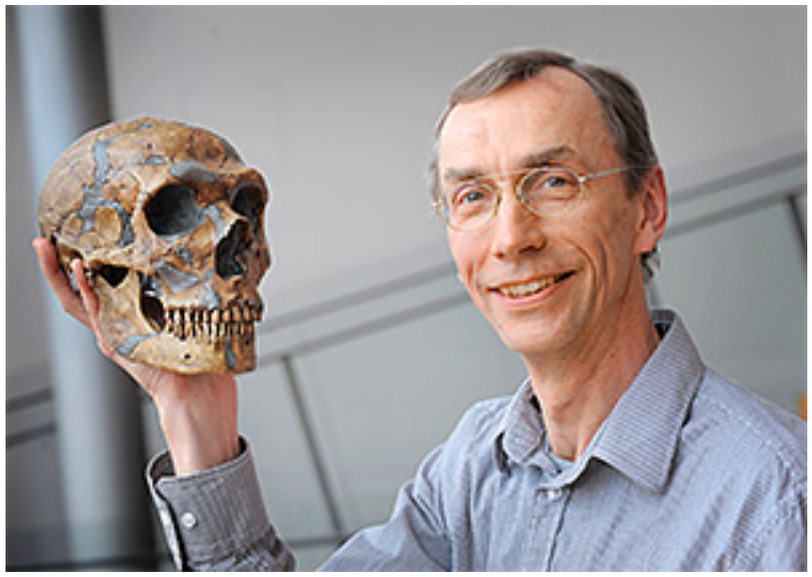
Darwin Day 2023 Lecture
Heroes of Evolution—Svante Pääbo

Stephen L. Gasior Ph.D.
Stephen Xootfly

February 12th, 2023
Science Circle

Svante Pääbo



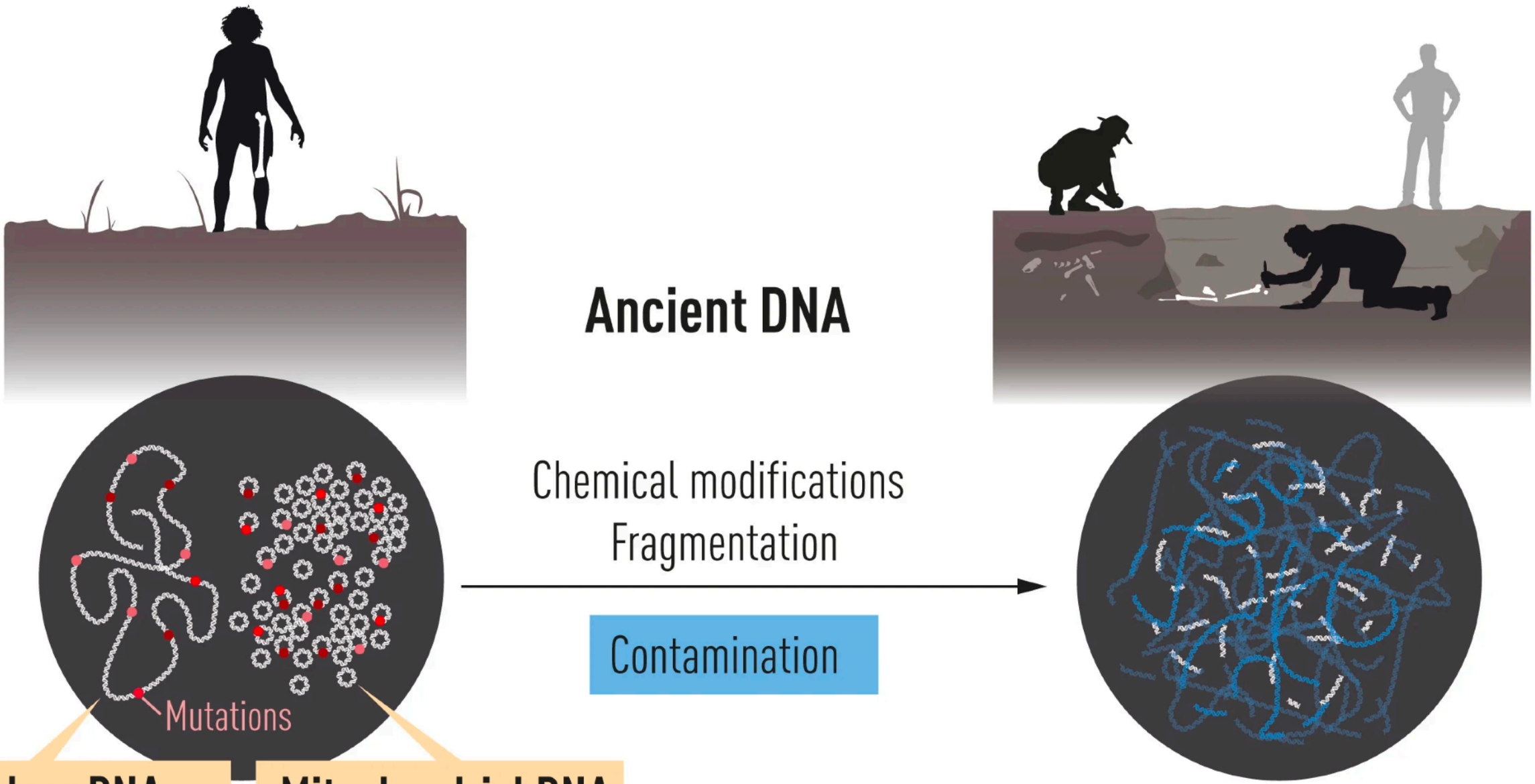
Director

Max Planck Institute for Evolutionary Anthropology

(from his faculty page)

- Born born 20 April 1955 in Stockholm, Sweden
- Mother: Karin Pääbo was a chemist and Father: Swedish biochemist Sune Bergström also a recipient of the Nobel Prize in Physiology or Medicine (in 1982) [not married]
- As an EMBO Postdoctoral Fellow, Pääbo moved to the United States in 1987 at the University of California, Berkeley, where he joined Allan Wilson's lab and worked on the genomes of extinct mammals
- In 1997, he became founding director of the Department of Genetics at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany
- Time Magazine 100 Most Influential People in the World (2007)
- In 2022, he was awarded the Nobel Prize in Physiology or Medicine "for his discoveries concerning the genomes of extinct hominins and human evolution”

Pääbo: Ancient DNA



Pääbo: Egyptian DNA (1985)

Artificial mummification was practised in Egypt from ~ 2600 BC until the fourth century AD. Because of the dry Egyptian climate, however, there are also many natural mummies preserved from earlier as well as later times.

To elucidate whether this unique source of ancient human remains can be used for molecular genetic analyses, 23 mummies were investigated for DNA content.

One 2,400-yr-old mummy of a child was found to contain DNA that could be molecularly cloned in a plasmid vector.

These analyses show that substantial pieces of mummy DNA (3.4 kilobases) can be cloned and that the DNA fragments seem to contain little or no modifications introduced postmortem.

Pääbo, Das Altertum, 1984

Pääbo: Alaskan and Siberian mammoths (1999)

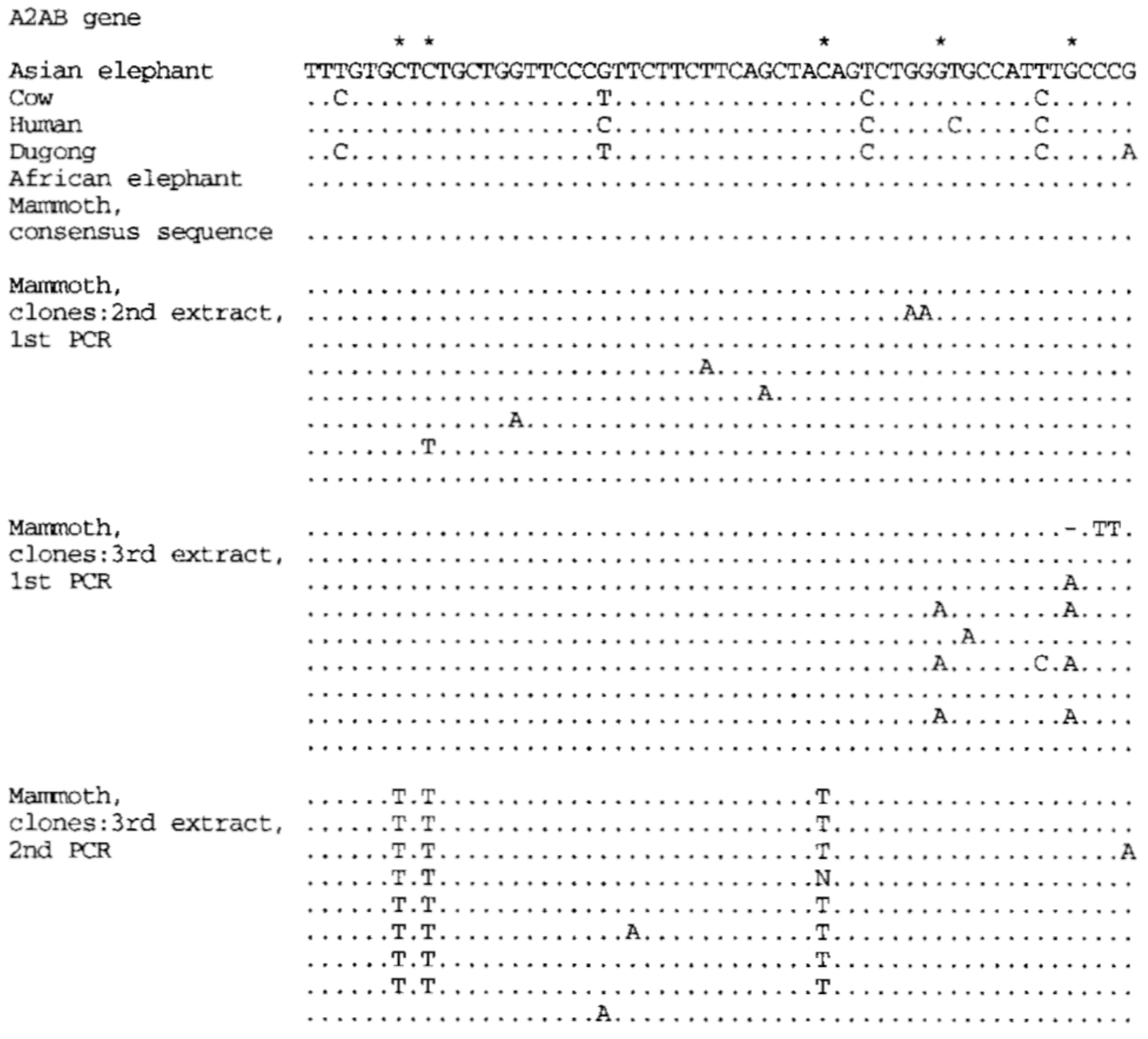
—Dentine sample from the Alaskan mammoth was dated by accelerator mass spectroscopy at 13,775 +/- 145 years
—The bone sample of the Croatian cave bear was dated at 33,335 +/- 145 years.
—The Siberian mammoth and the second Alaskan mammoth were assumed to be of late Pleistocene age (12,000-126,000 years ago)
—The estimated age of the ground sloth is approximately 13,000 years.

Thought nuclear DNA older than 10,000 was not amplifiable. So, they chose permafrost remains since a low ambient temperature may enhance preservation of biomolecules.

The results presented show that nuclear DNA sequences that exist in several copies per haploid genome as well as sequences that exist as single copies, such as the *vWF*, *A2AB*, and *IRBP* genes, can be amplified by PCR from a mammoth sample.

Pääbo: Alaskan and Siberian mammoths (1999)

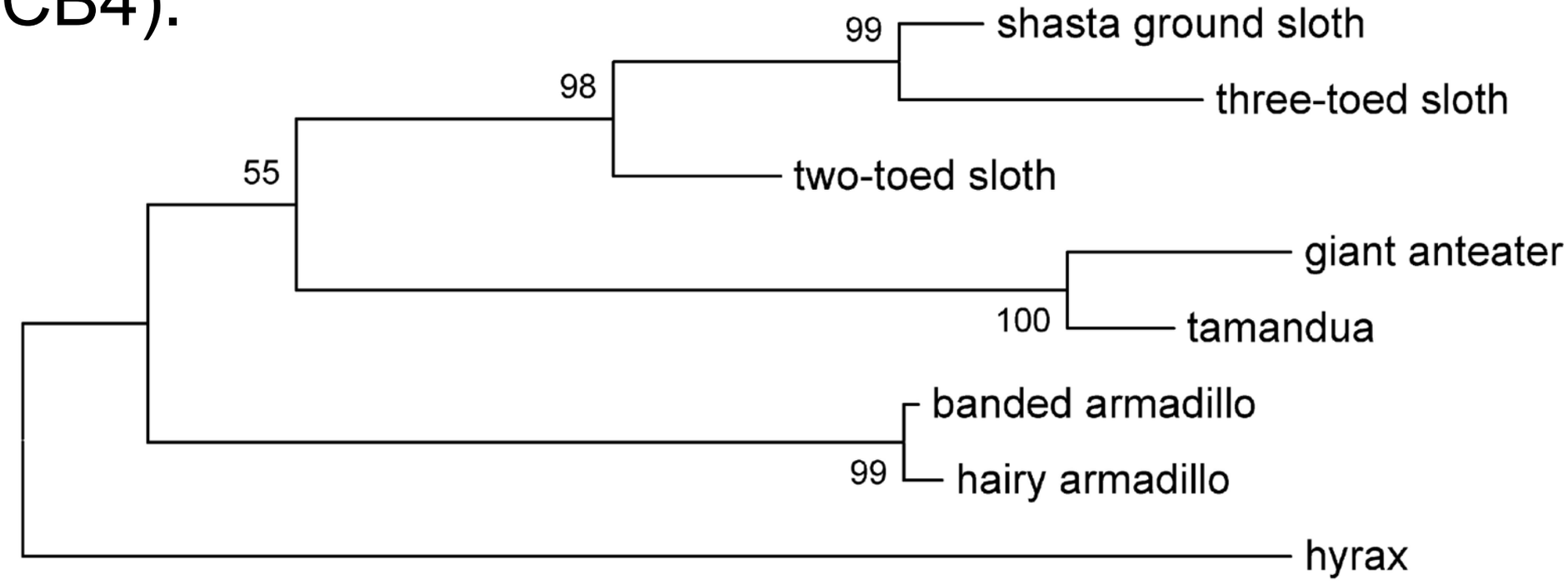
Alignment to modern species
only short stretches
sequence ambiguity
but can be used to develop/resolve phylogeny



Pääbo: Sloth (2003)

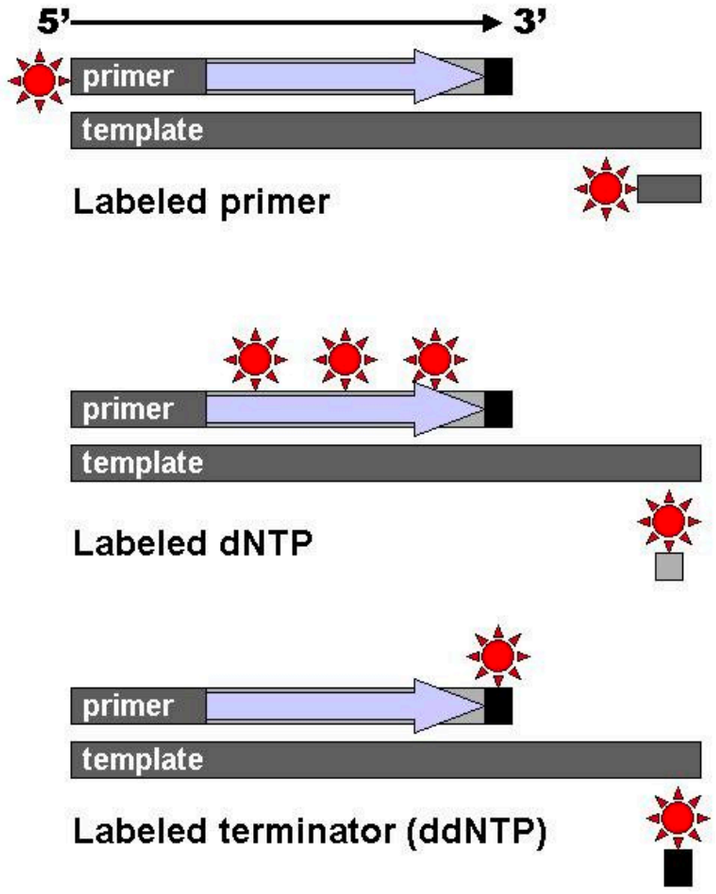
DNA extracts from a Shasta ground sloth coprolite from Gypsum Cave, Nevada (also late Pleistocene)

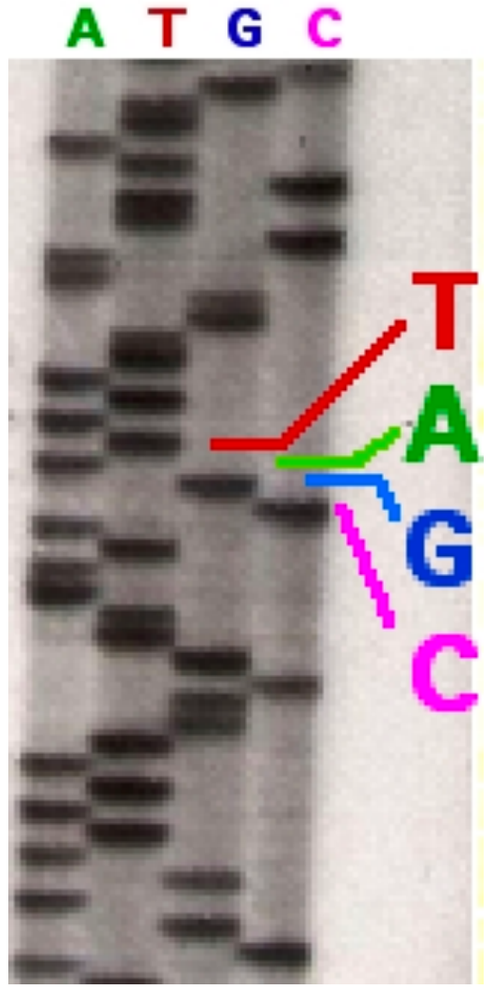
amplified a 74 bp fragment of the multicopy nuclear 28S rRNA gene and a several fragments of *vWF*, and a 120 bp fragment of *CREM* and a 94 bp product (with primers) of the *phospholipase C, β 4* gene (PLCB4).



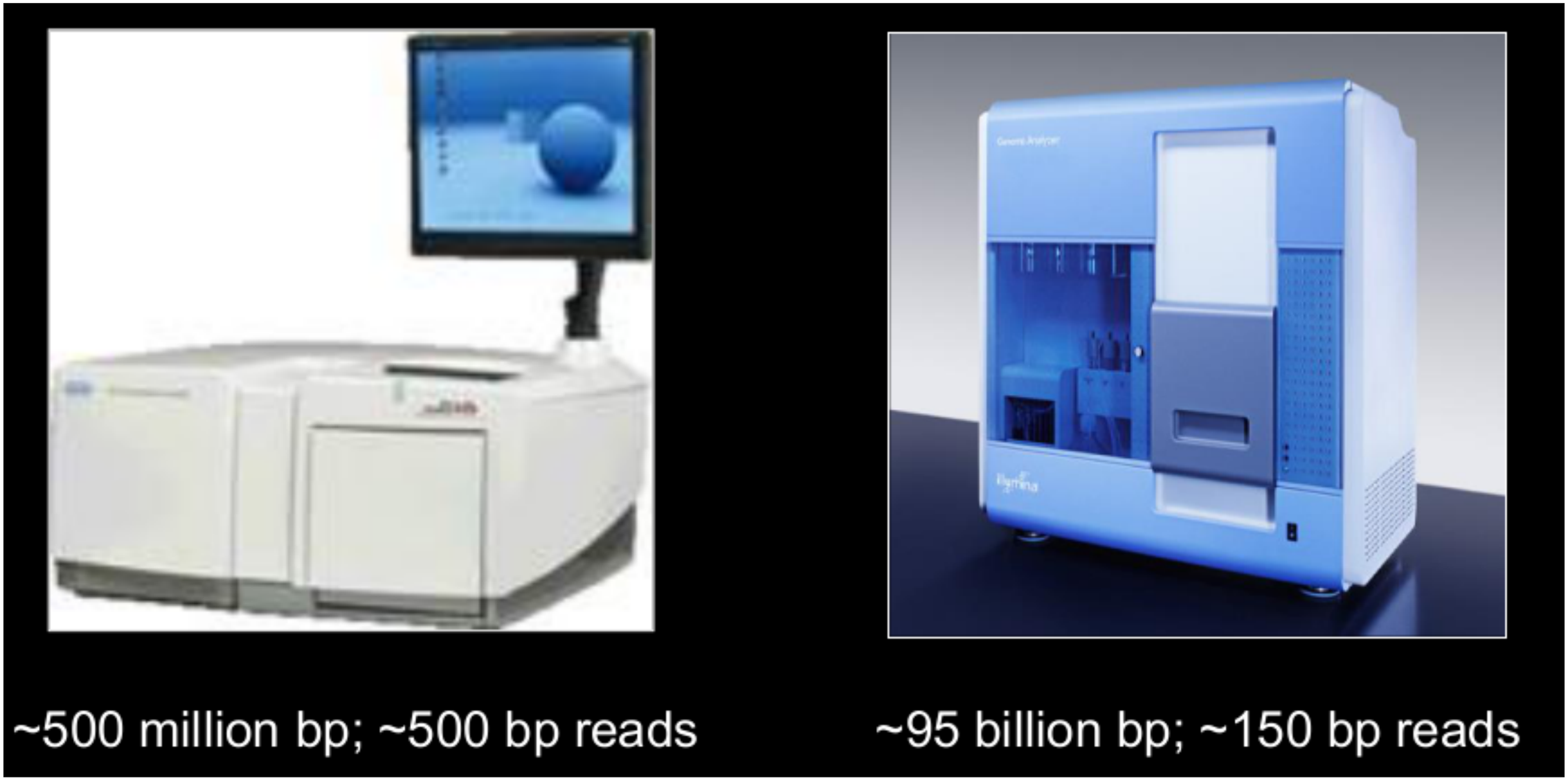
These results show that ancient single-copy nuclear DNA can be recovered from warm, arid climates. Thus, nuclear DNA preservation is not restricted to cold climates

Old School Sequencing for Genome Assembly





Pääbo: High Throughput Sequencing



up to date review: Orlando, L., Allaby, R., Skoglund, P. et al. Ancient DNA analysis. *Nat Rev Methods Primers* **1**, 14 (2021)

Pääbo: Sequencing Needles from Hay

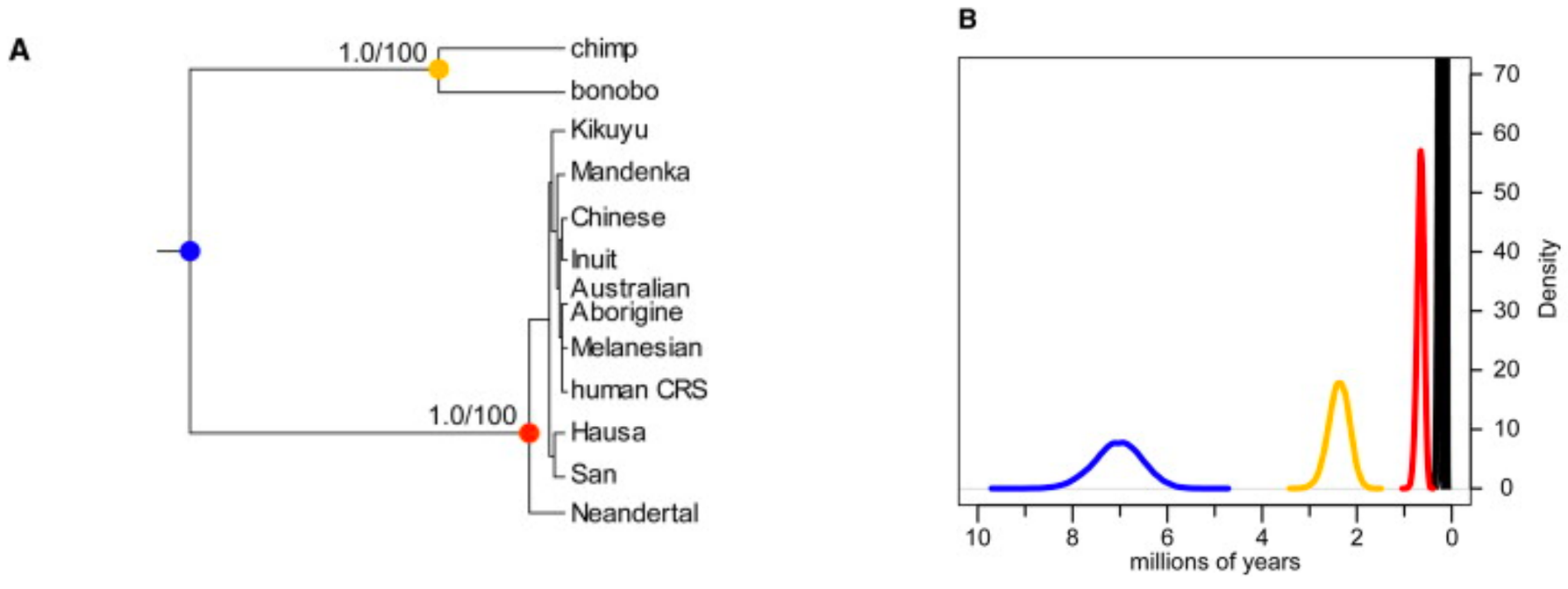
Pääbo: Neandertal Mitochondria (2008)

A complete mitochondrial (mt) genome sequence was reconstructed from a 38,000 year-old Neandertal individual excavated in 1980 from Vindija Cave, Croatia

with 8341 mtDNA sequences identified among 4.8 Gb of DNA generated from ~0.3 g of bone, 34.9-fold coverage

Alignment of the 16,565 nt Neandertal mtDNA to the 16,568 nt human revised Cambridge reference mtDNA sequence (rCRS) (Andrews et al., 1999) revealed 206 differences

Analysis of the assembled sequence unequivocally establishes that the Neandertal mtDNA falls outside the variation of extant human mtDNAs, and allows an estimate of the divergence date between the two mtDNA lineages of 660,000 ± 140,000 years.



===> Neandertal mtDNA is not present or related to modern day humans, suggesting they did NOT interbreed in particular when they overlapped geographies based on anthropologic data

Pääbo: Neandertal Draft Genome (2010)

(abstract only)

We present a draft sequence of the Neandertal genome composed of more than 4 billion nucleotides from three individuals.

Comparisons of the Neandertal genome to the genomes of five present-day humans from different parts of the world identify a number of genomic regions that may have been affected by positive selection in ancestral modern humans, including genes involved in metabolism and in cognitive and skeletal development.

We show that Neandertals shared more genetic variants with present-day humans in Eurasia than with present-day humans in sub-Saharan Africa, suggesting that gene flow from Neandertals into the ancestors of non-Africans occurred before the divergence of Eurasian groups from each other.

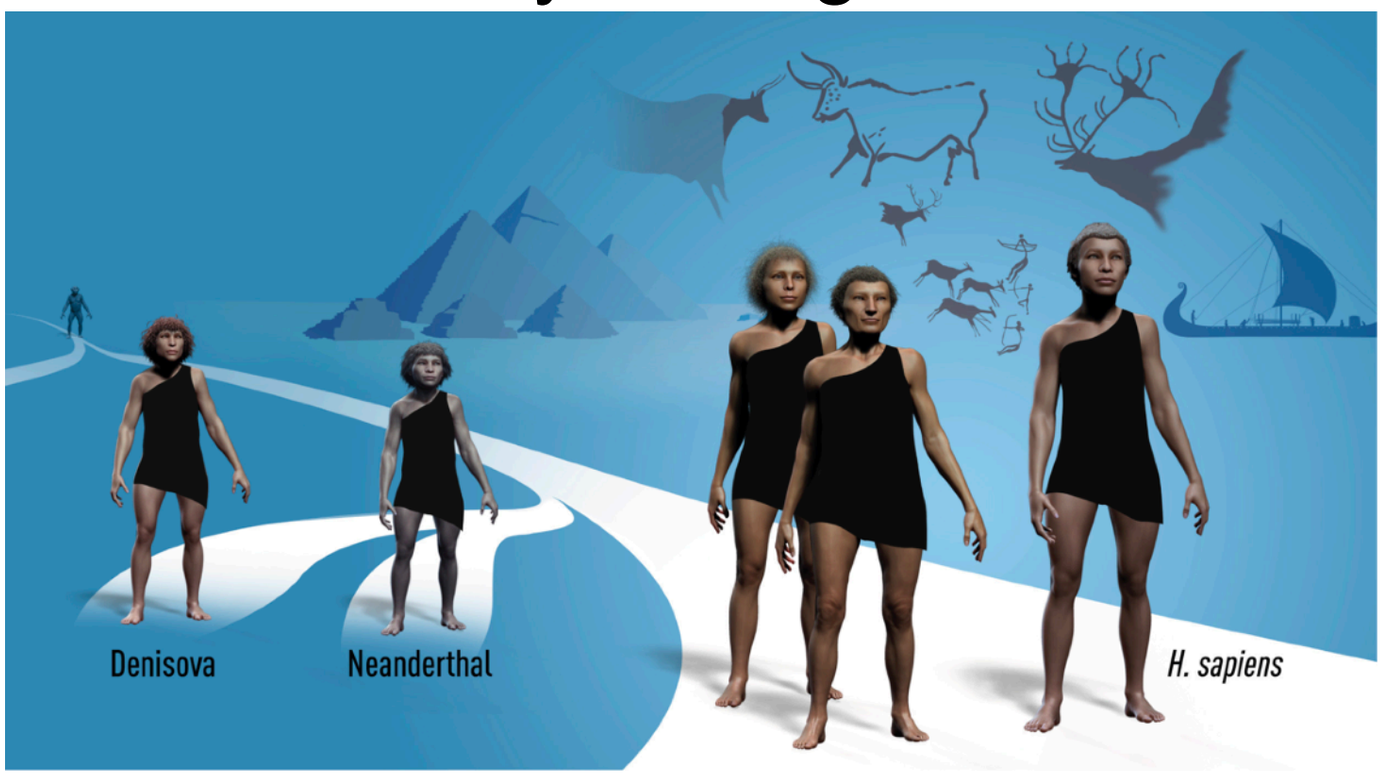
Pääbo: Denisovans (2010)

In 2008, the distal manual phalanx of a juvenile hominin was excavated at Denisova Cave. This site is located in the Altai Mountains in southern Siberia

mtDNA diverged from the common lineage leading to modern human and Neanderthal mtDNAs about one million years ago

We note that the stratigraphy and indirect dates indicate that this individual lived between 30,000 and 50,000 years ago

Representatives of three genetically distinct hominin lineages may all have been present in this region at about the same time.

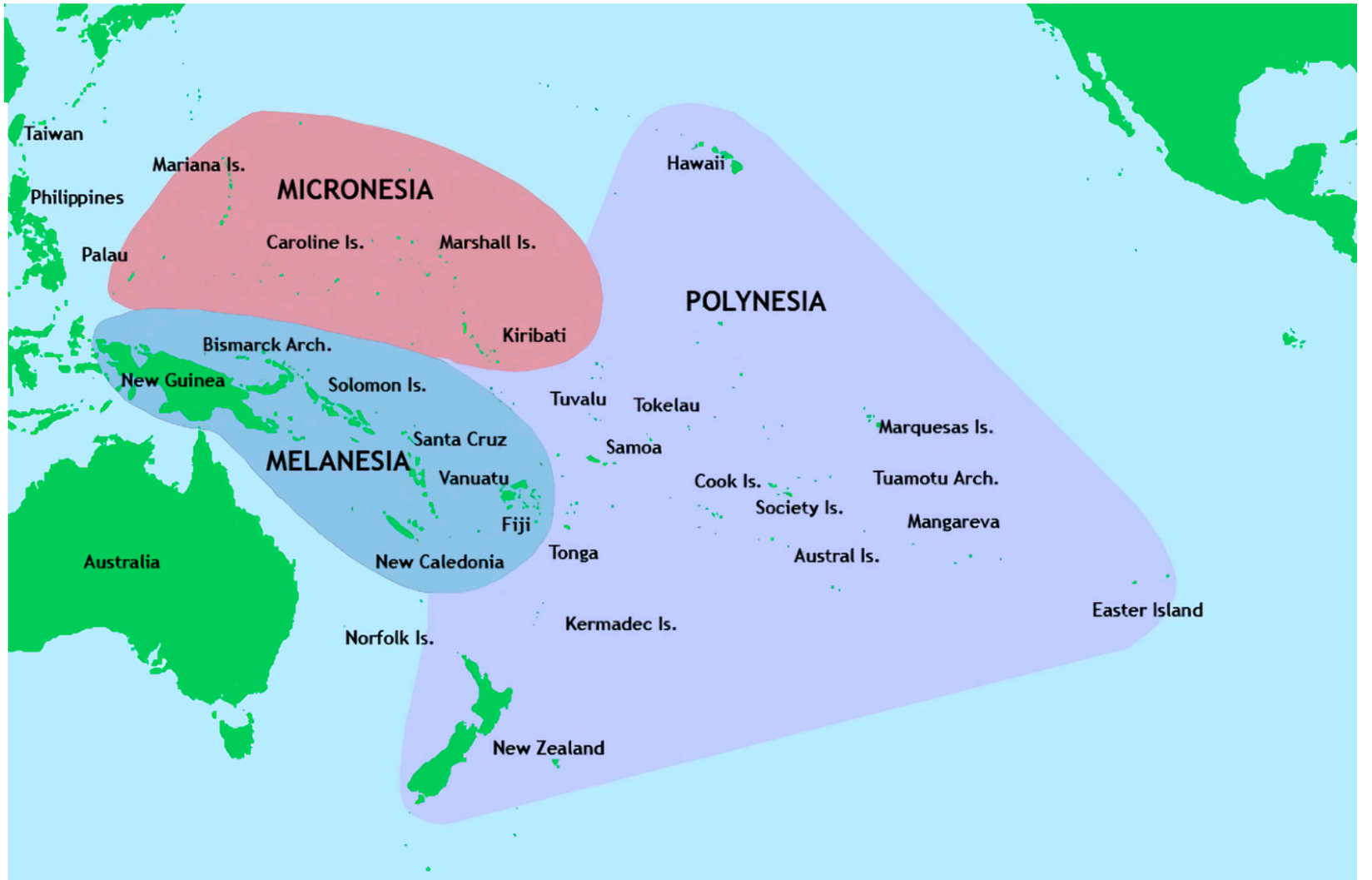


Pääbo: Denisovans (2010)

genome of an archaic hominin to about 1.9-fold coverage

Neanderthals and the Denisova individual diverged on average 640,000 years ago, and from present-day Africans 804,000 years ago.

data suggest that it contributed 4–6% of its genetic material to the genomes of present-day Melanesians



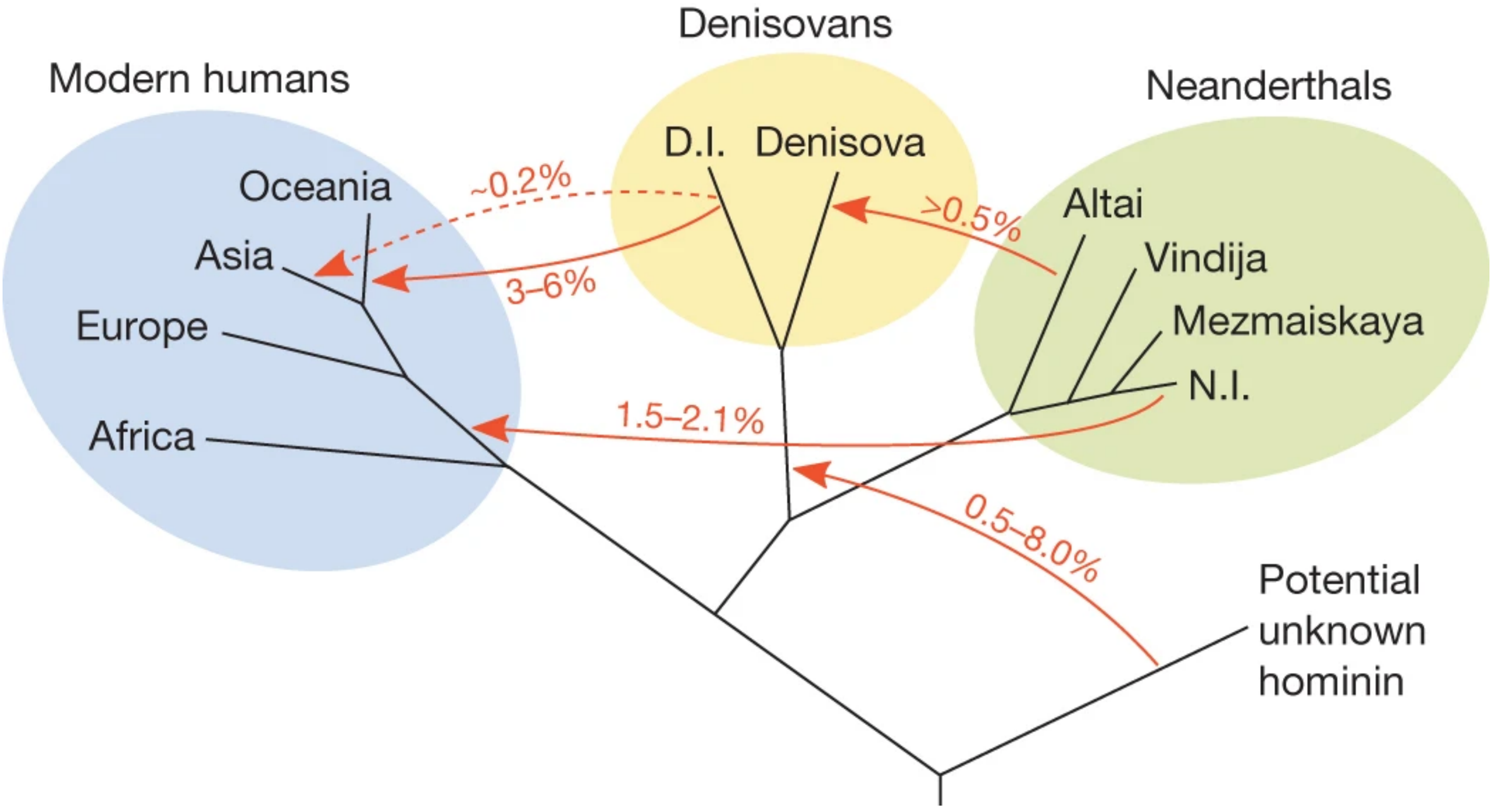
Pääbo: Neanderthal Genomic (2013)

We present a high-quality genome sequence of a Neanderthal woman from Siberia. We show that her parents were related at the level of half-siblings and that mating among close relatives was common among her recent ancestors. We also sequenced the genome of a Neanderthal from the Caucasus to low coverage.

Using the high-coverage Neanderthal genome in conjunction with the two other Neanderthal genomes, we now estimate that the proportion of Neanderthal-derived DNA in people outside Africa is 1.5–2.1%

Particularly strong signals of Neanderthal gene flow into Denisovans are found in the human leucocyte antigen (HLA) region and the CRISP gene cluster on chromosome 6 … which are involved in immunity and sperm function, respectively.

Pääbo: Neanderthal Genomic (2013)

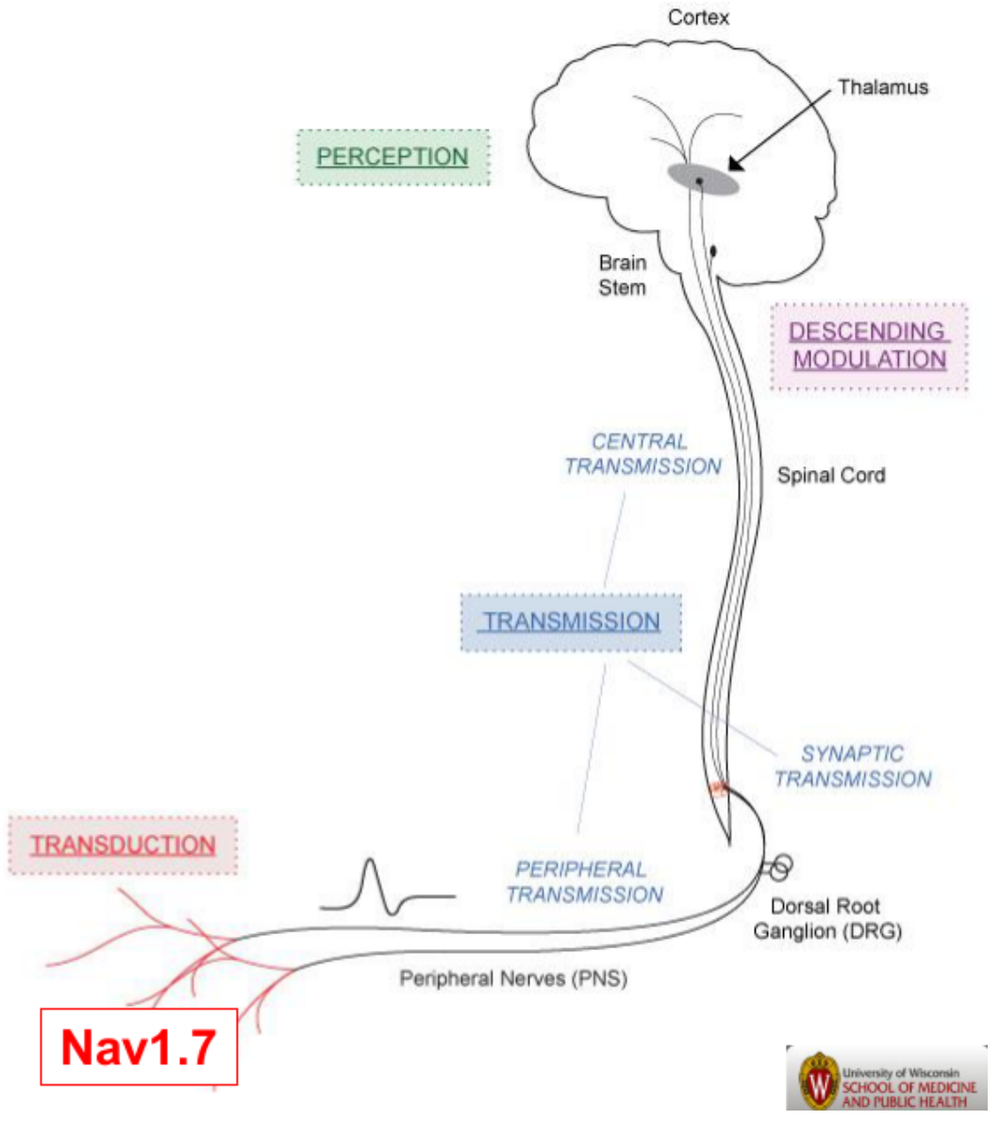


Pääbo: The Genes that Connect Us

Evolutionary geneticists found that the ancient human relatives carried three mutations in a gene encoding the protein NaV1.7, which conveys painful sensations to the spinal cord and brain

They also showed that in a sample of British people, those who had inherited the Neanderthal version of NaV1.7 tend to experience more pain than others.

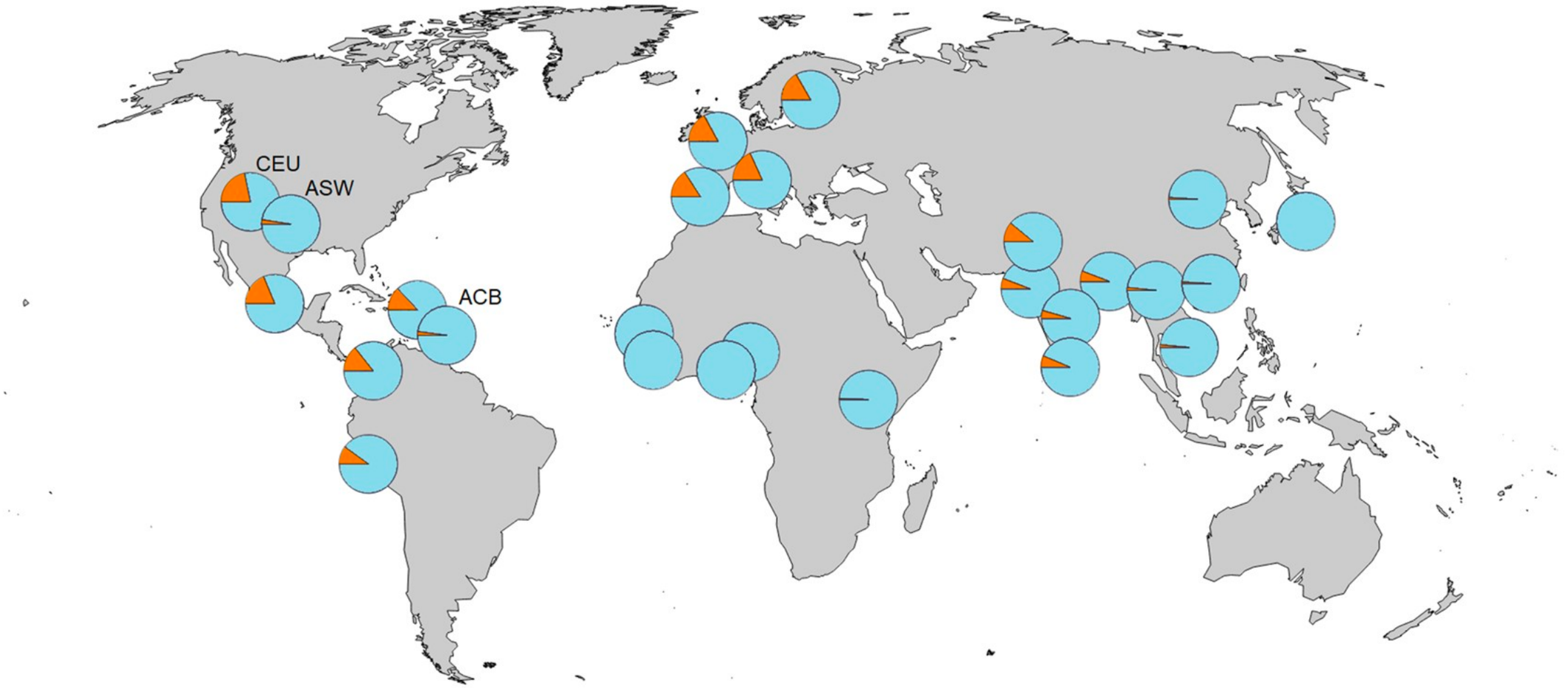
We expressed Nav1.7 proteins carrying all combinations of these substitutions and studied their electrophysiological effects. …
the full Neanderthal variant carrying all three substitutions … shows reduced inactivation



Pääbo: The Genes that Connect Us

The hormone progesterone is important for preparing the uterine lining for egg implantation and for maintaining the early stages of pregnancy.

We show that two Neandertal haplotypes carrying the PGR gene entered the modern human population and that present-day carriers of the Neandertal haplotypes express higher levels of the receptor.



Pääbo: The Genes that Connect Us

… we searched for associations between V660L polymorphism and phenotypes among 452,264 Britons in the UK Biobank using the Gene ATLAS tool.

Of 22 inpatient diagnoses related to pregnancy, childbirth and the puerperium, we find a negative association between the Neandertal allele and “hemorrhage in early pregnancy”.

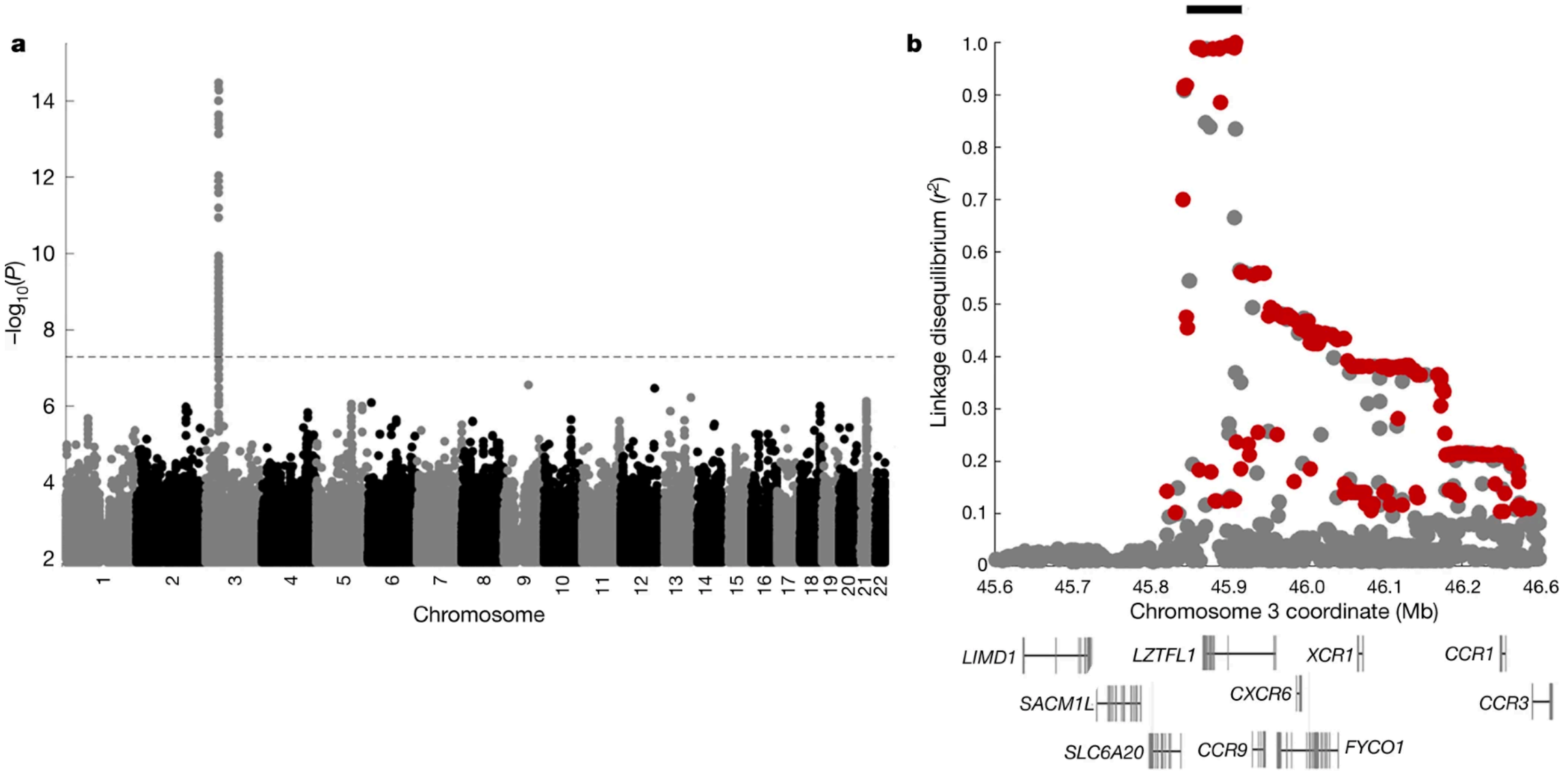
carriers of the Neandertal allele report less miscarriages

Nevertheless, individuals carrying the Neandertal V660L allele have significantly more sisters than those carrying the ancestral allele, whereas there is no difference for brothers.

(note to presenter, reflect on the biobank analyses)

Pääbo: The Genes that Connect Us

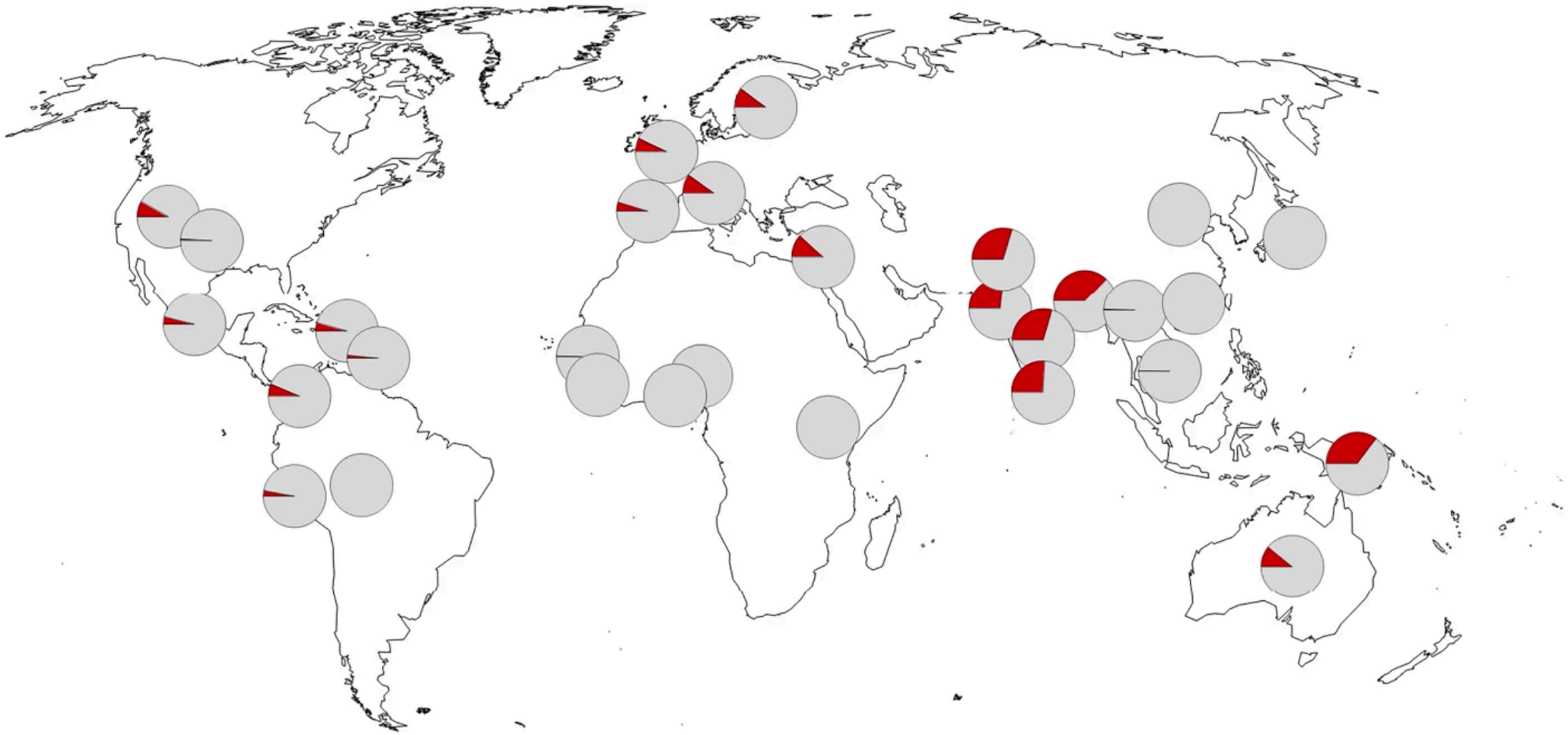
Genetic variants associated with severe COVID-19



Red circles indicate genetic variants for which the alleles are correlated to the risk variant (r2 > 0.1) and the risk alleles match the Vindija 33.19 Neanderthal genome. The core Neanderthal haplotype (r2 > 0.98) is indicated by a black bar. (note to presenter: comment on this being a **23 and me** thing)

Pääbo: The Genes that Connect Us

Geographical distribution of the Neanderthal core haplotype that confers risk for severe COVID-19.

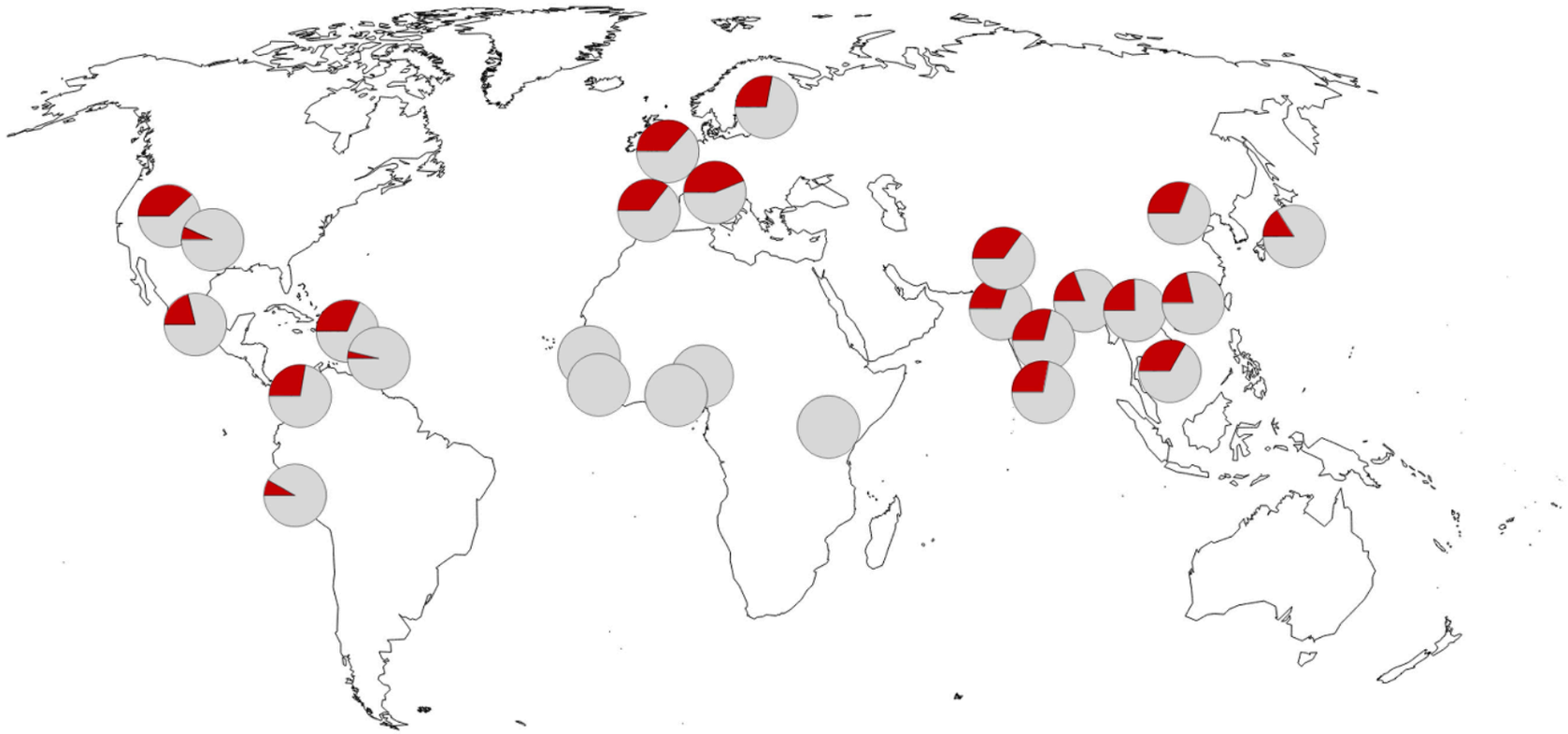


2022 follow-up: The risk-associated DNA segment modulates the expression of several chemokine receptors, among them CCR5, a coreceptor for HIV which is down-regulated in carriers of the COVID-19 risk haplotype. Here I show that carriers of the risk variant have an ~27% lower risk of HIV infection.

Pääbo: The Genes that Connect Us

Genetic variants associated with LESS severe COVID-19

Geographic distribution of the allele indicative of the Neandertal haplotype protective against severe COVID-19.

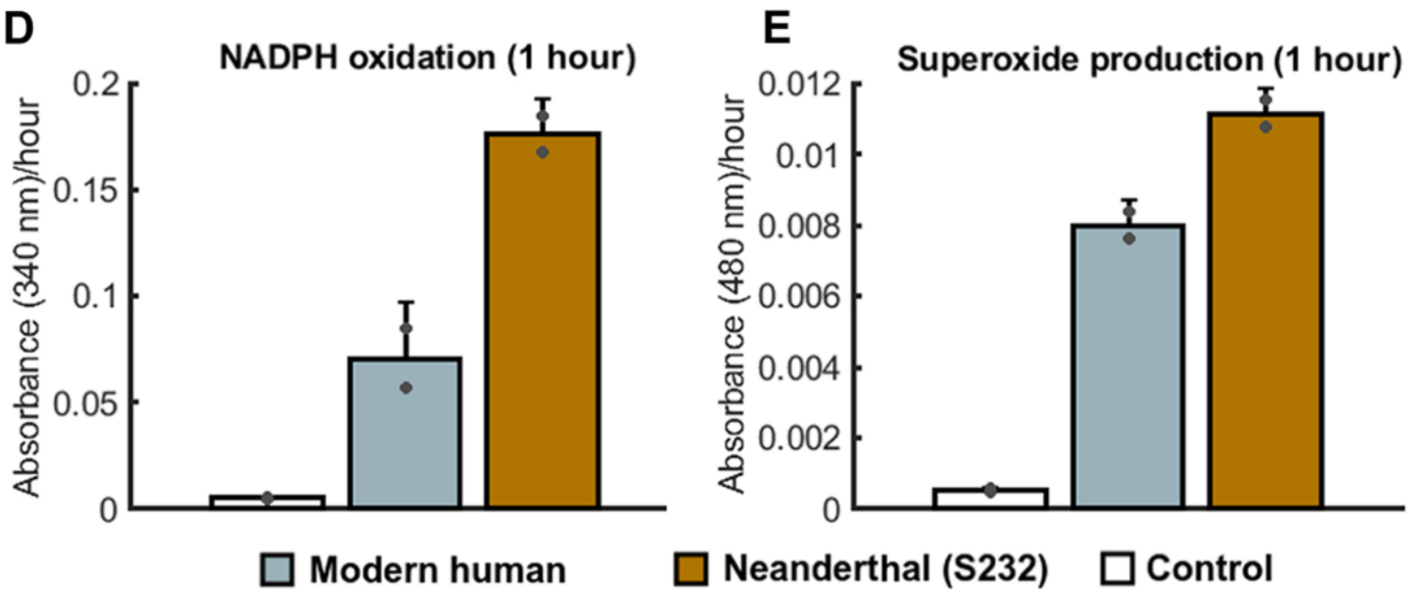


The Neandertal haplotype protective against severe COVID-19 on chromosome 12 contains parts or all of the three genes OAS1, OAS2, and OAS3, which encode oligoadenylate synthetases. These enzymes are induced by interferons and activated by double-stranded RNA. They produce short-chain polyadenylates, which, in turn, activate ribonuclease L, an enzyme that degrades intracellular double-stranded RNA and activates other antiviral mechanisms in cells infected by viruses.

Pääbo: The Genes that Define Us

Glutathione reductase is a critical enzyme for preventing oxidative stress and maintaining a reduced intracellular environment. Almost all present-day humans carry an amino acid substitution (S232G) in this enzyme relative to apes and Neanderthals.

(Fixed in humans, all had it, until breeding with Neanderthals)



the ancestral T allele occurs at a carrier frequency of
1.0 to 3.9% in Indian populations,
3.5% in Bangladeshis,
1.0% in Sri Lankan Tamils, and
1.0% in Puerto Ricans,
while it is missing in other 1000 Genomes populations

—In the Michigan Genomics Initiative cohort, we detected a single phenome-wide significant association with “Disorders involving the immune mechanism”
—We find that carriers of the Neanderthal allele have ~4 times higher numbers of“terminally differentiated effector memory cells reexpressing CD45RA” (TEMRA) … are involved in chronic immunological disorders such as graft-versus-host diseas, chronic hepatitis C infection, and inflammatory bowel disease (IBD)

Pääbo: The Genes that Define Us

The *CYP2C9* gene, which encodes the cytochrome P450 enzyme *CYP2C9*, is highly polymorphic in present-day humans.

Importantly, people with lower enzymatic activity are at risk of toxic reactions from standard doses of warfarin and phenytoin, which are substrates of the enzyme.

Approximately 50 kilobases upstream of the *CYP2C9*, is the gene *CYP2C8*, which encodes the cytochrome CYP2C8. This enzyme is a crucial part of the metabolism of several pharmacological agents.

The two variant alleles *CYP2C9*2* and *CYP2C8*3* have previously been shown to frequently co-segregate in families

Here we show that two of the most important alleles in pharmacogenetics are inherited from Neandertals. Although this knowledge itself does not change clinical practice, it explains differences observed across ancestries seen in clinical practice.

Pääbo: Summary of variants discussed

NaV1.7 — nerve receptor

PGR — progesterone receptor, pregnancy

CCR5 (indirectly) — COVID susceptibility/HIV resistance

OAS1-3 — viral defenses, COVID resistance

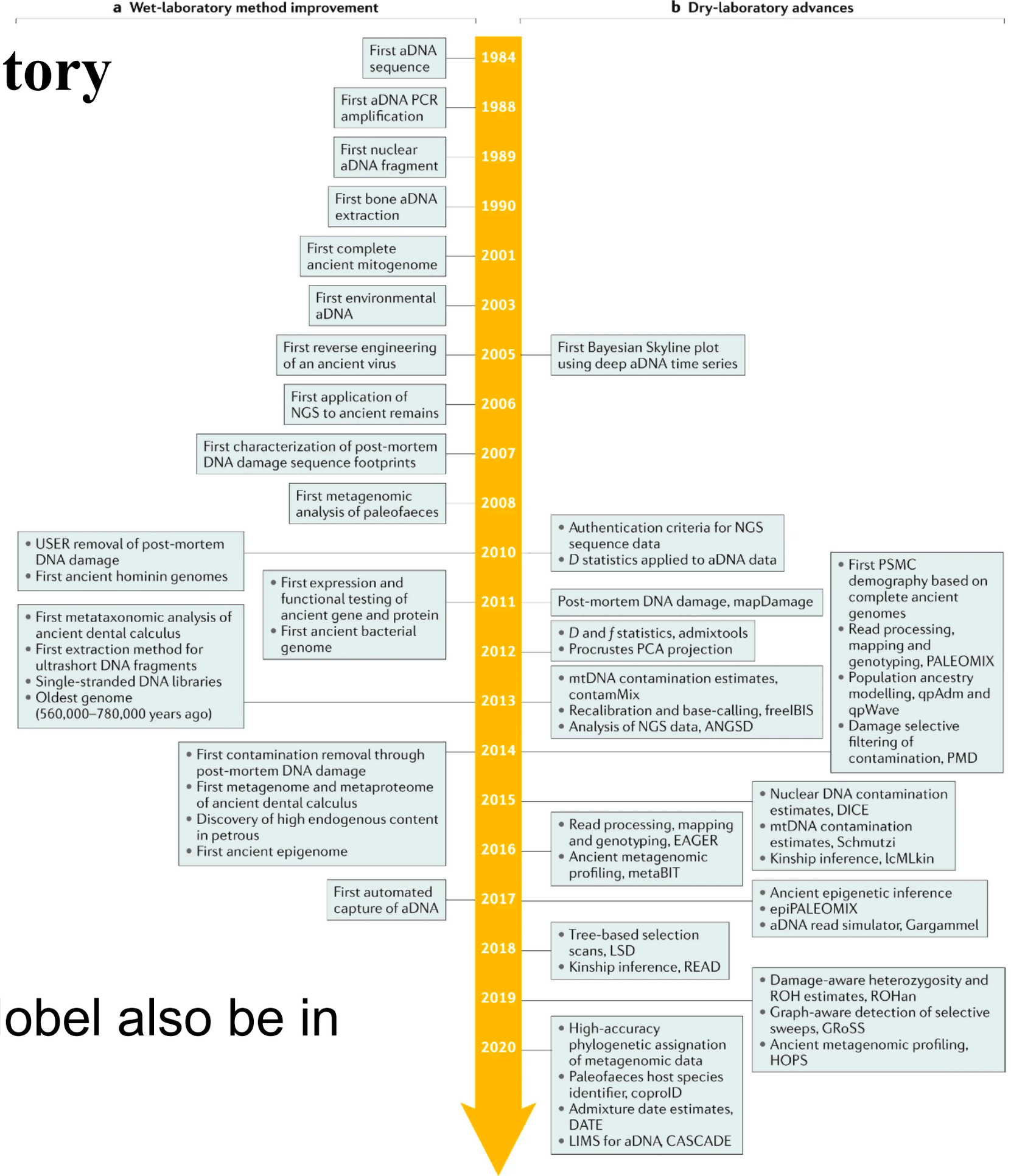
Glutathione reductase — immune and oxidative metabolism

CYP2C8 & 9 — drug metabolism

————————————————- more

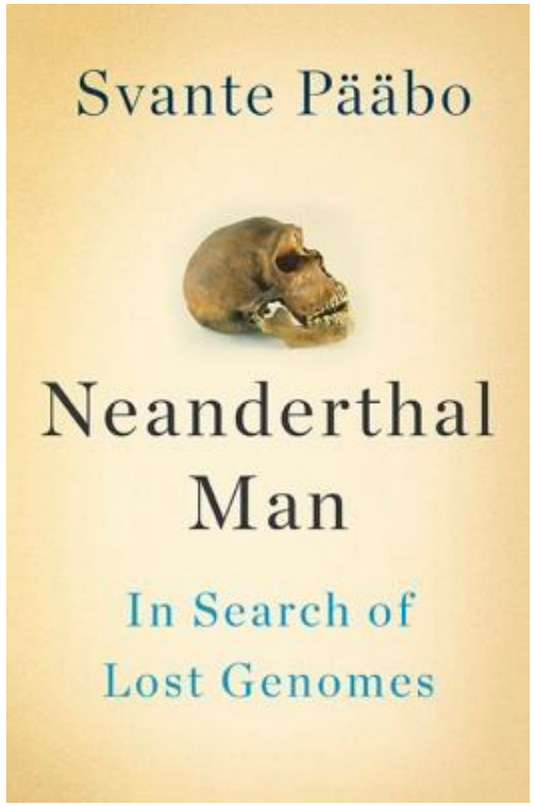
FOXP2 — TF in language/speech; *KIF18a* and *KNL1* — chromosome separation/metaphase length; *NOVA1* — development of brain organoids;

aDNA Analysis History



Could a Chemistry Nobel also be in the works?

Pääbo: Media



2014 *Neanderthal Man: In Search of Lost Genomes*

2011 *Origins of Us* (BBC series)
2015 *First Peoples* (PBS series)

Heroes of Evolution 2023