Lecture 18. Ancient and Modern Humans

Michael Schatz

April 6, 2020

JHU 600.749: Applied Comparative Genomics

Preliminary Project Report

Assignment Date: March 30, 2019
Due Date: Monday, April 13, 2019 @ 11:59pm

Each team should submit a PDF of your preliminary project proposal (2 to 3 pages) to GradeScope by 11:59pm on Monday April 13.

The preliminary report should have at least:

- Title of your project
- List of team members and email addresses
- 1 paragraph abstract summarizing the project
- 1+ paragraph of Introduction
- 1+ paragraph of Methods that you are using
- 1+ paragraph of Results, describing the data evaluated and any any preliminary results
- 1+ paragraph of Dicsussion (what you have seen or expect to see)
- 1+ figure showing a preliminary result
- 5+ References to relevant papers and data

The preliminary report should use the Bioinformatics style template. Word and LaTeX templates are available at https://academic.oup.com/bioinformatics/pages/submission_online. Overleaf is recommended for LaTex submissions. Google Docs is recommended for non-latex submissions, especially group projects. Paperpile is recommended for citation management.

Later, you will present your project in class starting the week of April 22. You will also submit your final written report (5-7 pages) of your project by May 13

Please use Piazza if you have any general questions!

2020 Applied Genomics Midterm Exam

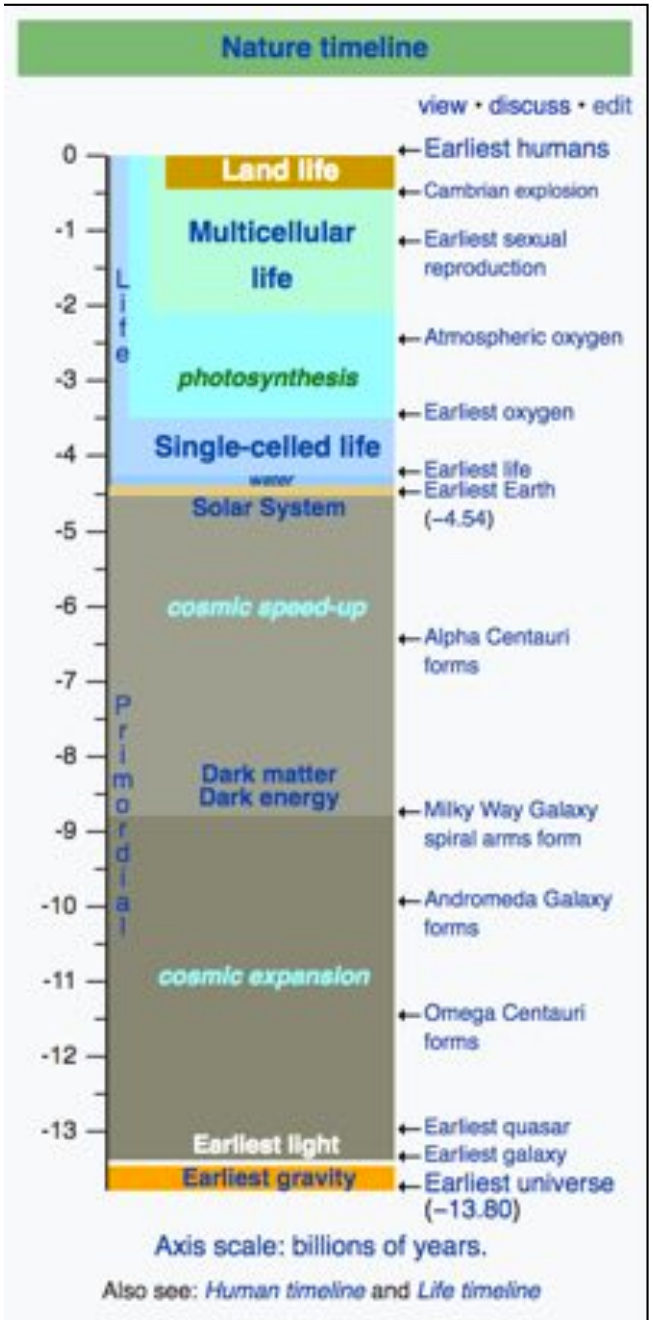
Exam Date: Wednesday, April 1, 2020
Submission Deadline: Thursday, April 2, 2020 by 11:59 pm (no late days allowed)

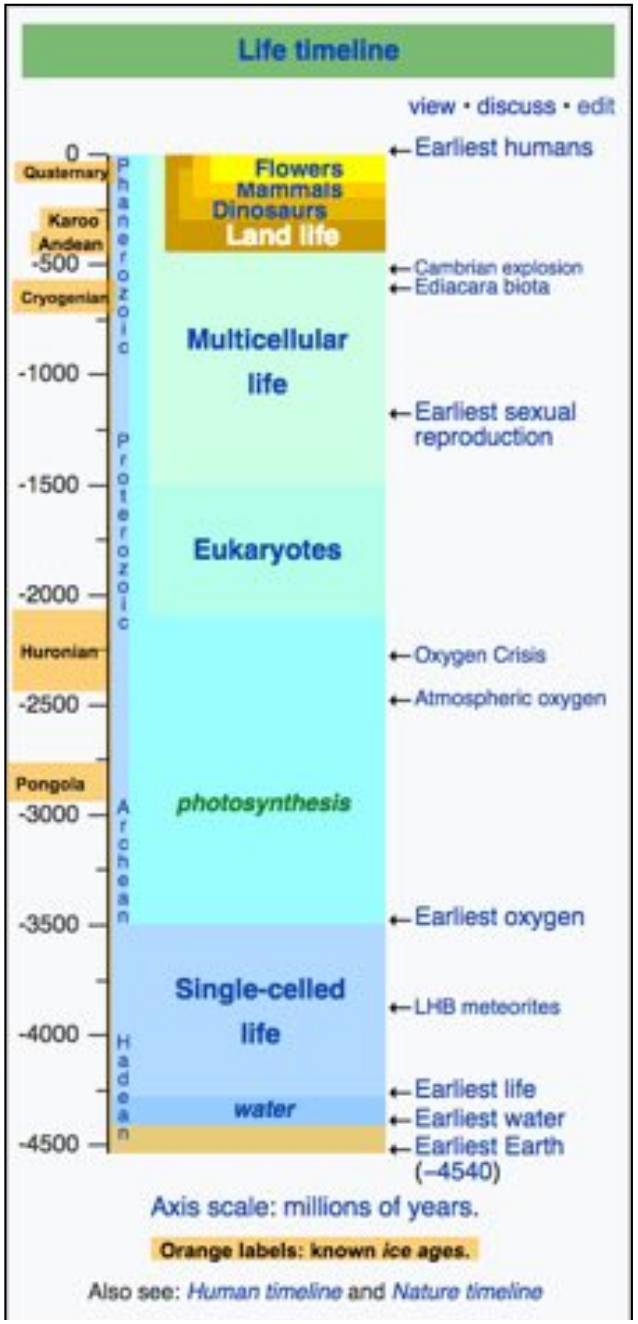
Instructions:

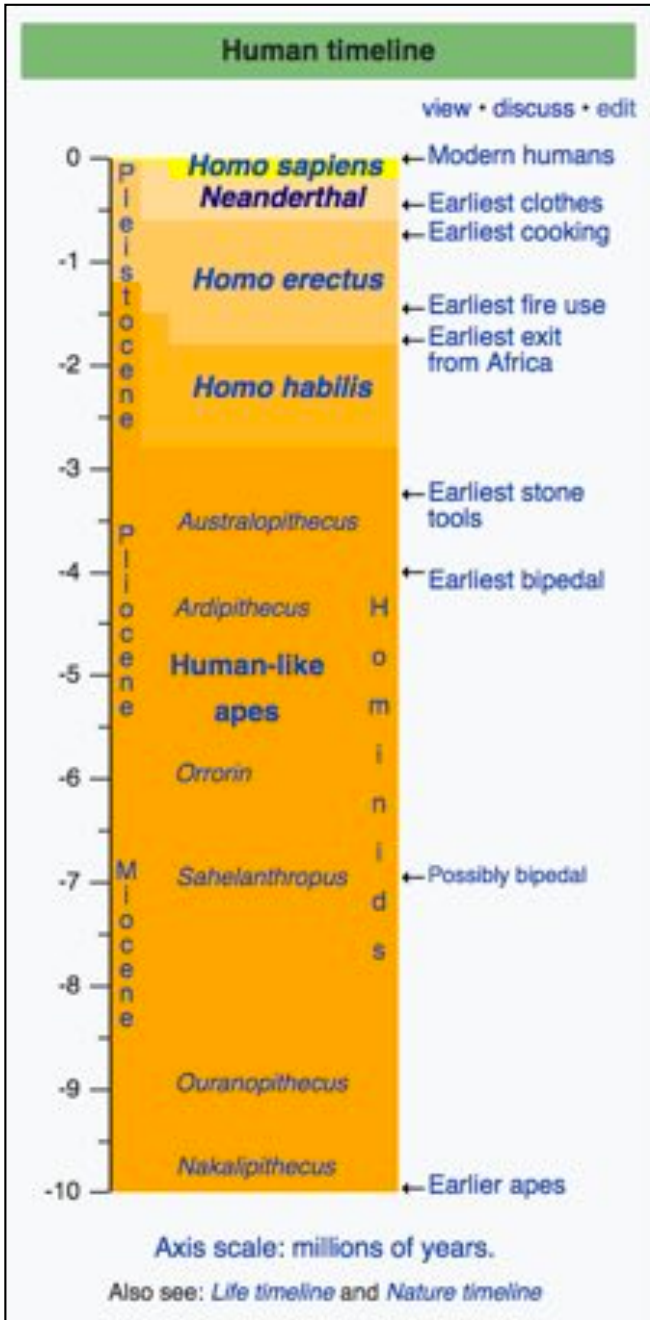
- Submit your solutions to GradeScope as a single PDF file.
- You are allowed to use class notes but you should not discuss the exam with other students.
- Please post to Piazza if you have any questions about the exam. Please submit your questions privately, and then we can adjust the visibility if others should see the information.

Part 1:
Ancient Hominds

Our Origins


Nature timeline
view • discuss • edit
Life
Primordial
Land life
Multicellular life
photosynthesis
Single-celled life
water
Solar System
cosmic speed-up
Dark matter
Dark energy
cosmic expansion
Earliest light
Earliest gravity
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-11
-12
-13
Earliest humans
Cambrian explosion
Earliest sexual reproduction
Atmospheric oxygen
Earliest oxygen
Earliest life
Earliest Earth (–4.54)
Alpha Centauri forms
Milky Way Galaxy spiral arms form
Andromeda Galaxy forms
Omega Centauri forms
Earliest quasar
Earliest galaxy
Earliest universe (–13.80)
Axis scale: billions of years.
Also see: Human timeline and Life timeline


Life timeline
view • discuss • edit
Phanerozoic
Proterozoic
Archean
Hadean
0
Quaternary
Karoo
Andean
-500
Cryogenian
-1000
-1500
-2000
Huronian
-2500
Pongola
-3000
-3500
-4000
-4500
Flowers
Mammals
Dinosaurs
Land life
Multicellular life
Eukaryotes
photosynthesis
Single-celled life
water
Earliest humans
Cambrian explosion
Ediacara biota
Earliest sexual reproduction
Oxygen Crisis
Atmospheric oxygen
Earliest oxygen
LHB meteorites
Earliest life
Earliest water
Earliest Earth (–4540)
Axis scale: millions of years.
Orange labels: known ice ages.
Also see: Human timeline and Nature timeline


Human timeline
view • discuss • edit
Pleistocene
Pliocene
Miocene
Hominids
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
Homo sapiens
Neanderthal
Homo erectus
Homo habilis
Australopithecus
Ardipithecus
Human-like apes
Orrorin
Sahelanthropus
Ouranopithecus
Nakalipithecus
Modern humans
Earliest clothes
Earliest cooking
Earliest fire use
Earliest exit from Africa
Earliest stone tools
Earliest bipedal
Possibly bipedal
Earlier apes
Axis scale: millions of years.
Also see: Life timeline and Nature timeline

Sequencing ancient genomes

Janet Kelso
Max-Planck Institute


Engis
Neandertal
Spy
Arcy-sur-Cure
La Quina
Saint-Césaire
Le Moustier
La Ferrassie
Steinheim
Châtelperron
La Chapelle-aux-Saints
Maula
Külna
Sipka
Tata
Erd
Krapina
Vindija
Sukhaya Mechetka
Molodovo
Kiyik-Koba
Starosillya
Figueira Brava
Zaferraya
Forbe's Quarry
Saccopastore
Guattari
Shanidar
Amud
Tabun
sites ayant livré des fossiles de Néandertaliens classiques
(les lignes de rivages et l'extension des glaciers correspondent à un maximum glaciaire)

Homo neanderthalensis

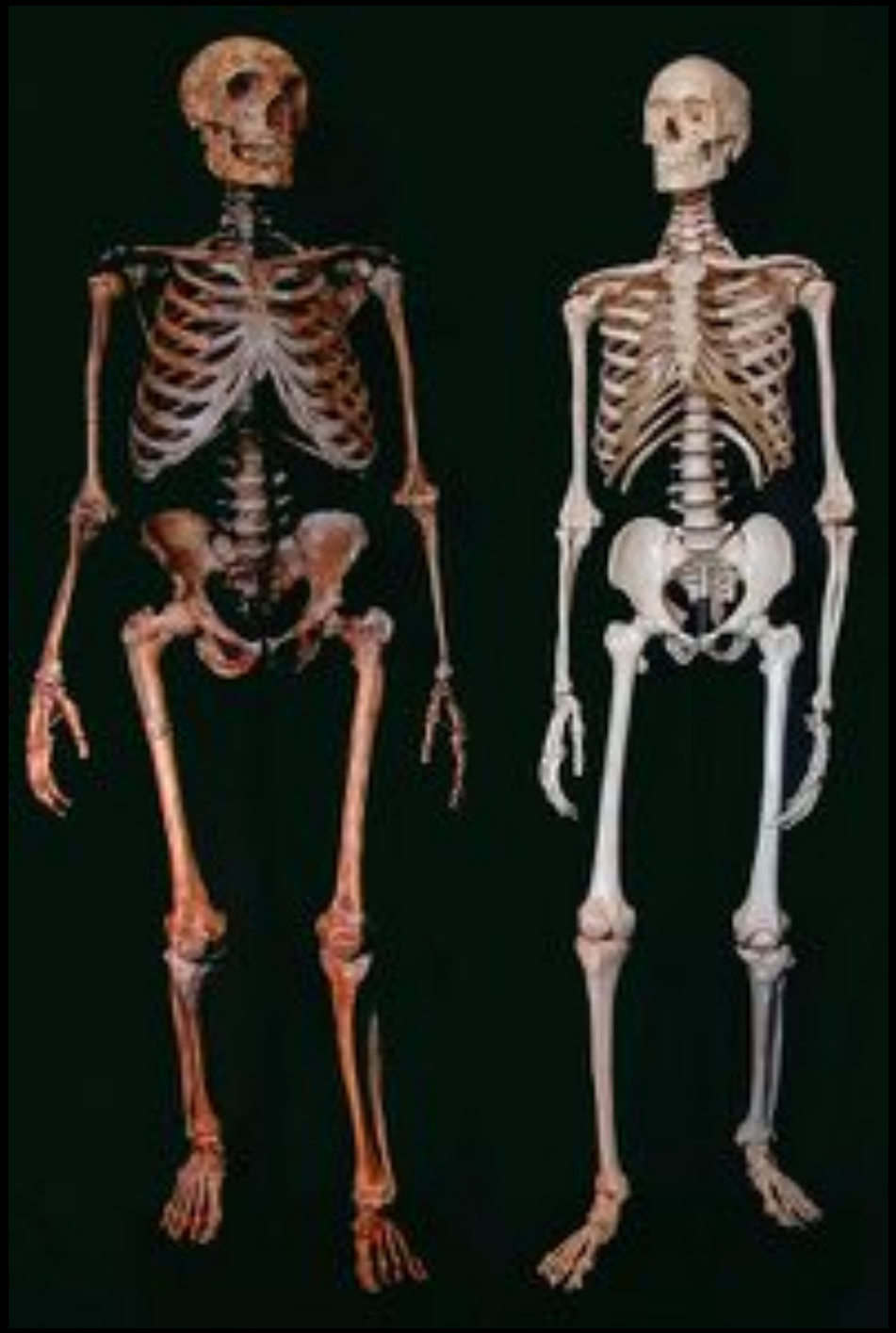
•Proto-Neanderthals emerge around 600k years ago

•“True” Neanderthals emerge around 200k years ago

•Died out approximately 40,000 years ago

•Known for their robust physique

•Made advanced tools, probably had a language (the nature of which is debated and likely unknowable) and lived in complex social groups



Homo sapiens sapiens

- Apparently emerged from earlier hominids in Africa around 50k years ago
- Capable of amazing intellectual and social behaviors
- Mostly Harmless ☺

Science
AAAS

A Draft Sequence of the Neandertal Genome

Richard E. Green, *et al.*

Science **328**, 710 (2010);
DOI: 10.1126/science.1188021

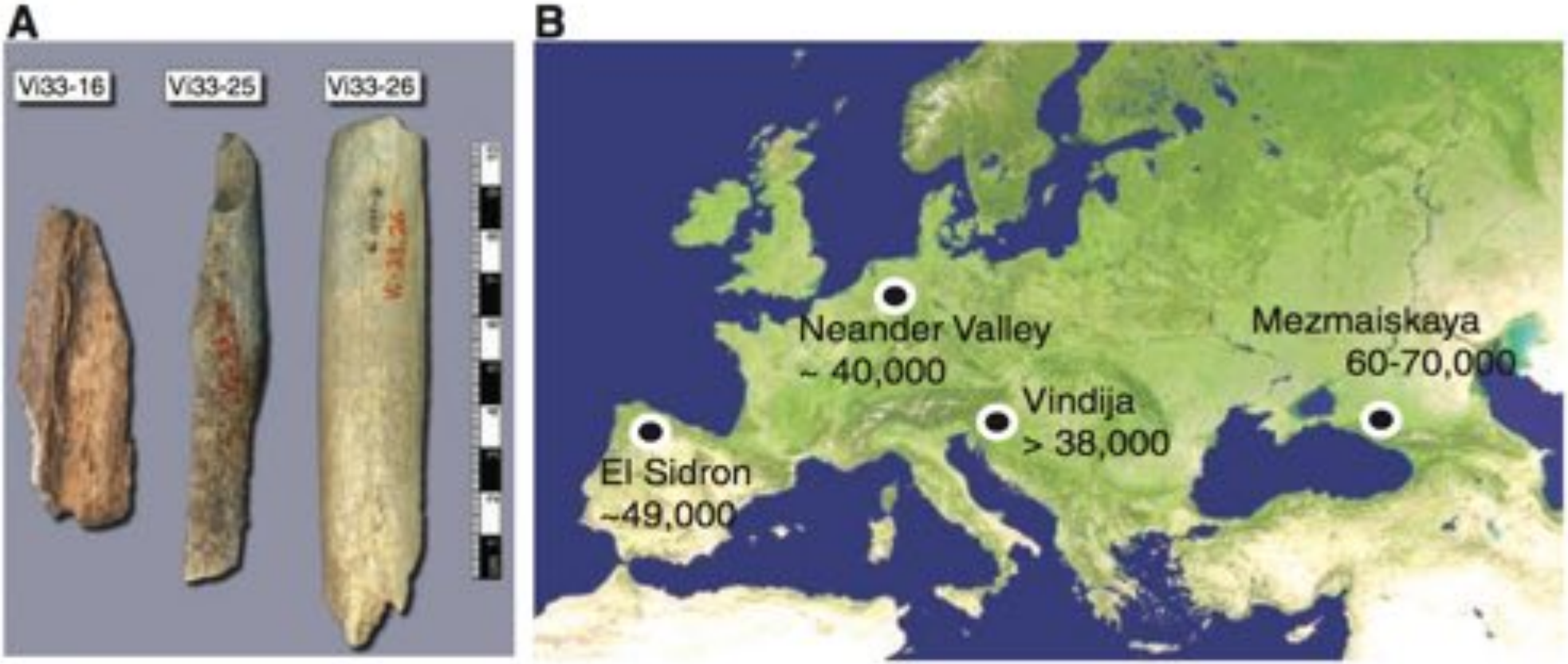
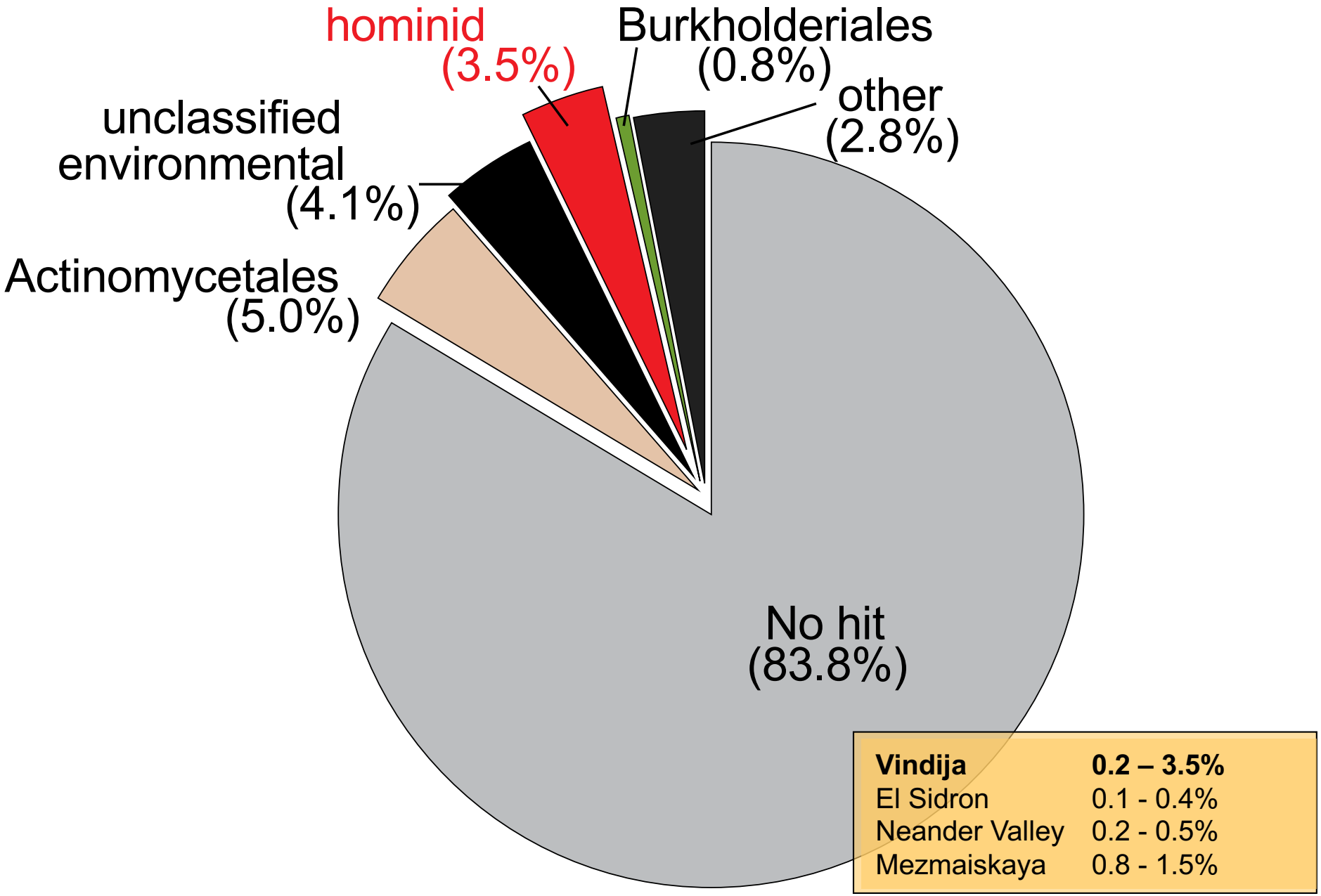


Fig. 1. Samples and sites from which DNA was retrieved. (**A**) The three bones from Vindija from which Neandertal DNA was sequenced. (**B**) Map showing the four archaeological sites from which bones were used and their approximate dates (years B.P.).

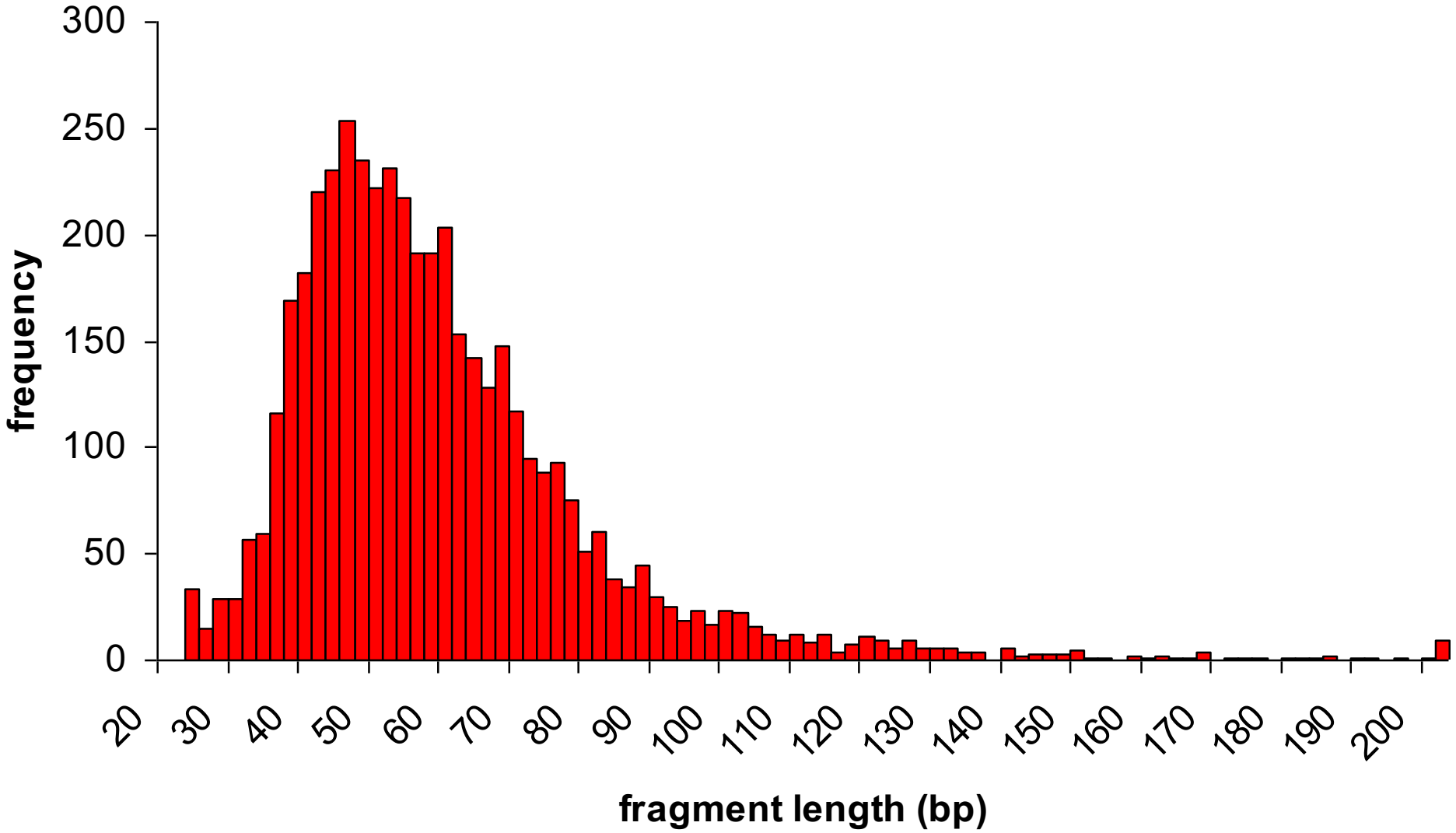
Extracting Ancient DNA

DNA is from mixed sources

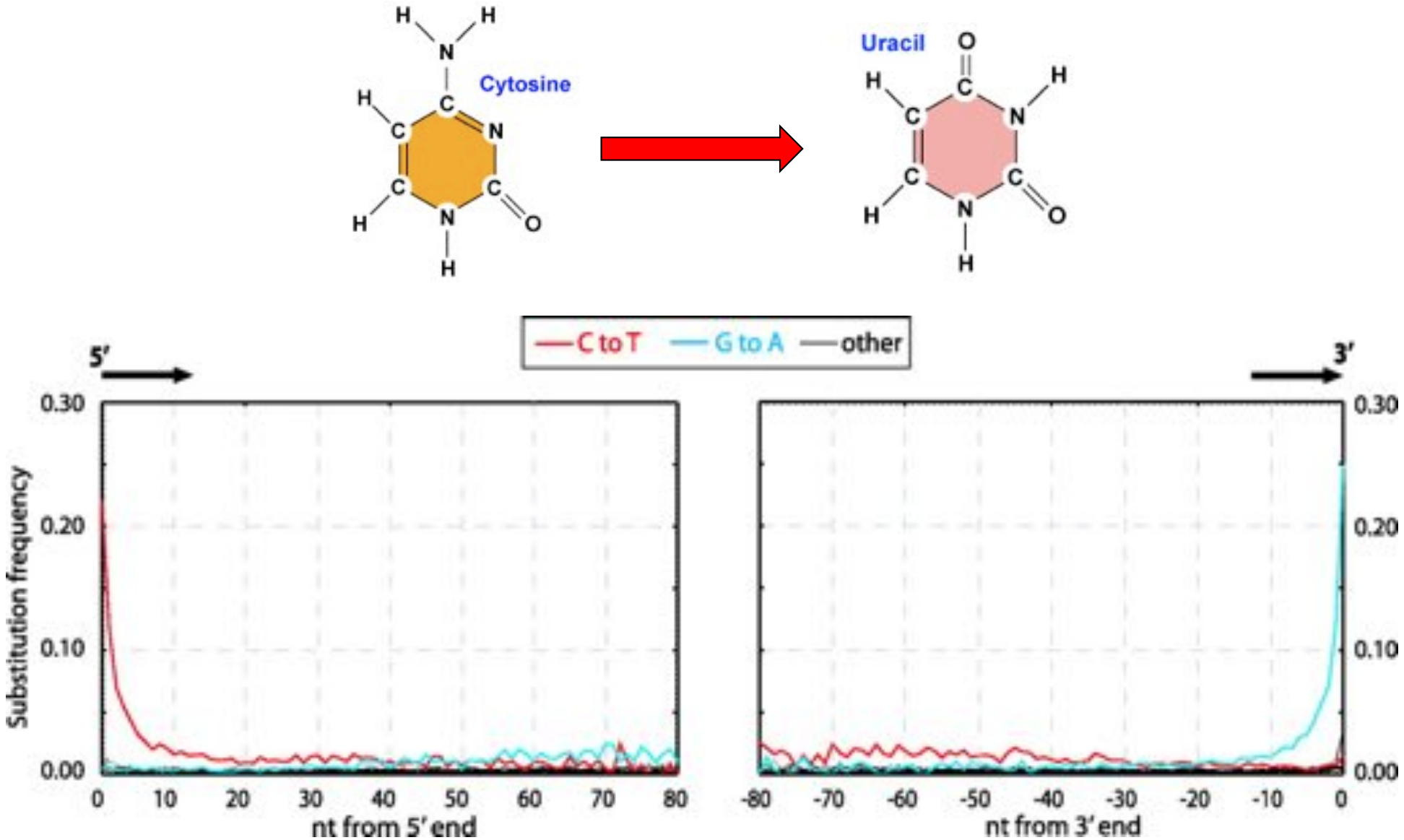


Vindija	**0.2 – 3.5%**
El Sidron	0.1 - 0.4%
Neander Valley	0.2 - 0.5%
Mezmaiskaya	0.8 - 1.5%

DNA is degraded



DNA is chemically damaged



Briggs A W et al. PNAS 2007;104:14616-14621

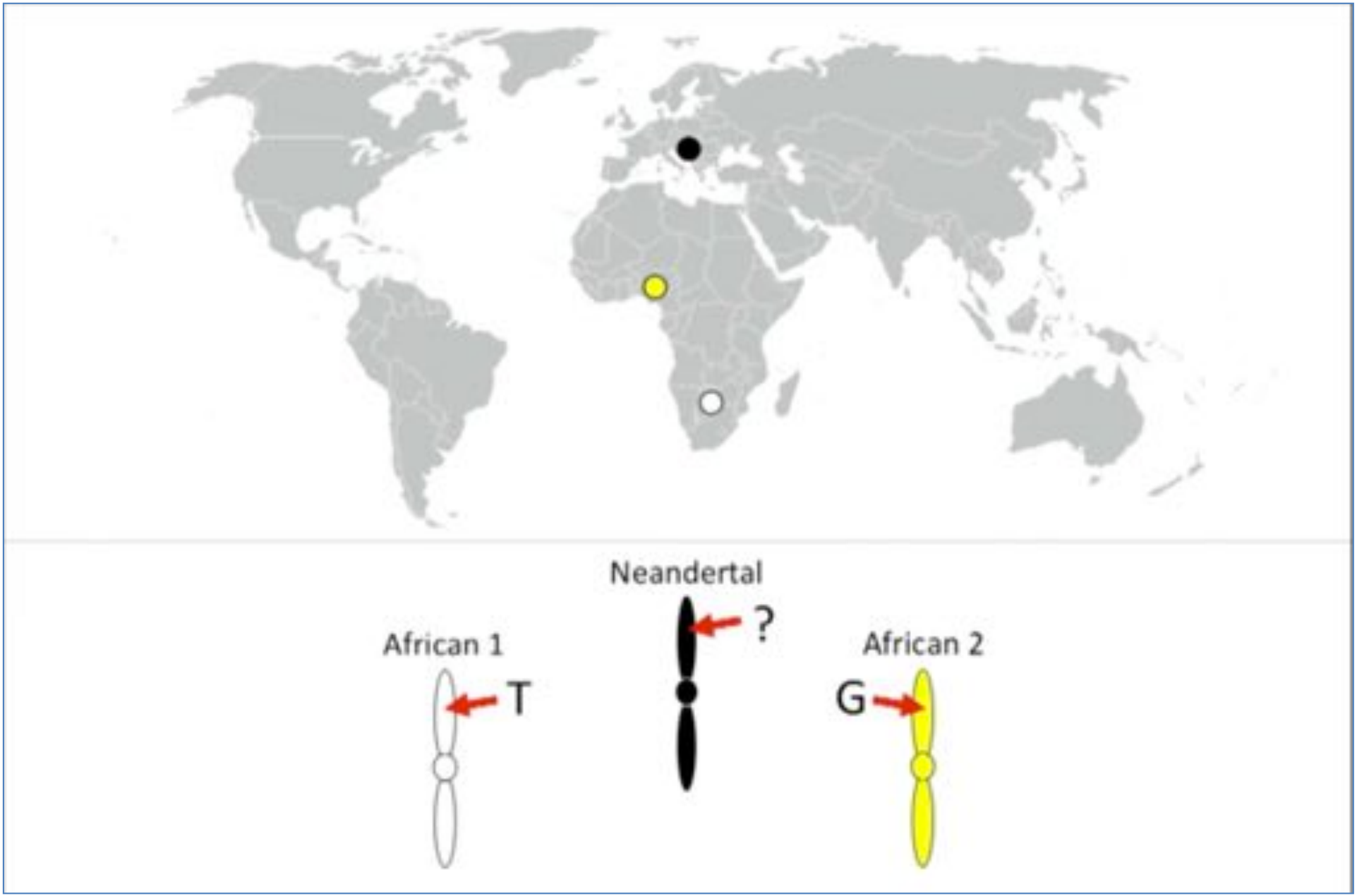
Green et al. 2010

Vindija	33.16	~1.2 Gb
	33.25	~1.3 Gb
	33.26	~1.5 Gb
El Sidron (1253)		~2.2 Mb
Feldhofer 1		~2.2 Mb
Mezmaiskaya 1		~56.4 Mb

~35 Illumina flow cells

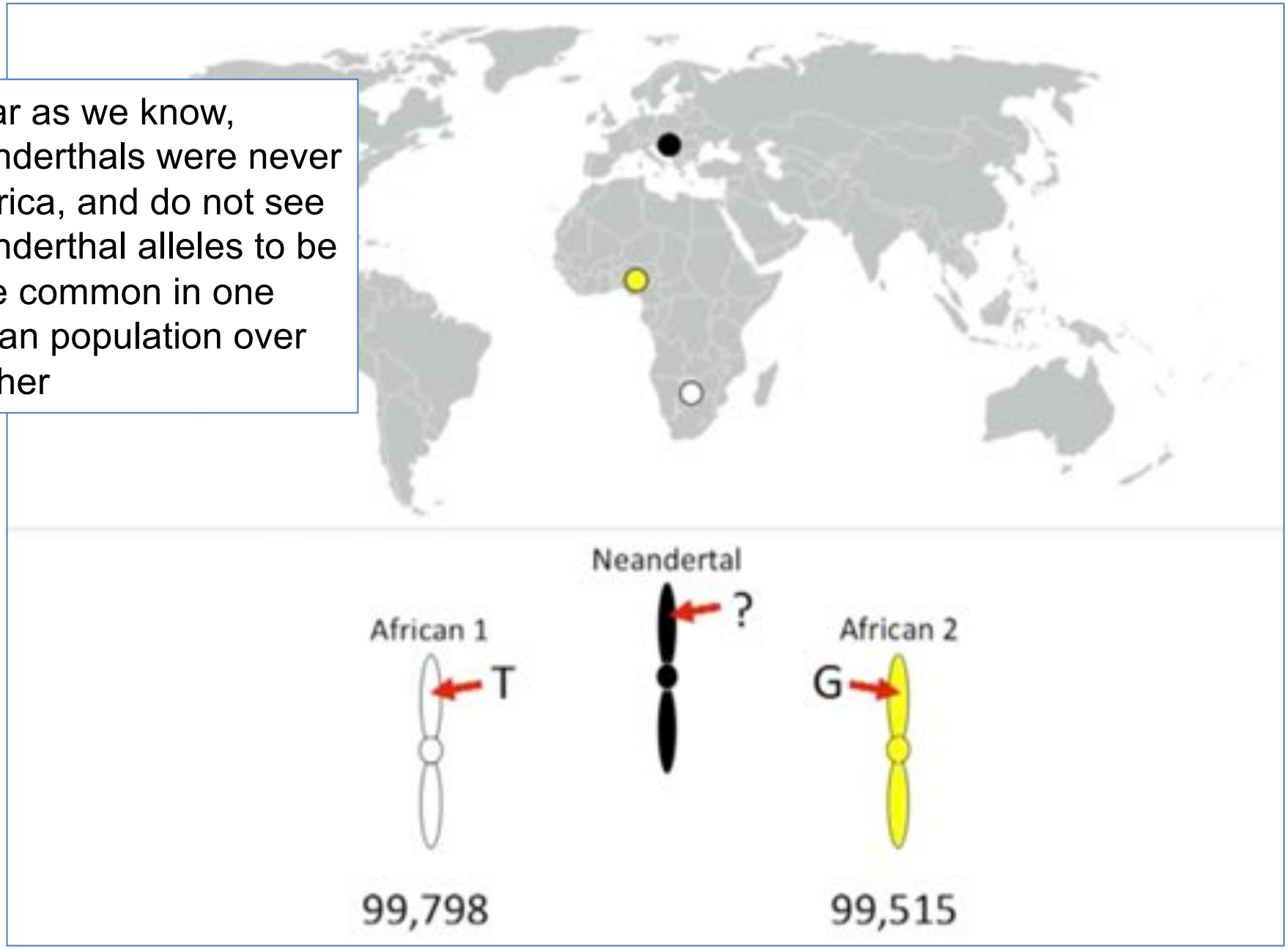
Genome coverage ~1.3 X

Did we mix?



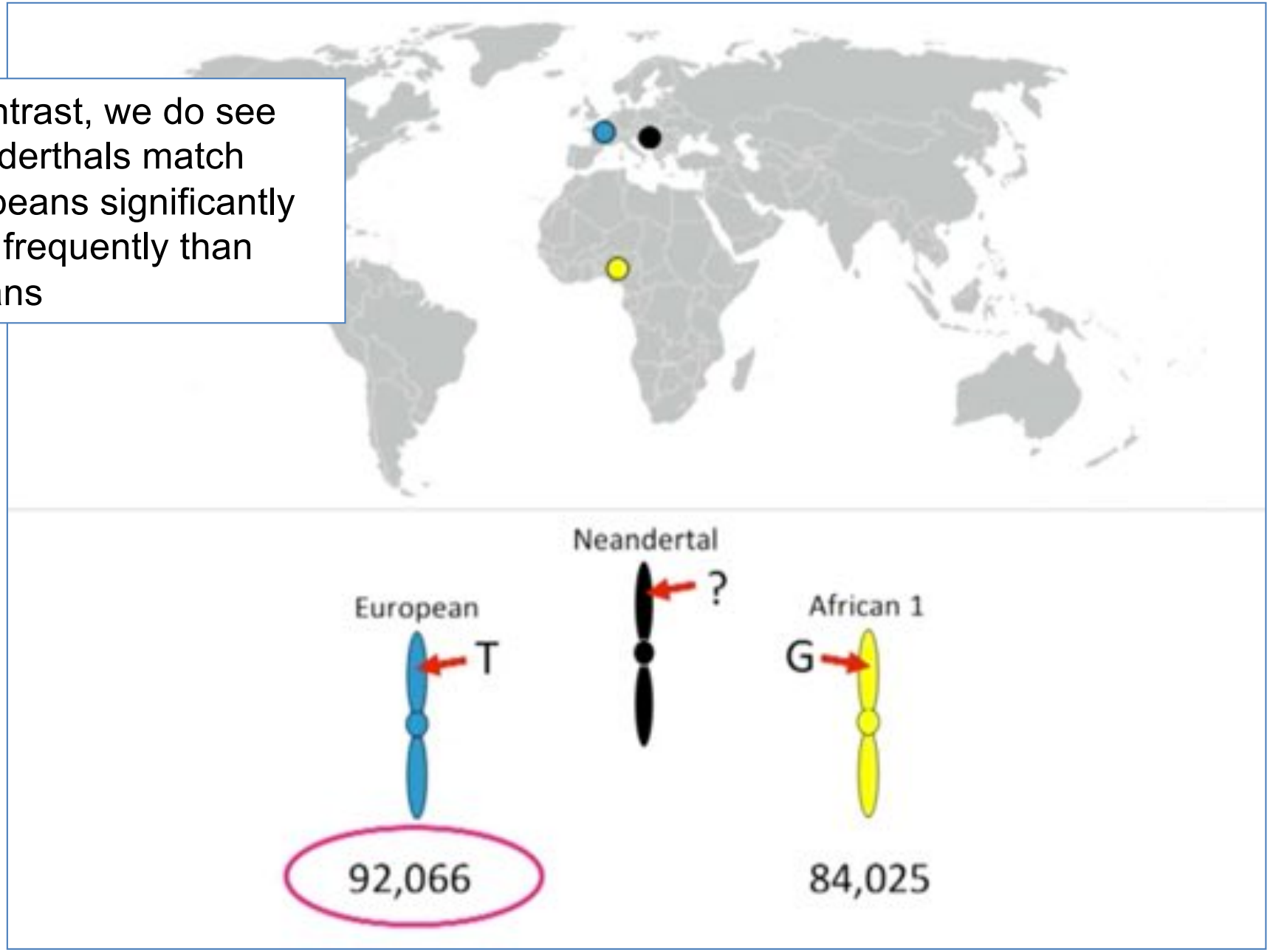
Did we mix?

As far as we know, Neanderthals were never in Africa, and do not see Neanderthal alleles to be more common in one African population over another



Did we mix?

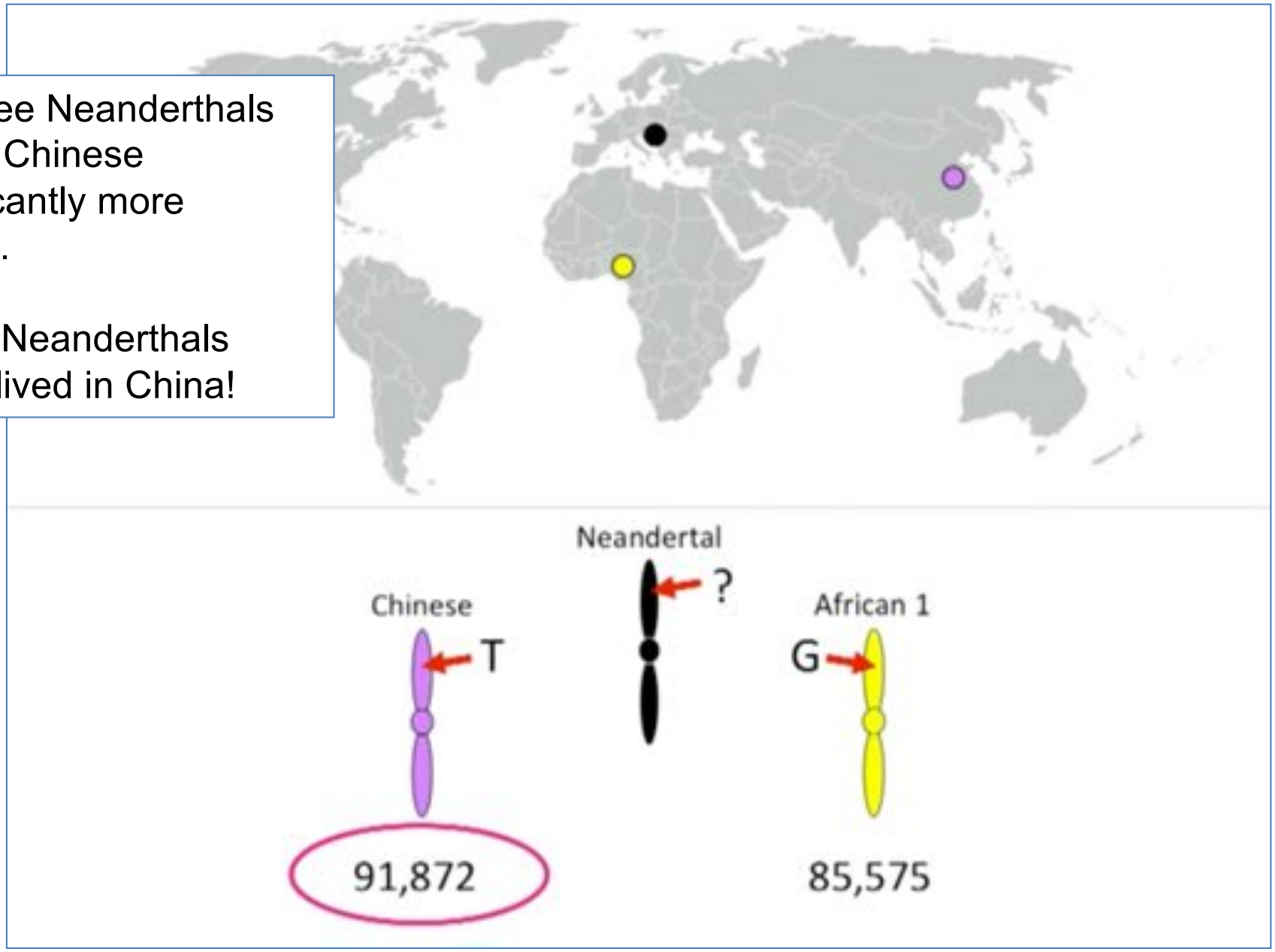
In contrast, we do see Neanderthals match Europeans significantly more frequently than Africans



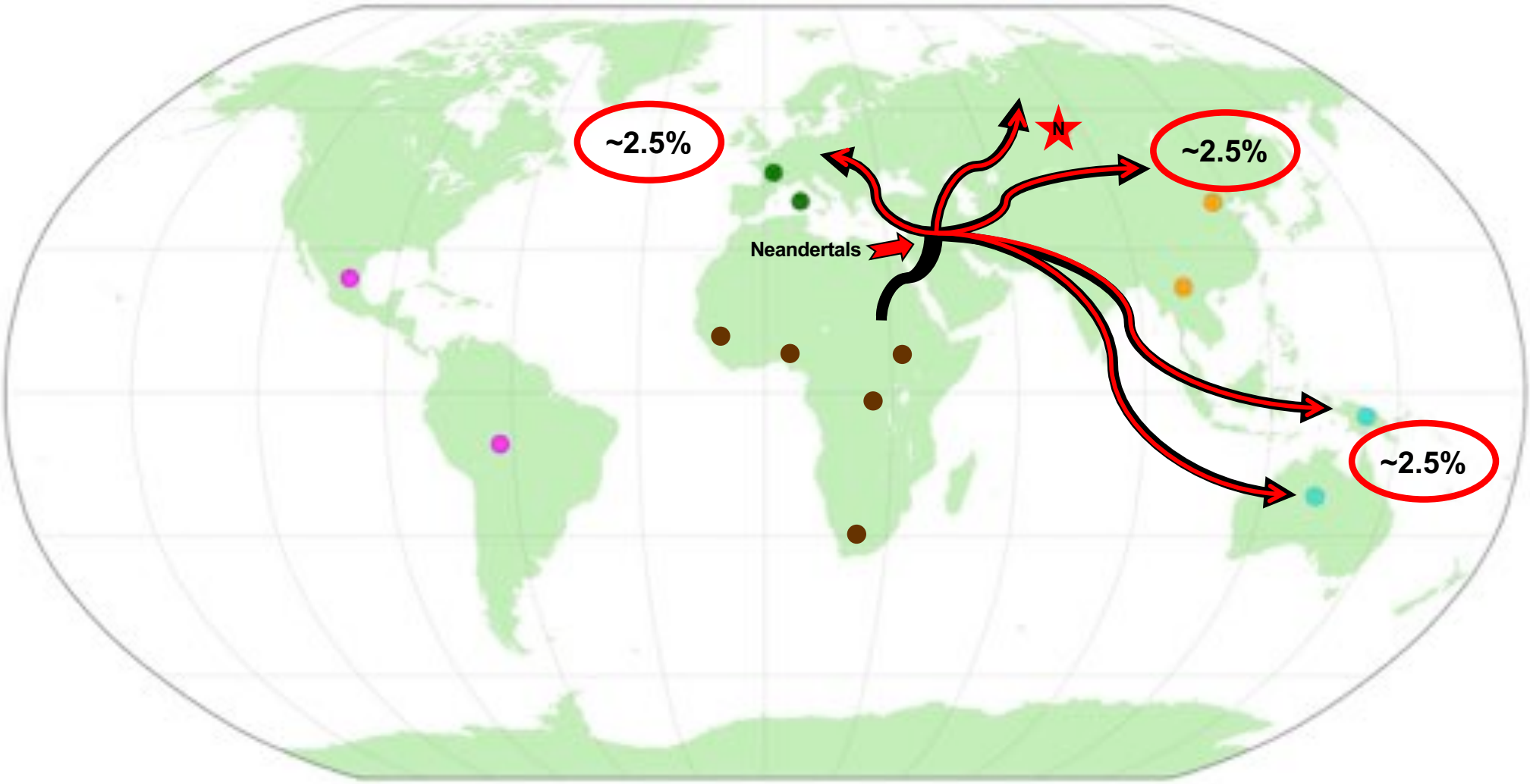
Did we mix?

Also see Neanderthals match Chinese significantly more often…

… but Neanderthals never lived in China!



Neanderthal Interbreeding

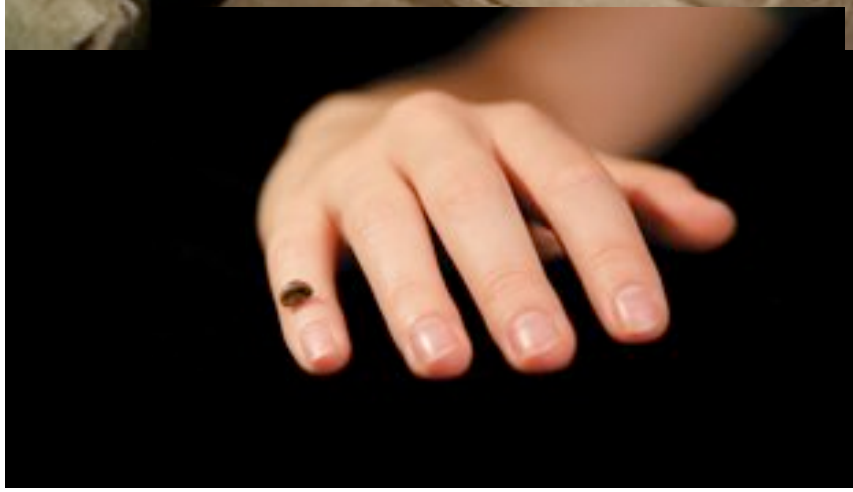


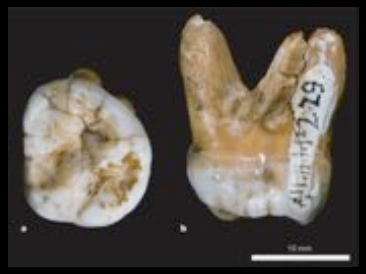
As modern humans migrated out of Africa, they apparently interbred with Neanderthal's so we see their alleles across the rest of the world and carry about 2.5% of their genome with us!

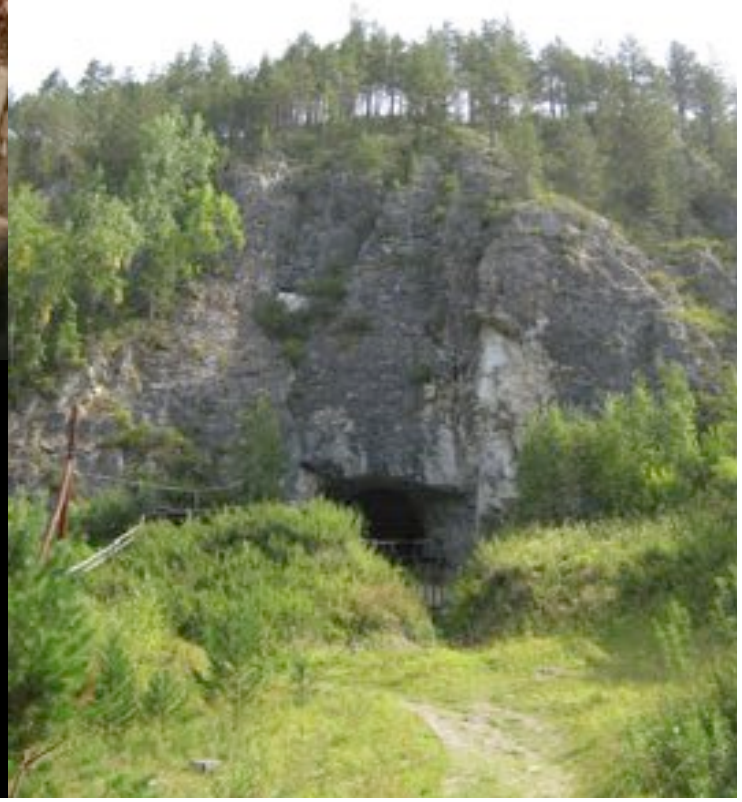
What about other ancient hominids?

Denisova cave
Altai mountains
Russia

Academician A.P. Derevianko

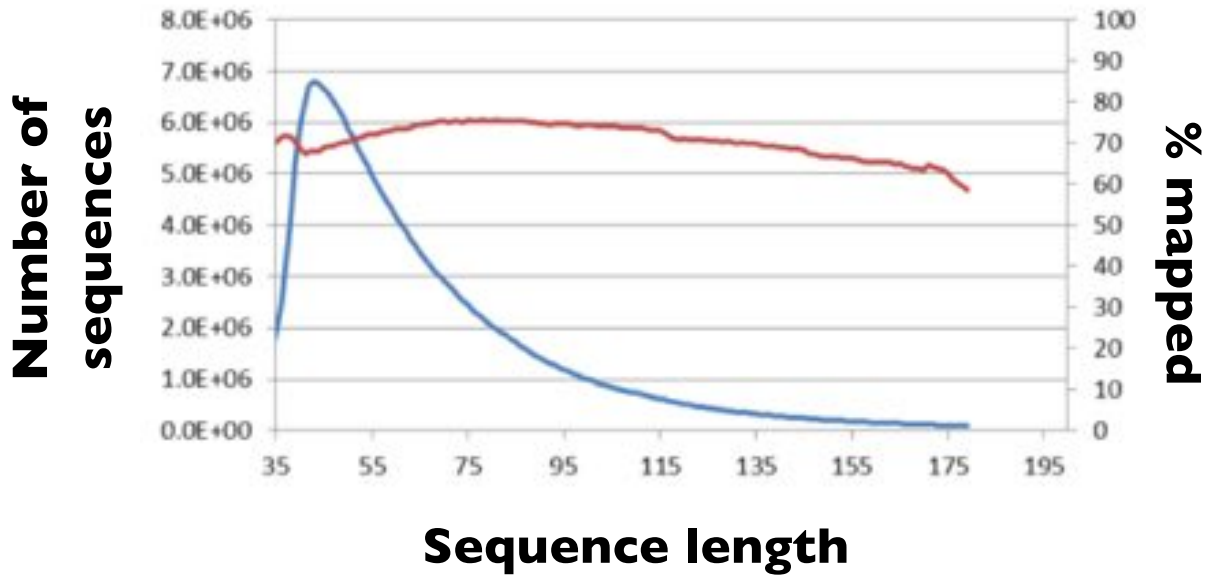






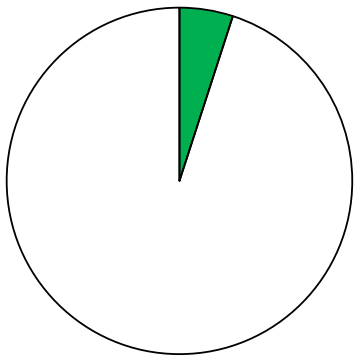

UNITED STATES OF AMERICA
E PLURIBUS UNUM
ONE CENT

Extraordinary preservation

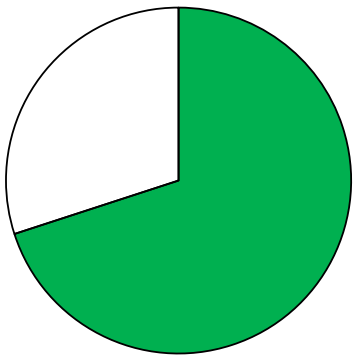


5% endogenous DNA

Best Neandertal bone

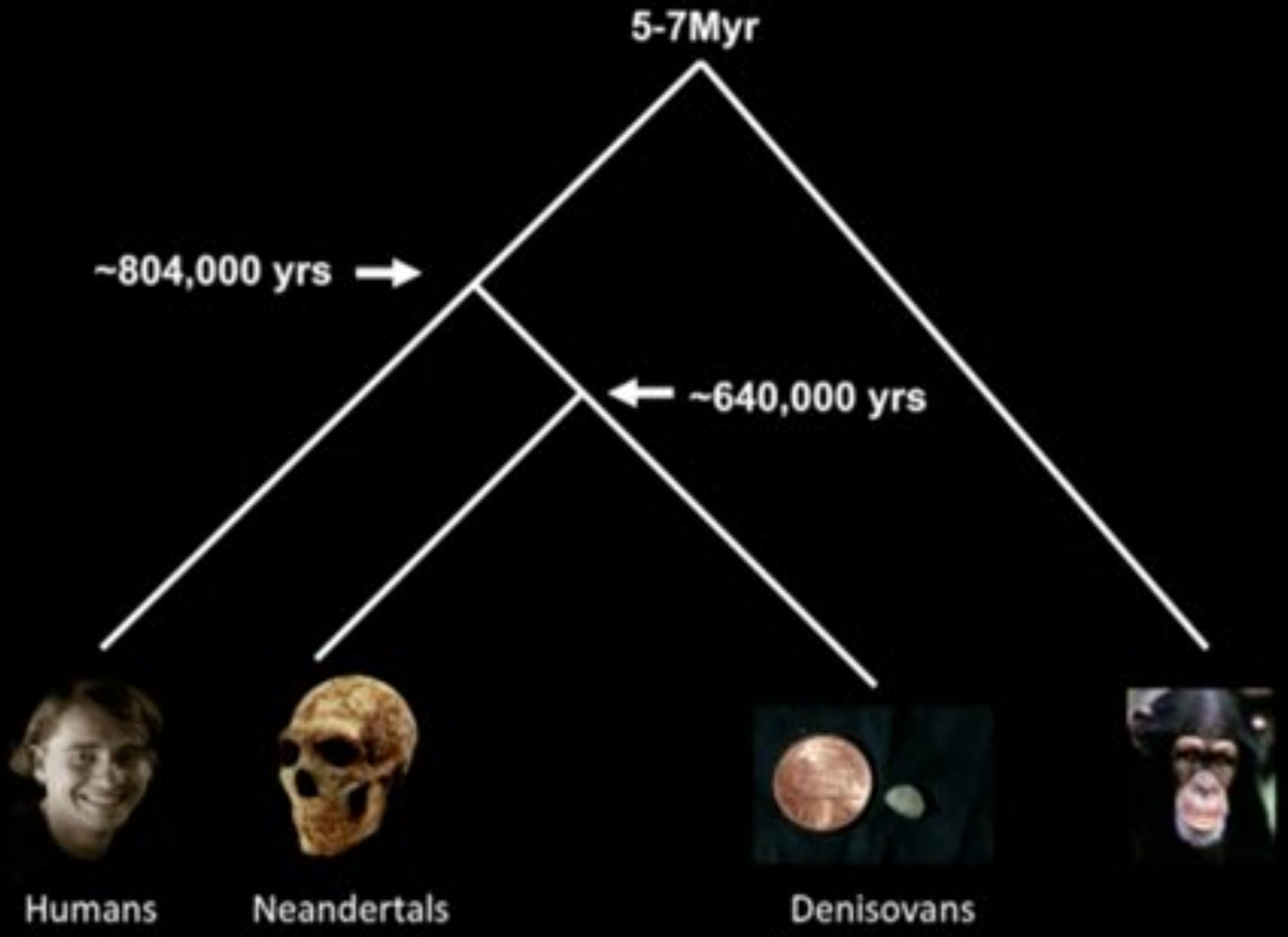


>70% endogenous DNA



Denisova bone

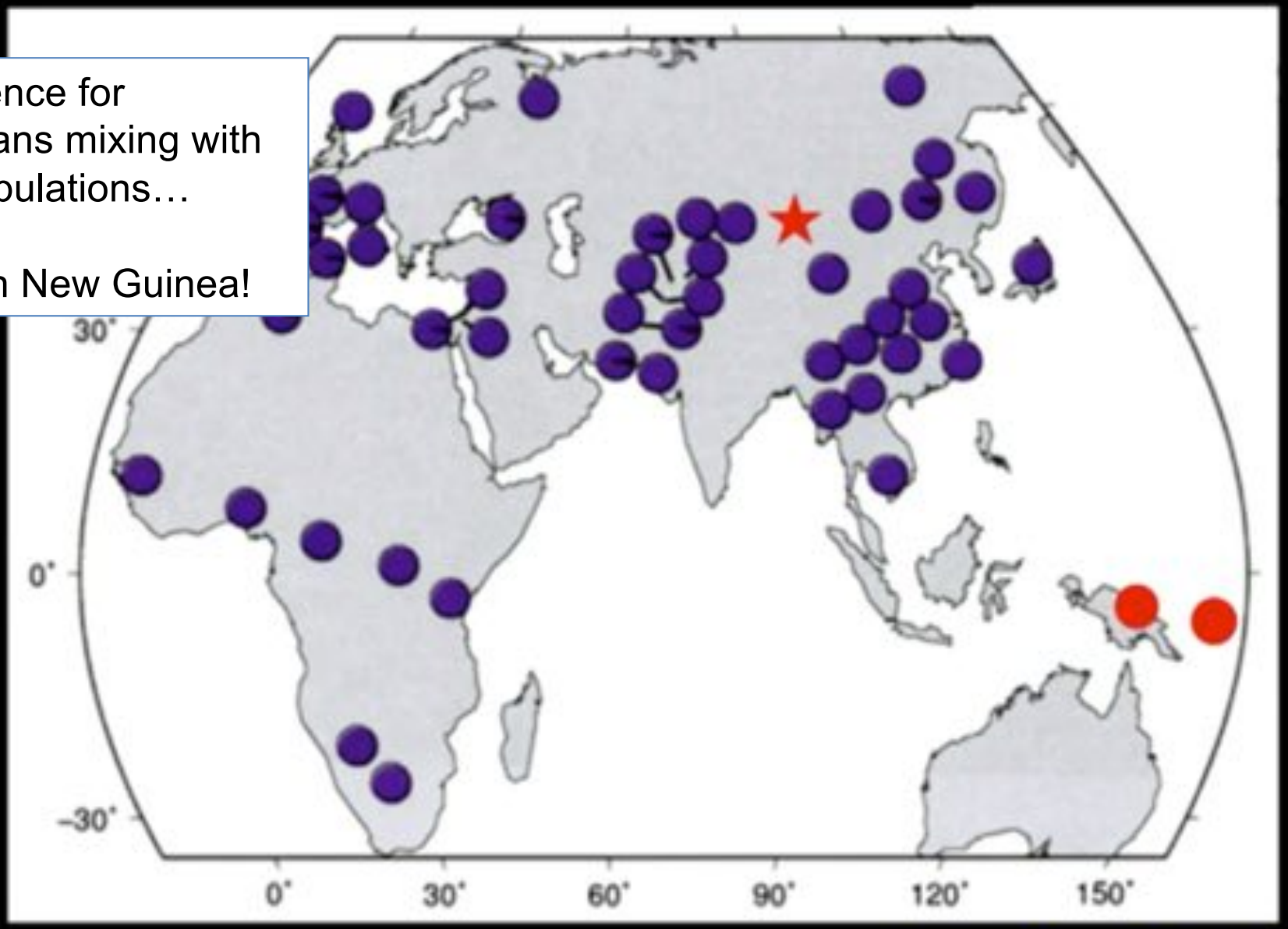
Denisovans & Neandertals



Did we mix?

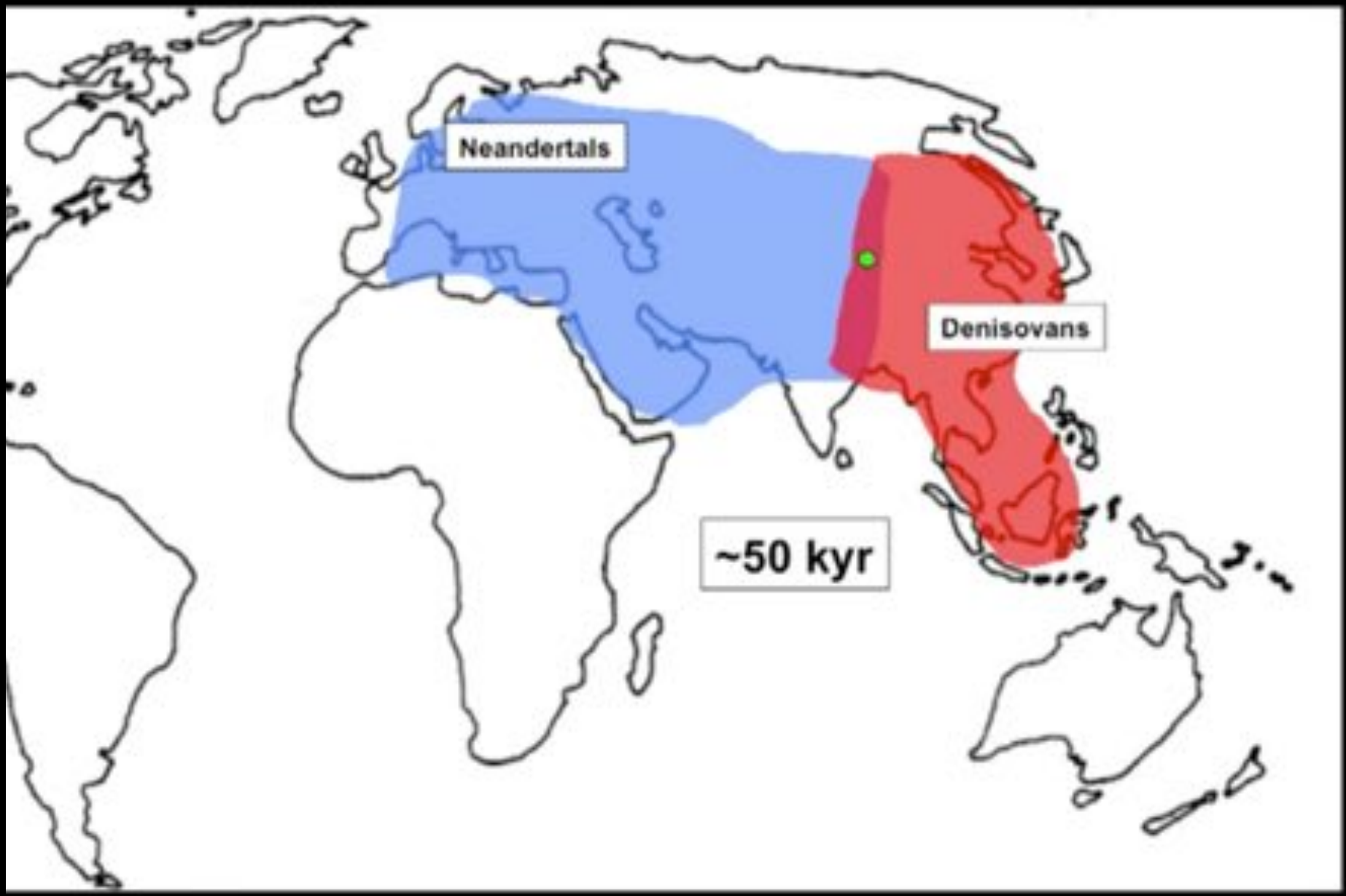
No evidence for Denisovans mixing with other populations…

Except in New Guinea!

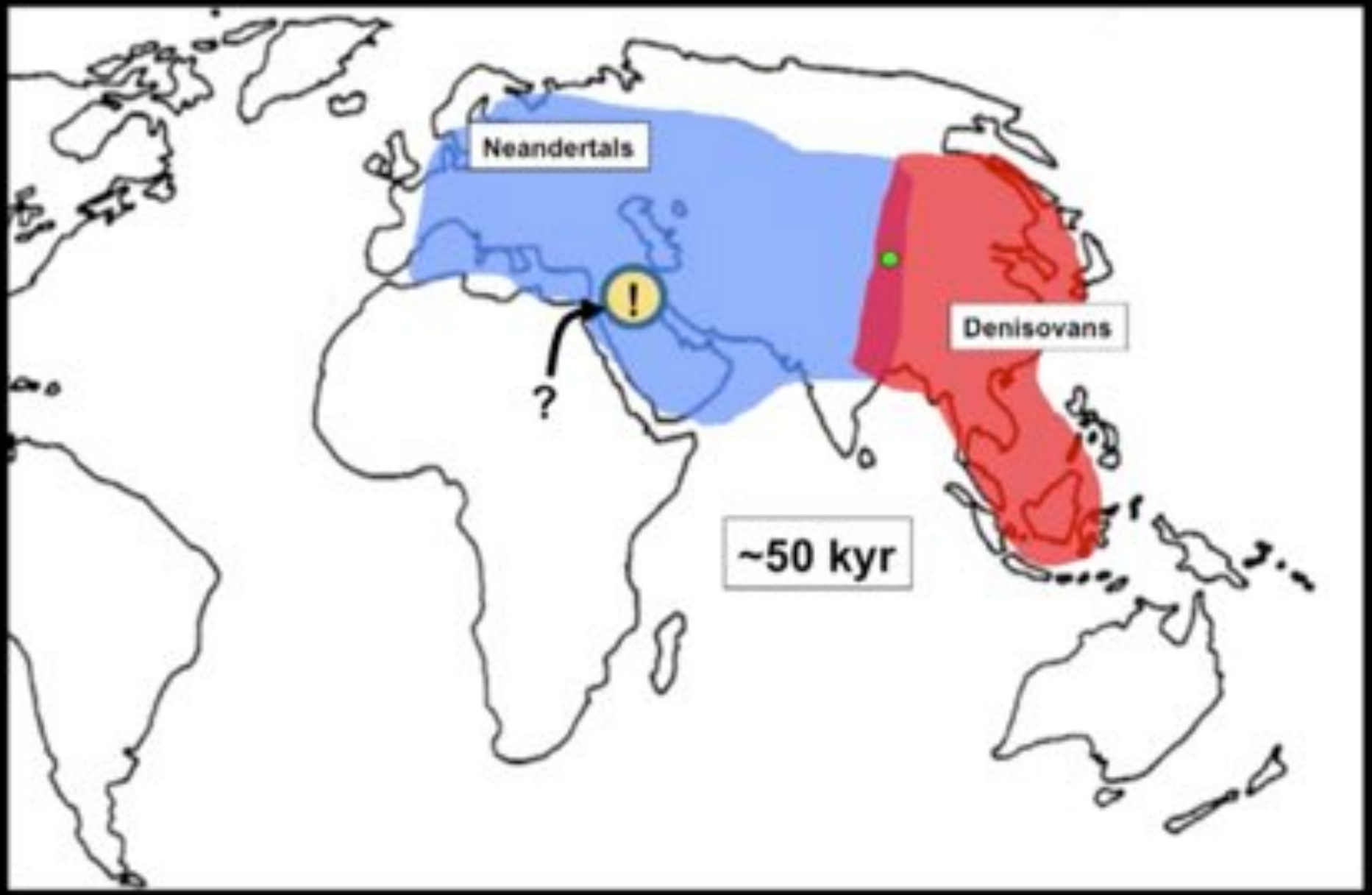


Map after Pickrell et al., 2009

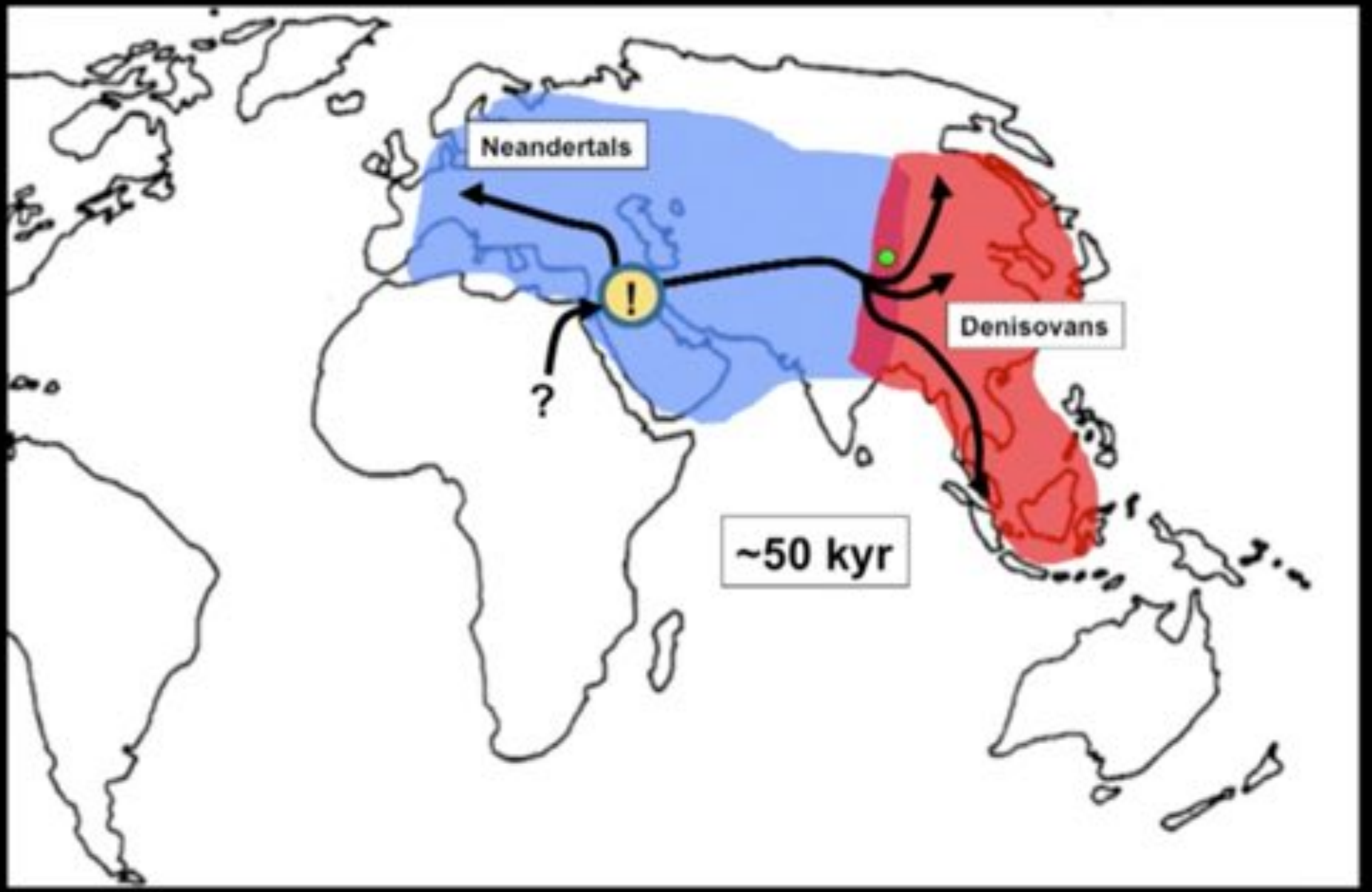
Timeline of ancient hominids



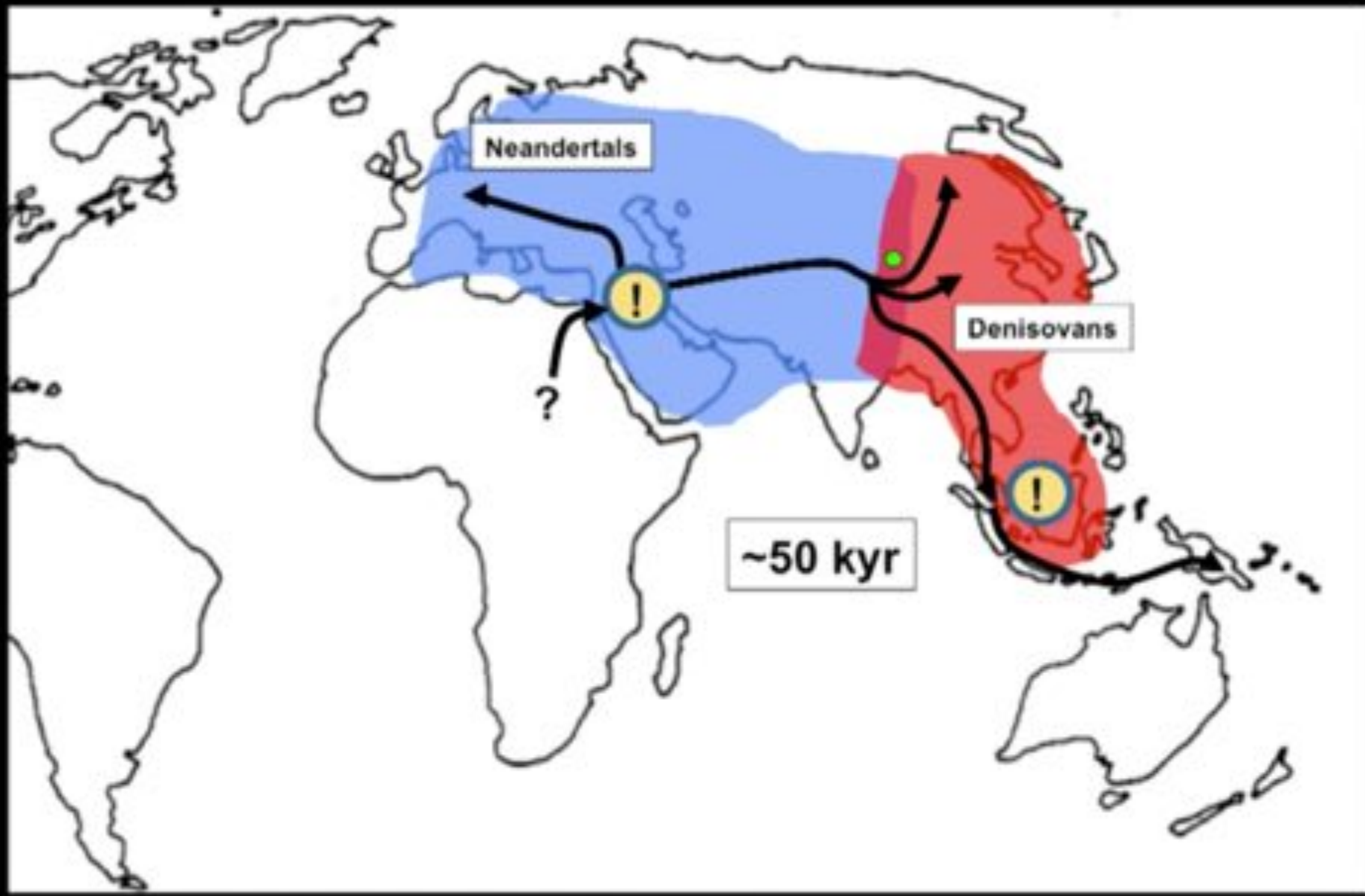
Timeline of ancient hominids



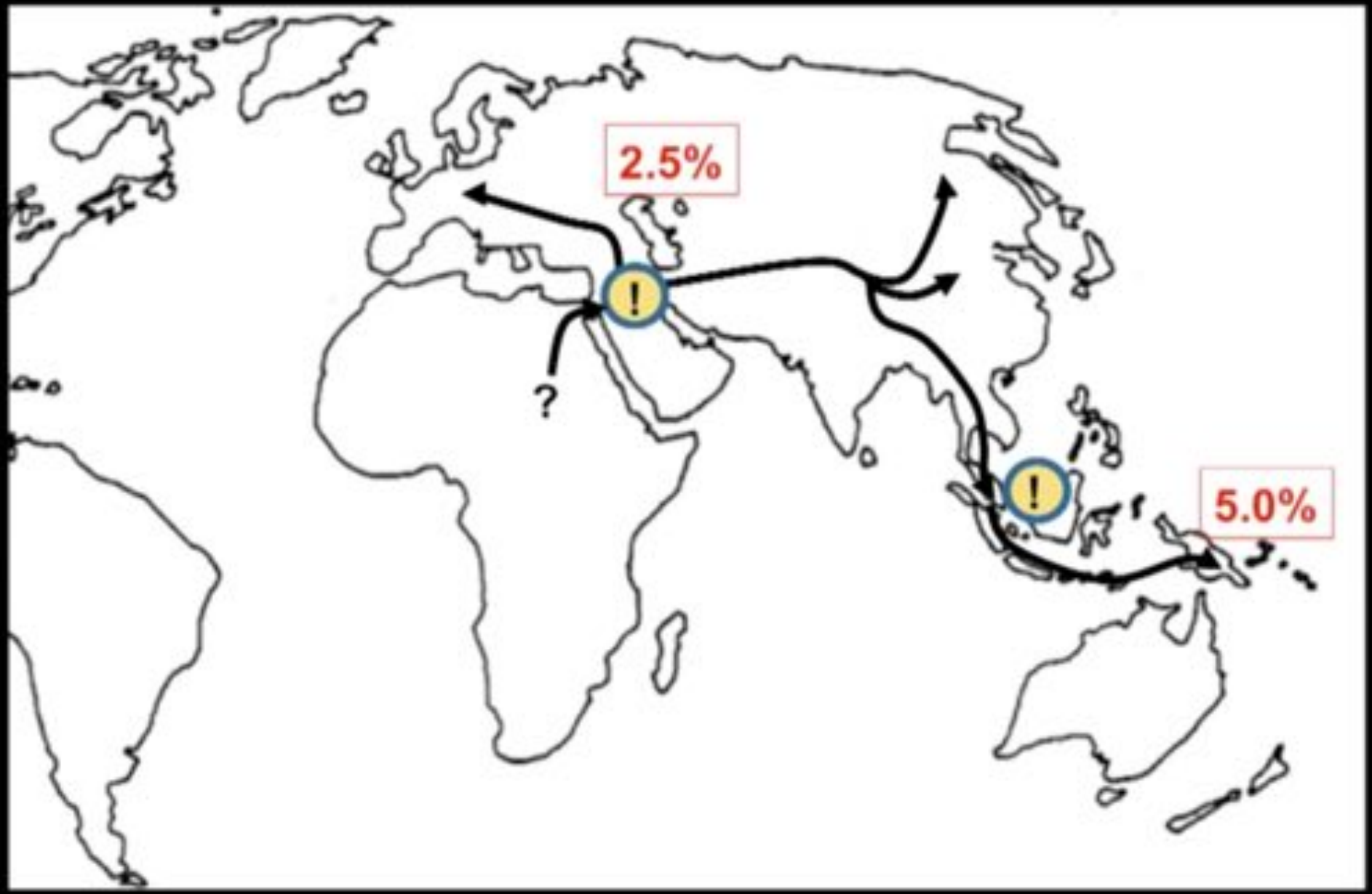
Timeline of ancient hominids



Timeline of ancient hominids



Timeline of ancient hominids



We have always mixed!

Science

REPORTS

Cite as: B. Vernot *et al.*, *Science* 10.1126/science.aad9416 (2016).

Excavating Neandertal and Denisovan DNA from the genomes of Melanesian individuals

Benjamin Vernot,[1] Serena Tucci,[1,2] Janet Kelso,[3] Joshua G. Schraiber,[1] Aaron B. Wolf,[1] Rachel M. Gittelman,[1] Michael Dannemann,[3] Steffi Grote,[3] Rajiv C. McCoy,[1] Heather Norton,[4] Laura B. Scheinfeldt,[5] David A. Merriwether,[6] George Koki,[7] Jonathan S. Friedlaender,[8] Jon Wakefield,[9] Svante Pääbo,[3]* Joshua M. Akey[1]*

[1]Department of Genome Sciences, University of Washington, Seattle, Washington, USA. [2]Department of Life Sciences and Biotechnology, University of Ferrara, Italy. [3]Department of Evolutionary Genetics, Max-Planck-Institute for Evolutionary Anthropology, Leipzig, Germany. [4]Department of Anthropology, University of Cincinnati, Cincinnati, OH, USA. [5]Coriell Institute for Medical Research, Camden, NJ, USA. [6]Department of Anthropology, Binghamton University, Binghamton, NY, USA. [7]Institute for Medical Research, Goroka, Eastern Highlands Province, Papua New Guinea. [8]Department of Anthropology, Temple University, Philadelphia PA, USA. [9]Department of Statistics, University of Washington, Seattle, Washington, USA.

*Corresponding author. E-mail: paabo@eva.mpg.de (S.P.); akey@uw.edu (J.M.A.)

Although Neandertal sequences that persist in the genomes of modern humans have been identified in Eurasians, comparable studies in people whose ancestors hybridized with both Neandertals and Denisovans are lacking. We developed an approach to identify DNA inherited from multiple archaic hominin ancestors and applied it to whole-genome sequences from 1523 geographically diverse individuals, including 35 new Island Melanesian genomes. In aggregate, we recovered 1.34 Gb and 303 Mb of the Neandertal and Denisovan genome, respectively. We leverage these maps of archaic sequence to show that Neandertal admixture occurred multiple times in different non-African populations, characterize genomic regions that are significantly depleted of archaic sequence, and identify signatures of adaptive introgression.

Recipe for a modern human

109,295 single nucleotide changes (SNCs)

7,944 insertions and deletions

Changes in protein coding genes

277 cause fixed amino acid substitutions

87 affect splice sites

Changes in Non-coding & regulatory sequences

26 affect well-defined motifs inside regulatory regions

Enrichment analysis

skin pigmentation

skeletal morphologies (limb length, digit development)

morphologies of the larynx and the epiglottis

Nonsynonymous	None	- Giant melanosomes in melanocytes (p-6.77e-6; FWER=0.091;
Splice sites		
3' UTR	None	- 1-3 toe syndactyly (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - 1-5 toe syndactyly (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - Aplasia/Hypoplasia of the distal phalanx of the thumb (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - Bifid or hypoplastic epiglottis (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - Central polydactyly (feet) (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - Distal urethral duplication (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - Dysplastic distal thumb phalanges with a central hole (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - Laryngeal cleft (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - Midline facial capillary hemangioma (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - Preductal coarctation of the aorta (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - Radial head subluxation (p=1.34288e-05; FWER=0.538; FDR=0.0887928) - Short distal phalanx of the thumb (p=1.34288e-05; FWER=0.538; FDR=0.0887928)

FOXP2 Analysis

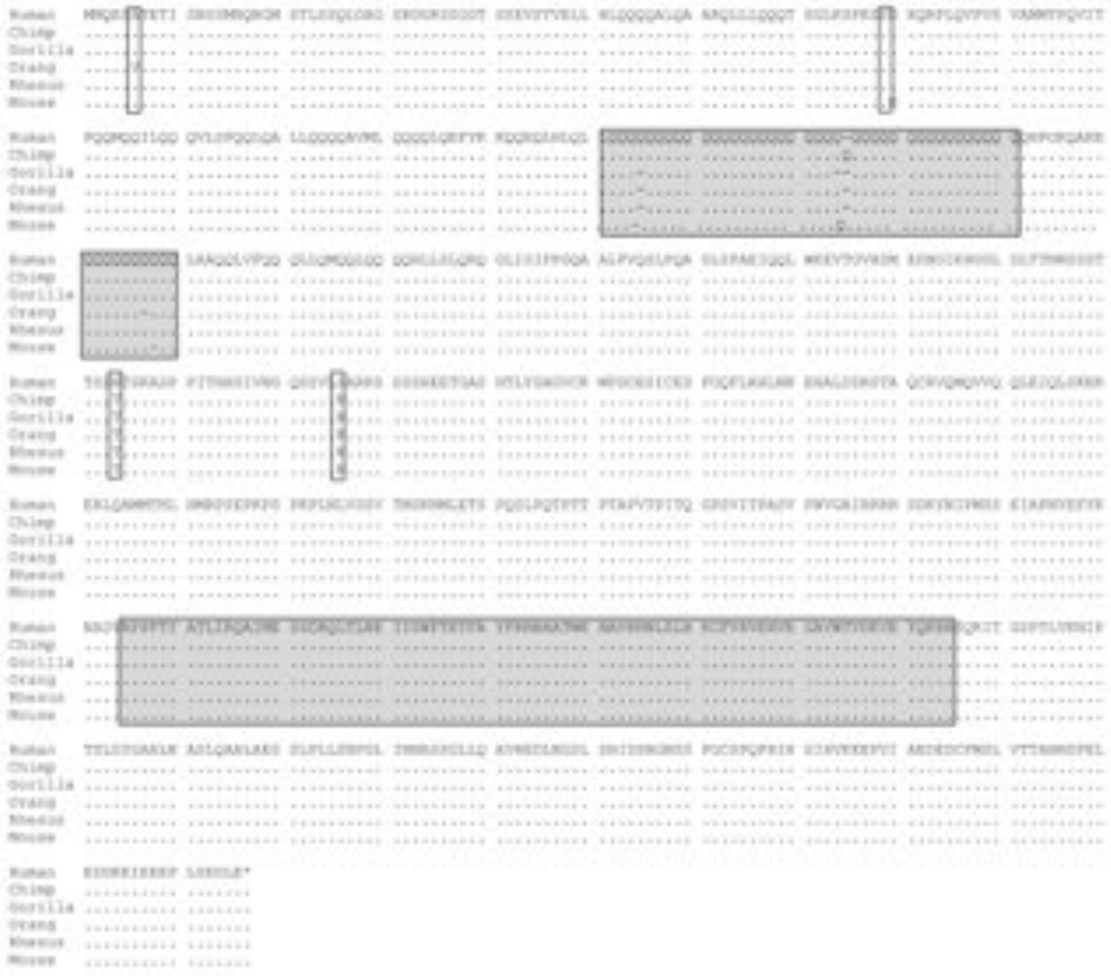


Figure 1 Alignment of the amino-acid sequences inferred from the *FOXP2* cDNA sequences. The polyglutamine stretches and the forkhead domain are shaded. Sites that differ from human sequence are boxed.

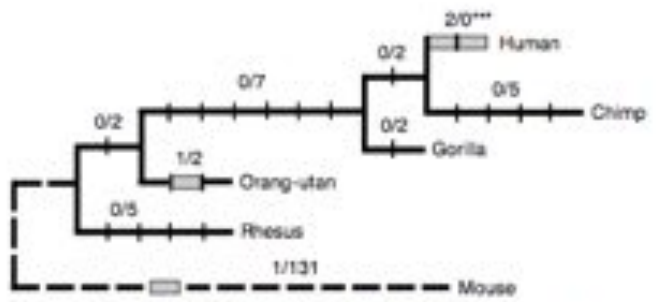


Figure 2 Silent and replacement nucleotide substitutions mapped on a phylogeny of primates. Bars represent nucleotide changes. Grey bars indicate amino-acid changes.

- Mutations of FOXP2 cause a severe speech and language disorder in people
- Versions of FOXP2 exist in similar forms in distantly related vertebrates; functional studies of the gene in mice and in songbirds indicate that it is important for modulating plasticity of neural circuits.
- Outside the brain FOXP2 has also been implicated in development of other tissues such as the lung and gut.

Molecular evolution of FOXP2, a gene involved in speech and language

Enard *et al* (2002) *Nature*. doi:10.1038/nature01025