Paleogenetics, 2022

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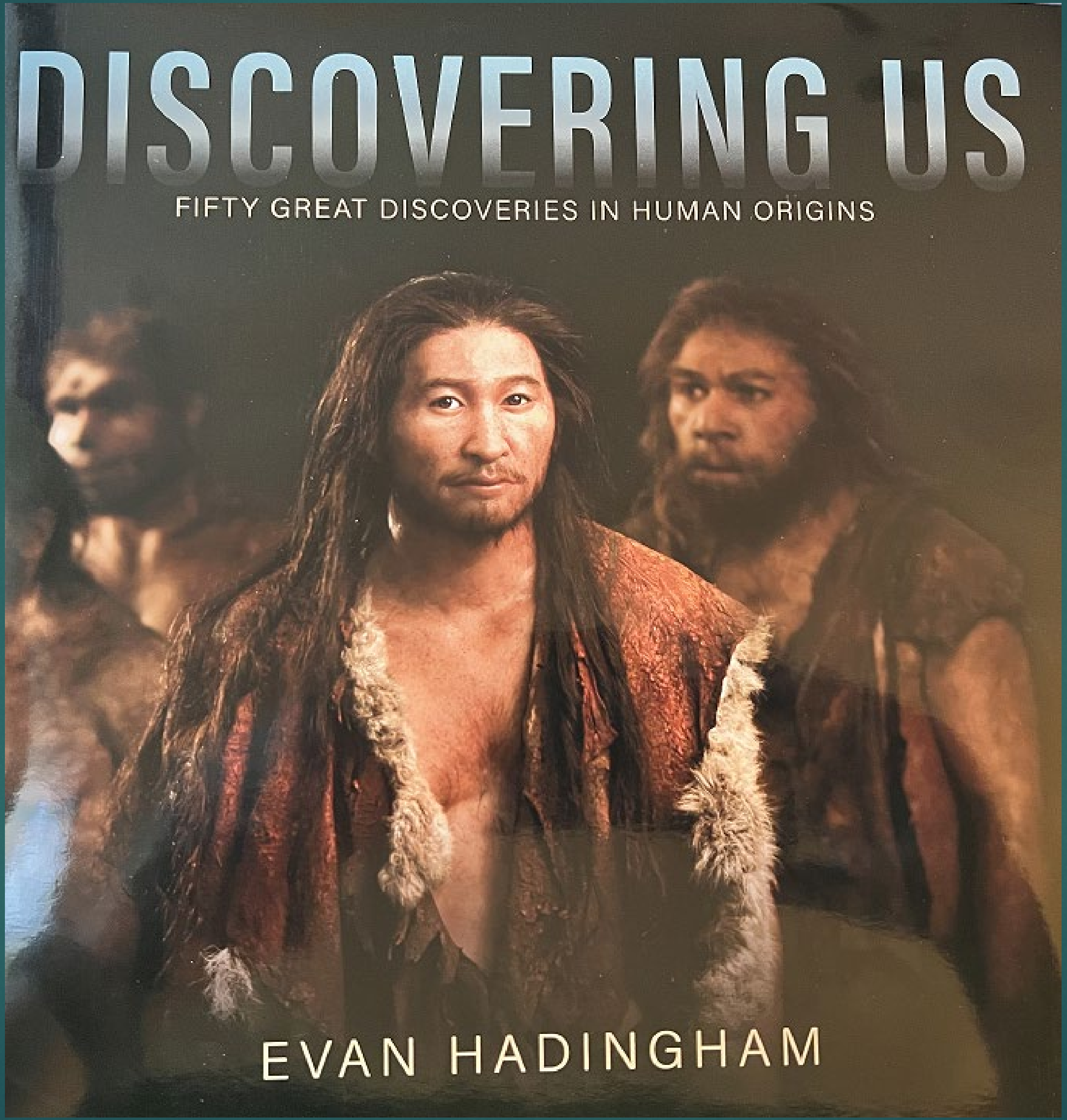
March 23 Updates

New Leakey Foundation Coffee Table Book

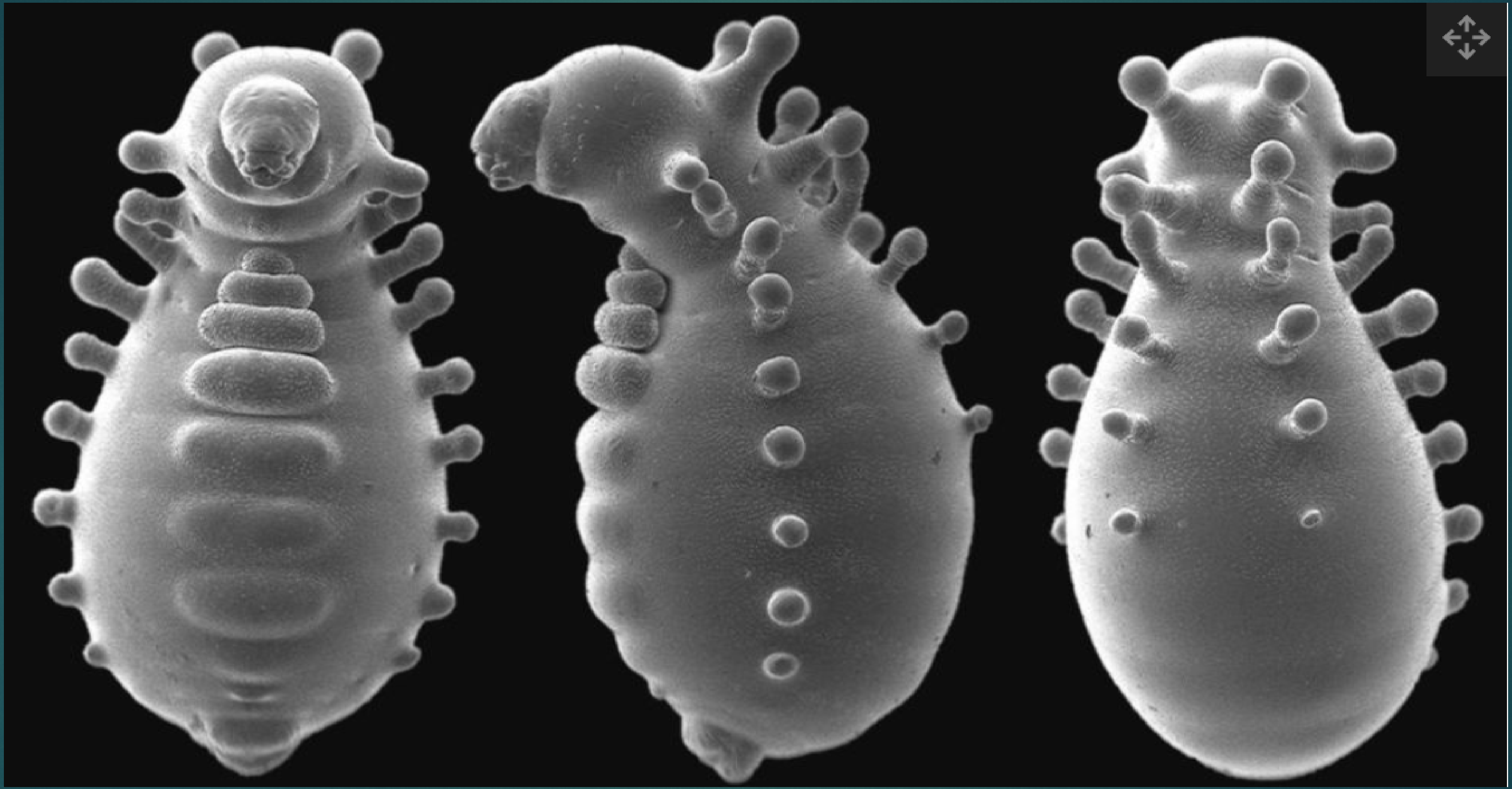


DISCOVERING US

FIFTY GREAT DISCOVERIES IN HUMAN ORIGINS

EVAN HADINGHAM

Larva of the queen ant *Monomorium triviale*



Massive Beringia Ice Wall

- There are two main hypotheses as to how people first migrated to North America.
  - The older idea suggested that people made this journey when Beringia — the landmass that once connected Asia with North America, now divided by the Bering Strait — was relatively free of ice.
  - The more recent theory suggested that travelers made their way on watercraft along the Pacific coasts of Asia, Beringia and North America.
- New study: An icy barrier up to 300 stories high — taller than any building on Earth — may have prevented the first people from entering the New World over the land bridge that once connected Asia with the Americas.
- These findings suggest that the first people in the Americas instead arrived via boats along the Pacific coast.

Ice Wall

- Based on stone tools dating back as much as 13,400 years, archaeologists had long suggested that Clovis people were the first to migrate from Asia to the Americas. Prior work regarding the age of the ice-free corridor suggested it might have served as the migration route for Clovis people.
- in 2021, 60 ancient footprints in New Mexico suggested humans were there about 23,000 years ago, and in 2020, archaeologists discovered stone artifacts in central Mexico that were at least 26,500 years old.
- Recent estimates suggested the ice-free corridor did not open until about 14,000 to 15,000 years ago, which would mean that the earliest Americans may have relied on a coastal route instead of an overland one.

Ice Wall

- New investigation of 64 geological samples taken from six locations spanning 745 miles (1,200 kilometers) along the zone where the ice-free corridor was thought to have existed.
- Examined boulders that glaciers once carried far from their original homes, much as rivers might wash pebbles down riverbeds over time. They analyzed how long these rocks were exposed on Earth's surface — and thus how long they sat on ice-free ground
- The new findings suggest that the ice-free corridor did not fully open until about 13,800 years ago, and the ice sheets "may have been 1,500 to 3,000 feet (455 to 910 m) high in the area where they covered the ice-free corridor. Compare: the tallest building in the world, the Burj Khalifa in Dubai, stands about 2,722 feet (829.8 m) high.

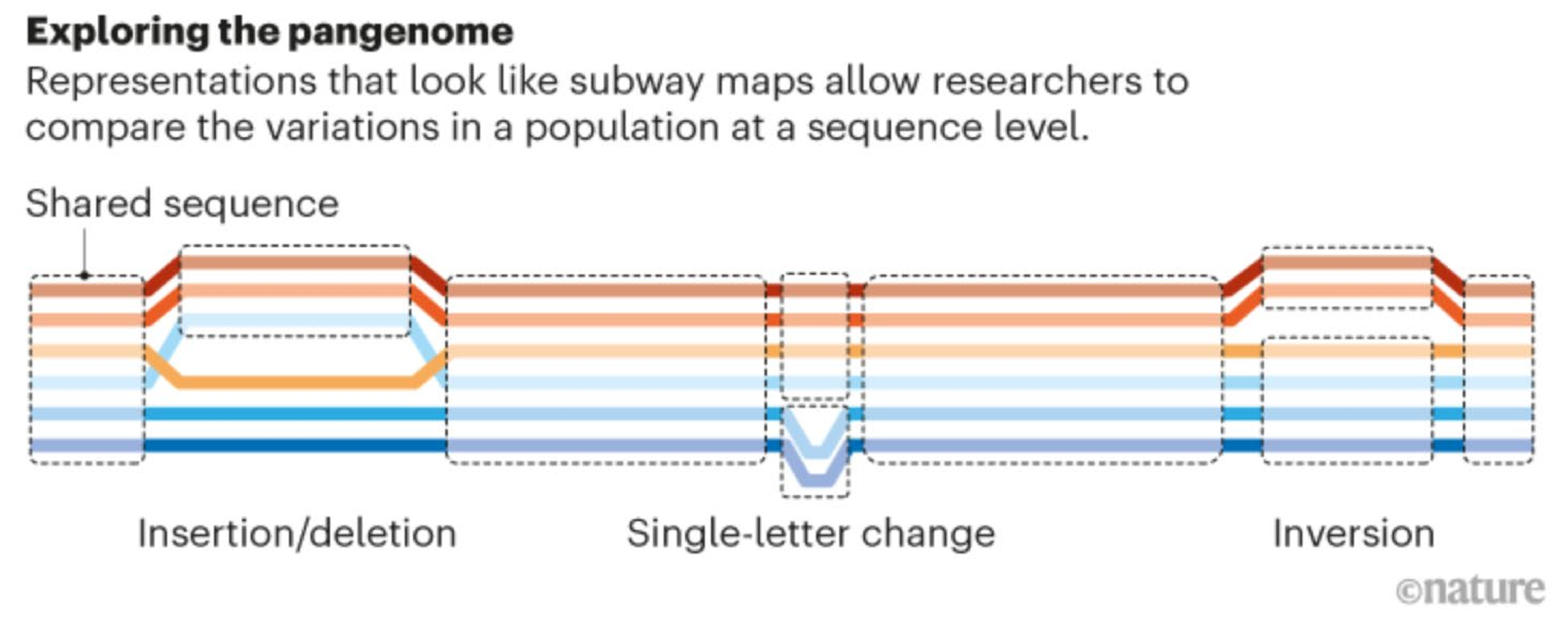
Human Pangenome Project

- Evan Eichler, a geneticist at the University of Washington in Seattle, and his colleagues spotted a massive stretch of DNA, about 400,000 letters long, that contained extra copies of Denisovan genes. This DNA stretch appeared in about 80% of people living in Papua New Guinea, but practically nowhere else.
- Human Genome Project, reference genome, known as GRCh38; 93% of its sequence came from just 11 individuals (recruited through a newspaper advertisement in Buffalo, New York); a whopping 70% of the DNA comes from just one man.
- Genome maps still don't adequately capture humanity's vast diversity.
- For example, in 2018, one group of researchers sequenced 910 individuals of African descent and discovered a sequence consisting of 300 million DNA letters, or bases, that was unknown. That's roughly 10% of the entire genome.

Human Pangenome Project

- Human Pangenome Project: New attempt to capture almost all human genetic variability; would represent the varieties of sequence that can be found in different populations; currently evaluating 350 genomes
- Using ‘long-read sequencing’, which analyses bigger stretches of DNA at a time.
- Recent study: first telomere-to-telomere genome sequence corrected numerous errors from previous references and uncovered around 100 unnoticed genes that probably code for proteins.

Human Pangenome Project: population genetic variations



Exploring the pangenome

Representations that look like subway maps allow researchers to compare the variations in a population at a sequence level.

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History of gene studies: Gene stars come and go

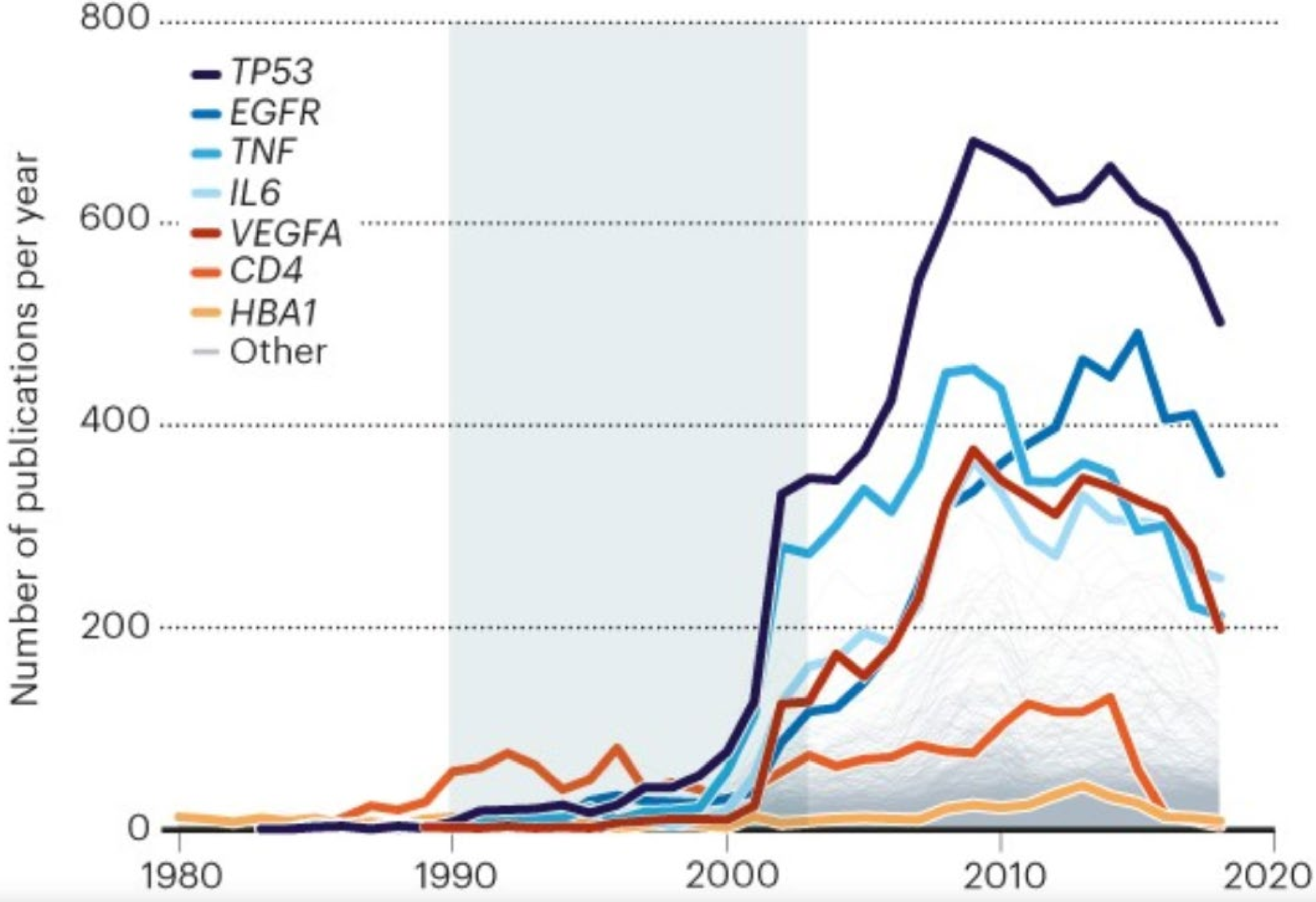
- Before the mid-1980s, for example, much genetic research centered on hemoglobin, the oxygen-carrying molecule found in red blood cells. More than 10% of all studies on human genetics before 1985 were about hemoglobin in some way.
- *HBB* Hemoglobin subunit beta and related genes were among the first to be linked to hereditary diseases such as sickle-cell anemia.
- *CD4* This T-cell receptor protein became in vogue owing to its role in HIV infection.
- *GRB2* Growth factor receptor-bound protein 2 helped launch the field of signal transduction (cellular communication).
- *TP53 A cancer repressor, the* ‘guardian of the genome' is the most studied gene (and protein) of all time.
- *APOE* Apolipoprotein E briefly interrupted TP53’s reign owing to its role in cholesterol metabolism and Alzheimer's disease.

Historical focus on just a few genes

- Interest has focused largely on just a few genes.
- Before 1990, *HBA1* was the most studied because it encodes one of the proteins in adult hemoglobin, and involved in sickle cell disease.
- From 1990, attention then shifted to *CD4* (based on the cumulative number of publications) given the protein's involvement in T-cell immunity and as the cell receptor for HIV.
- Yet the interest in these two genes pales next to the explosion of attention on individual genes following the draft 2001 HGP sequence.
- Some superstar genes, including *TP53*, *TNF* and *EGFR*, became the subject of hundreds of publications a year, with most other genes receiving scant attention
- We find that, by 2017, 22% of gene-related publications referenced just 1% of genes.

Star genes

The HGP gave rise to an explosion in research concentrated on just a few genes.



The ten most studied genes of all time are described in more than 40,000 papers – 6 of 10 related to cancer research

TP53	9,232 papers	Tumor suppressor; mutated in 50% of cancers
TNF	5,314	Tumor necrosis factor
EGFR	4,583	Epidermal growth factor mutated in drug-resistant cancers.
VEGFA	4,059	Vascular endothelial growth factor (cancer growth)
APOE	3,977	Cholesterol metabolism – Alzheimer's
IL6	3,930	Interleukin 6 -- roles in immunity
TGFB1	3,715	Transforming growth factor beta 1: cell proliferation/differ
MTHFR	3,256	Processes amino acids
ESR1	2,864	Breast cancer
AKT1	2,791	Activation of proteins

Genes: only select few are studied

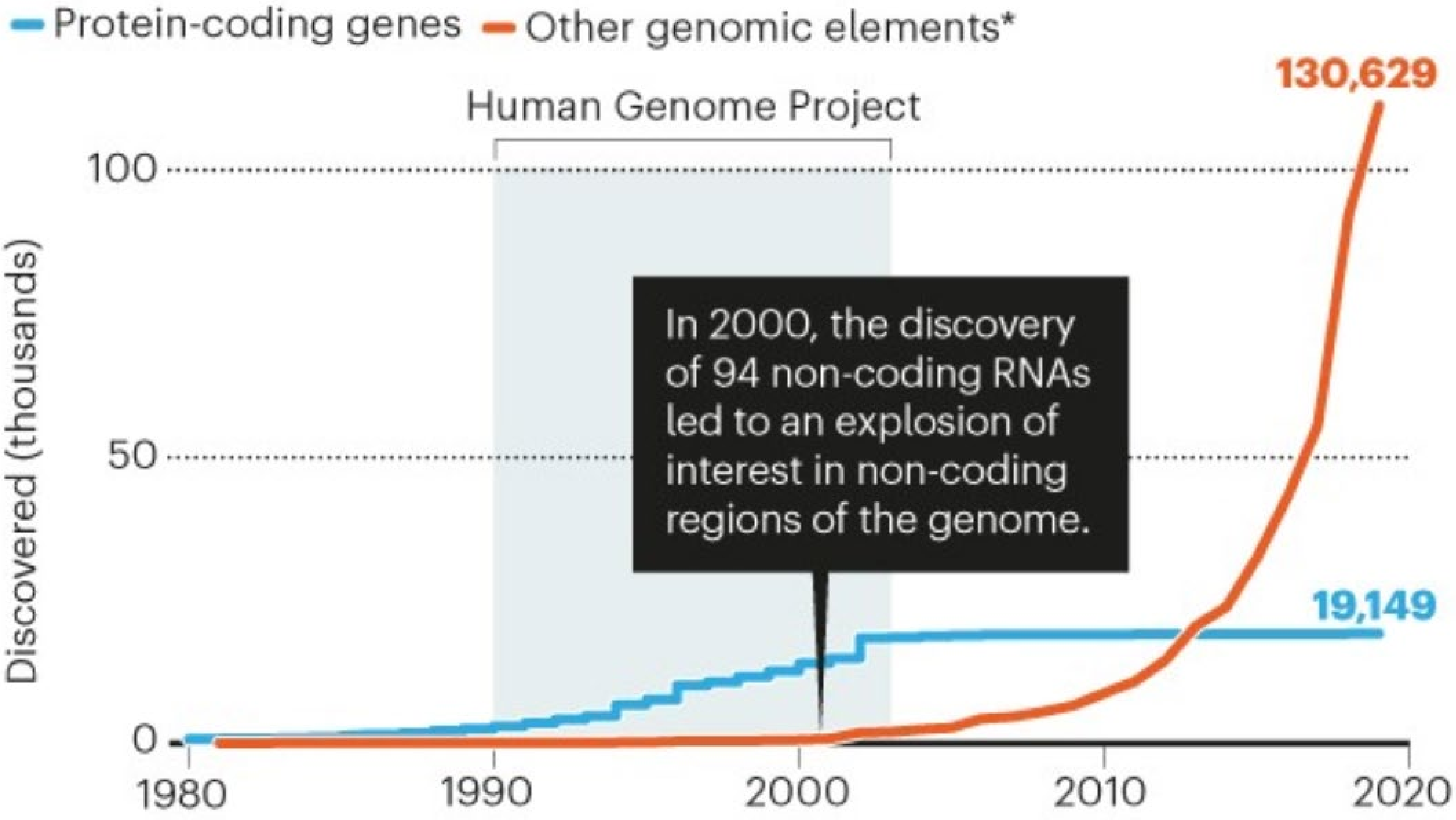
- Long story The gene TP53 on chromosome 17 was discovered in 1979. Associated with most cancers, it has since accumulated 9,232 publications. Leads to cancer when inactivated or altered. It is mutated in roughly half of all human cancers. Variations in this gene are found in more than 50% of tumor sequences. Two papers about it are published each day. The gene is a tumor suppressor, and widely known as the 'guardian of the genome'.
- Continued TP53 work because it is a safe bet. In network science, this phenomenon is called preferential attachment. Indeed, we find that the number of new yearly publications focusing on a given gene is linearly proportional to the size of previous literature on it
- The gene ADRA1A is targeted by 99 different drugs, 5% of all those approved. It is the subject of just 130 publications.
- TNF is associated with 160 known diseases, the most of any gene.

Should junk DNA (dark matter of the genome) be studied?

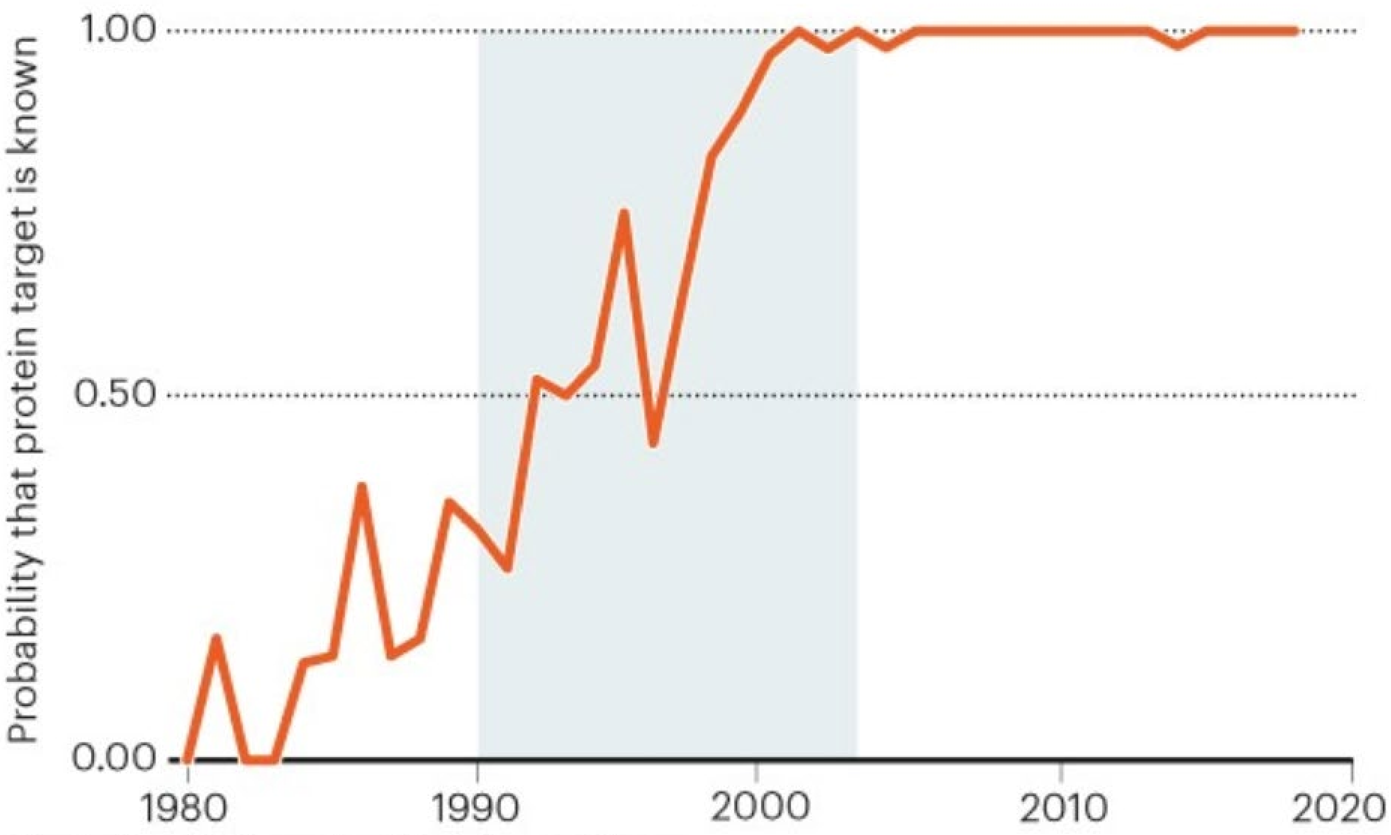
- The majority of functional sequences in the human genome do not encode proteins.
- Rather, elements such as long non-coding RNAs, promoters, enhancers and countless gene-regulatory motifs work together to bring the genome to life. Variation in these regions does not alter proteins, but it can perturb the networks governing protein expression.
- There are now thousands of papers on non-coding RNAs, which regulate gene expression.
- More than 30,000 papers per year linking SNPs and traits.
- Most of these associations are in the once-dismissed non-coding regions. more than 300,000 regulatory network interactions have been charted — proteins binding with non-coding regions or with other proteins.

Non-coding elements

Most protein-coding genes were discovered before the first draft of the Human Genome Project (HGP) in 2001. Many other genomic elements, previously called junk DNA, came in for scrutiny after that.



In 2000, the discovery of 94 non-coding RNAs led to an explosion of interest in non-coding regions of the genome.



Drug targets

Since 2001, nearly 100% of US drugs licensed in any given year have had all their potential protein targets identified.

*Including single nucleotide polymorphisms, pseudogenes, non-coding RNAs, promoters and so on.

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Drug targets

- Of the roughly 20,000 proteins revealed by the HGP as potential drug targets, only about 10% — 2,149 — have so far been targeted by approved drugs.

- That leaves 90% of the proteome untouched by pharmacology

- Five per cent of all approved drugs currently approved (99 distinct molecules) target the protein ADRA1A, which is involved in cell growth and proliferation.

- That said, the majority of successful drugs do not directly target individual disease genes. Instead, they target proteins one or two interactions away, modulating the consequences of faulty components.

Australian Magpie: a smart corvid

Australian Magpies: Escape artists

- The Australian magpie is one of the cleverest birds on earth. It has a beautiful song of extraordinary complexity, with more than 300 separate elements,. It can recognize and remember up to 30 different human faces.
- Magpies' latest mischief has been to outwit the scientists who would study them.
- Researchers took 6 months to develop undetachable tracking devices and then attached them to 5 magpies. Within three days, the magpies had removed all five devices.
- "Altruistic rescue behavior" — where birds help other birds without receiving tangible benefits in return
- Exhibited a special combination of helping but also problem solving, of being really social and having this cognitive ability to solve puzzles.

Why leaded gas was banned in 1996: Lower IQ in children

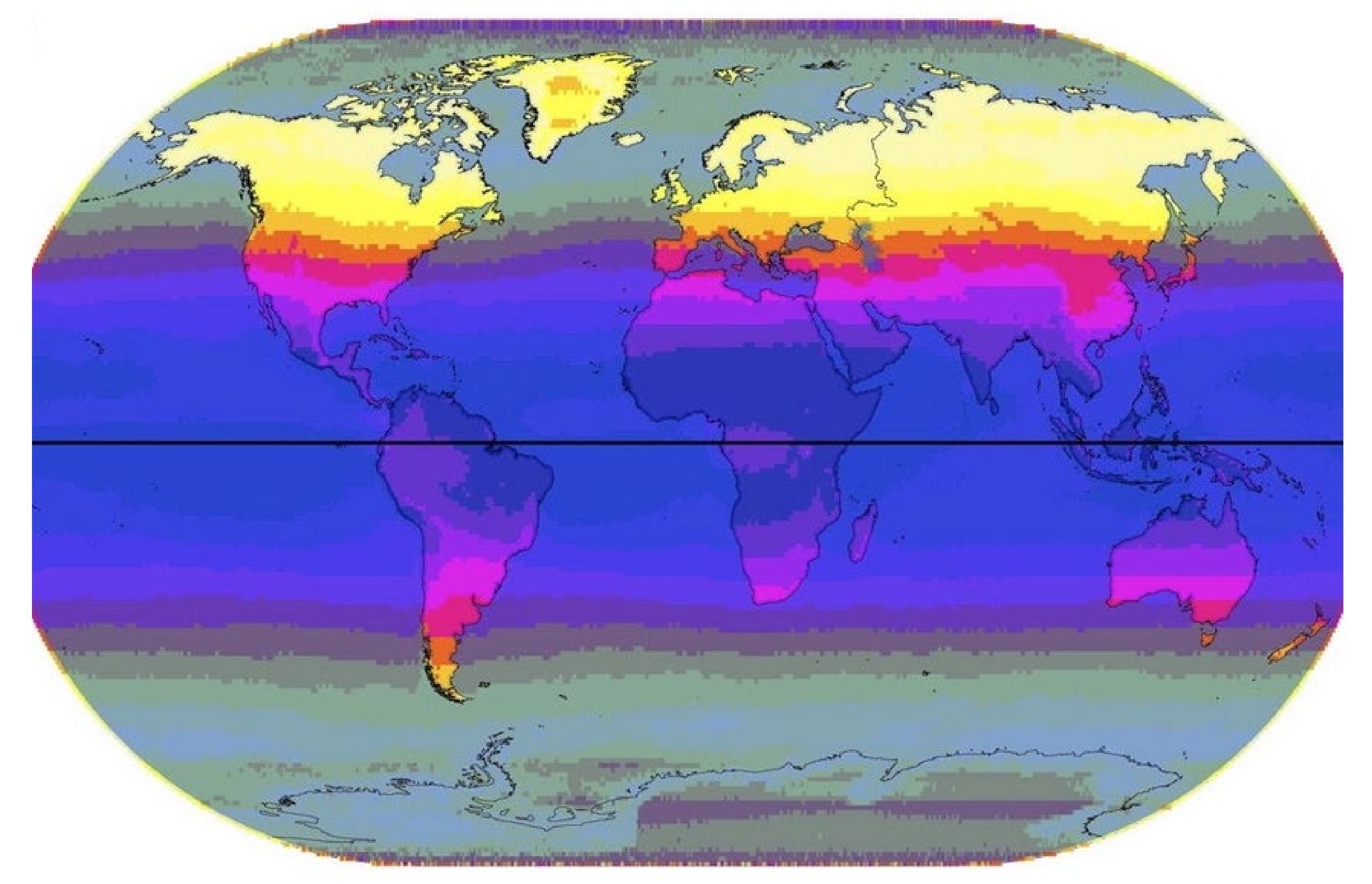
- Study: 170 million people in US have slightly diminished IQ due to leaded gas fume inhalation as children.
- Effect worse among those born in 1960s and 1970s, when leaded gas was at its peak.
- Known effect of lead exposure on IQ in children: An increase in blood lead from 10 to 20 micrograms/dl is associated with a decrease of 2.6 IQ points
- Analysis of 11,600 children aged from1 to 5 from blood samples taken from 1976 to 2016; estimated blood lead levels from 1940 to 1975
- Results: half current US population had elevated blood levels as children; estimate that this caused IQ drop of 2.6 points; for those born in mid to late 1960s, 5.9 point drop

Oldest mummies in the world

Oldest mummies: Portugal, 8000 years old

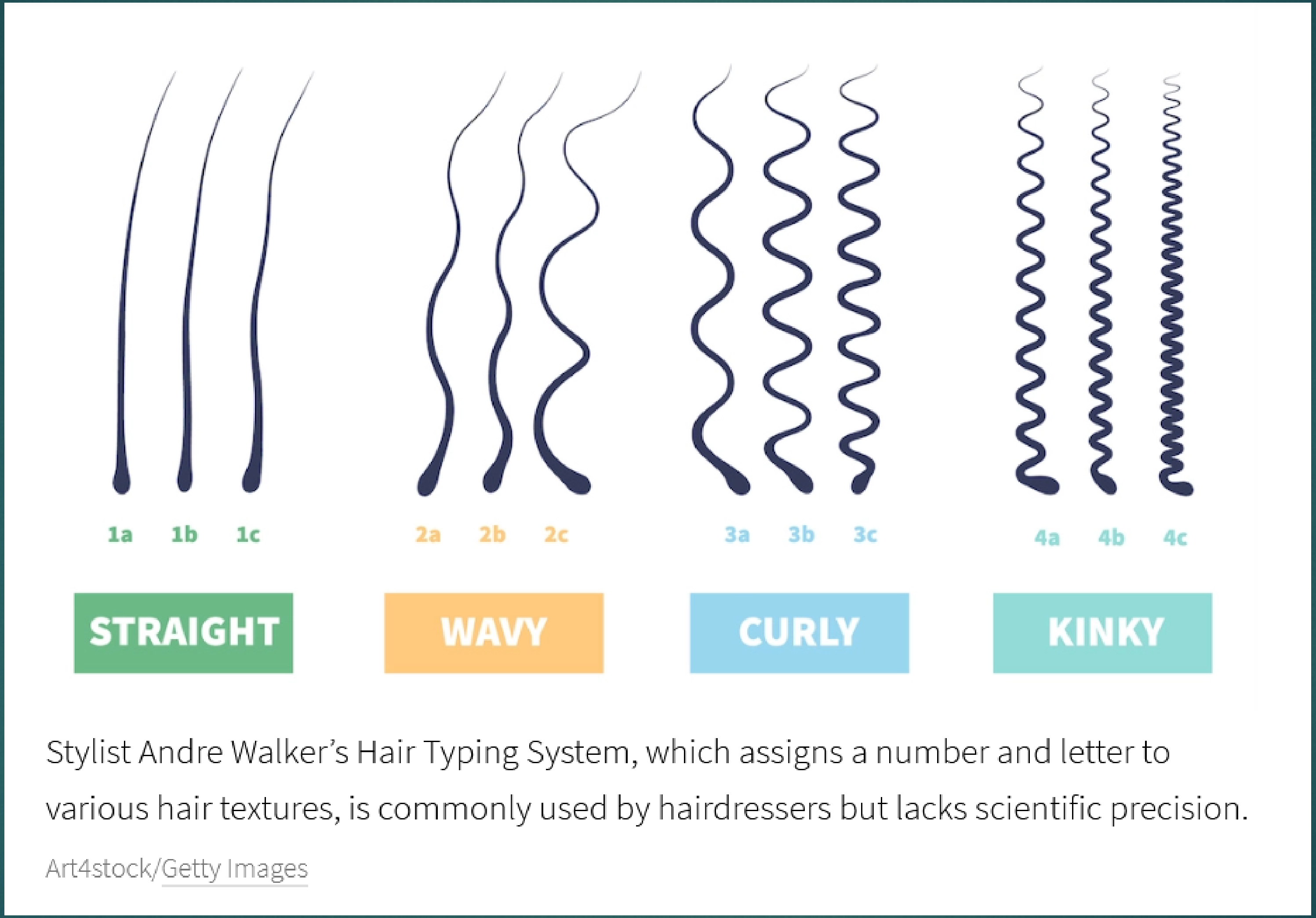
- Roughly 60 years ago, an archaeologist snapped photos of several skeletons buried in 8,000-year-old graves in southern Portugal. Now, a new analysis of these previously undeveloped photos suggests that the oldest human mummies don't hail from Egypt or even Chile, but rather Europe.
- More than a dozen ancient bodies were found in Portugal's southern Sado Valley during excavations in the 1960s, and at least one of those bodies had been mummified, possibly to make it easier to transport before its burial, researchers said after analyzing the images and visiting the burial grounds.
- Identified mummification in skeletal remains
- Suggestions of 10,000-year-old mummifications had been found at El Wad and Ain Mallaha in Israel, and there were signs of mummifications 30,000 years ago at Kosteni in Belarus.

Levels of ultraviolet radiation from the sun are highest around the equator



This created strong evolutionary pressure for humans living near this region to increase production of melanin, which protects skin and hair from UV rays.

Hair types: Oprah's Hair stylist created this



Stylist Andre Walker's Hair Typing System, which assigns a number and letter to various hair textures, is commonly used by hairdressers but lacks scientific precision.

Art4stock/Getty Images

Race

- In apartheid-era South Africa, authorities developed a pencil test to determine someone's race. They placed a pencil in a person's hair, and if it stayed in place due to their tight curls, they were classified as "Native" (Black) or "Colored" on their identity documents and segregated accordingly.
- Today the concept of race is recognized as not having any basis in biology but is entirely a cultural construct—one that has led to genocide, massacres, severe exploitation, and other human rights abuses.
- Hair and skin color are still often used as proxies for race.
- Only a few studies over the past six decades that quantitatively look at hair diversity.

Curly hair

- The most obvious, racialized, and quantifiable quality of hair is hair curvature or straightness.
- Just as melanated skin protects against UV rays, tightly curled hairs also protect humans from the sun.
- Tight curls create lofted, airy ventilation structures for the head, allowing it to breathe while providing extra protection from solar radiation

Race Is Real, But It's Not Genetic

- Example: The view that black people don't need a bone density test is a longstanding and common myth.
- FRAX, a widely used calculator that estimates one's risk of osteoporotic fractures, is based on bone density combined with age, sex, and, yes, "race." because "blacks do not get osteoporosis."
- Humans share the vast majority (99.9%) of our DNA in common.
- Race is a purely sociopolitical construction with powerful consequences.

Alan Goodman

Race

- When medical professionals or researchers look for a *genetic* correlate to "race," they are falling into a trap:

- They assume that geographic ancestry, which does indeed matter to genetics, can be conflated with race, which does not.

- Sure, different human populations living in distinct places may statistically have different genetic traits—such as sickle cell trait but such variation is about *local populations* (people in a specific region), not race.

Race and genetics

- Race does not describe human genetic variation.
- In 1972, Richard Lewontin had the idea to test how much human genetic variation could be attributed to “racial” groupings. Only about 6 percent of genetic variation in humans could be statistically attributed to race categorizations.
- The variation between any two individuals is *very* small, on the order of one single nucleotide polymorphism (SNP), or single letter change in our DNA, per 1,000. That means that racial categorization could, at most, relate to 6 percent of the variation found in 1 in 1,000 SNPs. Put simply, race fails to explain much.
- Genetic variation can be greater *within* groups that societies lump together as one “race” than it is between “races.” 0.88 per 1,000 nucleotides

Race: Location is what is important

- On average, two individuals in Africa are *more* genetically dissimilar from each other than either one of them is from an individual in Europe or Asia.

- Genetic variation across Europe and Asia, and the Americas and Australia, is essentially a subset of the genetic variation in Africa.

- What all these data show is that the variation that scientists think is “race” is actually much better explained by a population’s *location*.

Race and geography

- Genetic variation is highly correlated to geographic distance. Ultimately, the farther apart groups of people are from one another geographically, and, secondly, the longer they have been apart, can together explain groups' genetic distinctions from one another.

- Compared to "race," geographic factors better describe human variation; they invoke evolutionary processes to explain variation.

“If race is not real, explain sickle cell anemia to me.”

- Sickle cell is a genetic trait: It is the result of an SNP that changes the amino acid sequence of hemoglobin, the protein that carries oxygen in red blood cells.
- When someone carries two copies of the sickle cell variant, they will have the disease.
- In the United States, sickle cell disease is most prevalent in people who identify as African American, creating the impression that it is a “black” disease.
- It is common in West-Central Africa but also parts of the Mediterranean, Arabian Peninsula, and India.
- Globally, it does not correlate with continents or socially defined races.

Sickle Cell Disease and Malaria

- Correlated with places with a long history of agriculture and endemic malaria have a high prevalence of sickle cell trait (a single copy of the allele).
- Sickle cell trait helped people resist malaria. Evolution and geography, not race, explain sickle cell anemia.
- See American Association of Physical Anthropologists' Statement on Race & Racism: https://physanth.org/about/position-statements/aapa-statement-race-and-racism-2019/

Venus of Willendorf

The original Venus from Willendorf. Left: lateral view. Right-top: hemispherical cavities on the right haunch and leg. Right bottom: existing hole enlarged to form the navel. All images by Lois Lammerhuber[4].

Long-Unknown Origins of the Venus of Willendorf

- Mystery of the origins of the famous Venus of Willendorf, the famed 30,000-year-old figurine that was found in 1908 at a Paleolithic site in lower Austria.
- The work was made from oolitic limestone and painted red, possibly with ochre, which was almost entirely removed by the time of discovery. Oolitic limestones are otherwise absent in and around Willendorf,
- The material used in the Venus most likely originates from a region in Northern Italy around 400 miles away. This marks the first time the geologic origins of the object have been confirmed with such specificity.
- Indicates considerable mobility of Gravettian people and long-time transport of artifacts from South to North by modern human groups before the Last Glacial Maximum."

Stonehenge: A Calendar

Stonehenge

- Stonehenge has long been thought to be an ancient calendar due to its alignment with the summer and winter solstices, but exactly how the calendar system worked was a mystery.
- New analysis shows that it could have functioned like the solar calendar used in ancient Egypt, based on a year of 365.25 days, with each of the stones of the large sarsen circle representing a day within a month.
- It's a perpetual calendar that recalibrates every winter solstice sunset. This would have enabled the ancient people who lived near the monument in what is now Wiltshire, UK, to keep track of days and months of the year.

Stonehenge

- Recent discovery in 2020 that most of the sarsen stones were quarried from the same location 25 kilometers away, and were placed at Stonehenge at around the same time.
- The sarsens were arranged in three different formations at Stonehenge around 2500 BC: 30 formed the large stone circle that dominates the monument, 4 "station stones" were placed in a rectangular formation outside this circle, and the rest were constructed into 5 trilithons – consisting of two vertical stones with a third stone laid horizontally across the top like a lintel – located inside the stone circle.
- 30, 5 and 4 are interesting numbers in a calendrical kind of sense. Those 30 uprights around the main sarsen ring at Stonehenge would fit very nicely as days of the month. Multiply that by 12 and you get 360, add on another 5 from the central trilithons you get 365.
- To adjust the calendar to match a solar year, the addition of one extra leap day every four years is needed, and Darvill thinks that the four station stones may have been used to keep track of this.

Genetic Bottlenecks in MHs

- MHs lost much of their genetic diversity in two dramatic bottlenecks that sharply squeezed down the population of modern humans as they moved out of Africa between 60,000 and 50,000 years ago.
- Africans are the most genetically diverse people in the world.
- Humans outside of Africa are missing many genetic variants found only in Africans and, indeed, the farther a group lives from Africa, the less diversity it has in its genes and morphological traits, including skull shape.

Genetic Bottlenecks in MHs

- Genetic diversity is usually considered a good thing: the more a population has, the more likely individuals will have gene variants that will help them adapt better to new climates, diets, and life-threatening diseases, such as malaria or smallpox.

- Many scientists have suggested that those who left Africa went through a bottleneck, where only a small number of individuals had offspring, thus reducing genetic diversity.
- But until recently, little research has been done to pinpoint how that diversity was lost.

Bottlenecks: two models

- One model proposes that genetic diversity was lost in two distinct bottlenecks,
  - One, where groups of migrating people were quickly decimated by disease, starvation, warfare, or some other cause, dramatically reducing the number of adults who bore children that survived.
  - Another model suggests that genetic diversity was reduced gradually in a stepwise fashion as an initial group of about 100,000 or so people moved out around the globe, gradually leaving behind more and more people in settlements along the way.
- With the recent publication of a large data set of 763 microsatellite markers--short stretches of DNA that are repeated in the genome--from 53 populations in the Human Genome Diversity Project: able to test both models.

Bottlenecks: two models

- Using a software program called BOTTLENECK, the two searched for the signature of bottlenecks or founder effects in each population to see if the loss of diversity occurred suddenly or gradually as adjacent populations moved farther from Africa.
- Different genetic markers of diversity decline at different rates, creating an imbalance. The larger the imbalance, the stronger the evidence of a bottleneck.
- The team uncovered strong signs of this imbalance between rare alleles and heterozygosity in two populations--one, in people living today in the Middle East, and the other in the Yakut, who live near the Bering Strait.

Bottlenecks: Effect of barriers

- That indicated to the researchers that
  - first bottleneck occurred as people migrated out of Africa to the Middle East about 50,000 to 60,000 years ago, and
  - second, 19,000 kilometers away, when they crossed the ancient land bridge in the Bering Strait to the Americas.
- What caused the bottlenecks?
- Amos suggests that obstacles--such as the sea, glaciers, or mountains--on the route from Africa to the Middle East, across the Himalayas and over the Bering Strait, held many migrants back, so that a much smaller group moved on, producing offspring to inhabit new parts of the globe. Changes in climate may also have opened and closed new routes out of Africa, creating new barriers.

Essential Genes Protected from Mutations

- Epigenetic structures appear to reduce the rate of changes in genes essential for survival and reproduction, a study finds, challenging the notion that mutations are evenly distributed throughout the genome prior to selection.
- Conventional wisdom suggests that evolution is driven by mutations that randomly occur throughout an organism's genome, and that those that make the organism better at surviving or reproducing are then propagated thanks to natural selection.
- However, a new study cements the alternate idea that the process of mutation isn't evenly distributed across genomes.
- There's a discrepancy in the rates of mutations among genes in model plant *Arabidopsis thaliana*. Specifically, genes playing a crucial role in survival and reproduction mutate far less often than those that are less important.

Protected genes: mutation bias across the human genome

- There was 58 percent lower mutation rate within genes than in the areas of the genome around them.
- On top of that, genes considered essential for survival had a 37 percent lower mutation rate than those in which modifications would be less likely to prove disastrous.
- Challenges the idea that mutations are equally likely throughout the genome and clarifies how evolution occurs,
- More important genes seem protected from mutation; found evidence of methylation that prevent mutations from occurring in those regions, not unlike protective barriers.
- Challenges the notions that mutation is random and that evolution is directionless

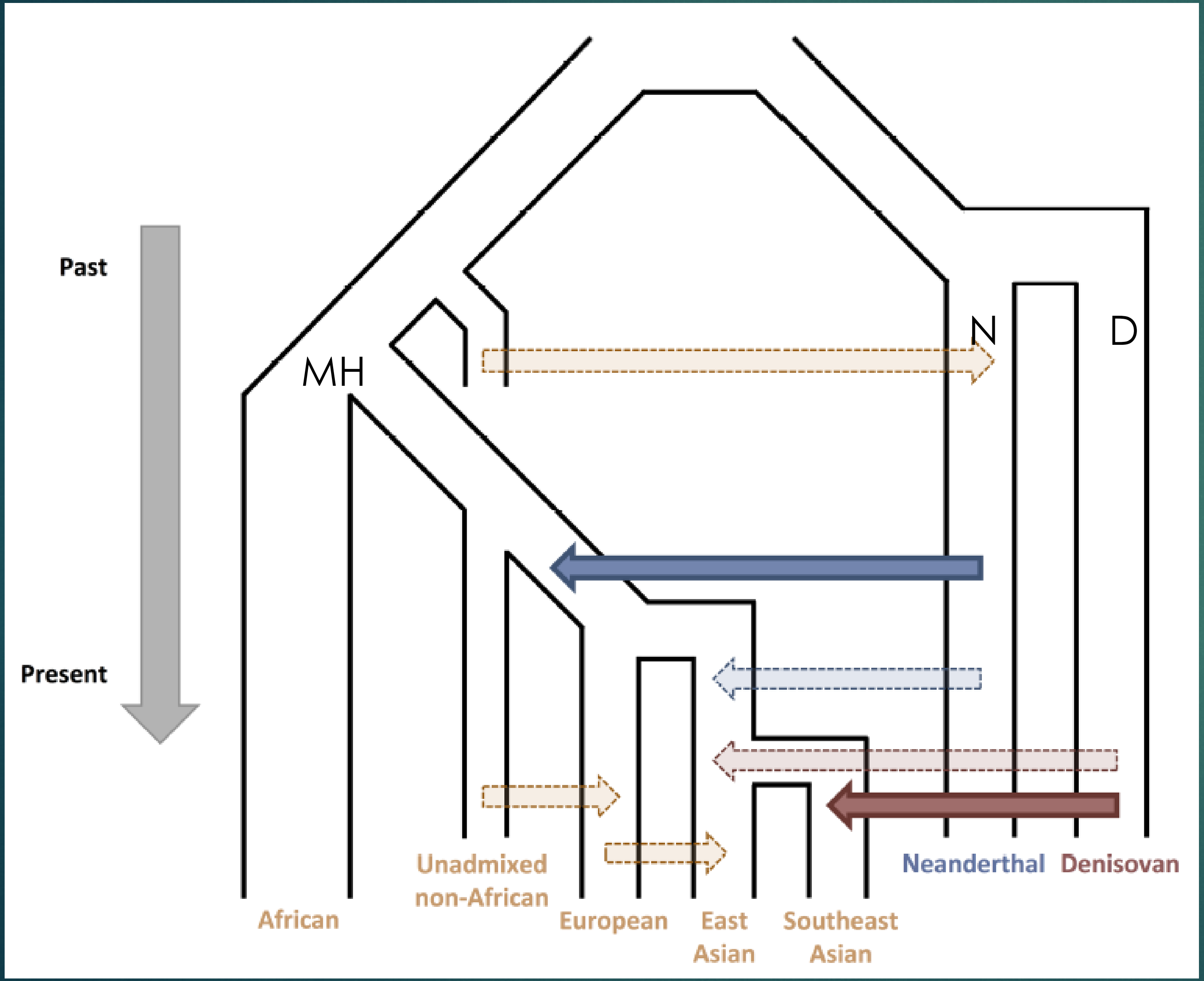
Paleogenetics, Part 6

The Introgression of
Neandertal & Denisovan DNA
into the
Modern Human Genome

Outstanding questions in the study of archaic hominin admixture – A. B. Wolf, J. M. Akey, 2018

- The complete genetic sequencing of archaic and modern human genomes has revolutionized the study of human history and evolution.
- Here, we review some of these questions, which include
  - how frequent archaic-modern human admixture was in history,
  - to what degree genetic drift and selection are responsible for the loss and retention of introgressed sequences in modern human genomes,
  - how surviving archaic sequences affect human phenotypes.

Wolf & Akey, 2018: A model of admixture history between archaic and anatomically modern human populations



- Consensus: two independent gene-flow events occurred (solid arrows) admixture from Neanderthals into an ancestral Eurasian population (solid blue) and from Denisovans into an ancestral Southeast Asia population (solid red). It is likely that additional instances of admixture occurred, explaining the variation in the percentage of archaic sequence across different global populations.
- These additional instances include a pulse of admixture from Neanderthals (dashed blue) and from Denisovans (dashed red) into an ancestral East Asian population.
- Alternatively, or in addition, global variation in archaic ancestry could be the result of admixture within human populations (dashed orange) diluting archaic sequence.
- Admixture from human populations may also have introduced sequence into archaic populations.

How much N DNA in MHs

- Prüfer et al. (2013) estimated the proportion of N DNA in MHs:
  - 1.5–2.1% for non-Africans,
  - revised in 2017 to a higher 1.8–2.6% for non-Africans outside Oceania.
- Lohse and Frantz (2014) infer a higher rate of 3.4–7.3% in Eurasia.
- Prüfer et al. (2017) noted that
  - East Asians carry more Neandertal DNA (2.3–2.6%) than Western Eurasians (1.8–2.4%).

Wolf & Akey, 2018: MHs have 1.8 to 2.6% N DNA

- High-coverage Vindija Cave Neanderthal genome:
  - improved estimates of the Neanderthal effective population size = small size
  - admixing Neanderthal population to be closer to the Vindija, Croatia N populations than the Altai, Siberia one,
  - Determining that MHs have 1.8 to 2.6% N ancestry
- Non-African MHs share more genetic ancestry with Ns and Ds than do African MHs, due to occurrence of hybridization between Ns and Ds and the ancestors of all non-African MHs

Archaic human ancestry

- All modern non-African genomes are estimated to carry approximately 2%-7% archaic human sequence:
  - approximately 2% ancestry from Neanderthals
  - additional 2%-5% ancestry from Denisovans in Melanesian populations.
  - Present-day levels of archaic ancestry need not reflect initial admixture levels, which were higher

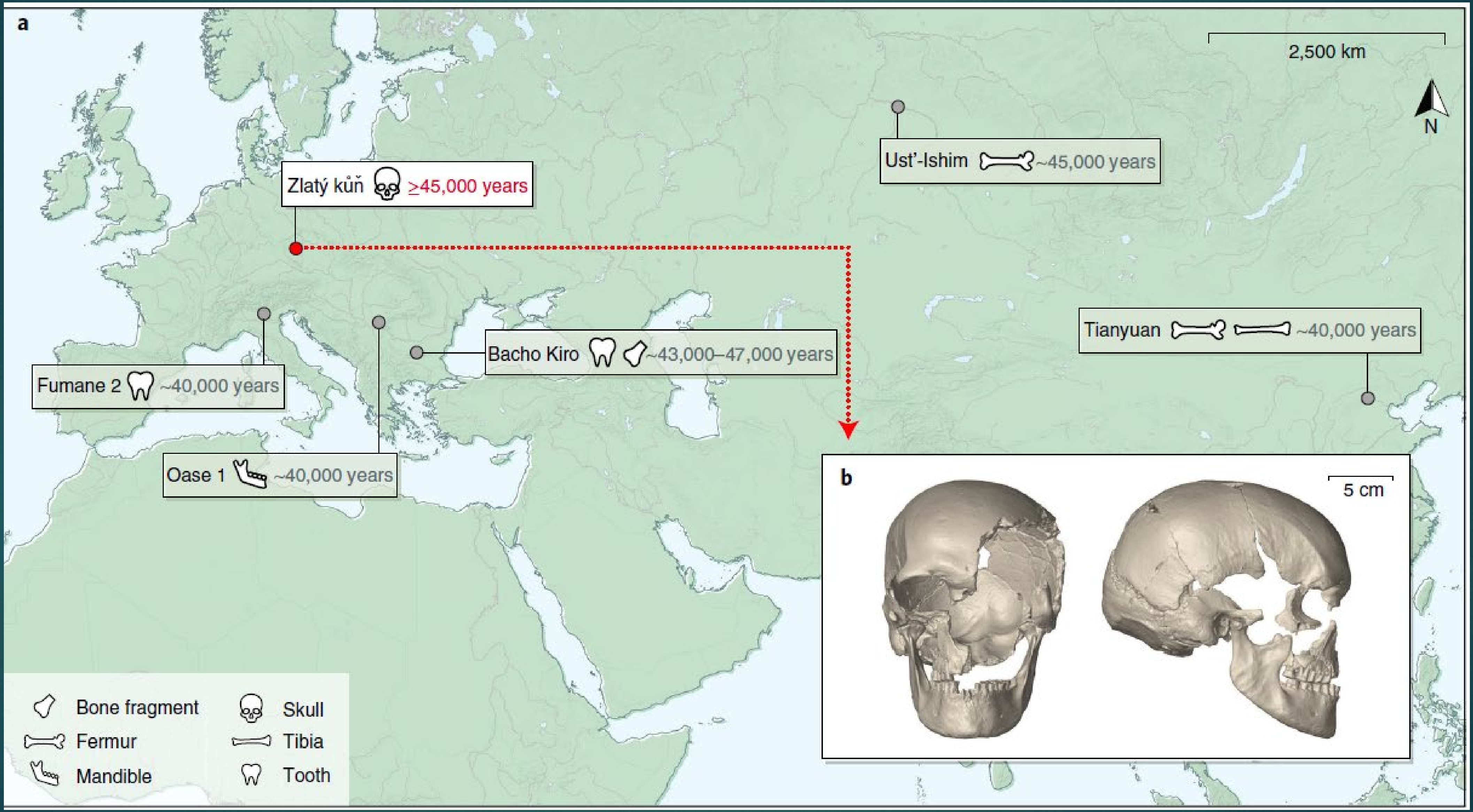
Wolf & Akey, 2018: what % N DNA

- Following the discovery of approximately 2% Neanderthal ancestry in modern non-Africans, it was originally estimated the initial level of admixture between Neanderthals and modern humans was also 2%.

- Further analyses revealed large depletions of Neanderthal ancestry across the human genome, suggesting widespread purging of deleterious Neanderthal sequence.

- This lead to conclusion that the initial proportion of Neanderthal ancestry after admixture was dramatically higher than 3%.

Sites of Earliest MHs in Europe



Wolf & Akey, 2018: early MHs had more N DNA

- Consistent with this hypothesis is the discovery of an ancient East Asian individual, dated to 40 Ka, who was an ancestor of modern Asians and who carried 4 to 5% Neanderthal ancestry.
- Data from a 42 Ka AMH from Pęstera cu Oase, Romania, reveal this individual shared 6% to 9% of his genome with Neanderthals, more than 3× any contemporary modern humans.
- Pęstera cu Oase individual had a very recent Neanderthal ancestor (within 4-6 generations) and likely did not contribute any ancestry to modern populations.

N and MH sex

- Currat and Excoffier suggest that either modern humans and Neanderthals didn’t have sex very often, or their hybrids weren’t very fit.
- They favor the first idea.
- According to their model, it would only have taken between 197 and 430 liaisons between ancient humans and Neanderthals to fill 1-3 percent of modern Eurasian genomes with Neanderthal DNA.
- Considering that they two groups probably interacted for 10,000 years or so, it would have been enough for one human to sleep with one Neanderthal every 23 to 50 years.

Oase 1: Erik Trinkaus

- To Erik Trinkaus, the jaw of the oldest modern human found in Europe has always looked strange. Its huge wisdom teeth and hefty, buttressed lower jaw reminded him of Neandertals, and he argued that this fossil, 37,000 to 42,000 years old, was the product of generations of mixing between modern humans and our extinct cousins. “It wasn't a popular idea,” admits Trinkaus, a paleoanthropologist at Washington University in St. Louis.
- Other paleoanthropologists insisted that the young man whose remains were found in 2002 in Peştera cu Oase cave in Romania was just a chunky example of our own species.

Oase 1

- Trinkaus has been vindicated by ancient DNA.
- The young Oase man inherited as much as one-tenth of his DNA from a Neandertal ancestor, and that ancestor lived only 200 years or so previously,
- So researchers proposed that modern humans and Neandertals had rare and relatively early encounters, perhaps in the Middle East, when moderns swept out of Africa 60,000 to 50,000 years ago.
- The DNA from Oase 1, a lower jaw without a skull, complicates that picture
- They found that the Oase man had far more Neandertal DNA—composing 4.8% to 11.3% of his genome—than either the ancient modern humans from Russia or living Europeans and Asians

Oase 1

- Oase 1 had inherited the Neandertal DNA in "large chunks," including several segments more than 50 million base pairs long; one chunk spanned half the length of chromosome 12.
- Those unbroken stretches of Neandertal DNA suggest that the interbreeding must have been just four to six generations back. If the mixing had been more ancient, the long DNA segments would have been broken up by the reshuffling of chromosomes that takes place every generation.
- The team concluded that the Oase man himself was an evolutionary dead end, who did not pass his DNA along to living Europeans.

We are a genetic mosaic

- Humans today are mosaics, our genomes rich tapestries of interwoven ancestries.
- With every fossil discovered, with every DNA analysis performed, the story gets more complex: We, the sole survivors of the genus *Homo*, harbor genetic fragments from other closely related but long-extinct lineages.
- Modern humans are the products of a sprawling history of shifts and dispersals, separations and reunions — a history characterized by far more diversity, movement and mixture than seemed imaginable a mere decade ago.

Paleo Hooking Up

- It turns out that ancient human species hooked up a lot.
- *Homo heidelbergensis, Homo sapiens*, Neanderthals, and Denisovans, had numerous intergroup sexual encounters
- Geneticists call these events "archaic introgression events"
- But over time, the footprints of introgression are being relentlessly erased from their genomes by the power of natural selection.
- Some of this archaic ancestry was clearly deleterious, but some was beneficial.

Not Us and Them

- Pääbo now recommends against imagining separate species of human evolution altogether: not an Us and a Them, but one enormous "metapopulation" composed of shifting clusters of essentially human-ish things that periodically coincided in time and space and, when they happened to bump into one another, occasionally had sex.
- Finlayson: "Each valley could have told a different story. In one, they may have hit each other over the head. In another, they may have made love. In another, they ignored each other."
- Jon Mooallem: "a superlong elevator ride with strangers."

Homo neanderthalensis Genome

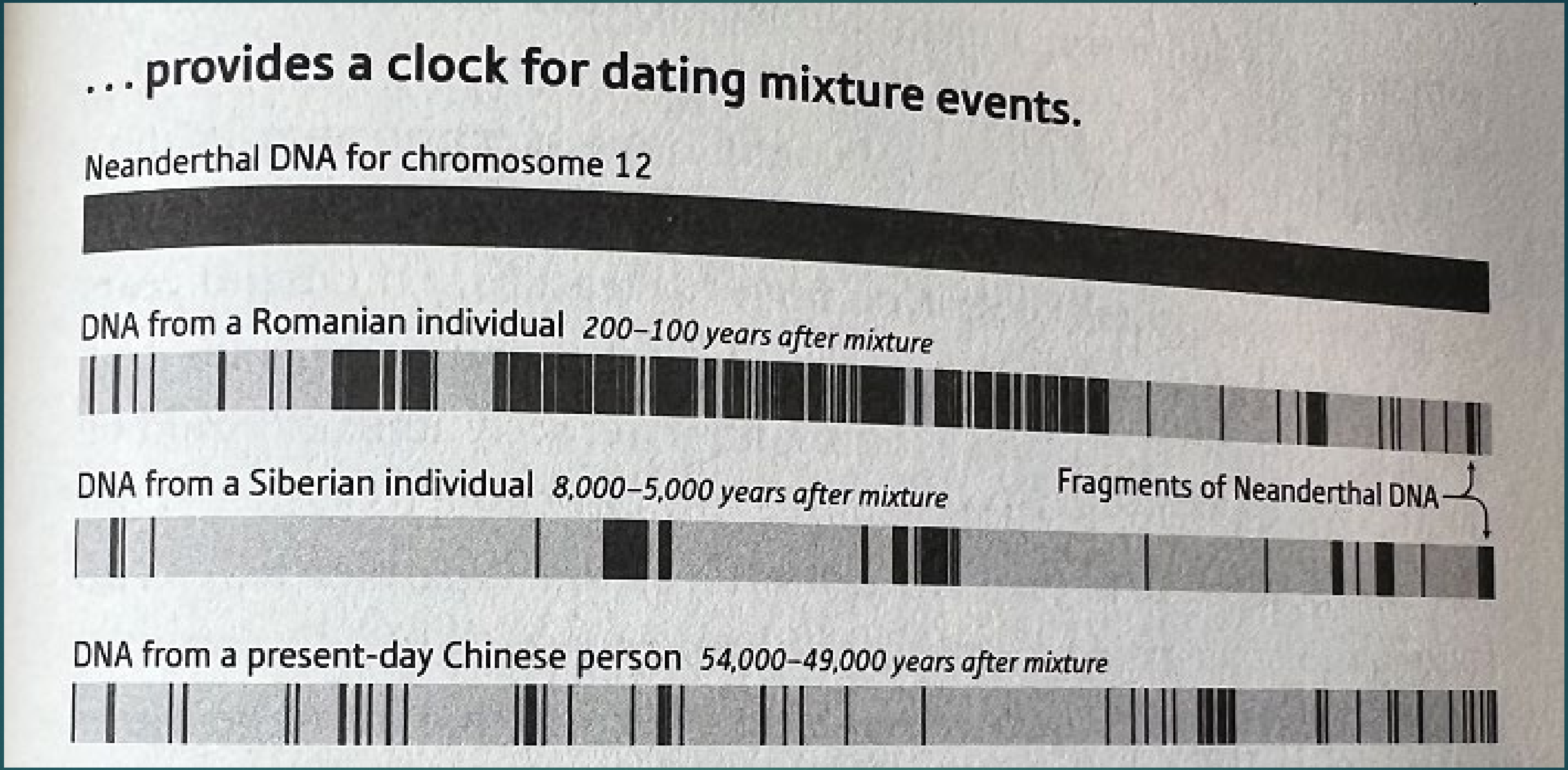
- Information about the Neanderthal genome was published in 2010. At that time, it was determined that modern humans, living outside of Africa, carry between 1% and 4% of Neanderthal DNA.
- One explanation might be that modern humans migrating out of Africa mated with Neanderthals living in the Middle East, producing viable offspring before these descendants fanned out across Europe and Asia.
- The date of that interbreeding has been pinned down to between 50,000 and 60,000 years ago.

MH & Ns share 99.7% of 3 billion SNPs

- 2010 study: Compared Neanderthal genome to the genomes found in DNA from the five people, as well as to chimpanzee DNA. An analysis of the genetic variation showed that
  - Neanderthal DNA is 99.7 percent identical to present-day human DNA,
  - 98.8 percent identical to chimpanzee DNA.
  - Equals 9 million SNPs difference
- 2 percent of the genomes (nucleotide sequences) of present-day humans living from Europe to Asia - and as far into the Pacific Ocean as Papua New Guinea - was inherited from Neanderthals.

Denisova genome

- Denisova hominin in Siberia revealed that it differed from that of modern humans by
  - 385 bases (nucleotides) in the mtDNA strand out of approximately 16,500,
  - whereas the difference between modern humans and Neanderthals is around 202 bases.
- N and D mtDNA types have not contributed to the modern human mtDNA pool.
- Based on the analysis of mitochondrial DNA, the split of the N and MH lineages is estimated to date to between 760 to 550 Ka



. . . provides a clock for dating mixture events.

Neanderthal DNA for chromosome 12

DNA from a Romanian individual *200–100 years after mixture*

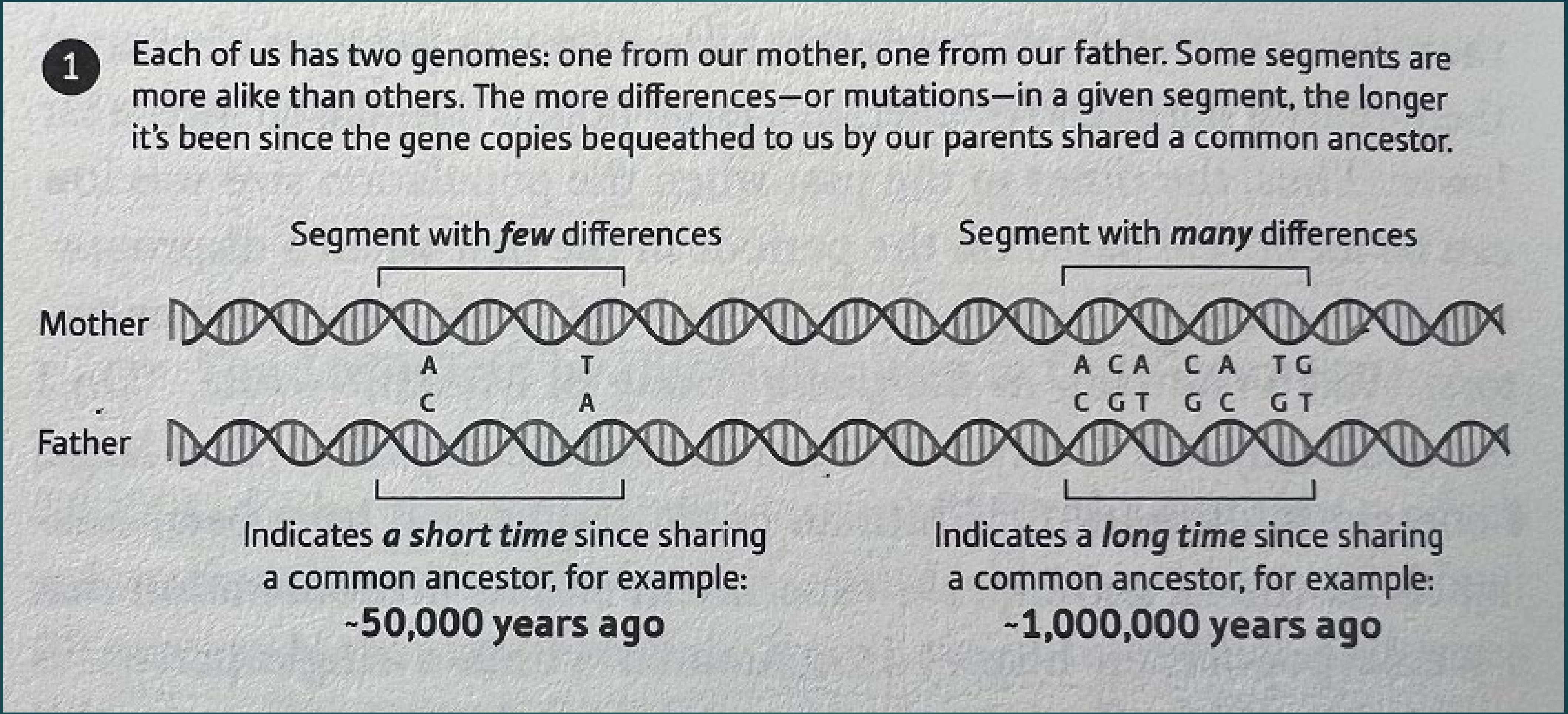
DNA from a Siberian individual *8,000–5,000 years after mixture*

Fragments of Neanderthal DNA

DNA from a present-day Chinese person *54,000–49,000 years after mixture*

N DNA dilution in MH: Amount of Neandertal DNA lessens with amount of time from original admixture. There is no N DNA in more than 50% of MH genome. Evidence of systematic removal of N DNA by natural selection, esp. gene regions, & X & Y chromosomes

How We Can Tell How Long It Has Been Since Our Genes Shared Common Ancestor: More mutations, longer time to LCA



① Each of us has two genomes: one from our mother, one from our father. Some segments are more alike than others. The more differences—or mutations—in a given segment, the longer it's been since the gene copies bequeathed to us by our parents shared a common ancestor.

Segment with ***few*** differences

Segment with ***many*** differences

Mother

A T

C A

A C A C A T G

C G T G C G T

Father

Indicates ***a short time*** since sharing a common ancestor, for example: **~50,000 years ago**

Indicates a ***long time*** since sharing a common ancestor, for example: **~1,000,000 years ago**

A Multiplicity of Archaic Human Lineages – based on David Reich

- 1,400,000-900.000 ya: Last Common Ancestor of MHs. Neanderthals, and Denisovans separates from their superarchaic lineage.
- 1,000,000-800,000 ya: The Denisovan and Sima de los Huesos mitochondrial DNA splits from those of Neanderthals and MHs.
- 770,000-550,000 ya: Genetic estimate of population separation between Neanderthals and MHs
- 700,000-50,000 ya: The "Hobbits" inhabit the island of Flores in Indonesia.
- 470,000-380,000 ya Genetic estimate of Neanderthal-Denisovan population split

A Multiplicity of Archaic Human Lineages: Ns: 470 to 39 Ka

- 470,000-360,000 ya Estimated date at which Neanderthal & MH mitochondrial DNA separation
- -430,000 ya Sima de los Huesos skeletons and DNA show that the Neanderthal lineage was already evolving in Europe.
- 400,000-270,000 ya: Separation of Siberian Denisovans and Australo-Denisovans
- 54,000-45,000 ya Neanderthals and modern humans interbreed
- 49,000-44.000 *ya* Denisovans and modern humans interbreed

The Age of Modern Humans: 350,000 years ago – present

- 330,000-300,000 ya: Oldest fossils with anatomical features shared with anatomically modern humans (Jebel Irhoud. Morocco)

- -320,000 ya: Date of the most recent shared ancestor of all present-day humans anywhere on chromosomes 1-22

- 300,000-250.000 ya Middle Stone Age/Middle Paleolithic Transition

- 180,000 ya: "Mitochondrial Eve" -- Date of the most recent shared ancestor of all present-day humans along the entirely maternal line

- 70.000-50,000 ya: Later Stone Age/ Upper Paleolithic Transition

- Dates of Origins by regions: San (300 Ka), West Africans (~275 Ka), East Africans (~140 Ka), West Eurasians (~80 Ka), East Asians (~50 Ka), Native Americans (~20 Ka)

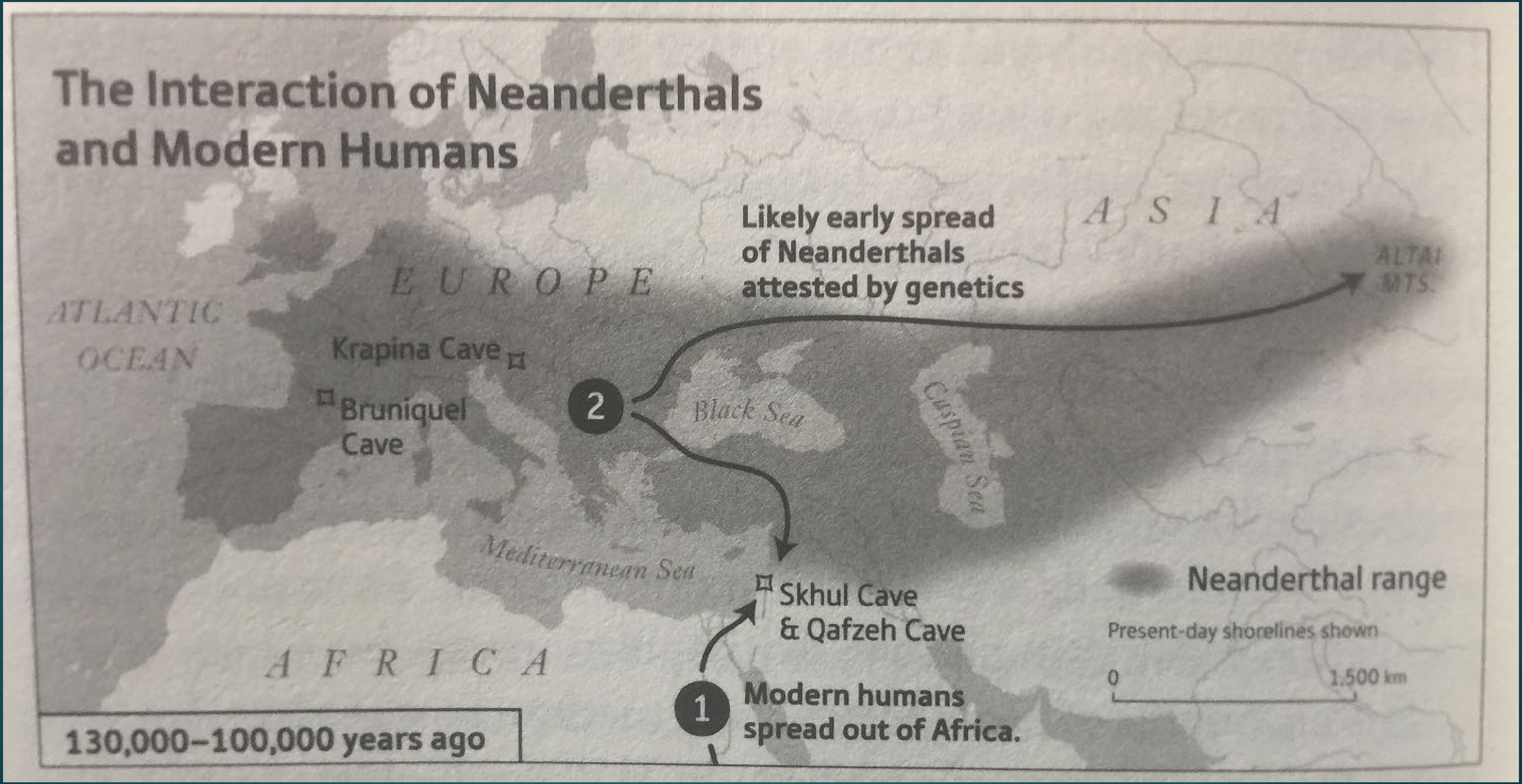
150,000 to the Present

- 130,000 -100,000 ya: Anatomically modem humans spread to the Near East (Skhul and Qafzeh Caves. Israel)
- -70.000 ya: Neanderthals spread south and east out of Europe.
- -60,000 ya: Neanderthal skeleton in Middle East (Kebara Cave, Israel)
- < 50,000 ya: Modem humans spread out of Africa and the Near East.
- -40,000 ya: Neanderthal/ modern human hybrid (Oase, Romania)
- -39-29,000 ya: Last Neanderthals in Europe disappear.

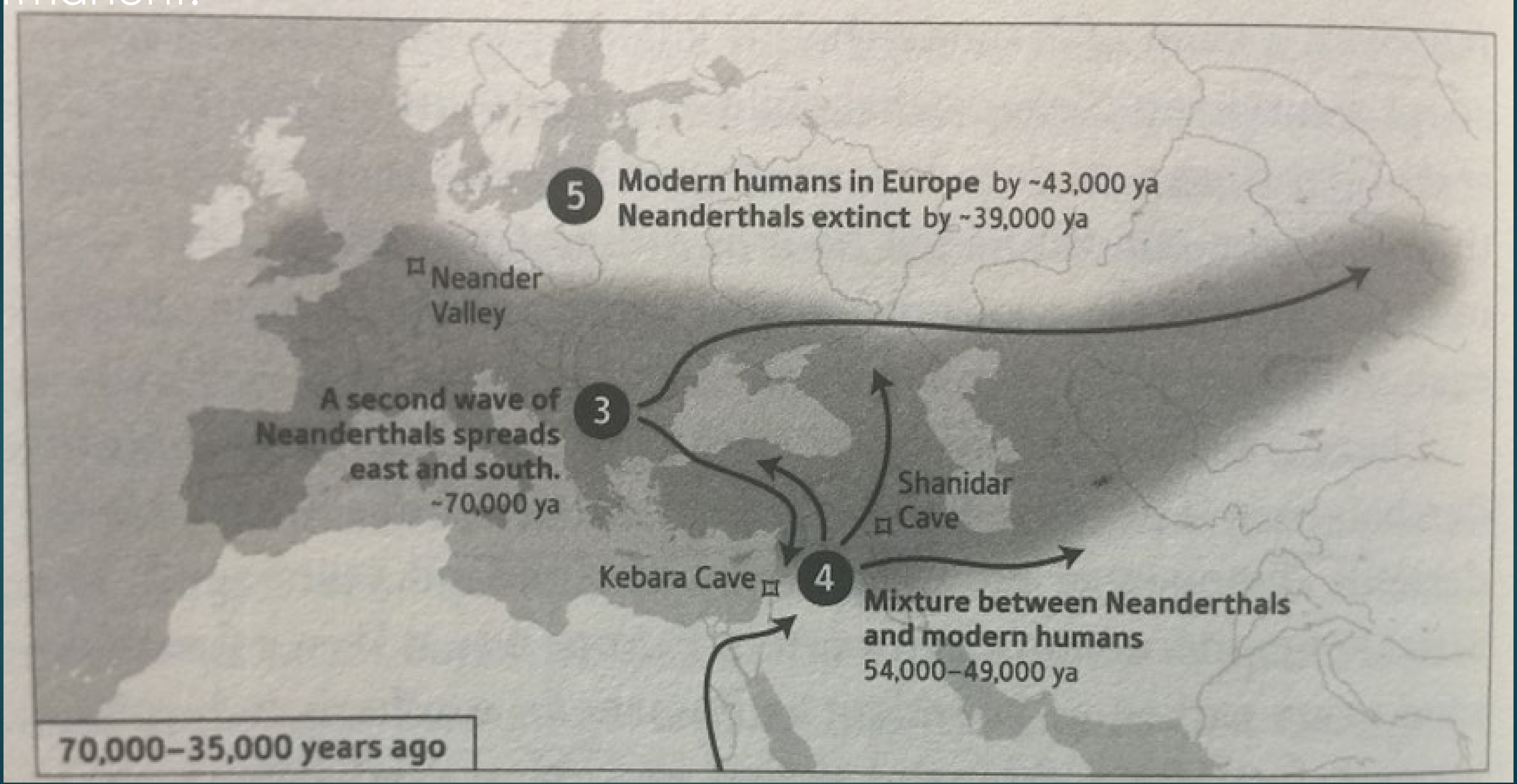
33,000 to Present

- 33,000-22.000 *ya:* *Gravettian* culture and a new type of genetic ancestry spread through Europe from the east.
- *25.000-19.000 ya* Lost Glacial Maximum
- -24.000 ya The Mal'ta boy from Siberia: an ancient North Eurasian
- 19.000-14,000 ya Magdalenian culture and a new type of genetic ancestry spread through Europe from the southwest.
- 14,000-8.000 ya Bolling-Allerod warming period allows a new group of hunter-gatherers to spread into Europe from the southeast.
- -11.500 ya Farming begins in the Near East and is practiced by highly divergent populations.
- 10.000-4,000 ya West Eurasian populations integration.
- Present

After 400 Ka, Ns were the dominant humans in western Eurasia, extending to Siberian Altai Mountains. They survived several influxes of MHs prior to 60 Ka.



Ns spread E and S ~70 Ka; MH & N admixture in Levant; After 60 Ka, MHs made a final influx into Western Eurasia that was permanent.



Did we mix?

Current aDNA findings underscore how it is not a question o
whether our ancestors interacted with other hominins,
but it is a question of when, where, & who did the interbree

** A history of multiple
interbreeding events:

When we have met,
we have always mixed!

Continuous interbreedings: when populations meet, they mix

- Humans have been continuously evolving through the mixing of varied populations for hundreds of thousands of years, including multiregional interactions in Africa
- Clues are emerging about the unexpected influence of gene flow from ancient hominins on modern human populations before the latter left Africa.
- What is curious is that the only migration that seems to have left modern human descendants in Europe and Asia was the one from 60,000 years ago. The groups that migrated earlier apparently all died out or got absorbed into Neanderthal or other ancient populations.

Pre-60 Ka Out of Africa Migrations

- Well-known out-of-Africa diaspora 60,000 years ago.
- There were multiple unsuccessful MH dispersals from Africa, perhaps due to greening of the Sahara and Arabian deserts, which happened every 100 K years

Archaic Admixture

- Did our ancestors interbreed with archaic humans?
- Hybridization did indeed happen between our ancestors and Neanderthals
- All non-Africans inherited approximately 2% of their genome from Neanderthal ancestors

(Selina Vattathil and Joshua M. Akey, 2015 , Green et al., 2010; Yang et al., 2012; Sankararaman et al., 201
Prufer et al., 2014) and Denisovans (Reich et al., 2010; Reich et al., 2011).

Archaic admixture

- Individuals of Melanesian ancestry inherited approximately 4%–6% of their genome from Denisovan ancestors.
- Number of hybridization events compatible with the observed levels of archaic ancestry is currently unknown and difficult to estimate precisely as it requires tenuous assumptions about a range of parameters such as historical population sizes and fitness of hybrid offspring

Archaic Admixtures

- More recently, the focus of admixture studies has shifted from testing the hypothesis that archaic admixture occurred to identifying the specific sequences that were inherited from archaic ancestors.
- The two largest studies to date searched for surviving Neanderthal sequences in whole-genome sequence data from individuals of European and East Asian ancestry (Sankararaman et al., 2014; Vernot and Akey, 2014).
- The key population genetics signatures that allow archaic sequences to be identified are
  - unusually high genetic divergence from the human reference genome and
  - high sequence similarity to the Neanderthal reference genome over long (30–100 kb) stretches of DNA.

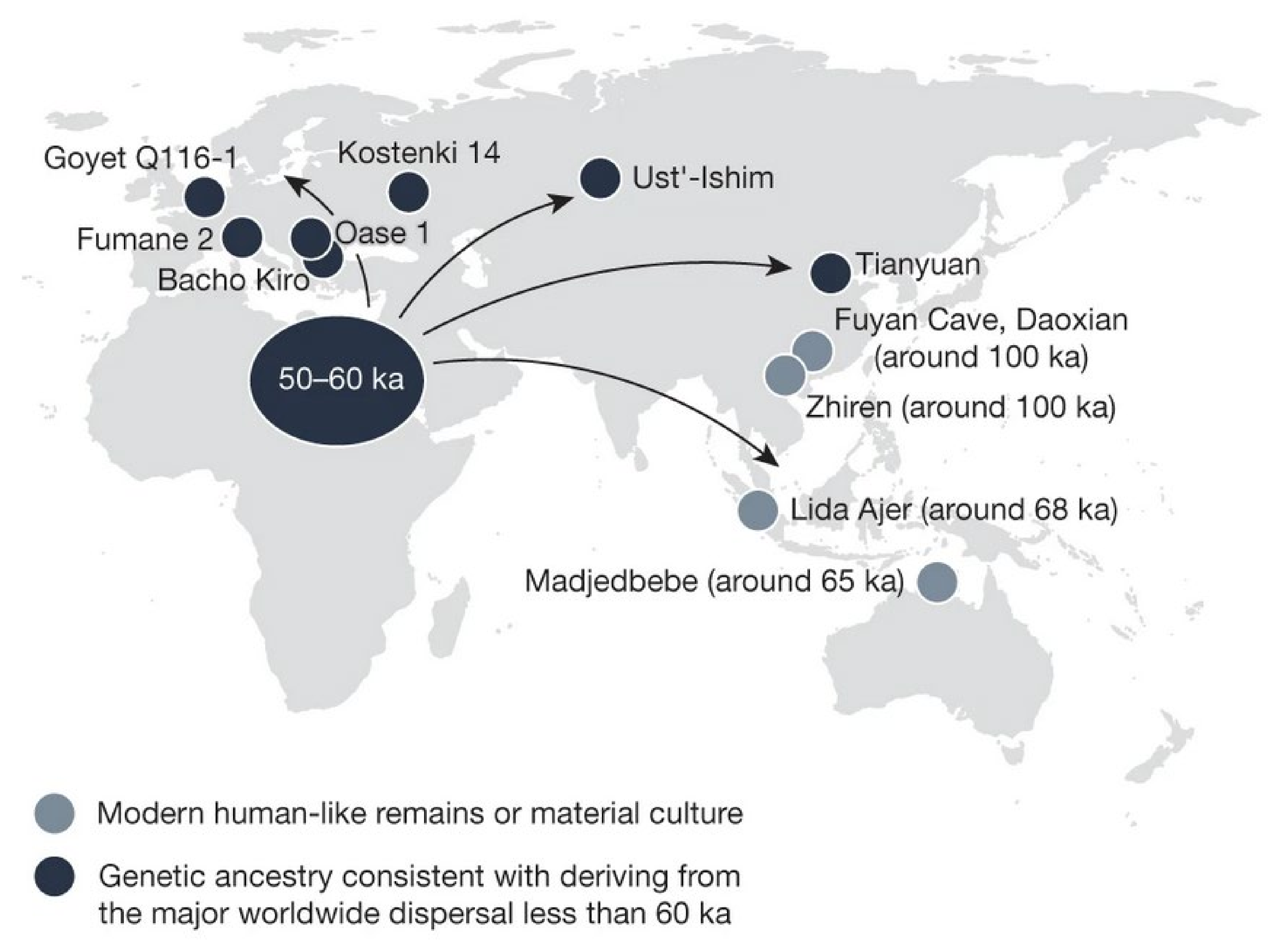
Archaic Admixtures

- In total, Vernot and Akey (Vernot and Akey, 2014) identified 600 Mb of introgressed Neanderthal sequence and Sankararaman et al. (Sankararaman et al., 2014) reported 1.1 Gb of introgressed sequence,
- representing 20% and 35%, respectively, of the Neanderthal genome.

Morphological evidence of multiple Out of Africa migrations: 210 to 50 Ka, but left no descendants

- Apidima Cave, Greece (dated to more than 210 ka): skull
- Misliya Cave, Israel (180 ka): mandible
- Israeli caves of Skhul and Qafzeh (90–130 ka): skulls[1]
- Al Wusta in Saudi Arabia (90 ka): finger
- Chinese fossils (113 -80 ka): teeth
- Teeth from Sumatra (70 ka)
- Artefacts from northern Australia (65 ka)
- Cranial and mandibular fossils from Laos (50 Ka)

MHs in Eurasia: 60 Ka vs Earlier dispersals



Locations of early individuals with modern human DNA ancestry in Eurasia, together with sites that may indicate an earlier dispersal in Asia and Sahul (the continental shelf centered on Australia).

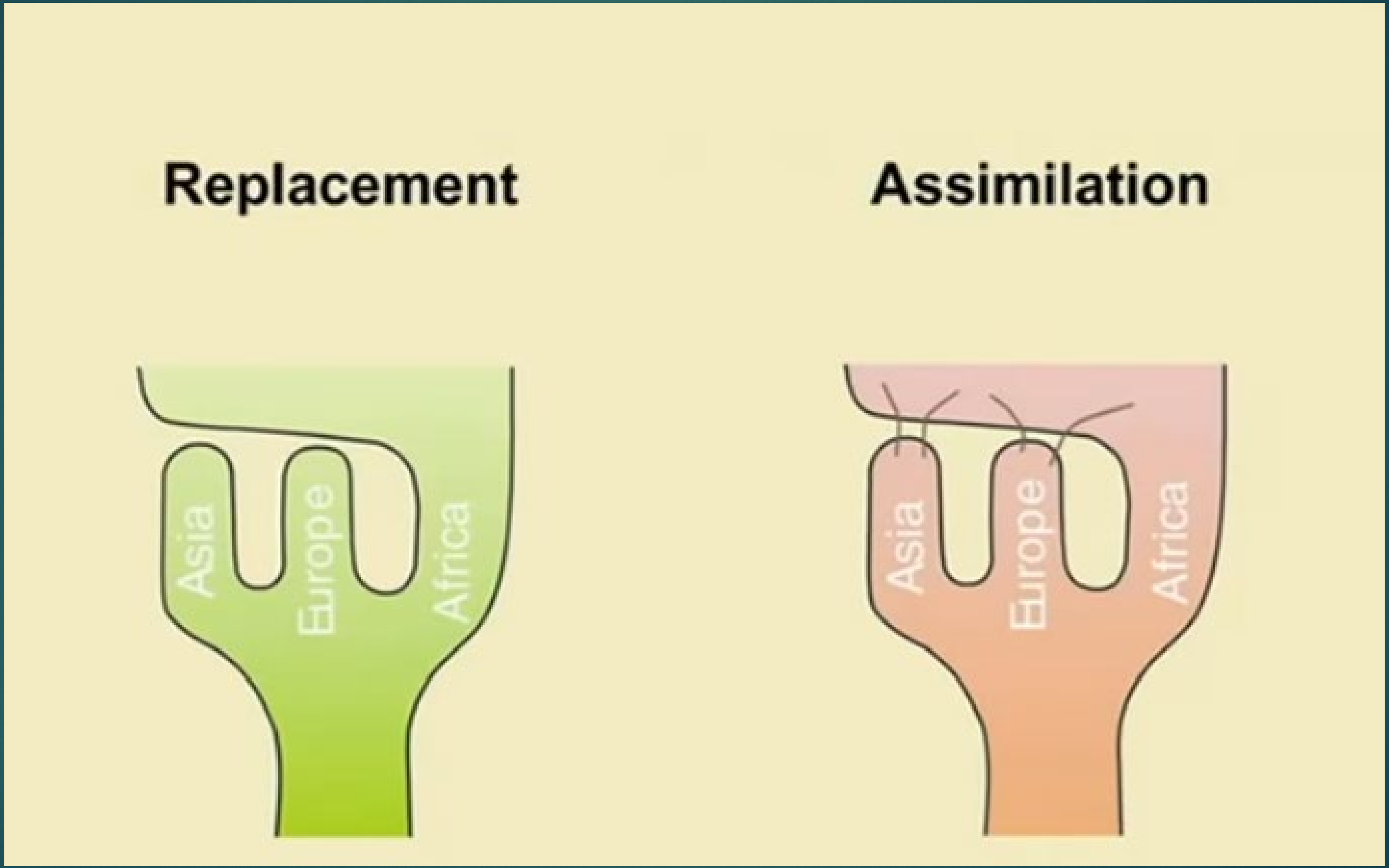
A complex history of MH, N, D, + archaics, interbreeding

- Sexual encounters among different ancient human species were commonplace throughout their history.

- Multiple ancestors of MHs interbred at a variety of times and places with other hominins.

- MHs, Ns, Ds, & multiple archaic Homo “ghost” lineages interbred inside and outside of Africa.

Neandertals: complete replacement vs genetic assimilation (admixture via gene-flow)



Admixture vs common ancestor

- Original theory disagreement: Difficult to verify if DNA change was introduced by genetic admixture or by the fact that it is shared from a common ancestor.
- One method of finding N sequences in MH: divergence (different variants at 1 locus) and how long sequences are: if common ancestor (incomplete lineage sorting), expect chunks to be much smaller in size
- While interbreeding was viewed as the most parsimonious interpretation of the genetic discoveries, the 2010 study still could not conclusively rule out an alternative scenario, in which the source population of non-African modern humans was already more closely related to Neanderthals than other Africans were, because of ancient genetic divisions within Africa.

Akey

Debate: Gene Flow vs Introgression

- Debate:
  - Is this gene flow between populations that occurred,
  -
  - or rather introgression, the genetic exchange of elements between separate species associated with incomplete reproductive isolation?

- It's clear that modern human origins is not simply a tale of anatomically-modern humans evolving over the last 300,000 years, expanding out of Africa and replacing everything that existed = complete replacement theory
-

Debate: Gene Flow vs Introgression

- AMHs did evolve in Africa in the last 300,000 years.

- They did expand out. But part of that expansion was associated with genetic exchange between existing archaic populations that existed outside of Africa.

- Admixed genetic variants are not just these neutral genetic elements floating around in us, but in many cases seem to be elements that were selected for, at least locally, and have been retained because of the selected advantages they provide MHs.

Did MHs and Ns interbreed? Are Ns ancestral to MHs?

- Skeletal evidence for hybridization:
- Erik Trinkaus identified remains, such as those from Oase, Romania, as N-MH hybrids
- But shared skeletal features can reflect adaptation to same environmental pressures, not shared genetics
- Need genetic evidence to prove hybridization

The Species Problem

- Generally speaking, different species can’t have fertile descendancy. But weren’t N & MH separate species? Doesn’t a species, by definition, breed only with others of that species?
- The question of how to define a species has divided researchers for centuries. Darwin’s words in *On the Origin of Species* still hold: “No one definition has satisfied all naturalists.”
- How you define a species. Ernst Mayr: “Are species realities of nature or are they simply theoretical constructs of the human mind?”
- Most scientists use the biological species concept proposed by Ernst Mayr: “groups of actually or potentially interbreeding natural populations, which are reproductively isolated from other such groups.”

Species Controversy

- If you apply Mayr's definition strictly, and MR, N, & Ds must be considered *Homo sapiens*. This is John Hawks position. "They mated with each other. We'll call them the same species" . A minority view.

- J. Hublin: Differences between MH and N are significant, greater than in all MHs. In the real world, he says, Mayr's concept doesn't hold up.

- There are 330 closely related species of mammals that interbreed, and at least 30% can produce fertile hybrids. 10 percent of all animal species are known to hybridize.

- Species Interbreed: For example different kinds of baboons (genus *Papio*), wolves and wild dogs (*Canis*), bears (*Ursus*) and large cats (*Panthera*).

- At least 16% of all bird species interbreed with each other in the wild.

Species

- Under strict biological speciation, implies these were not separate species but divergent groups of same species; evolving largely independently but not to the point of developing genetic isolation and full reproductive isolation.

- The reality is that in most cases in mammals and birds, species diverge from each other gradually.

- It may take millions of years for full reproductive isolation to develop, something that clearly had not yet occurred for *H. neanderthalensis* and *H. sapiens*.

- Svante Pääbo dodges the species question & refers to N, MHs, D as “populations”. He considers species discussion “a sterile academic endeavor

Species Problem

- Low levels of interbreeding between N, H, Ds suggest that
  - either archaic people mated with moderns only rarely or
  - their hybrid offspring had low fitness and so produced few viable offspring.

- The MH/N hybrids proved to be fertile for the simple reason that the two species shared sufficient genetic similarity for it to be possible, without genetic complications arising in the hybrid species that rendered it sterile.

Species problem

- MH X chromosome is almost devoid of Neanderthal DNA. Male human-Neandertal hybrids may have been infertile.
- The Y-chromosome of male Neanderthals proved to be unviable in hybrids; only the female hybrids proved to be fertile.
- The DNA on the Y chromosome from a male Neandertal who lived at El Sidrón, Spain, 49,000 years ago has not been passed onto modern humans.
- Despite inheriting 2% N DNA from their ancestors' interbreeding with Neandertals, MHs are missing chunks of Neandertal DNA on their Y chromosomes.

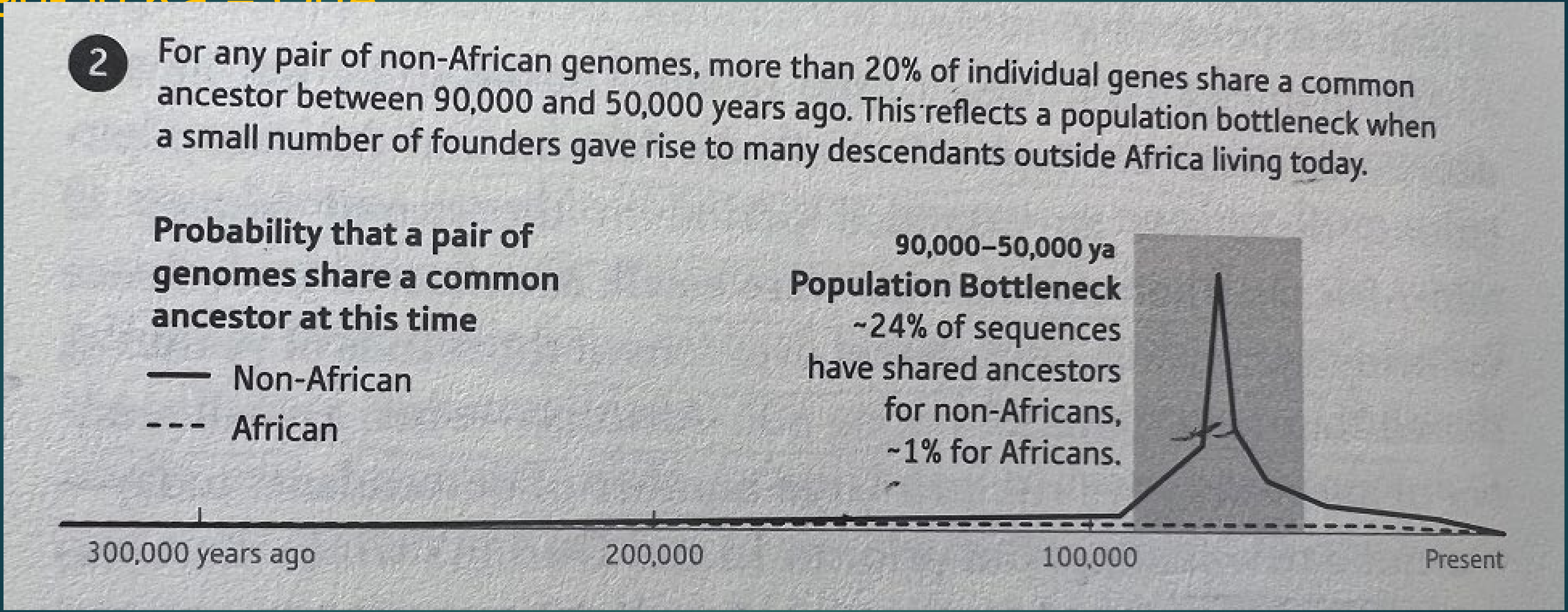
Species problem

- This has suggested that female modern humans and male Neandertals were not fully compatible and that male Neandertals may have had problems with sperm production.
- The El Sidrón Neandertal had mutations in three immune genes, including one that produces antigens that can elicit an immune response in pregnant women, causing them to reject and miscarry male fetuses with those genes.
- So even though male Neandertals and female modern humans probably hooked up more than once over the ages, they may have been unable to produce many healthy male babies—and, thus, hastened the extinction of Neandertals.

Species problem

- Tellingly, 10 of 10 N mitochondrial sequences are outside the current MH range, suggesting that mating of MH males with N females generated nonviable progeny.
- In contrast, progeny of female MHs and N males may have had the opportunity to survive within MH groups, with sufficient mating success rates to allow transmissions of a few alleles valuable to the newcomers, probably related to ecological adaptation.

How We Can Tell How Long It Has Been Since Our Genes Shared Common Ancestor: Bottleneck at 90-50 Ka = OoA

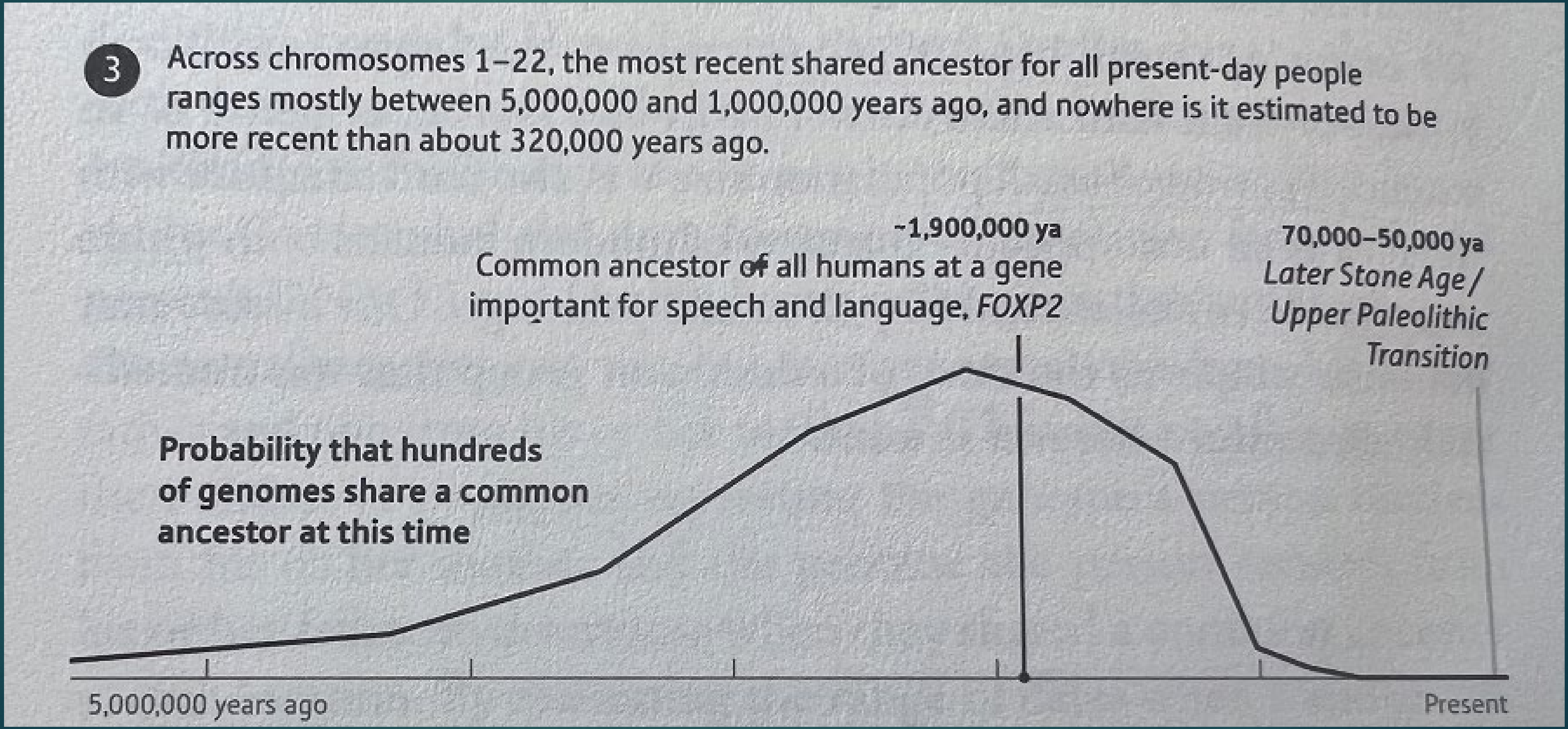


② For any pair of non-African genomes, more than 20% of individual genes share a common ancestor between 90,000 and 50,000 years ago. This reflects a population bottleneck when a small number of founders gave rise to many descendants outside Africa living today.

Probability that a pair of genomes share a common ancestor at this time

90,000–50,000 ya
Population Bottleneck
~24% of sequences have shared ancestors for non-Africans, ~1% for Africans.

How We Can Tell How Long It Has Been Since Our Genes Shared Common Ancestor: Most recent shared ancestor is ~320 ya



③ Across chromosomes 1–22, the most recent shared ancestor for all present-day people ranges mostly between 5,000,000 and 1,000,000 years ago, and nowhere is it estimated to be more recent than about 320,000 years ago.

Most recent shared ancestor of MHs is ~320 ya

- MH genome: there is no gene location where all people living today share a common ancestor earlier than ~320 K ya; in effect, the approximate origin date of MHs

- This is far older time than required by Richard Klein's theory of genetic switch that made us MH ~50 Ka; disproves his theory; if he was right, would find genetic variants that were shared within last 100 Ka; but there are none

A Review of 15 known introgression events: from 320 Ka to recent

1) Svante Pääbo Lab: 1997: Neandertal mtDNA

- mtDNA sequence from N1, type specimen of "*neanderthalensis*"
- N mtDNA fell far outside all MH variation
- 379 base sequence compared to 994 human lineages
- 1) mtDNA difference among 2 human lineages: mean of 8 base substitutions
- 2) Mean differences (base-pair substitutions) between N sequence &
    - European lineages: 28.2
    - African lineages: 27.1
    - Asian lineages: 27.7
    - North American lineages: 27.4
    - Australian/Oceanic lineages: 28.3
    - Conclusion: No N DNA in MHs – no interbreeding

2) mtDNA research (2008): 38,000 Ka Croatian Neandertal

- 38 Ka Croatian Neandertal
- Complete mtDNA has been sequenced (16,000 bp)
- Compared to 53 living humans
  - Modern human and modern humans (2-188 differences)
  - Modern humans and Neandertals (201-234 differences)
- Neandertal mtDNA is not found in modern humans
- Evidence for validity of *Homo neanderthalensis*?
- Estimate of divergence date between the two mtDNA lineages: 660,000 ± 140,000 ybp

N and AMH admixture

- No evidence for interbreeding had been found as of 2008.
- As of 2009, analysis of about one third of the full genome of the Altai N individual was still reported as showing "no sign of admixture".
- The variant of microcephalin common outside Africa, responsible for rapid brain growth in humans, was not found in Neanderthals. Nor was the MAPT variant, a very old variant found primarily in Europeans.

Neandertal Y chromosome & DNA

- Originally had only have female N DNA sample
- No information on N's Y chromosome
- Now know that some modern humans have up to 3% N DNA in their genome
- Two scenarios:
  - If we had N genes because we had common ancestor of both N and MH, all would have some N DNA
  - If we had N ancestry, then unequal distribution of N DNA, which is what we have; only in those who are non-African – N was geographically never in Africa

More samples of N mitochondrial DNA

- Mathias Krings (Svante Pääbo’s lab in Leipzig):
- mtDNA from humerus of Neandertal 1 – well outside the range of variation of diverse sample of MHs
- Then 8 samples: mtDNA from 2nd N from Neander type site; from Mezmaiskaya, Russia N child; 2 Ns from Vindija, Croatia; Engis, Belgium N child; La Chapelle-aux-Saints, France N adult, & from sites in Western Asia & Spain;\
- Range from these Ns the same as mtDNA of same number of MHs, but differences between them and mtDNA of MHs are substantial and significant; imply N are separate species

2010: First N DNA extraction

Vindija Cave:

3 different female Ns

Sequenced 55% of total N genome

3) 2010: N is separate species

- Green et al., 2010:
  - Positive evidence for admixture was first published in May 2010.
  - "The proportion of Neanderthal-inherited genetic material is about 1 to 4 percent [later refined to 1.5 to 2.1 percent].
- It is suggested in this study that ~20 percent of Neanderthal DNA survived in modern humans,

Media

SCIENCE 02/17/2016 05:06 pm ET | Updated Feb 17, 2016

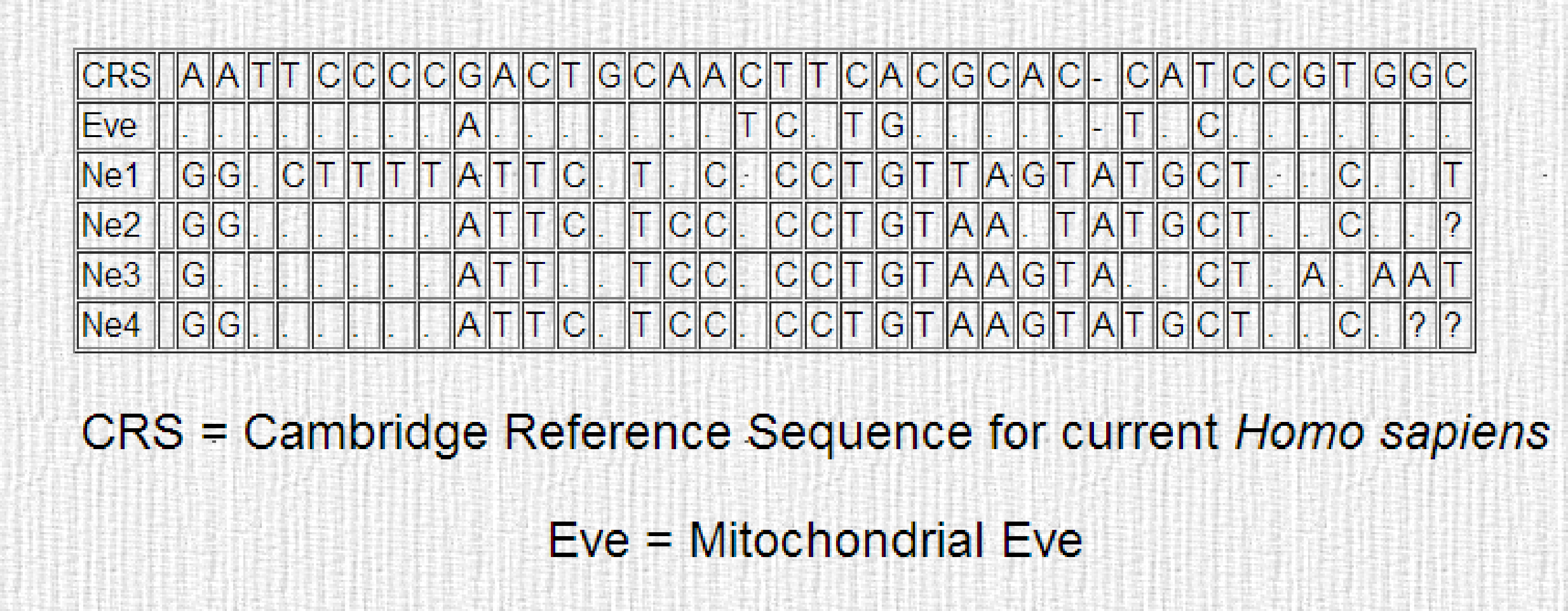
Humans Were Likely Boinking Neanderthals Earlier Than We Thought

The discovery actually says something important about modern humans' migration out of Africa.

By Hilary Hanson

Neanderthals mated with modern humans much earlier than previo..

N are different



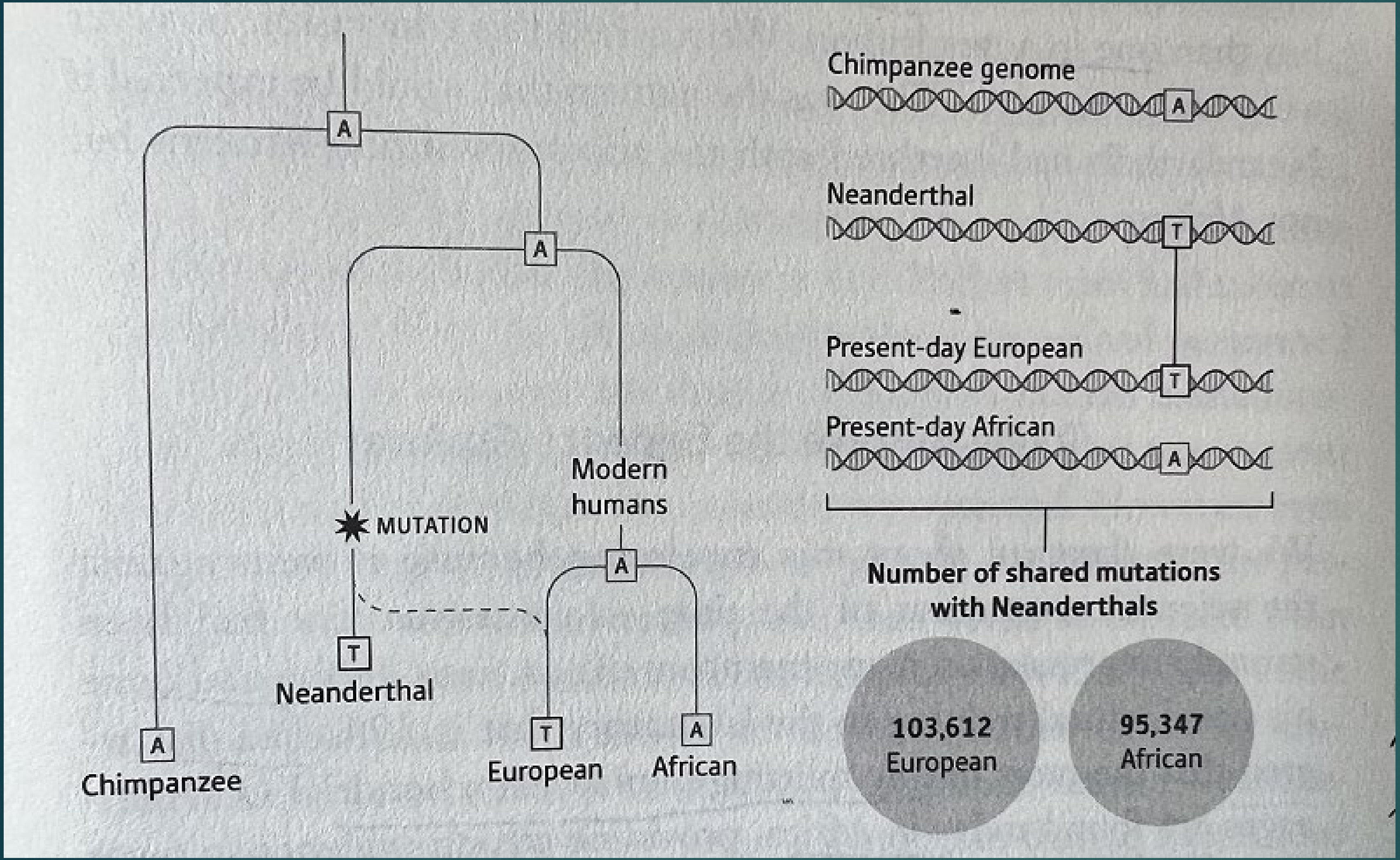
CRS		A	A	T	T	C	C	C	C	G	A	C	T	G	C	A	A	C	T	T	C	A	C	G	C	A	C	-	C	A	T	C	C	G	T	G	G	C
Eve		.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	T	C	.	T	G	.	.	.	.	.	-	T	.	C	.	.	.	.	.	.	.
Ne1		G	G	.	C	T	T	T	T	A	T	T	C	.	T	.	C	.	C	C	T	G	T	T	A	G	T	A	T	G	C	T	.	.	C	.	.	T
Ne2		G	G	.	.	.	.	.	.	A	T	T	C	.	T	C	C	.	C	C	T	G	T	A	A	.	T	A	T	G	C	T	.	.	C	.	.	?
Ne3		G	.	.	.	.	.	.	.	A	T	T	.	.	T	C	C	.	C	C	T	G	T	A	A	G	T	A	.	.	C	T	.	A	.	A	A	T
Ne4		G	G	.	.	.	.	.	.	A	T	T	C	.	T	C	C	.	C	C	T	G	T	A	A	G	T	A	T	G	C	T	.	.	C	.	?	?

CRS = Cambridge Reference Sequence for current *Homo sapiens*

Eve = Mitochondrial Eve

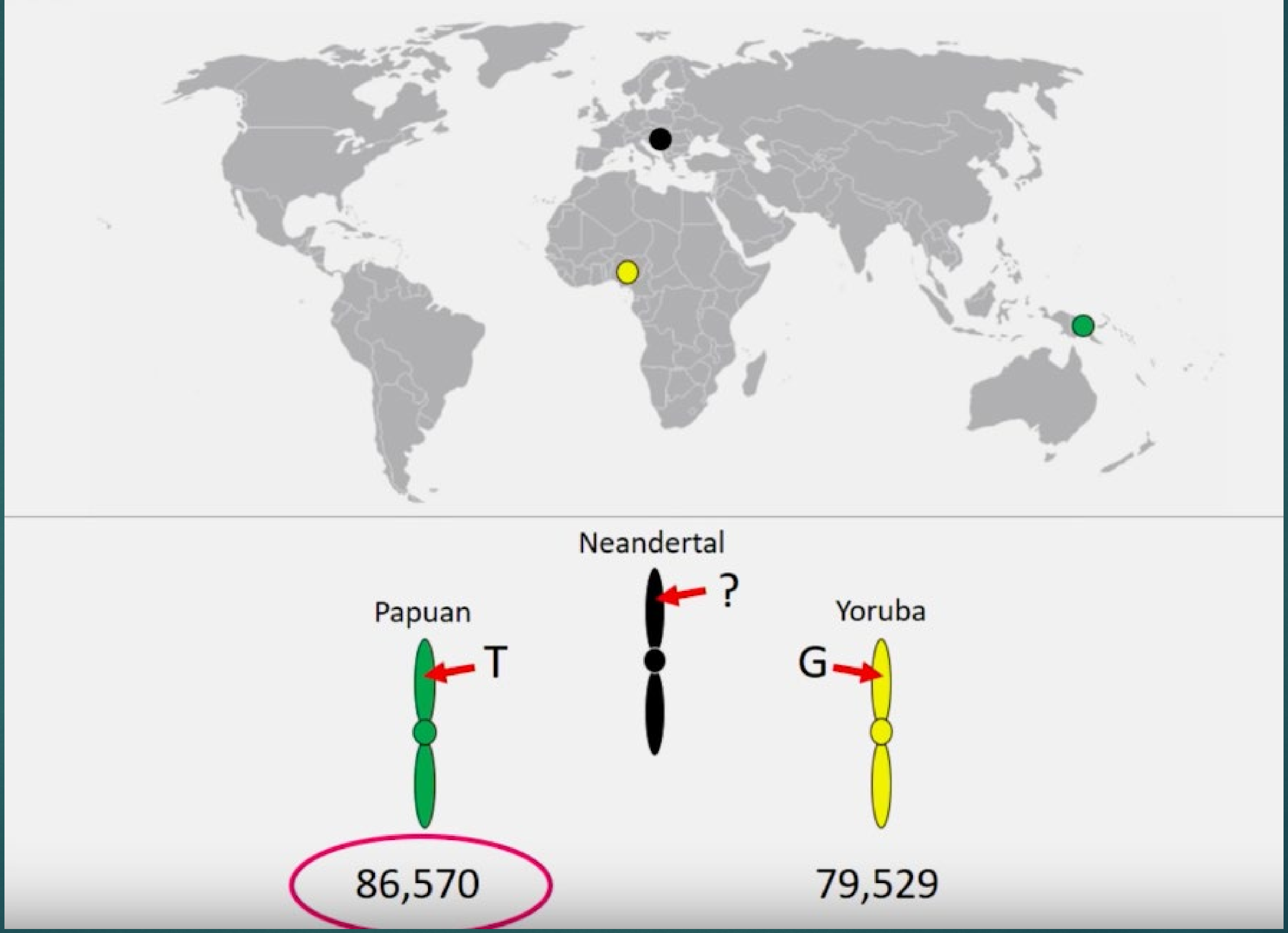
- Sample of MH, mEve, 4 N:
  - Clearly, *Homo sapiens* and *Homo Neanderthals* are quite different,
  - whereas the Neanderthals represent a pretty homogeneous group.
- The implication is that Ns are not the ancestors of modern humans.
- A divergence time for the two lines is estimated at 741 to 317 Ka.

Four Population Test: Chimp, N, 2 MHs



- Evaluation of whether two populations are consistent with descending from a common ancestral population through the "Four Population Test."
- For example, consider a mutation that occurred in the ancestors of the Neanderthal (letter T. above) that is not seen in chimpanzee DNA.
- There are about 9 percent more of these mutations shared with Europeans than with African genomes, reflecting a history of Neanderthal interbreeding into the ancestors of Europeans.

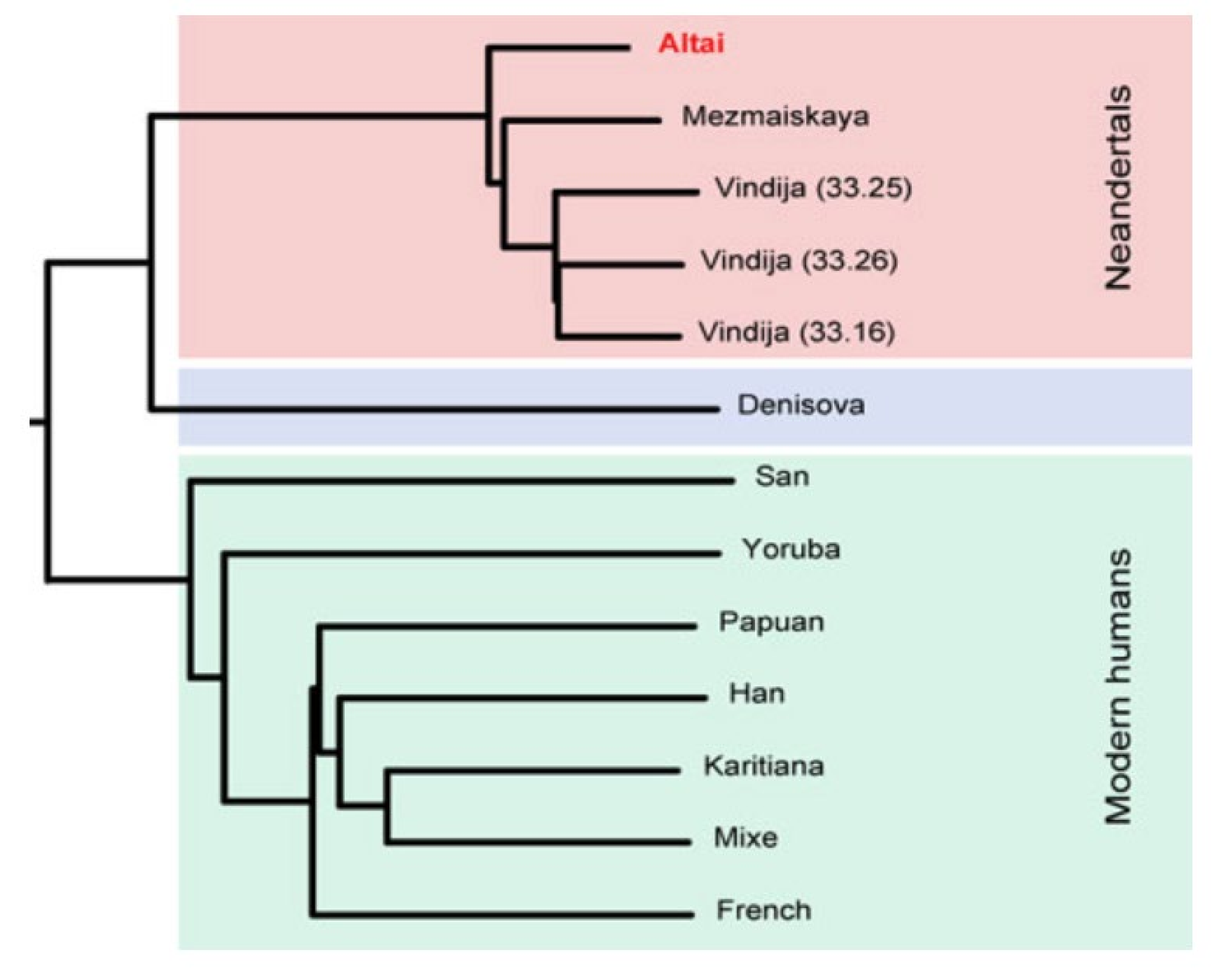
Expectation: If N and MHs interbreed, then Europeans should have more N matches than Africans or Asians



2010 Green study: Prediction

- If N-MH intermixing, predict more sharing of N genetic variation in Europe and Eurasia than in Africa between N and Africans, where N had never been
- Sample: 5 non-African people sequenced & compared to Africans
- Europeans matched more with N than with Africans
- Modern Humans have ~2.5% N DNA

2010: N and MH


Altai
Mezmaiskaya
Vindija (33.25)
Vindija (33.26)
Vindija (33.16)
Neandertals
Denisova
San
Yoruba
Papuan
Han
Karitiana
Mixe
French
Modern humans

Interbreeding in Middle East

- Interbreeding occurred in the Middle East between 45,000 and 80,000 years ago. (New genetic material places dates between 50,000 and 60,000 years ago. Balter, Michael, 2015).
- According to this scenario, some Neanderthal populations moved into the Middle East from Southern Europe and interbred with our species before modern humans did final Out of Africa migration.
- Thus, all non-African human populations carry between 1.5 to 2% Neanderthal DNA.

N DNA

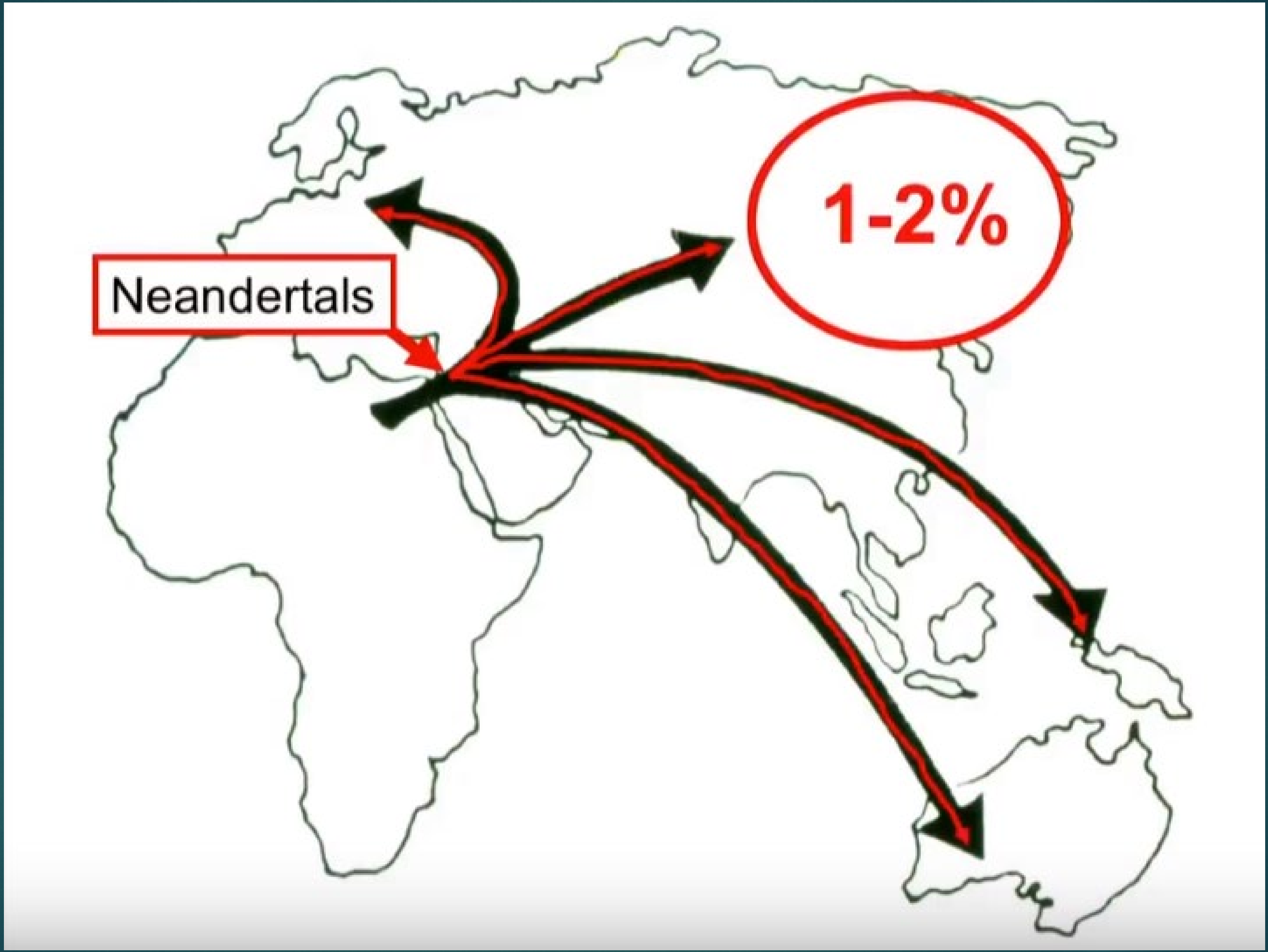
- MH and N share 99.85% of their DNA;
- only .15% different;
- 10 x more similar to MH than chimp to MH

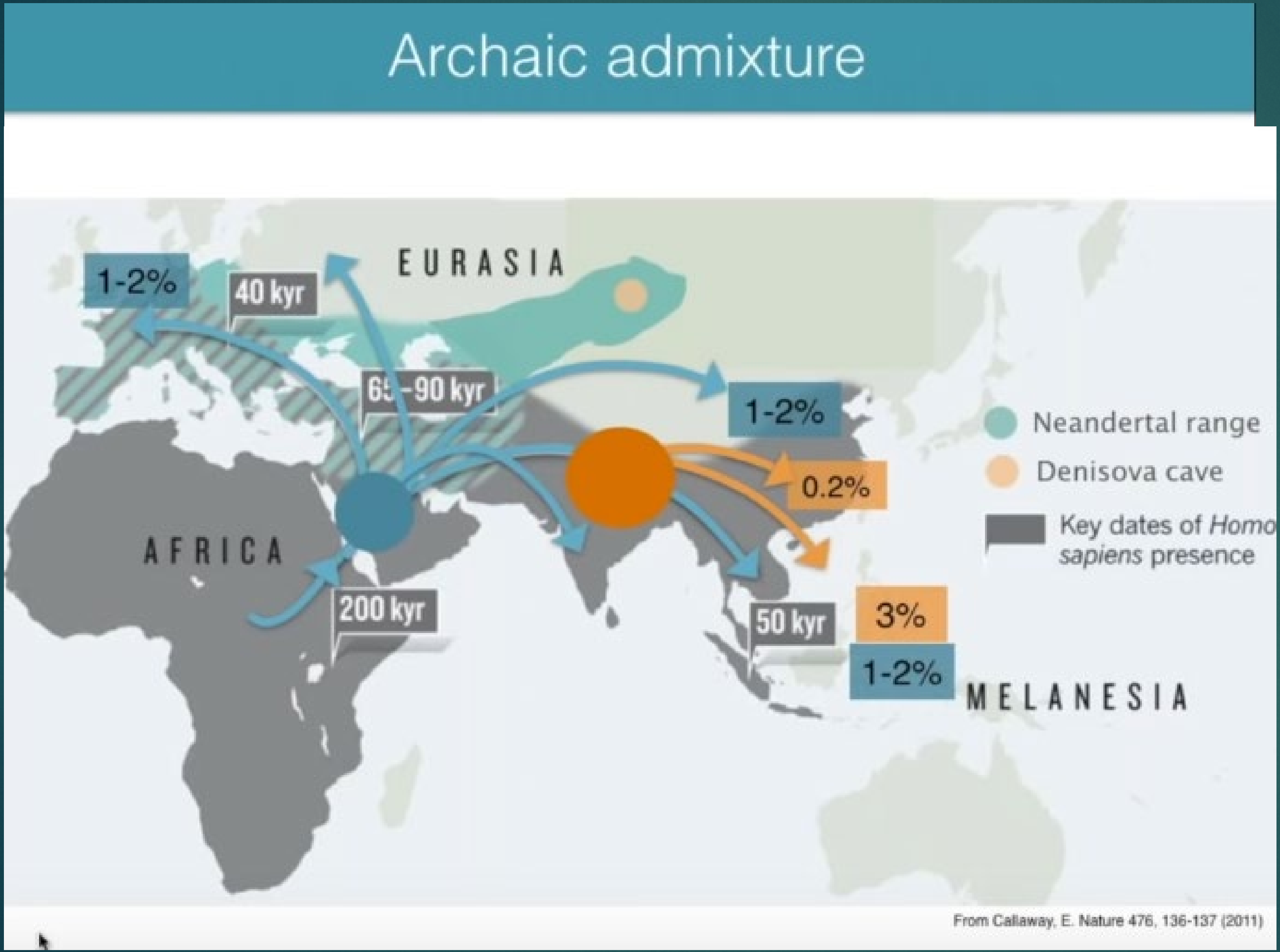
- All Non sub-Saharan MHs have N DNA; even N Africans and E Africans have some N DNA

- Later discovery of Ns in San and other African Tribes

N admixture: can evaluate population history

- If you compare 2 Africans with N, no difference
- If compare N with European or Chinese, see difference
- Pääbo model: MH mixed with Ns in Middle East,


Neandertals
1-2%



Archaic admixture

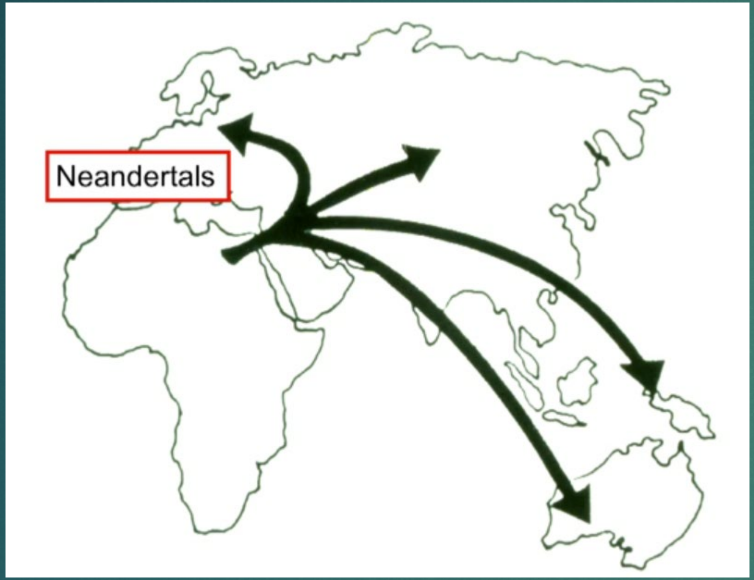
From Callaway, E. Nature 476, 136-137 (2011)

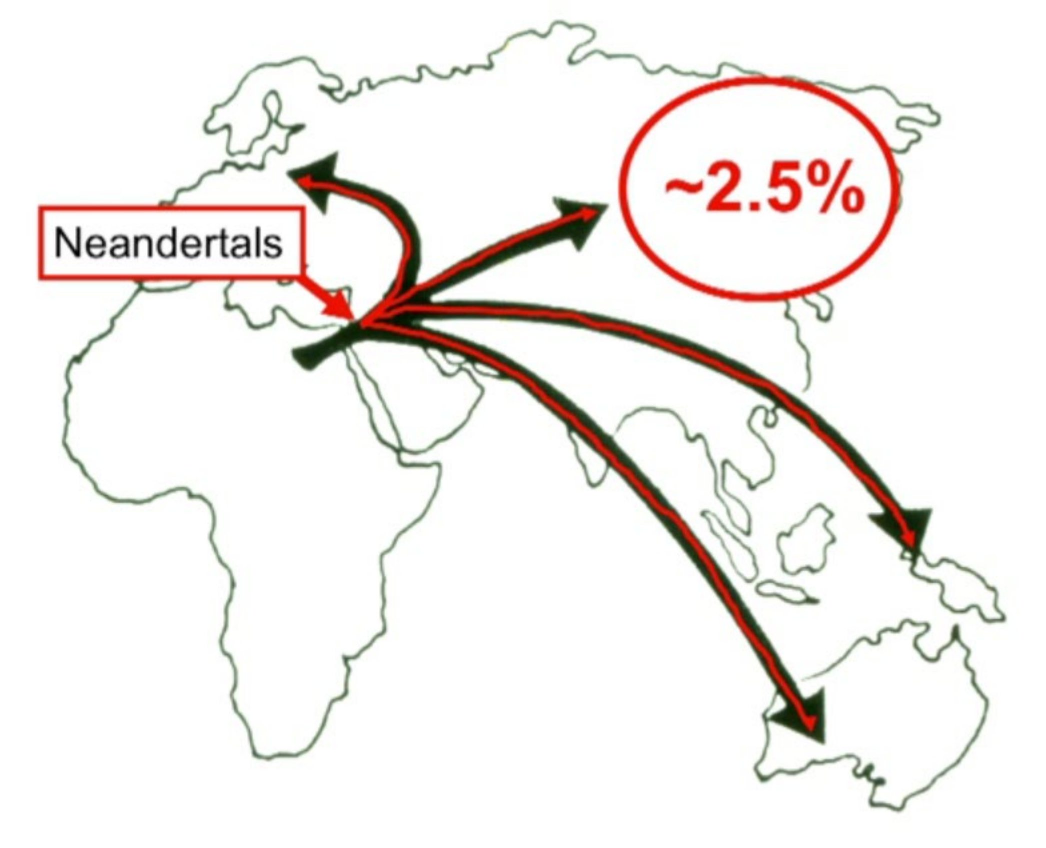
MH admixture with Ns

In all comparisons of non Africans with Africans, the non African had an excess of derived variants; applied to all non-African populations; Shared 2% N variants

Then came admix with Ds: .2% in Asia and 3-6% in New Guinea

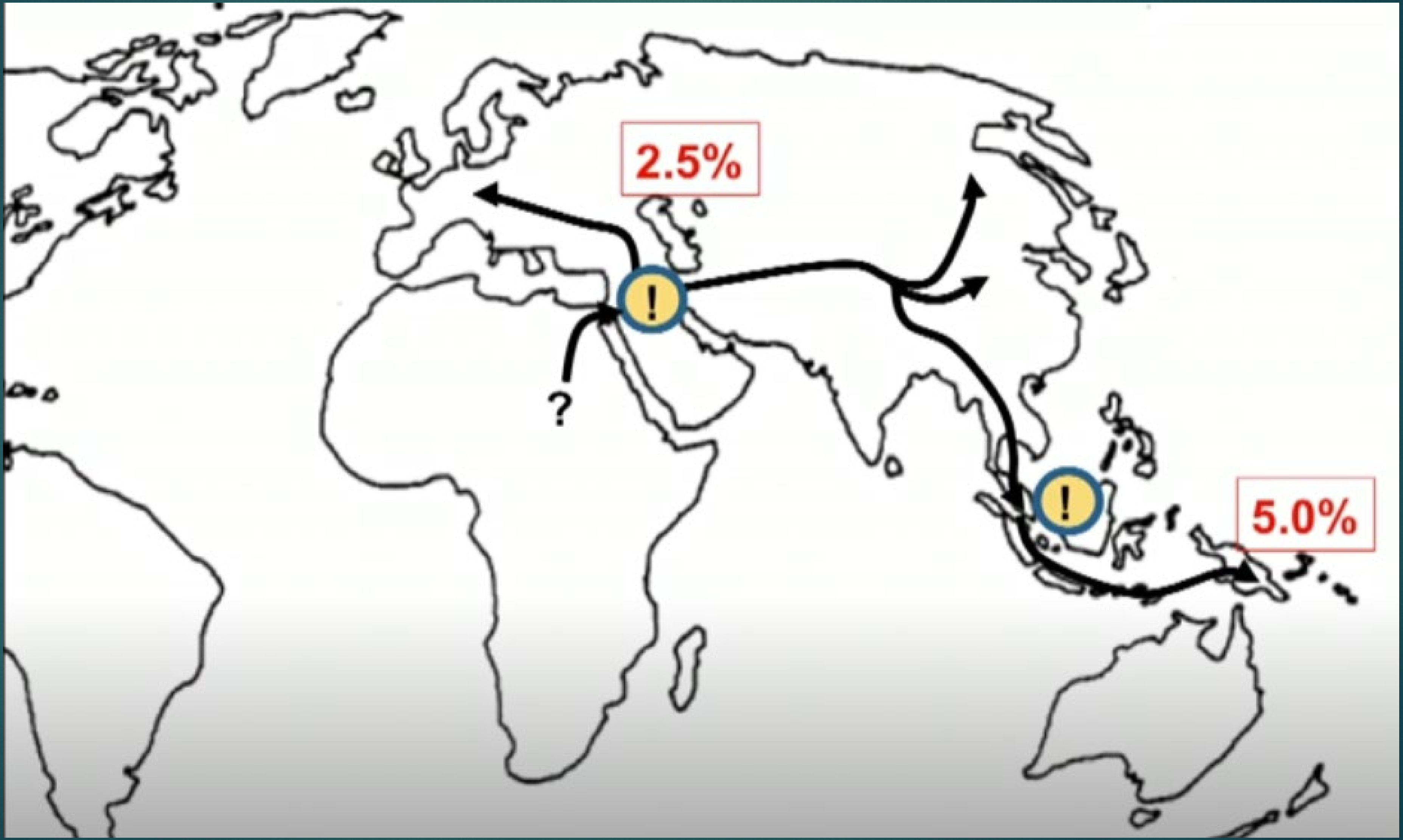
First MH and N contact in Middle East





- MH mixed first with N in Middle East ~50-90 Ka, then continued on to rest of world with N DNA
- Original theory: 20% more N DNA in Eurasia than in Europe

Denisovans, Ns & MHs: We have always mixed



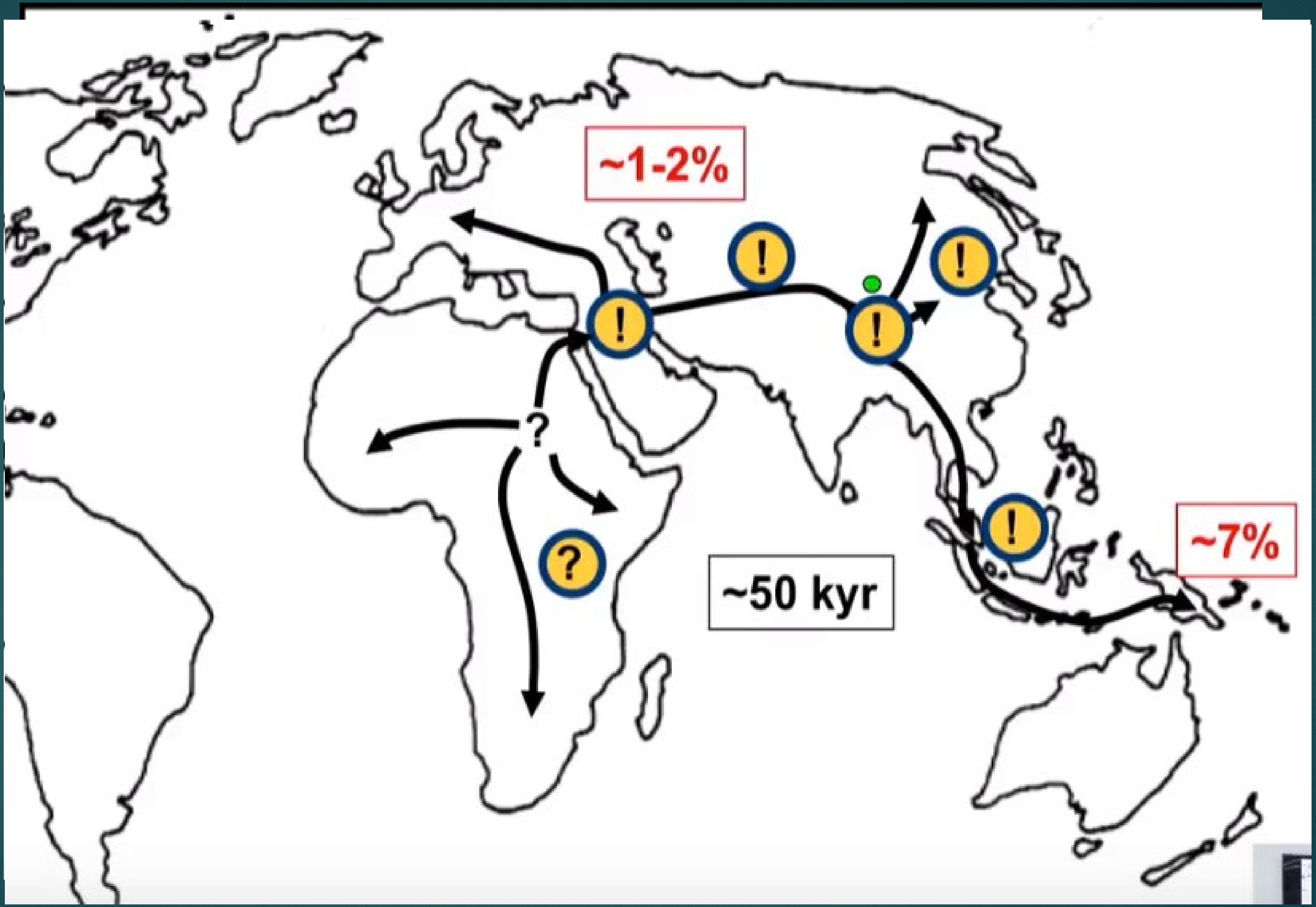
N and D regions and admixtures with MHs

MHs emerged from Africa Had several introgressions with N and Ds

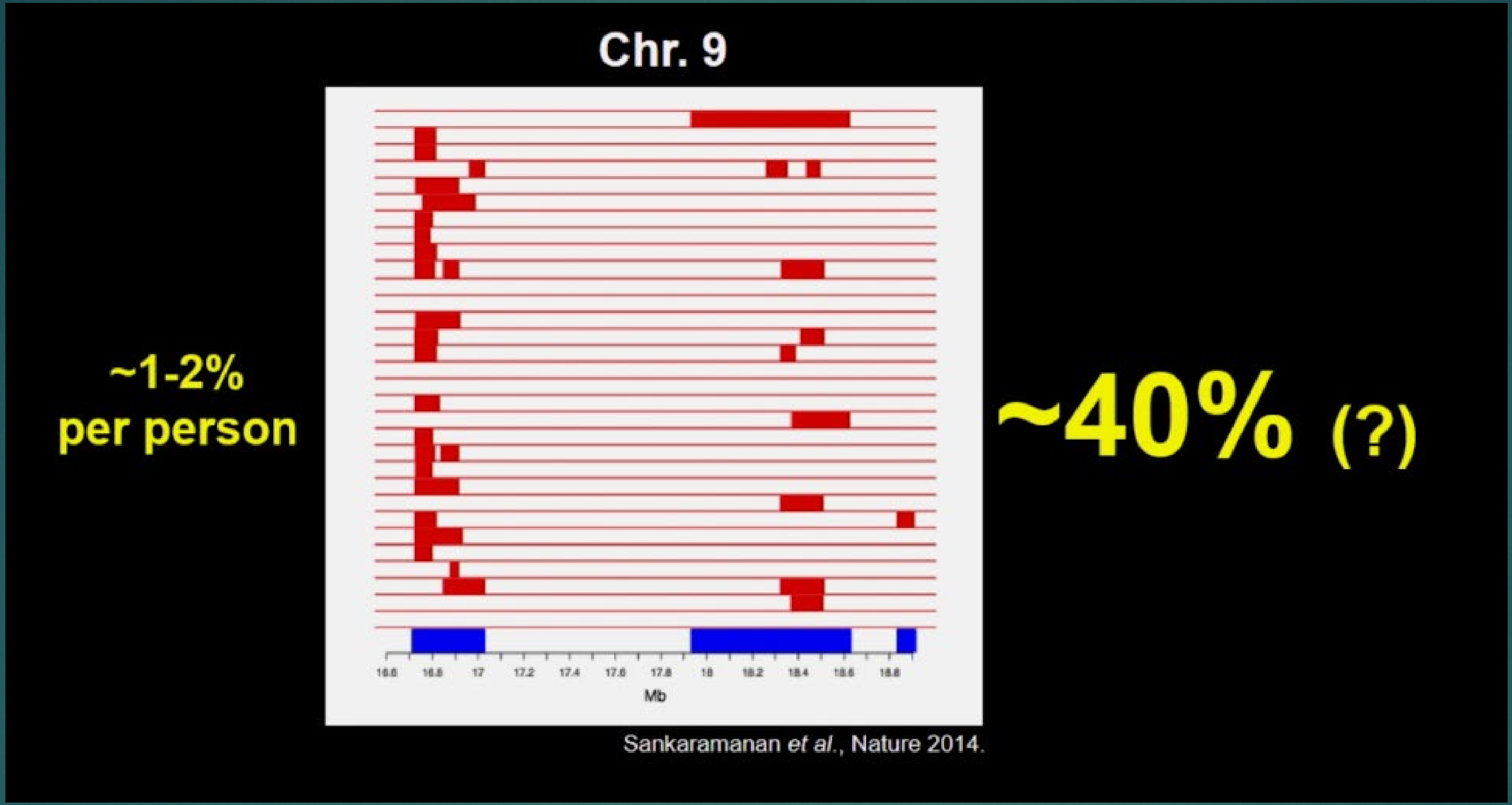
Asians carry 20-30% more N DNA than Europeans

Several D admixtures in Asia & Papua New Guinea

MHs in Africa: Introgression from archaic types; but no DNA yet



Example of N DNA fragments on Chromosome 9



Sankaramanan *et al.*, Nature 2014.

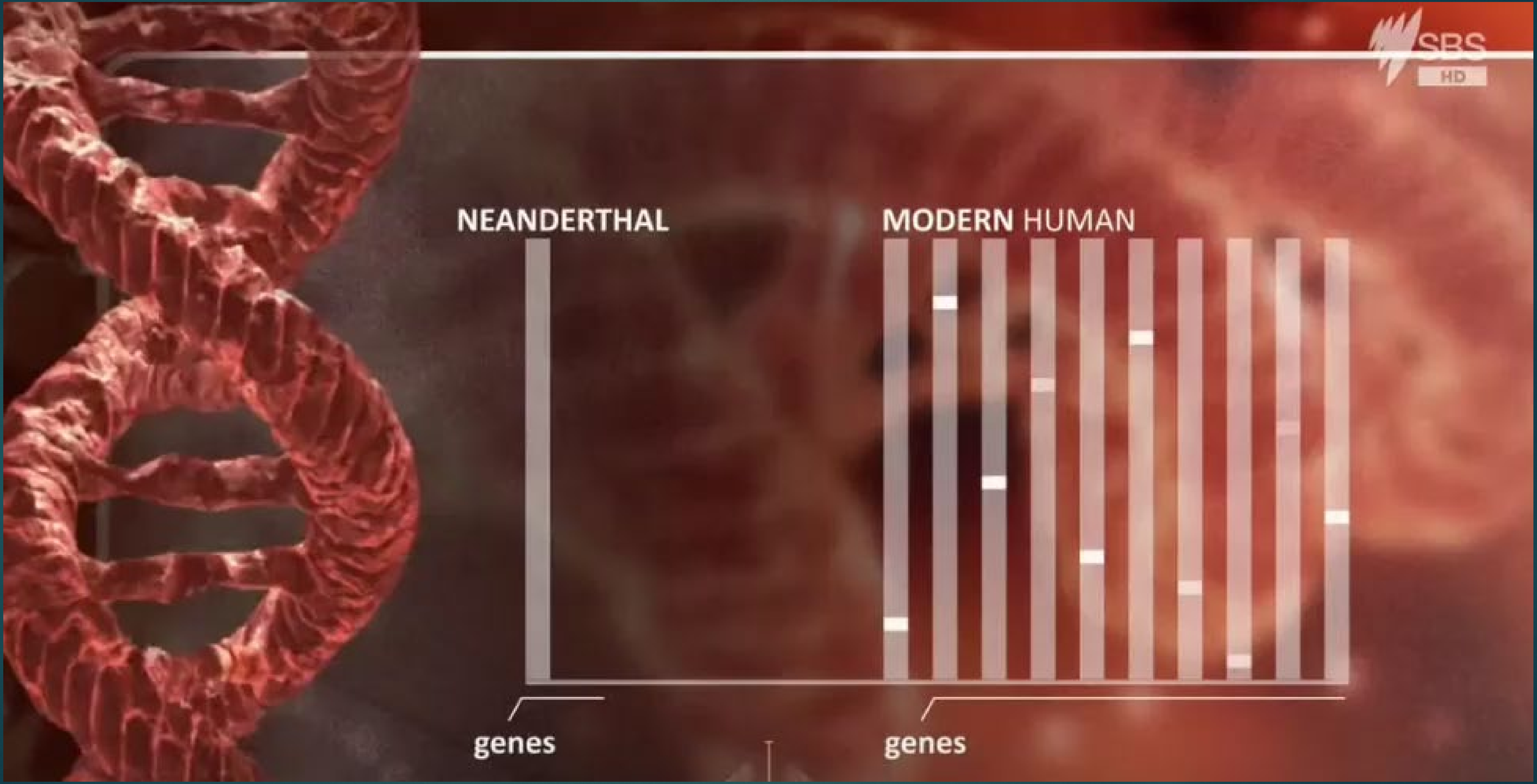
Different N fragments in different people:
totals to ~1-2% N DNA in each individual;
Total amount of N DNA in all people = ~40 % of N genome

S. Sankararaman:
Neandertal DNA in Different Modern Humans Not Same

- While only 1-2% of the total genome of moderns is Neandertal, this represents 20-40% of total Neandertal genome.

- Living Europeans have inherited around 1.2% and East Asians about 1.4% of their DNA from our Neandertal cousins.

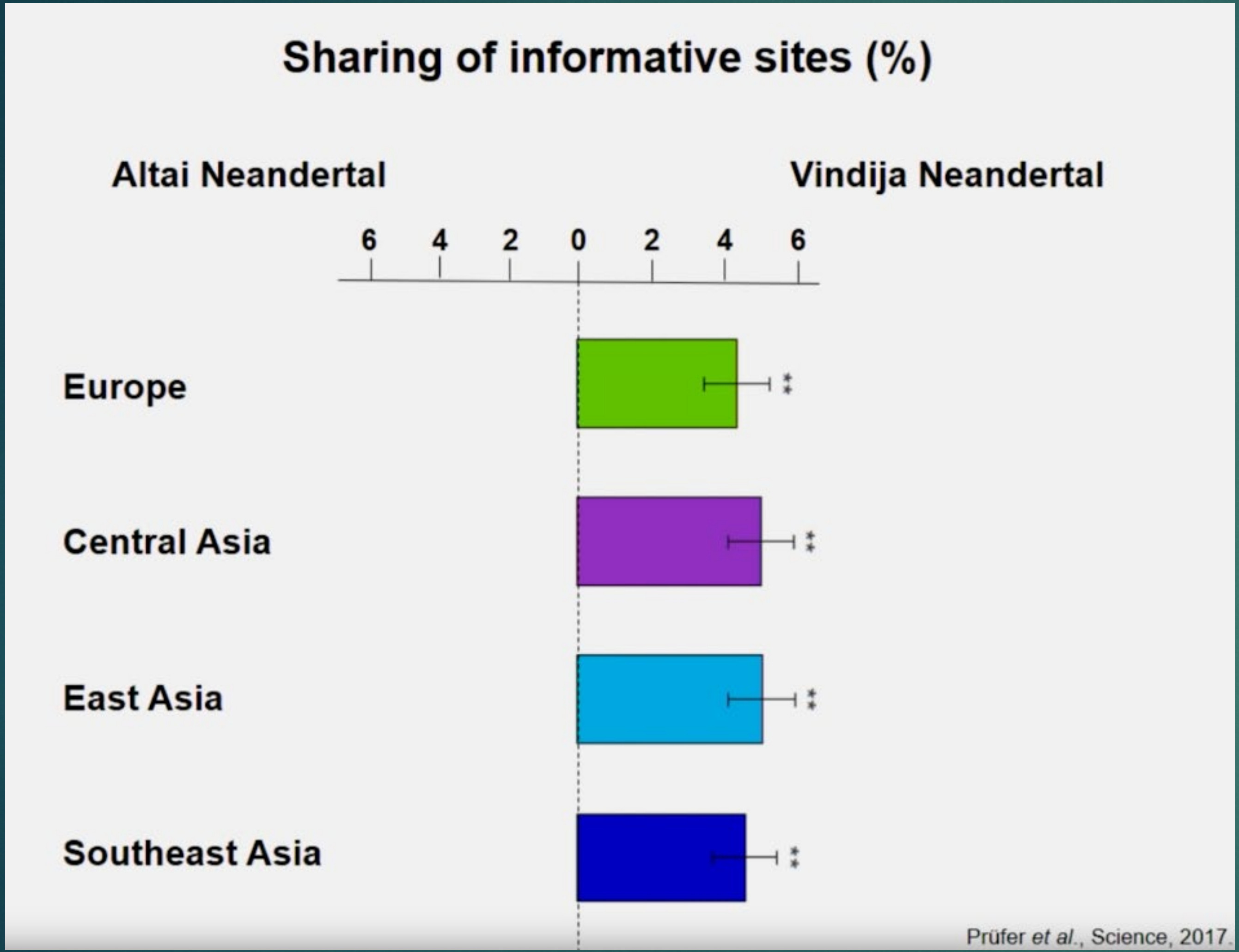
N genome: 20-40 % of N represented in MH genome



Introgressed genome: 40% in all MHs

- About 40% of the Neanderthal genome has been found introgressed or assimilated in the modern human population
- **Subpopulation admixture rate**
- A higher Neanderthal admixture was found in East Asians than in Europeans, which is estimated to be about 20% more introgression into East Asians.
- This could possibly be explained by
  - the occurrence of further admixture events in the early ancestors of East Asians after the separation of Europeans and East Asians,
  - dilution of Neanderthal ancestry in Europeans by populations with low Neanderthal ancestry from later migrations,
  - or natural selection that may have been relatively lower in East Asians than in Europeans.

Ns from Vindija, Croatia and from Denisova cave in Altai Mts.



Prüfer *et al.*, Science, 2017.

Modern humans share more N DNA from Vindija N than from Altai N

Ancient Nuclear DNA

- Oldest current ancient DNA is dated to 430 Ka: Sima de los Huesos
- Have been able to extract DNA of fossil hominin species, i.e. Ns, Ds
- Clear evidence of N DNA in MH DNA
- Denisovan DNA also has shown intrusion into MH DNA; variable amounts in MHs, esp. those from SE Asia

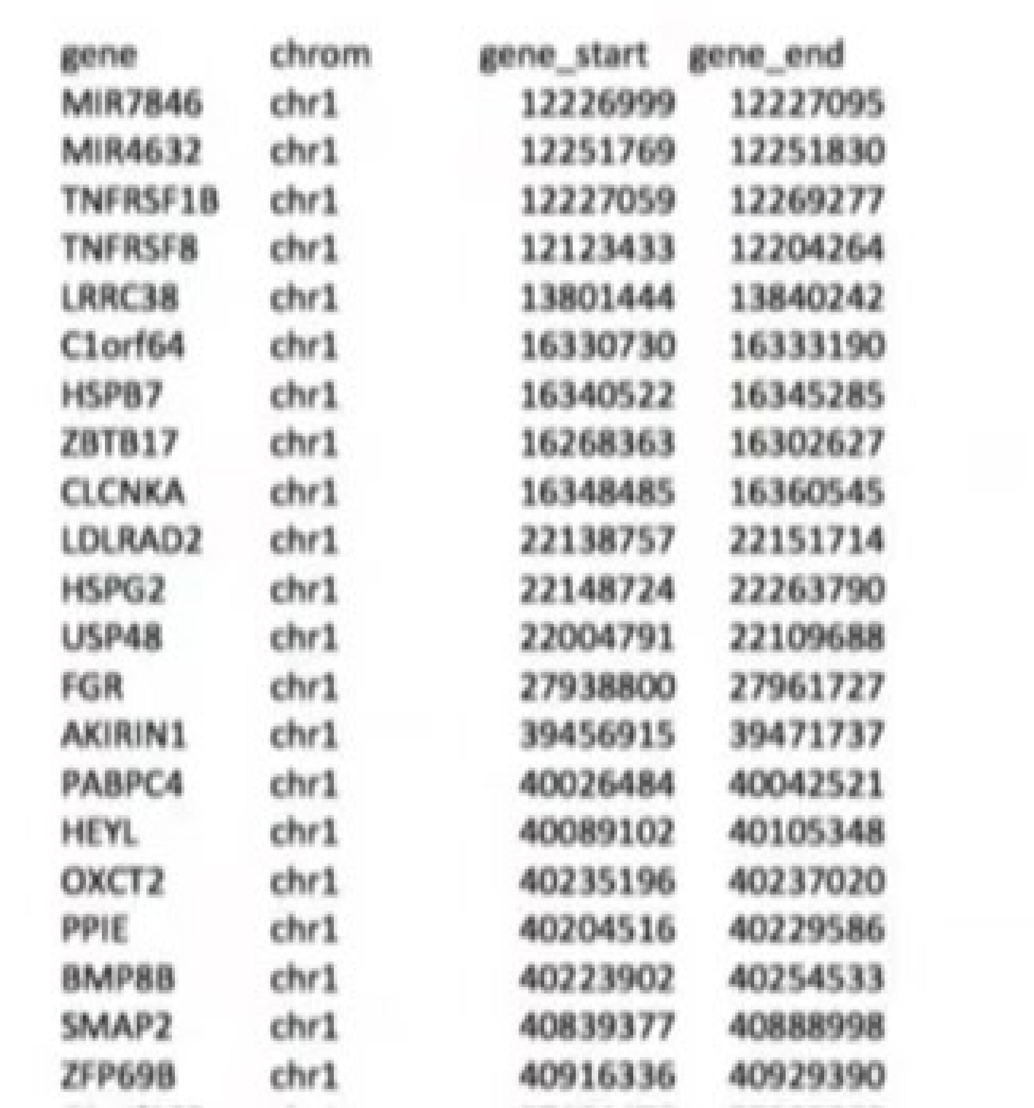
N genes in MHs & vice versa

- The Neanderthal genome project (2010 and 2014):
  - Neanderthals contributed to the DNA of modern humans, through interbreeding, likely between 50 to 60 Ka

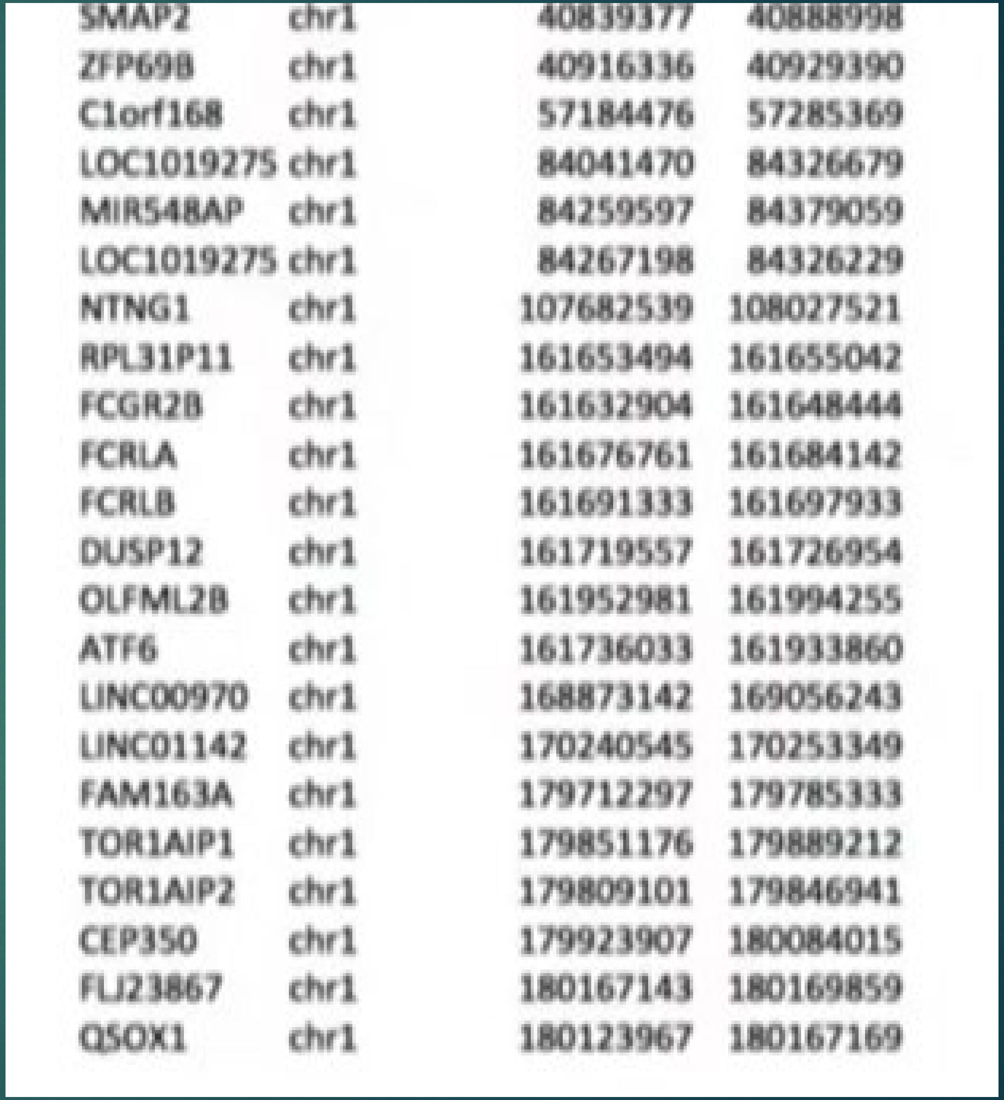
- A few Neanderthals began mating with ancestors of modern humans long before the large "out of Africa migration" of the present-day non-Africans, as early as 100,000 years ago.

- In 2016, research indicated that there were three distinct episodes of interbreeding between modern humans and Neanderthals:
  - the first encounter involved the ancestors of non-African modern humans, probably soon after leaving Africa, at ~100 Ka
  - the second, after the ancestral Melanesian MH group had branched off (and subsequently had a unique episode of interbreeding with Denisovans);
  - the third, involving the ancestors of East Asians only.

Some N genes

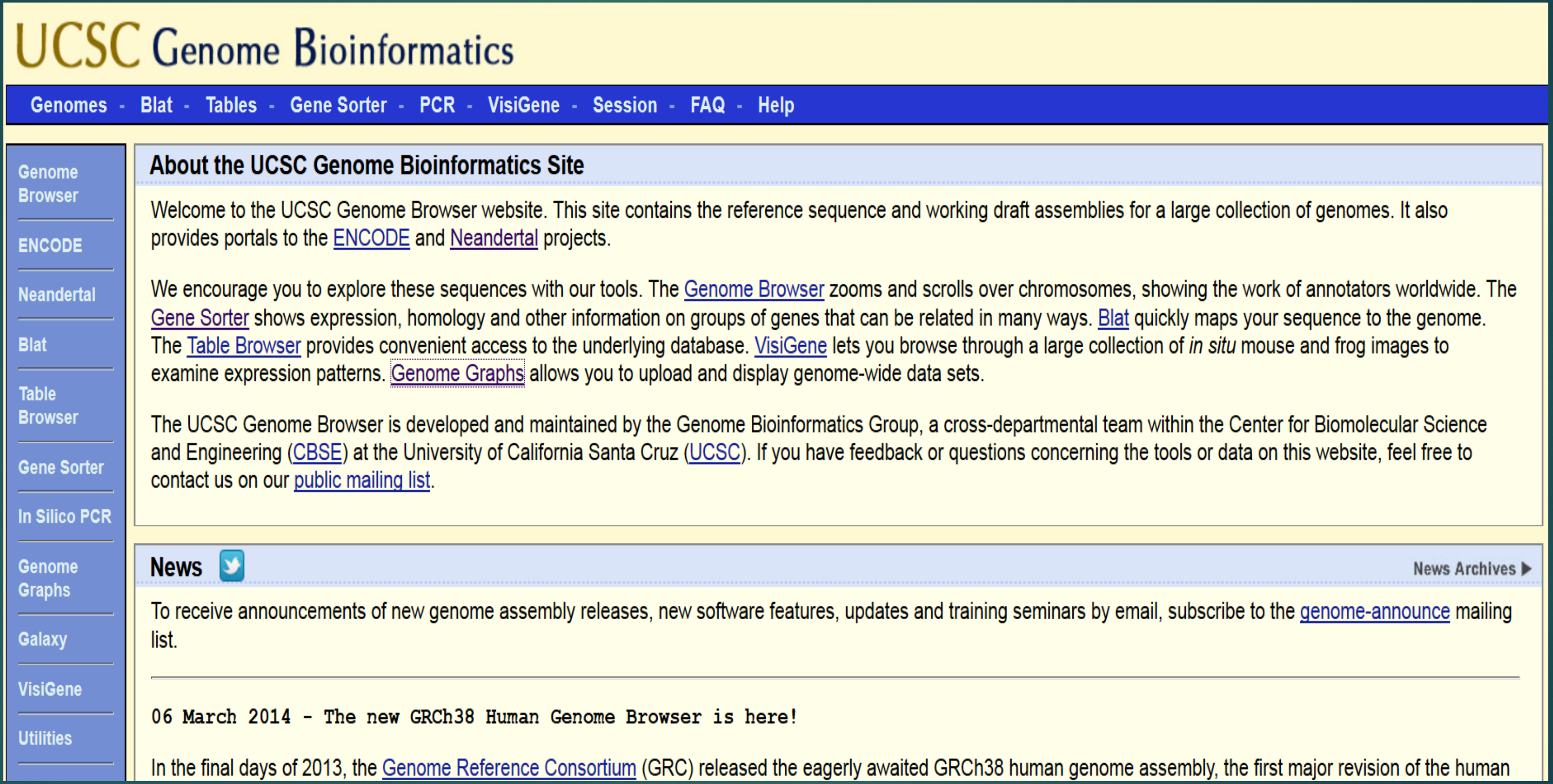


gene	chrom	gene_start	gene_end
MIR7846	chr1	12226999	12227095
MIR4632	chr1	12251769	12251830
TNFRSF1B	chr1	12227059	12269277
TNFRSF8	chr1	12123433	12204264
LRRC38	chr1	13801444	13840242
C1orf64	chr1	16330730	16333190
HSPB7	chr1	16340522	16345285
ZBTB17	chr1	16268363	16302627
CLCNKA	chr1	16348485	16360545
LDLRAD2	chr1	22138757	22151714
HSPG2	chr1	22148724	22263790
USP48	chr1	22004791	22109688
FGR	chr1	27938800	27961727
AKIRIN1	chr1	39456915	39471737
PABPC4	chr1	40026484	40042521
HEYL	chr1	40089102	40105348
OXCT2	chr1	40235196	40237020
PPIE	chr1	40204516	40229586
BMP8B	chr1	40223902	40254533
SMAP2	chr1	40839377	40888998
ZFP69B	chr1	40916336	40929390



SMAP2	chr1	40839377	40888998
ZFP69B	chr1	40916336	40929390
C1orf168	chr1	57184476	57285369
LOC1019275	chr1	84041470	84326679
MIR548AP	chr1	84259597	84379059
LOC1019275	chr1	84267198	84326229
NTNG1	chr1	107682539	108027521
RPL31P11	chr1	161653494	161655042
FCGR2B	chr1	161632904	161648444
FCRLA	chr1	161676761	161684142
FCRLB	chr1	161691333	161697933
DUSP12	chr1	161719557	161726954
OLFML2B	chr1	161952981	161994255
ATF6	chr1	161736033	161933860
LINC00970	chr1	168873142	169056243
LINC01142	chr1	170240545	170253349
FAM163A	chr1	179712297	179785333
TOR1AIP1	chr1	179851176	179889212
TOR1AIP2	chr1	179809101	179846941
CEP350	chr1	179923907	180084015
FLJ23867	chr1	180167143	180169859
QSOX1	chr1	180123967	180167169

UCSC Genome Site:
Browse N Genome



About the UCSC Genome Bioinformatics Site

Welcome to the UCSC Genome Browser website. This site contains the reference sequence and working draft assemblies for a large collection of genomes. It also provides portals to the ENCODE and Neandertal projects.

We encourage you to explore these sequences with our tools. The Genome Browser zooms and scrolls over chromosomes, showing the work of annotators worldwide. The Gene Sorter shows expression, homology and other information on groups of genes that can be related in many ways. Blat quickly maps your sequence to the genome. The Table Browser provides convenient access to the underlying database. VisiGene lets you browse through a large collection of *in situ* mouse and frog images to examine expression patterns. Genome Graphs allows you to upload and display genome-wide data sets.

The UCSC Genome Browser is developed and maintained by the Genome Bioinformatics Group, a cross-departmental team within the Center for Biomolecular Science and Engineering (CBSE) at the University of California Santa Cruz (UCSC). If you have feedback or questions concerning the tools or data on this website, feel free to contact us on our public mailing list.

News

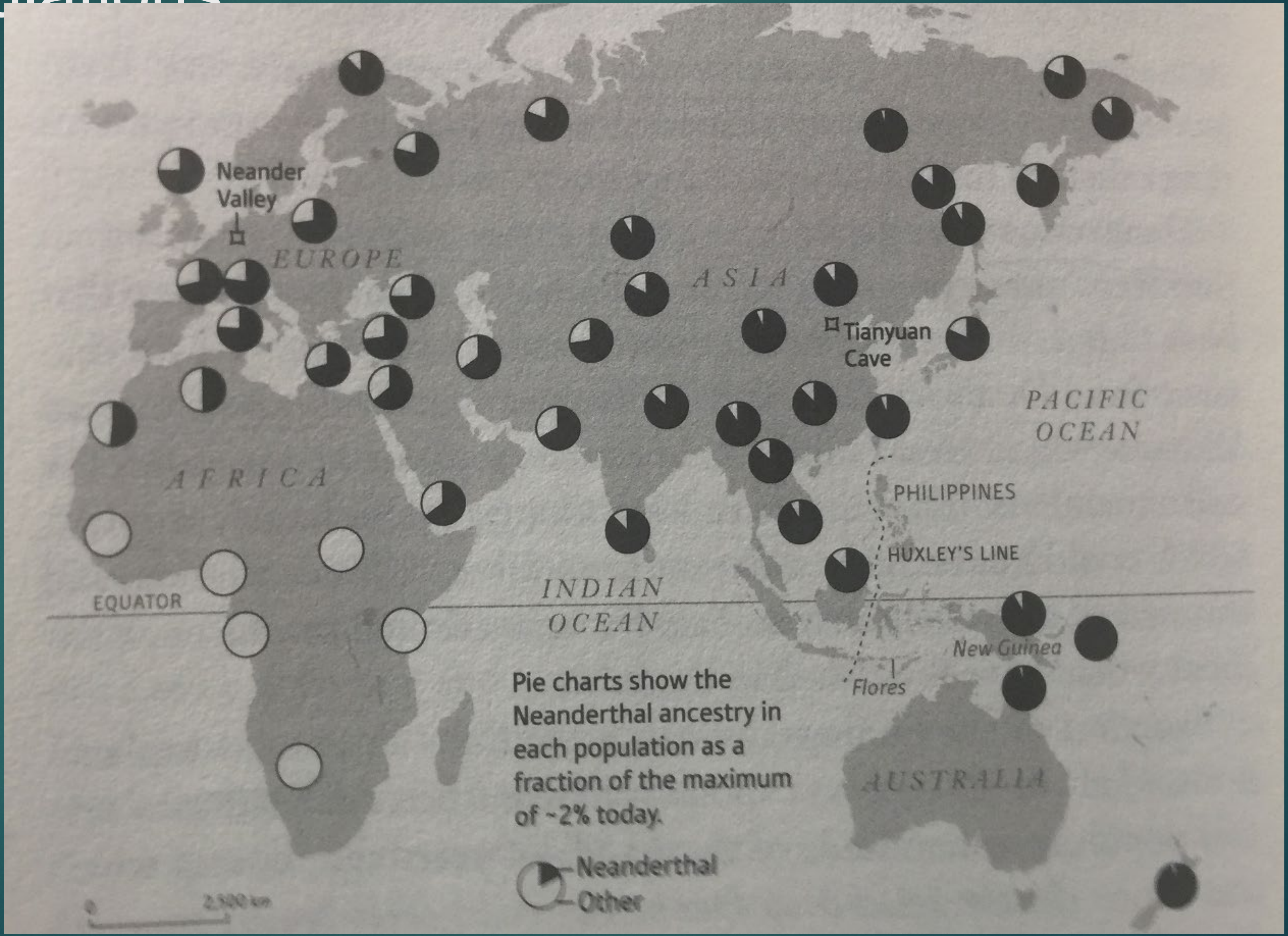
To receive announcements of new genome assembly releases, new software features, updates and training seminars by email, subscribe to the genome-announce mailing list.

`06 March 2014 - The new GRCh38 Human Genome Browser is here!`

In the final days of 2013, the Genome Reference Consortium (GRC) released the eagerly awaited GRCh38 human genome assembly, the first major revision of the human

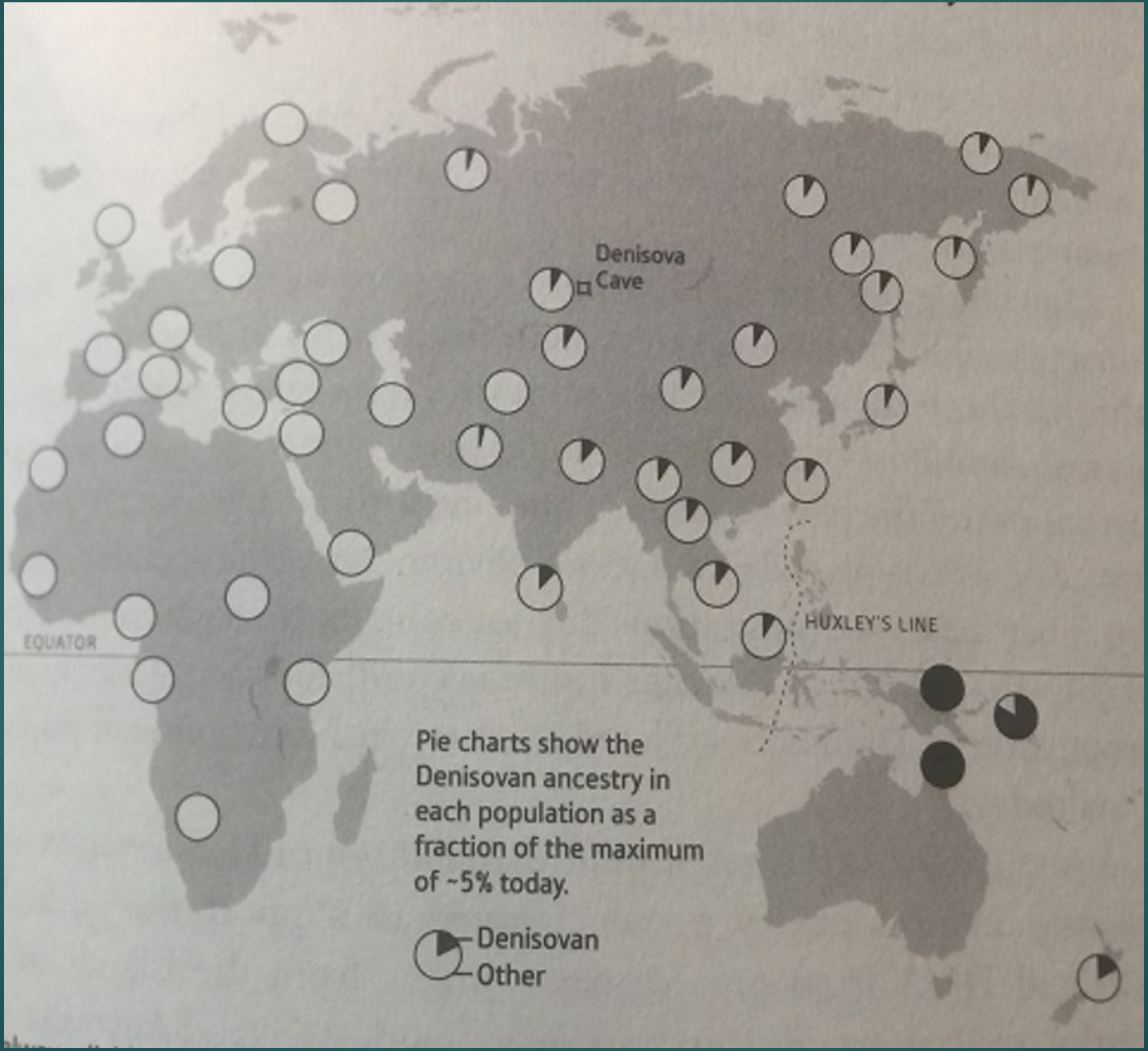
http://genome.ucsc.edu/

N ancestry (fraction of maximum 2%) in various Eurasian populations



Pie charts show the Neanderthal ancestry in each population as a fraction of the maximum of ~2% today.

Proportions of Denisovan Ancestry (fraction of max 5%)in People Tod



Pie charts show the Denisovan ancestry in each population as a fraction of the maximum of ~5% today.

A Plausible Scenario in Which Modem Human Ancestors Were Not Always in Africa – David Reich

- Conventional View: Our Lineage was always in Africa – at least 4 major migrations
  - 1 - ~1,800,000 ya: First major migration of humans to Eurasia from Africa
  - 2- After 1,400.000- 900,000 ya: Second archaic lineage enters Eurasia from Africa, giving rise to superarchaic human lineage. (found in D DNA)
  - 3 - After 770,000-550,000 ya Third archaic lineage enters Eurasia from Africa, giving rise to ancestors of Neanderthals and Denisovans.
  - 4 – After ~50,000 ya: Modern humans expand out of Africa & Near East

- Alternative View: As few as 3 major migrations
  - 1 - ~1,800,000 ya: First major migration of humans to Eurasia from Africa
    - Ancestors of Denisovans. Neanderthals, and superarchaic humans develop outside of Africa.
  - 2 - Before 300,000 *ya:* Ancestors of modern humans return to Africa.
  - 3 - After ~50,000 ya: Modern humans expand out of Africa & Near East.

Maria Martinon-Torres & Roin + +-Dennell

Origins of modern human ancestry

- 4 Episodes of gene flow from Eurasian archaic humans:
- 1. Gene flow from Neanderthals
- The first archaic admixture event resulted in approximately 2% Neanderthal ancestry in present-day populations outside of sub-Saharan Africa and is found in all non-African modern human genomes (up to around 45 ka), including early ancient individuals in Belgium, western Siberia and China.
- Neanderthal ancestry is also present in smaller amounts in East and West Africa, from later gene flow from Eurasia.

Gene flow: SW Asia

- The geographical ubiquity of Neanderthal ancestry outside of Africa has suggested that the admixture occurred in or close to Southwest Asia, but no explicit evidence is available so far.

- Late Neanderthals in Europe do not appear to have contributed ancestry to present-day populations.
- A central feature of the geographical distribution of Neanderthal ancestry today is
  - an approximately one fifth to one tenth lower proportion in western compared to eastern Eurasian populations, with intermediate levels in South and Central Asia.
  - This reflects multiple admixture events, but currently, the most likely explanation is a process of dilution by early ‘basal Eurasian’ groups that carried little to no Neanderthal ancestry.

Origins of modern human ancestry

- Comparisons of Neanderthal DNA segments in present-day humans indicate that, while the diversity of the N source population was low, more than a few individuals must have contributed.
- Neanderthal ancestry today is depleted by about one third around noncoding genic regions and promoters, probably due to genetic load accumulated because of low Neanderthal population sizes.
- Natural selection rapidly brought an initial N gene proportion as high as around 10% down to the present-day levels of about 2%.
- We cannot presently rule out an 'assimilation' scenario in which Neanderthals were absorbed into a larger expanding modern human population.

Bergström

3) Origins of modern human ancestry - Denisovans

- 2 Gene flow from Denisovans

- The second strongly supported admixture event gave rise to up to approximately 4-6% Denisovan-related ancestry in present-day Oceanian individuals.

- Ancestry deriving from this admixture event is present across Southeast Asia and Oceania, and in very small amounts (around 0.1-0.2%) in East Asian, South Asian and Native American populations.

- A major enduring question is where this admixture took place, as the Denisovan individual from Siberia is only distantly related to the source population of hypothetical ‘southern Denisovans’.

Origins of modern human ancestry - Denisovans

- Denisovan segments in present-day Oceanian genomes are longer than Neanderthal segments, and it has therefore been estimated that this admixture occurred more recently than Neanderthal admixture, around 45–55 ka.

- Like Neanderthal ancestry, Denisovan ancestry today is depleted around functional regions of the genome and was therefore probably subject to a similar process of negative selection.

Gene Flow: 2 Denisovan lineages

- 3. The third strongly supported admixture event in the ancestry of present-day people is from a second, distinct Denisovan population into the ancestors of present-day East Asian people, found in proportions in the order of 0.1%.

- This population was more closely related to the Denisovans from Siberia.

- East Asian populations can thus trace very small amounts of ancestry to two distinct Denisovan-related groups.

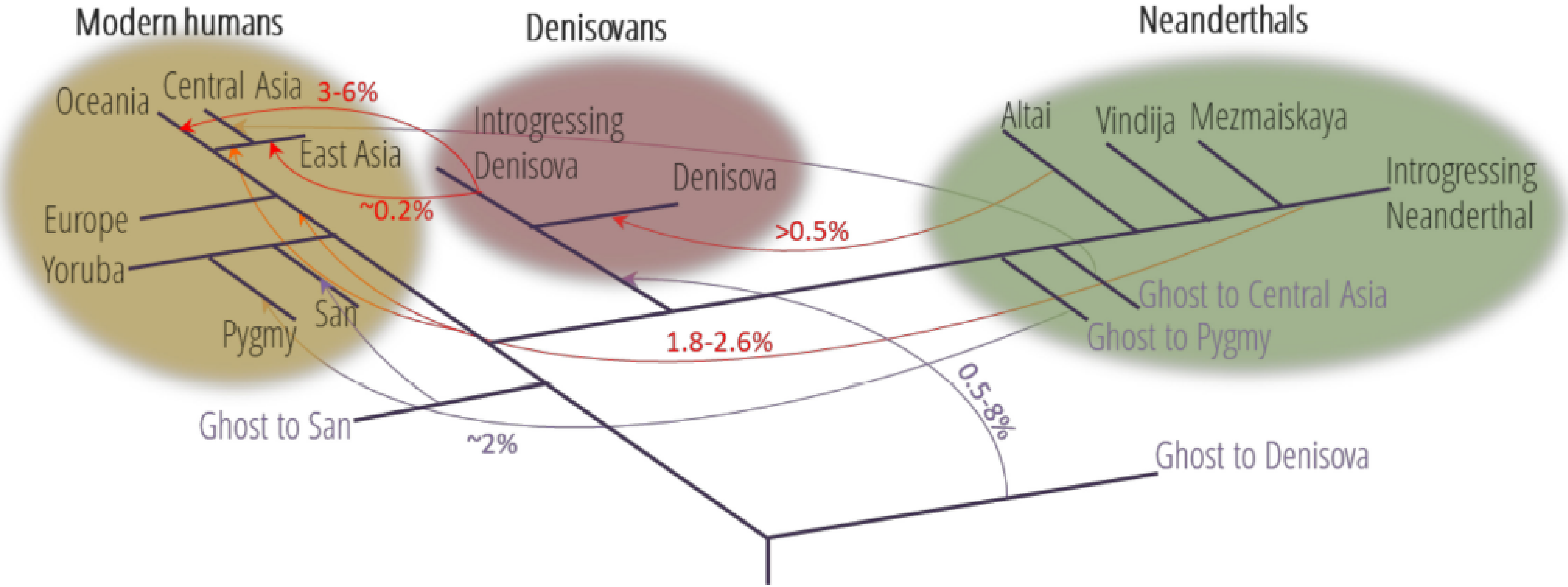
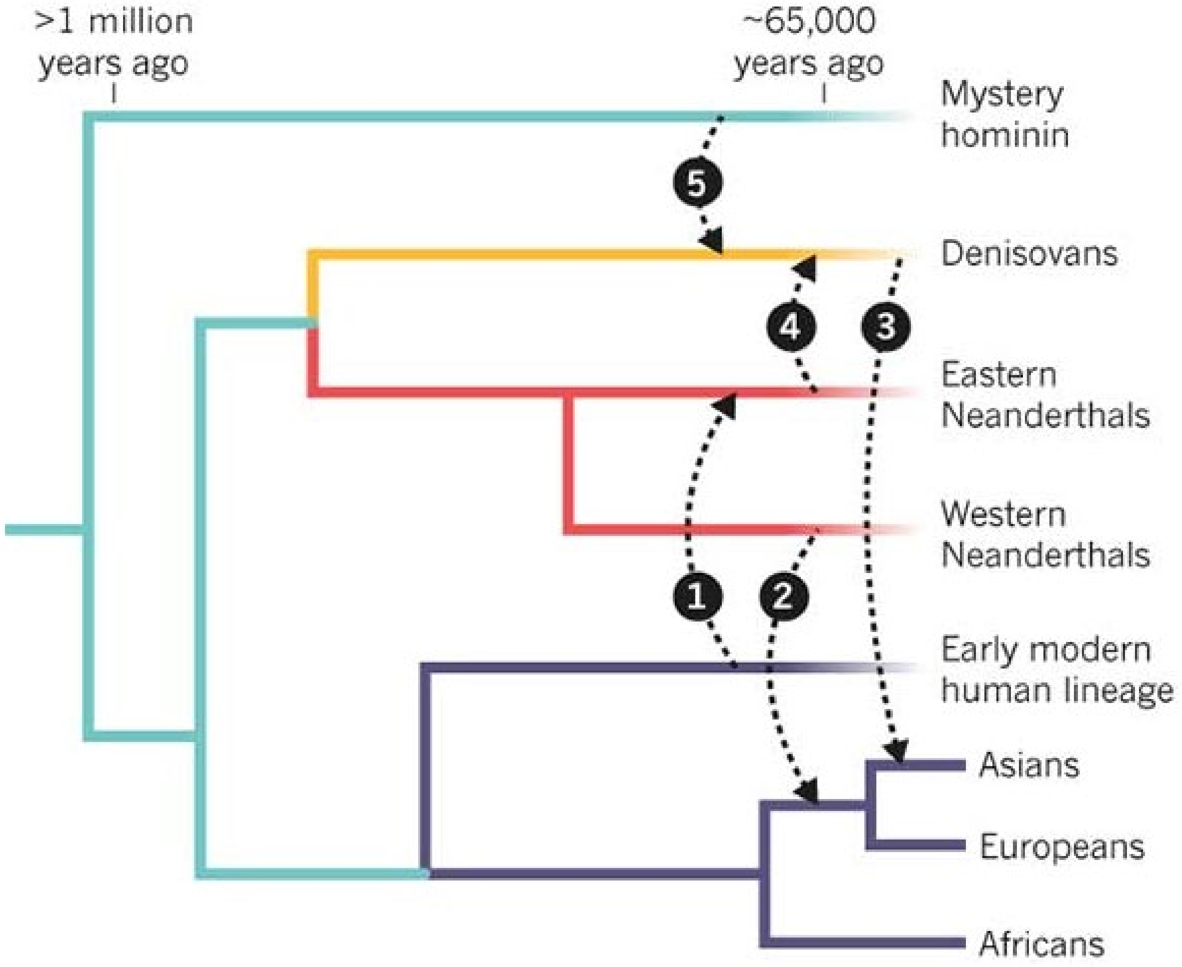


Figure 1. Family tree of the four groups of early humans living in Eurasia 50,000 years ago and the inferred gene flow between the groups due to interbreeding (based on [12–16]). The direction and estimated magnitude of inferred gene flow events are shown. Branch lengths and timing of gene flows are not scaled. Light violet color indicates introgression events from unknown archaic populations (Ghost).

A HISTORY OF INTERBREEDING

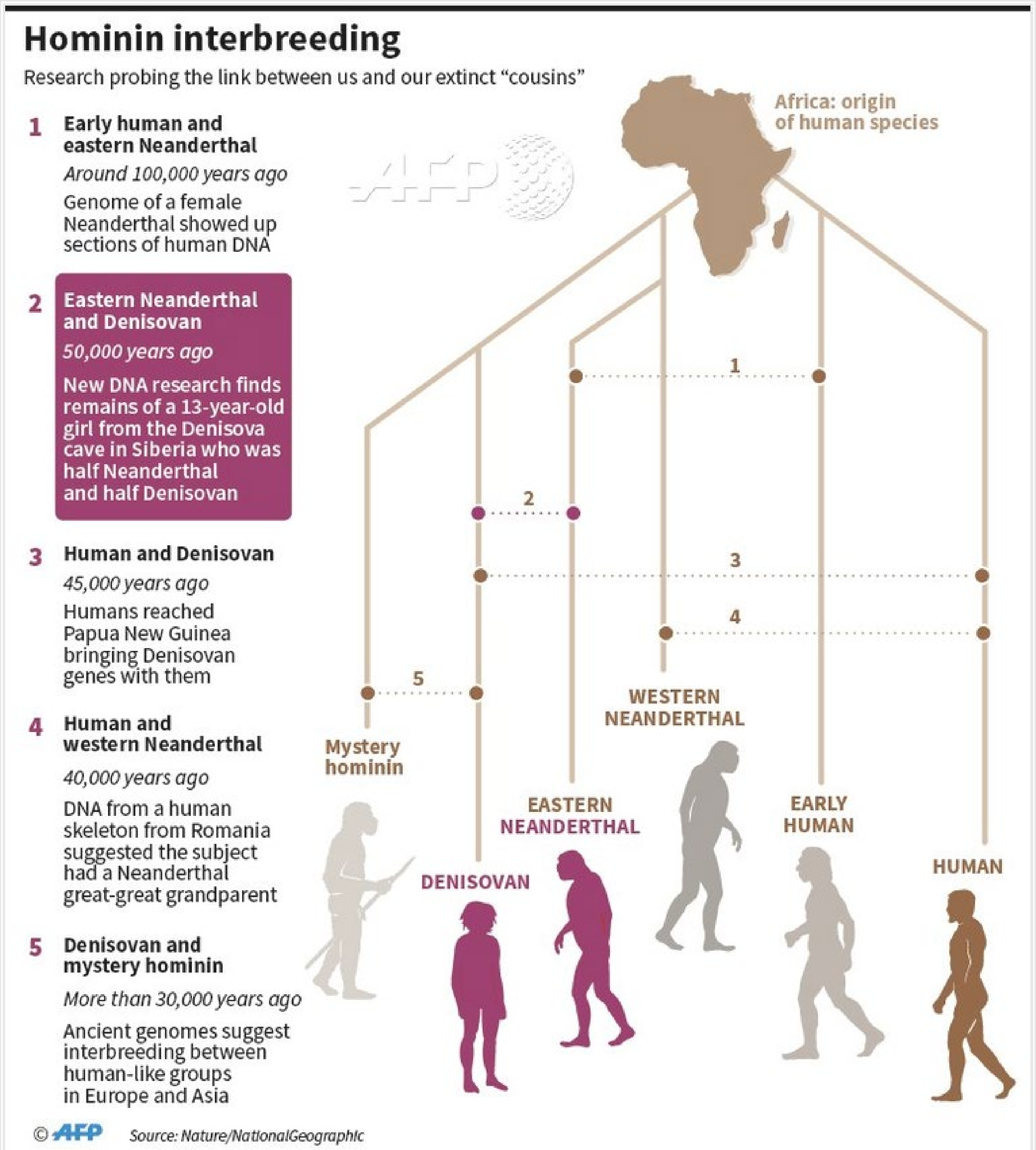
Early modern humans, Denisovans, and Neanderthals all interbred with each other on multiple occasions in the past 100,000 years.



---- Interbreeding episode/event

©nature

NATURE NEWS, FEBRUARY 17, 2016 DOI:10.1038/NATURE.2016.19394



Hominin interbreeding

Research probing the link between us and our extinct “cousins”

1 Early human and eastern Neanderthal

Around 100,000 years ago

Genome of a female Neanderthal showed up sections of human DNA

2 Eastern Neanderthal and Denisovan

50,000 years ago

New DNA research finds remains of a 13-year-old girl from the Denisova cave in Siberia who was half Neanderthal and half Denisovan

3 Human and Denisovan

45,000 years ago

Humans reached Papua New Guinea bringing Denisovan genes with them

4 Human and western Neanderthal

40,000 years ago

DNA from a human skeleton from Romania suggested the subject had a Neanderthal great-great grandparent

5 Denisovan and mystery hominin

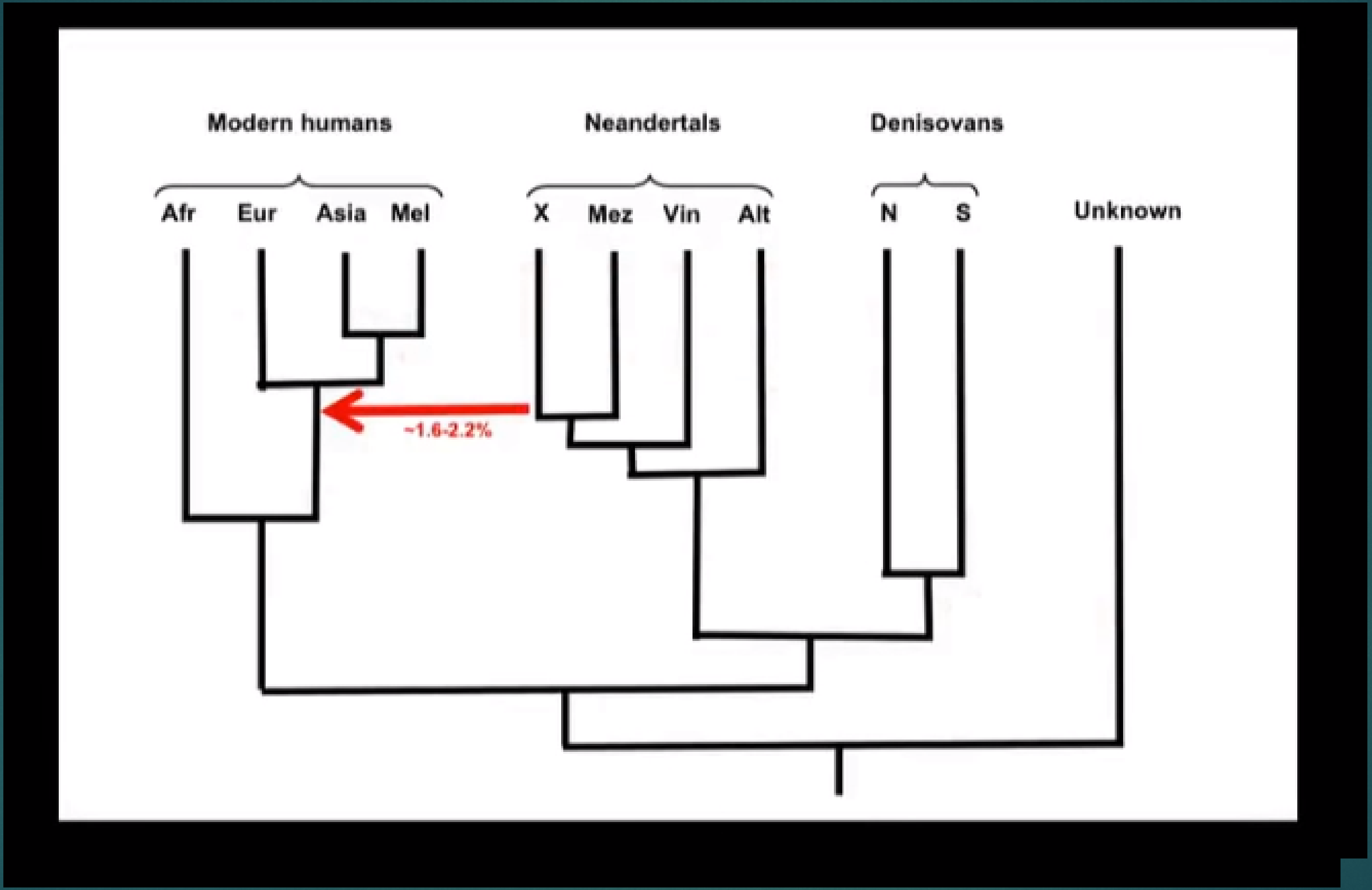
More than 30,000 years ago

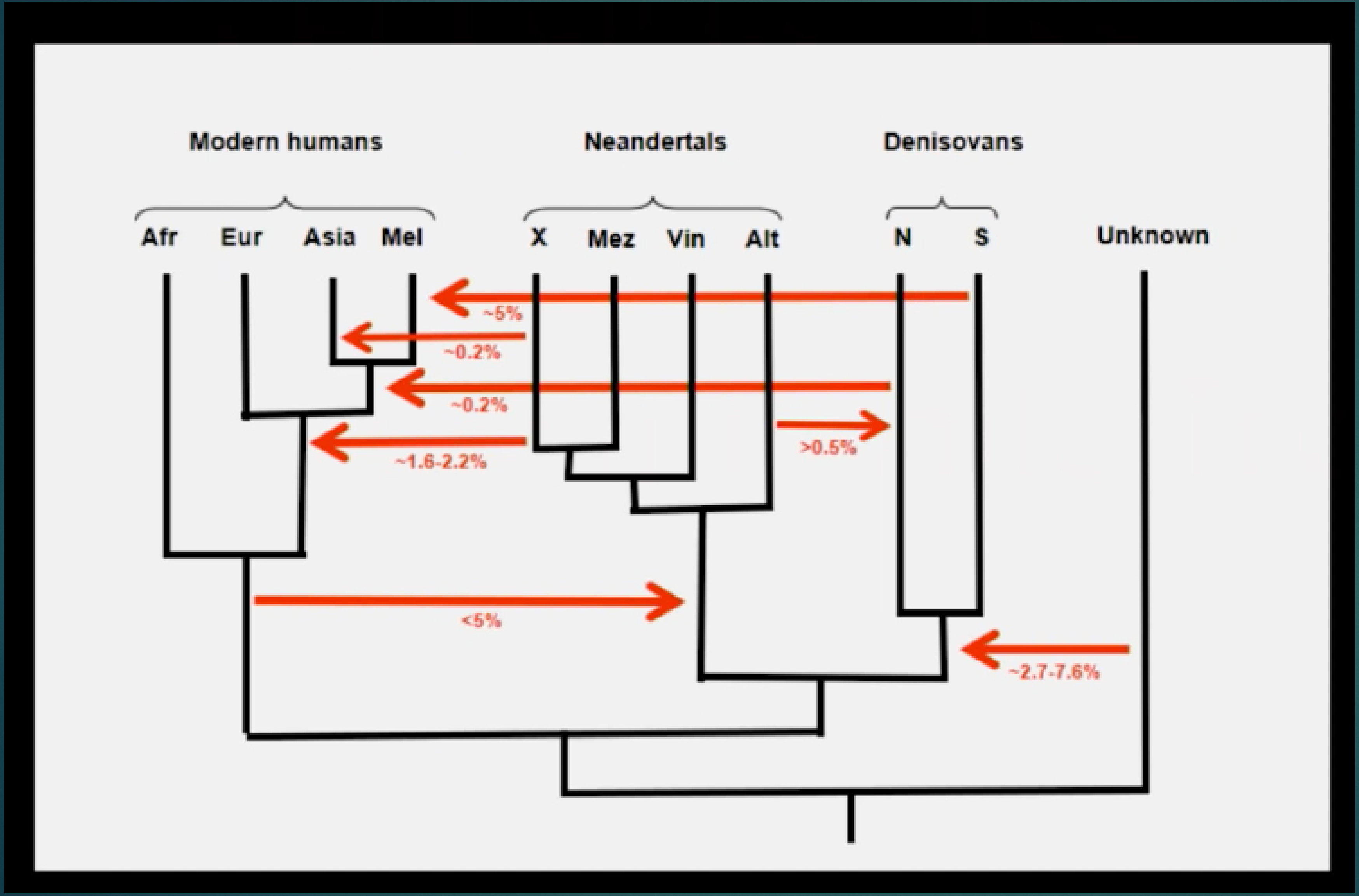
Ancient genomes suggest interbreeding between human-like groups in Europe and Asia

© AFP

Source: Nature/NationalGeographic

Introgressions





7 gene flow events / genetic introgressions:

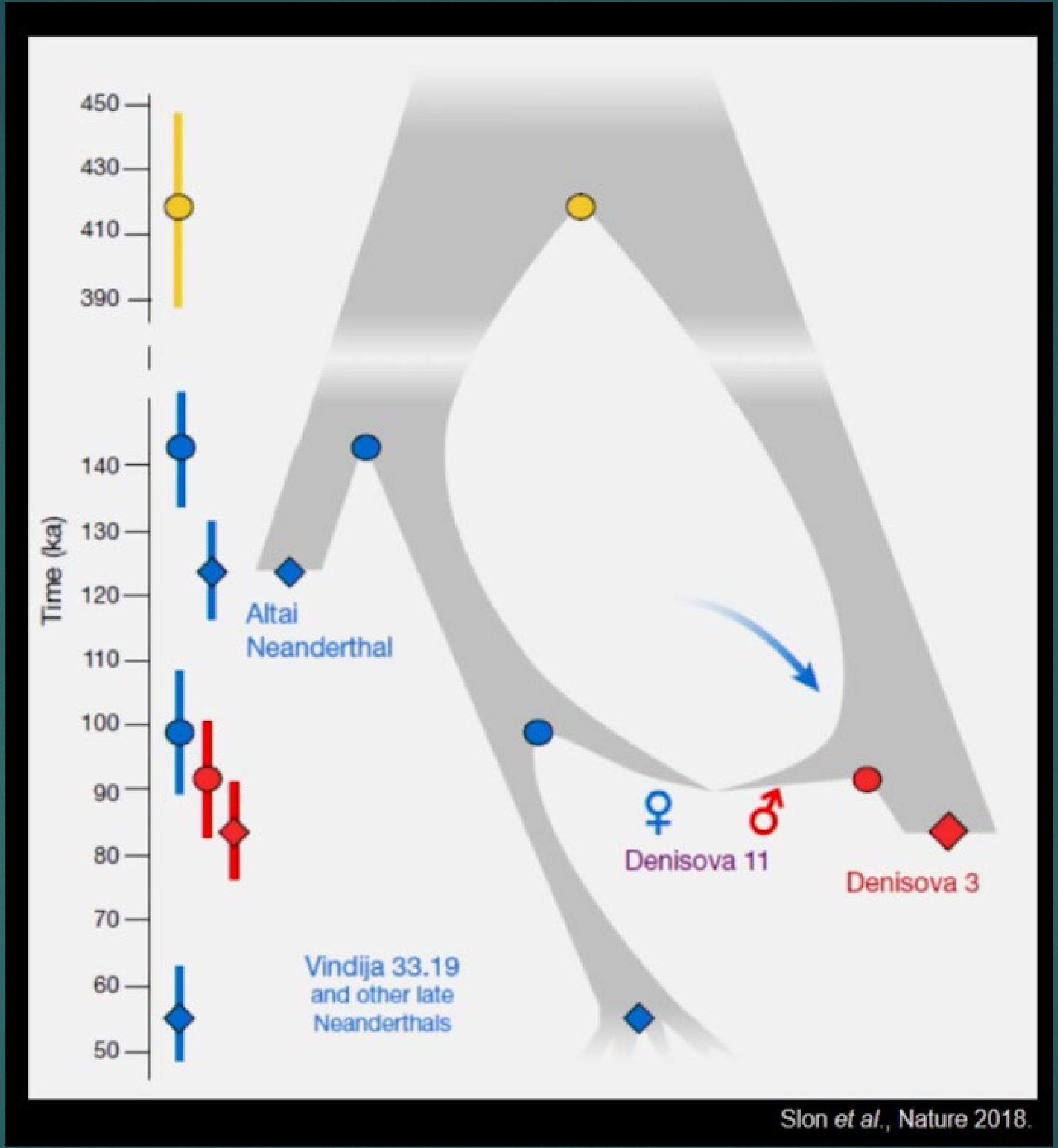
2 D to MH

2 N to MH

1 N to D

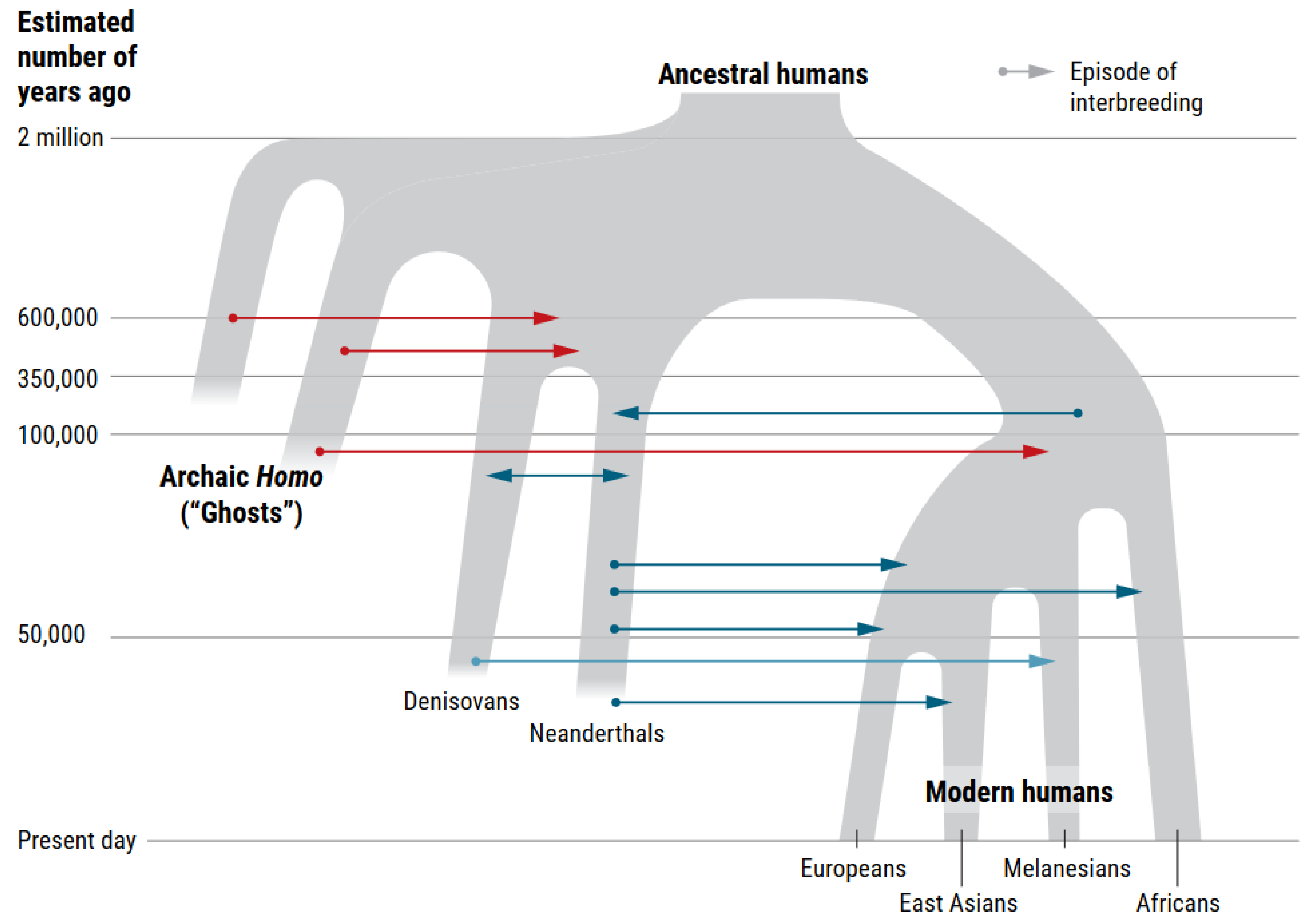
1 MH to N

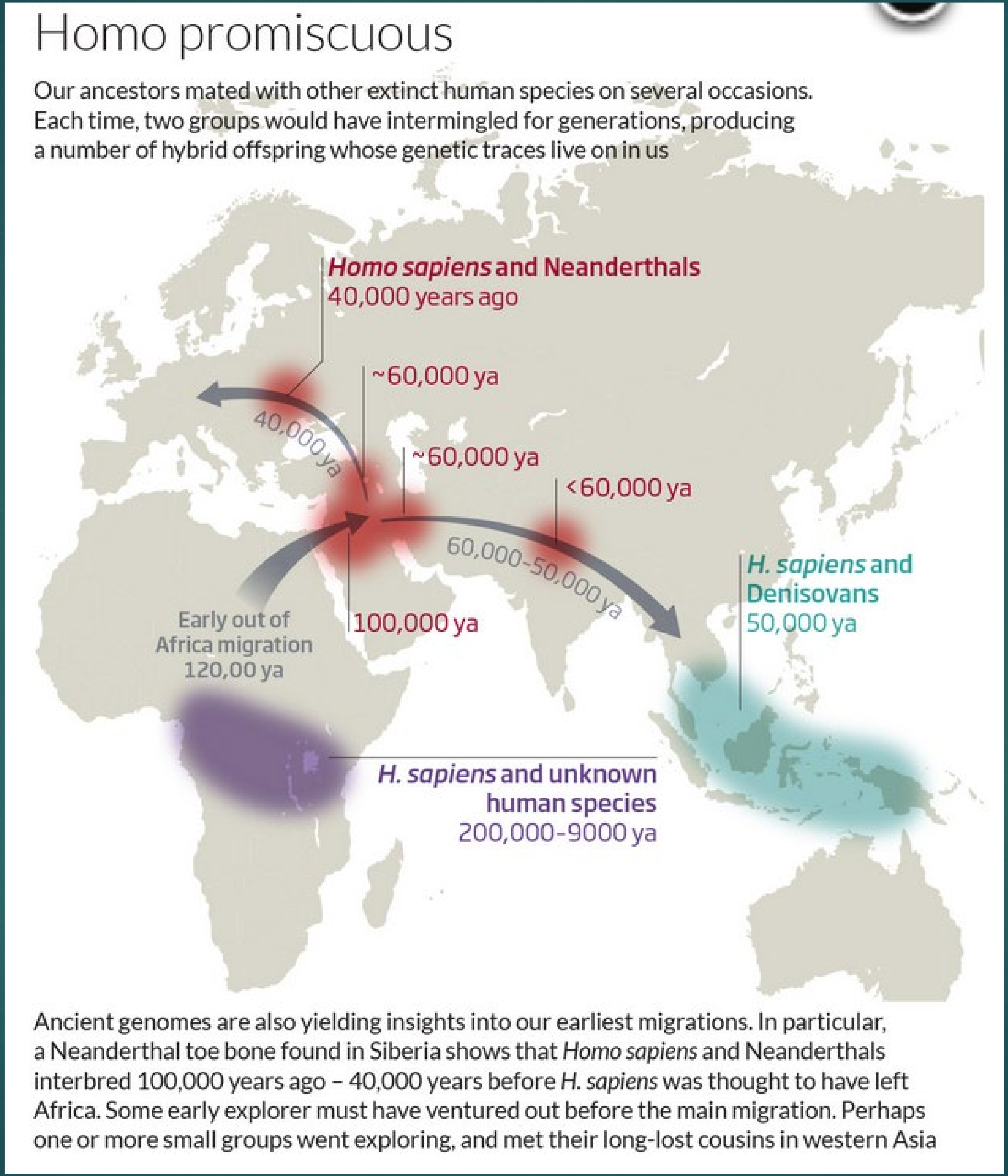
1 older (H. erectus?) to D



Slon *et al.*, Nature 2018.

F = D, more related to Ds in Denisova cave
M = N, more closely related to later Ns, than to N in the same D cave;
Implies N migration from W to E, replacing earlier Ns


Estimated number of years ago
Ancestral humans
Episode of interbreeding
2 million
600,000
350,000
100,000
Archaic *Homo* ("Ghosts")
50,000
Denisovans
Neanderthals
Modern humans
Present day
Europeans
East Asians
Melanesians
Africans



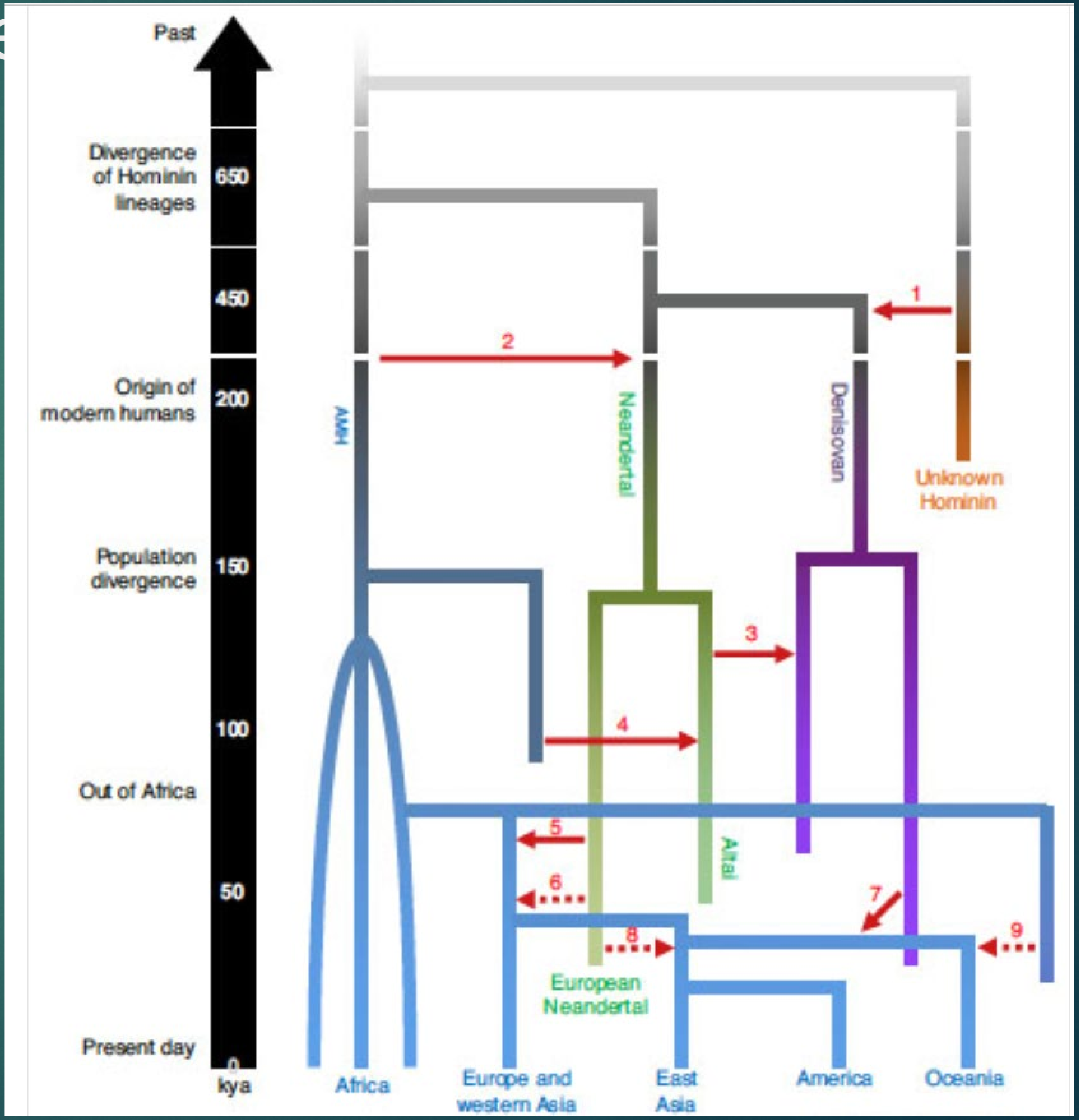
Homo promiscuous

Our ancestors mated with other extinct human species on several occasions. Each time, two groups would have intermingled for generations, producing a number of hybrid offspring whose genetic traces live on in us

Ancient genomes are also yielding insights into our earliest migrations. In particular, a Neanderthal toe bone found in Siberia shows that *Homo sapiens* and Neanderthals interbred 100,000 years ago – 40,000 years before *H. sapiens* was thought to have left Africa. Some early explorer must have ventured out before the main migration. Perhaps one or more small groups went exploring, and met their long-lost cousins in western Asia

Various interbreeding events between *Homo sapiens* and other hominin specie

Schematic representation of human evolution (based on focusing on the lineages leading to ourselves (blue), Neanderthals (green) and Denisovans (magenta) and highlighting probable interbreeding (numbered red arrows). 1: 2.5–5.8% Denisova genome from archaic hominin having diverged 0.9–1.4 mya [16]; 2: mtDNA introgressed c. 270 kya into a Neanderthal (Hohlenstein-Stadel, Germany) from an African lineage leading or related to AMH; 3: at least 0.5% genome coming from a Neanderthal population closer related to the Atai Neanderthals [16]; 4: 1.0–7.1% gene flow from AMH into Altai Neanderthals; 5,6,8,9: multiple introgressions from Neanderthals into various modern human populations outside Africa resulting in about 2% (regionally and inter-individually variable, slightly more in East Asia) Neanderthal DNA; 7: Denisova introgression resulting in about 2–4% Denisovan DNA in Melanesia (less in e.g. South Asia).



N-D Divergence

- The common ancestor of modern humans, Neanderthals and Denisovans, lived between 765 and 550 Ka
- The picture painted by nuclear DNA (nDNA) is that, between 765 and 550 Ka, our ancestors in Africa diverged into two groups
- The proto-Neanderthal/Denisovan group left Africa for Eurasia at some point; sometime between 445 and 473 Ka, they diverged into distinct Neanderthals and Denisovans.

4) N DNA into Ds and vise versa

- Denisova Cave: Teeth dating to 80 Ka yield DNA from a Denisovan individual; first to confirm the existence, via DNA, of a third group of ancient hominins, the Denisovans, that coexisted with Neanderthals and human ancestors.

- There are indications of early Neanderthal and Denisovan interbreeding

5) Archaic Hominin into Denisovan DNA

- Earlier study: Archaic hominin DNA (from 0.9-1.4 Ma) (Homo erectus?), constitutes .5-8.0%(later 2.5–5.8%) of Denisova genome -- Waddell et al. 2011. This DNA was passed on to New Guineans
- 2017: Model indicates that 1% of the Denisovan genome was introgressed from an archaic hominin ancestor. (27 Mb of sequence)
- About 15% of these "super-archaic" regions—comprising at least about 4 Mb— were, in turn, introgressed into modern humans and continue to exist in the genomes of people alive today

Denisovan + Ghost species

- Denisovans and a 'ghost' population of hominins:
- A ghost population of hominins that may have left Africa some million years ago.
- The mystery species could be an Asian offshoot of *Homo erectus*, which lived in Indonesia, perhaps as recently as 100,000 years ago, or possibly even relatives of *Homo floresiensis*, the 'hobbit' species discovered more than a decade ago on an Indonesian island.

Ewen Callaway

Ghost species in Ds

- Discordance between the Denisovan and modern human divergence times estimated from mitochondrial DNA and nuclear DNA -1 million years ago versus 500,000 years ago, respectively - has been interpreted as evidence that Denisovans also interbred with another archaic hominin distinct from Neanderthals or humans.
- Possible candidates for such interbreeding include *Homo erectus* and *H. heidelbergensis*, archaic human species that archaeological data suggest inhabited East and Southeast Asia as recently as 100 kya .

Wolf & Akey, 2018

Admixtures in Africa

- **Did archaic hominin admixture happen in Africa?**
- Too few genomic databases of Africans; and challenging climate impeding the recovery of ancient DNA.
- Studies indicate admixture occurred between an unidentified archaic hominin ancestor and several African populations and contributed functionally relevant genetic variation at specific loci
- New African Multiregional Theory

6) Archaic hominin DNA into MHs

- 2004 study led by Daniel Garrigan: DNA sequences from a nonfunctional region of the X chromosome known as RRM2P4.

- Analyses of its reconstructed tree pointed to an origin for the sequence, not in Africa but in East Asia around 1.5 million years ago (*H. erectus*?), implying that the DNA came from an archaic Asian species that intermixed with the *H. sapiens* originally from Africa; occurs at frequencies up to 53% in south China; found at less than 1% in African populations

- This ancient lineage is a remnant of introgressive hybridization between expanding anatomically modern humans emerging from Africa and archaic populations in Eurasia.

N genes: not in coding genes, but in regulatory regions

- “We’ve known for a long time that gene expression variation is an important source of phenotypic variation within populations and phenotypic divergence between species,” says Akey.

- “We were interested in asking whether Neanderthal sequences make any contribution to gene expression variability.”

- The answer was a resounding yes.

- Rotival et al.: found a strong depletion of Neanderthal variants in coding portions of genes, and a slight enrichment of the archaic sequences in regulatory regions (*Am J Hum Genet*,)

7) MH DNA into Ns – 200 Ka

- Evidence of early introgressions – pre 60 Ka
- 2017, Adam Siepel lab: early interbreeding between MHs and Ns occurred between 300 and 200 KA
- Adam Siepel: around 3% of Neanderthal DNA — and possibly as much as 6% — came from modern humans who mated with the Neanderthals more than 200,000 years ago.
- So Ns who gave us 2%, already had 3% of MH DNA in their DNA

Melissa J. Hubisz, et al., 2017

3-6% MH DNA into Ns ~200 Ka

- Study sample: 2 Africans, 2 Neanderthal, 1 Denisovan, and 1 chimpanzee outgroup; a new method, called ARGweaver-D,
- We identify 3% of the Neanderthal genome that is introgressed from ancient MHs, and estimate that the gene flow occurred between 200-300kya.
- 3% in both the Altai and Vindija Neanderthal. This number is almost certainly an underestimate, By contrast, only 0:37% of regions are classified as MH to Denisovan.
- Neanderthal genome was likely more influenced by introgression from ancient humans, than non-African MH genomes are by Neanderthal introgression.

8) Ns inherited their mtDNA from MHs

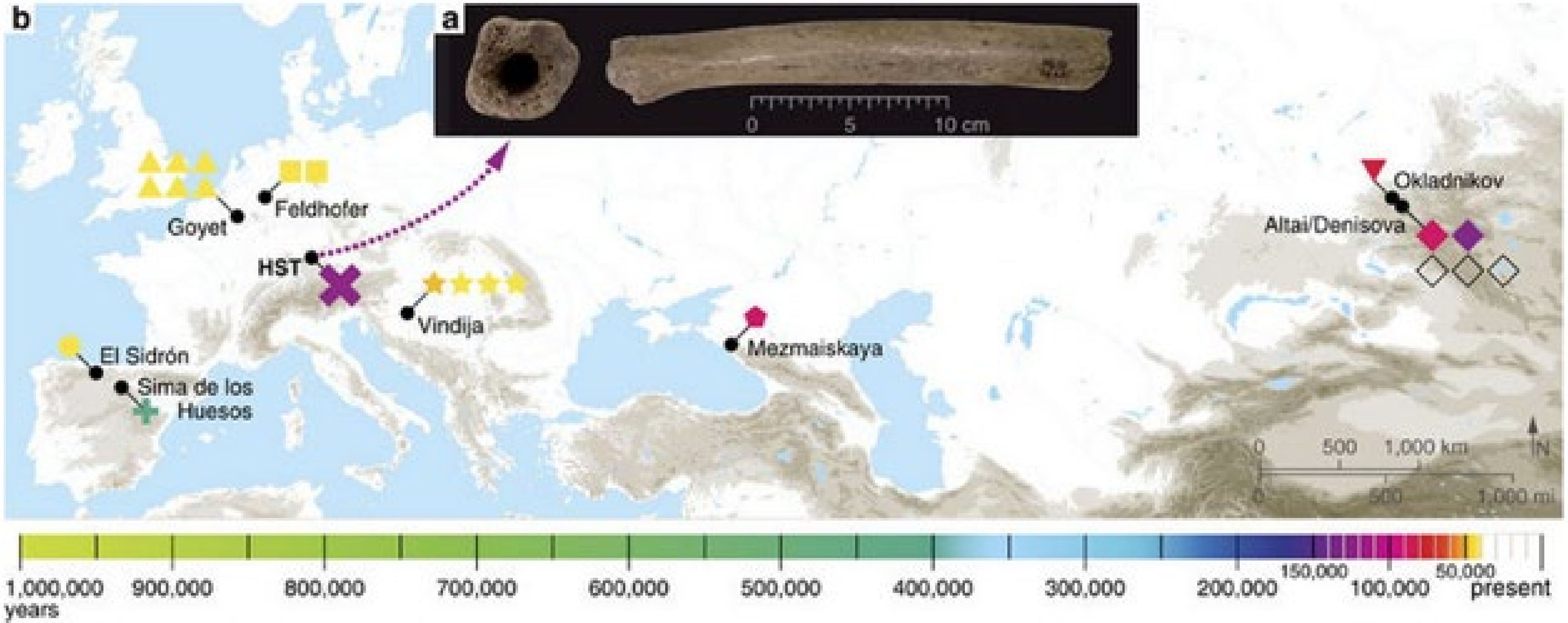
- Svante Pääbo in 2016: the “Neandertal” mtDNA actually came from modern humans.
- A Neandertal femur found in 1937 in this cave in Germany had inherited modern human mtDNA; from a Neandertal thighbone found in 1937 in the Hohlenstein-Stadel cave (HST) in Germany.
- An early MH female mated with a Neandertal male more than 220,000 years ago. In time her African mtDNA completely replaced the ancestral Neandertal mtDNA.

Cosimo Posth, et al., 2017

Femur bone from HST: 124 Ka

MtDNA: Since the bone is 124,000 years old, implies that that Homo sapiens and Neanderthals met and interbred sometime between 470,000 and 220,000 years ago.

From: Deeply divergent archaic mitochondrial genome provides lower time boundary for African gene flow into Neanderthals



(**a**) Pictures of the HST femur,
(**b**) map of archaeological sites where complete mtDNA from archaic humans were reconstructed,
They are still trying to get nuclear DNA from the bone,

HST

- Used mutational rates to calculate that the bone is 124 Ka. The approach also indicates that this Neanderthal split from all other known Neanderthals sometime between 316 and 219 Ka.
- This means that modern human ancestors must have interbred with Neanderthals before 219 Ka and hence could have migrated out of Africa and into Europe much earlier than we thought.
- The results also suggest that Neanderthals had a much greater genetic diversity and larger population at this time
- .

A complex history of MH, N, D, +, interbreeding:

MH DNA into Ns

- 270 Ka: early MH mtDNA introgressed into a Neanderthal (Hohlenstein-Stadel, Germany)
- Estimated the divergence time between HST and all other Neanderthals to ~ 270 ka (316–219 ka), while the TMRCA for the Altai N branch was inferred to be ~160 ka (199–125 ka).
- Dating: The three oldest N mtDNAs: Sima, age of 430 Ka; HST with an age of 124 ka (183–62 ka) and Altai Neanderthal with an age of 130 ka (172–88 ka).
- An early MH female mated with a Neandertal male more than 220 Ka.
- All known Neanderthals inherited their mitochondrial DNA from an ancestor who lived before 220 Ka.

HST: N mtDNA

- In time her African MH mtDNA completely replaced the ancestral Neandertal mtDNA.
- That means a human mother carried a mixed-species baby to term *and*, in turn, her offspring spread her mtDNA to his or her mixed-subspecies descendants.
- The evidence suggests that Ns eventually discarded their original mitochondrial DNA for mDNA inherited from this human mitochondrial Eve.
- Yet their nuclear DNA was more closely related to the mysterious Denisovans, from whom they split about 450,000 years ago.

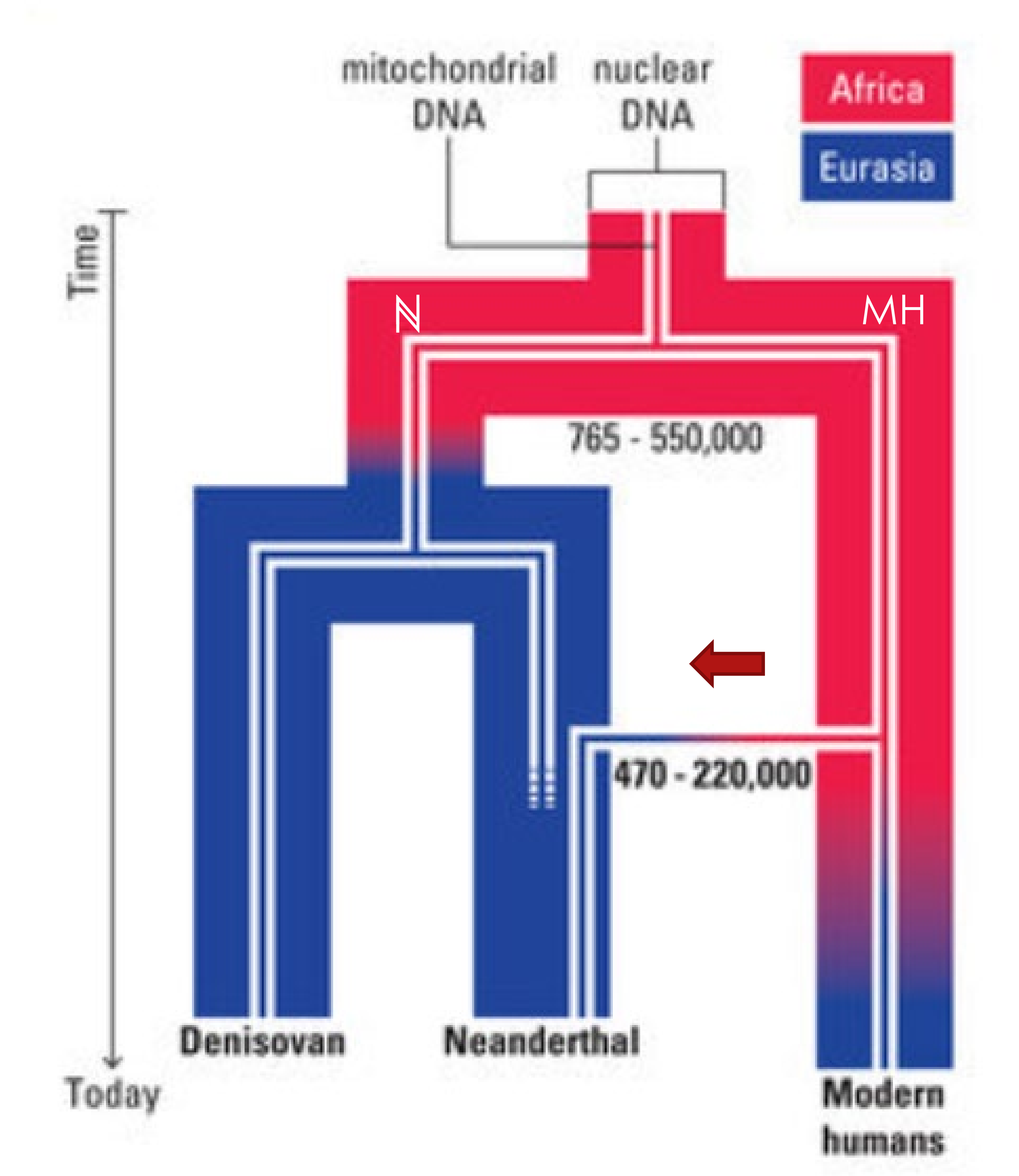
Hohlenstein-Stadel Neandertal mtDNA

- HST Neandertal's mtDNA was significantly different even from that of proto-Neandertals that date to 430 Ka at Sima de los Huesos in Spain, suggesting that their mtDNA had been completely replaced.

- HST mtDNA split from that of all other Neandertals at least 220 Ka. The ancient *H. sapiens*' mtDNA must have entered the Neandertal lineage before this time, but after 470 Ka.

- That's early enough for the new form of mtDNA to have spread among Neandertals and replaced all their mtDNA.

- Conclusion: The mtDNA of Neandertals is not actually from Neandertals, but from an early modern human from Africa


mitochondrial DNA
nuclear DNA
Africa
Eurasia
Time
N
MH
765 - 550,000
470 - 220,000
Denisovan
Neanderthal
Today
Modern humans

HST: mtDNA dating

- Neanderthal mtDNA is more similar to modern humans than it is to Denisovan mtDNA.
- And the divergence date between us and them, when estimated based on mtDNA, is much more recent—between 498 and 295 Ka.
- Some researchers have suggested that you can explain this mixed genetic evidence if Neanderthals interbred with another, more recent African group of humans. This would provide them with different mtDNA after they split from Denisovans.
- And that, in turn, means that there must have been humans, closely related to our own species, who left Africa for Europe far earlier than previously suspected.

HST: Ns, Ds, MHs

- The common ancestors of Neanderthals and Denisovans spread across Europe and Asia over half a million years ago.

- In the east, they, genetically, became Denisovans. In the west, they became Neanderthals.

- The 430 Ka fossils at Sima de los Huesos — Neanderthals with Denisovan like mt DNA — capture the early stage of that split.

- A wave of early Homo sapiens made their way from Africa to Europe before 270K. There, they interbred with Neanderthals. Then the ancient African migrants disappeared. But their mtDNA endured in later generations of Neanderthals.

MH mtDNA in Ns

- That helps to narrow down the time frame of the genetic mixture with African humans: the mixing must have happened before 270 Ka. This suggests that the early migration out of Africa must have happened sometime before that.

- Their DNA entered the Neanderthal gene pool. Over many generations, most of that new DNA disappeared.

- But the mitochondrial DNA survived, passed down from mothers to their children. In fact, eventually all the Neanderthals inherited it; for some reason discarding the mitochondrial DNA that the species once had.

- Another example: The mtDNA in some grizzly bears has been completely replaced by that of polar bears

HST: 1 MH female had child of male N

- This is evidence that some early members of our own species moved from North Africa into Europe.
-
- Supporting this idea was the discovery of fossils of Homo sapiens in Morocco dating back 300,000 years.
- Somewhere in prehistory, at least one female human from Africa must have carried the child of a male Neanderthal.

Divergence

- Molecularly dated the split of the HST lineage from other Neanderthal mtDNAs to ~270 ka; to replace the pre-existing Denisovan-like mtDNA (a la Sima de los Huesos N).
- Proposed that the Neanderthal population in western Europe underwent a demographic turnover followed by a subsequent recolonization.
- Under that scenario, the HST lineage would have been largely replaced towards the end of the Neanderthal temporal range by mtDNAs descendants on the Altai branch.
- The African introgression hypothesis suggests that Late Pleistocene Neanderthal mtDNAs originated through gene flow from an African source, which took place more than ~270ka

8) MH DNA into nuclear N genome in Middle East ~100 Ka

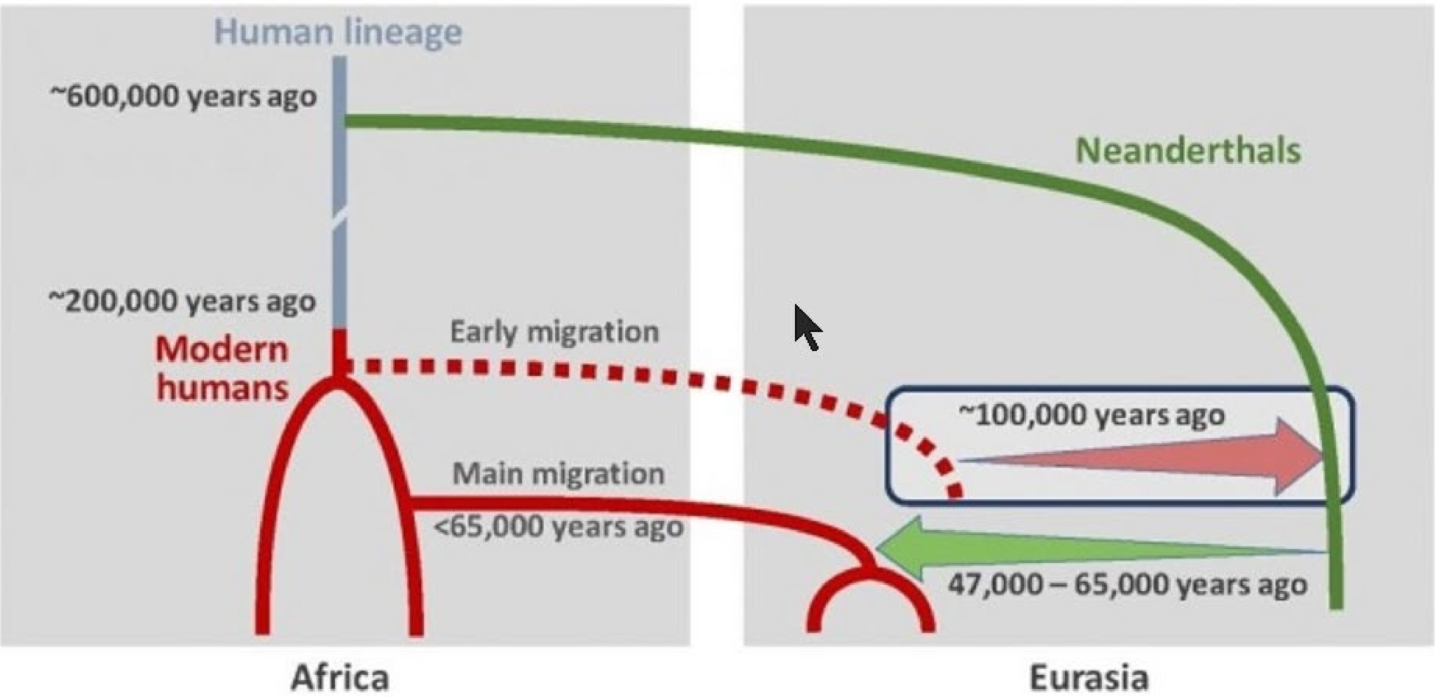
- ~100 Ka: An ancient population of *Homo sapiens* migrated from Africa into Asia. In the Near East they met a population of Neandertals, probably around the Persian Gulf, the Arabian Peninsula or the eastern end of the Mediterranean Sea in Western Asia.
- Then an introgression of MH into N = MH DNA in the genome of a female neandertal from the Denisova Cave in the Altai Mountains, south Siberia; but not in western Ns.
- This means that probably those hybrid Neandertals + *H.sapiens* from 100 Ka migrated to East Asia. No descendants?
- They are probably related with the 90 Ka populations from the Skhul and Qafzeh caves in Israel, as well as with the 47 human teeth dated to 80-120 Ka found in a limestone cave system in Daoxian, China.

Kahlil et al. (2016).

When did they hook up?

- Morphological changes in human fossils can be directly dated and compared with time estimates for genetic evidence of interbreeding between Neanderthals and non-African modern humans.
- Currently, the greatest amount of gene flow is thought to have occurred around 77 to 114 Ka, long before the claimed skeletal evidence for interbreeding at 45,000–35,000 years ago.
- This seeming asynchronicity between genetic and skeletal patterning has yet to be explained.

MHs meet Neandertals at least Twice



Interbreeding around 60,000 years ago (green arrow) accounts for Neanderthal DNA in modern humans; human DNA in the Neanderthal genome likely came about due to earlier interbreeding (red arrow).

© ILAN GRONAU

<u>MH DNA in N genome</u>

<u>N DNA in MH genome</u>

<u>MHs interbred with Neanderthals;</u>

1- earliest interbreeding between MHs and Neanderthals took place <u>at least 100 kya (put MH DNA in N genome)</u>,

2 - when Neanderthals migrating east from Europe to Asia; <u>N interbreed with MHs ~60 kya (N DNA in MH genome)</u>

Altai N into East Asians at 100 Ka

- Altai N DNA into East Asians

- Castellano: humans and the ancestors of the Altai Neanderthals interbred about 100,000 years ago — long before people were thought to have left Africa; or humans expanding into the Middle East encountered and interbred with Neanderthals there.
- The Neanderthals then migrated east to Siberia, taking human DNA with them.

Neandertal Sites

N DNA in MHs is related to Mezmaiskaya & Vindija N

- Neanderthal component in non-African MHs is
  - more related to the western Mezmaiskaya Neanderthal (Caucasus)
  - than to the Altai Neanderthal (Siberia)
  - or the Vindija Neanderthals (Croatia).

Multiple N Populations

- Neanderthal component in non-African MHs is more closely related to the Vindija and Mezmaiskaya Neanderthals than to the Altai Neandertal.
- These results suggest that a majority of the admixture into modern humans came from Neanderthal populations that had diverged (about 80–100 Ka) from the Vindija and Mezmaiskaya Neanderthal lineages before the latter two diverged from each other.

9) MH DNA into Altai Ns ~100 Ka

- El Sidrón and Vindija Neanderthals display significant rates of gene flow (0.3–2.6%) into modern humans, suggesting that the El Sidrón and Vindija Neanderthals are more closely related than the Altai Neanderthal is to the Neanderthals that interbred with MHs about 47-65 Ka.
- Significant rates of modern human gene flow into Neanderthals occurred—of the three examined lineages—for only the Altai Neanderthal (0.1–2.1%), suggesting that MH gene flow into Neanderthals mainly took place after the separation of the Altai Neanderthals from the El Sidrón and Vindija Neanderthals that occurred at ~110 Ka.

MH genes into Ns

- The findings show that the source of modern human gene flow into Neanderthals originated from a population of early MHs humans from about 100 Ka, predating the out-of-Africa migration of the modern human ancestors of present-day non-Africans.

10) N DNA into Ds

- At Denisova: at least 0.5% N genome coming from a Neanderthal population closer related to the Altai Neanderthals
- Denny: The 90 Ka remains of a Denisovan-Neanderthal hybrid in Denisova Cave laid bare the fact that the two groups interbred: N mother and D father

11) The most referenced introgression: 2% N DNA into MH

- Green et al., 2010:
  - Dated to 40-60 Ka
  - N DNA into MH = 1.5-2.1% (current =1.8-2.6%)
  - More in E. Asians than European
  - Neanderthal genes into out-of-Africa MHs, in Middle East
  - Multiple introgressions from Neanderthals into various modern human populations outside Africa resulting in about 2% (regionally and inter-individually variable) Neanderthal DNA
- First conclusive evidence that humans and Neanderthals mated came from analyzing a draft Croatian Neanderthal genome.

What else have we learned from the Neandertal genome?

1. People from Eurasia share 1-4% of their genomic variations with Neandertals:

“It may not sound like a lot -- between 1 and 4 percent. But that's the equivalent of one great-great-great grandparent's DNA contribution. In the case of the Neandertal contribution, more than 1500 generations ago, it's an enduring legacy of an ancient group of people, spread across many lines of the genealogies of living people.”--from John Hawk's (Associate Professor of Anthropology, U. of Wisconsin) weblog, May 6, 2010

N DNA into MHs

- As a result of these encounters, humans from outside Africa carry traces of Neanderthal DNA — about 1–2% of their genomes.
- The two populations may have met in the Middle East 50,000 to 60,000 years ago, as humans leaving Africa encountered resident Neanderthals.

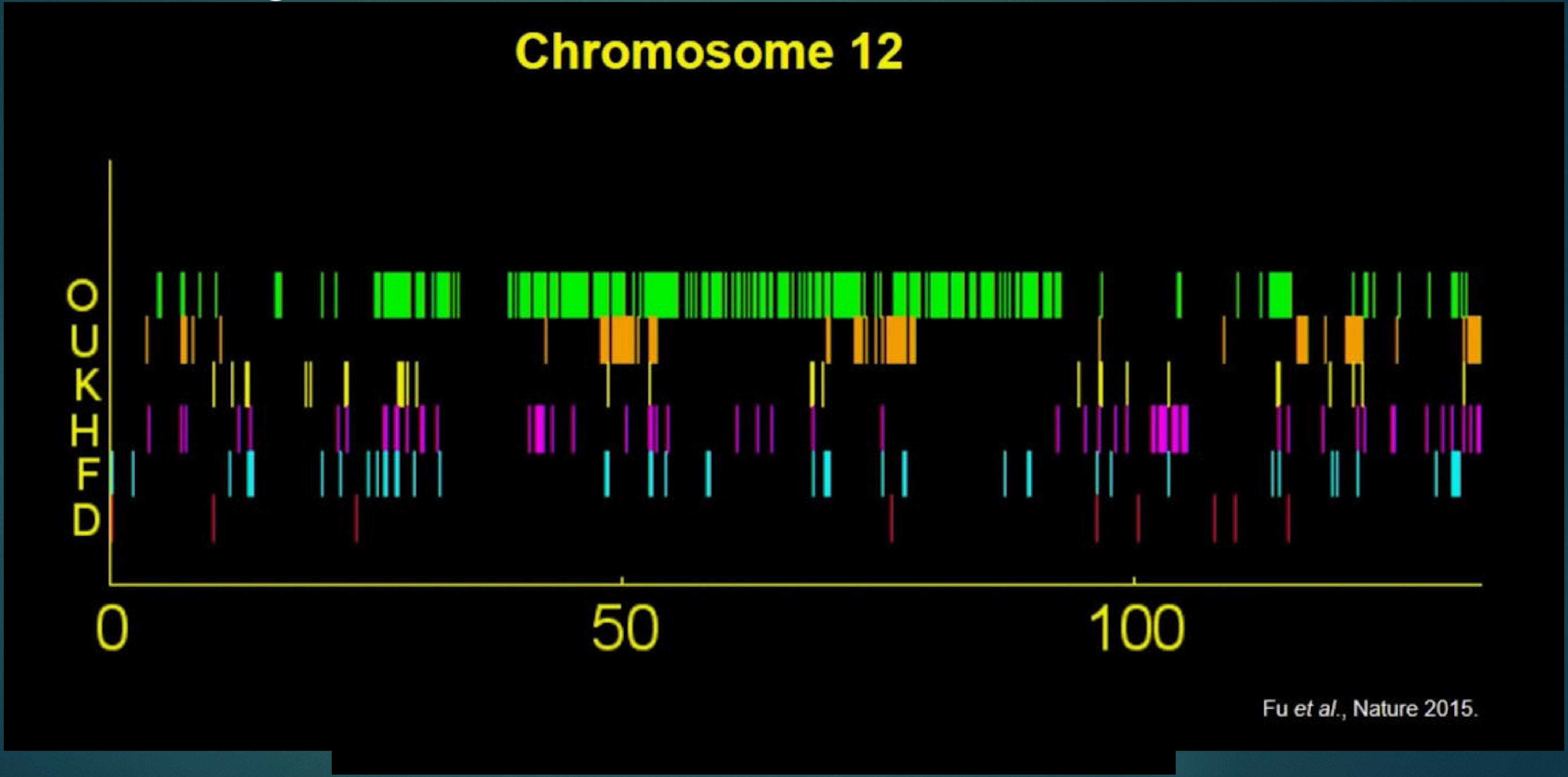
N into MH

- 60,000 ya -- In later migrations from Africa into Asia between 40-60 Ka *Homo sapiens* successfully began colonizing the world.
- They interbred with Neandertals probably again in western Asia. The consequence is the 1 to 2% neandertal trace that is kept in all modern humans' DNA
- Some researchers contend that the ancestors of East Asians had a second Neanderthal affair, leaving them with slightly more Neanderthal heritage than Europeans have.

Latest Studies:

- Reich: 1-1.2% N in every one, but different pieces; 35% total of N genome
- N & MH hybrids may have been infertile (no N genes in male germ area)
- No N mitochondrial DNA exists today; no Neandertal Y chromosome today
- One of the Y chromosome genes that differ in Neanderthals has been implicated in transplant rejection when males donate organs to women; a woman's immune system might attack a male fetus carrying Neanderthal H-Y immune genes
- Backflow into Africa: Eurasian genes (with N Dna) in the San

Romanian Cave, Oase 1: 50% of Chr. 12 is N; full N ancestor 6 generations back



Fu *et al.*, Nature 2015.

Oase-1

- 45,000 ya -- evidence of another hybridization in East Europe = The Oase-1 mandible from Romania is one of the oldest European *Homo sapiens* specimens.
- Its DNA has an amazing 6 to 9% of neandertal genome.
- This means he had a full Neandertal ancestor only 4 to 6 generations before him.

12) D DNA into MHs

- Denisova introgression resulting in about 2–6% Denisovan DNA in Melanesia ~ 45 Ka (less in South Asia, ~0.2%)
- Denisovans once lived all across Asia, giving them ample opportunity to interbreed with MHs there.
- Flow of Southern Denisovan DNA into Papuans (Reich et al. 2010)): People from Papua New Guinea and elsewhere in Oceania carry fragments of Denisovan DNA, as do East Asians

(Skoglund and Jackobsson 2011),

13) Archaic hominin into MHs in Africa

- Sub-Saharan archaic hominin into MH (MUC7 in saliva)
- A salivary antibacterial mucin

Khoe-San: most genetically diverse; deepest split time

- In all the world, genetic diversity is greatest today among the Khoe-San peoples of southern Africa.

- Until recently, geneticists have thought that their ancestral lineage has existed for as long as 200,000 years. That origin, the deepest split between human populations that still exist, points to the stem population of all living people.

- It doesn’t divide Africans from non-Africans, it reflects a deep history of diversity among African populations—the founder effect leading to non-African peoples was much later.

14) Archaic DNA in the San

- Gene flow from archaics into MHs - San, ~2% (Hammer et al. 2011).

15) Ghost lineage in 4 West African Groups

- Four West African groups — Yoruba in southwestern Nigeria, Esan in southern Nigeria, Gambians in western Gambia, and Mende in Sierra Leone —
- Derive 2% to 19% of their DNA from an archaic ghost lineage. Ghost lineage diverged from the ancestors of Neanderthals and modern humans up to 1.02 Ma and interbred with the ancestors of modern West Africans from 124 Ka up to the present day.
- A number of previous studies have found evidence for deeply diverged lineages contributing genetic ancestry to the Pygmy (and Yoruba populations).
- Stone-age hunter-gatherers from South Africa diverged from other modern-day populations >260,000 years

3 episodes: N into MH

- The Neanderthals interbred with anatomically modern humans (AMH) on at least three occasions,
  - when MHs first came into the Levant 100–120 Ka
  - during MH’s move into glacial Europe ~50 Ka
  - The third would have involved Neanderthals and the ancestors of East Asians only.

3 episodes

- A 2016 study presented evidence that Neanderthal males might not have had viable male offspring with AMH females. This could explain why no modern man to date has been found with a Neanderthal Y chromosome.
- Virus exchange: A 2018 study concluded that interbreeding between Neanderthals and modern humans led initially to the
  - exposure of each species to unfamiliar viruses.
  - Later on, the exchange of genes granted resistance to those viruses, too.

Evidence of Interbreeding: MH shared organisms with Ns

- MH and N contact is also revealed by other lines of evidence:
  - the oral commensal Archaea microbe Methanobrevibacter oralis from a Spanish Neanderthal pointing to his ancestors having had contact with an African strain presumably from the AMH in the Levant ~126 kya,
  - the sexually transmitted oncogenic MH papillomavirus 16 which shows strains having split ~450 kya mirroring the divergence between Neanderthals and AMH, but later with the Neanderthal strain re-infecting AMH after c. 120 kya.

Percentage of admixture

- The proportion of Neanderthal-derived ancestry was estimated by Green, et al., 2010 to be 1–4% of the Eurasian genome.
- Prüfer et al. (2013) revised the proportion to an estimated 1.5–2.1%,
- Lohse and Frantz (2014) infer an even higher rate of 3.4–7.3%.

Modeling: Eurasian MHs have 3-7% Neandertal genes

- Lohse & Frantz: Neandertal Admixture in Eurasia Confirmed by Maximum Likelihood Analysis of Three Genomes:
  - Strong support for Neandertal admixture in Eurasia at a higher rate (3.4%-7.3%)
  - Rejects hypothesis that humans who left Africa evolved from the same ancestral subpopulation that had previously given rise to the Neanderthals.

Konrad Lohse and Laurent A. F. Frantz, 2014

Sex between N and MHs

- Either Quest for Fire or Dancing with Wolves; the difference is the music
- Kidnapping or Romance?
- No way to tell currently
- Less mixture in X chromosome than in other chromosomes
- What’s it been like in last 2000 years between different cultures

Sex Bias in hybridization

- Was there sex bias in hybridization
  - MH male to N female,
  - N male to MH female,
- Sex-biased hybridization has been invoked an explanation for the reduced level of Neanderthal ancestry along the X chromosome (~ 20% that of the autosomes).
- Selection against Neanderthal sequence on the X chromosome was greater than on the autosomes

Wolf & Akey, 2018

Sex bias

- Or: more frequent Neanderthal male and human female pairings-potentially as great as 3× more frequent than the complementary pairing.

- A bias towards Neanderthal male and human female pairings could also help explain why investigations of Neanderthal and human mitochondrial DNA, which is inherited maternally, show no indication of Neanderthal-human admixture

Non-consensual sex? Or slumming MH females?

- Genetic evidence for type of sex: The discovery that only nuclear DNA and not mitochondrial DNA (exclusively via the maternal line) are shared between Neanderthals and Homo sapiens means that successful interbreeding only occurred between male Neanderthals and female Homo sapiens, with male offspring rendered infertile

- This could be used to support a non-consensual sex hypothesis (especially given the robustness of the Neanderthal physique).

- An identical claim can of course be made that a male Homo sapiens could have forced himself upon a female Neanderthal, but this cannot be proven genetically

(Mason and Short 2011; Wang et al. 2013)

MH-N Hybrids

- What do we know about these first bi-species people?
- It’s likely that they were less healthy than their single-species peers. It’s possible not all hybrid offspring were fertile.
- And there’s evidence that the Neanderthal genes actually introduced disadvantageous traits into the population.
- 20-40% of Ns in MHs: But what’s more interesting is figuring out what Neanderthal genes didn’t get passed on. These would be Neanderthal traits that are not advantageous for survival.
- These Neanderthal-gene-less regions are involved in speech, language, and neural functions; those genes didn’t survive natural selection.

Denisovan gene flow into MH

- There was Denisovan gene flow in mainland Asia (the Han Chinese, the Dai in southern China, and the Karitiana)

- And D mix in the Americas; contribution about 0.2% and thus about 25 times smaller than the Denisovan contribution to populations in Papua New Guinea and Australia

Kay Prüfer, et al., *Nature, 2013*

How many distinct pulses of admixture occurred with Neanderthals?

- Original model involved a single pulse of N and OoA MHs before the ancestral Eurasian population split into European and Asian lineages.

- Analyses of high-quality Altai N reference genome noted:
  - more N DNA in Asian and American populations than European ones
  - More N in East Asian populations compared to European populations
  - Less N in Melanesians compared to either East Asians or Europeans.

Wolf & Akey, 2018

Admixtures

- Models can only account for the higher proportion of Neanderthal ancestry in East Asians compared to Europeans by including multiple pulses of admixture.
- Even a ªtwo-pulseº model may be too simplistic a representation for the history of human and Neanderthal admixture

East vs West

- Akey’s group also identified another potential bias in how researchers have interrogated modern genomic data.
- Analyses identified Neanderthal sequences in modern human genomes by comparing them to the Neanderthal reference genome. But as a result of interbreeding with modern humans, Neanderthals carried modern human DNA in their genomes.
- This means that all current methods, even this new one, are overestimating the amount of Neanderthal DNA in modern human genomes across the board—African, European, and Asian, “We’re finding similar sequences, not because of introgression from Neanderthals to modern humans, but from this old hybridization event where humans gave Neanderthals their DNA.”

East vs West

- More Neandertal genes in Asians than in Europeans; Akey sees this as possible evidence that Neanderthals interbred with ancient humans on at least two separate occasions: once with the ancestors of all Eurasians, and later with a population ancestral only to east Asians.
- Ancient East Asians mixed and mingled multiple times with Neandertals
- East Asians got a double dose of Neandertal ancestry. That's the conclusion of two new studies seeking to explain why East Asians inherited 15 to 30 percent more Neandertal DNA than Europeans did
- East Asians' ancestors interbred with Neandertals more than once.

Multiple interbreeding events

- Conclude
  - Altai Neanderthal lineage "represents the ancestral lineage of Neanderthals and was sampled only in Asia and late Neanderthals
  - another lineage "replaced the ancestral Neanderthal lineage in Europe ~50,000 years ago.
- In the far distant past, ancestors of East Asians and Western Europeans intermixed with different Neanderthal lineages on multiple occasions as they spread out of Africa.
- We probably met different Neanderthal populations at different times in our expansion into other parts of the globe.

Ozgur Taskent, et al., 2020: Multiple Archaic Introgression Events, Including from Altai Neanderthal Lineage

- Modern humans share different amounts of single nucleotide as well as large deletion polymorphisms from the two Neanderthal lineages.
  - The Altai Neanderthal lineage, on the one hand, represents the ancestral lineage of Neanderthals and was sampled only in Asia.
  - Late Neanderthals (Vindiga, Mezmaiskaya) on the other hand, represents a more derived Neanderthal lineage that replaced the ancestral Neanderthal lineage in Europe 50,000 years ago.
- Current 2020 study: introgressed haplotypes detected in modern human genomes from Western Europe and East Asia are on average closer to the Vindija Neanderthal genome (a late Neanderthal genome) than to the Altai Neanderthal genome, there are more than expected haplotypes that show excess distances to Vindija Neanderthal genome under a single-pulse introgression model in both East Asia and Western Europe.

Ozgur Taskent, et al., 2020

- This indicates that multiple pulses of introgression from different lineages of Neanderthals into modern humans occurred for both East Asians and Western Europeans.
- In line with these results, we found a deletion variant that is located within a 366 kb introgressed haplotype detected in East Asian genomes and exclusively shared between Altai Neanderthal and extant humans from East and Southeast Asia.
- Coalescent simulations indicate that the allele sharing observed for this locus is highly unlikely under single-pulse introgression from a lineage closer to Vindija Neanderthal.
- A second pulse of introgression from a late Neanderthal lineage into the ancestors of Europeans after they split from the East Asians is the most likely scenario.

Ozgur Taskent, et al., 2020: Altai N into East Asians

- It has been suggested that the main gene flow from Neanderthals into the ancestors of present-day Eurasian populations originated from the Vindija branch of the Neanderthal phylogeny (Prüfer et al. 2017).
- It was further suggested that this branch belongs to a late Neanderthal population from which the Vindija Neanderthal descended, which replaced earlier Neanderthal populations, including the population that is represented by the Altai Neanderthal (Hajdinjak et al. 2018).
- Our results are support a second pulse of Neanderthal introgression into both East Asians and Europeans
- Conclusion: Introgression from the Altai lineage, specifically into the ancestors of East Asian populations. Our results are mostly in line with a model of low-level Altai Neanderthal lineage-specific introgression.

Latest research: Closer to Altai N

- Various Neanderthal populations contributed to extant human genetic variation in a population-specific manner.
- Analyzing the DNA of hundreds of people with Eurasian ancestry, researchers have found:
  - genetic material linked to Neanderthals in the Altai mountains of modern Siberia into East Asians
  - This is an entirely different lineage from the Croatian population of Neanderthals identified in past genomic research.

Ozgur Taskent, et al., Genetics, 2020

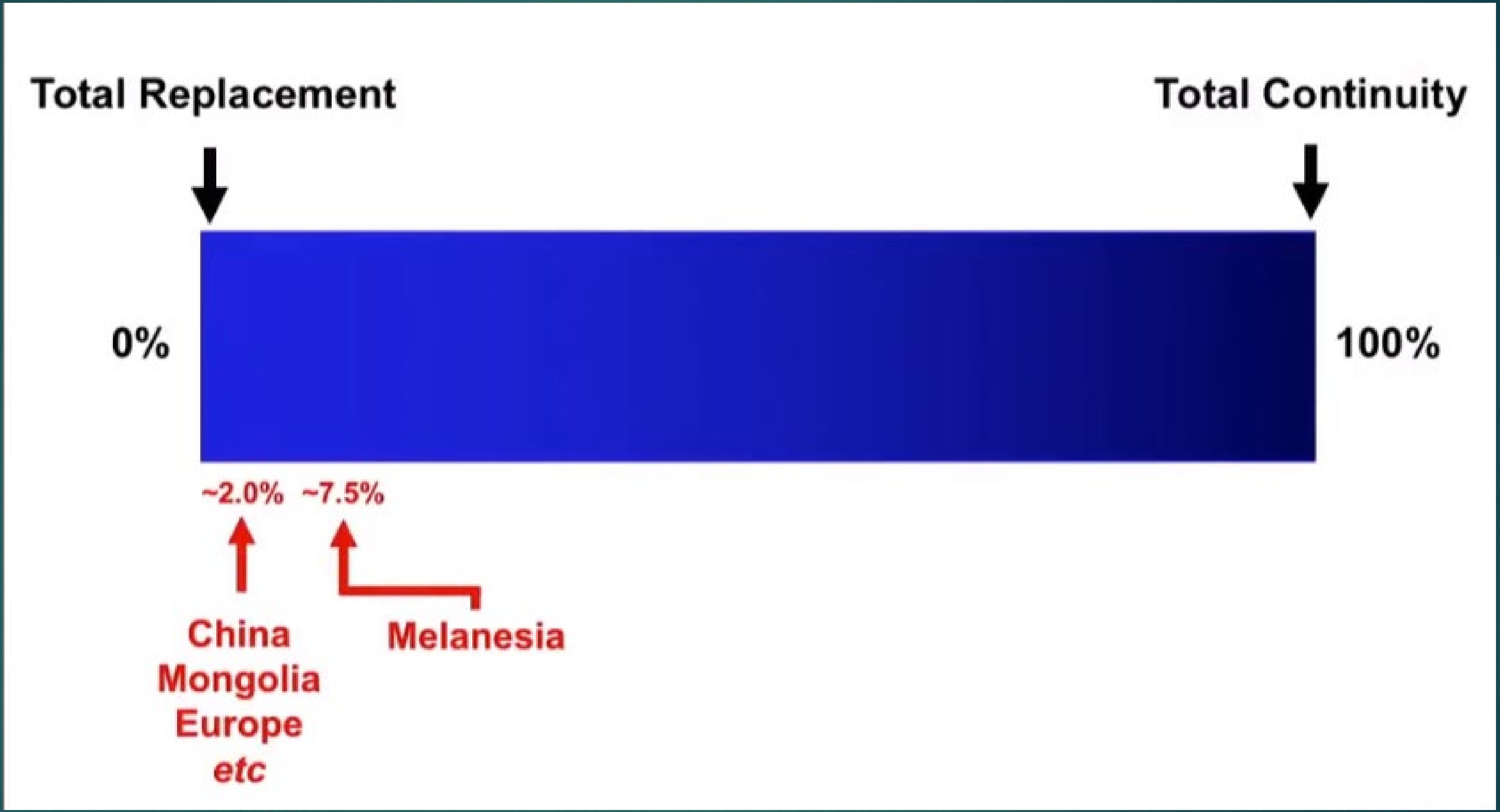
Why the replacement?

- Why was N DNA replaced in MHs?
- Because Ns had such small populations and accumulation of deleterious variants, when MH variants were introduced, they fixated because they were functional

Replacement vs Continuity of DNA: mtDNA

1997: N mtDNA has been totally replaced

DNA rejects total replacement theory: Denisovan DNA



Neandertals from Genome

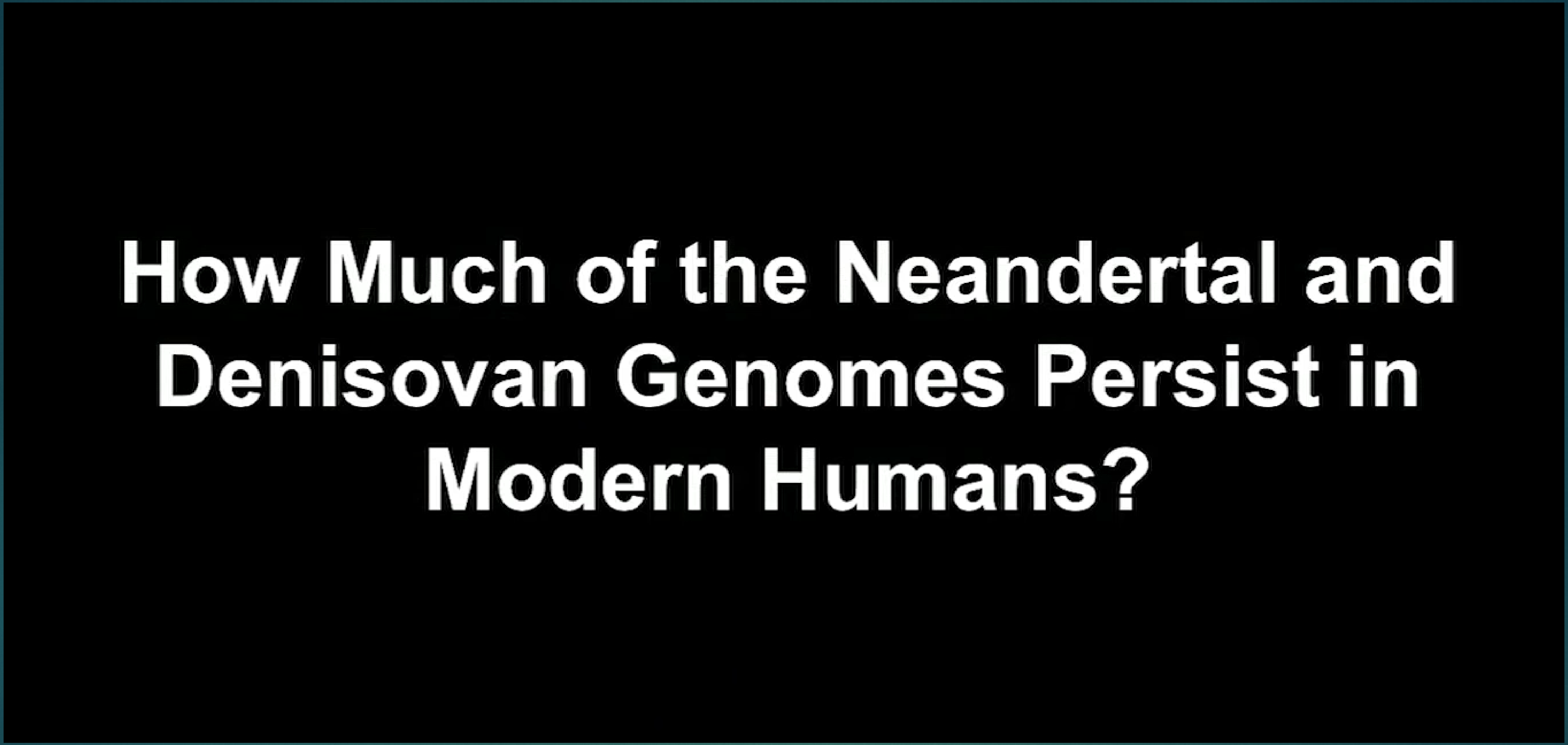
- Low genetic variability: heterozygosity in Neanderthals as well as Denisovans appears to have been lower than in present-day humans and is among the lowest measured for any organism.
- All genomes analysed show evidence of a reduction in population size that occurred sometime before 1.0 million years ago.
- Subsequently, the population ancestral to present-day humans increased in size, whereas the Altai and Denisovan ancestral populations decreased further in size.

mtDNA datings

- A synthesis of mtDNA studies concluded that an early exodus out of Africa, evidenced by the remains at Skhul and Qafzeh by 135,000 to 100,000 years ago, has not left any descendants in today’s Eurasian mtDNA pool.
- The successful exodus of women carrying M and N mtDNA, ancestral to all non-African mtDNA today, at around 60,000 years ago may coincide with the unprecedented low sea-levels at that time, probably opening a route across the Red Sea to Yemen.

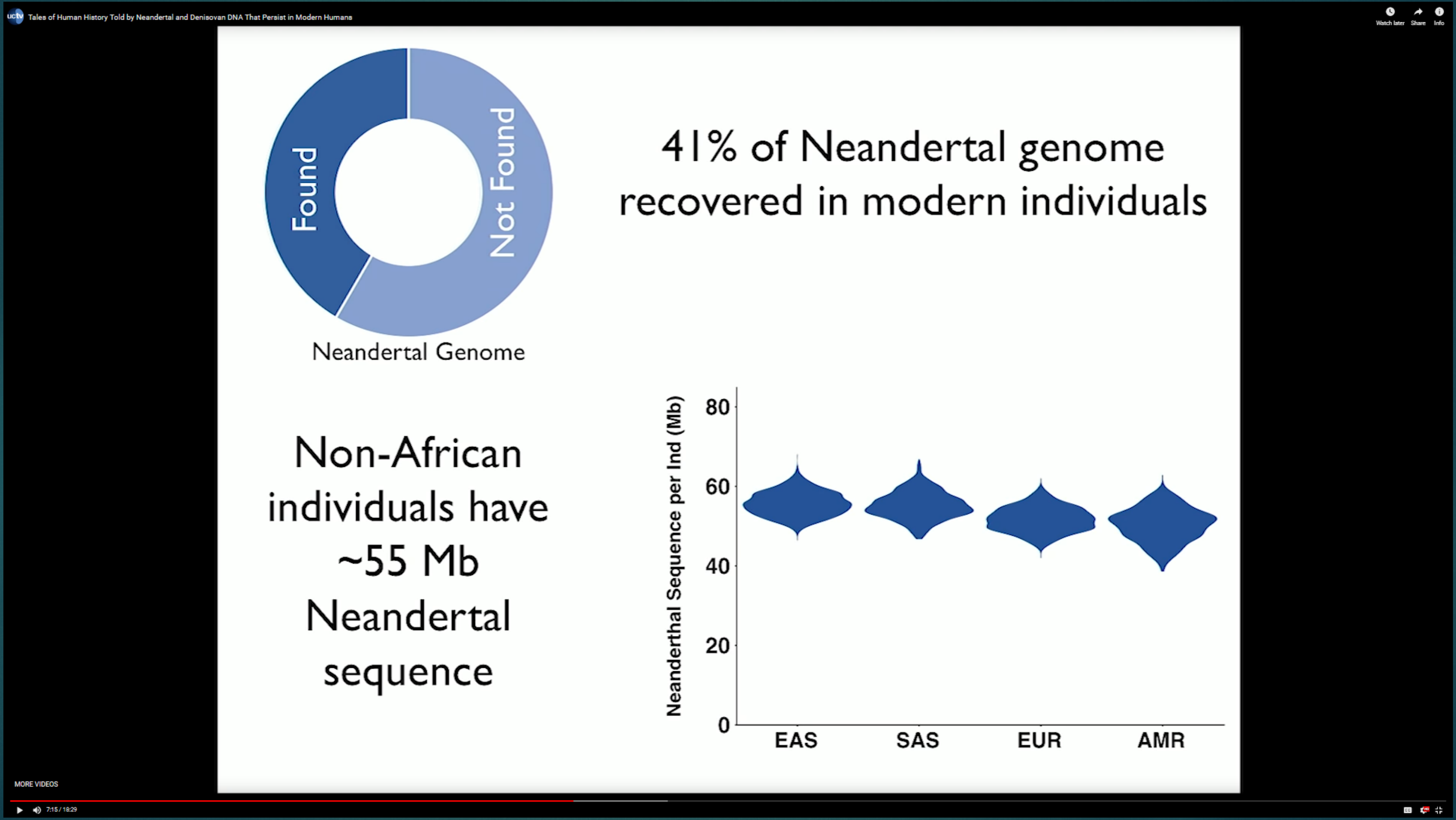
mtDNA datings

- Another study of a subset of the human mtDNA sequence yielded similar results, finding that the most recent common ancestor of all the Eurasian, American, Australian, Papua New Guinean, and African lineages
  - dates to between 73,000 and 57,000 years ago,
  - while the average age of convergence, or coalescence time, of the three basic non-African founding haplogroups M, N, and R is 45,000 years ago.



How Much of the Neandertal and Denisovan Genomes Persist in Modern Humans?

41% of total N genome present today in MHs

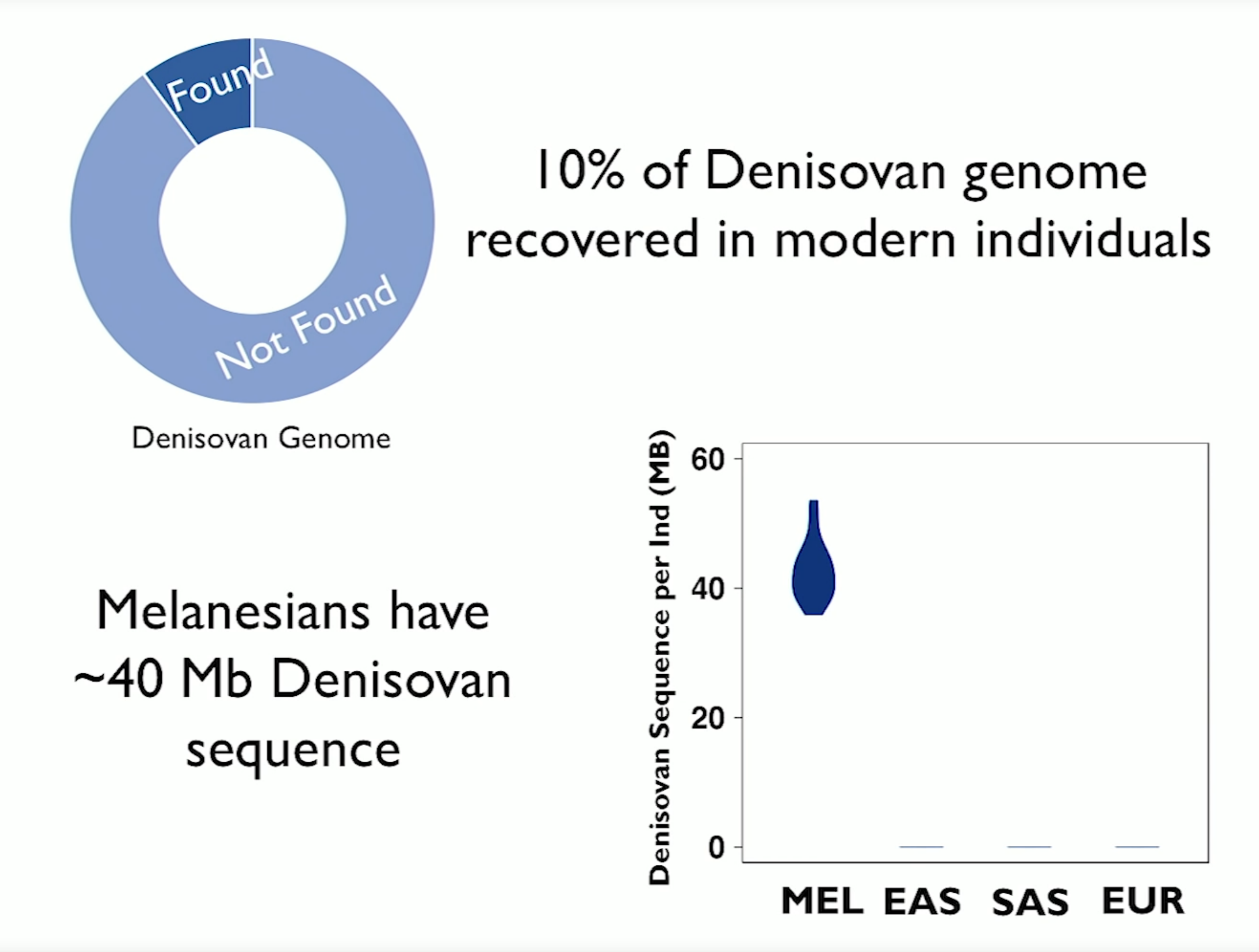


Tales of Human History Told by Neandertal and Denisovan DNA That Persist in Modern Humans

41% of Neandertal genome recovered in modern individuals

Non-African individuals have ~55 Mb Neandertal sequence

10% of total Denisovan genome is present in MHs



Denisovan Genome

10% of Denisovan genome recovered in modern individuals

Melanesians have ~40 Mb Denisovan sequence

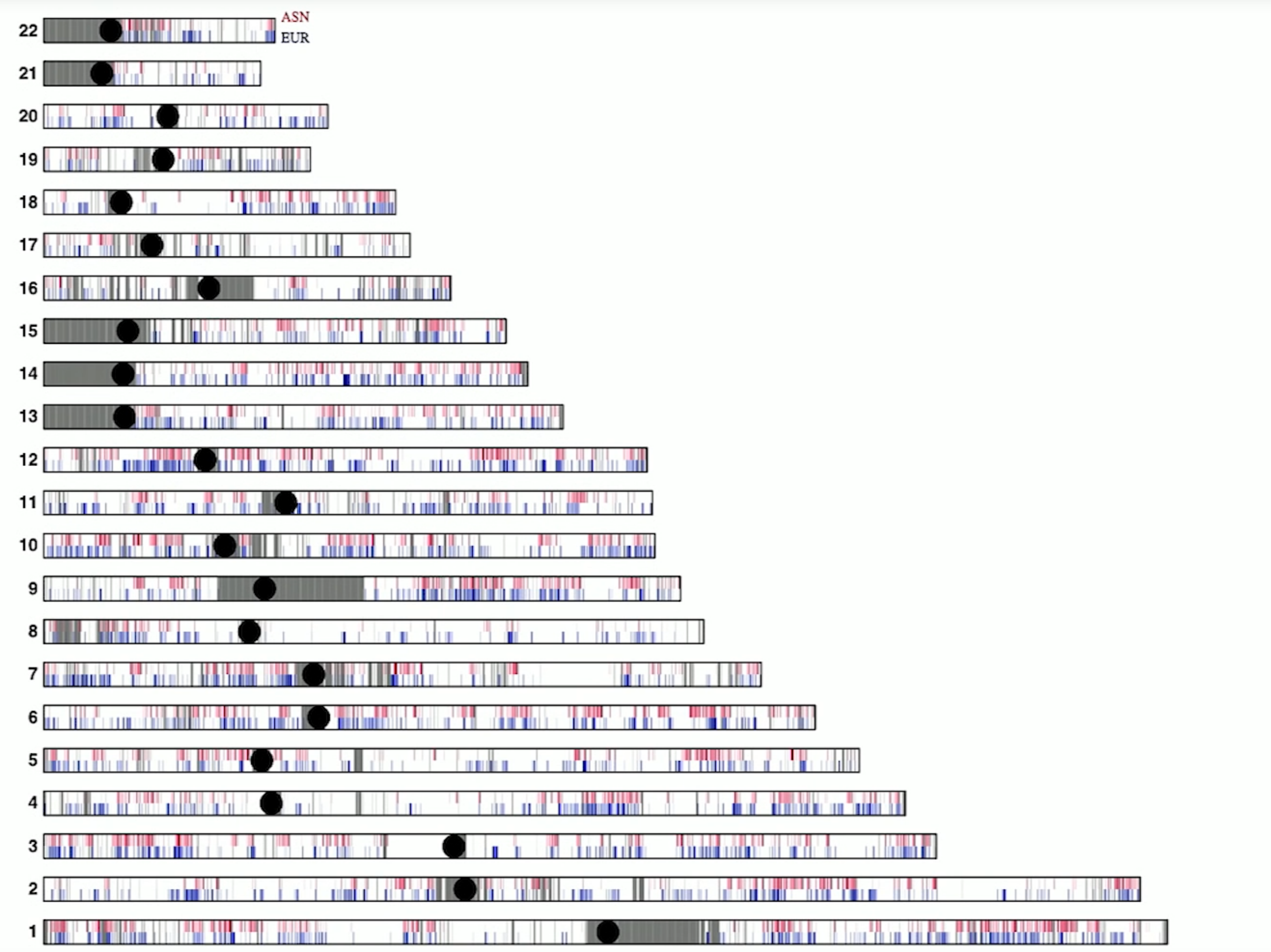
Based only on n=35 who are Melanesians ; more to be found

Was admixture an interesting side note in human history or something more significant

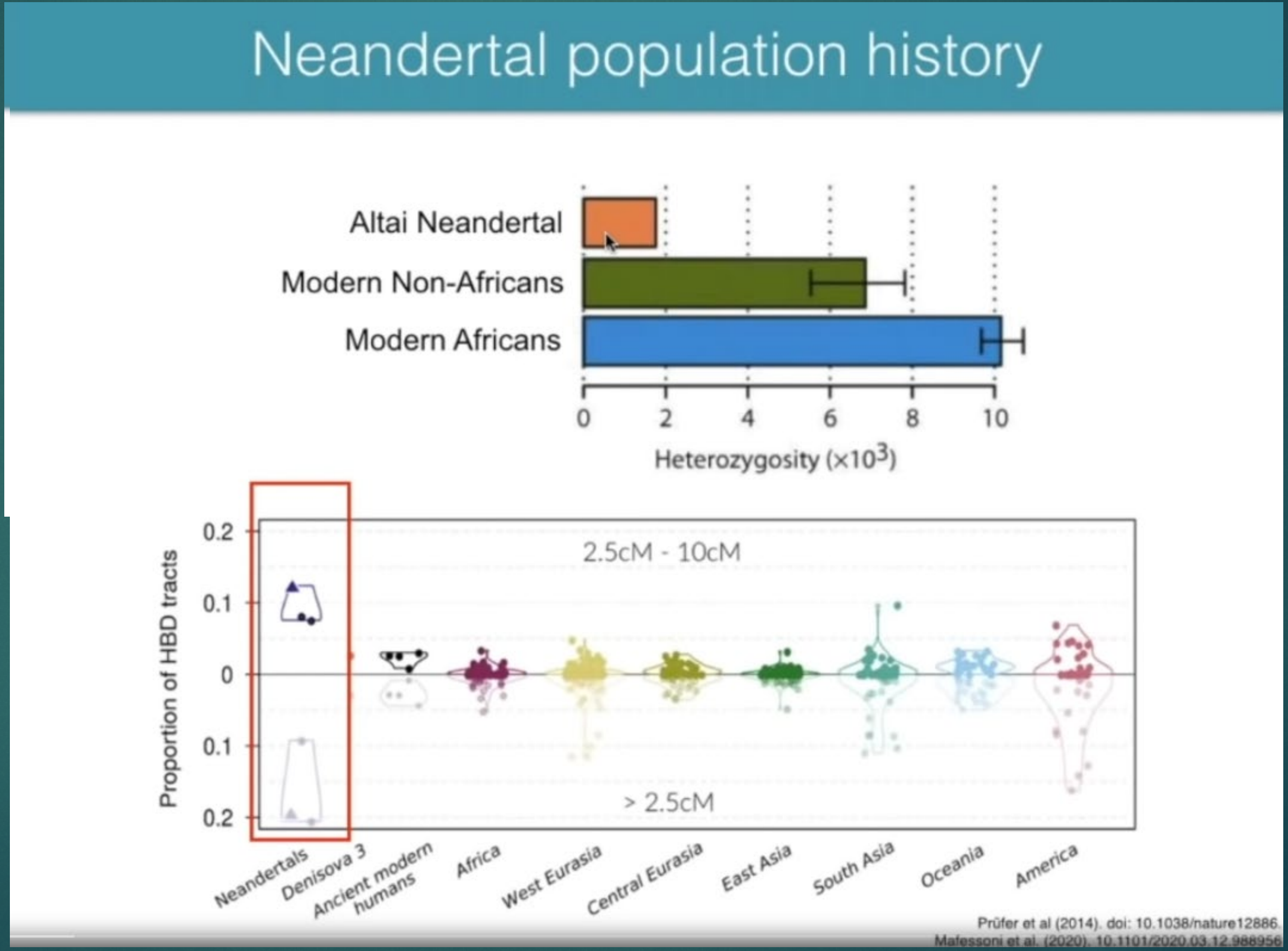
- Negative fitness consequences?
- Positive fitness consequences?
- Phenotypic consequences

N sequences in Modern Humans today

Europeans = Blue
East Asians = Red



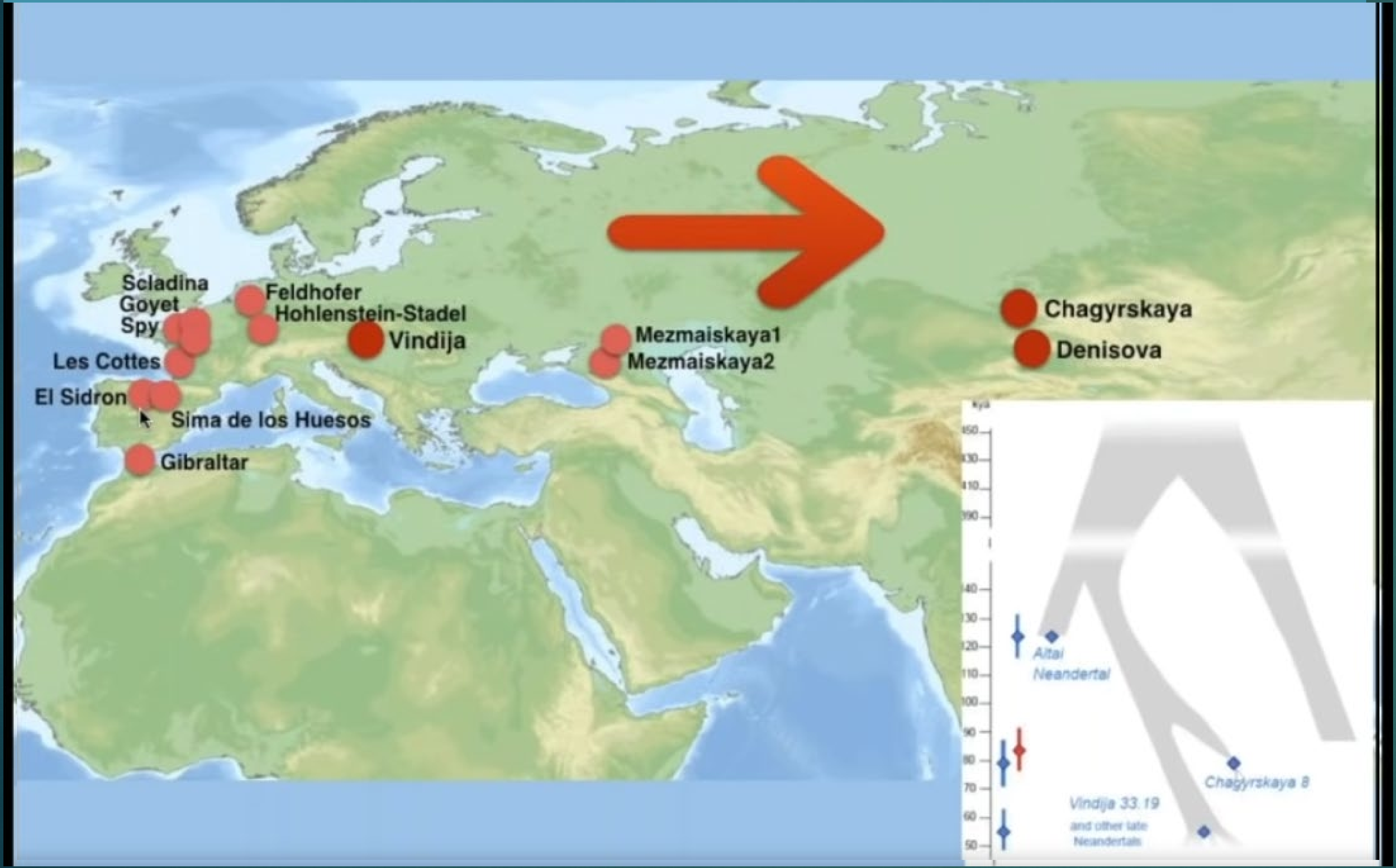
Very Low N Genetic diversity: long stretches of homozygosity; lots of interbreeding; implies closely related parents



Neandertal population history

Prüfer et al (2014). doi: 10.1038/nature12886.
Mafessoni et al. (2020). 10.1101/2020.03.12.988956

Neandertal population history



Chagyskaya (80 K) more closely related to 40 K Vindija N than to Altai N, next door

All Western Ns more closely related to each other than to Denisova Altai N

Reason: significant movement of Ns from W to E

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End of Paleogenetics, Part 6