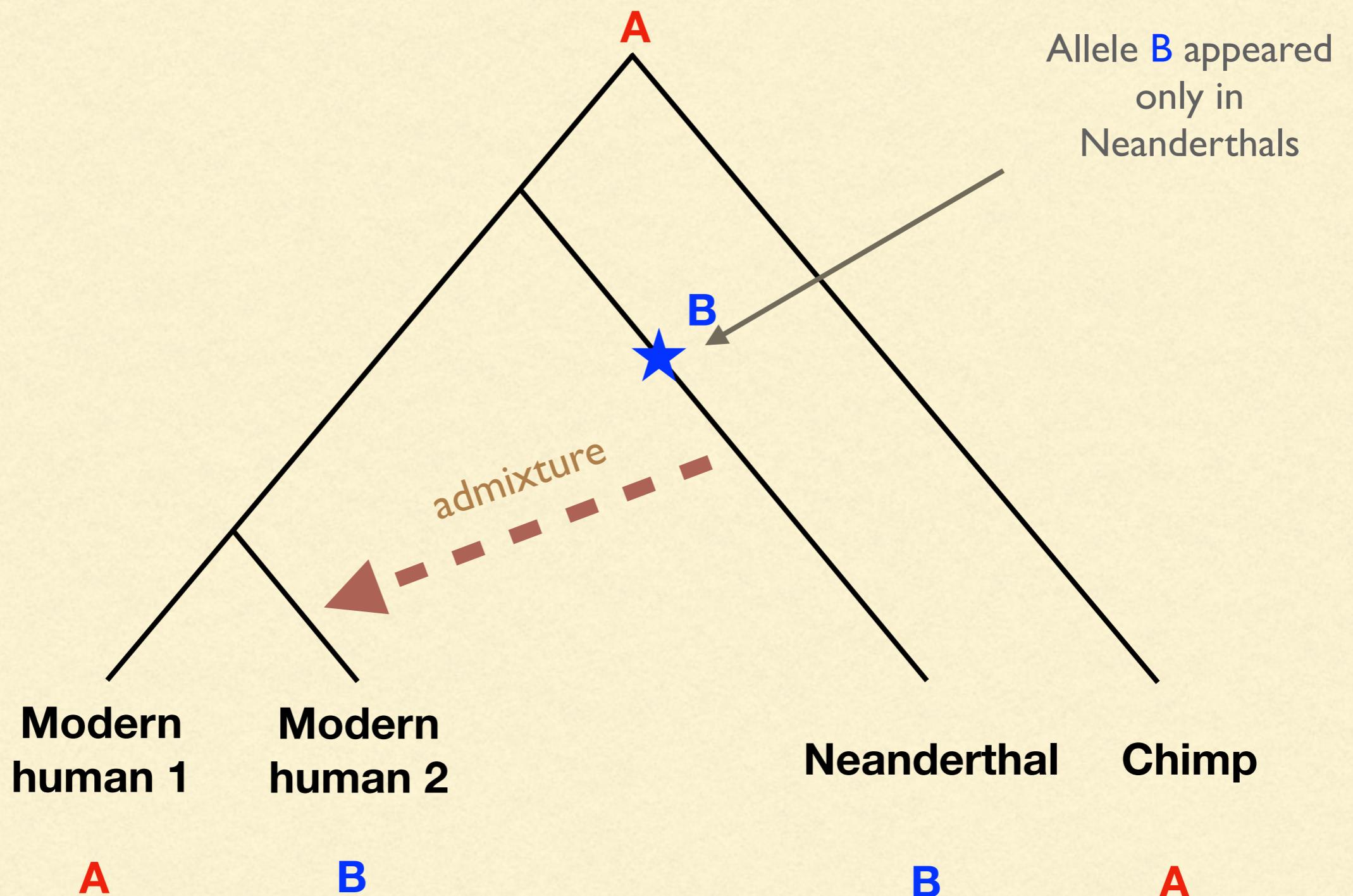
No admixture: $f_4 = \# BABA - \# ABBA \sim 0$











Admixture: $f4 = \# BABA - \# ABBA < 0$

EXAMPLE

$f4(\text{Yoruba}, \text{X}; \text{Neanderthal}, \text{Chimp}) \dots \text{X} = \text{Dinka or French}$

EXAMPLE

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X	#BABA	#ABBA	#sites	f4	p-value
French	44409	46865	1436967	-0.0017	< 0.000001
Dinka	43025	43182	1436978	-0.0001	0.3