Paleogenetics, Part 10

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Scientific Update, August 2022

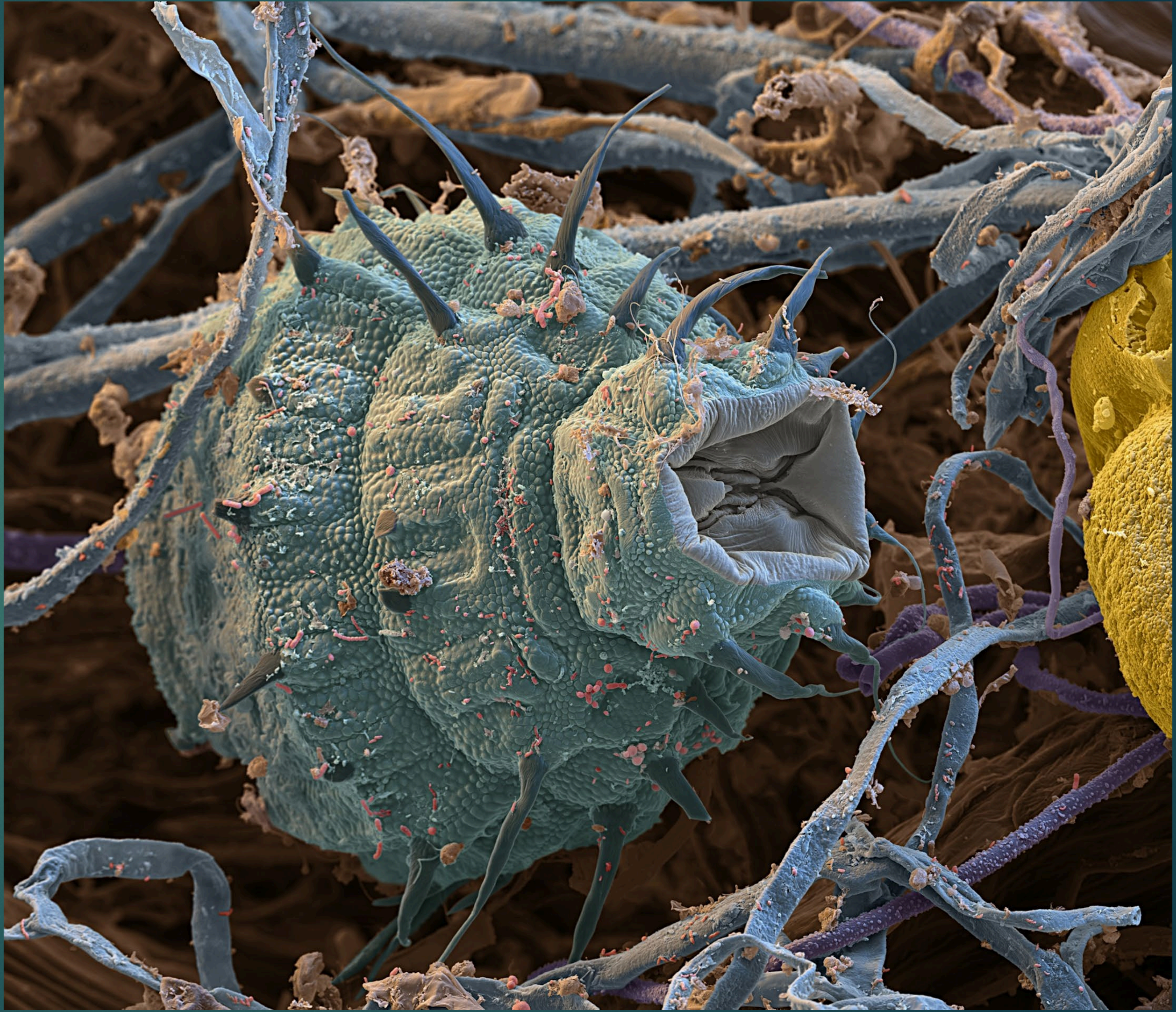
National Geographic: At the microscopic level, soil from Germany’s Black Forest is a fantastical realm: a tardigrade

Resinicium bicolor fungi

Scales of silica cover the single-celled body of a testate amoeba: 14 Kx

A single piece of woody debris can be a bustling hub for forest microbes. Here, a bristle worm (at left) and two types of mites

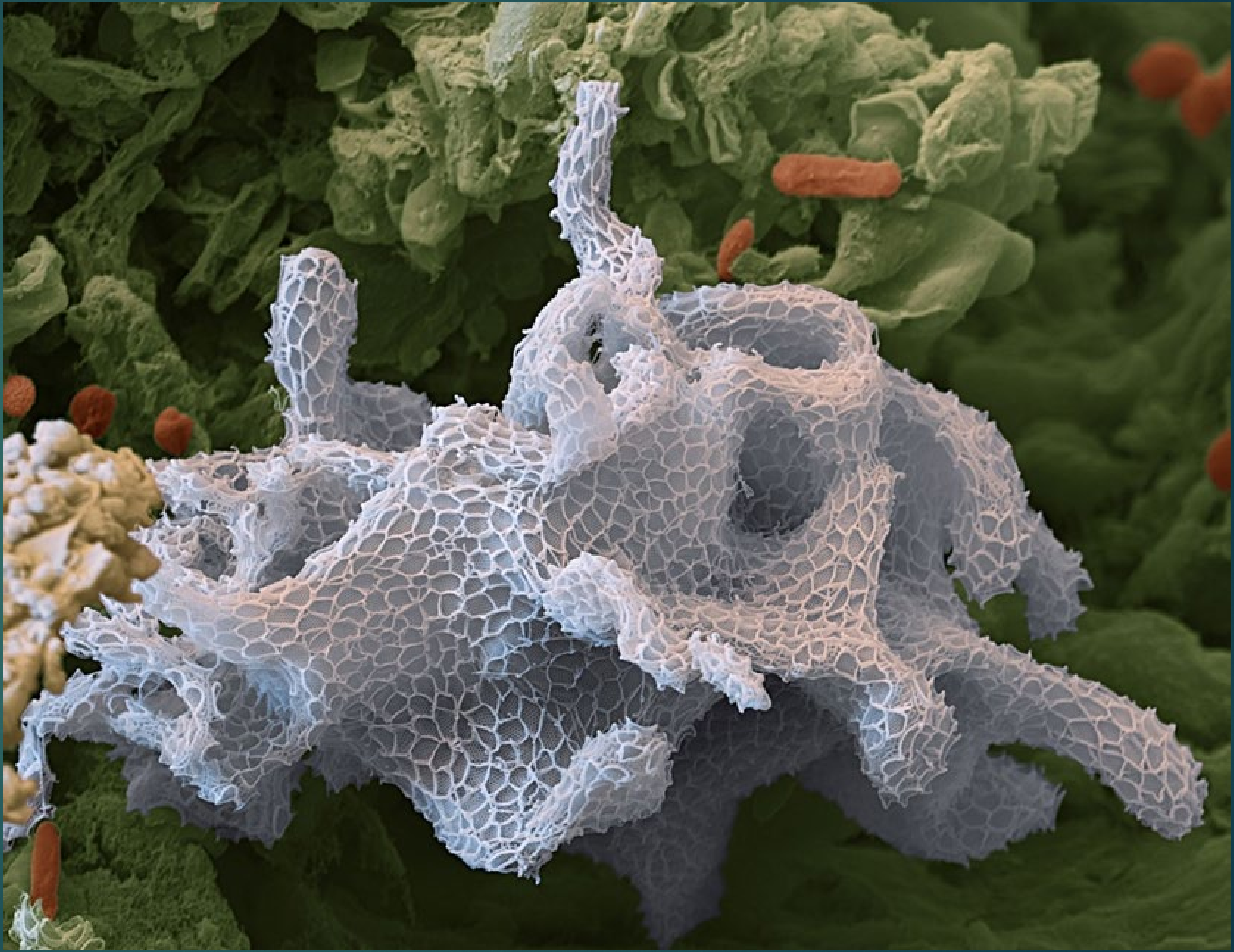
Fungal filaments frame a spiky-bodied rotifer



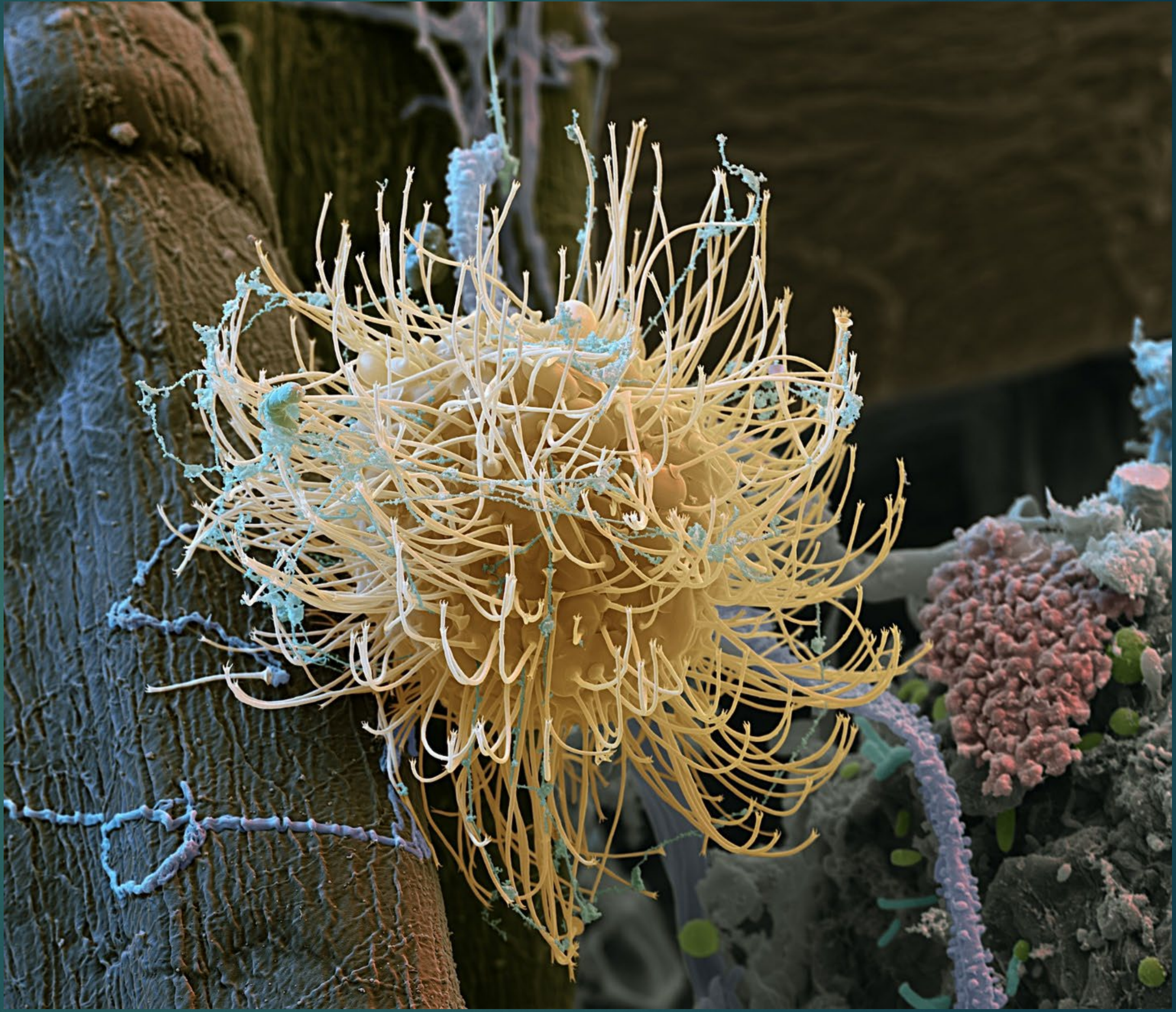
Slime Mold + spores

Bacteria

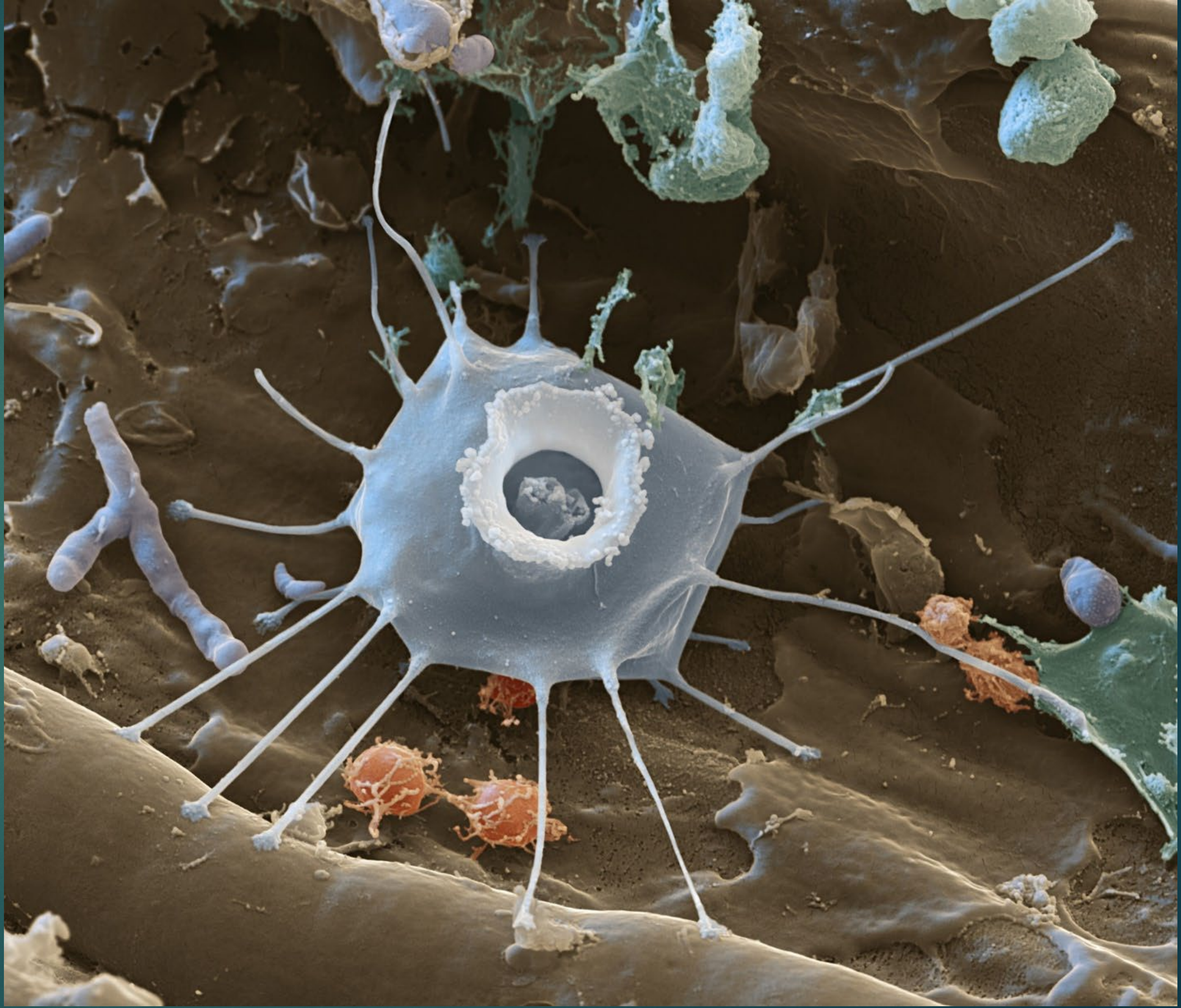
Amoeba from the genus Korotnevella



Heliozoan

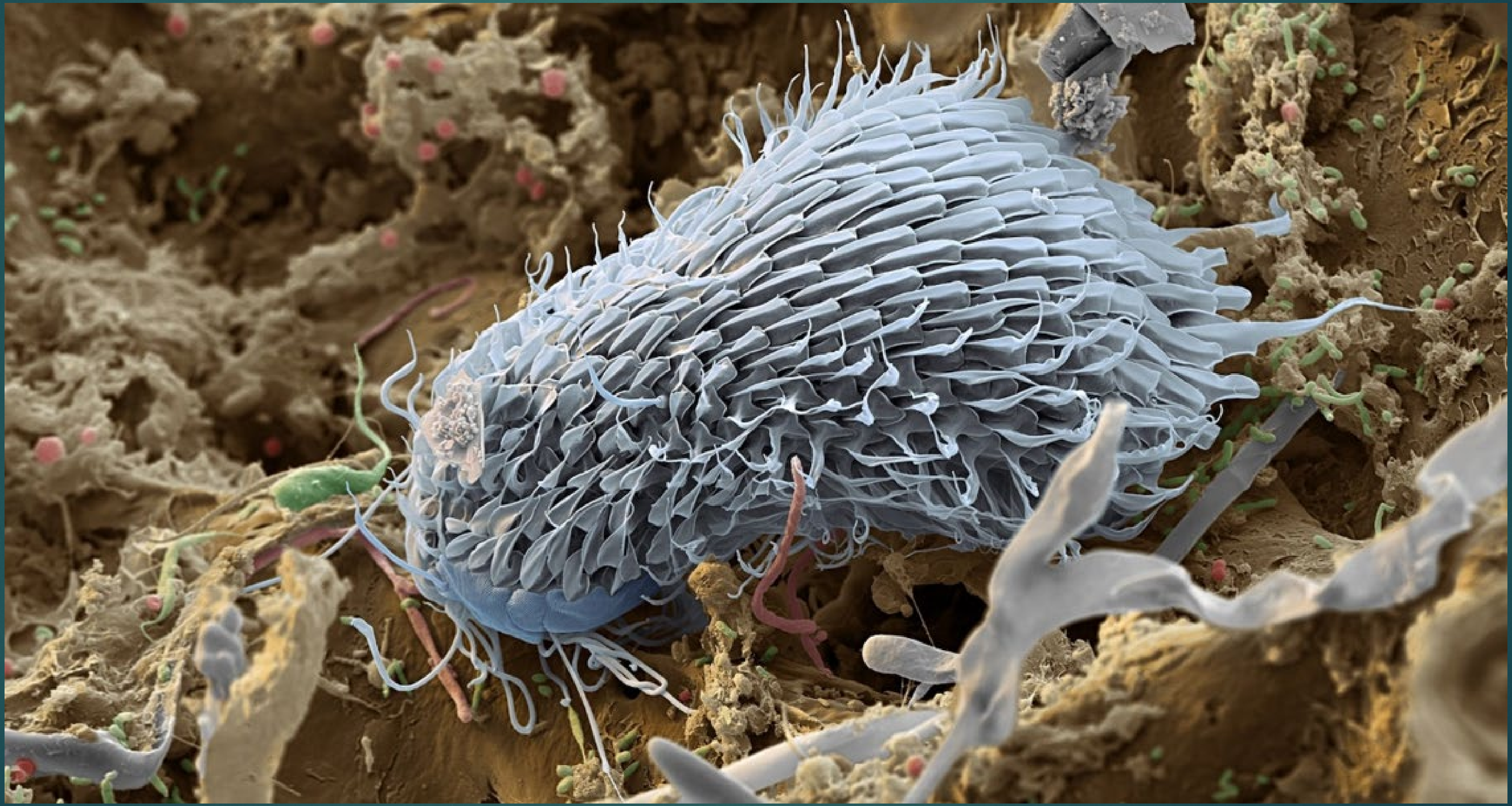


Single-celled choanoflagellate

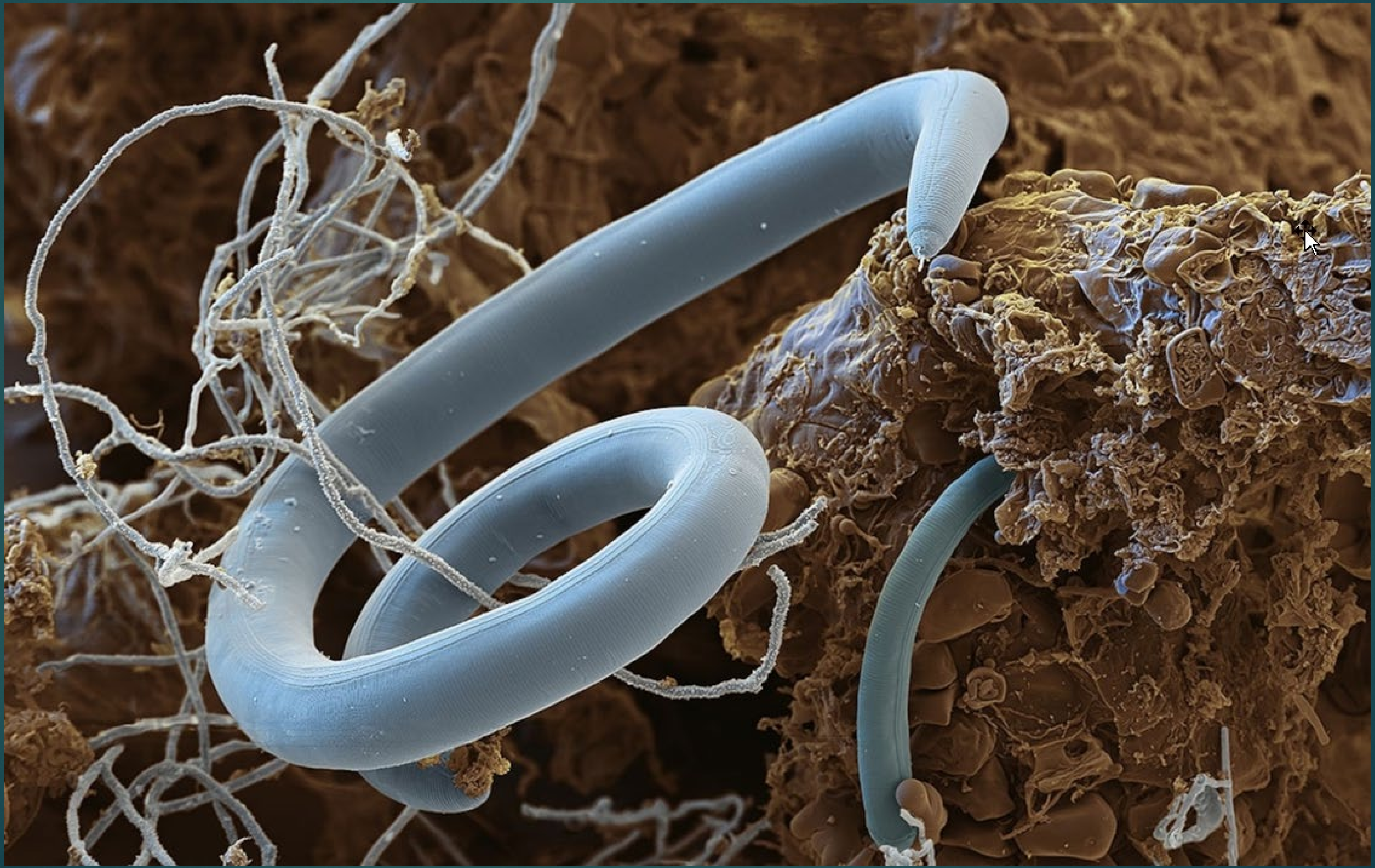


Ciliate: can swim

Hairybacks, the microscopic animals in the phylum Gastrotricha



A pair of nematodes curl around delicate fungal filament: 60 billion nematodes for every human on Earth



Springtails grow no larger than a fifth of an inch. The name comes from the tail-like appendage that allows them to leap more than 20 times their own body length to escape danger. 100 X

Oribatid mite: In search of food, one mite typically walks no more than half the length of a bowling lane in its lifetime

Oribatid mite

Mycorrhizal fungi make their homes inside plant cells, as seen in this cross section of a European blueberry root. This symbiosis allows soil residents of very different sizes to exchange nutrients

The Stairway to Heaven

Located at the top of Tianmen Mountain,

24,500 feet above the city of Zhangjiajie

in China's Hunan province.

Tianmen Mountain is a mountain located within *Tianmen Mountain* National Park, Zhangjiajie, in the northwestern part of Hunan Province, China.

1118 miles north of Hong Kong = 12 hrs.

Road to *Tianmen Mountain:* 7 miles, 40 minutes

99 hairpin turns

You can take a bus.

Or 2nd longest 25-minute gondola ride

999 steps up to Gateway

The 999 steps to Tianmen Cave, which is the world's highest naturally formed arch, the Gateway To Heaven.

4700 feet high walkway

Glass bottom walkway

Inspiration for alien landscapes of James Cameron’s Avatar film

Should you get your whole genome sequenced?

- Would you have your baby's whole genome sequenced at birth? A groundbreaking trial that used whole-genome sequencing to predict newborns' future health, is starting to reveal the impact it has had on the whole family, seven years later.
- The implications are a minefield, said ethicists. Who will have access to the data? Will it be useful? How will it affect parents and children over the course of their lives? But others say the benefits could be worth the risk.
- MedSeq: which began in 2012 and was the first study to examine the use of whole-genome sequencing in people with suspected genetic cardiac disease. It also looked at people who were in good health with no family history that suggested they were at risk of a genetic disease.

Whole genome

- One of the most surprising outcomes of this work was the discovery that a significant percentage of the latter group carry deleterious mutations – gene variants that increase a person's susceptibility to a certain condition. Found 20 per cent of healthy adults carrying something that might put them at risk of a disease
- The UK already routinely screens babies for nine rare conditions that can affect long-term health by looking for biomarkers in a few drops of blood from the newborn's heel. States in the US screen for at least 29 conditions.
- BabySeq -- 2015 study: focused on 954 genes that were related to childhood diseases and included a limited list of adult-onset conditions in the study. It meant that some of the results could indicate a parent was at risk, too.

Whole genome

- When the team actually went to maternity wards to enroll volunteers, only 7 per cent of the parents they asked signed up.
- Another issue was figuring out how to break bad news to parents whose results showed their newborn was at risk of a severe disease.
- Not all those with a bad genetic variant will go on to develop the disease; could be a big deal, but might not happen,
- Parents of 325 newborns completed surveys: when they enrolled in the trial, immediately after their child's results were disclosed, three months later and 10 months later. Half of the children received standard newborn screening plus a family history report, the rest received standard newborn screening plus a report based on whole-genome sequencing.

Whole genome

- Found no long-term negative psychological harm in a parent having knowledge about their child's genome, even in families where the sequencing found an increased risk for a disease
- Genetic sequencing of ill babies has a long history of having a positive impact on health; 7 hours and 18 minutes = world record for fastest genetic diagnosis
- The consequences of screening healthy babies has been less clear until now. BabySeq's latest results show that 18 per cent of 159 babies with no current medical problems who had their genome sequenced at birth had a mutation for a childhood-onset or adult-onset genetic condition. All of the conditions had available clinical interventions. In eight cases, the results prompted screening for at-risk family members, too.

Whole genome

- For instance, the maternal grandfather of a child in the study had been previously diagnosed with a heart condition. The baby was shown to carry the variant that predisposes them to the same heart condition. Consequently, the child’s mother now has routine echocardiography.

- Issues: One is that sequencing the entire genome has the potential to give results that aren’t significant or actionable, causing worry without any pay-off. And although BabySeq has been running for a while now, there is limited understanding of how such early knowledge of your genes affects your life over the long term.

Whole genome

- We know from a 2019 study, for instance, that being given genetic information can change behavior. When people were told they had a genetic propensity for either obesity or lower exercise capacity, it altered the way their body responded to a meal and exercise (even though the result was, in fact, fake). And of course, when screening newborns, you are making these decisions on behalf of an individual who, as an adult, may not want to know about them.
- A paper, published last year, found that more than a third of people whose genetic information showed a disease-causing variant with an actionable outcome chose not to receive the information.

To know or not to know. That is the question

- Privacy and consent are among biggest concerns.
- An individual’s medical information is private. If a child is sick and must be treated without their consent, the parents may get information about the child’s health. But it isn’t the case that our parents have the right to total knowledge about our health. We’re talking about basically subjecting all members of society to a medical investigation that will yield huge amounts of private information, which will be somewhere, available to whoever, without the individual’s consent. It isn’t clear who will hold the genetic information, how it will be tied to public health records or how often each genetic risk leads to actual disease.

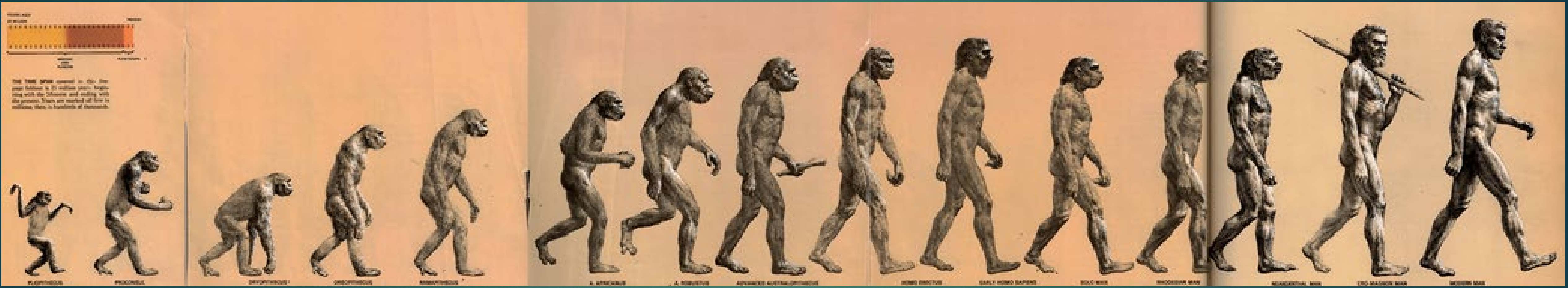
Whole genome

- Although researchers are currently focused on the medical outcomes of newborn genetic screening, it may be possible to correlate the data with other outcomes in the future.
- Would you want to know whether your baby is predisposed to having a high IQ or excellent sporting ability?
- A 2018 study of 1.1 million people found correlations between certain genes and educational attainment

2nd meteor may have struck at end of dinosaur era

- 9 km crater discovered buried beneath the sea floor near the coast of West Africa. It was made around the time of the larger Chicxulub impact that wiped out most dinosaurs, leading to speculation that it was caused by a chunk that broke off the Chicxulub asteroid.
- Spotted the feature in seismic reflection data supplied by the oil and gas industry. The likely crater, named the Nadir crater after a nearby seamount, is on the continental shelf a few hundred kilometers off the coast of Guinea, buried beneath around 300 meters of sediment in an area where the water is 900 meters deep.
- The structure has all the features characteristic of an impact crater of this size, including a raised rim and signs of ejected material outside the crater itself.
- Asteroid size = 400 meters round
- Nadir crater appears to have formed around 66 million years ago, the same time as the 180 kilometer-wide Chicxulub crater in what is now Mexico. This asteroid was 13 km wide

1965 March of Progress: wrong view of evolution – Nature does not evolve toward higher complexity or modern human beings



Demise of March of progress by Alexander Werth

- Simplistic, linear views of evolution incorrectly portray humans as more evolved than other species
- Herschel Walker, the former football star–turned–U.S. Senate candidate from Georgia, made headlines when he recently asked at a church-based campaign stop, if evolution is true, “Why are there still apes?”
- We did not evolve from apes; we had a common ancestor.
- A more fruitful query might be, “If evolution is true, why are there still humans?” Why is our species almost universally seen as the logical endpoint of evolution, with all other species serving as inferior detours or temporary placeholders on an inevitable march toward humanity?

Evolution

- It is not necessarily surprising that non-scientists might see Earth’s history as a progression toward higher levels of complexity, with humans representing the most complex. What is startling is that traces of this view remain in scientific thought.
- As if humans are the benchmark by which all characteristics should be measured,
- It’s exemplified by the iconic “March of Progress”—a linear sequence of slumped apes eventually supplanted by upright humans. And it persists in the ideas that certain “lower” ancestral human populations gave rise to, and were succeeded by, more complex people, who are often depicted as having lighter skin tones.

Evolution

- People must unlearn this idea that biological diversity is an ascending ladder of complexity, with humans on top and nonhuman species as imperfect transitions and lesser beings. The chief result of this misguided worldview is our casual disregard for the natural environment,
- The last universal common ancestor of all living things on Earth was a bacterium-like organism that arose around 4 billion years ago. All living species today are equally evolved from and similarly distant from that microbe.
- As paleontologist Stephen Jay Gould argued in his 1996 book *Full House*, the apparent trend toward complexity is a bit of a mirage. Instead, Earth has remained, since life appeared, in an “Age of Bacteria” because of both their staggering abundance and overwhelming influence on all other organisms.

Evolution: There Are No Higher or Lower Creatures

- Consider that bacteria do countless things humans cannot, including orienting by magnetic fields, encysting to survive hundreds of years in “suspended animation,” and incorporating stray bits of DNA lying around their environment. Many bacteria make their own food by chemosynthesis or photosynthesis. Others glow in the dark, survive in anoxic muck or boiling water, or pick up metal particles to shield themselves from toxic and radioactive environments.
- Naturalist Charles Darwin drafted a note to himself to “Never use the words higher or lower.” Apes did not appear just so they could morph into humans. Nor did reptiles evolve solely to give rise to mammals, nor fish to amphibians.

Evolution

- Robust herbivorous australopithecines, sometimes placed in the genus *Paranthropus*, continued to exist for at least a million or more years after smaller meat-eaters in the genus *Homo* appeared.
- Archaic *Homo* species did not disappear just as anatomically modern humans appeared, and Neanderthals had brains that were on average larger than those of our more gracile species.
- Anthropologists studying genetic diversity have learned how fragile humanity is: During multiple population “bottlenecks,” our ancestors came within a hair’s breadth of extinction. Life has never been about attaining humanity. Humans evolved as a result of chance contingencies and random mutations.

Evolution

- As Gould famously argued in his 1989 book *Wonderful Life*, if evolution's "tape were to be rolled back," humans might not reappear. The world would surely be different if humans had never evolved, but frogs and butterflies might be better off, especially given humanity's frequent disregard for the welfare of Earth and its inhabitants.

- People naturally think categorically and are primed to see differences rather than similarities between humans and other animals. Further, numerous studies show that people are instinctively teleological—tending to see goal-driven progress everywhere, starting at a very young age.

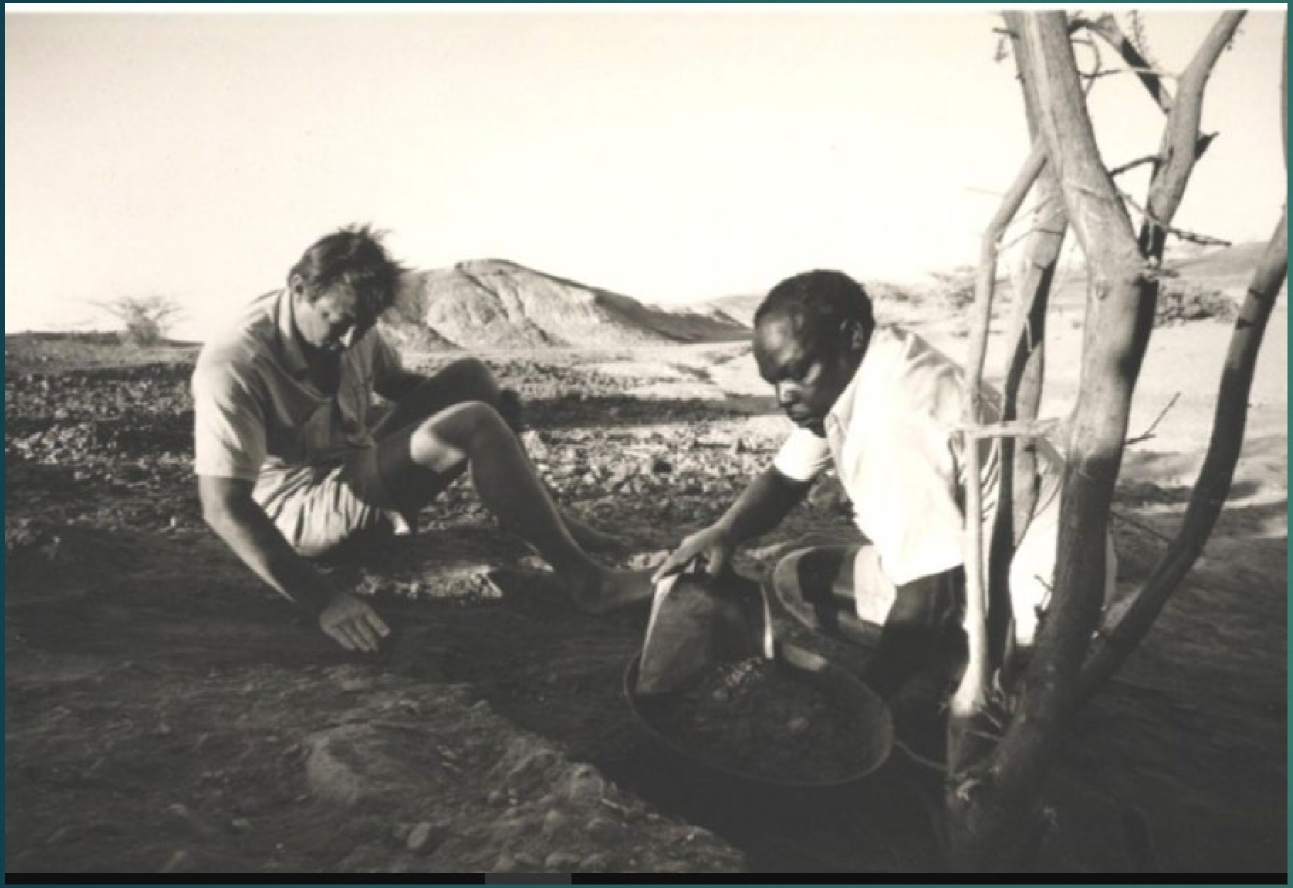
Evolution

- Anthropocentrism is merely one way of seeing the world. Religions such as Jainism and Buddhism are less anthropocentric than Abrahamic faith traditions. But they are still less ecocentric than philosophical Taoism, and most Native American and Aboriginal worldviews, which typically put all life on a level playing field.
- In numerous Indigenous cultures, humanity does not exist on an elevated platform from which it looks down on other species. There is modesty and equity. There is appreciation and gratitude for all of nature rather than a sense that nature exists solely for humanity’s benefit, to use and squander as it sees fit

Evolution

- So, perhaps the best retort to Herschel Walker and like-minded people is to wonder why, if evolution is true, humans do not live up to our potential. Why do all people not fully use their impressive brains and touted foresight? Why do they not accept and embrace science? Why do some sneer down on other species as lesser or lower? Why do they not care for all living things?
- All peoples must learn to accept what science clearly shows: that ours is simply one among many extraordinary species, and that humanity must be seen as a part of—not apart from—nature.

Remembering Kamoya Kimeu: “digging for bones”



Kamoya Kimeu, the legendary paleontologist and fossil finder behind some of the world’s most important hominin fossil discoveries, passed away on July 21, 2022.

Kimeu began working with Louis and Mary Leakey in 1960, then with Richard Leakey. His finds, including the KNM-ER-1813 skull of *Homo habilis* and the remarkable Turkana Boy skeleton,

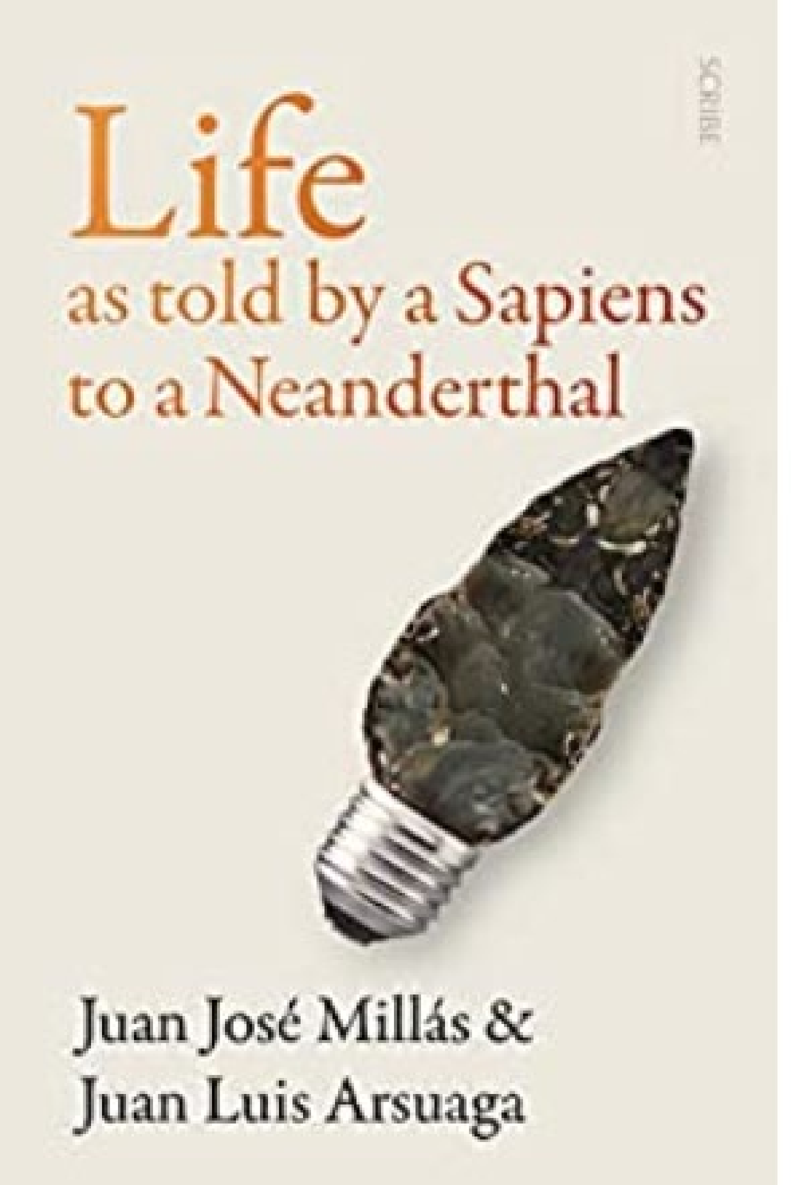
Head of his Hominid Gang

Kamoya Kimeu discoveries

- In January of 1964 at the Peninj site near Lake Natron in Tanzania, Kimeu, working with Richard Leakey and Glynn Isaac, found an entire mandible of a *Paranthropus boisei; not ancestral to Homo habilis*
- In 1968, again on an expedition with Richard in the Omo valley of Ethiopia, Kimeu discovered an early *Homo sapiens* skull. no one believed *Homo sapiens* could be this old. Dated at 130,000 years old, until this discovery, many anthropologists believed that Homo sapiens had not appeared until after the Neanderthals, or approximately 60,000 years ago at the latest. This discovery also proved that Neanderthals and *Homo sapiens* were contemporaries
- In 1973, Kamoya Kimeu located a new fossil, KNM-ER 1813, a Homo habilis specimen with a relatively small braincase.

Kimeu

- 1984: Probably Kimeu’s most famous fossil discovery was that of an almost complete Homo erectus skeleton labeled KNM-WT 15000 but known in paleoanthropological circles as Turkana or Nariokotome boy.
- In 1994: with Meave Leakey at Kanapoi in Southwest Turkana, Kimeu found two parts of a hominid shinbone; 4 Ma, Australopithecus anamensis.
- In 1985 Kimeu was awarded the National Geographic Society La Gorce Medal by Ronald Reagan at the White House.
- Two fossil primates have been named after him: *Kamoyapithecus hamiltoni* and *Cercopithecoides kimeui*.
- In 1977 he became the National Museums of Kenya's curator for all prehistoric sites in Kenya; He was awarded a honorary Doctorate of Science degree from Case Western Reserve University in 2021



SCRIBE

Life
as told by a Sapiens
to a Neanderthal

Juan José Millás &
Juan Luis Arsuaga

New book by Juan Luis Arsuaga, Spanish Paleoanthropologist

He works at Atapuerca archeological site

A journey thru human origins

Human Y chromosome sequences from Q Haplogroup reveal a South American settlement pre-18,000 years ago

- Found chromosomal evidence of people living in South America at 18,000 years ago.
- Collected tissue samples from 13 people living in Argentina who were believed to be descended from ancient migrants to the region (members of the Q Haplogroup), rather than the New World. The researchers then studied their Y chromosomes as a means of establishing a timeline. The Y chromosome has the longest stretch of non-recombinant DNA
- Used the data from the volunteers to help create de novo phylogenetic trees where the lengths of the branches were proportionate to the number of single-nucleotide polymorphisms, which they note correspond to time. They then compared the data with samples collected from 80 other people belonging to the Q Haplogroup, who lived in other places, such as Eurasia and that allowed them to make estimates regarding how long people in South America must have been living there for their Y chromosomes to have the characteristics that they have today—approximately 18,000 years.

'Ghost footprints' left by ancient hunter-gatherers discovered in Utah desert: only appear when it rains

“Ghost” footprints

- They become visible only after it rains and the footprints fill with moisture and become darker in color, before disappearing again after they dry out in the sun.
- At least 88 individual footprints belonging to a range of adults and children, potentially as young as 5 years old. Used ground-penetrating radar
- The ghostly prints were left by bare human feet, dated to 10,000 to 12,000 years ago when the area was still a vast wetland.
- People appear to have been walking in shallow water, with the sand rapidly infilling their print behind them, much as you might experience on a beach. But under the sand was a layer of mud that kept the print intact after infilling. The footprints have since been filled in with salt as the wetlands dried out.

Ghost footprints

- Less than a mile (1.6 kilometers) away from where the tracks were uncovered, a previous research group uncovered a hunter-gatherer camp dating to 12,000 years ago, where the humans who left the prints might have lived. Archaeological finds at the site included an ancient fireplace, stone tools used for cooking, a pile of more than 2,000 animal bones and charred tobacco seeds, which are the earliest evidence of tobacco use in humans.
- This region is a hotspot for ancient human trackways. In September 2021, a study revealed that 60 human footprints in White Sands National Park in New Mexico dated to between 21,000 and 23,000 years ago, making them the oldest "unequivocal evidence" of humans in the Americas.

37,000-year-old mammoth butchering site

- A 37,000-year-old mammoth butchering site, uncovered in New Mexico, might be the earliest evidence of humans in North America. Some of the bones at the site show signs of being handled by humans or even being used as tools
- The new site was discovered on the Colorado Plateau in northern New Mexico
- An excavation of the Hartley site revealed the incomplete remains of two mammoths, believed to be an adult female and a juvenile. Most of the bones were grouped in a large pile, with the adult female's skull lying on top. By carbon-dating collagen in the bones, researchers estimated the remains could date to between 36,250 and 38,900 years ago.

New mammoth discovery

Potential butchering marks on mammoth ribs. The top rib shows a fracture from blunt force impact; the middle rib shows a puncture wound, potentially made by a tool; the bottom rib shows chopping-like cut marks. (Image credit: Timothy Rowe et al. / The University of Texas at Austin)

37,000-year-old mammoth butchering site

- Until now, the most conclusive evidence of a pre-LGM settlement for pre-Clovis people comes from a 2021 study, which revealed a set of 60 bare human footprints uncovered at White Sands National Park in New Mexico. The fossilized tracks date to between 21,000 and 23,000 years ago based on organic material trapped inside the footprints, which suggests pre-Clovis people may have moved into North America before or during the LGM. But this discovery has not been enough to settle the debate.
- Criticism: "The researchers certainly have a solid date for the death of the mammoths, but they lack definitive evidence of human activity,"

Other recent studies

- Other recent archeological discoveries placing humans in the Americas during or before the Last Glacial Maximum (LGM). These include:
  - multiple in situ human footprints from New Mexico that date from 22,860 to 21,130 cal BP (Bennett et al., 2021),
  - and footprints from Argentina that date to 30,000 cal BP (Azcuy et al., 2021).
  - Simple stone tools discovered in Chiquihuite Cave, Mexico, date from 26,500 to 19,000 cal BP and represent a previously unknown tradition (Ardelean et al., 2020; Becerra-Valdivia and Higham, 2020).
  - At Coxcatlan Cave, Mexico, re-dating butchered small mammals associated with minimally worked stone tools established a 33,448 to 28,279 cal BP date for the site's lowest cultural level (Somerville et al., 2021).

Other recent studies

- Simple flaked stone artifacts are known from numerous ancient South American sites. These include
  - Toca da Tira Peia, Brazil, which dates to 20,000 cal BP (Lahaye et al., 2013),
  - and Vale da Pedra Furada, Brazil, which dates to 24,000 cal BP (Boëda et al., 2021); older artifacts dating to 32,000 cal BP are also reported from this site (Guidon and Delibrias, 1986; Guidon et al., 1994).
  - At Toca do Serrote das Moendas, Brazil, faunal remains associated with human bones were dated to between 29,000 and 24,000 cal BP (Kinoshita et al., 2014).
  - And at Arroyo del Vizcaíno, Uruguay, a fossil-rich 30,000 years old megafaunal locality with cut-marked bones (Fariña et al., 2014)
  - adds to a growing record of probable human occupation sites in the Americas that predate arrival of the Native American clade by millennia.

All Hooting Aside: Did a Vocal Evolution Give Rise to Language?

- The loss of certain muscles in the human larynx may have helped give our species a voice.
- A study of 43 primates found that they all possessed an extra set of vocal membranes in the larynx, just above the vocal cords. Only humans lack the structure. The vocal lips and the vocal cords vibrated in unison
- Vibrations of the vocal cords form the foundations of the human voice.
- The presence of vocal lips destabilized the other primates' voices, rendering their tone and timbre more chaotic and unpredictable. Animals with vocal lips have a more grating, less controlled baseline of communication, the study found; humans, lacking the extra membranes, can exchange softer, more stable sounds

Vocal muscles

- Propose that the absence of vocal lips — and their complicating vibrations — in humans was a key factor in the evolution of language (?) in our species. Vibrating in splendid isolation, our vocal cords allowed for subtle changes in inflection and register that characterize our own speech.

Silent Witness British Detective Series

- Over the past twenty years, DNA analysis has revolutionized forensic science, and has become a dominant tool in law enforcement. Today, DNA evidence is key to the conviction or exoneration of suspects of various types of crime

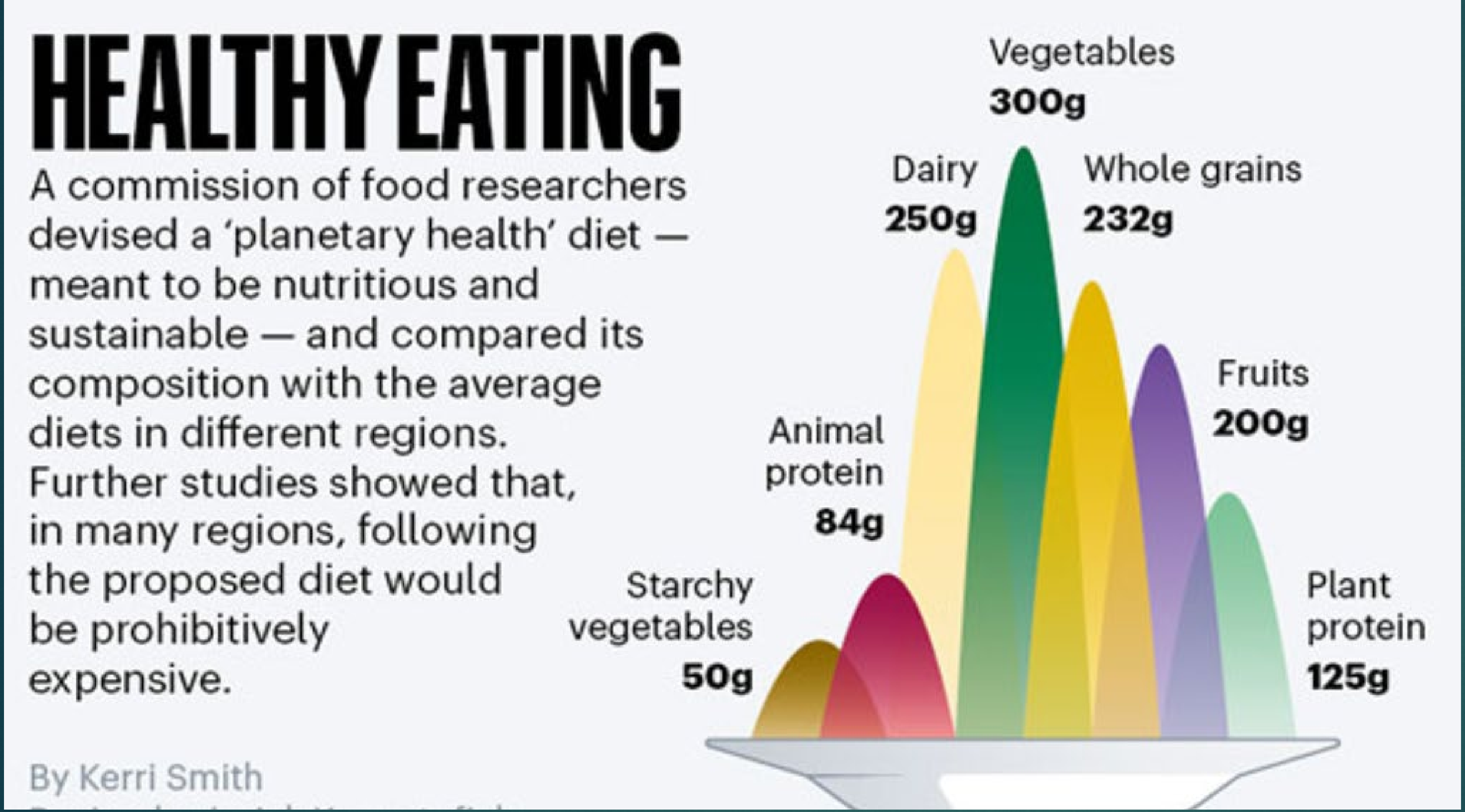
- Forensic DNA can be fabricated via PCR technology, molecular cloning, GW amplification.

- If you have access to a DNA profile in a database, you could construct a sample of DNA to match that profile without obtaining any tissue from that person.

DNA fabrication and authentication

- Using some of the same techniques, it is possible to scavenge anyone's DNA from a discarded drinking cup or cigarette butt and turn it into a saliva sample that could be submitted to a genetic testing company that measures ancestry or the risk of getting various diseases.
- But…Real DNA has epigenetic markers that fabricated DNA does not
- So forensic pathology still continues

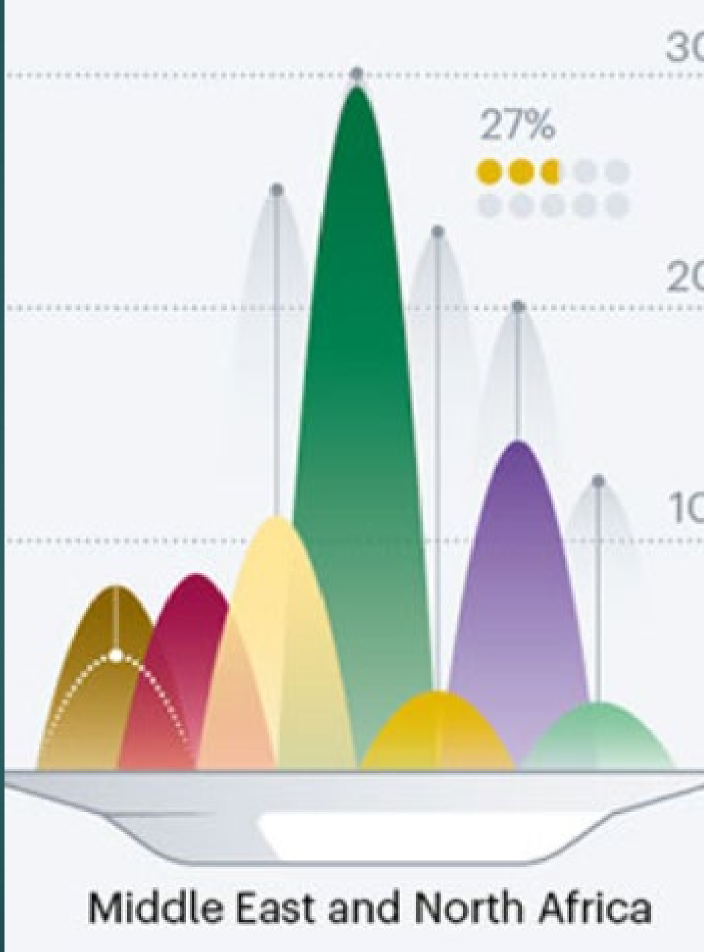
Food Sustainability: what we should be eating vs what we are



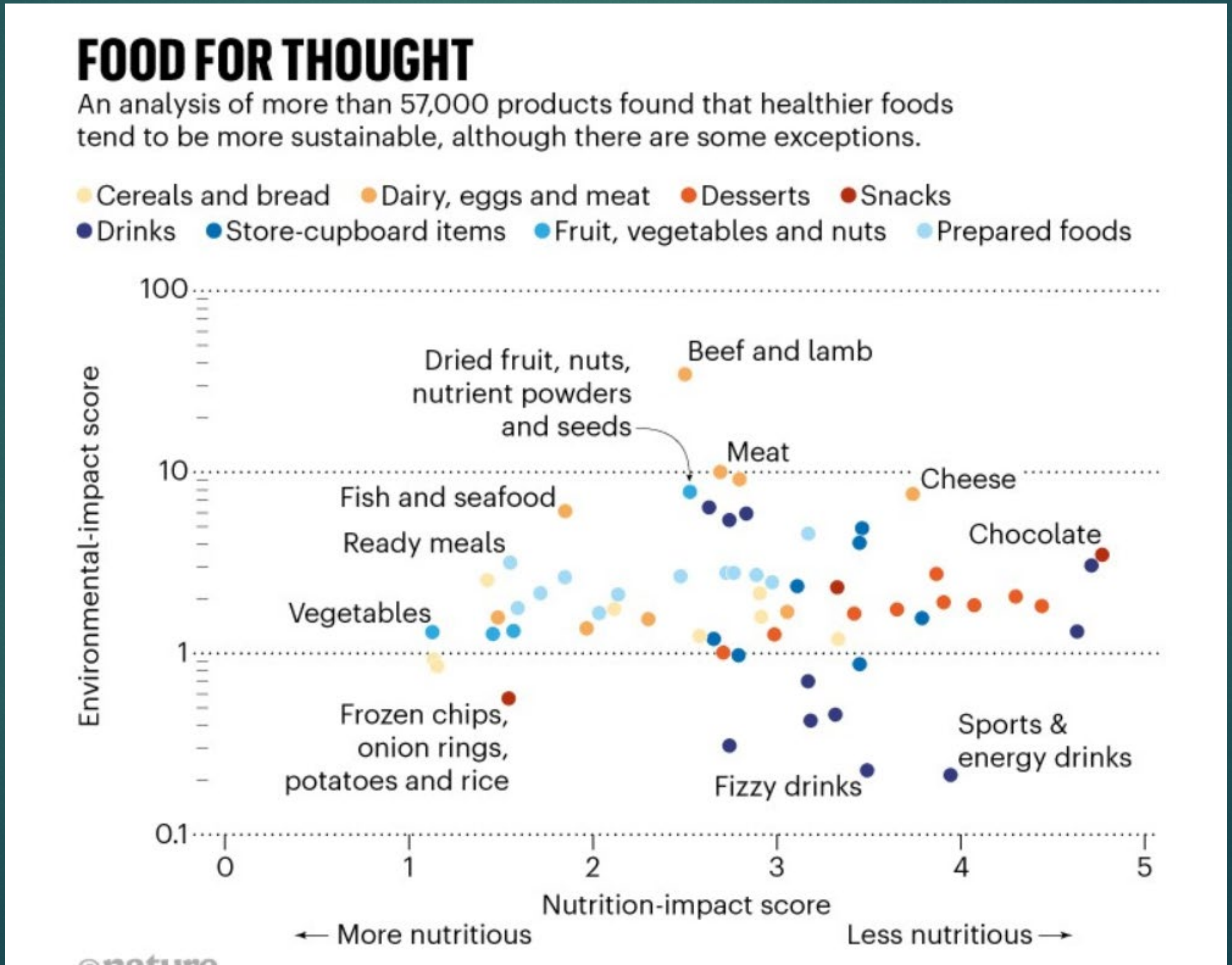
HEALTHY EATING

A commission of food researchers devised a ‘planetary health’ diet — meant to be nutritious and sustainable — and compared its composition with the average diets in different regions. Further studies showed that, in many regions, following the proposed diet would be prohibitively expensive.

By Kerri Smith



Healthier foods are better for the planet: Analysis of 57,000 multi-ingredient foods reveals which have the best and worst environmental impacts.



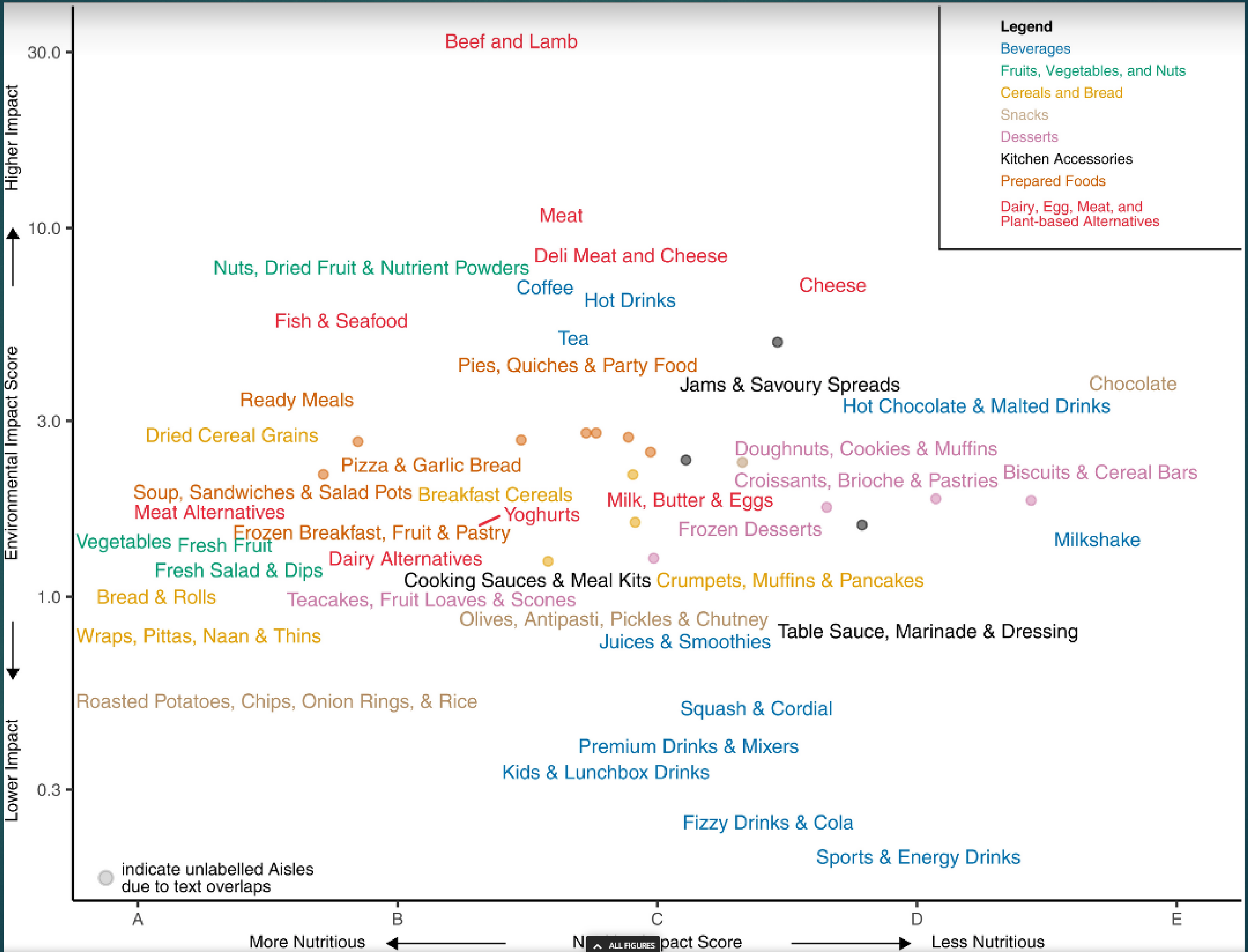
FOOD FOR THOUGHT

An analysis of more than 57,000 products found that healthier foods tend to be more sustainable, although there are some exceptions.

Michael Clark

Healthy food

- Food production is a major contributor to climate change. A 2020 study found that, even if emissions from burning fossil fuels ended immediately, current trends in food systems could derail efforts to limit global warming to 2 °C above pre-industrial levels.
- Some foods — such as red meat, dairy — produce far more greenhouse gases than others. Food products containing lamb and beef — such as ready-made meat pies — had the most serious environmental impact,
- The lowest-impact foods tended to be made with plants and included bread products, fruits, vegetables, grains and beverages rich in sugar.
- Healthier foods tended to have low environmental impacts. There were some notable exceptions: both nuts and seafood had a good nutrition score but relatively high environmental impacts.


Legend
Beverages
Fruits, Vegetables, and Nuts
Cereals and Bread
Snacks
Desserts
Kitchen Accessories
Prepared Foods
Dairy, Egg, Meat, and Plant-based Alternatives
Higher Impact
Environmental Impact Score
Lower Impact
30.0
10.0
3.0
1.0
0.3
Beef and Lamb
Meat
Deli Meat and Cheese
Nuts, Dried Fruit & Nutrient Powders
Coffee
Hot Drinks
Cheese
Fish & Seafood
Tea
Pies, Quiches & Party Food
Jams & Savoury Spreads
Chocolate
Ready Meals
Hot Chocolate & Malted Drinks
Dried Cereal Grains
Doughnuts, Cookies & Muffins
Pizza & Garlic Bread
Biscuits & Cereal Bars
Croissants, Brioche & Pastries
Soup, Sandwiches & Salad Pots
Breakfast Cereals
Milk, Butter & Eggs
Meat Alternatives
Yoghurts
Frozen Breakfast, Fruit & Pastry
Frozen Desserts
Vegetables
Fresh Fruit
Milkshake
Dairy Alternatives
Fresh Salad & Dips
Cooking Sauces & Meal Kits
Crumpets, Muffins & Pancakes
Bread & Rolls
Teacakes, Fruit Loaves & Scones
Olives, Antipasti, Pickles & Chutney
Table Sauce, Marinade & Dressing
Wraps, Pittas, Naan & Thins
Juices & Smoothies
Roasted Potatoes, Chips, Onion Rings, & Rice
Squash & Cordial
Premium Drinks & Mixers
Kids & Lunchbox Drinks
Fizzy Drinks & Cola
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What is their function?

The dawn of dairy farming in Europe occurred thousands of years before most people evolved the ability to drink milk as adults without becoming ill. This ability was almost non-existent in early dairy farmers.

Now *researchers think they know why*: lactose tolerance was beneficial enough to influence evolution only during occasional episodes of famine and disease, explaining why it took thousands of years for the trait to become widespread[1].

Earliest date for milk use in the Near East and southeastern Europe linked to cattle herding – Evershed, et al., 2008

- Organic residues preserved in archaeological pottery have provided direct evidence for the use of milk in the fourth millennium in Britain, and in the sixth millennium in eastern Europe, based on the delta(13)C values of the major fatty acids of milk fat.
- Here we apply this approach to more than 2,200 pottery vessels from sites in the Near East and southeastern Europe dating from the fifth to the seventh millennia bc.
- We show that milk was in use by the seventh millennium; this is the earliest direct evidence to date.
- Milking was particularly important in northwestern Anatolia, pointing to regional differences linked with conditions more favorable to cattle compared to other regions, where sheep and goats were relatively common and milk use less important.

Got milk? How humans' ability to digest milk evolved from famine and disease

- Examination of ancient dairy fat and protein residues shows that consumption of animal milk began in Anatolia in the seventh millennium bc. By 5000 bc, this behavior had spread across Europe and the Eurasian steppe, and into northern Africa.
- Although milk use was widespread in each of these regions by at least 5000 bc, the genetic lactase persistence that enable adults to digest milk were extremely rare.
- Today, about one-third of the world's population can be categorized as being lactase persistent, yet early milk consumers in Eurasia (between approximately 9,000 and 2,000 years ago) lacked a version (allele) of the gene needed for LP, and this adaptation did not start to become common in Europe until roughly 3,000 years ago.

Got Milk?

- A rise in genetic changes that help adults to digest milk, a phenomenon termed lactase persistence (LP), occurred long after the onset of dairy consumption
- The ability to digest milk thanks to LP alleles does not seem to offer any benefit in terms of evolutionary fitness (as assessed through characteristics such as lifespan or having children).
- These data, combined with extensive archaeological data supporting the consumption of milk fats (lipids) from ceramic vessels, have enabled Evershed and colleagues to present two hypotheses for how and why LP spread across Europe over the past two millennia.

Got Milk?

- Until about 3,000 years ago, LP ability was typically mainly ‘switched off’ after weaning.
- People lacking lactase in adulthood are described as lactase non-persistent (LNP). After consuming milk, LNP individuals can experience mild to severe symptoms that might include bloating, cramps and diarrhea.
- Although up to 95% of modern Europeans, in certain regions, are lactase persistent, this has not always been the case.
- Suggests that the ability to drink milk without negative side effects was probably not a strong factor driving the ancient spread of LP alleles.

Got Milk?

- Examination of ancient dairy fat and protein residues shows that consumption of animal milk began in Anatolia (a region corresponding to the bulk of what is Turkey today) ~7000 bc.
- By 5000 bc, this behavior had spread across Europe and the Eurasian steppe, and into northern Africa.
- Although milk use was widespread in each of these regions by at least 5000 bc, genetic lactase persistence that enable adults to digest milk were extremely rare.
- Such genetic changes enable expression of the milk-digesting enzyme lactase to be retained beyond childhood, a state termed lactase persistence (LP).

Got Milk?

- In European and many African, Middle Eastern and southern Asian populations, lactase persistence (LP) is the most strongly selected monogenic trait to have evolved over the past 10,000 years.
- Today, about one-third of the world's population can be categorized as being lactase persistent, yet early milk consumers in Eurasia (between ~9,000 and 2,000 years ago) lacked a version (allele) of the gene needed for LP, and this adaptation did not start to become common in Europe until roughly 3,000 years ago

Got Milk?

- Evershed et al. 2022: analysis of present-day UK health data, that the ability to digest milk thanks to LP alleles does not seem to offer any benefit in terms of evolutionary fitness (as assessed through characteristics such as lifespan or having children). British population studied, regardless of whether they were lactase persistent or LNP, typically consumed fresh milk regularly.

- <u>This suggests that the ability to drink milk without negative side effects was probably not a strong factor driving the ancient spread of LP alleles.</u>

Dairying, diseases and the evolution of lactase persistence in Europe - Evershed, R. P. *et al. Nature, 2022*

- Question of how the selection of LP and the consumption of prehistoric milk were linked.
- Study provides detailed distributions of milk exploitation across Europe over the past 9,000 years using around 7,000 pottery fat residues from more than 550 archaeological sites.
- European milk use was widespread from the Neolithic period onwards but varied spatially and temporally in intensity.

Milk and LP

- In the UK Biobank cohort of 500,000 contemporary Europeans, LP gene was only weakly associated with milk consumption and did not show consistent associations with improved fitness or health indicators.
- This suggests that other reasons for the beneficial effects of LP should be considered for its rapid frequency increase.
- Propose that lactase non-persistent individuals consumed milk when it became available but, under conditions of famine and/or increased pathogen exposure, this was disadvantageous, driving LP selection in prehistoric Europe.
- Population fluctuations, settlement density and wild animal exploitation—proxies for LP drivers—provide better explanations of LP selection than the extent of milk exploitation.

Got Milk?

- Lactose tolerance was beneficial enough to influence evolution only during occasional episodes of famine and disease, explaining why it took thousands of years for the trait to become widespread. Explains how the ability to digest milk became so common in modern Europeans, despite being almost non-existent in early dairy farmers.
- Many had presumed that the variation proved beneficial only after ancient peoples started routinely consuming dairy products.

Evershed, R. P. *et al. Nature, 2022*

Got Milk? Milk consumption unrelated to lactose intolerance

- Evershed found milk-fat residues on ancient potsherds dating from the dawn of animal domestication.
- Examined genomes of more than 1,700 ancient Eurasian people.
- aDNA showed that these early animal farmers were lactose intolerant, and that tolerance for milk did not become common in Europe until after the Bronze Age, 5,000–4,000 years ago.
- There was little overlap between leaps in lactose tolerance and heightened milk consumption, inferred by the presence of milk-fat residues from some 13,000 potsherds from more than 550 archaeological sites across Europe

Got Milk?

- In the UK Biobank, found little correlation between milk consumption and lactose tolerance, with 92% of lactose-intolerant participants preferring fresh milk over alternatives. And lactose tolerance showed no clear health or fertility benefits, which might drive natural selection.

- This suggests that, for most lactose-intolerant people, the costs of drinking milk aren’t that high today — and probably weren’t in ancient times, either. “If you’re healthy, you get a bit of diarrhea, you get cramps, you fart a lot. It’s unpleasant, but you’re not going to die.”

Got Milk?

- Increased milk use in China, where LP is low.
- These findings bring into question the widely held belief that selection against LNP was the result of detrimental effects of milk consumption in otherwise healthy individuals—for example, through inducing stomach cramps, diarrhea and flatulence.
- Milk has little or no adverse health effect when consumed by LNP adults in a contemporary population.
- Propose that the consequences of milk drinking among lactose-intolerant people long ago would have been much more severe for those who were in ill health, as a result of famine or infection.

Got milk?

- Fluid loss, through diarrhea, contributes to deaths through malnutrition and infection, especially in places with poor sanitation.
- The researchers’ model found that lactase persistence was more likely to occur in ancient populations exposed to animal pathogens and famine than in those exposed to other factors examined.
- Propose that the consequences of milk drinking among lactose-intolerant people long ago would have been much more severe for those who were in ill health, as a result of famine or infection.
- The team proposes that natural selection for lactase tolerance was turbocharged during such periods, when lactose-intolerant individuals would have been more likely to die than people who lacked the suddenly beneficial LP gene variation.

Got Milk?

- Ancient DNA (aDNA) data indicate that most, if not all, Early Neolithic people were lactase non-persistent and that LP only reached appreciable frequencies in the Bronze and Iron Ages.
- Such an allele frequency trajectory indicates strong selection favoring LP and is consistent with selection starting in the Early Neolithic period
- Milk use was a very widespread activity across all periods in European prehistory and at the broadest scale this was congruous with the spread of farming across the continent

Got Milk? Amount of milk usage did not drive LP selection

- The overarching picture is that, whilst dairying persisted throughout the Neolithic period, its intensity fluctuated substantially in space and through time, suggesting regionally specific instabilities in food production and cultural changes in dietary preferences.

- This is consistent with previous studies showing regional ‘boom and bust’ fluctuations in population density across Europe over the same period.

- Analysis of potsherd lipid residue and ancient LP allele data suggest that intensity of milk usage—beyond its mere presence—did not drive selection on LP

Got Milk?

- Aside from dietary change, a number of other factors are likely to have influenced fecundity and mortality following the establishment of farming communities in Europe, including increased population and settlement density, increased mobility, proximity to animals, frequent crop failure, famine and population collapse and general poor hygiene and sanitation.
- Most, if not all, of these factors are likely to have increased infectious disease loads, particularly zoonoses (diseases that can be spread from animals to humans under natural conditions)
- Propose two related mechanisms for the evolution of LP.

Got Milk?

- First, the detrimental health consequences of high-lactose food consumption by LNP individuals would be acutely manifested during famines, leading to high but episodic selection favoring LP.

- This is because lactose-induced diarrhea can shift from an inconvenient to a fatal condition in severely malnourished individuals and high-lactose (unfermented) milk products are more likely to be consumed when other food sources have been exhausted.

- Called this the ‘crisis mechanism’, which predicts that LP selection pressures would have been greater during times of subsistence instability.

Got Milk?

- A second mechanism relates to the increased pathogen loads—especially zoonoses—associated with farming and increased population density and mobility.
- Mortality and morbidity due to pathogen exposure would have been amplified by the otherwise minor health effects of LNP in individuals consuming milk—particularly diarrhea—due to fluid loss and other gut disturbances, leading to enhanced selection for LP. Called this the ‘chronic mechanism’, which predicts that LP selection pressures would have increased with greater pathogen exposure.

Got Milk? milk consumption has little detrimental health impact on current healthy LNP individuals.

- These findings suggest a different picture. Milk consumption did not gradually grow throughout the European Neolithic period from initially low levels but rather was widespread at the outset in an almost entirely LNP population.
- We show that the scale of prehistoric milk use does not help to explain European LP allele frequency trajectories and thus it also cannot account for selection intensities.
- Show that LP status has little impact on modern milk consumption, mortality or fecundity and milk consumption has little or no detrimental health impact on contemporary healthy LNP individuals.

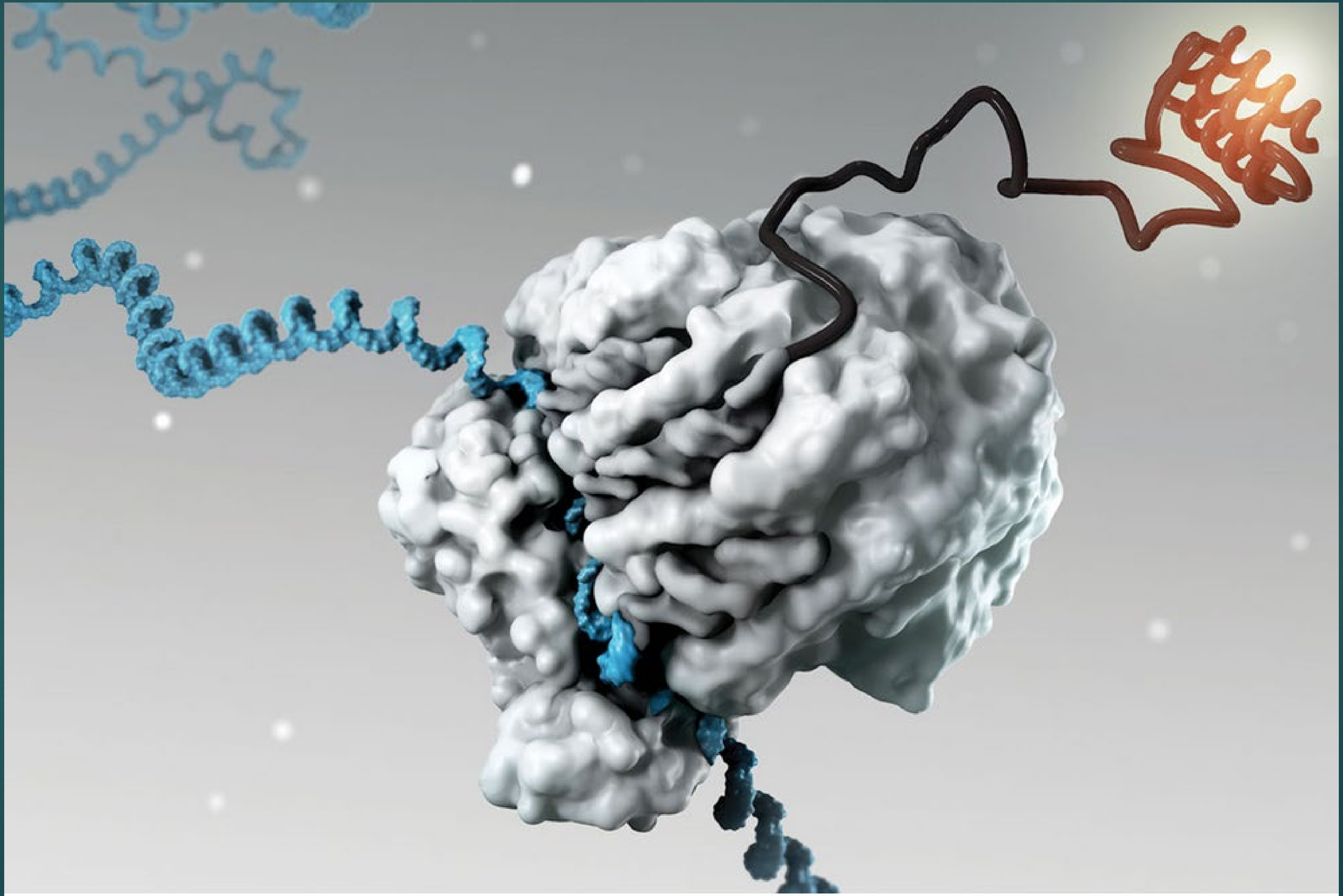
Got Milk?

- Find support for two related hypotheses: that LP selection was driven episodically and acutely by famine and/or on a more continuous basis by synergies between pathogen exposure and the otherwise benign consequences of milk consumption in LNP individuals.
-
- Propose that these mechanisms would have applied in the disease- and malnutrition-prone environment existing during the period of rapid increase in LP frequency but would not be expected to apply outside these circumstances.
- In contemporary populations, LP genotype associates strongly with aspects of the gut microbiome but only in consumers of milk. This suggests that when milk entered the diet of a LNP population it would have altered the gut microbiome.

Got milk?

- We postulate that, when combined with the changing pattern and prevalence of circulating infections consequent on increasing population density and settlement size, diarrheal disease mortality in late childhood could have been increased in LNP individuals drinking milk.
- Over the period in which LP prevalence increased, the ratio of late childhood (5–18 yr) to early childhood (2–5 yr) mortality increased.
- The ‘crisis’ and ‘chronic’ mechanisms are, of course, not mutually exclusive, nor do they exclude other LP selection mechanisms, especially outside western Eurasia

RNAs (blue) that are converted to functional small proteins (orange) by ribosomes (center).

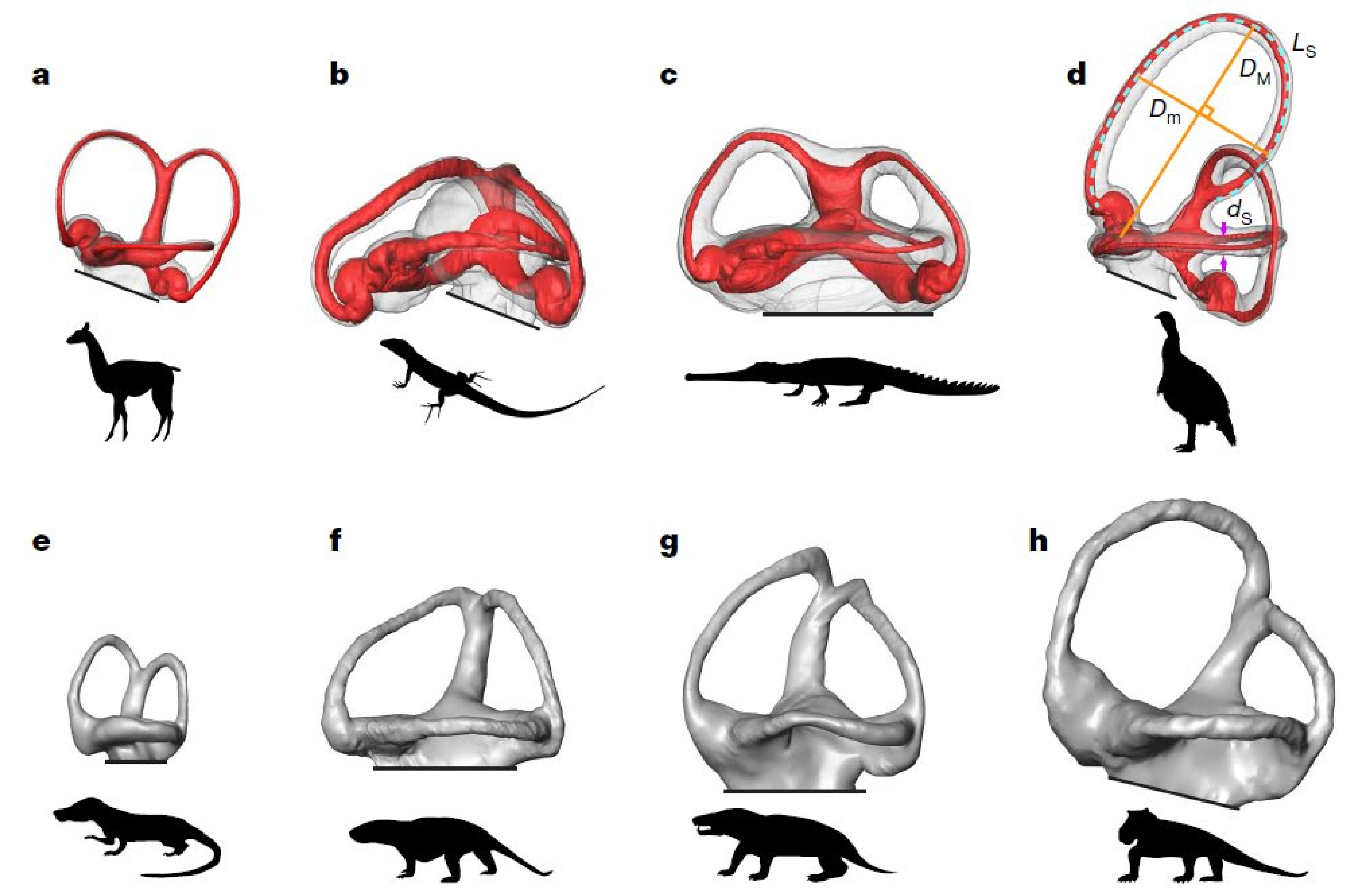


n international consortium will search for RNAs (blue) that are converted to functional small proteins (orange) by ribosomes (center). V. ALTOUNIAN/*SCIENCE*

Gold mine of unexplored biology: Short protein sequences could dramatically expand human genome

- New consortium will vet whether 7000-plus RNAs make stable proteins with cellular functions
- Concerted effort to search for new genes that encode short proteins.
- Only 19,370 human genes are known to code for proteins.
- But current catalogs only include genes for proteins containing at least 100 amino acids each, a cutoff chosen in part because longer DNA sequences make it easier for geneticists to look for commonalities between species. Many smaller proteins are known to exist, but they've largely flown under the radar even though some have been shown to play crucial roles in regulating the immune system, blocking other proteins, and destroying faulty RNAs.
- 7264 candidates to become new genes

Origins of endothermy



Endothermy

- The origin of mammalian endothermy can be investigated using the morphology of the endolymph-filled semicircular ducts of the inner ear

- The results suggest that endothermy evolved abruptly during the Late Triassic period in Mammaliamorpha, correlated with a sharp increase in body temperature (5–9 °C) and an expansion of aerobic and anaerobic capacities.

Dementia pathway review

- Review of 200 K dementia literature for “dementia” and “pathway”
- Goal: evidence for each biological pathway’s association with AD.
- Identified 91 of 341 pathways found in AD
- Despite major technological advances, the same set of top-ranked pathways have been consistently related to AD for 30 years, including *AD, immune system, metabolic pathways, cholinergic synapse, long-term depression, proteasome, diabetes, cancer,* and *chemokine signaling*.
- AD pathways studied appear biased: animal model and human subject studies prioritize different AD pathways. Surprisingly, human genetic discoveries and drug targeting are not enriched in the most frequently studied pathways. Our findings suggest that AD is incredibly biologically complex.

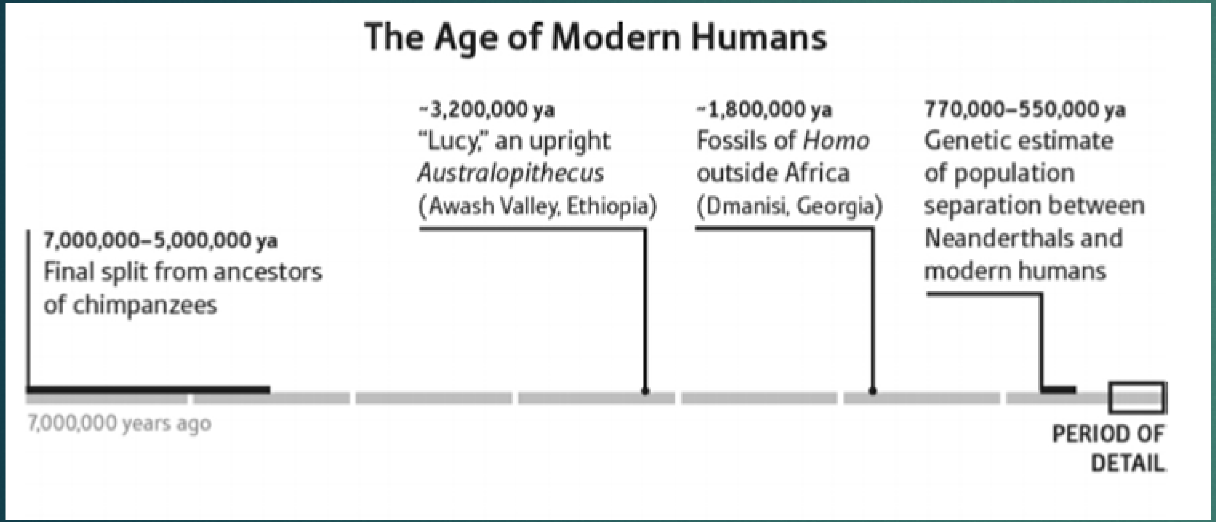
Reduce your AD risk

- Get your flu vaccination: 40% less likely risk
- Vaccine for Varicella zoster virus to prevent chickenpox and shingles—has been shown to considerably reduce the risk of dementia
- Chores, exercise, and frequent social family visits linked to lower risk of dementia; 11-year follow-up
- Ultra-processed foods (high in added sugar, fat and salt) like soft drinks, salty and sugary snacks, ice cream, sausage, deep-fried chicken, yogurt, canned baked beans and tomatoes, ketchup, mayonnaise, packaged guacamole and hummus, packaged breads and flavored cereals; have a higher risk of developing dementia
- Vitamin D supplements are probably worthless

Who We Are and How We Got Here

- Reich's *Who We Are and How We Got Here* is divided into three parts.
- Part I, "The Deep History of Our Species," describes how the human genome contains within it the history of our species.
- Part II, "How We Got to Where We Are Today," is about how the genome revolution and ancient DNA have transformed our understanding of our own particular lineage of modern humans, and it takes readers on a tour around the world with population mixture as a unifying theme.
- Part III, "The Disruptive Genome," focuses on the implications of the genome revolution for society.

Part I
“The Deep History of Our Species”



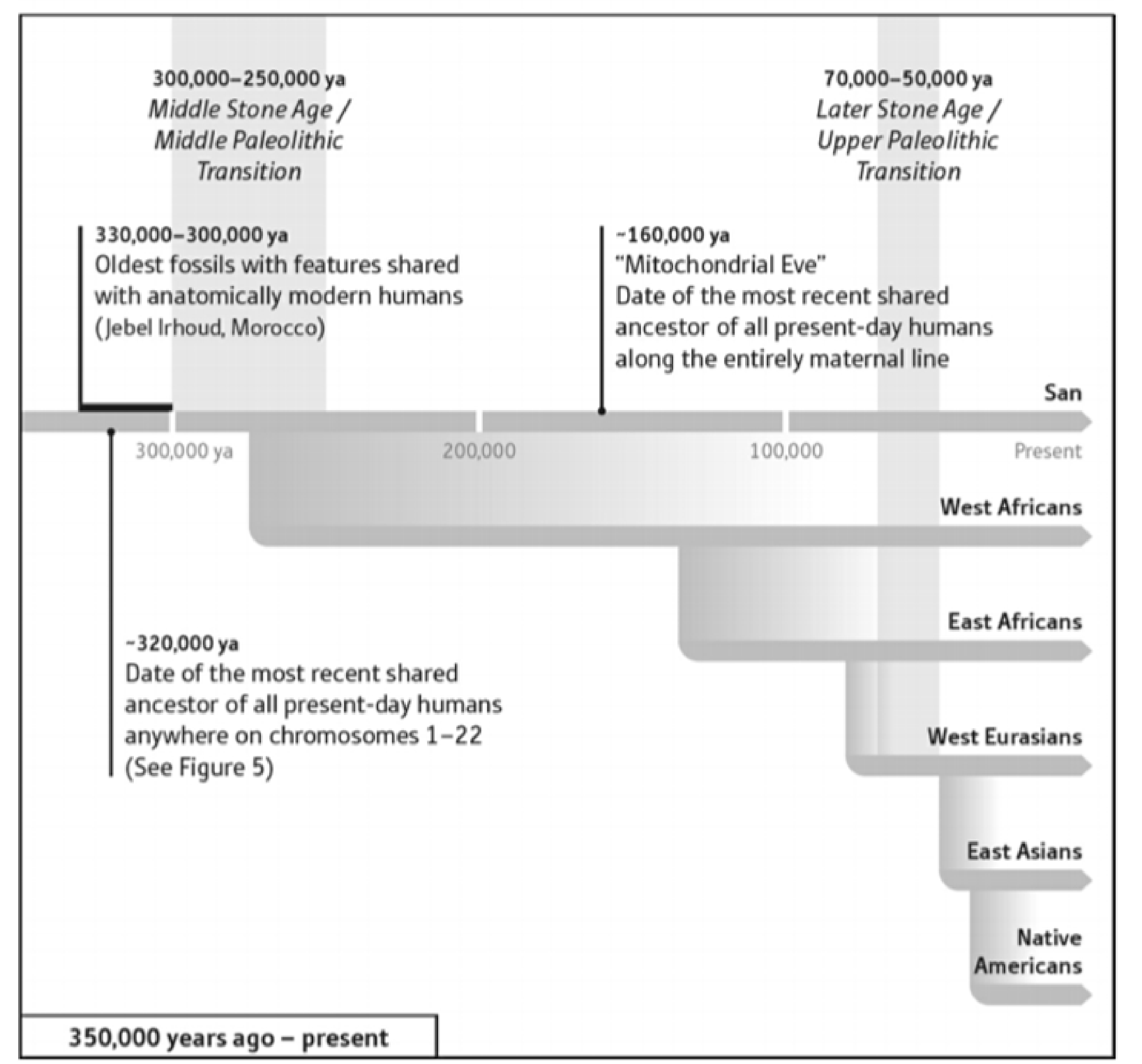
The Age of Modern Humans

~3,200,000 ya
“Lucy,” an upright *Australopithecus*
(Awash Valley, Ethiopia)

~1,800,000 ya
Fossils of *Homo* outside Africa
(Dmanisi, Georgia)

770,000–550,000 ya
Genetic estimate of population separation between Neanderthals and modern humans

7,000,000–5,000,000 ya
Final split from ancestors of chimpanzees



300,000–250,000 ya
Middle Stone Age / Middle Paleolithic Transition

70,000–50,000 ya
Later Stone Age / Upper Paleolithic Transition

330,000–300,000 ya
Oldest fossils with features shared with anatomically modern humans
(Jebel Irhoud, Morocco)

~160,000 ya
"Mitochondrial Eve"
Date of the most recent shared ancestor of all present-day humans along the entirely maternal line

~320,000 ya
Date of the most recent shared ancestor of all present-day humans anywhere on chromosomes 1–22
(See Figure 5)

Every chapter has one of these summary graphs.- but they're hard to read

The Age of Modern Humans

- 7 to 5 Ma: Final split of hominins and chimpanzees
- -3.2 Ma: "Lucy," an upright *Australopithecus* (Awash Valley. Ethiopia)
- -1.8 Ma: Fossils of *Homo* outside Africa (Dmanisi, Georgia)
- 770 to 550 Ka: Genetic estimate of population separation between Neanderthals and modern humans

Who We Are and How We Got Here

- Chapter 1, "How the Genome Explains Who We Are," argues that the genome revolution has taught us about who we are as humans not by revealing the distinctive features of our biology compared to other animals but by uncovering the history of migrations and population mixtures that formed us.

- Origin in Africa: Deepest branch of the mtDNA tree—the branch that left the main trunk earliest—is found today only in people of sub-Saharan African ancestry, suggesting that the ancestors of modern humans lived in Africa. Mitochondrial Eve at 160 Ka.

Genetics: 350,000 ya to Present

- 330 to 300 Ka: Oldest fossil with features shared with AMHs (Jebel Irhoud. Morocco)
- ~320 Ka: Date of the most recent shared ancestor of all present-day humans anywhere on chromosomes
- 300 to 250 Ka: Middle Stone Age/Middle Paleolithic Transition
- ~160 Ka: "Mitochondrial Eve"-- Date of the most recent shared ancestor of all present-day humans by mtDNA
- 70 to 50 Ka: Later Stone Age/Upper Paleolithic Transition
- Subpopulations evolved post 60 Ka: San, West Africans, East Africans, West Eurasians, East Asians, Native Americans

Richard Klein's genetic cognitive change theory for AMH behavior

- Klein's genetic brain change hypothesis (~50 Ka) to explain AMH behavior

- It came under intense criticism almost as soon as he suggested it, most notably from the archaeologists Sally McBrearty and Alison Brooks,

- They showed that almost every trait that Klein considered to be a hallmark of distinctly modern human behavior was evident in the African and Near Eastern archaeological records tens of thousands of years before the Upper Paleolithic and Later Stone Age transitions.

Richard Klein's genetic cognitive change theory

- Reich: But even if no single behavior was new, Klein had put his finger on something important.
- The intensification of evidence for modern human behavior after fifty thousand years ago is undeniable, and raises the question of whether biological change contributed to it.

An evolutionary Manhattan Project

- Reich: It will take an evolutionary Manhattan Project to understand the function of each mutation that MHs have and that Neanderthals do not.

- This Manhattan Project of human evolutionary biology is one to which we as a species should commit ourselves.

- But even when it is carried out, he expects that the findings will be so complicated—with so many individual genetic changes contributing to what makes humans distinctive—that few people will find the answer comprehensible.

An evolutionary Manhattan Project

- He does not expect that an intellectually elegant and emotionally satisfying molecular explanation for behavioral modernity will ever be found.
- There is a new picture of how we got to be the way we are.
- This explanation, based on migrations and population mixture, is the subject of this book.

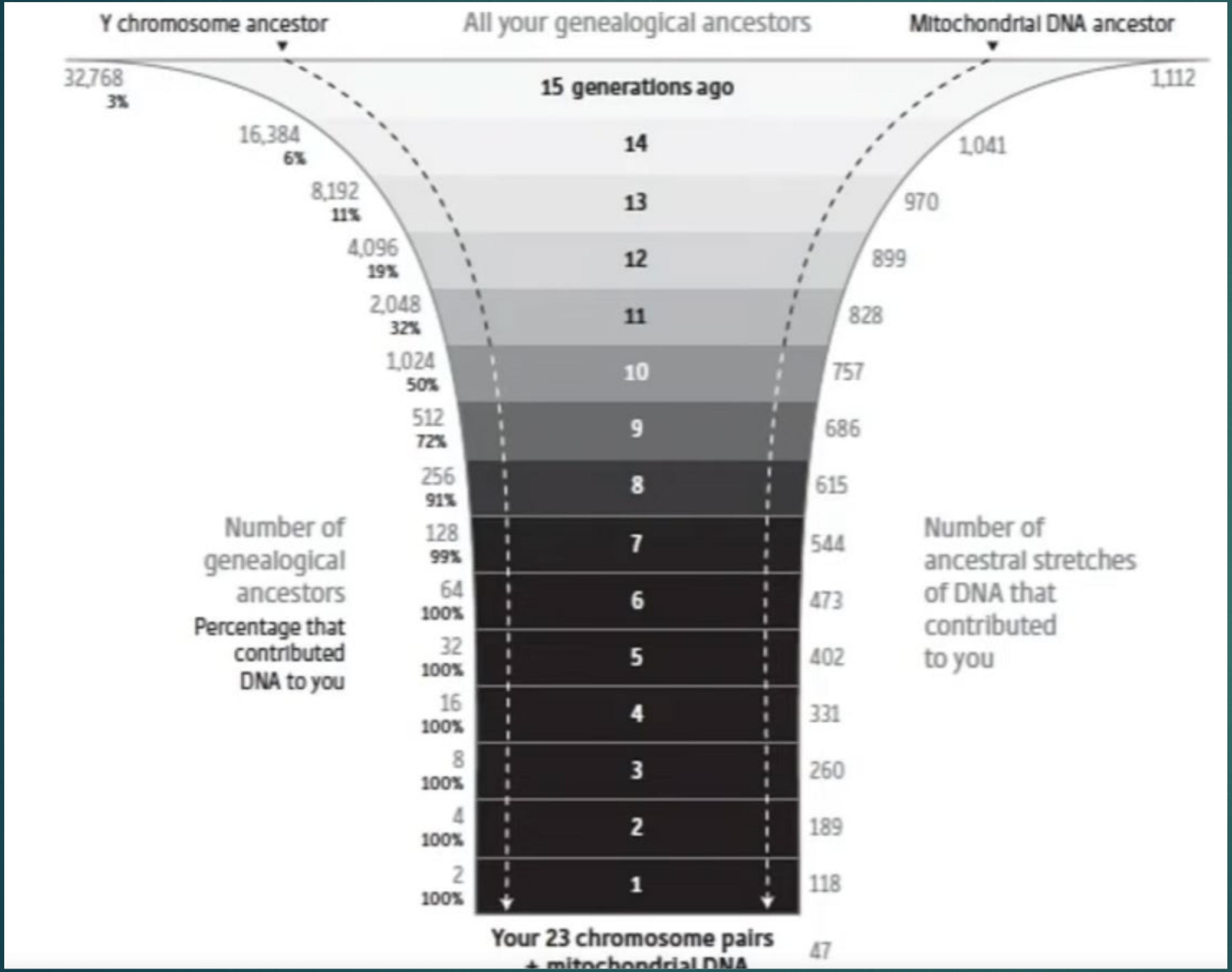
The genome: a mosaic of ancestors

- The genome contains the stories of many diverse ancestors—tens of thousands of independent genealogical lineages, not just your parent’s Y chromosome and mitochondrial DNA.

- The genome is not one continuous sequence from a single ancestor but is instead a mosaic of your ancestors.

- Seventy-one new genetic splices (variants) per generation: Females create an average of about forty-five new splices (introns excised; exons joined), when producing eggs, while males create about twenty-six splices when producing sperm

You are not one person. You contain multitudes.



10 generations = 1000 ancestors

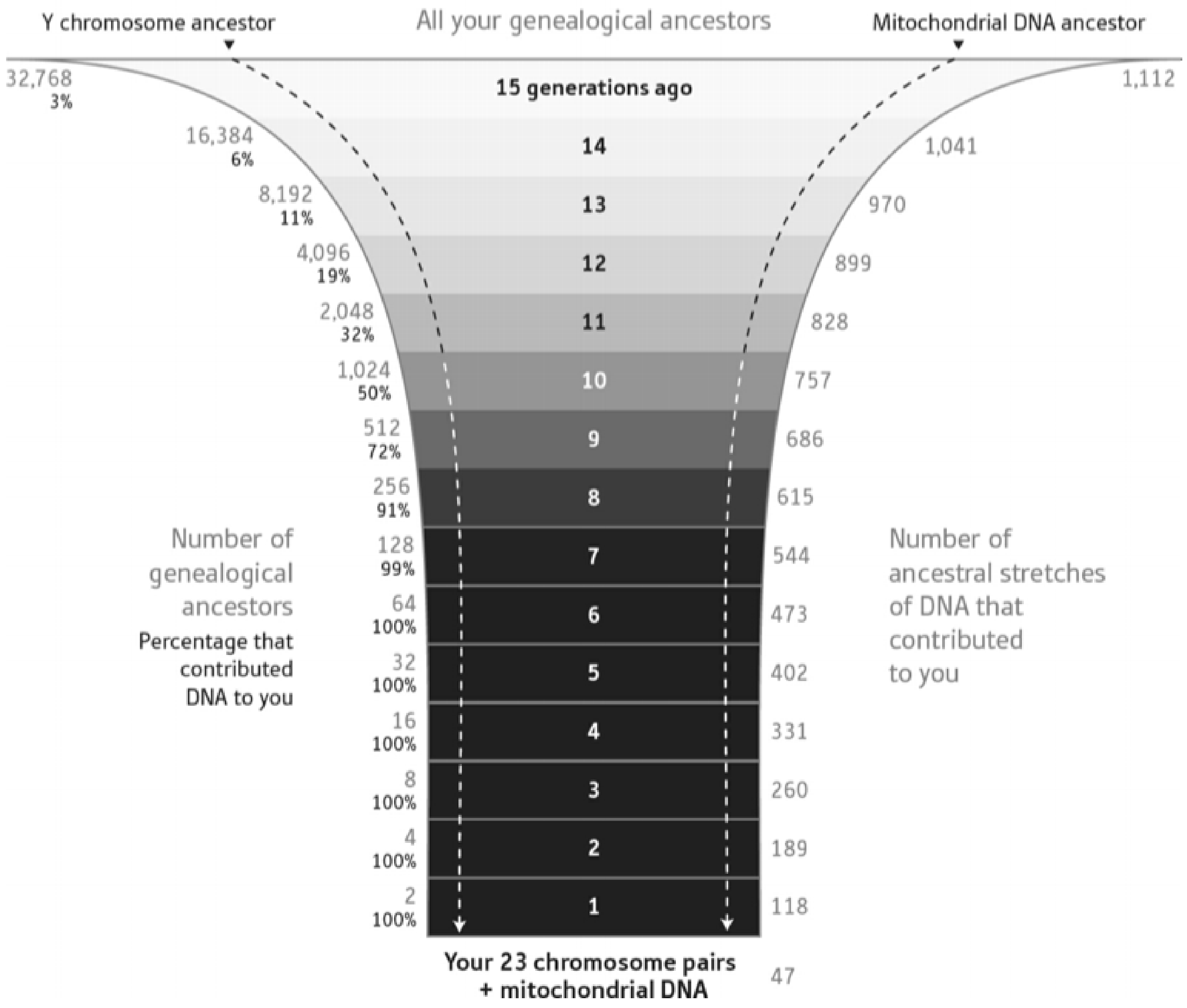
Contain recombined fragments of 100 K ancestors

DNA starts with 46 sections;
Then fragments; breaks an additional 70 times per generation

At 10 generations, more fragments than there are ancestors: you have ancestors who did not contribute any DNA to you

The Far Richer Story Told by the Whole Genome

Y chromosomes and mitochondrial DNA reflect information only from the entirely male or entirely female lineages (dashed lines). The whole genome carries information about tens of thousands of others.



The number of ancestors you have doubles every generation back in time.
However, the number of stretches of DNA that contributed to you increases by only around seventy-one per generation

Go back fifteen generations and the probability that any one ancestor contributed directly to your DNA becomes exceedingly small.
Tracing back fifty thousand years in the past, our genome is scattered into more than one hundred thousand ancestral stretches of DNA, greater than the number of people who lived in any population at that time, so we inherit DNA from nearly everyone in our ancestral population who had a substantial number of offspring at times that remote in the past.

Our genome: not all your ancestors

- Twenty generations in the past, the number of a person's ancestors is almost a thousand times greater than the number of ancestral stretches of DNA in a person's genome, so it is a certainty that each person has not inherited any DNA from the great majority of his or her actual ancestors.

- These calculations mean that a person's genealogy, as reconstructed from historical records, is not the same as their genetic inheritance.

Genome

- About 70 percent of the original Human Reference sequence came from a single individual, an African American male
- 100 Ka, the vast majority of lineages of African American ancestors, like those of everyone today, were in Africa.
- We are all African by origin
- Thus it is possible to count the number of mutations separating the genome a person receives from their mother and the genome the person receives from their father to determine when they shared a common ancestor

Inference of Human Population History From Whole Genome Sequence of A Single Individual -- Heng Li and Richard Durbin, 2011

- Various studies have found evidence for a founder event (bottleneck) in East Asian and European populations associated with the human dispersal out-of-Africa event ~ 60 Ka.

- We present a more detailed history of human population sizes between approximately ten thousand to a million years ago, using the pairwise sequentially Markovian coalescent (PSMC) model applied to the complete diploid genome sequences of 7 individuals

Human Population History

- European and Chinese populations had very similar population size histories before 20–10 Ka.

- Both populations experienced a severe bottleneck between 60–10 Ka while African populations experienced a milder bottleneck from which they recovered earlier.

- Earlier, between 250–60 Ka, all three populations had an elevated effective population size

Bottleneck after OoA: small population lasted over long period

- Evidence for Bottleneck after OoA: The times in the past when the population size was low can be identified based on the periods in the past when a disproportionate fraction of lineages have evidence of sharing common ancestors.
- Li and Durbin study: evidence that after the OoA event, there was an extended period in the shared history of non-Africans when populations were small, as reflected in evidence for many shared ancestors in genomes.
- This small population lasted over long period

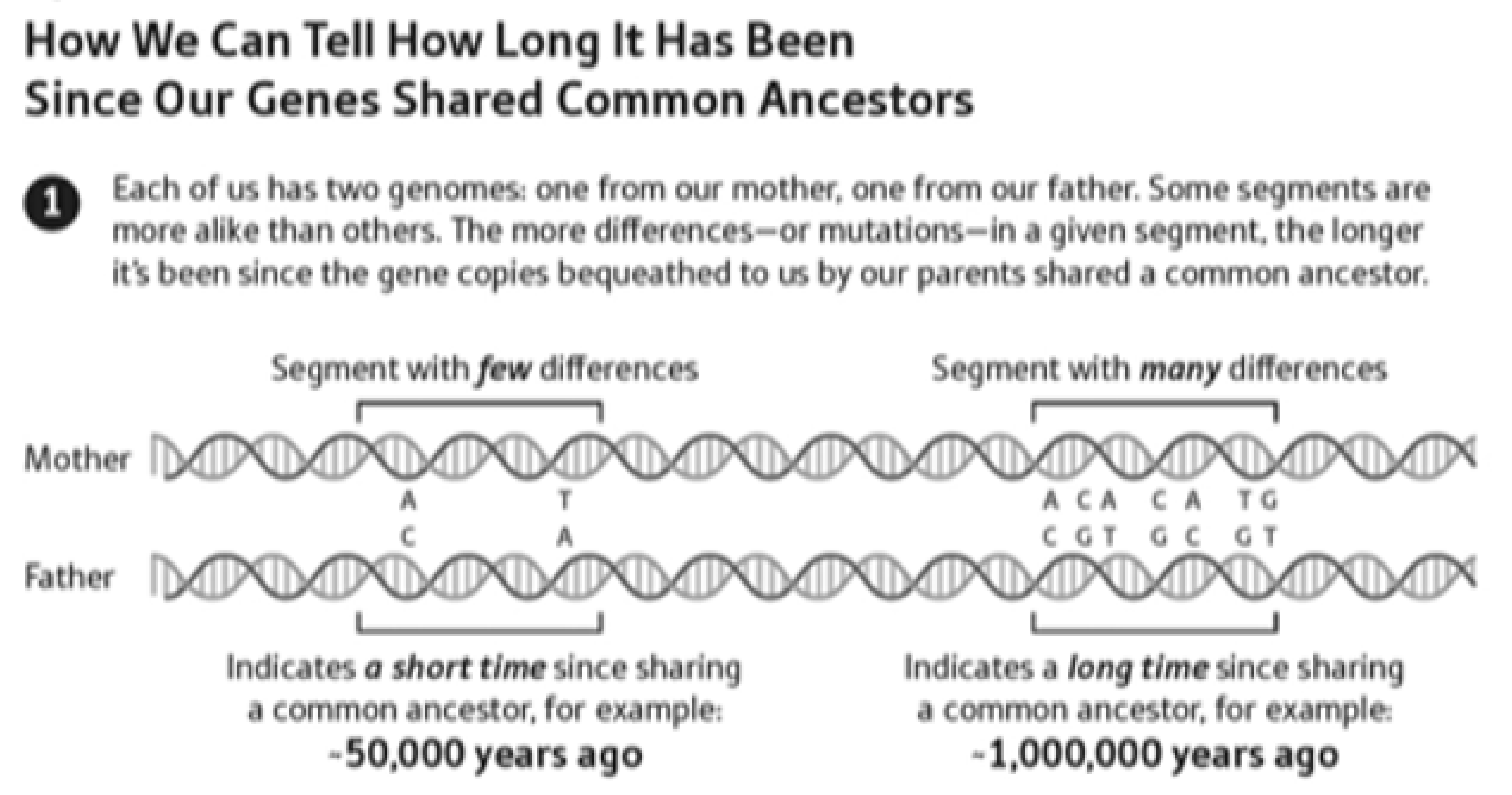
Bottleneck after OoA: lasted for a long period

- But prior to Li and Durbin’s work, there was no good information about the duration of this event, and it seemed plausible that it could have transpired over just a few generations—for example, a small band of people crossing the Sahara into North Africa, or from Africa into Asia.

- The Li and Durbin evidence of an extended period of small population size was also hard to square with the idea of an unstoppable expansion of modern humans both within and outside Africa around fifty thousand years ago.

- Our history may not be as simple as the story of a dominant group that was immediately successful wherever it went.

More mutations in a segment, further back to common ancestor



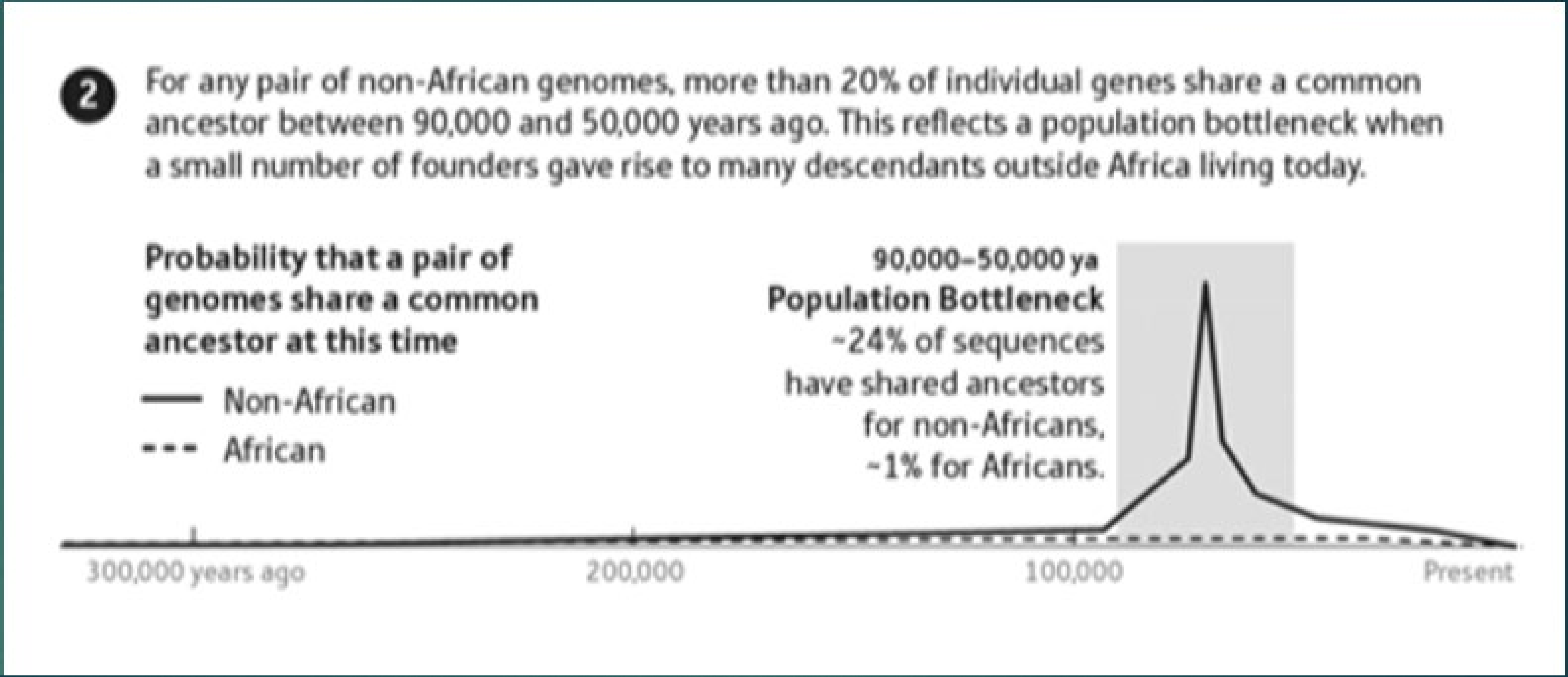
How We Can Tell How Long It Has Been Since Our Genes Shared Common Ancestors

❶ 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.

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

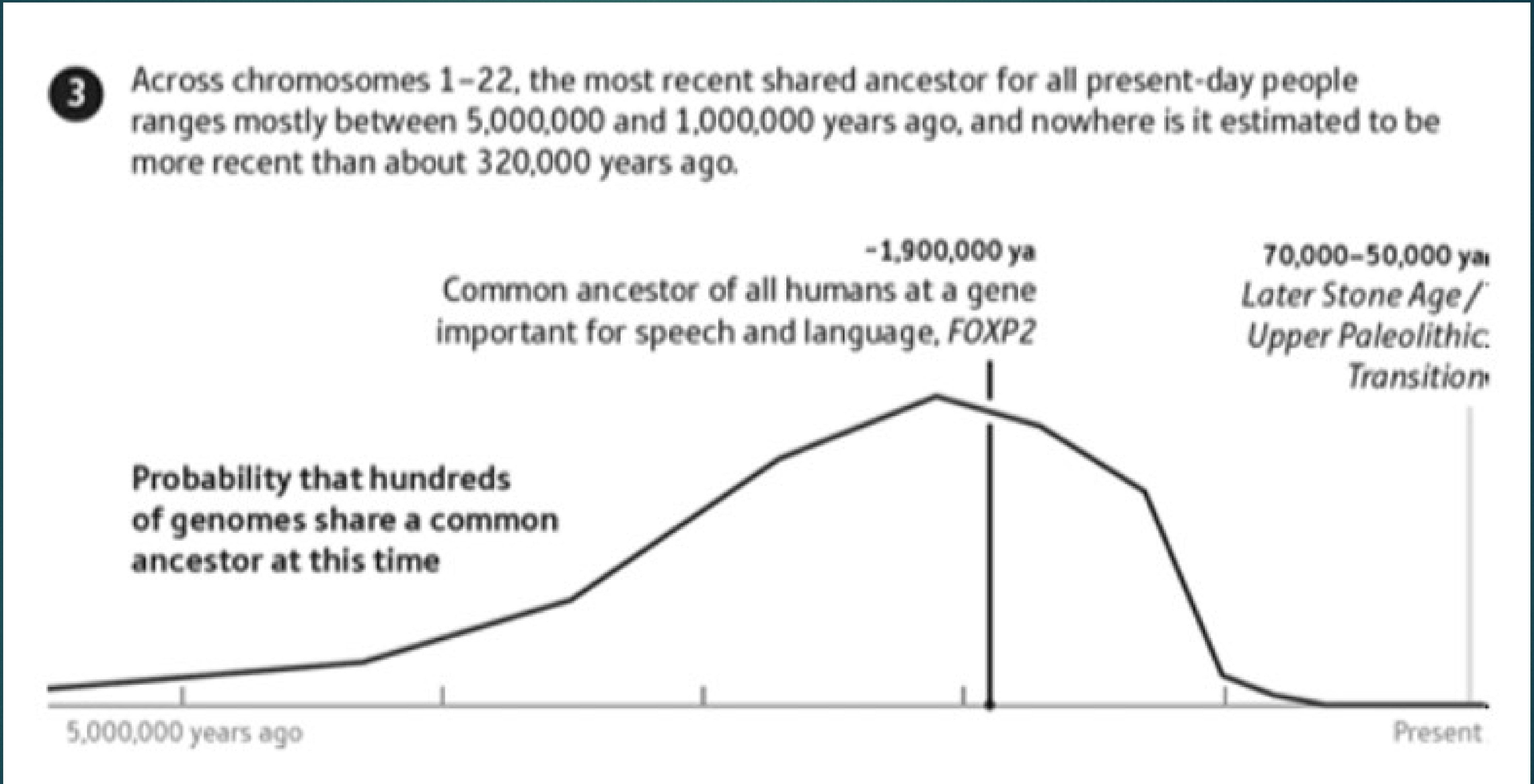
Indicates a *long time* since sharing a common ancestor, for example:
~1,000,000 years ago

Evidence for bottleneck between 90 to 50 Ka: 24% have common ancestor



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.

320 Ka = most recent common ancestor of MHs



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.

Whole genome studies: Most current MH ancestry from the San

- Whole-genome has allowed reconstruction of population history in far more detail than had been previously possible.

- Failed theories: Simple picture from mitochondrial DNA, and the theories about one or a few changes (i. e. R. Klein) propelling the LSA and UP cultural changes when recognizably modern human behavior became widespread as reflected in archaeological sites across Africa and Eurasia, are no longer tenable.

- The earliest branching modern human lineage that has contributed a large proportion of the ancestry of a population living today is the one that contributed the largest share of ancestry to the San hunter-gatherers of southern Africa.

No more simple answers, i. e. 1 gene answers

- This human population separation had begun by 200 Ka and was mostly complete by more than 100 Ka.
- Density of mutations separating San genomes from non-San genomes is uniformly high, implying few shared ancestors between San and non-San in the last hundred thousand years.
- At FOXP2, found that the common ancestor of everyone living today (that is, the person in whom modern humanity's shared copy of FOXP2 last occurred), lived more than one million years ago.

Klein was wrong

- In whole genome, they could not find any location—apart from mtDNA and the Y chromosome—where all people living today share a common ancestor less than about 320,000 years ago

- This is a far longer time scale than the one required by Klein's hypothesis. If Klein was right, it would be expected that there would be places in the genome where almost everyone shares a common ancestor within the last hundred thousand years. But these do not exist.

Who We Are and How We Got Here

- Chapter 2, "Encounters with Neanderthals," reveals how

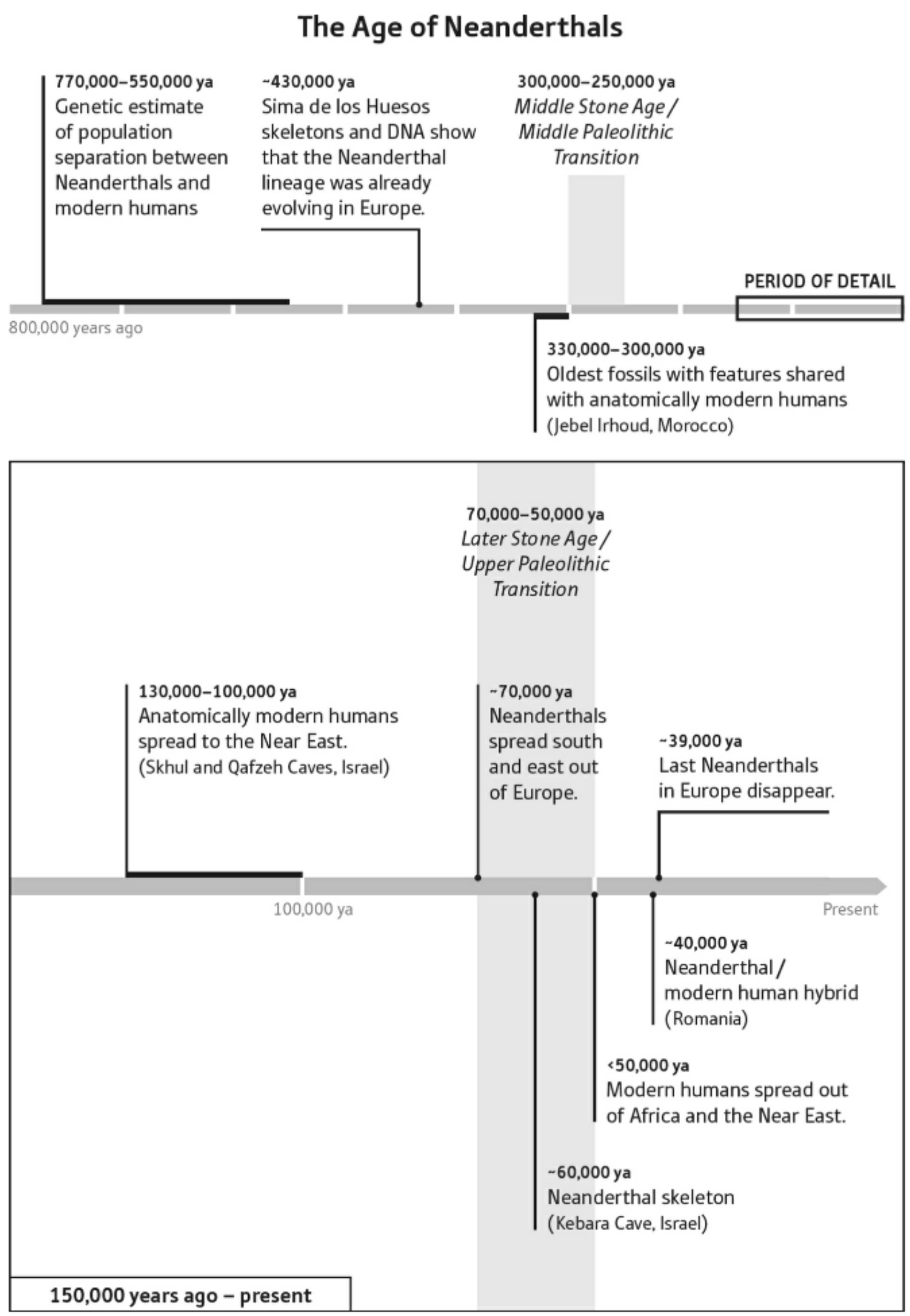
- the breakthrough technology of ancient DNA provided data from Neanderthals and
- showed how they interbred with the ancestors of all modern humans living outside of Africa.

- The chapter also explains how genetic data can be used to answer the question that the archaeological record cannot answer—but the DNA record can—is how those archaic people were related to us.

Encounters with Neanderthals

- In the Near East there were at least two opportunities for encounters between Neanderthals and MHs:
  - when early modern humans first peopled the region before around one hundred thousand years ago and established a population that met the expanding Neanderthals,
  - and when modern humans returned and displaced the Neanderthals there sometime around sixty or fifty thousand years ago.

Age of Neanderthals



The Age of Neanderthals

770,000–550,000 ya
Genetic estimate of population separation between Neanderthals and modern humans

~430,000 ya
Sima de los Huesos skeletons and DNA show that the Neanderthal lineage was already evolving in Europe.

300,000–250,000 ya
Middle Stone Age / Middle Paleolithic Transition

330,000–300,000 ya
Oldest fossils with features shared with anatomically modern humans
(Jebel Irhoud, Morocco)

70,000–50,000 ya
Later Stone Age / Upper Paleolithic Transition

130,000–100,000 ya
Anatomically modern humans spread to the Near East.
(Skhul and Qafzeh Caves, Israel)

~70,000 ya
Neanderthals spread south and east out of Europe.

~39,000 ya
Last Neanderthals in Europe disappear.

~40,000 ya
Neanderthal / modern human hybrid
(Romania)

<50,000 ya
Modern humans spread out of Africa and the Near East.

~60,000 ya
Neanderthal skeleton
(Kebara Cave, Israel)

The Age of Neanderthals

- 770 to 550 Ka: Genetic estimate of population separation between Neanderthals and modern humans
- -430 Ka: Sima de los Huesos skeletons and DNA show that the Neanderthal lineage was already evolving in Europe.
- 330 to 300 Ka: Oldest fossils with features shared with AMHs (Jebel Irhoud. Morocco)
- 300 to 250 Ka: *Middle Stone Age/ Middle Paleolithic Transition*

The Age of Neanderthals: 150 Ka to Present

- 130 to 100 Ka: Anatomically modern humans spread to the Near East (Skhul and Qafzeh Caves. Israel)
- 70 to 50 Ka: *Later Stone Age/Upper Paleolithic Transition*
- -70 Ka: Neanderthals spread south and east out of Europe.
- -60 Ka: Neanderthal skeleton (Kebara Cave, Israel)
- < 50 Ka: OoA - Modern humans spread out of Africa and the Near East.
- -40 Ka: Neanderthal/modern human hybrid (Oase 1, Romania)
- -39 Ka: Last Neanderthals in Europe disappear.

Neandertals

- After 400 Ka, Neanderthals were the dominant humans in western Eurasia, eventually extending as far east as the Altai Mountains.

- Ns survived an initial influx of modern humans circa 120 Ka. Then, after 60 Ka, modern humans made a second push out of Africa into Eurasia. Before long, the Neanderthals went extinct.

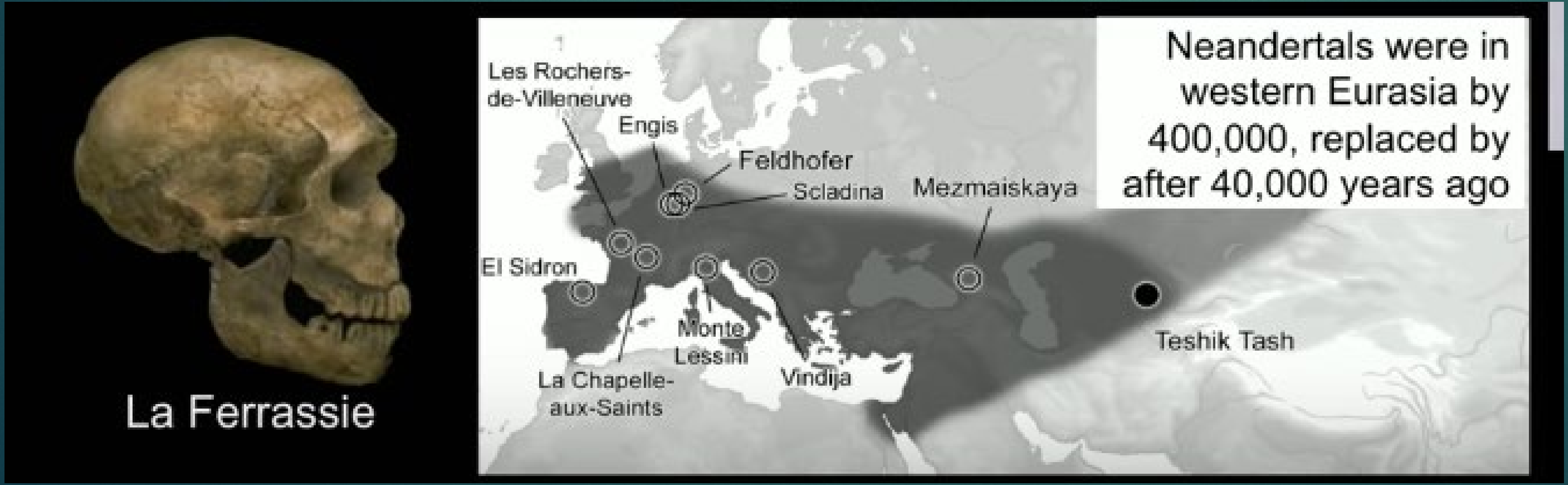
- Did the two populations interbreed? As of 2009, we did not know!

Neandertals

- There was originally some skeletal evidence for hybridization. Erik Trinkaus identified remains such as those from Oase Cave in Romania that he argued were intermediate between modern humans and Neanderthals.
- However, shared skeletal features sometimes reflect adaptation to the same environmental pressures, not shared ancestry. This is why archaeological and skeletal records cannot determine the relatedness of Neanderthals to us.
- Studies of the genome can.

1st lesson in humility for Reich: We are not 100% African

“Modern” humans evolve Africa by 300,000 years ago, explode out of Africa after 50,000 years ago

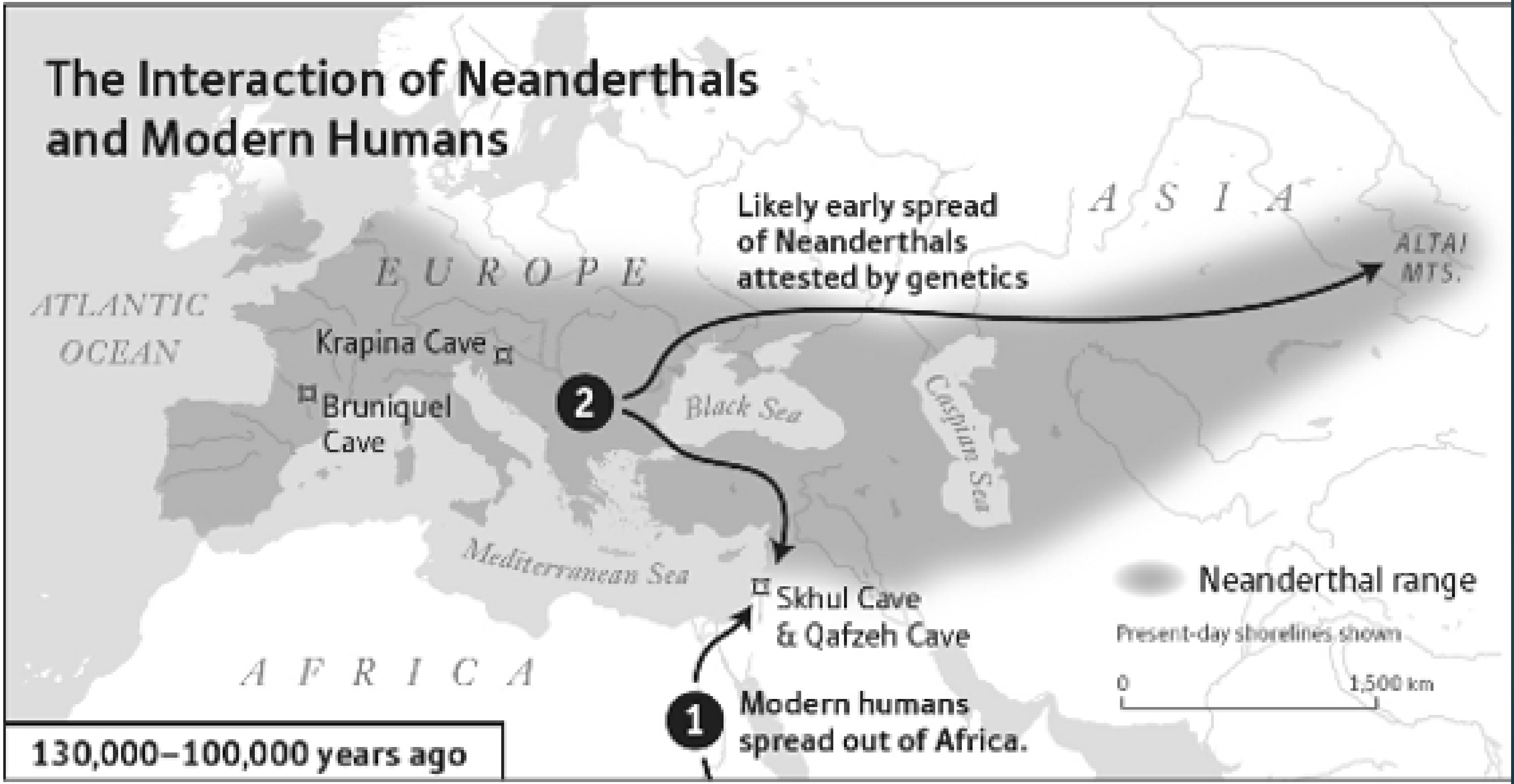


Neandertals were in western Eurasia by 400,000, replaced by after 40,000 years ago

Great majority of our ancestry is African, …but not all.

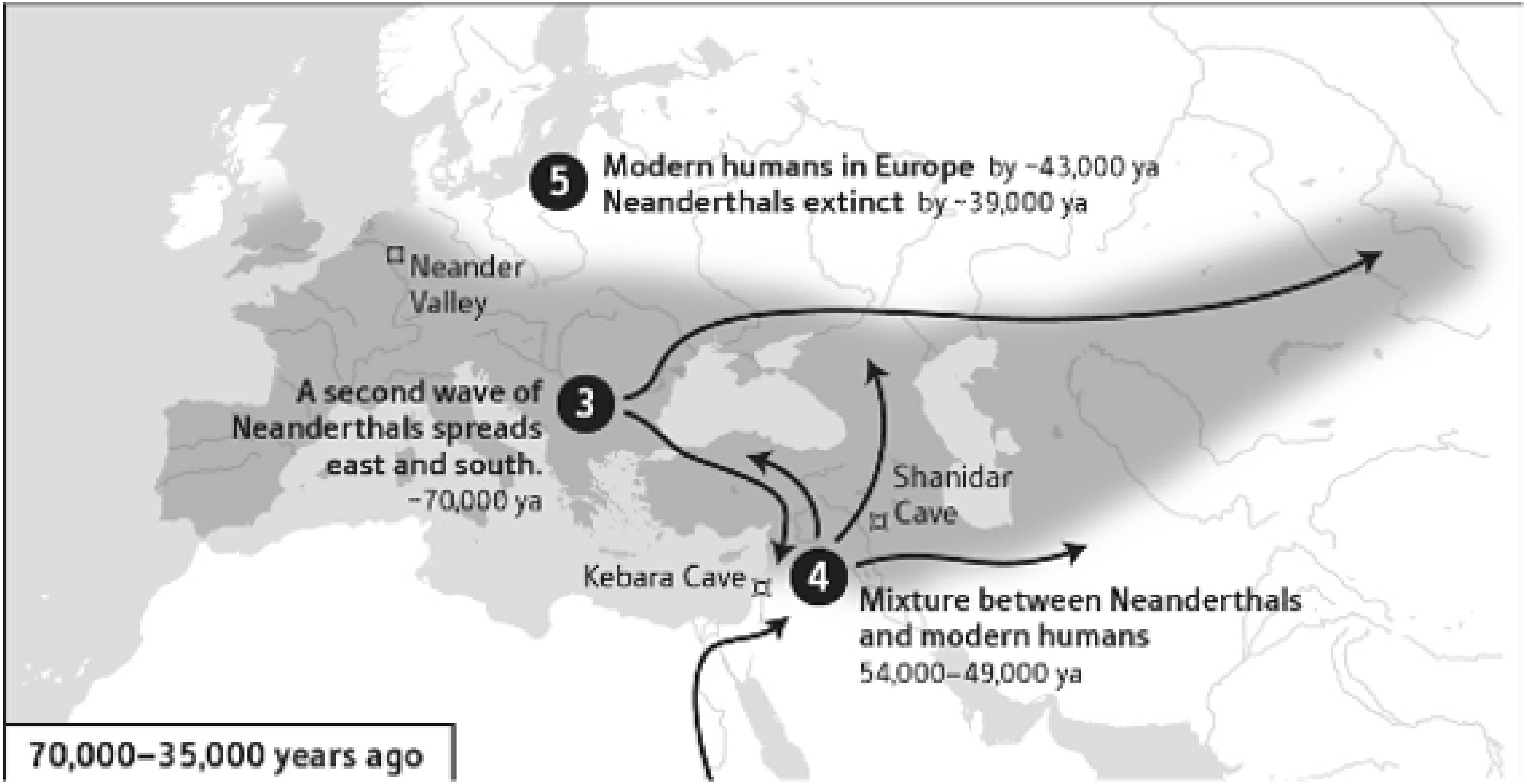
In 1990s, idea was that all Eurasian DNA traced back to Africa.

Reality:
Only 98% of non-African DNA is from Africa;
2% is from Ns



The Interaction of Neanderthals and Modern Humans

130,000–100,000 years ago


5
Modern humans in Europe by ~43,000 ya
Neanderthals extinct by ~39,000 ya
Neander Valley
3
A second wave of Neanderthals spreads east and south.
~70,000 ya
Shanidar Cave
Kebara Cave
4
Mixture between Neanderthals and modern humans
54,000–49,000 ya
70,000–35,000 years ago

Original N MtDNA study

- Original Mitochondrial data analysis confirmed that Neanderthals shared maternal-line ancestors with modern humans, circa 470 to 360 Ka. Mitochondrial DNA analysis also confirmed that the Neanderthals were highly distinctive.

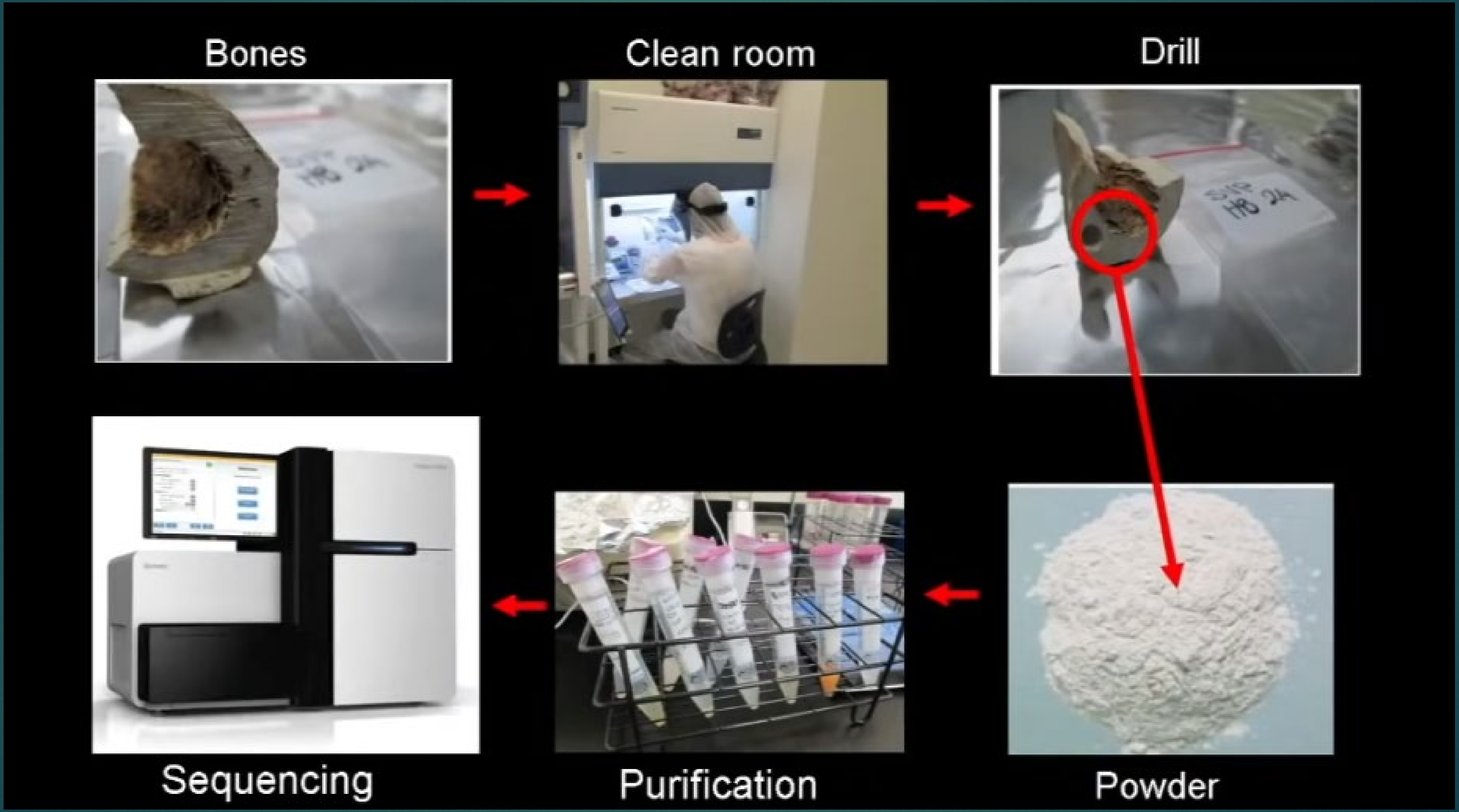
- Their DNA type was outside the range of present-day variation in modern humans.

- Neanderthal mitochondrial DNA provided no support for the theory that Neanderthals and modern humans interbred when they encountered each other.

Neandertal mtDNA and whole genome

- The view that Neanderthals and modern humans did not mix remained the scientific orthodoxy until Svante Pääbo’s team extracted DNA from the whole genome of a Neanderthal in 2010.
- The rate of bp genetic differences between modern humans and Neanderthals is about one per six hundred letters, so it is sometimes impossible to tell whether a particular stretch of DNA comes from the bone or from someone who handled it.

2010 Discovery of new scientific technology (like microscope, telescope, etc.): aDNA extraction



Million times less expensive now

Clean Rooms for aDNA

- Clean spaces used in microchip fabrication facilities in the computer industry were model for aDNA extraction.

- There was an overhead ultraviolet (UV) light of the same type used in surgical operating suites that was turned on whenever researchers were not present, in order to convert contaminating DNA into a form that cannot be sequenced (the light also destroys ancient DNA on the outside of samples, but researchers drill beneath the surface and so are able to access DNA that is not destroyed).

Clean Rooms for aDNA

- The air was ultra-filtered to remove tiny dust particles—anything more than one thousand times smaller than the width of a human hair—that might contain DNA.
- The suite was pressurized so that air flowed from inside to outside, to protect the samples from any contaminating DNA wafting in from outside the lab.
- There were three separate rooms in the suite.

Clean Rooms

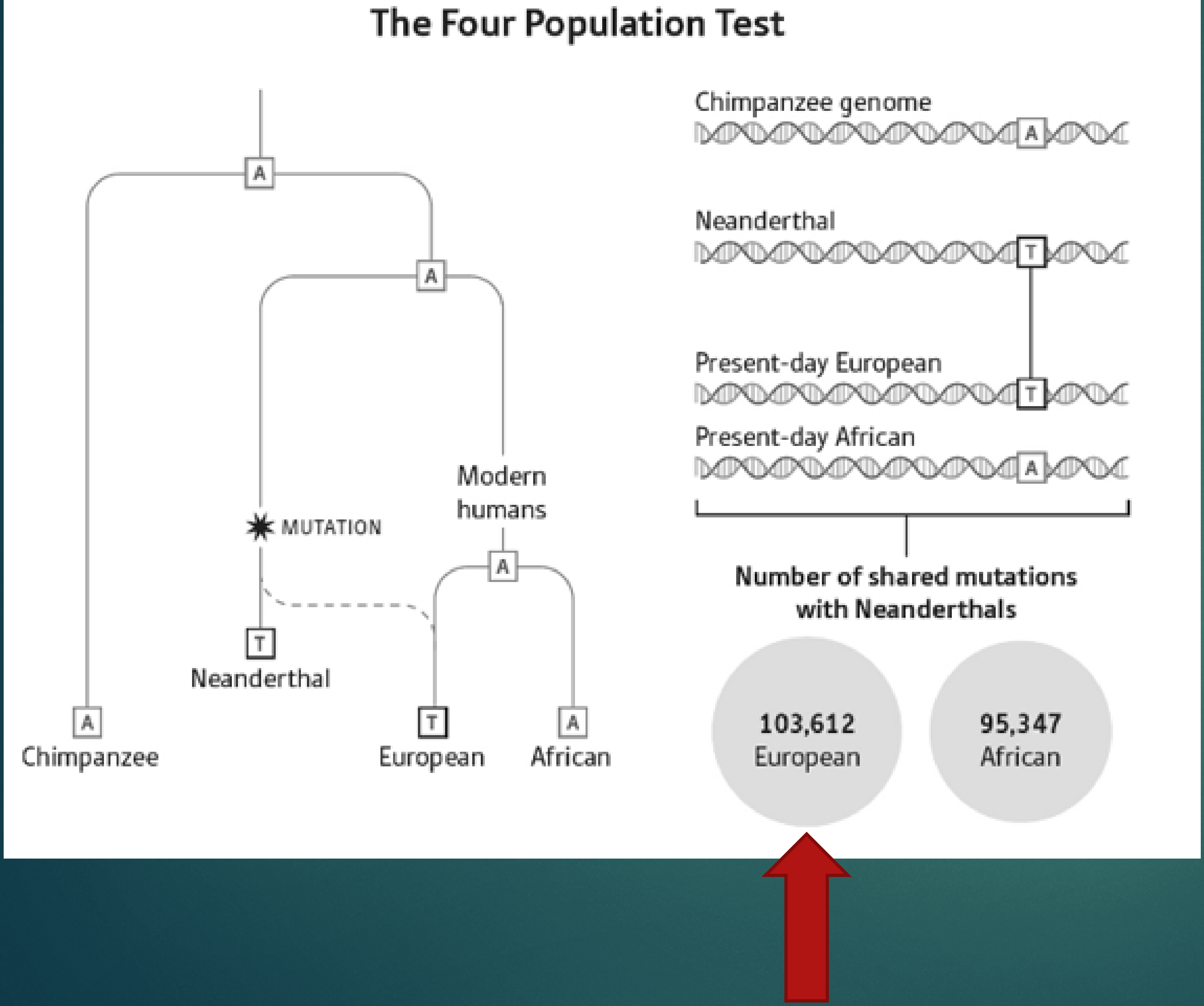
- In the first, the researchers donned full-body clean suits, gloves, and face masks.
- In the second, they placed the bones chosen for sampling into a chamber where they were exposed to high-energy UV radiation, again with the goal of converting the contaminating DNA that might be lying on the surface into a form that cannot be sequenced
- The researchers then cored the bones using a sterilized dental drill, collected tens or hundreds of milligrams of powder onto UV-irradiated aluminum foil, and deposited this powder into a UV-irradiated tube.

Clean Rooms

- In the third chamber, they immersed the powder into chemical solutions that removed bone minerals and protein, and ran the solution over pure sand (silicon dioxide), which binds the DNA while removing the compounds that poison the chemical reactions used for sequencing.
- The researchers then transformed the resulting DNA fragments into a form that could be sequenced.
- First, they chemically removed the ragged ends of the DNA fragments that had been degraded after tens of thousands of years buried under the ground.
- The best-preserved Neanderthal samples turned out to be three 40 Ka old arm and leg bones from Vindija Cave in the highlands of Croatia.

Reich joins Pääbo

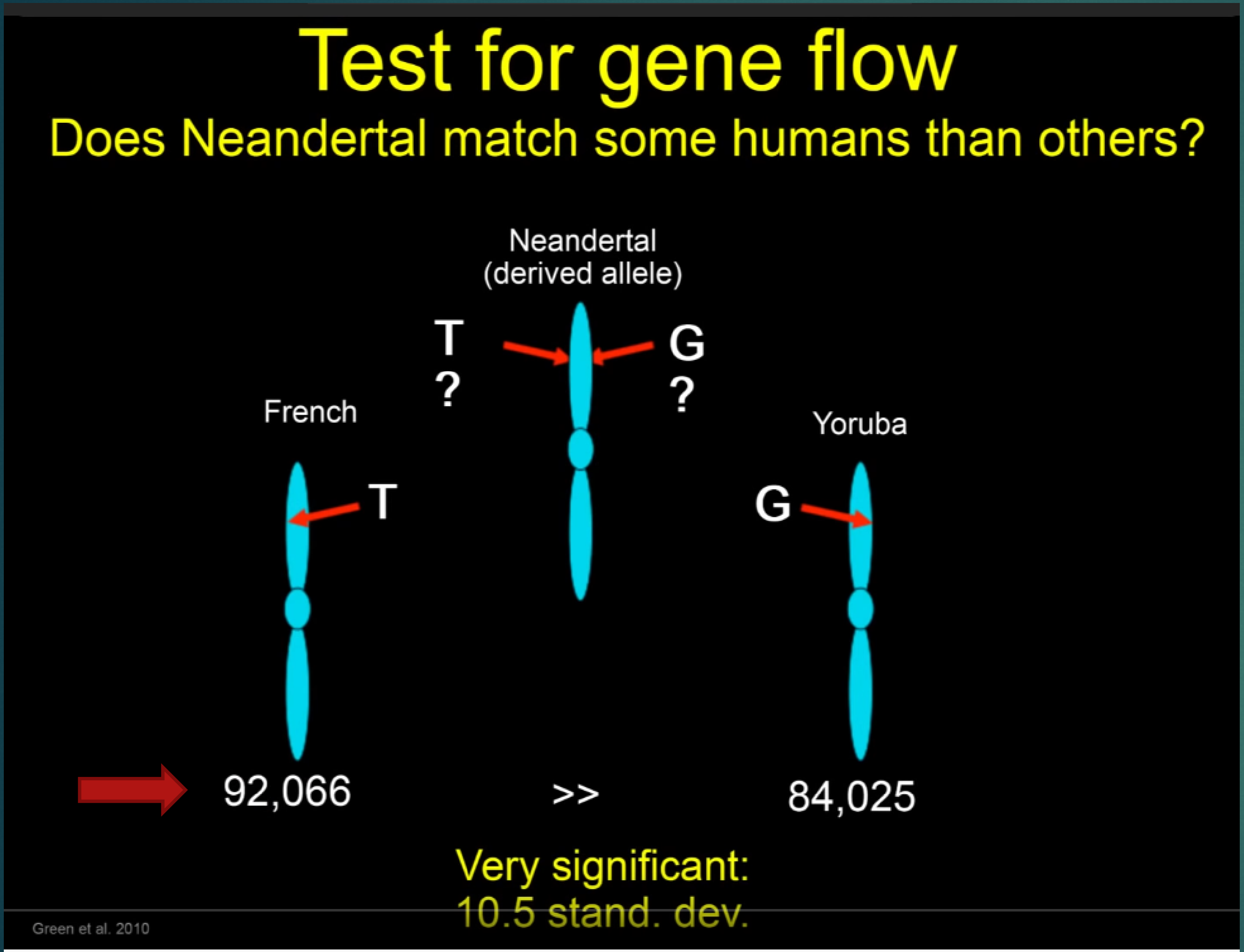
- Once Pääbo realized in 2007 that he would be able to sequence almost the entire Neanderthal genome, he assembled an international team of experts with the goal of ensuring that the analysis would do justice to the data.
- This is how Reich got involved, together with his chief scientific partner, the applied mathematician Nick Patterson. Pääbo reached out to them because over the previous five years we had established themselves as innovators in the area of studying population mixture.
- Based on the degree of excess mutations on the Neanderthal lineage, we estimated that these Neanderthal sequences had a mistake approximately every two hundred DNA letters.



Designed a mathematical test for measuring whether Neanderthals were more closely related to some present-day humans than to others. The test takes as its input the DNA letters seen at the same position in four genomes:

We can evaluate whether two populations are consistent with descending from a common ancestral population.

If Neanderthals and some modern humans interbred, the modern human population descended from the interbreeding will share more mutations with Neanderthals.



Test for gene flow

Does Neandertal match some humans than others?

Very significant:
10.5 stand. dev.

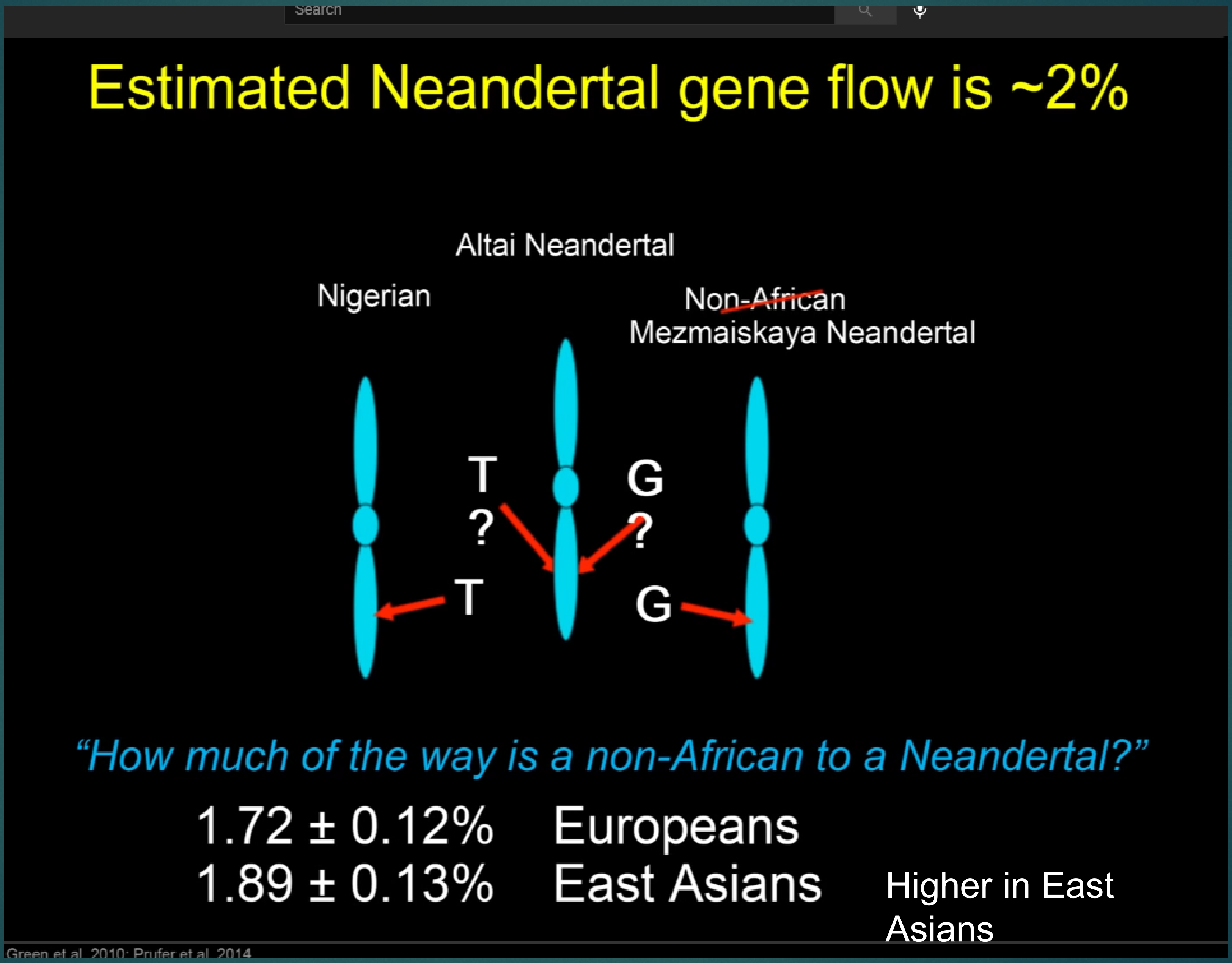
Green et al. 2010

Test for gene flow:
If no admixture, N would be equidistant in Africans and Europeans;
If there was admixture, then N would be closer to European than to African; N is a T

On 1 chromosome,
1 variant:
Ns matches European more than African

Also compare European to 2nd N:

Close to 2% N DNA in MHs; more in Asians



Estimated Neandertal gene flow is ~2%

"How much of the way is a non-African to a Neandertal?"

1.72 ± 0.12%	Europeans
1.89 ± 0.13%	East Asians

Higher in East Asians

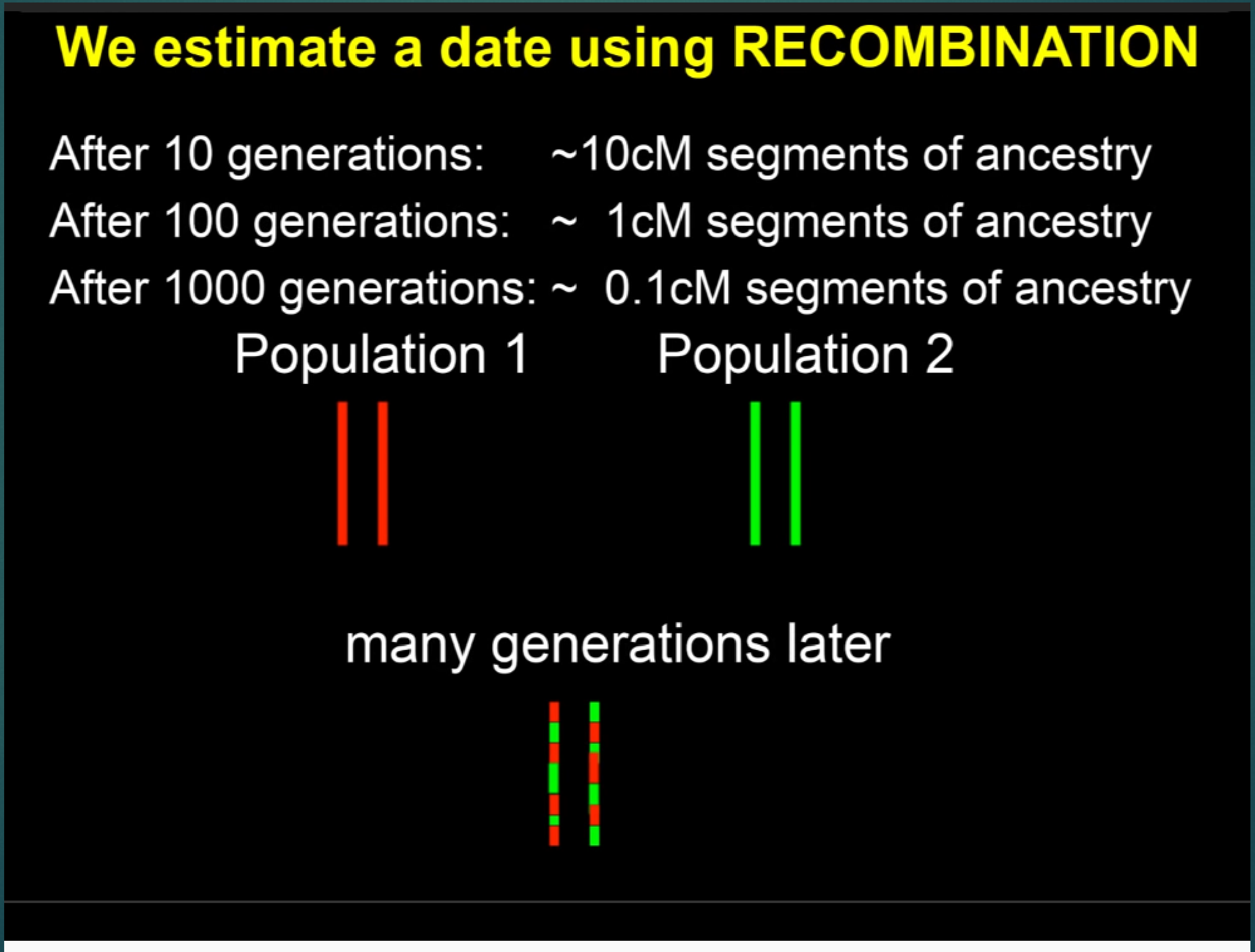
Green et al. 2010; Prufer et al. 2014

= 2% N

Neandertals

- Found Neanderthals to be about equally close to Europeans, East Asians, and New Guineans, but closer to all non-Africans than to all sub-Saharan Africans
- Leipzig team were deeply suspicious of the evidence they were finding for interbreeding with Neanderthals.
- Reich came into the Neanderthal genome project with a strong bias against the possibility of Neanderthal interbreeding with modern humans; that Africa was origin of all humans, with no interbreeding.
- Method for identifying how long ago interbreeding occurred by measuring size of N segments

Estimating age since mixture: estimation of introgression date by size of fragments = smaller equals more recent



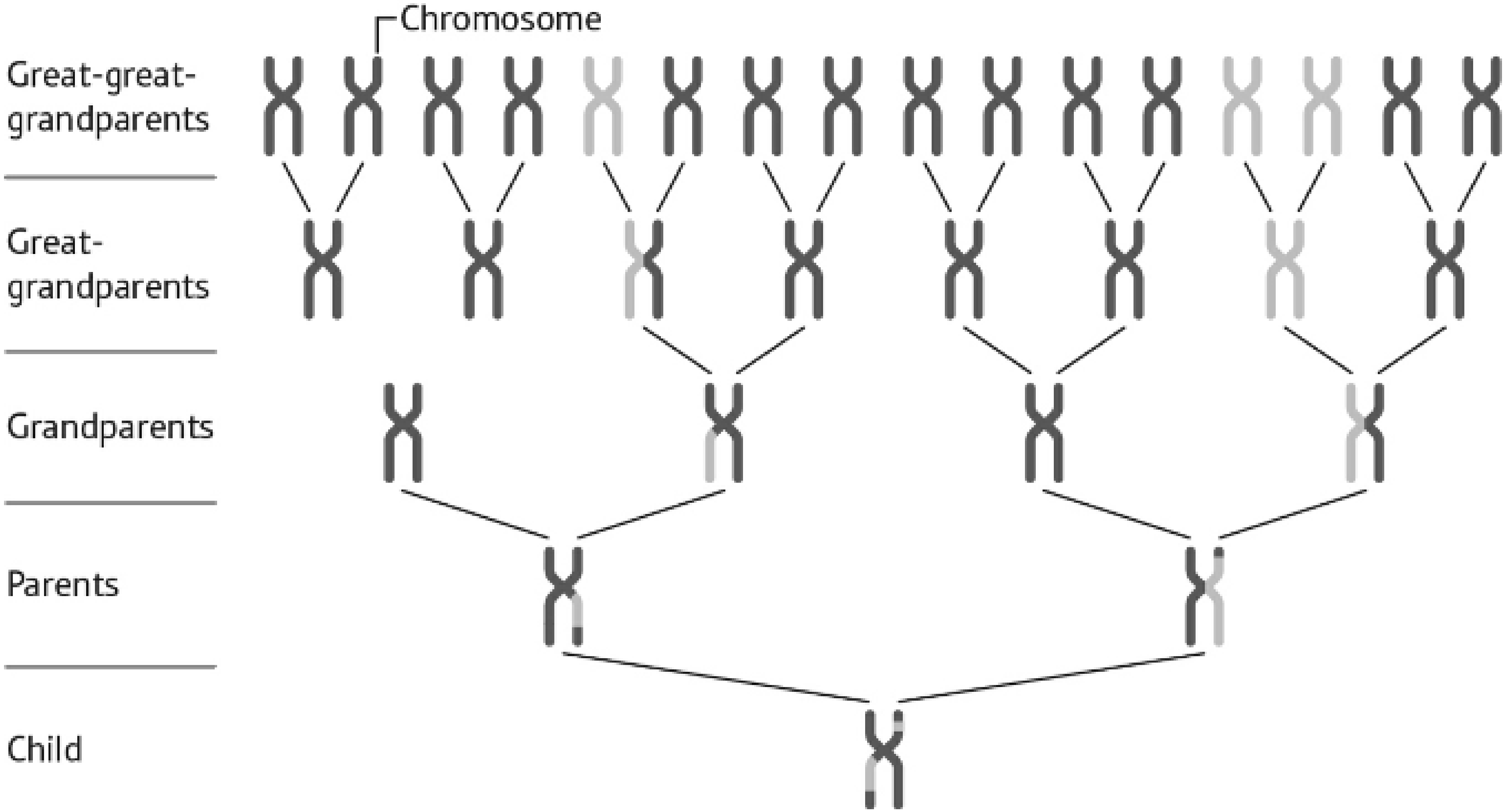
We estimate a date using RECOMBINATION

After 10 generations: ~10cM segments of ancestry

After 100 generations: ~ 1cM segments of ancestry

After 1000 generations: ~ 0.1cM segments of ancestry

The chopping up of chromosomes every generation . . .



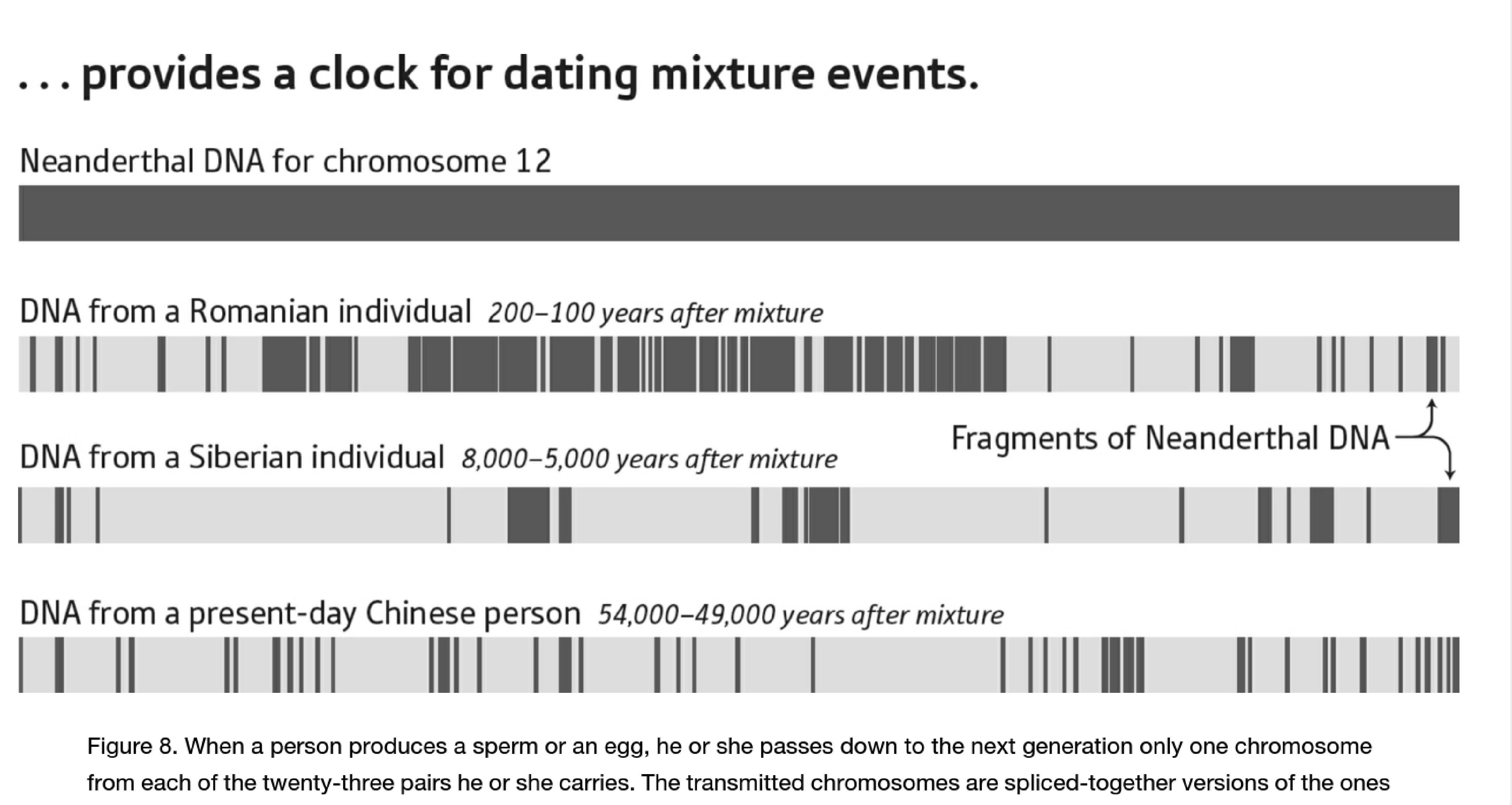


Figure 8. When a person produces a sperm or an egg, he or she passes down to the next generation only one chromosome from each of the twenty-three pairs he or she carries. The transmitted chromosomes are spliced-together versions of the ones

Dating method based on size of segments: Increasingly chopped up segment size = more recent

Dating MH-N admixture: 54 to 49 Ka

- Transmitted chromosomes from parents are spliced-together versions of the ones inherited from the mother and father. This means that the sizes of the bits of Neanderthal DNA in modern human genomes became smaller as the time since mixture increased (above slide, real data from N chromosome 12).

- Originally estimated that at least some Neanderthal-related genetic material came into the ancestors of present-day non-Africans, 86 to 37 Ka.

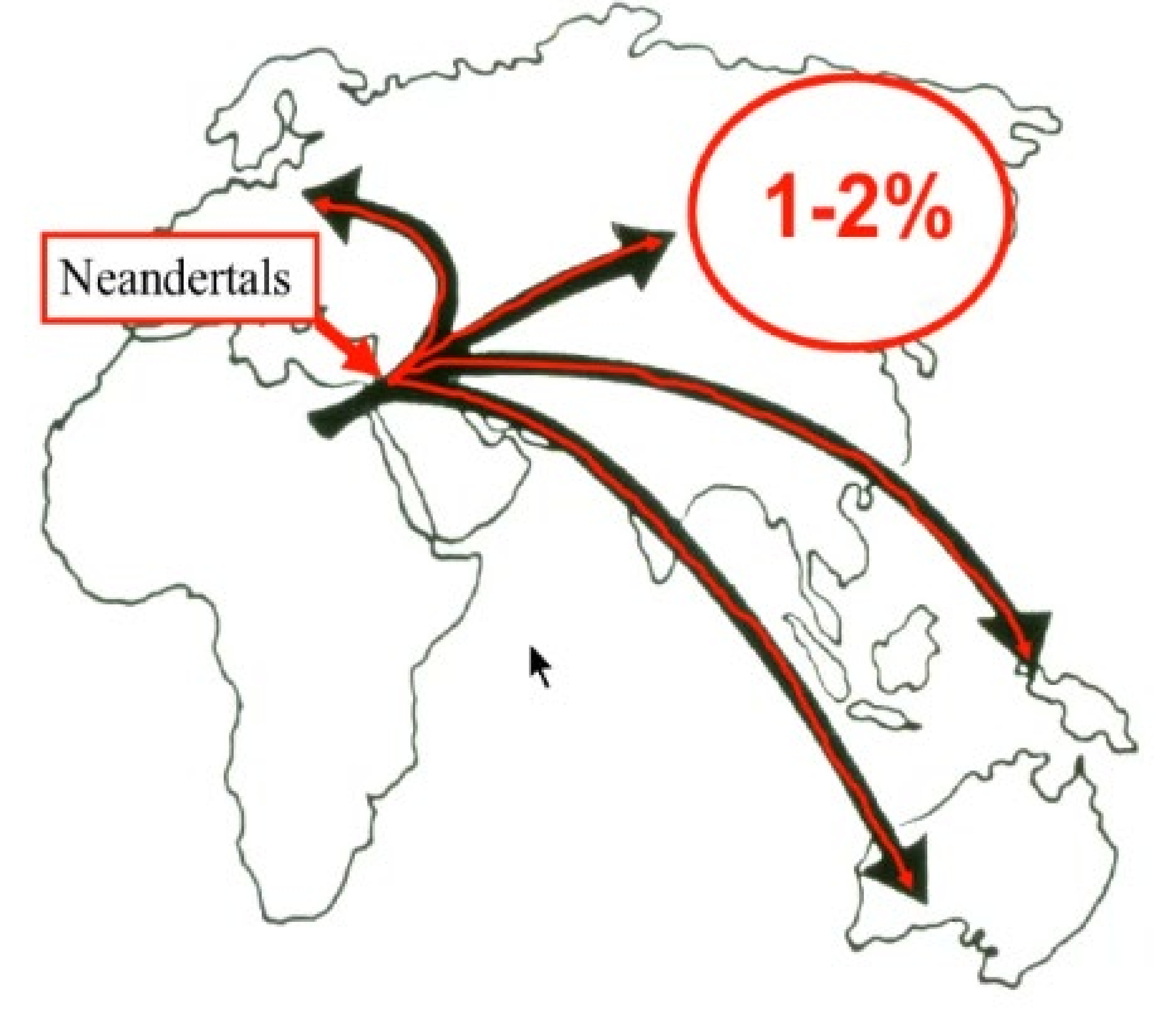
- Have since refined this date by analyzing ancient DNA from a modern human from Siberia who, radiocarbon dating studies show, lived around forty-five thousand years ago. The stretches of Neanderthal-derived DNA in this individual are on average seven times larger than the stretches of Neanderthal-derived DNA in modern humans today,

- Updated Admixture date: 54 to 49 Ka

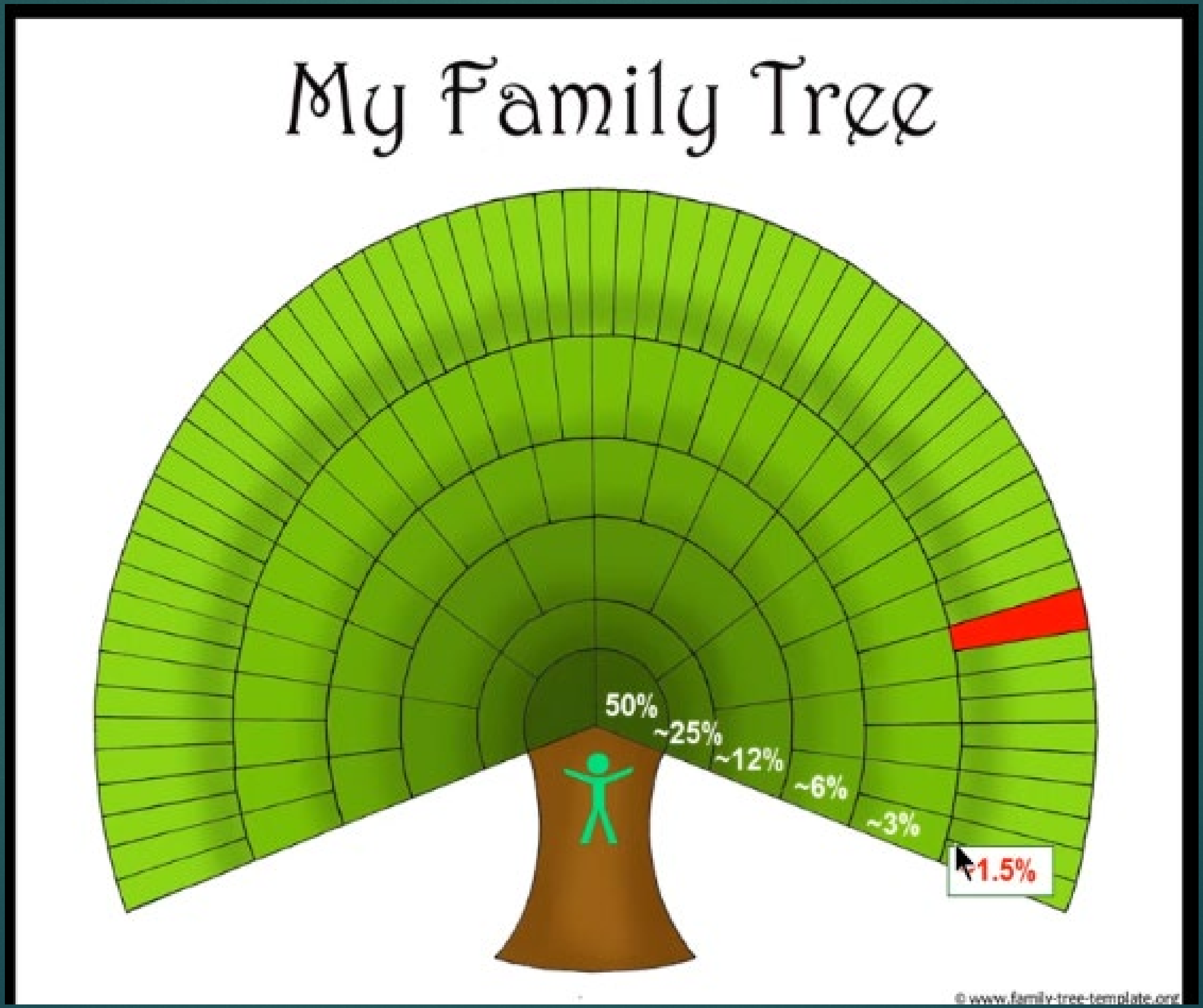
N admixtures

- We found that non-African genomes today are around 1.5 to 2.1 percent Neanderthal in origin, with the higher numbers in East Asians and the lower numbers in Europeans.
- Part of the explanation is dilution.
- Pre-farming Europeans at 9000 Ka had just as much Neanderthal ancestry as East Asians do today.
- The spread of farmers with this inheritance diluted the Neanderthal ancestry in Europe, but not in East Asia.
- The low fertility of hybrids may also have reduced Neanderthal ancestry in the DNA of people living today. [Long discussion in book].

Neandertal & MH interbreeding



2% = same as 5th great grandparent; 6 generations back in amount; MHs today have ~40% of total N genome



N DNA

- In more than half the MH genome, no Neanderthal DNA has been detected in anyone.
- But in some unusual places in the genome, more than 50 percent of DNA sequences are from Neanderthals.
- N DNA reduced in sex cells and around the great majority of genes
- Neanderthal ancestry decreased continually from 3 to 6 percent in most of the samples analyzed from earlier times to its present-day value of around 2 percent
- Driven by widespread natural selection against Neanderthal DNA.

Location of admixture

- In the Near East, Neanderthals and modern humans traded places as the dominant human population at least twice between 130,000 and 50,000 years ago; might have met during this period.

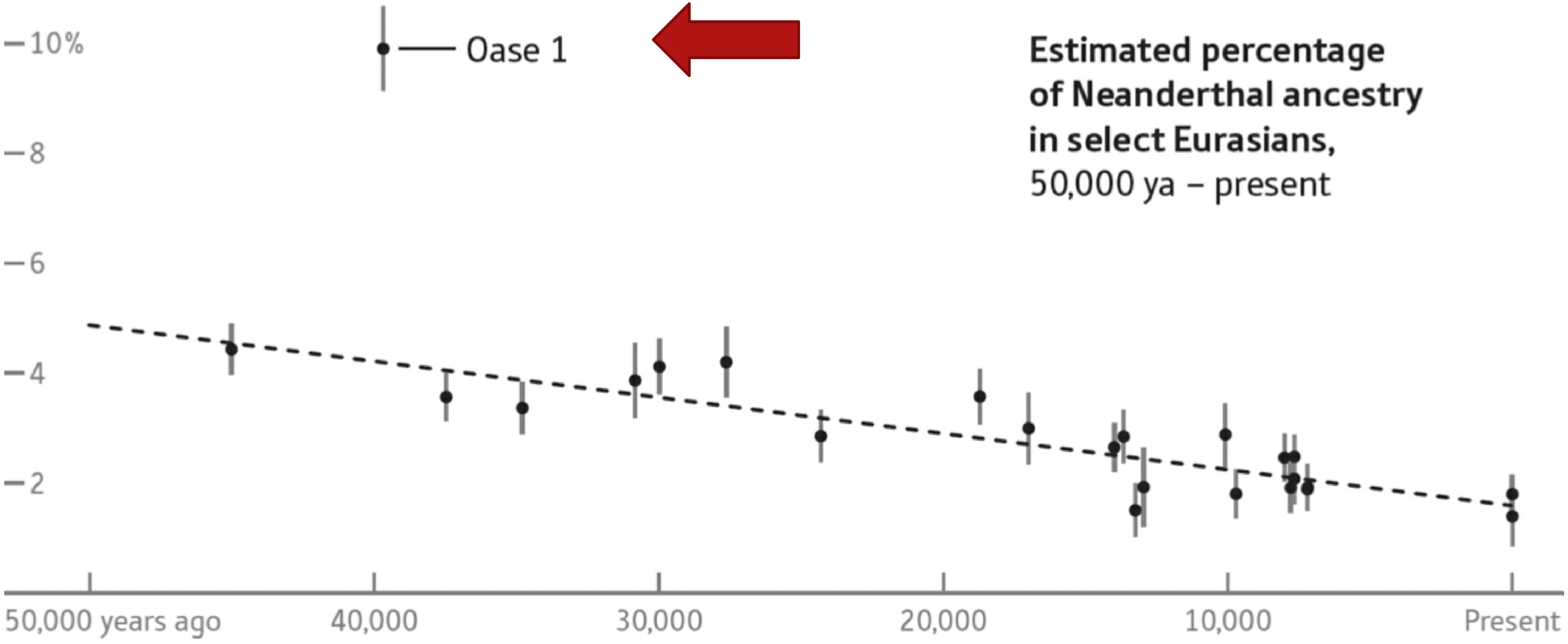
- So interbreeding in the Near East provides a plausible explanation for the Neanderthal ancestry that is shared by Europeans and East Asians.

- The Romanian Oase 1 individual, at 42 Ka, had 6 to 9 percent N ancestry.

- Some stretches of his Neanderthal DNA extend a third of the length of his chromosomes— Oase individual had an actual Neanderthal no more than six generations back in his family tree. suggested that modern humans and Neanderthals also hybridized in Europe.

- But his was a dead end population.

Neanderthal ancestry has been removed over time by natural selection.



Estimated percentage of Neanderthal ancestry in select Eurasians,
50,000 ya – present

N population sizes

- A large part of the Neanderthal range was in a region where ice ages caused periodic collapses of the animal and plant populations that Neanderthals depended on.

- There is genetic confirmation
  - for smaller Neanderthal
  - than modern human population sizes
  - from the fact that the diversity of their genomes was about four times smaller than MHs.

N population sizes

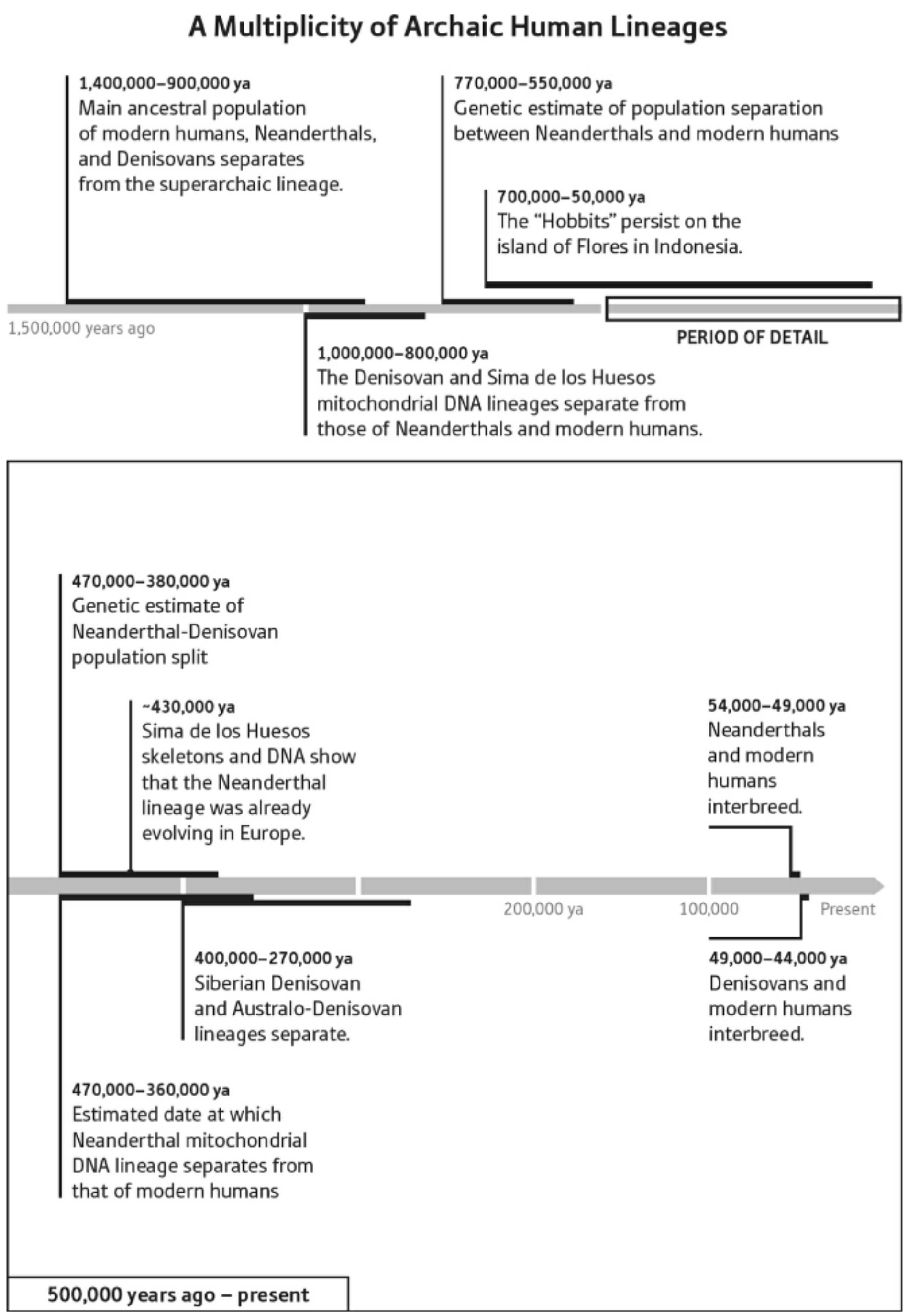
- A history of small size is problematic for the genetic health of a population, because the fluctuations in mutation frequency that occur every generation are substantial enough to allow some mutations to spread through the population even in the face of the prevailing wind of natural selection that tends to reduce their frequencies.

- So in the half million years since Neanderthals and modern humans separated, Neanderthal genomes accumulated mutations that would prove detrimental when later, Neanderthal/modern human interbreeding occurred.

Who We Are and How We Got Here

- Chapter 3, “Ancient DNA Opens the Floodgates,”
  - highlights how ancient DNA can reveal features of the past that no one had anticipated,
  - starting with the discovery of the Denisovans, a previously unknown archaic population that had not been predicted by archaeologists and that mixed with the ancestors of present-day New Guineans.
- The sequencing of the Denisovan genome unleashed a cavalcade of discoveries of additional archaic populations and mixtures, and demonstrated unequivocally that population mixture is central to human nature.

Multiplicity of Archaic Human Lineages



A Multiplicity of Archaic Human Lineages

1,400,000–900,000 ya
Main ancestral population of modern humans, Neanderthals, and Denisovans separates from the superarchaic lineage.

770,000–550,000 ya
Genetic estimate of population separation between Neanderthals and modern humans

700,000–50,000 ya
The "Hobbits" persist on the island of Flores in Indonesia.

1,000,000–800,000 ya
The Denisovan and Sima de los Huesos mitochondrial DNA lineages separate from those of Neanderthals and modern humans.

470,000–380,000 ya
Genetic estimate of Neanderthal-Denisovan population split

~430,000 ya
Sima de los Huesos skeletons and DNA show that the Neanderthal lineage was already evolving in Europe.

54,000–49,000 ya
Neanderthals and modern humans interbreed.

400,000–270,000 ya
Siberian Denisovan and Australo-Denisovan lineages separate.

49,000–44,000 ya
Denisovans and modern humans interbreed.

470,000–360,000 ya
Estimated date at which Neanderthal mitochondrial DNA lineage separates from that of modern humans

500,000 years ago – present

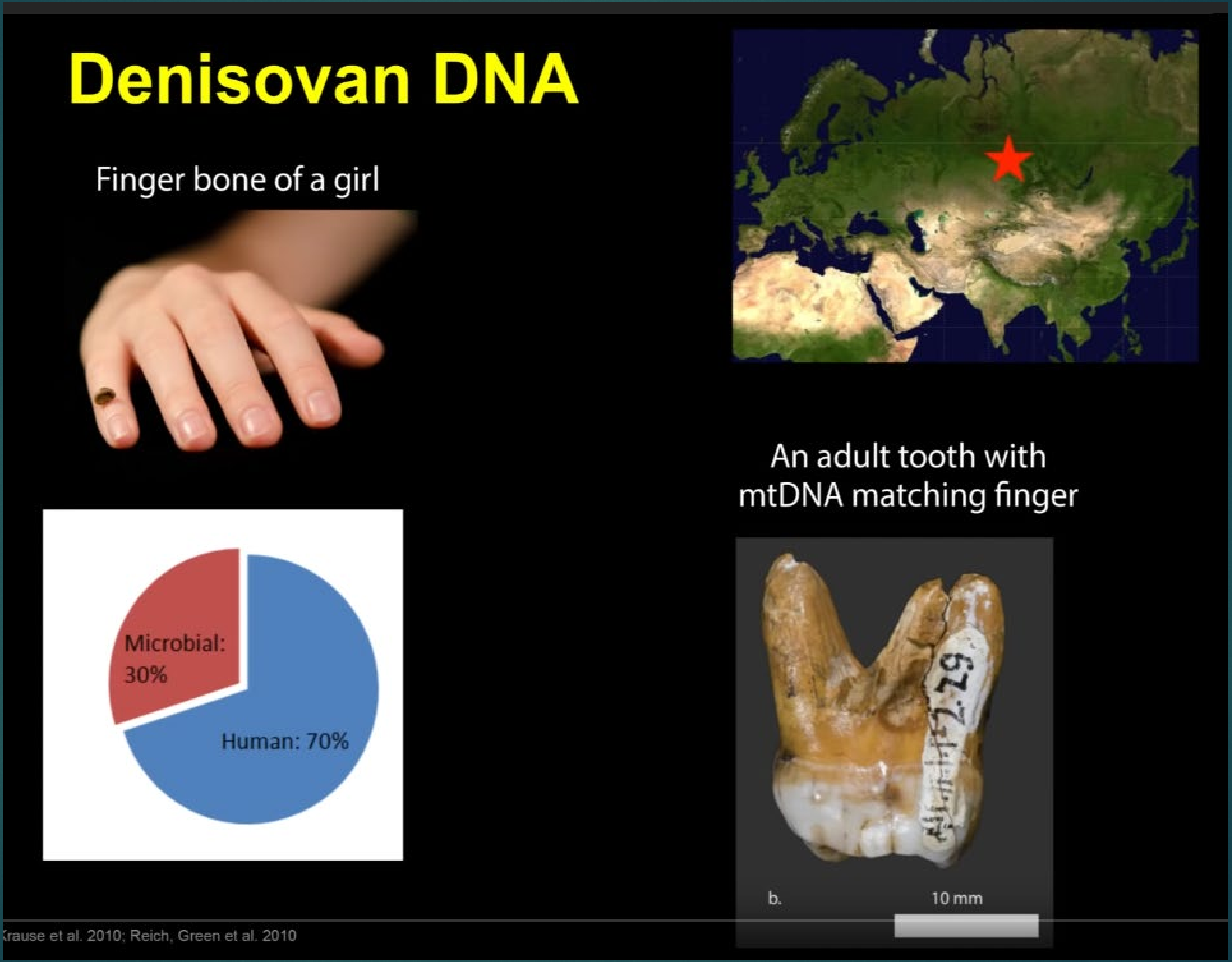
A Multiplicity of Archaic Human Lineages: 1,500,000 years ago

- 1.4 Ma-900 Ka: -- Main ancestral population of modern humans, Neanderthals, and Denisovans separates from the superarchaic lineage.
- 770 to 550 Ka: Genetic estimate of population separation between Neanderthals and modern humans
- 1 Ma to 800 Ka: The Denisovan and Sima de los Huesos mitochondrial DNA lineages separate from those of Neanderthals and modern humans.
- 700 to 50 Ka: The “Hobbits" exist on the island of Flores in Indonesia.

A Multiplicity of Archaic Human Lineages

- 470 to 380 Ka: Genetic estimate of Neanderthal-Denisovan population split
- 470 to 360 Ka: Estimated date at which Neanderthal mitochondrial DNA lineage separates from that of modern humans
- -430 Ka: Sima de los Huesos skeletons and DNA show that the Neanderthal lineage was already evolving in Europe.
- 400 to 270 Ka: Siberian Denisovan and Australo-Denisovan lineages separate.
- 54 to 49 Ka: Neanderthals and modern humans interbreed.
- 49 to 44 Ka: Denisovans and modern humans interbreed.

2010



Denisovan DNA

Finger bone of a girl

An adult tooth with mtDNA matching finger

Krause et al. 2010; Reich, Green et al. 2010

Denisova Cave

- Pääbo’s team, led by Johannes Krause, extracted mitochondrial DNA from the Denisova Cave bone. Its sequence was of a type that had never before been observed in more than ten thousand modern human and seven Neanderthal sequences.
- There are around two hundred mutational differences separating the mitochondrial DNA of people living today from that of Neanderthals.
- The new mitochondrial DNA from the Denisova finger bone featured nearly four hundred differences from the mitochondrial DNA of both present-day humans and Neanderthals.

A Genome in Search of a Fossil

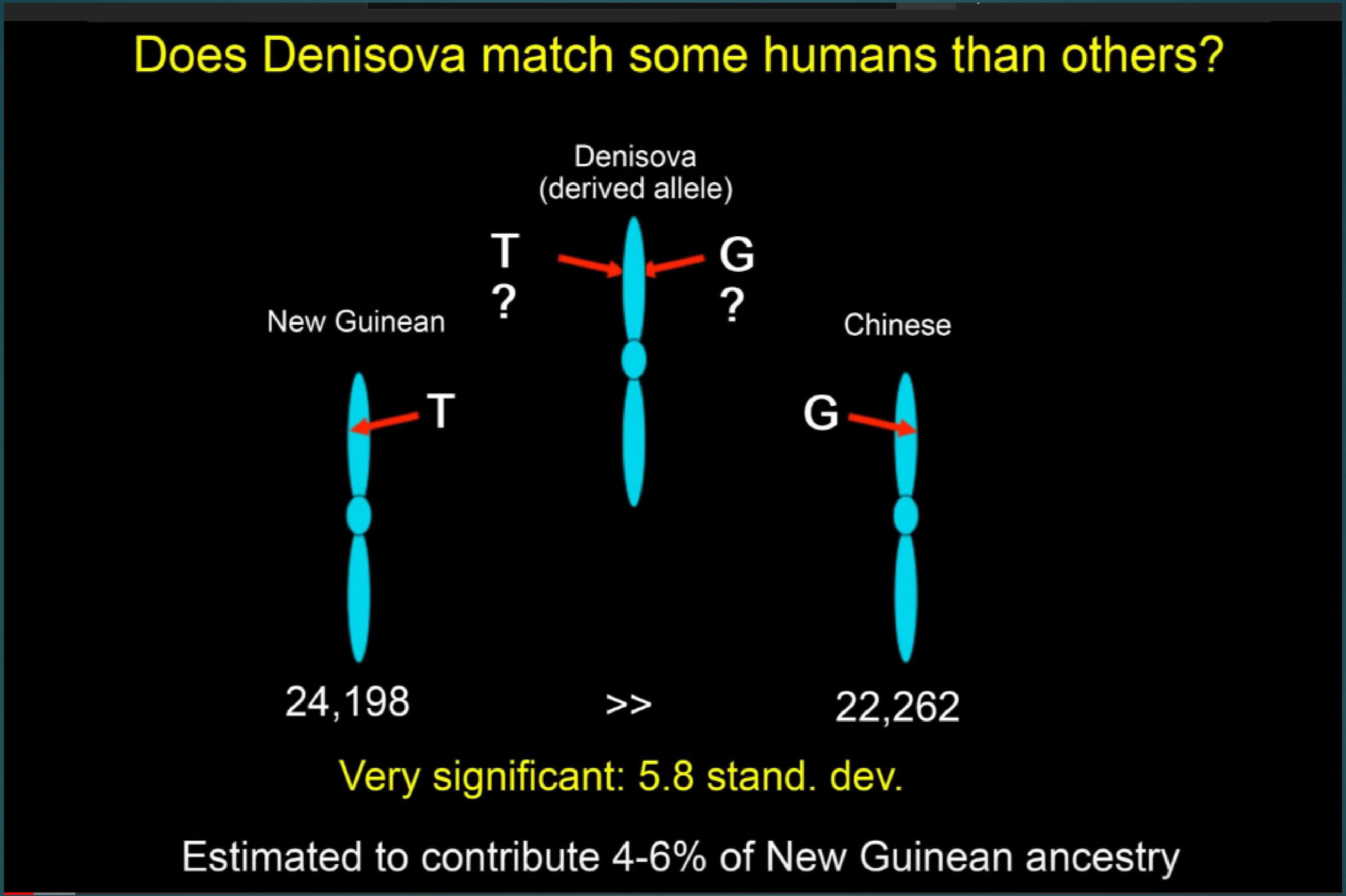
- While Pääbo had screened dozens of Neanderthal samples to find a few with up to 4 percent primate DNA, this Denisovan finger bone had about 70 %.
- Reich: The invitation to analyze the Denisovan genome was the greatest piece of good fortune I have had in my scientific career.
- Neanderthals and Denisovans were more closely related to each other than either to MHs
- Separation between the common ancestor of Ns and Ds and MHs to have occurred 770 to 550 Ka.
- Separation between the Neanderthal and Denisovan ancestral populations to have occurred 470 to 380 Ka,

“Denisovans”, not *H. altaiensis*

- We had a heated debate about what to call the new population, and decided to use a generic non-Latin name, “Denisovans,” after the cave where they were first discovered, in the same way that Neanderthals are named after the Neander Valley in Germany.
- This decision distressed some of our Russian colleagues, who lobbied for a new species name—perhaps *Homo altaiensis*, after the mountains where Denisova Cave is located.
- *Homo altaiensis* is now used in a museum exhibit in Novosibirsk in Russia that describes the discovery at Denisova.
- The geneticists, however, were reluctant to use a species name.

Denisovans

- Fact that Neanderthals interbred successfully with modern humans and in fact did so on multiple occasions seems to undermine the argument that they are distinct species.
- Our data showed that Denisovans were cousins of Neanderthals, and thus if we are uncertain about whether Neanderthals are a species, we need to be uncertain about whether Denisovans are a species as well.

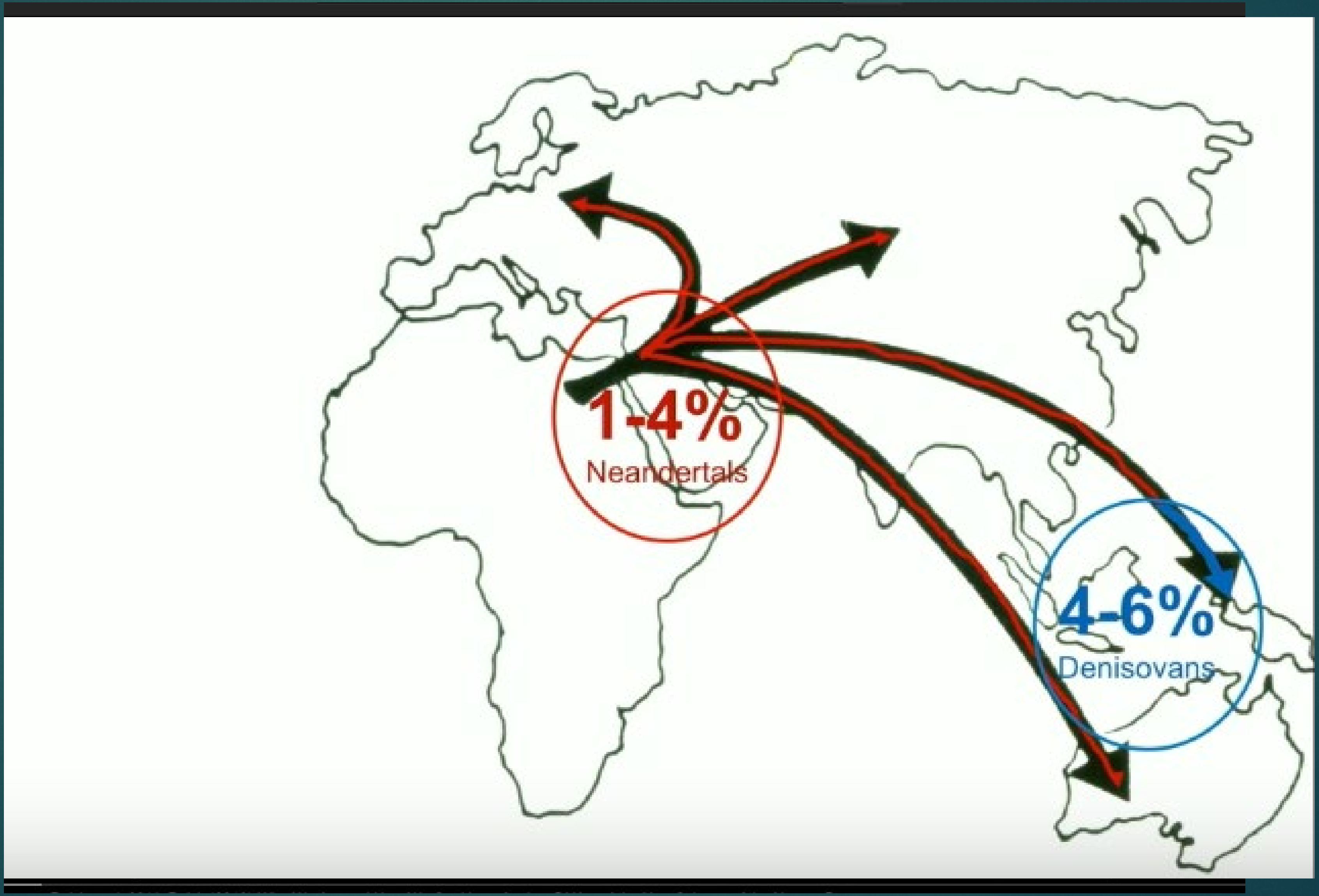


Does Denisova match some humans than others?

Very significant: 5.8 stand. dev.

Estimated to contribute 4-6% of New Guinean ancestry

6% Denisovan DNA East of Wallace line; 20th of that in Asia; none in Europe



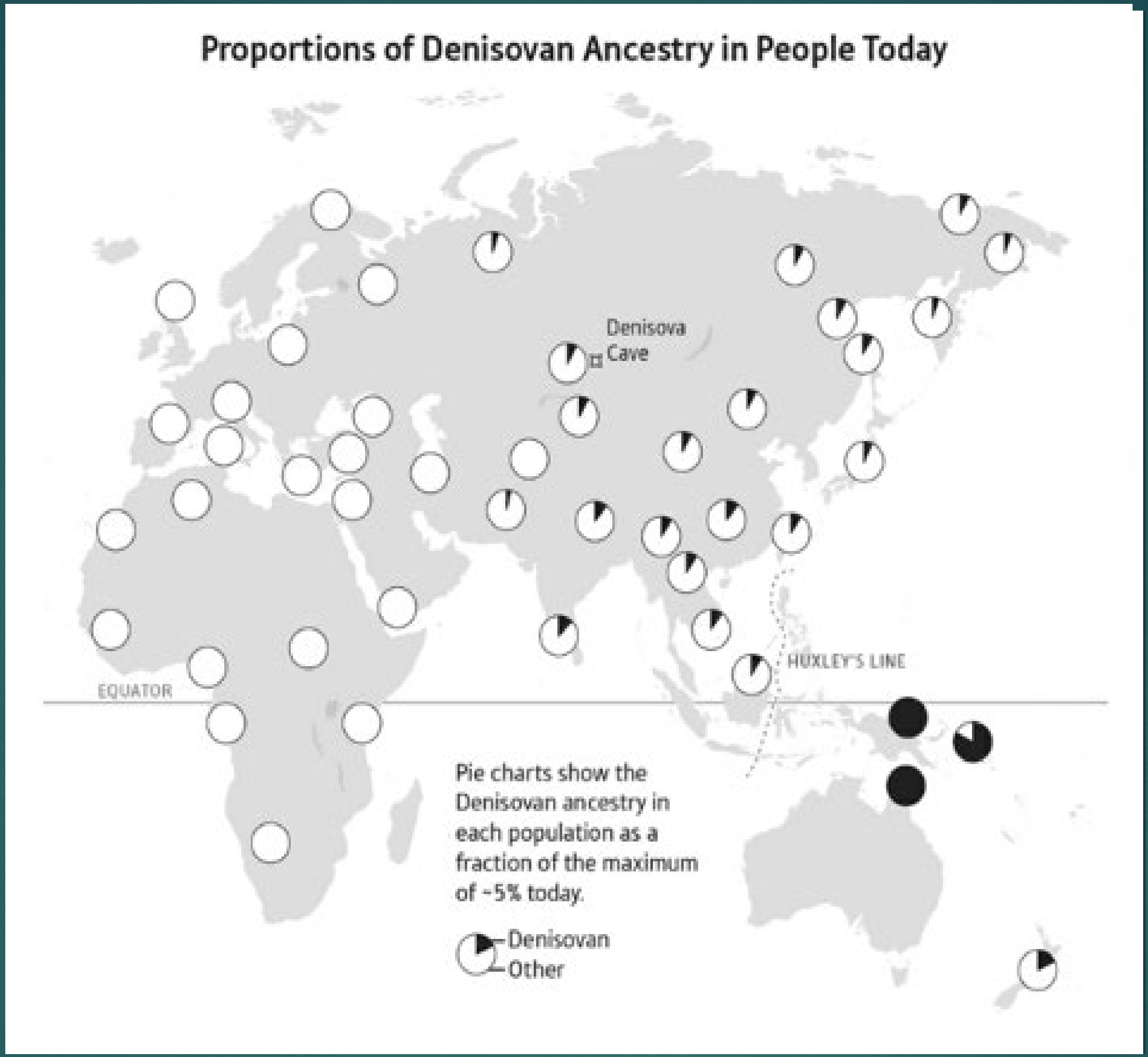
Denisovans

- Denisovans were genetically a little closer to New Guineans than they were to any population from mainland Eurasia, suggesting that New Guinean ancestors had interbred with Denisovans. Yet the distance from Denisova Cave to New Guinea is around nine thousand kilometers, and New Guinea is separated by sea from the Asian mainland.

- We were able to measure the size of intact archaic ancestry segments, and found that the ones related to Denisovans were about 12 percent longer than those from Neanderthals, implying that the Denisovan-related segments had been introduced that much more recently on average.

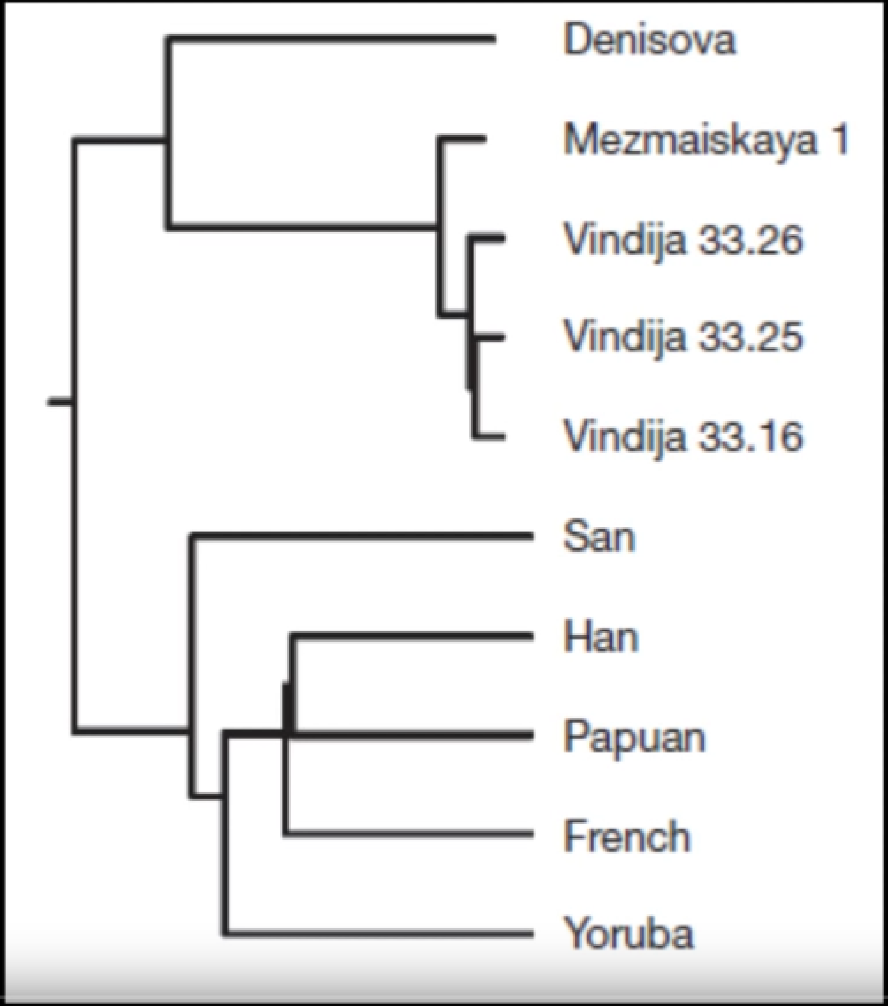
- Based on how much longer the Denisovan segments were in New Guineans, we could conclude that the interbreeding between Denisovan and New Guinean ancestors occurred 59 to 44 Ka.

Neanderthal ancestry in each population as a fraction of the maximum of *-2%* today



3 to 6 % of New Guinean ancestry derives from Denisovans. Thus in total, 5 to 8 % of New Guinean ancestry comes from archaic humans. This is the largest known contribution of archaic humans to any present-day human population.

“Denisovans” are distinct from both Neandertals and modern humans



Tooth morphology and mtDNA are also distinct

Krause et al. 2010

Denisovans in Indonesia

- The simplest explanation for the large fractions of Denisovan-related ancestry on the islands off the southeastern tip of Asia and in New Guinea and Australia would be the occurrence of interbreeding near the islands—on the islands themselves or in mainland Southeast Asia. But there are no skeletal findings.
- Reich: it is more likely that interbreeding occurred in southern China or mainland Southeast Asia.
- There are Chinese archaic human remains from Dali in Shaanxi province in north-central China, from Jinniushan in Liaoning in northeastern China, and from Maba in Guangdong in southeastern China, all dating to around two hundred thousand years ago, all of which are more plausible skeletal matches for the Denisovans.

Australo-Denisovans

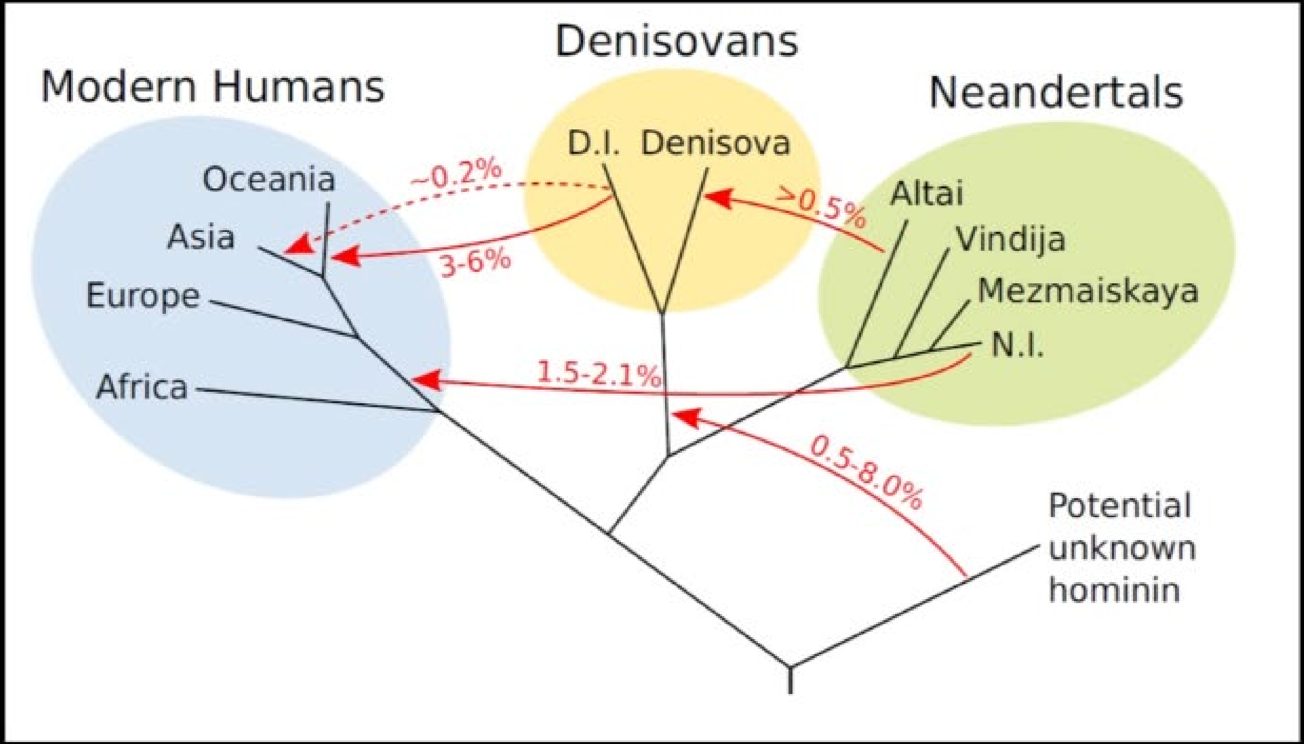
- A Denisovan population split (Siberian vs Australo) that occurred 400 to 280 Ka.
- This meant that the ancestors of the Siberian Denisovans separated from the Denisovan lineage that contributed ancestry to New Guineans
- Reich likes to call them "Australo-Denisovans" to highlight their likely southern geographical distribution. Anthropologist Chris Stringer prefers "Sunda Denisovans" after the landmass that joined most of the Indonesian islands to the Southeast Asian mainland.
- One of the profound implications of the Denisovan discovery was that East Eurasia is a central stage of human evolution and not a sideshow as westerners often assume.

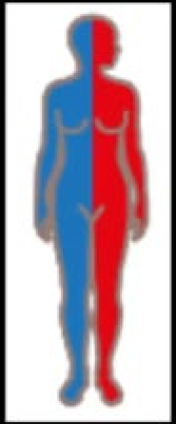
N and D Hybrid Denny

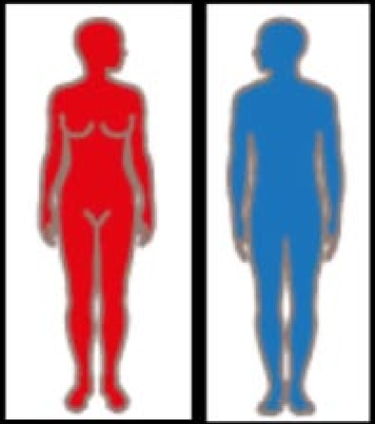
Genome of a girl with a
Neanderthal mother

and a Denisovan father

The Pandora's Box of Mixtures Between Archaic Humans Opened by Ancient DNA







Denisovans in Asia

- The Denisovan ancestry in East Asians is about a 25th of that seen in New Guineans—it comprises about 2 percent of East Asians' genomes, rising to up to 3–6 percent in parts of South Asia.
- Denisovan adaptation to high altitude inherited by ancestors of Tibetans inherited through Denisovan interbreeding.
- Ghost lineage in Denisovans: an unknown archaic population that interbred into Denisovans which first split off from the lineage leading to modern humans 1.4 to 0.9 Ma and that this unknown archaic population contributed at least 3 to 6 % of Denisovan-related ancestry.

Major Population Splits

- At least four major population separations involving modern and archaic human lineages over the last two million years.
  - 1- The skeletal evidence: *H. erectus* to Eurasia from Africa at least 1.8 Ma.
  - 2 - The genetic evidence suggests a second lineage split from the one leading to modern humans around 1.4 to 0.9 MA, giving rise to the superarchaic group that we have evidence of through its mixture with the ancestors of Denisovans and that plausibly contributed the highly divergent Denisovan mitochondrial DNA sequence that shares a common ancestor with both Neanderthals and modern humans in this time frame.

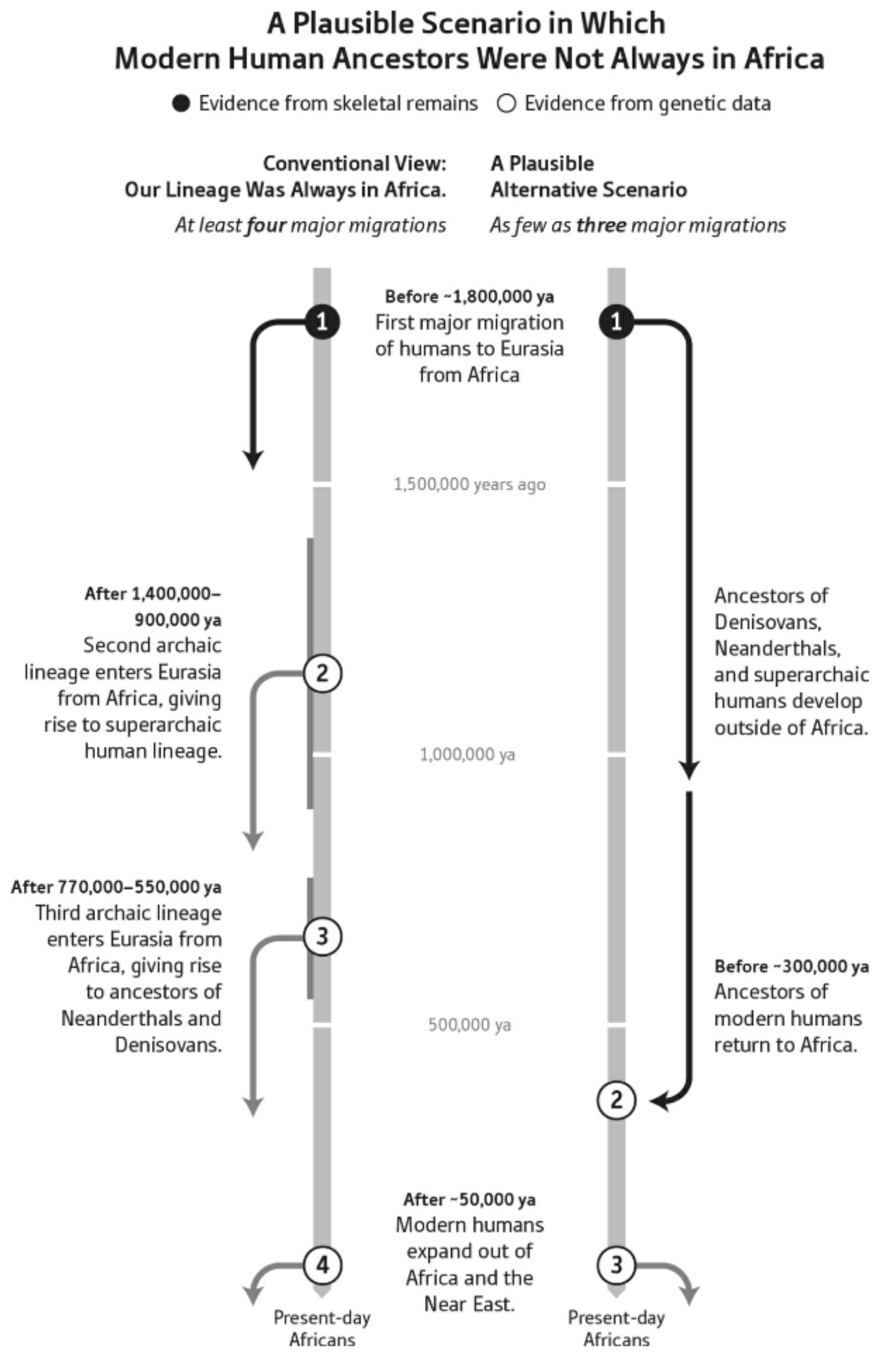
Eurasia as a Hothouse of Human Evolution

- 3 - A major split 770 to 550 Ka: ancestors of modern humans separated from Denisovans and Neanderthals,

- 4 - Denisovans and Neanderthals split from each other 470 to 380 Ka.

Reich: controversial idea

- Reich also proposes a controversial theory in which he suggests that modern human ancestors actually may have lived in Eurasia, not in Africa, calling Eurasia a “hothouse of human evolution.”
- According to this theory, ancestral humans, including Neandertals and Denisovans, descended from the African *Homo erectus*, left Africa for Eurasia, and later returned to serve as the founders of what would eventually evolve into modern humans.
- This provocative proposal is sure to generate debate.



But another possibility suggests itself, which is that the ancestral population of modern humans, Neanderthals, and Denisovans actually lived in Eurasia, descending from the original Homo erectus spread out of Africa.

In this scenario, there was later migration back from Eurasia to Africa, providing the primary founders of the population that later evolved into modern humans.

The attraction of this theory is its economy:

It requires one less major population movement between Africa and Eurasia to explain the data. The superarchaic population and the ancestral population of modern humans, Denisovans, and Neanderthals could both have arisen within Eurasia, without requiring two further out-of-Africa migrations, as long as there was just one later migration back into Africa to establish shared ancestry with modern humans there.

Eurasia: ancestor of MHs?

- María Martinón-Torres and Robin Dennell theory: The genetic evidence that the ancestors of modern humans may have spent a substantial part of their evolutionary history in Eurasia.
- They argue that humans they call *Homo antecessor*, found in Atapuerca, Spain, and dating to around one million years ago, show a mix of traits indicating that they are from a population ancestral to modern humans and Neanderthals.
- Combining this evidence with archaeological analysis of stone tool types, Martinón-Torres and Dennell argue for the possibility of continuous Eurasian habitation from at least 1.4 million years ago until the most recent common ancestor of humans and Neanderthals after 800 Ka, at which point one lineage migrated back to Africa to become the lineage that evolved into modern humans.

The Most Ancient Hominin DNA Yet

- 2014, Matthias Meyer, Svante Pääbo: mitochondrial DNA from a 430 K-old *Homo heidelbergensis* individual from the Sima de los Huesos cave system in Spain where twenty-eight ancient humans were found at the bottom of a thirteen-meter shaft.

- The Sima skeletons have early Neanderthal-like traits, and the archaeologists who excavated them have interpreted them as being on the lineage leading to Neanderthals

- 2016: Full genome of Simas de los Huesos: confirmed that the Sima humans were on the Neanderthal lineage. The Sima humans were more closely related to Neanderthals than they are to Denisovans. These results provided direct evidence that Neanderthal ancestors were already evolving in Europe at 400 Ka,

Sima de los Huesos mtDNA: Denisovan

- Sima de los Huesos:
    - mitochondrial DNA = Denisovan,
    - genome = Neanderthal

- Siberian Denisovan individual has mitochondrial DNA twice as divergent from modern humans and Neanderthals as they were from each other despite being closer to Neanderthals in the rest of the genome.

- Krause's idea: several hundred thousand years ago, an early modern human population migrated out of Africa and mixed with groups like the one that lived in Sima de los Huesos, replacing their mitochondrial DNA along with a bit of the rest of their genomes and creating a mixed population that evolved into true Neanderthals.

Sima de los Huesos mtDNA: Denisovan

- Explains: Neanderthals had a mitochondrial sequence much more similar to modern humans than it did to either the Sima de los Huesos individual or the Siberian Denisovan

- Could account for the fact that the estimated date of the common ancestor of humans and Neanderthals in mitochondrial DNA (470 to 360 Ka) is paradoxically more recent than the estimated date of separation of the ancestors of these two populations based on the analysis of the whole genome (770 to 550 Ka).

Sima de los Huesos: MH mtDNA in Ns & MH DNA in Ns

- Could explain how it was that Neanderthals and modern humans both used complex Middle Stone Age methods of manufacturing stone tools, even though the earliest evidence for this tool type is hundreds of thousands of years after the genetically estimated separation of the Neanderthals Sima and modern human lineages.

- Study led by Sergi Castellano and Adam Siepel that found up to 2 percent MH DNA in the ancestors of Neanderthals from early migration of MHs (100+ Ka)

- If Krause's theory is right, this could have been the lineage that spread the mitochondrial DNA found in all Neanderthals.