New Studies, September 2021

Charles J Vella, PhD

October meeting options

- October is pumpkin carving month for Vellas
- Request your permission to put off next Paleogenetics talk to November.
- Unless another group member has a book to review, etc., I can offer one of these lectures
  - Intelligence of birds
  - Mind control in insects
  - Neuroscience and the Law
  - Visual Illusions
  - The Social Brain

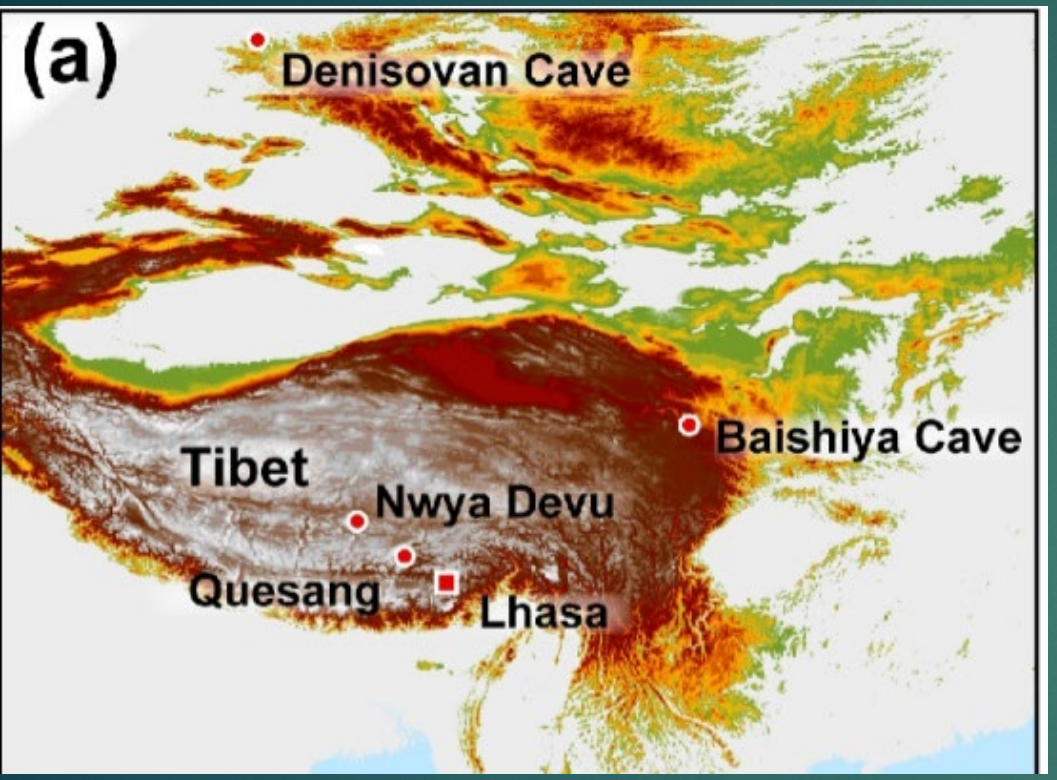
Kids' Fossilized Handprints May Be Some of the World's Oldest Art

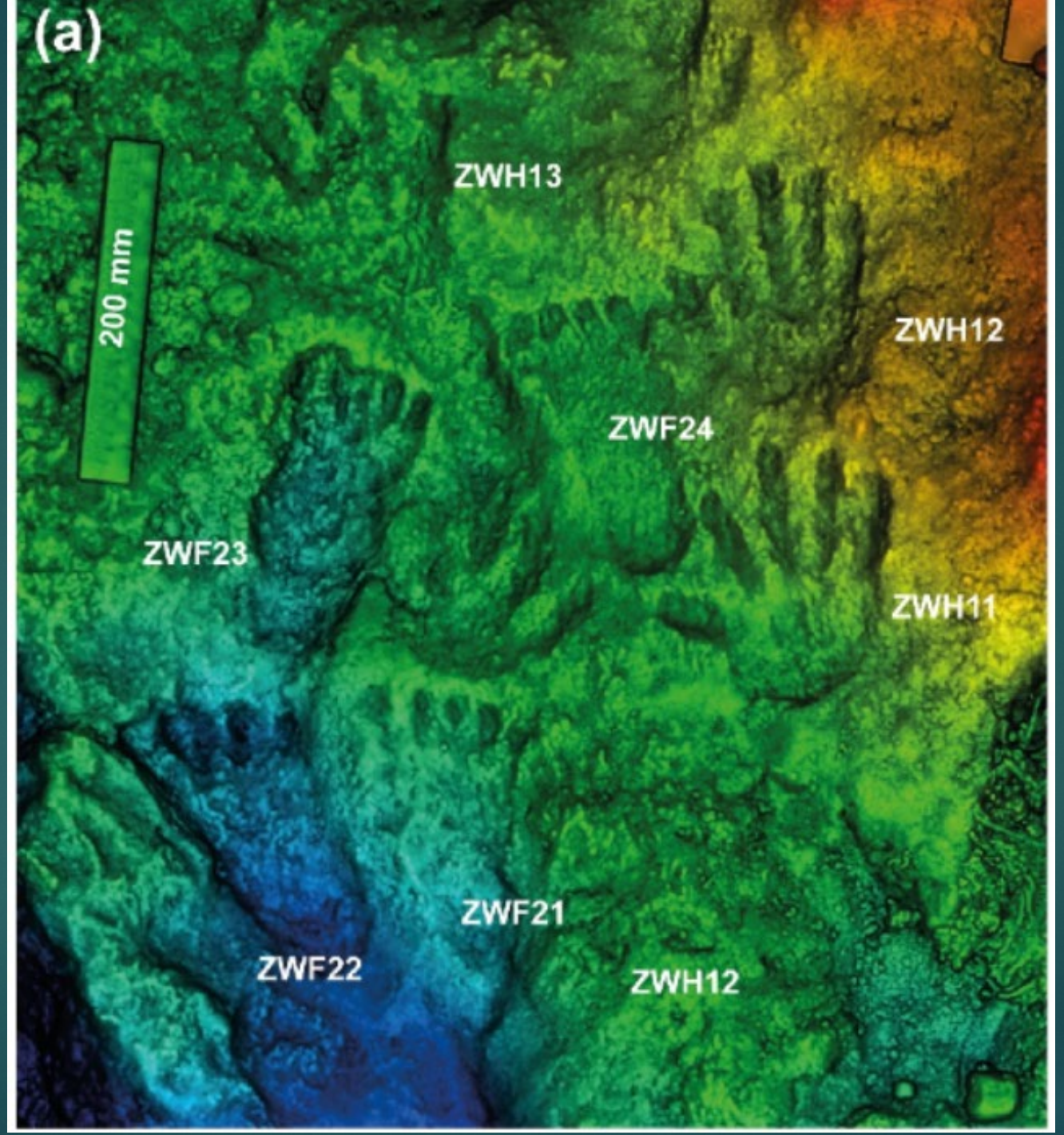
Handprints

- About 169,000 to 226,000 years ago, ice age children squished their hands and feet into sticky mud 13,100 feet above sea level on the Tibetan Plateau. These impressions, now preserved in limestone, provide some of the earliest evidence of human ancestors inhabiting the area and may represent the oldest art of their kind ever discovered.
- Hand and footprints should be considered "parietal" art
- Left by 2 children, ~7 and 12 year old, either *H. erectus* or Denisovan; earliest evidence of hominins at Quesang
- The handprints themselves are made of travertine, a kind of freshwater limestone

Nicoletta Lanese, 2021; David D.Zhang, et al.,

Quesang, Tibet




(a)
200 mm
ZWH13
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ZWF24
ZWF23
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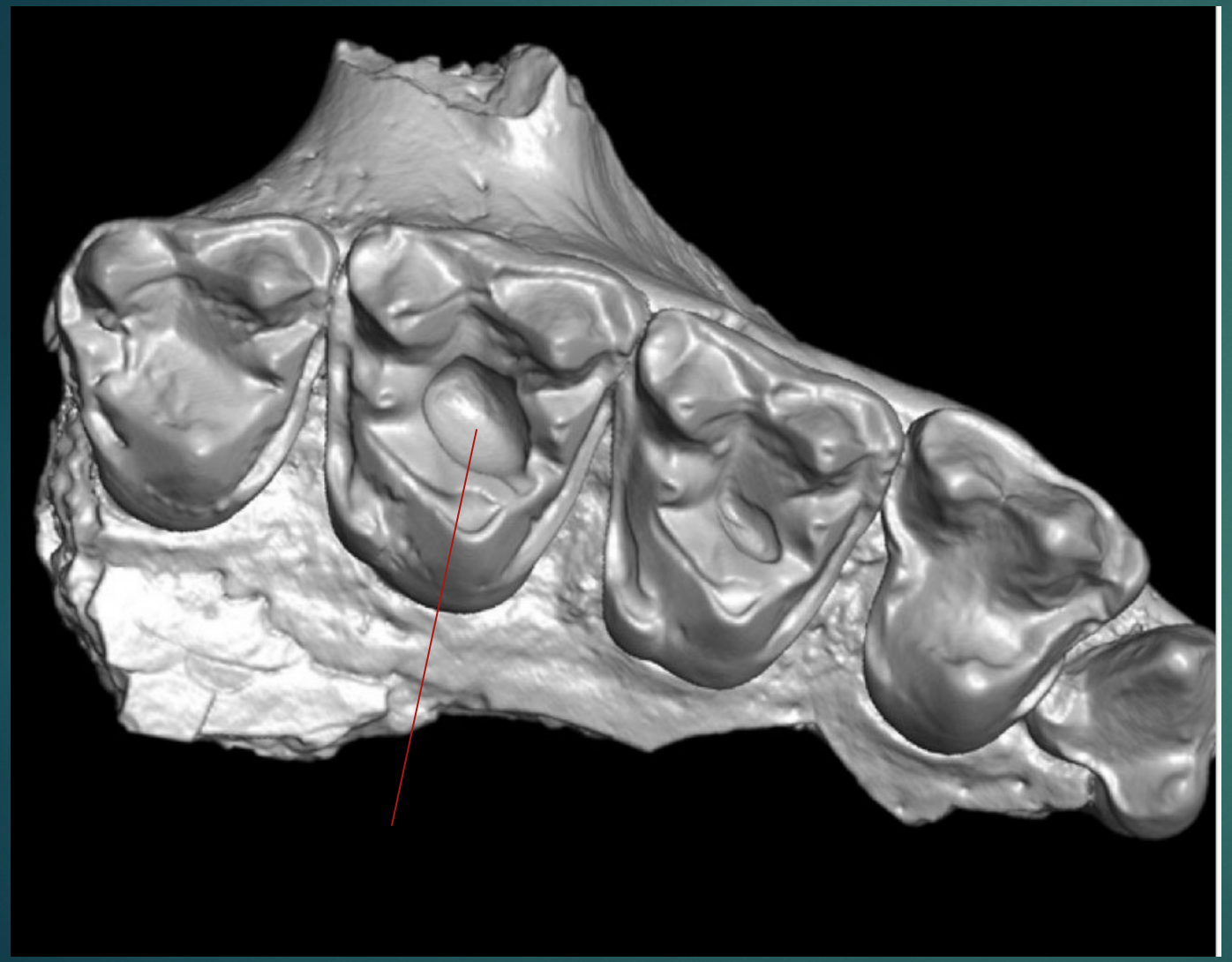
ZWH12

How we lost our tails

- For half a billion years or so, our ancestors sprouted tails. But then, roughly 25 million years ago, the tails disappeared.
- Researchers have identified more than 30 genes involved in the development of tails in various species
- A study has pinpointed the genetic mutation that may have erased our tails. When the scientists made this genetic tweak in mice, the animals didn't grow tails
- To search for those mutations, compared the DNA of six species of tail-less apes to nine species of tailed monkeys. Eventually, discovered a mutation shared by apes and humans — but missing in monkeys — in a gene called TBXT.
- The insertion of an individual *Alu* element into the genome of the hominoid ancestor. We demonstrate that this *Alu* element – inserted into an intron of the *TBXT* gene is the cause.
- The no tail mutant form of TBXT became the norm in living apes and humans; reason that we grow a coccyx instead of a tail.

Bo Xia, et al., 2021

1 - A sweet tooth gave ancient primates a mouthful of woe



- The earliest known evidence of mammals with cavities[1].
- A fossilized jaw (computer reconstruction) of *Microsyops latidens* has cavities — seen as oval depressions — in the teeth second and third from the bottom
- First appeared in the fossil record about 54 million years ago

Smoothers (*lissoirs)*

- Smoothers are a common Upper Paleolithic tool made from ungulate ribs, longitudinally split to produce two thin half ribs. These half ribs are then shaped by grinding and scraping, with a rounded end polished by use, showing wear facets and striations.
- By their similarity to ethnographic bone tools used by the Sami people (Lapps, indigenous people of northern Europe) they are interpreted as tools for smoothing dry hides. They are frequent in Aurignacian assemblages;
- Four come from two Neandertal Mousterian of Acheulian Tradition sites in France.
- The new Castel di Guido and Schöningen pieces with clearly smoothed and polished tips are very similar to the Aurignacian and Mousterian *lissoir*s and can be classed as smoothers.

2 - N invention of bone 'lissoirs‘ for leather working; 51Ka

Four views of the most complete lissoir found during excavations at the Neanderthal site of Abri Peyrony in France. Photograph: Abri Peyrony/Pech-de-l'Azé I Projects

Lissoirs, made of deer ribs, would have been used by Neanderthals to prepare hides. Eventually the tips would break off. Illustration: Abri Peyrony/Pech-de-l'Azé I Projects

The slender, curved implements called "lissoirs" were shaped from deer ribs and likely used to work animal hides to make them softer, tougher and more waterproof. Similar tools are still in use by leather workers today,

Found the first large piece of a lissoir at a cave called Pech-de-l'Azé I on a tributary of the Dordogne in southwest France, dated to 51K; also another site, 41-48 K

400 Ka Neandertal Smoothers (*lissoirs)*

Fig 14. Castel di Guido, smoother.

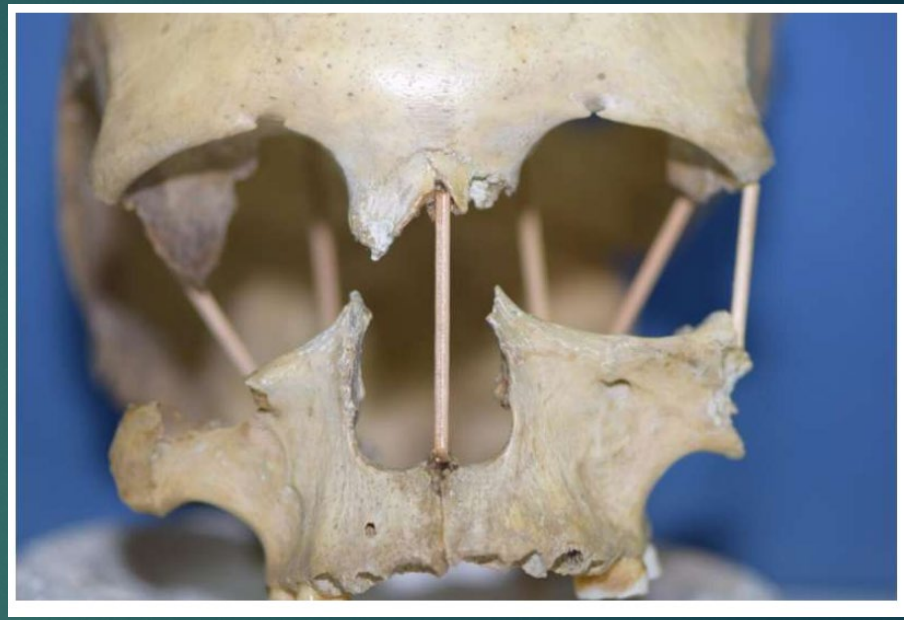
Neanderthal Hand-Carved, 400,000-Year-Old Bone Tool Used for Smoothing Leather Found in Italy

- The dig site at Castel di Guido in Italy featured numerous skeletons of straight-tusked elephants, from which many of the bone tools were produced
- Number of verified, human-made bone tools is 98. This is the highest number of flaked bone tools made by pre-modern hominins published so far. Moreover, the Castel di Guido bone assemblage is characterized by systematic production of standardized blanks (elephant diaphysis fragments) and clear diversity of tool types. Bone smoothers and intermediate pieces prove that some features of Aurignacian technology have roots that go beyond the late Mousterian, back to the Middle Pleistocene
- The view that early humans were incapable of developing sophisticated techniques diagnostic of behaviorally modern humans is unsupported. The emergence of complex bone technology at the end of the Mousterian period appears to be more a matter of technical evolution than an innovation due to higher levels of cognition.

Paola Villa, et al., 2021

3 - The entire genome from Peştera Muierii 1 sequenced

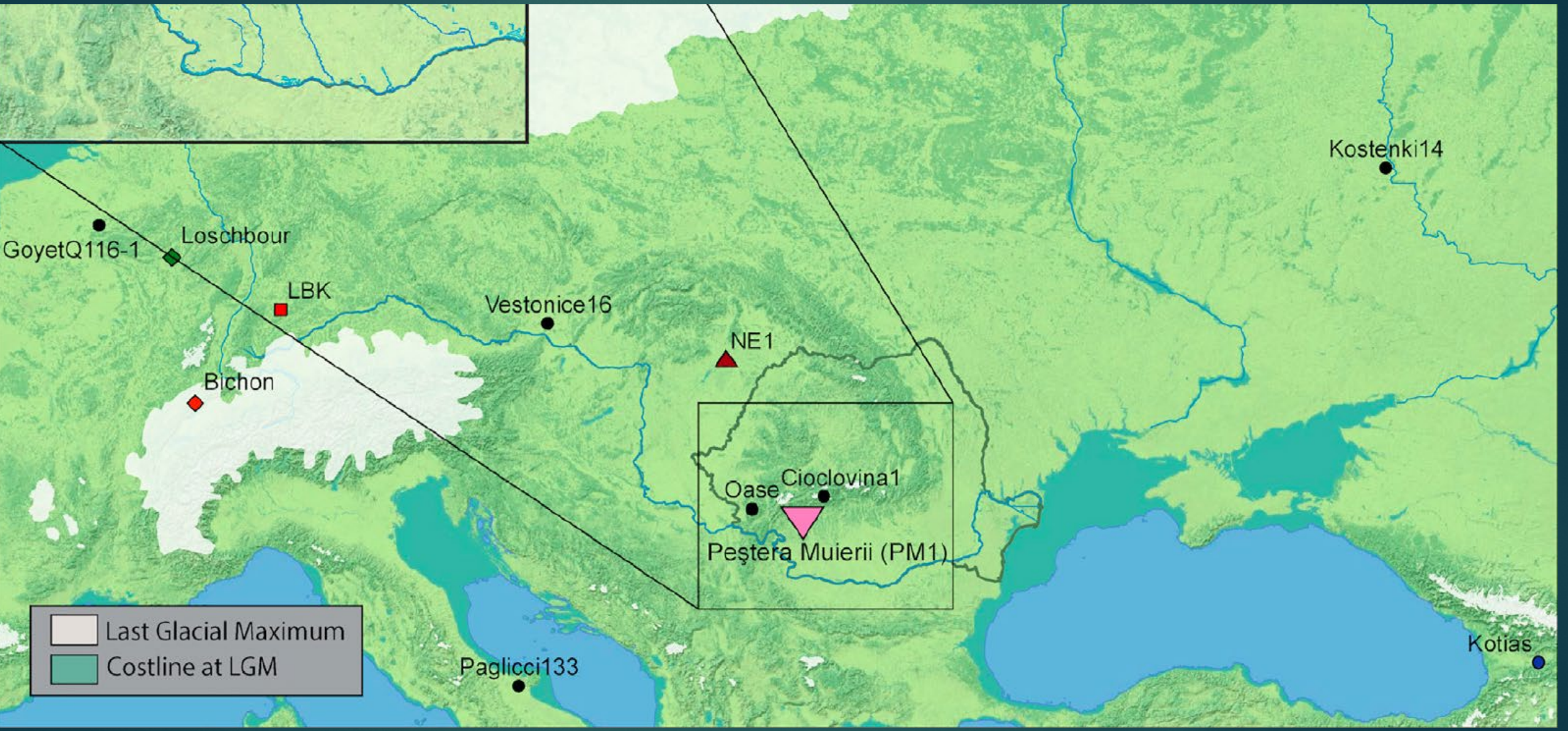
- Peştera Muierii woman, at 34 Ka, is related to Europeans, but she is not a direct ancestor
- Reduced diversity in Europe caused by Last Glaciation (24-19 Ka) , not out-of-Africa bottleneck
- New DNA extraction approach recovers up to 33 times more DNA from ancient remains



Entire genome from Peştera Muierii 1

- Svensson et al. sequenced the complete genome of a woman from ‘‘Pesxtera Muierii,’’ Romania, who lived 34,000 years ago.
- Found with Aurignacian tool. Her genome is similar to modern-day Europeans, but she is not a direct ancestor.
- *** Her genome shows high levels of diversity, revealing that much loss of diversity in non-Africans occurred after she lived rather than before her time.

10 MH genomes post 45 Ka



Genome of Peştera Muierii skull shows high diversity and low mutational load in pre-glacial Europe

- Lived in today's Romania 35,000 years ago. Her high genetic diversity shows that the out of Africa migration was not the great bottleneck in human development but rather this occurred during and after the most recent Ice Age
- not a direct ancestor of modern Europeans, but she is a predecessor of the hunter-gathers that lived in Europe until the end of the last Ice Age

- While previously assumed to have more N DNA because of morphological features, she has the same low level of Neanderthal DNA as most other individuals living in her time. Compared with the remains from some individuals who lived 5,000 years earlier, such as Peştera Oase 1, she had only half as much Neanderthal ancestry.

Emma Svensson, et al., 2021

Genome of Peştera Muierii

- Peştera Muierii 1 has high genetic diversity implies that the greatest loss of genetic diversity occurred during the last Ice Age.
- Shows that genetic variation outside of Africa was considerable until the last Ice Age, and that the Ice Age caused the decrease in diversity in humans outside of Africa.
- The researchers were also able to follow the genetic variation in Europe over the last 35,000 years and see a clear decrease in variations during the last Ice Age.

Peştera Muierii 1: dark skin, brown eyes

- Genome shows similar levels of Neanderthal admixture (3.1%) to most EUP humans but only half compared to the 40,000-year-old Pesxtera Oase 1.

- All UP European hunter-gatherers display high genetic diversity, demonstrating that the severe loss of diversity occurred during and after the Last Glacial Maximum (LGM) rather than just during the out-of-Africa migration.
- The prevalence of genetic diseases is expected to increase with low diversity; however, pathogenic variant load was relatively constant from UP to modern times, despite post-LGM hunter-gatherers having the lowest diversity ever observed among Europeans.

Peştera Muierii 1: dark skin, brown eyes

- Fewer but longer Neanderthal segments compared to post-LGM individuals and more but shorter segments than the older Ust'-Ishim individual, consistent with a single Neanderthal introgression event for these individual's ancestors.

- The 40-ky-old Romanian Pesxtera Oase 1 mandible showed a different pattern, with a Neanderthal ancestor just a few generations back and 6%–9% Neanderthal admixture.

- Hence, despite the fact that both Pesxtera Muierii 1 and Pesxtera Oase 1 have been suggested to carry archaic N morphological traits, they show distinctly different Neanderthal admixture levels and history.

- Pesxtera Muierii 1 carried the ancestral variants for known SNPs involved in pigmentation similar to other individuals from UP Eurasia and likely had relatively dark skin pigmentation and brown eyes

Impact of climate and demography

- Her genetic diversity illustrates the impact and importance of subsequent climatic and demographic events.

- The deep sequencing of the Peștera Muierii 1 woman enabled us to identify a surprising genetic diversity in pre-LGM populations.

- First, we can conclude that it is not the migration out of Africa that solely caused the reduction in diversity; rather, it appears that the low diversity was caused by the low population density outside Africa for an extended period of time coupled with population turnovers, as seen in Europe.

- Second, after the LGM, Europe was likely recolonized by relatively small hunter-gatherer groups from one or very few glacial refugia, and only later large-scale migrations associated with farming practices led to an increase of genetic diversity approaching the levels before the LGM

Peştera Muierii 1: high immunity capacity

- Pre-LGM hunter-gatherers to be much more diverse than their post-LGM counterparts. the loss of genetic diversity during and after the LGM was likely caused by the harsh climate conditions during those times, coupled with recolonizations and population turnovers initiated from small groups.

- Overall, these data suggest that Peștera Muierii 1 individual was a high responder in terms of cytokine production capacity, although less than 4% of modern-day Europeans display this combination of high-cytokine polymorphisms.

- Considering the protective effects of high immune responses in the context of high infection burden, it is likely that this genetic makeup represents an adaptive state conferring protection against pathogenic microbes.

Peştera Muierii 1

- A novel paradigm, in which early AMH populations after migration out of Africa were much more diverse than previously believed, and the bottlenecks associated with loss of diversity were caused by glacial climatic periods in northern latitudes.

- In line with the high diversity observed in UP genomes, the burden of damaging variants in these individuals was largely the same as in modern-day individuals.

- This is clearly a different pattern from the high burden of deleterious variants found in small isolated populations.

Peştera Muierii 1: Limits of study

- However, these ancient high-coverage genomes represent a very small sample size, and it is unclear whether the results can be extrapolated to the entire populations living during these time periods.

- Finally, using novel methodologies employed in medical genomics, we mined the genomes of ancient individuals for potential pathogenic variants. We have identified several interesting rare variants with medical consequences in the EUP genomes.

- One variant AIPL1 indicated blindness. Note that care for individuals with congenital disorders or injuries is present in the archaeological record since the Middle Pleistocene, and if the variant was verified as causing blindness, we could add another example of early human care for an individual with a severe disorder.

4 - Shifting Climate & early MH migrations

- Classic hypothesis = modern humans left Africa in one enormous exodus around 65,000 years ago, based on genetic and archeological data.

- But a new climate model suggests that modern humans had several windows of opportunity to leave the continent far earlier. There were multiple instances of our species' dispersal beyond Africa prior to the main one.

- Reconstruction of the climate of northeastern Africa over the last 300,000 years. The scientists identified when there would have been enough rainfall to allow a group of hunter-gatherers to survive the journey to the Arabian Peninsula.

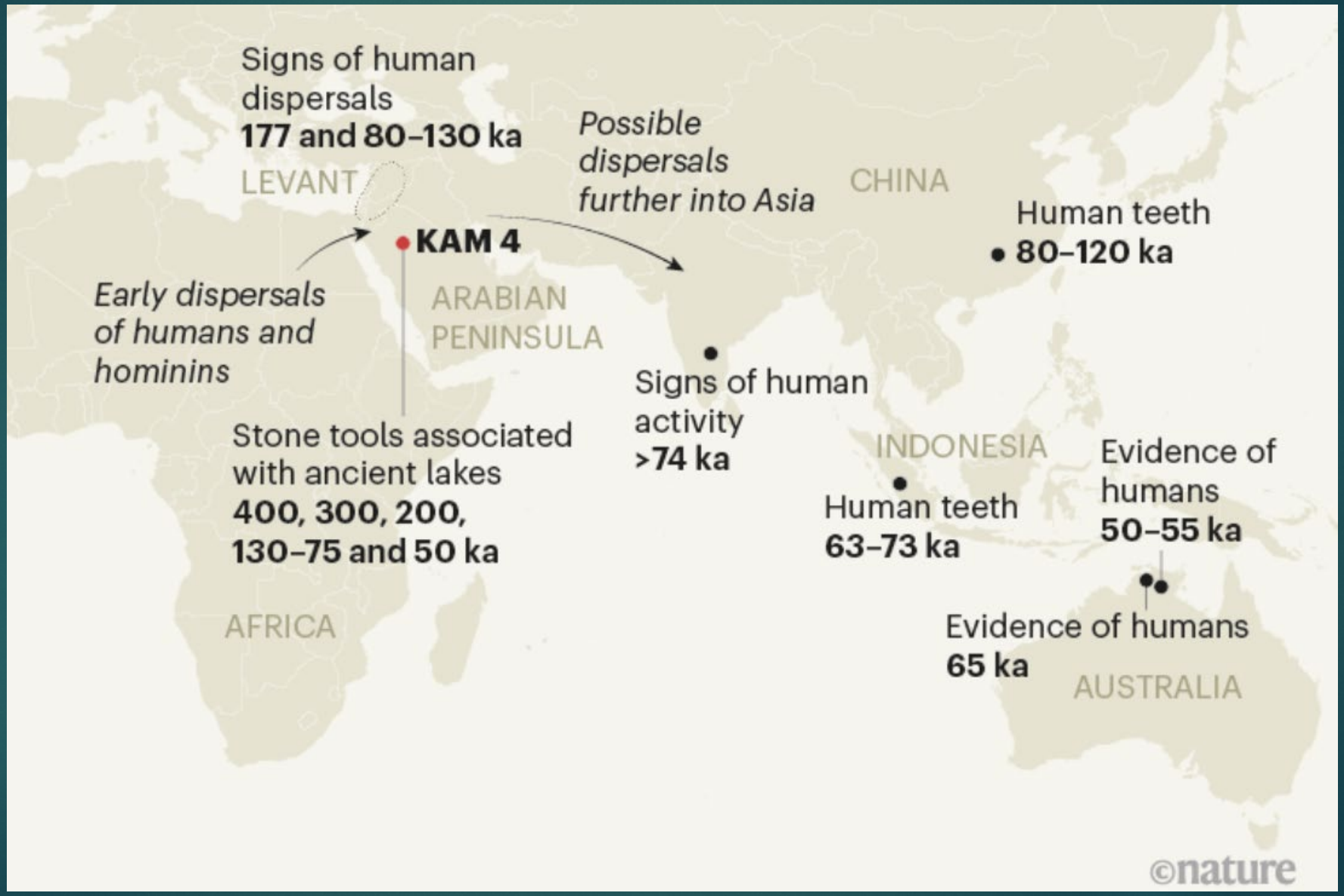
Andrea Manica et al., 2021

Multiple early, unsuccessful migrations out of Africa

- It bolsters the theory that Homo sapiens had multiple migrations out of Africa.

- Some of *Homo sapiens*' false starts:
  - part of a middle finger from 85,000 years ago, found in Arabia;
  - a human jawbone from at least 177,000 years ago, found in Israel;
  - Chinese teeth from 80-120 Ka; a skull from 210,000 years ago, found in Greece.

Early MH migrations



Shifting Climate & human migrations

- Found that modern human populations are generally not recorded in areas where precipitation falls below 3.5 inches of rain per year.

- Modeled travel through two possible routes into Eurasia: the Sinai Peninsula up north and, further south, the Strait of Bab-el-Mandeb , which separates the Horn of Africa from contemporary Yemen.

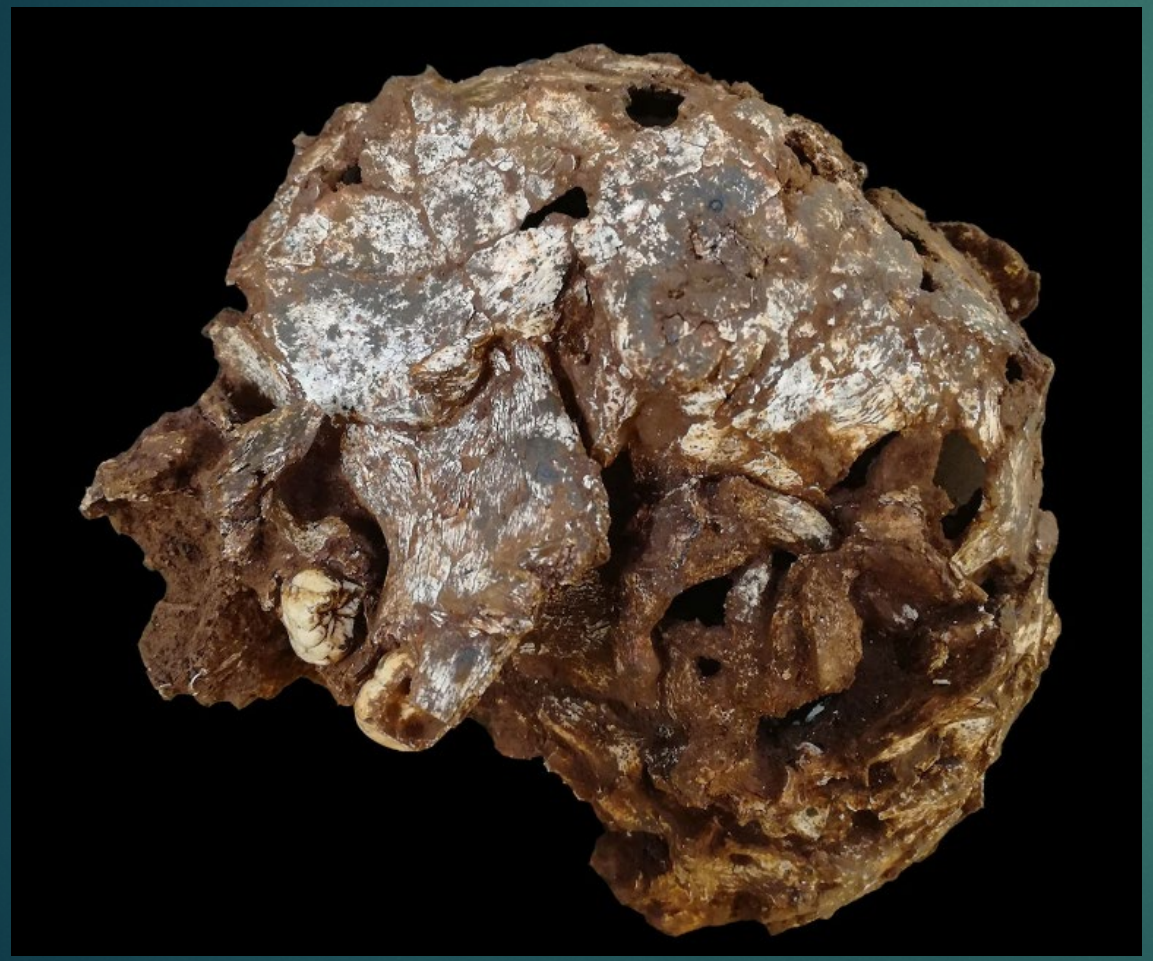
- Their model revealed a handful of historical windows during which there was enough rainfall and relatively low sea levels to sustain a human migration out of Africa. The Sinai land bridge was crossable several times, as early as 246,000 years ago, and the southern strait had even more favorable windows, including the period 65,000 years ago.

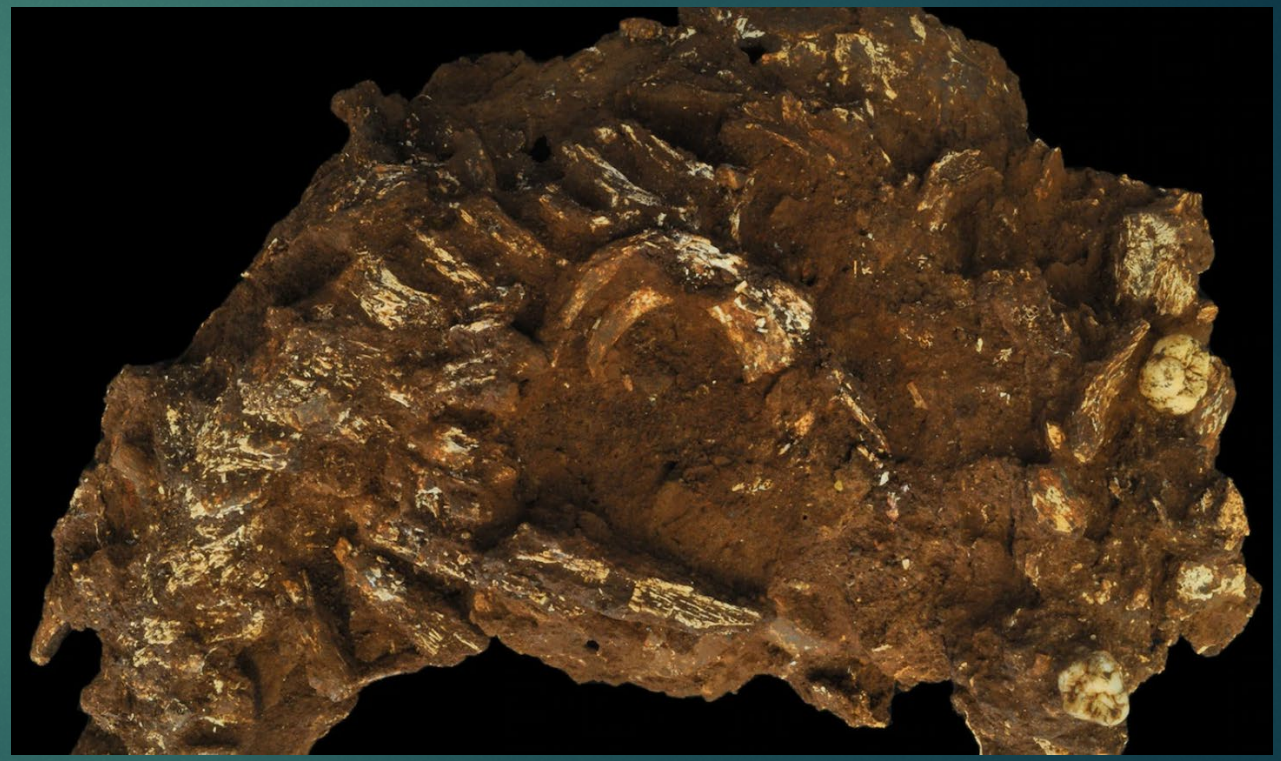
Shifting Climate & human migrations

- So the question still stands: If some Homo sapiens were able to colonize Eurasia far earlier, why were they not successful?

- If early humans could have moved out of Africa much earlier, they would have faced stiff competition from other early human species;
  - the north was a Neanderthal stronghold, and
  - much of East Asia was likely populated by the Denisovans.
  - The models also suggest that dry periods often followed the favorable windows, which could have isolated any populations undertaking an exodus.
  - As always, there were multiple critiques of the model.

5 - Oldest known African burial at 78 Ka: 2 yo child





Oldest African burial

- Wrapped in a shroud, head nestled on a pillow, the remains of a MH child unearthed in in Panga ya Saidi, a massive cave system sprawled along an escarpment paralleling the Kenyan coast.
- Fossil has been nicknamed “Mtoto”—Swahili for "child”

6 - Wonderwerk Cave in South Africa's Kalahari Desert

Magnetostratigraphy and cosmogenic dating of Wonderwerk Cave

- Confirmed the oldest cave dwelling at Wonderwerk Cave in South Africa's Kalahari Desert, dating back nearly two million years.
- Our human ancestors were making simple Oldowan stone tools inside the Wonderwerk Cave 1.8 million years ago.
- Wonderwerk is unique among ancient Oldowan sites, a tool-type first found 2.6 million years ago in East Africa, precisely because it is a cave and not an open-air occurrence

Shaar, et al., 2021

Wonderwerk Cave

- Able to identify the shift from Oldowan tools — mainly sharp flakes and chopping tools — to early handaxes over one million years ago.
- They were also able to date the deliberate use of fire by our prehistoric ancestors to one million years ago, in a layer deep inside Wonderwerk Cave.
- Cave contained a full array of fire remnants: burnt bone, sediment and tools as well as the presence of ash.

7 - Parasitic Wasps - Warning: Nature’s horror video

Genes Shared With Viruses Protect Caterpillars from Parasitic Wasps

- Not all caterpillars infected with parasitoid wasps will meet this same grisly end.
- A newly identified gene family named "parasitoid killing factor" (PKF) that kill parasitoid larvae
- PKFs are found in both insect-infecting viruses and their caterpillar hosts
- *PKF* genes were found in several large double-stranded DNA viruses that infect lepidopteran insects (moths and butterflies), but also within the genomes of several Lepidoptera species themselves, suggesting that the genes have been swapped between viruses and infected hosts over the course of evolutionary history.

Genes Shared With Viruses Protect Caterpillars from Parasitic Wasps

- Studies of host-pathogen interactions often reveal evidence of evolutionary arms races, as organisms hone their strategies for virulence and defense.

- Viruses usually only encode genes that are absolutely necessary for viral replication and that are involved in adaptation to the host. In this case, however, the viral *PKF* genes adapted to the virus's potential parasitoid competitors.

- When the caterpillars were infected with the virus, they were protected from certain parasitoid wasp species.

Parasitic wasp viruses

- In the 1970s, entomologist Harry Kaya noticed that virally-infected caterpillars were protected from parasitoid wasps, but didn't understand the mechanism of protection.

- PKFs induce apoptosis (cell suicide) in susceptible parasitoids.

- Why ascoviruses, which carry *PKF*s, are transmitted to Lepidopteran hosts by the very parasitoid wasps they can kill. "Why would ascovirus kill its vector?"

8 - Horizontal gene transfer between a plant and an animal

Horizontal gene transfer between a plant and an animal

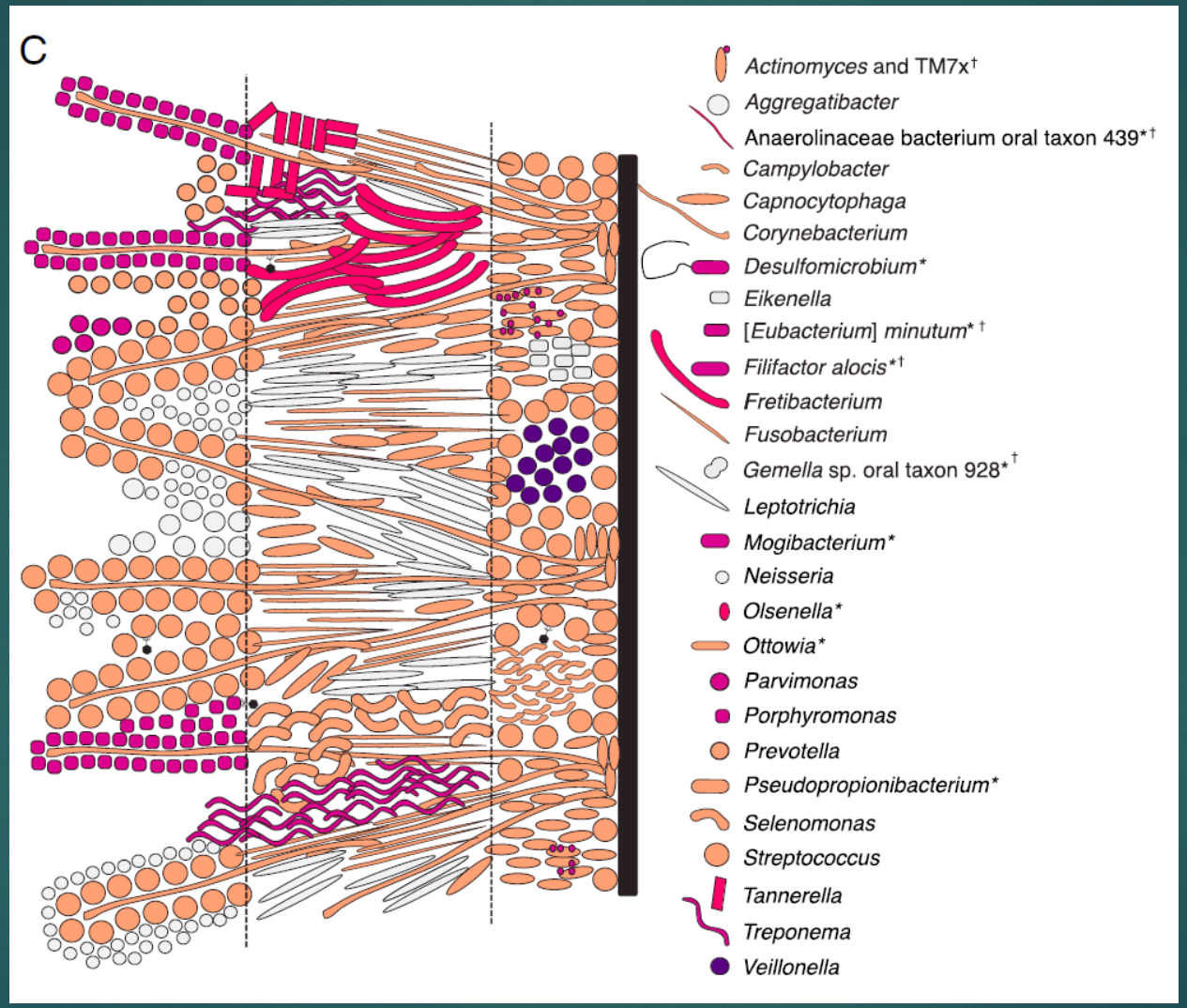
- In the first known example of horizontal gene transfer between a plant and an animal, a common pest known as the whitefly (*Bemisia tabaci*) acquired a gene from one of the various plants it feeds on.
- The gene, *BtPMaT1*, originally protects plants from phenolic glycosides, toxins that they produce to defend themselves against such pests; but now the whiteflies with the gene can feast on the plant.
- Horizontal gene transfer is the nonsexual swapping of genes between species.
- There are a number of ways that horizontal gene transfer can occur. Genetic material can be transferred via phages or other viruses, and some organisms may take up free DNA from the environment.

9 - Environmental DNA Can Be Pulled from the Air

- Prior study at Denisova Cave proved you can collect DNA from dirt as well as from bones.
- eDNAir: proof of concept that animal DNA can be collected from air sampling
- eDNA can be collected from air and used to identify mammals (naked mole rats).
- Proof of concept study successfully demonstrated that eDNA sampled from air contained mixed templates which reflect the species known to be present within a confined space and that this material can be accessed using existing sampling methods

Elizabeth Clare, et al., 2021

10 - Seven-year study: Core taxa of the human oral microbiome



James A. Fellows Yates, et al., 2021

Neandertals & Starch: The evolution and changing ecology of the African hominid oral microbiome, J. Fellows Yates, et al., 2021

- Analysis 124 dental biofilm genomes from humans, Neanderthals and Late Pleistocene to present-day MHs, chimps, gorillas, & New World howler monkeys

- Found that a core microbiome of primarily biofilm structural taxa has been maintained throughout African hominid evolution, and in howler monkeys, suggesting that they have been important oral members since before the catarrhine (old world monkeys)–platyrrhine (new world) split ca. 40 Mya.

- Reconstructing oral metagenomes from up to 100 Ka, show that the microbial profiles of both Neanderthals and modern humans are highly similar, sharing functional adaptations in nutrient metabolism.

Microbial archeology: Oral biome and starch digestion

- Reconstructed the 100,000-year-old oral microbiome of a Neanderthal from Pešturina Cave in Serbia

- Identified a core group of 10 bacterial species within the African hominid primate oral microbiome that are also shared with howler monkeys; played a key role in oral biofilms for over 40 million years.

- Identified 27 genus-level members of the *Homo* core oral microbiome, such as *Streptococcus* and the pathogens *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*.

- Found major taxonomic and functional differences between the oral microbiomes of *Homo* and chimpanzees but a high degree of similarity between Neanderthals and modern humans, including a *Homo*-specific acquisition of starch digestion capability in oral *Streptococcus* bacteria.

Homo-Specific Shifts in Oral Biofilm Are Linked to Dietary Starch Availability

- The biggest surprise from the study was the presence of particular strains of oral bacteria that are specially adapted to break down starch.
- These members of the genus *Streptococcus* have a unique ability to capture starch-digesting enzymes from human saliva, which they then use to feed themselves.
- This bacteria is only active when starch is part of the regular diet.
- Both the Neanderthals and ancient humans had these starch-adapted strains in their dental plaque while most of the primates, who eat exclusively on non-starchy plant parts, like fruits, stems, and leaves, had almost no streptococci that could break down starch.

Starch digestion is ancient

- Dental plaque of 124 individuals. The one Neanderthal microbiome, dated to 100 Ka, is the oldest oral microbiome genome reconstructed to date.
- The microbiome of bacteria in the mouths of preagricultural humans and Neanderthals strongly resembled each other.
- Humans and Neanderthals harbored an unusual group of *Streptococcus* bacteria in their mouths. These microbes had a special ability to bind to an abundant enzyme in human saliva called amylase, which frees sugars from starchy foods.
- The presence of the strep bacteria that consume sugar on the teeth of Neanderthals and ancient modern humans, but not chimps, shows they were eating more starchy foods

Streptococci and Starch

- Streptococci: amylase-binding capability by oral streptococci.
- Amylase binding is an apparent Homo-specific trait, suggestive of microbial coadaptation to starch-rich diets early in human evolution.
- These Streptococcus groups and abpB are a general feature of Homo, suggesting that
  - starch-rich foods, possibly modified by cooking, first became important early in Homo evolution prior to the split between Neanderthal and modern human lineages more than 600 ka,
  - Implication for what caused larger Homo-associated encephalization (starch rather than meat)

Oral biome: starch by 600 Ka in MHs and Ns

- Found that ancient humans living in Ice Age Europe shared some bacterial strains with Neanderthals.
- Found that Neanderthal-like bacterial strains were no longer found in humans after 14,000 years ago, a period during which there was substantial population turnover in Europe at the end of the last Ice Age.
- A subgroup of *Streptococcus* bacteria present in both modern humans and Neanderthals appears to have specially adapted to consume starch early in *Homo* evolution.
- This suggests that starchy foods became important in the human diet prior to the split between Neanderthal and modern human lineages more than 600,000 years ago.

Starch

- Oral microbiomes of Neanderthals and today's humans were almost indistinguishable.
- The findings also push back on the idea that Neanderthals were top carnivores, given that the "brain requires glucose as a nutrient source and meat alone is not a sufficient source."
- ** Reinforces view about Neanderthals that their diets were the same as *H. sapiens:* starch-rich and cooked.
- For human ancestors to efficiently grow a bigger brain, they needed energy dense foods containing glucose. Meat is not a good source of glucose.
- The starchy plants gathered by many living hunter-gatherers are an excellent source of glucose,

Neanderthals carb loaded, helping grow their big brains

- Shows that Ns ate so many roots, nuts, or other starchy foods that they dramatically altered the type of bacteria in their mouths.

- MHs & Ns had adapted to eating lots of starch by at least 600,000 years ago—about the same time as they needed more sugars to fuel a big expansion of their brains.

- And they had already adapted to eating more starchy plants long before the invention of agriculture 10,000 years ago.

Starch: Common Ancestor = gatherer-hunter

- Suggests they inherited these microbes from their common ancestor, who lived more than 600,000 years ago.
- Although earlier studies found evidence that Neanderthals ate grasses and tubers and cooked barley, the new study indicates they ate so much starch that it dramatically altered the composition of their oral microbiomes.
- Because the amylase enzyme is much more efficient at digesting cooked rather than raw starch, the finding also suggests cooking, too, was common by 600,000 years ago.
- Reveals how much Ns depended on plants. Like modern hunter-gatherers, it's often the gathering that ends up providing a substantial portion of the calories.

11 - African Ghost lineage

- An ancient, humanlike population still undiscovered in fossils left a genetic legacy in present-day West Africans
- These extinct relatives of *Homo sapiens* passed genes to African ancestors of modern Yoruba and Mende people starting around 124,000 years ago or later.
- Surviving DNA of those ancient hominid is different enough from that of Neandertals and Denisovans to suggest an entirely different hominin was the source.
- Yoruba and Mende groups' genomes contain from 2 to 19 percent of genetic material from this mysterious "ghost population.. Some of this DNA influence survival-enhancing functions, including tumor suppression and hormone regulation. Those genes likely spread rapidly among modern West Africans,
- This ancient ghost population is present in genomes of Han Chinese in Beijing and Utah residents with northern and western European ancestry

A. Durvasula & Sankararaman, 2020

Ghost genes

- *H. sapiens* groups interbred with European Neandertals before taking Neandertal DNA back to Africa starting around 20,000 years ago.

- That study found that Neandertal DNA accounts for, on average, about 0.5 percent of individual Africans' genomes, compared to 1-2% N DNA in non-Africans.

- Researchers lack any fossils from the ancient ghost population from which to extract examples of its DNA,

- Durvasula and Sankararaman compared genomes of 405 West Africans — more than half either Yoruba or Mende — with ancient DNA from a roughly 44,000-year-old Eastern European Neandertal fossil and a Denisovan fossil from Siberia dating to at least around 51,000 years ago.

Ghost lineages

- Found DNA variants that were inherited from a line of ancient hominins other than Neandertals and Denisovans.
- That ghost population diverged from direct ancestors of present-day Yoruba and Mende more than 1 million years ago,
- A 2012 investigation suggested that 15 modern African hunter-gatherers had inherited about 2 percent of their DNA from an unknown hominid species that split from ancestors of people today around 1.1 million years ago.
- It's unclear if this is same DNA as in current study.

12 - Arabia was repeatedly inhabited

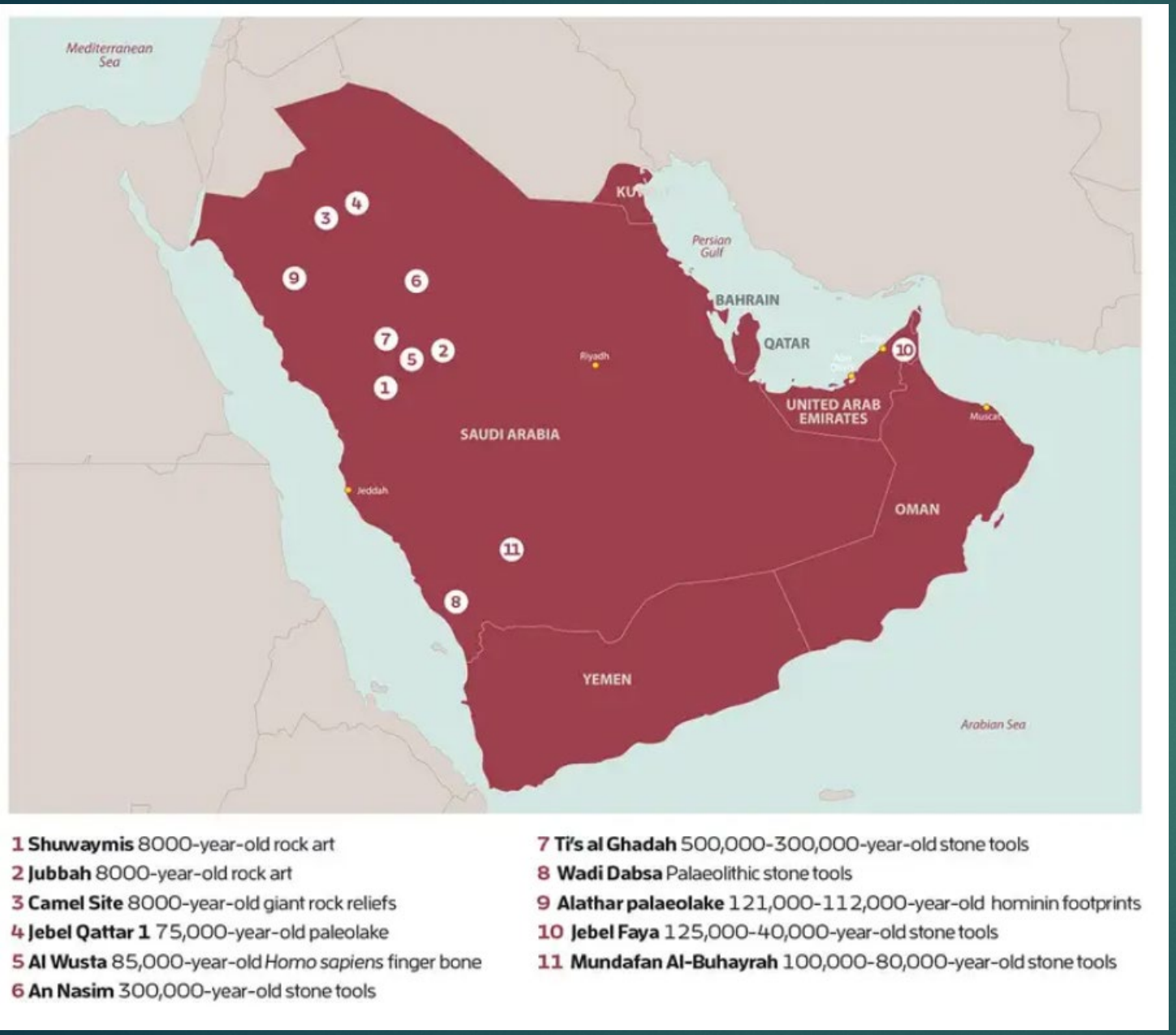
- Arabia lends weight to the idea that there were multiple migrations, every time the climate and ecosystems became favorable.

- There are about 10,000 paleolakes of Arabia. Have explored a couple of hundred. On 70 per cent of those, fossils or archaeology have been discovered.. At Mundafan Al-Buhayrah, a flat region that was once a lake, stone tools discovered that date from 100-80 Ka.

- Occupations tended to follow climatic fluctuations: hominins came in when the climate was wet, and either left or died out when it dried. This cyclicity is key to everything.

- Nevertheless, conditions were wet enough for hippopotamuses to have inhabited the peninsula. Hippos need perennial water, meters deep

Arabian sites with stone tools



- Evidence unearthed in the past decade reveals that hominins were living in Arabia up to 500,000 years ago, and spent long periods there at times when the climate was wetter and the environment lusher

Arabia: stone tools, but only 1 finger bone fossil

- Geography of Arabia had powerful effects on the communities living there. Those residing in northern Arabia probably still had contact with populations in Africa and elsewhere. Shared stone tool traditions.

- In contrast, the inhabitants of southern Arabia tended to develop distinctive tools, suggesting they were isolated.

- The 85,000-year-old Al Wusta finger bone is still the only known hominin bone found in Arabia

- Petraglia and his colleagues claimed that a set of footprints made between 121,000 and 112,000 years ago at Alathar paleolake in Saudi Arabia belonged to modern humans.

Arabia as part of greater Africa

- The stone tool record goes back much further. Stone tools found at An Nasim in Saudi Arabia are 300,000 years old.
- In 2018, discoveries at Ti's al Ghadah. There, a dried-up lake was once surrounded by fertile grasslands, inhabited by elephants, Asiatic wild asses and water birds. Evidence of stone tools and cutmarked bones. The animal remains were dated to between 300,000 and 500,000 years ago.
- Scerri thinks these early hominins were Neandertals, given similar stone tools in Israel.
- The discoveries in Arabia also show that modern humans didn't just stick to the coasts when migrating out of Africa. The lake finds show that they also crossed the center of the peninsula.

13 - 1000 Mustatils (rectangle sandstone walls) across 200,000 square kilometers –ranged from 20 meters to more than 600 meters in length, but their walls stood only 1.2 meters high.

ere are 1000 ancient monuments across one region of Saudi Arabia

Huge stone monuments in which low walls surround a central courtyard: Arabian cult may have built 1000 monuments; 5300 and 5000 BCE, when the area was a grassland

14 - What Indigenous Languages Reveal About Bear Genetics

- Bears and people have shared food and space for millennia.
- New research on Indigenous language groups in British Columbia shows a relationship between geographical patterns in genetic variation in grizzly bears and words used to identify these bear populations.
- A remarkable geographical alignment between distinct grizzly bear genetic groups and three Indigenous language families—Tsimshian, Northern Wakashan, and Salishan Nuxalk—in coastal territories, suggesting that the rich landscape has similarly shaped both bears and humans.
- Analyzed bear hair samples collected over a 23,500-square-kilometer area of the British Columbia central coast.

15 - Fossilized brain: This Brain Imprint Remained Intact in a 310 Million-Year-Old Horseshoe Crab Fossil

- 310 Ma extinct penny-size horseshoe crab was
- Siderite, an iron carbonate mineral, accumulated rapidly around the dead creature's body, forming a mold.
- With time, as the soft tissue decayed, a white-colored clay mineral called kaolinite filled the void left by the brain
- The internal brain architecture has

Isthmus of Panama and origin of Homo sapiens

16 - Importance of Isthmus of Panama: geography & evolution

- Twenty million years ago ocean covered the area where Panama is today. The waters of the Atlantic and Pacific Oceans flowed freely thru it. If the Isthmus of Panama had not formed, the world would be very different today.

- By shutting down the flow of water between the two oceans, the land bridge re-routed currents in both the Atlantic and Pacific Oceans. Atlantic currents were forced northward, and eventually settled into a new current pattern that we call the Gulf Stream today. With warm Caribbean waters flowing toward the northeast Atlantic, the climate of northwestern Europe grew warmer.

- Panama was a North American peninsula, possibly as early as 19 million years ago, because fossils that are closely related to North American land mammals, such as rhinos, horses, peccaries and dogs have been found in the Panama Canal during ongoing maintenance.

Formation of the Isthmus of Panama: importance of geology to evolution

- The formation of the Isthmus of Panama – tectonic plate movements led to a land bridge closure that created a strip of land that separates the Caribbean Sea from the Pacific Ocean and connects North and South America-- is considered one of the most important geologic, oceanographic, and biogeographic events ever. Occurred ~3 M years ago.
- This geological event involved the evolution of new species, genome evolution, alteration of global ocean circulation, the origin of modern fauna and flora in the Americas, the establishment of Caribbean reefs and Atlantic fisheries, and the origin of H sapiens.
- Marine taxa suddenly had their routes of migration blocked and gene flow between populations could no longer occur; enhanced biodiversity.
- Molecular clock of these new species point to closure at 3 Ma. There was interoceanic gene flow until approximately 3 Ma.

Isthmus

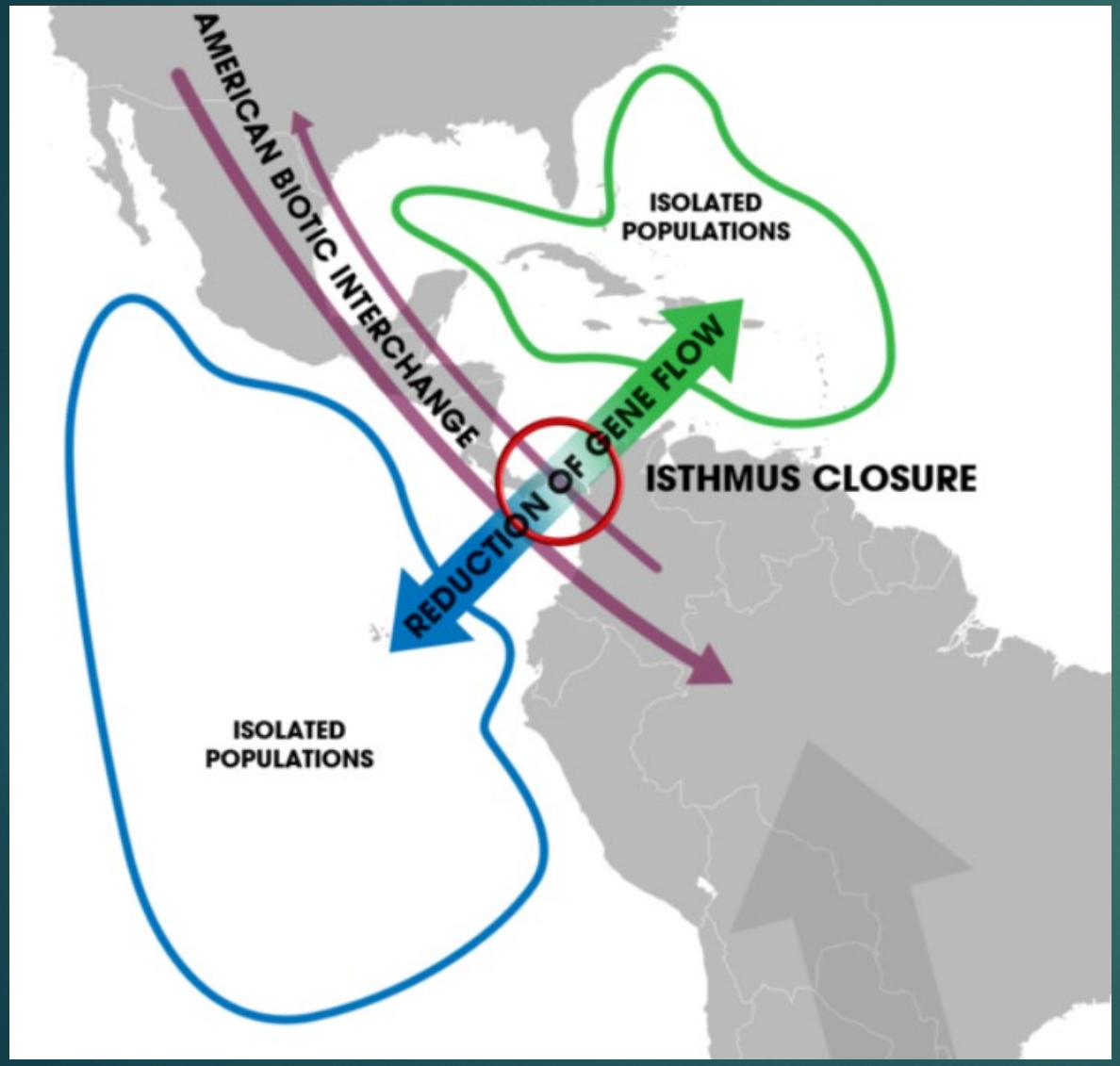
- The Central American Peninsula collided slowly with the South American continent through tectonic plate movement (the Pacific Cocos Plate slid under the Caribbean Plate) over millions of years.

- Isthmus of Panama was first a peninsula of southern Central America before the underlying tectonic plates merged it with South America 2.8 million years ago.

Isthmus of Panama

- This was first suggested in 1910 by North American paleontologist Henry Fairfield Osborn, based on the fossil record of mammals in Central America.
- This conclusion provided a foundation for Alfred Wegener when he proposed the theory of continental drift in 1912.
- Creation of this closed land mass and the subsequent warm, wet weather over northern Europe resulted in the formation of a large Arctic ice cap and contributed to the current ice age.
- That warm currents can lead to glacier formation may seem counterintuitive, but heated air flowing over the warm Gulf Stream can hold more moisture. The result is increased precipitation that contributes to more snow pack.

Species segregation and interchange



This event is known in paleontology as the Great American Interchange.

In North America, the opossum, armadillo, and porcupine all trace back to ancestors that came across the land bridge from South America.

Likewise, bears, cats, dogs, horses, llamas, and raccoons all made the trek south across the isthmus.

Isthmus also ended gene flow

Creation of Isthmus of Panama altered the world

- Land bridge joined North and South America, permitting interchange of previously isolated terrestrial organisms.
- Without the isthmus, all the animals of South America would be unique marsupials – no invasion of Northern animals
- Today corals reefs are abundant in the Caribbean but without large supplies of commercial fish, whereas the Pacific ocean has few small coral reefs and large important commercial fisheries. Would have become one whole.
- Humans from Asia might not have reached South America via the Bering Land Bridge from the north so different kinds of humans might have arrived, say, from Polynesia.
- The Ice Age would have been different, and Europe's ports might freeze every winter like the Saint Laurence seaway does. By carrying warm water northeast across the Atlantic, it makes Western Europe and especially Northern Europe warmer and milder than it otherwise would be.

Isthmus: weather and the Gulf Stream

- Following the development of the Isthmus of Panama, the Gulf Stream was diverted. The closure of the Isthmus of Panama strengthened the warm Gulf Stream Current. This current took warm waters high into northern latitudes providing moisture to the atmosphere so that snow formed to build the glaciers of the ice age.

- At the same time a strong current also flowed south along the eastern side of the Atlantic Ocean and affected the climate of north Africa causing it to become drier so that savannahs and open grasslands developed which provided the habitats that previously arboreal (tree living) primates then colonized. In the process one group became

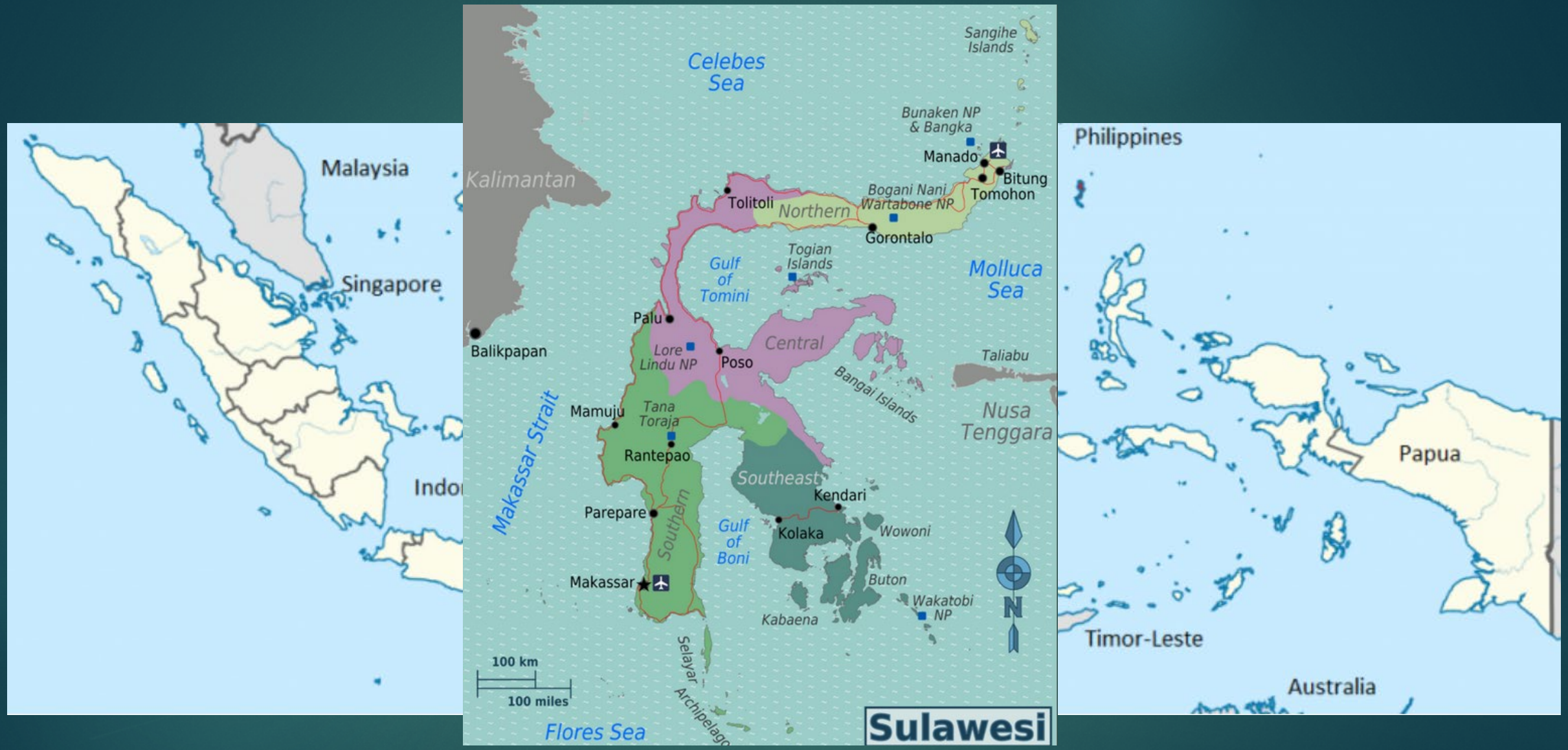
- Changes Earth's climate and weather patterns: altered ocean currents, even changing direction for some of them and eventually affected water temperatures. By altering the flow of water between the two oceans, the Isthmus of Panama contributed to the formation of the Gulf Stream, which covers much of the Atlantic and its warm waters affect weather and precipitation.
- So you could say the Isthmus directly and indirectly influenced ocean patterns, weather patterns and atmospheric conditions which in turn shaped landscapes over a wide area of the world.

17 - First ancient human DNA found from key Asian migration route

- 7,000-year-old skeleton of a teenage hunter-gatherer from Sulawesi in Indonesia could be the first remains found from a mysterious, ancient culture known as the Toaleans, whose existence is known from scant archaeological evidence, such as distinctively notched stone tools. Found alongside Toalean-type tools. Named the woman Bessé´, Bugis word for 'young woman'.

- Largely complete fossil of a roughly 18-year-old Stone Age woman was found in 2015 buried in a fetal position inside the Leang Panninge limestone cave on Sulawesi. The island is part of a region known as Wallacea, which forms the central islands of the Indonesian archipelago.

- DNA extracted from the skull suggests the woman shared ancestry with New Guineans and Aboriginal Australians, Denisovans, as well with an extinct species of ancient human. First time anyone's found ancient human DNA in


Malaysia
Singapore
Indo
Celebes Sea
Sangihe Islands
Bunaken NP & Bangka
Manado
Bitung
Tomohon
Kalimantan
Tolitoli
Northern
Bogani Nani Wartabone NP
Gorontalo
Togian Islands
Gulf of Tomini
Molluca Sea
Palu
Balikpapan
Lore Lindu NP
Poso
Central
Taliabu
Bangai Islands
Nusa Tenggara
Mamuju
Tana Toraja
Makassar Strait
Rantepao
Southeast
Kendari
Parepare
Southern
Gulf of Boni
Kolaka
Wowoni
Buton
Makassar
Wakatobi NP
Kabaena
Selayar Archipelago
100 km
100 miles
Flores Sea
Sulawesi
Philippines
Papua
Timor-Leste
Australia


WONDERFULL CAVE
LIANG PANNING

7 K fossil from Panning Sulawesi in Indonesia

Panning Sulawesi

- The woman's genome suggests a similar level of relatedness to present-day Aboriginal Australians and New Guineans, implying that her lineage split off before either of those groups diverged from one another around 37 Ka

- Question of whether this individual might be linked to 44,000-year-old cave paintings discovered in 2019 in Sulawesi

18 - Humans were drinking milk before they could digest it

- Our history with milk presents a chicken-or-egg conundrum: Humans couldn't digest the beverage before they evolved mutations that helped them do so, yet they had to already be consuming milk to change their DNA.
- "There's always been the question of which came first," says University of Pennsylvania geneticist Sarah Tishkoff. "The cultural practice or the mutation."
- Study: oldest evidence yet for dairy drinking: People in modern Kenya and Sudan were ingesting milk products beginning at least 6000 years ago. That's before humans evolved the "milk gene," suggesting we were drinking the liquid before we had the genetic tools to properly digest it.

Ability to drink and digest milk as adult

- All humans can digest milk in infancy. But the ability to do so as an adult developed fairly recently, likely in the past 6000 years.
- A handful of mutations allows adults to produce the enzyme lactase, which can break down the milk sugar lactose.
- Genes that enable lactase persistence (can digest as adult) are widespread in modern Africa, which has four known lactase persistence mutations. (European populations rely on just one.)
- It's one of the strongest signals of natural selection ever observe

Milk

- Africa, where societies have herded domesticated cows, sheep, and goats for at least 8000 years.
- The scientists examined dental calculus of eight skeletons excavated in Sudan and Kenya, which were between 2000 and 6000 years old.
- These people were consuming some sort of dairy product at least 6000 years ago. This is the earliest known direct evidence for dairy consumption in Africa, and perhaps the world.
- Dairying in Africa goes back just as far as it does in Europe—perhaps longer.

Milk

- Ancient Africans don’t appear to have evolved any milk digesting genes, per 2020 DNA study. They were drinking milk before they had lactase persistence.
- The mutations may have eventually arisen because they helped people get more nutrients from their milk,

- The selection pressure for lactase persistence might also have been environmental: Milking is a sustainable way to manage herds under tough conditions, allowing herders to get nutrition from their animals without killing them. During droughts, for example, lactase persistent herders could make better use of cattle and goats as four-legged water filters and storage containers. If you have cows, you have a source of liquid and proteins and nutrition

19 - Only 1.5 percent to 7 percent of the human genome contains uniquely human DNA

- Study examined every spot of DNA in the genomes of 279 people: For each basepair, determined whether it was MH, N, D, etc.
- Humans-only DNA tends to contain genes involved in brain development and function, hinting that brain evolution was important in making humans human. But don't yet know exactly what the genes do
- Sub-Saharan Africans: inherited 0.096 to 0.46 % N DNA
- Non-Africans: 0.73 percent to 1.3 percent N DNA

Unique 1.5-7 percent

- ~ 50 % of the MH genome contains N or D DNA
- Uniquely human DNA = 1.5 to 7 % of the genome.
- Study concluded that the uniquely human DNA distinctive arose in two bursts at 600 Ka and 200 Ka. 600 Ka = MH-N divergence time; 200 Ka = origin of MHs

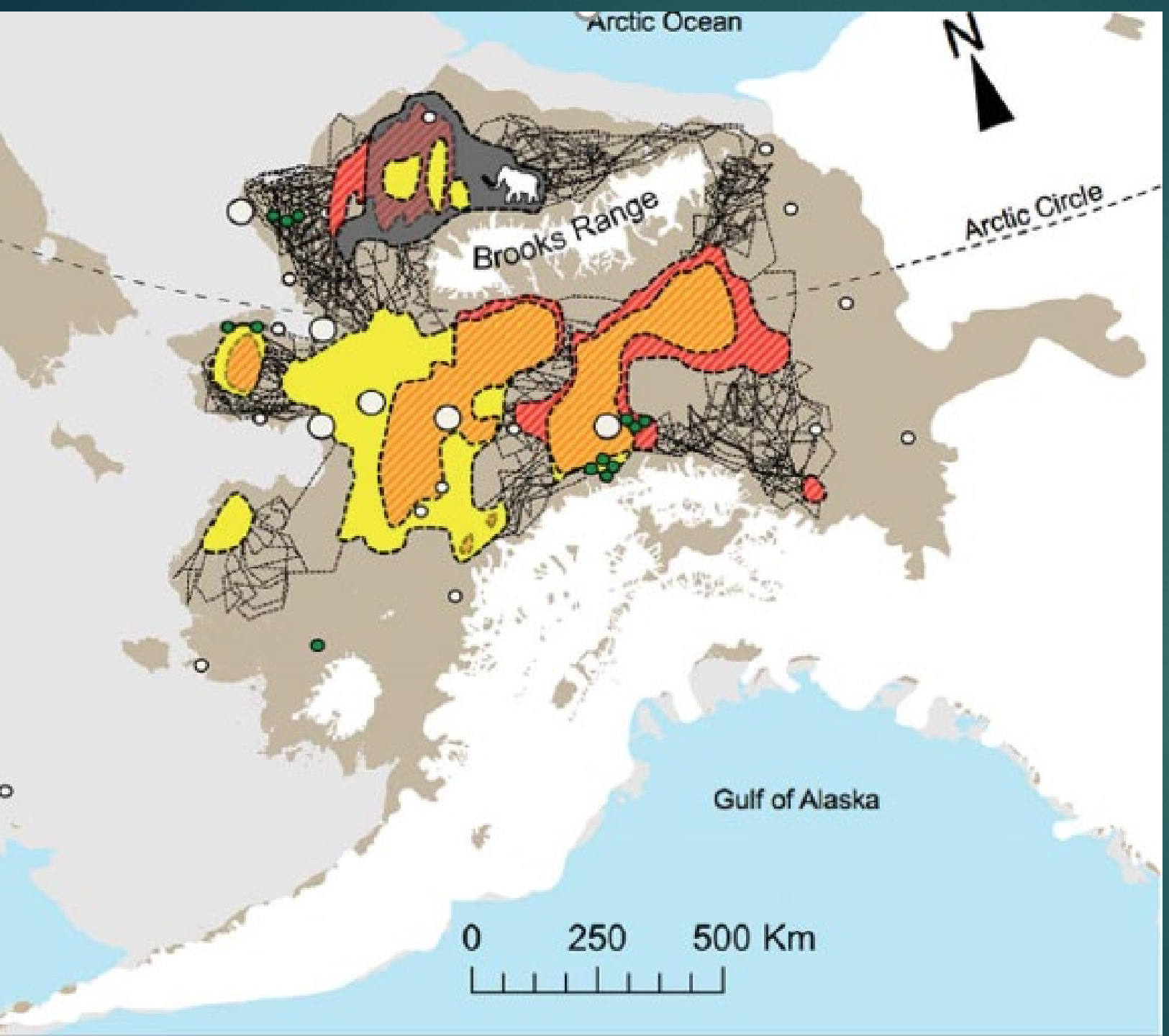
20 - Mammoth's epic travels preserved in tusk

- Chemical analysis of an ice age woolly mammoth's tusk reveals the huge distances it travelled during its lifetime more than 17,000 years ago.
- Researchers have reconstructed the geographical movements of a single woolly mammoth (*Mammuthus primigenius*) using chemical 'GPS tags' preserved in one of its tusks.
- The findings show that the animal travelled so widely across what is now Alaska that it could have circled Earth almost twice (49,000 miles)
- Every place on Earth has a distinct chemical signature based on differences in its geology. The ratios of various isotopes of elements such as strontium and oxygen in the bedrock and water create a unique profile specific to that location and is incorporated into soil and plants. As mammoths grazed on the Arctic plains, these isotopic signatures were integrated into their ever-growing tusks, creating a permanent record of the animals' whereabouts with almost daily resolution.

Matthew J. Wooller, et al., 2021

Mammoth ivory tusk record

- Analysis of the 1.7-meter-long tusk of a male mammoth that died around 17,100 years ago, when it was ~ 28 years old.
- The base of the tusk is the day that it died; the tip is the day that it was born. Everything in between is the lifespan of the mammoth.
- Used lasers to sample the tusk's chemical composition at approximately 340,000 points along the full length of the cone tips.
- They then compared the isotopic profiles at each of these data points with a geological map of Alaska and northwest Canada,
- The bull spent much of its early life in the Yukon River basin and wider Alaskan interior, where it made repeated, long-distance journeys between smaller territories.



This study:
Mammoth frequently used areas at different life stages[d]

- Neonate/Juvenile
- Adult
- Final two winters
- Death location

Mammoth

- At about 16 years old, the isotopic pattern in the tusk becomes more variable. The mammoth probably wandered longer distances in less regular patterns than during its juvenile years. This could indicate that it left its herd to roam freely,

- In the last year and a half of the animal's life, its stamping grounds shrank to a single region near the northern coast of Alaska within the Arctic Circle.

- A distinctive isotope pattern recorded at the base of the tusk showed the "telltale hallmark of starvation in mammals", which was probably what caused its death

- Their extinction coincided with a period when the planet was warming and much of the mammoth's Arctic range was becoming hotter, wetter and more forested. If mammoths regularly migrated as widely as this bull, that could explain why they were so negatively affected by habitat loss

21 - The Extinct Species Within: Ghost lineages

- The genomes of living animals are littered with DNA from long-gone relatives, evidence of past extinctions

- Adaptation via hybridization, or adaptive introgression, seems to happen all the time.

- Example: In Tibet *H. sapiens* interbred with Denisovans, while their domesticated dogs interbred with Tibetan wolves. And from those hybridizations, both picked up adaptive variants of the *EPAS1* gene, which encode version of the protein that help their bodies, and especially their blood, cope with lower levels of oxygen.

- Before wolves passed *EPAS1* along to dogs, the wild canids obtained the helpful *EPAS1* variant by breeding with another canine species— an extinct ghost species.

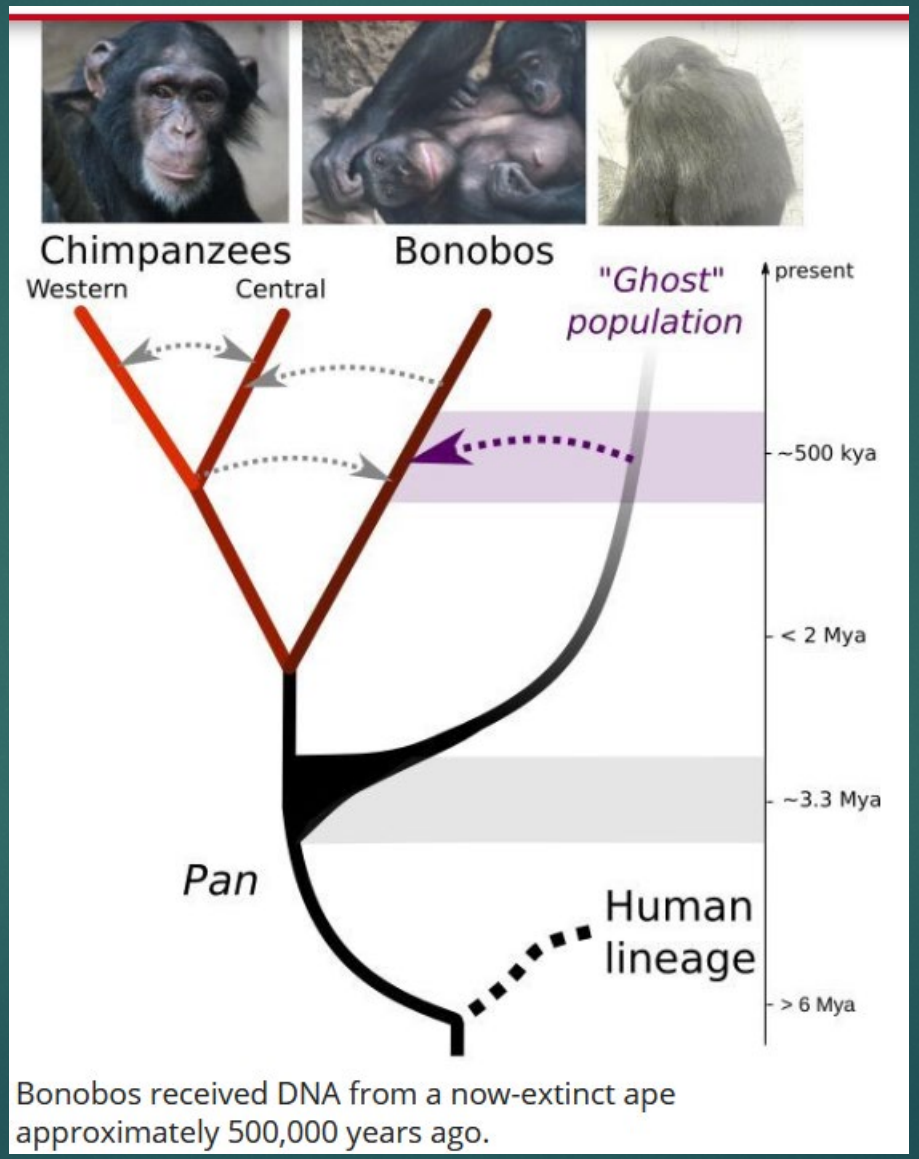
The Extinct Species Within: Ghost lineages

- Other examples of hybridization with extinct species:
  - brown bears cozied up to now extinct cave bears (and they continue to romp with polar bears)
  - elephant species interbred frequently back in the time of mammoths
  - cats apparently did it with now extinct felines
- The more genomes that have been sequenced from the more different lineages and species and places in the world, the more we see that when animals interact with each other and can interbreed, they do. Evidence is ghost DNA in modern species.

Adaptive introgression/hybridization is a key mechanism for evolution.

- Cold adaptation in northern pigs: One of the earliest pieces of evidence for adaptive introgression in mammals came from a 2015 study on domesticated Chinese pigs (*Sus scrofa domesticus*) where a ghost *Sus* lineage was uncovered, which introduced immunity genes.
- Western European house mice (*Mus musculus domesticus*) obtained a gene conferring resistance to the rodenticide warfarin from the Algerian mouse (*Mus spretus*)
- Gulf killifish (*Fundulus grandis*) can tolerate heavily polluted waters thanks to genes garnered from Atlantic killifish (*F. heteroclitus*).
- Species are not isolated—they're connected to other species, and when the environment changes, they can pick up DNA to adapt to new environmental conditions. Those genes that have been jumping from one species to another species and so on, they're probably the important genes for that environment.
- Domesticated cattle in China were bred with yak and banteng, a species of cattle endemic to Southeast Asia, to help them survive high altitudes and tropical environments, respectively.

22 - Ghost ape lineage



Bonobos received DNA from a now-extinct ape approximately 500,000 years ago.

Ghost ape lineage

- Introgression analyses run on 69 chimpanzee and bonobo genomes revealed that the two species had hybridized in the past.

- 0.9–4.2 percent of the bonobo genome was made up of DNA from an otherwise unknown ape.

- These segments contained genes related to immunity, physiology, and behavior, all of which suggests some of the notable differences between bonobos and chimpanzees may stem in part from the former's hybridization with another species.

23 - Ayta Magbukon, Philippine Negrito group, has most D DNA

- 2021 study: Philippine Negrito ethnic group known as the Ayta Magbukon have the highest level of Denisovan ancestry in the world.

- Carry considerably more Denisovan DNA than the Papuan Highlanders, who were previously known as the present-day population with the highest level of Denisovan ancestry.

- If we account for and masked away the East Asian-related ancestry in Philippine Negritos, their Denisovan ancestry can be up to 46 percent greater than that of Australians and Papuans.

- The average amount of Denisovan sequence detected in Ayta Magbukon and Papuans are 100.38 Mb and 79.35 Mb, respectively; a difference of 27%.

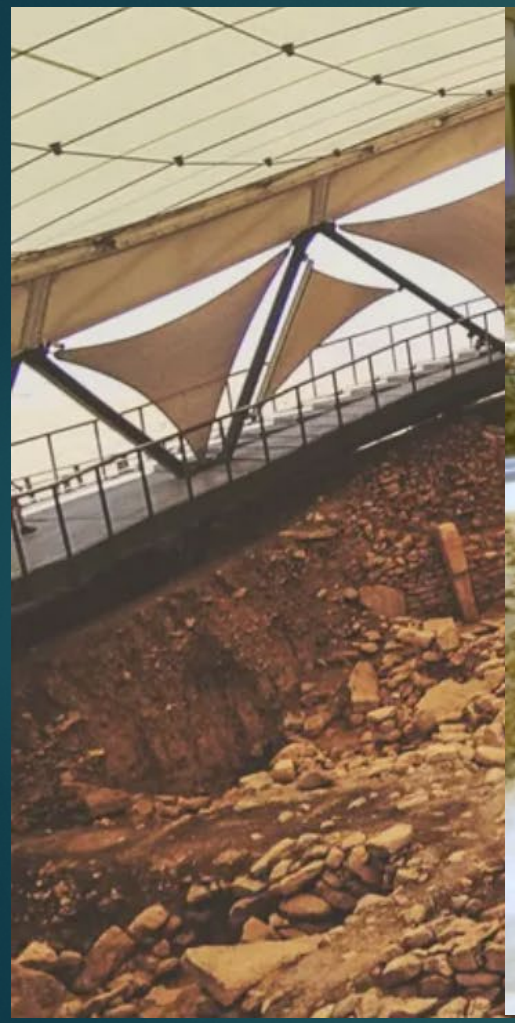
Larena et al.:, 2021

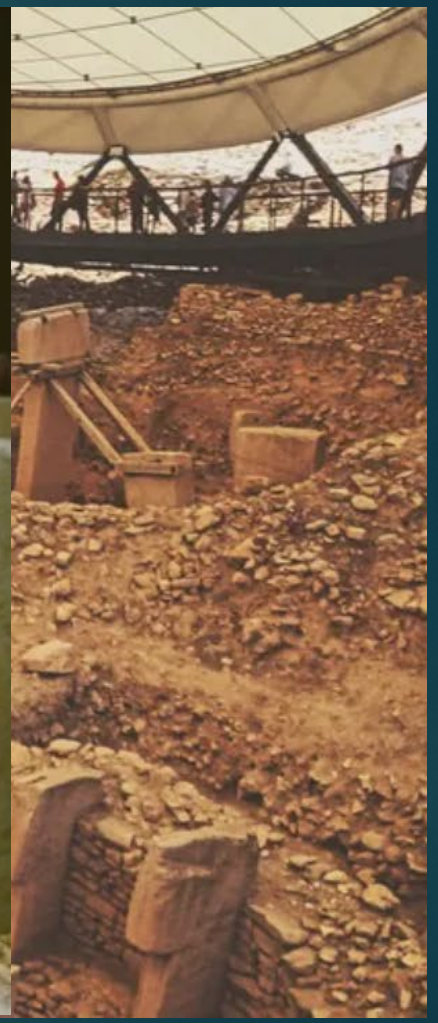
24 - Importance of porridge: Göbekli Tepe in Turkey – 9500-9000 years old; oldest temple in world – 20+ circular stone enclosures.

Göbekli Tepe follows a geometric pattern. The pattern is an equilateral triangle that connects enclosures A, B, and D.

Now a Tourist site

The Şanlıurfa Archaeology and Mosaic Museum, built nearby in 2015 in central Urfa - a full-scale partial replica

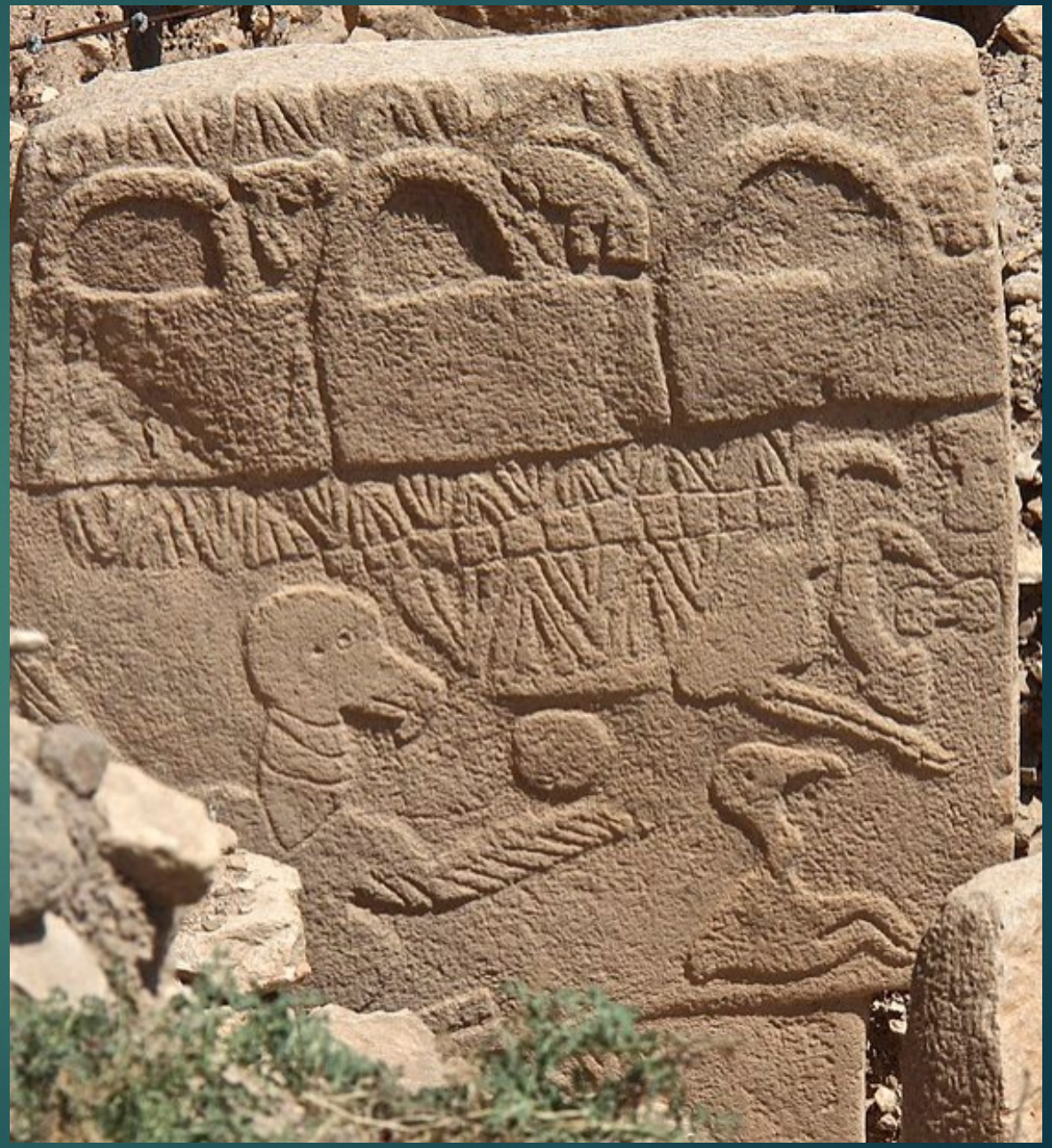




Göbekli Tepe: Schmidt theory

- German archaeologist Klaus Schmidt first began excavating on a Turkish mountaintop 25 years ago
- Circular enclosures had been built by hunter-gatherers, living off the land. Tens of thousands of animal bones that were uncovered were from wild species, and there was no evidence of domesticated grains or other plants.
- The site, Schmidt argued, was a ritual center, perhaps some sort of burial or death cult complex, rather than a settlement.
- It was firmly in the pre-Neolithic era, before agriculture.

In 2018, Gobekli Tepe designated as Unesco World Heritage site



Göbekli Tepe

- Pictographs of lions, boars, birds and insects
- The site was deliberately buried sometime after 8000 BCE: the buildings were buried under debris, mostly flint gravel, stone tools, and animal bones.
- Klaus Schmidt's view was that Göbekli Tepe is a stone-age mountain sanctuary. Radiocarbon dating indicate that it contains the oldest known megaliths yet discovered anywhere, and that these ruins may constitute the remains of a temple.
- Very close to where modern wheat was first domesticated.
- According to Lee Clare a revision of the temple-narrative is unavoidable due to new observations related to the "existence of domestic buildings and the harvesting and distribution of rain-water.

Gobekli Tepe

- Work on foundations needed to support the site's swooping fabric canopy required archaeologists to dig deeper that Schmidt ever had.

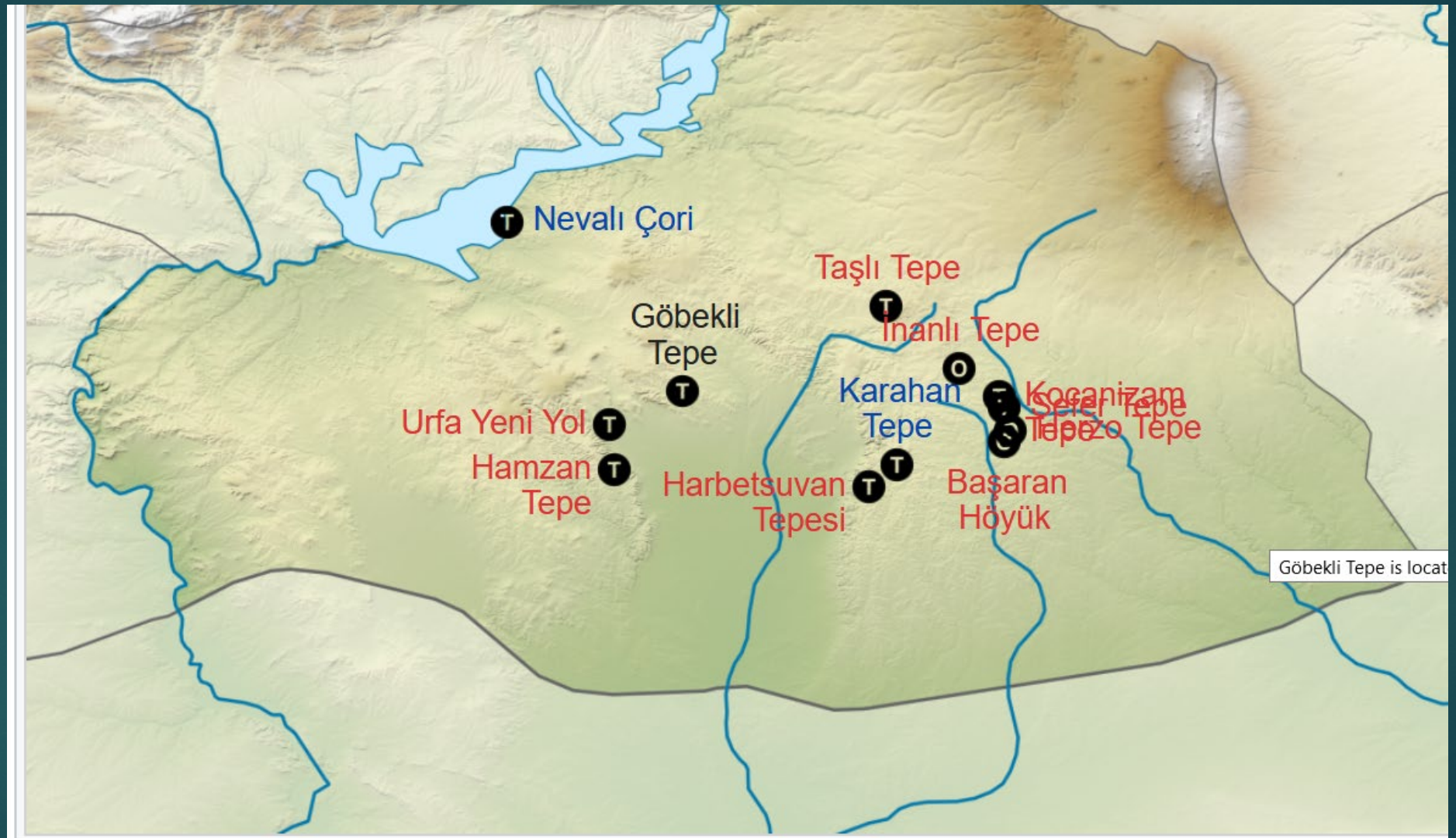
- Under the direction of Schmidt's successor, Lee Clare, a German Archaeological Institute team dug several "keyhole" trenches down to the site's bedrock, several meters below the floors of the large buildings

- The digs revealed evidence of houses and year-round settlement, suggesting that Gobekli Tepe wasn't an isolated temple visited on special occasions but a rather a thriving village with large special buildings at its center.

Gobekli Tepe

- The team also identified a large cistern and channels for collecting rainwater, key to supporting a settlement on the dry mountaintop
- It was a fully-fledged settlement with permanent occupation.
- Turkish archaeologists working in the rugged countryside around Urfa have identified at least a dozen other hill-top sites with similar – if smaller – T-pillars, dating from around the same time period.
- Rather than a centuries-long building project inspiring the transition to farming, Clare and others now think Gobekli Tepe was an attempt by hunter-gatherers clinging to their vanishing lifestyle as the world changed around them.
- Evidence from the surrounding region shows people at other sites were experimenting with domesticated animals and plants – a trend the people of "Belly Hill" might have been resisting.

Sites with T-shaped pillars in Urfa region



Known PPN sites in the Urfa region.[17][18][19] Sites with T-shaped pillars are marked with T.

Göbekli Tepe and ancient carb revolution

- Grains were on the menu at feasts that took place more than 9,000 years ago at Göbekli Tepe in Turkey, before Neolithic revolution of farming
- No signs of domesticated grain at Göbekli Tepe; signs of massive feasts; fueled by vat-fulls of porridge and stew, made from grain that the ancient residents had ground and processed on an almost industrial scale
- Ancient humans relied on grains much earlier than was previously thought — even before there is evidence that these plants were domesticated.
- These discoveries shred the long-standing idea that early people subsisted mainly on meat

Porridge at Göbekli Tepe

- The ‘garden’ area covered an area the size of a football field and contained more than 10,000 grinding stones and nearly 650 carved stone platters and vessels, some big enough to hold up to 200 liters of liquid; grinding grain to produce porridge and beer.

- Humans have more copies of the gene that produces enzymes to digest starch than do any of our primate relatives. Humans have up to 20 copies, and chimpanzees have 2. there’s a selective advantage to higher-starch diets for *Homo sapiens*

- Cooking hearths at sites in South Africa dating back 120,000 years: earliest evidence of ancient people cooking starch (roots & tubers)

Starch

- Neanderthals in Iran and Belgium between 46,000 and 40,000 years ago: Plant microfossils trapped and preserved in the hardened plaque showed that they were cooking and eating starchy foods including tubers, grains and dates
- Neanderthals had already genetically adapted to a plant-rich diet; evidence in microbiome
- It has become clear that early humans were cooking and eating carbs almost as soon as they could light fires.
- Evidence of burnt bread at 14.5 Ka in Jordan, based on wild wheat -- hunter-gatherers were using cereals.
- Göbekli Tepe suggests that even before farming took hold, cereals were a daily staple, not just part of an occasional fermented treat.
- Göbekli Tepe: mostly grinding grain coarsely, just enough to break up its tough outer layer of bran and make it easy to boil and eat as porridge or ferment into beer.

25 - GWAS: Alcohol & immune cells

- Alcoholism and immune gene *SPI1:* expression is enriched in some fetal brains, suggesting that people who are genetically predisposed to Alcohol Use Disorder and heavy drinking are also predisposed to developing an overactive immune system.
- When people with this gene variant drink heavily, their immune system is likely to become overactivated.
- That could cause microglia to start altering neuronal connections, pointing to a study in mice that found binge drinking activated microglia, which selectively pruned excitatory dopamine synapses, causing the animals to display anxiety-like behaviors.
- Potentially, the microglia prune connections to neurons the produce dopamine, the chemical responsible for the “rewarding” feeling of drinking alcohol.
- If people with certain versions of *SPI1* start drinking regularly, they’d have to drink more and more to get the same level of reward. And their immune system will get more activated, pruning more synapses. It becomes a vicious cycle.
- Gene also associated with neurodegeneration

M. Kapoor, et al., 2021

26 - GWAS: Externalizing behavior due to 579 genes

- Multivariate genomic analysis of 1.5 million people identifies genes related to externalizing behavior. A European sample
- Behaviors and disorders related to lack of self-regulation, such as substance use, antisocial conduct, and ADHD, are collectively referred to as *externalizing* and have a shared genetic liability (80%).
- Genetic correlates of 7 phenotypic externalizing behaviors: attention-deficit/hyperactivity disorder, problematic alcohol use, lifetime cannabis use, age at first sexual intercourse, number of sexual partners, general risk tolerance, and lifetime smoking.
- GWAS identified 579 SNPs associated with a general tendency toward externalizing. Mostly genes expressed in brain and neurodevelopment.

Richard Karlsson Linnér, et al., 2021

Externalizing behavior

- A polygenic score constructed from our results captures variation in a broad range of behavioral and medical outcomes: such as opioid use disorder, suicide, HIV infections, criminal convictions, and unemployment.
- Score captures 10% of variance of genetics. Predicts opioid use, age at first sex, being fired from work, being convicted of a crime, and are more likely to experience a variety of diseases, including cirrhosis of the liver and HIV infection, and are more likely to attempt suicide.
- A polygenic score is a risk factor. It is not free of environmental or social processes or causations.
- Persistent difficulties in self-regulation can be conceptualized as a neurodevelopmental condition.
- Move away from psychiatric diagnostic categories toward more biological markers

GWAS: Externalizing behavior due to 579 genes

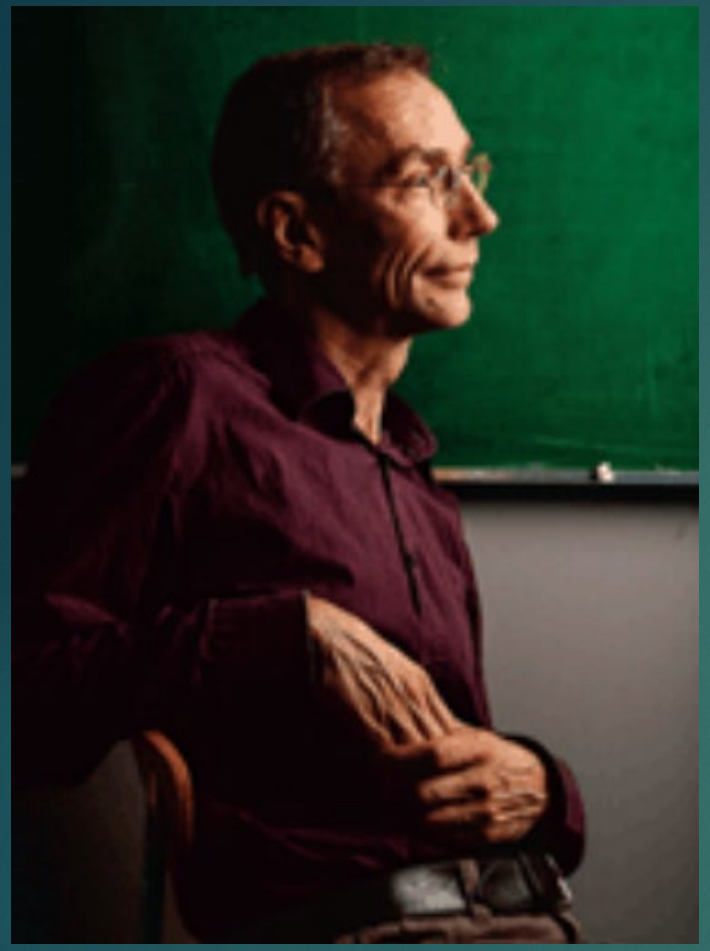
- Effect sizes were substantially attenuated in analyses of socioeconomic outcomes
- Cautions: These results are *not* evidence that some people are genetically determined to experience certain life outcomes or are "innately" antisocial. Examples = decriminalization of cannabis and imprisonment; childhood externalizing is associated with greater adult earnings, but only for children not raised in poverty
- Caution: https://externalizing.org/faqs/
- Currently, they urge extreme caution about using an externalizing polygenic score. It does not predict individual outcome. We do not know *how* the polygenic score is associated with externalizing, i.e. aggressive risk may be environmentally caused. Appropriate use is for research, not eugenics.

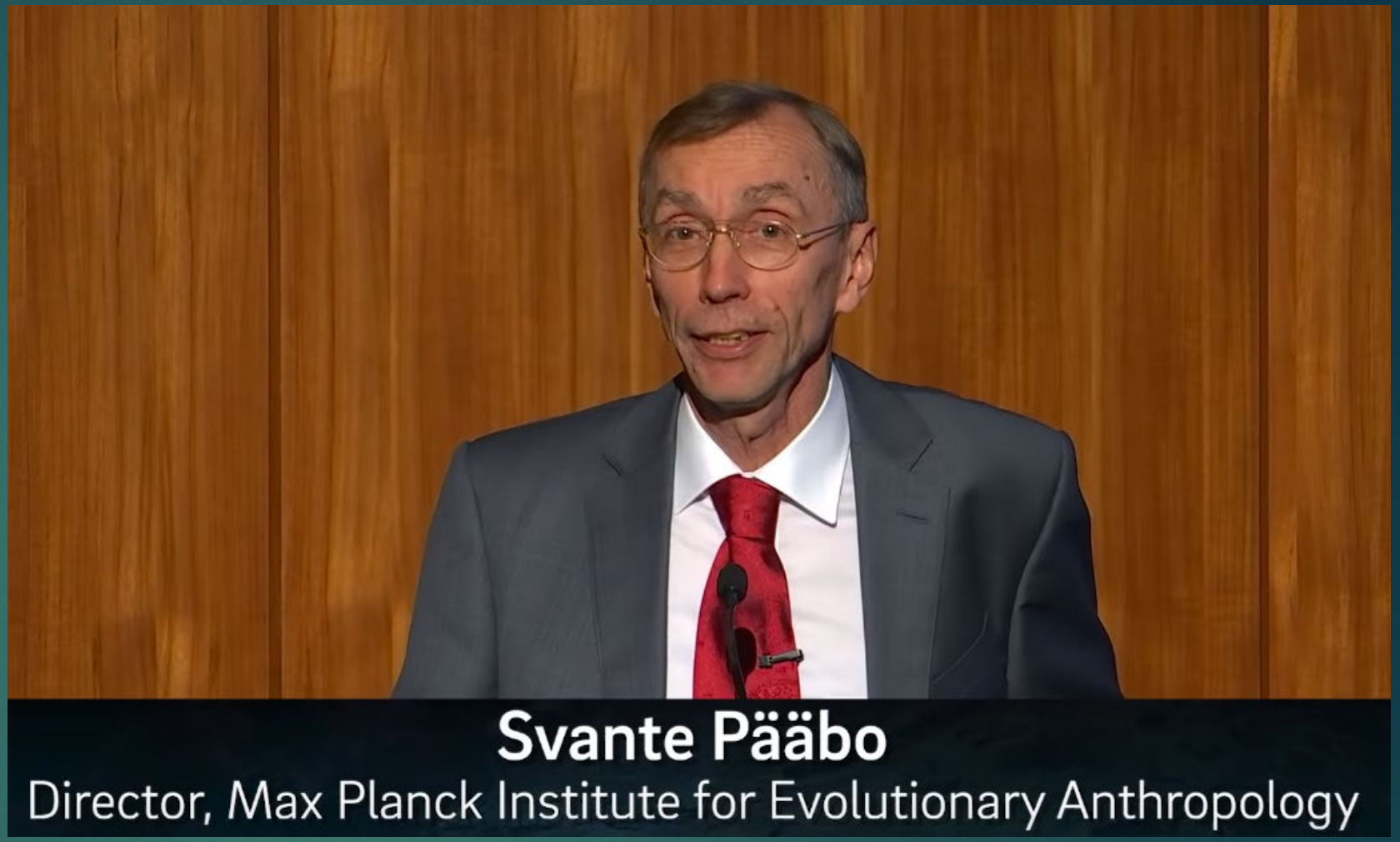
** Start

Ancient DNA: A History of Human Paleogenetics

CHARLES J VELLA, PHD

SEPTEMBER 2021





Dedicated to Svante Pääbo who has transformed our view of human evolution by sequencing the genomes of archaic humans.

Svante Pääbo
Father of Paleogenetics

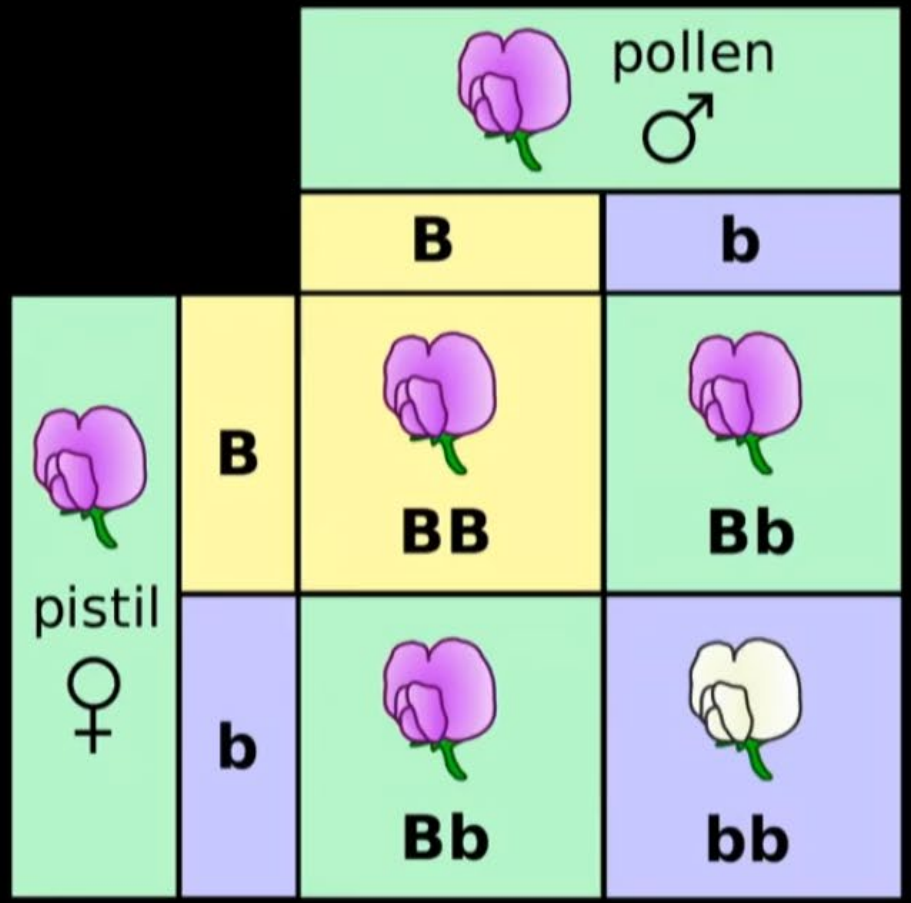
Director, Dept. of Evolutionary Genetics, Institute for Evolutionary Anthropolog
Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

Animal experimentation: Man who invented sheep, 1700s

Practical understanding of genetics via crossbreeding of animals. First to implement systematic selective breeding of livestock. His advancements not only led to specific improvements in sheep, cattle and horses, but contributed to general knowledge of artificial selection. In *On the Origin of Species* Darwin cited Bakewell's work as demonstrating variation under domestication

Gregor Mendel: Founder of the modern science of genetics. _Laws of Inheritance (dominant/recessive traits): Mendel grew over 10,000 pea plants over eight years (1856-1863) and he published his results in **1865**. Primarily a meteorologist.

Gregor Mendel
(1822-1884)



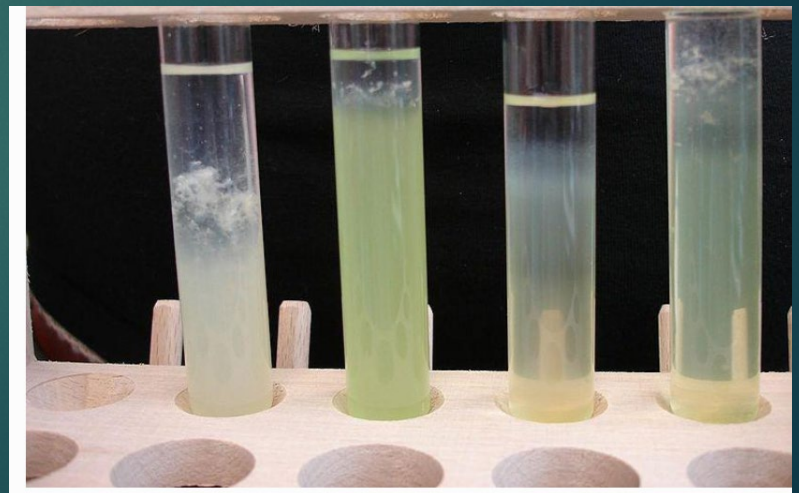
Wikipedia

Thomas Hunt Morgan (1866-1945)

- American evolutionary biologist, geneticist, embryologist
- Nobel Prize, 1933: elucidating the role that the chromosome plays in heredity
- Genetic characteristics of the fruit fly *Drosophila melanogaster*
- In his famous Fly Room at Columbia University, showed that genes are carried on chromosomes and are the mechanical basis of heredity.

Friedrich Miescher (1844-1895): “On the chemical composition of the pus cells”, 1869

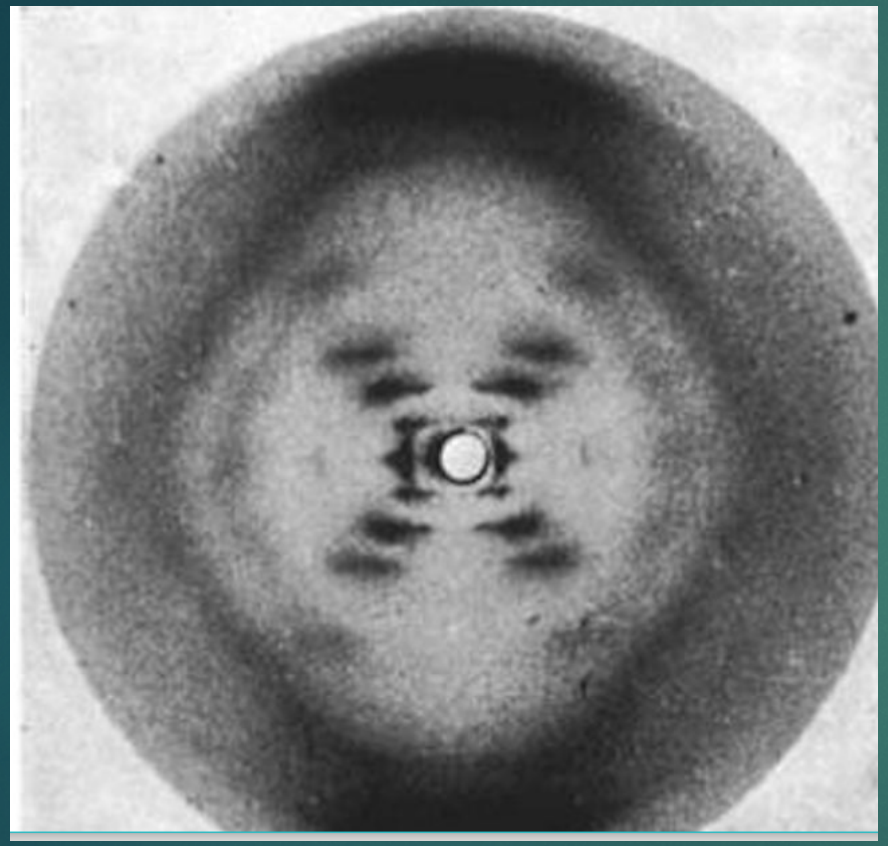
- Swiss physiological chemist Friedrich Miescher discovered, in a castle kitchen, what he called "nuclein" inside the nuclei of human white blood cells obtained from pus in 1869
- in a 1961 historical account of nineteenth-century science, Charles Darwin was mentioned 31 times, Thomas Huxley 14 times, but Miescher not even once

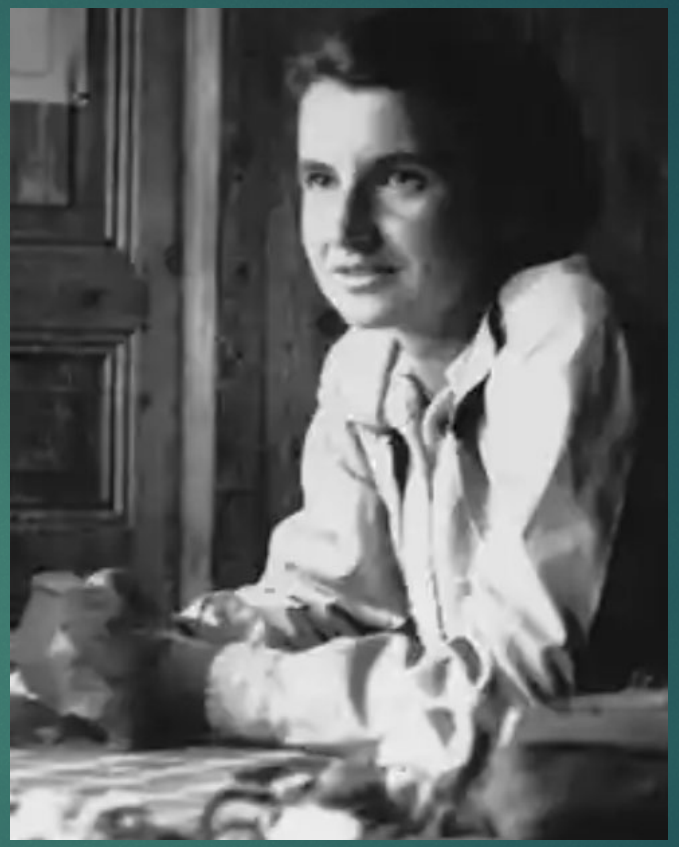


DNA isolated from a zucchini, visible as a white cloud in

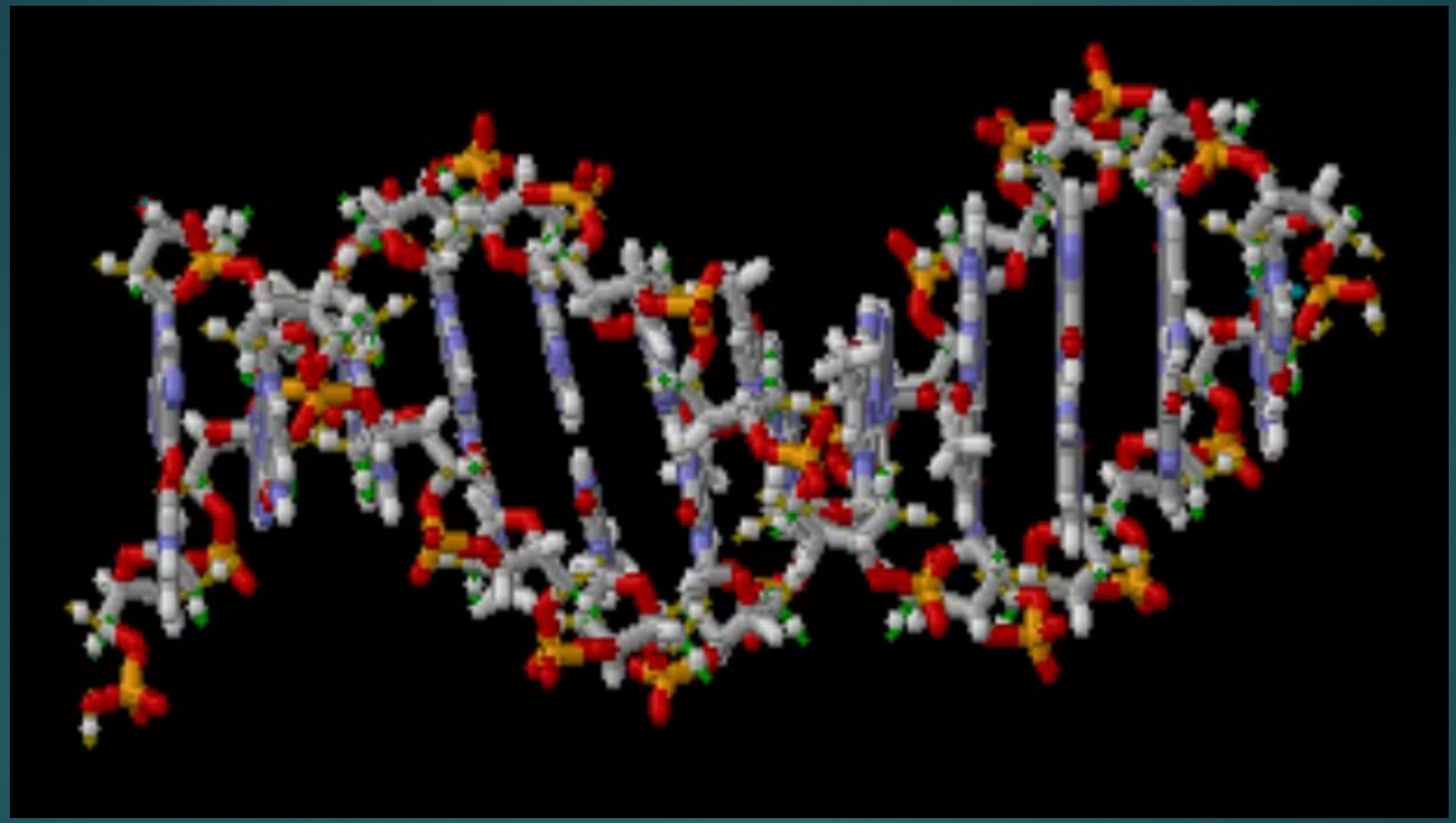
James Watson (left) was only 24 when together with Francis Crick (right) he published the paper that first described the structure of DNA

"Photo 51", from Rosalind Franklin's X-ray diffraction experiments





Maurice Wilkins, James Watson and Francis Crick won the 1962 Nobel Prize in Medicine for the DNA-related work. Franklin had died and was not mentioned.

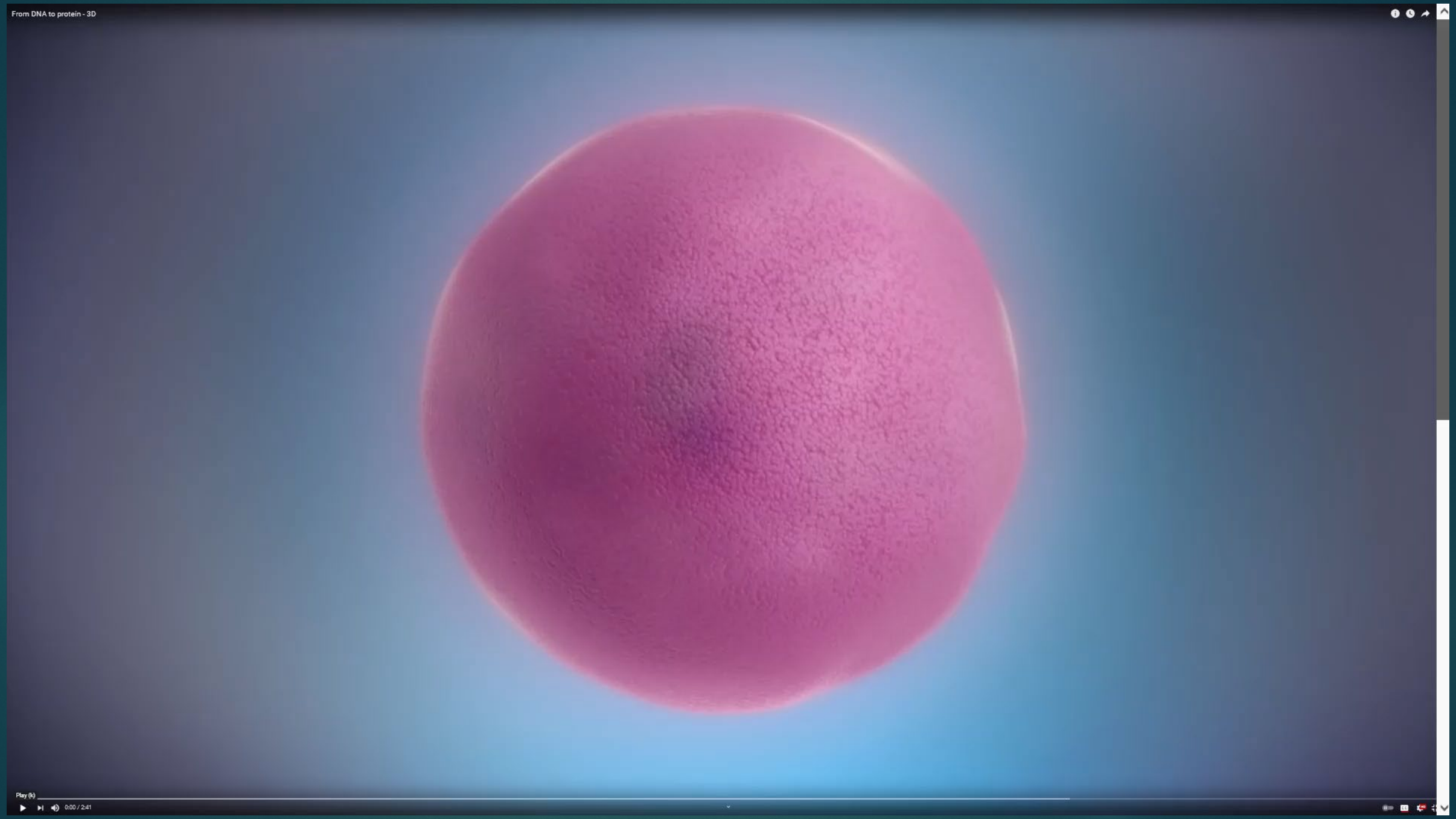


Molecular Biology

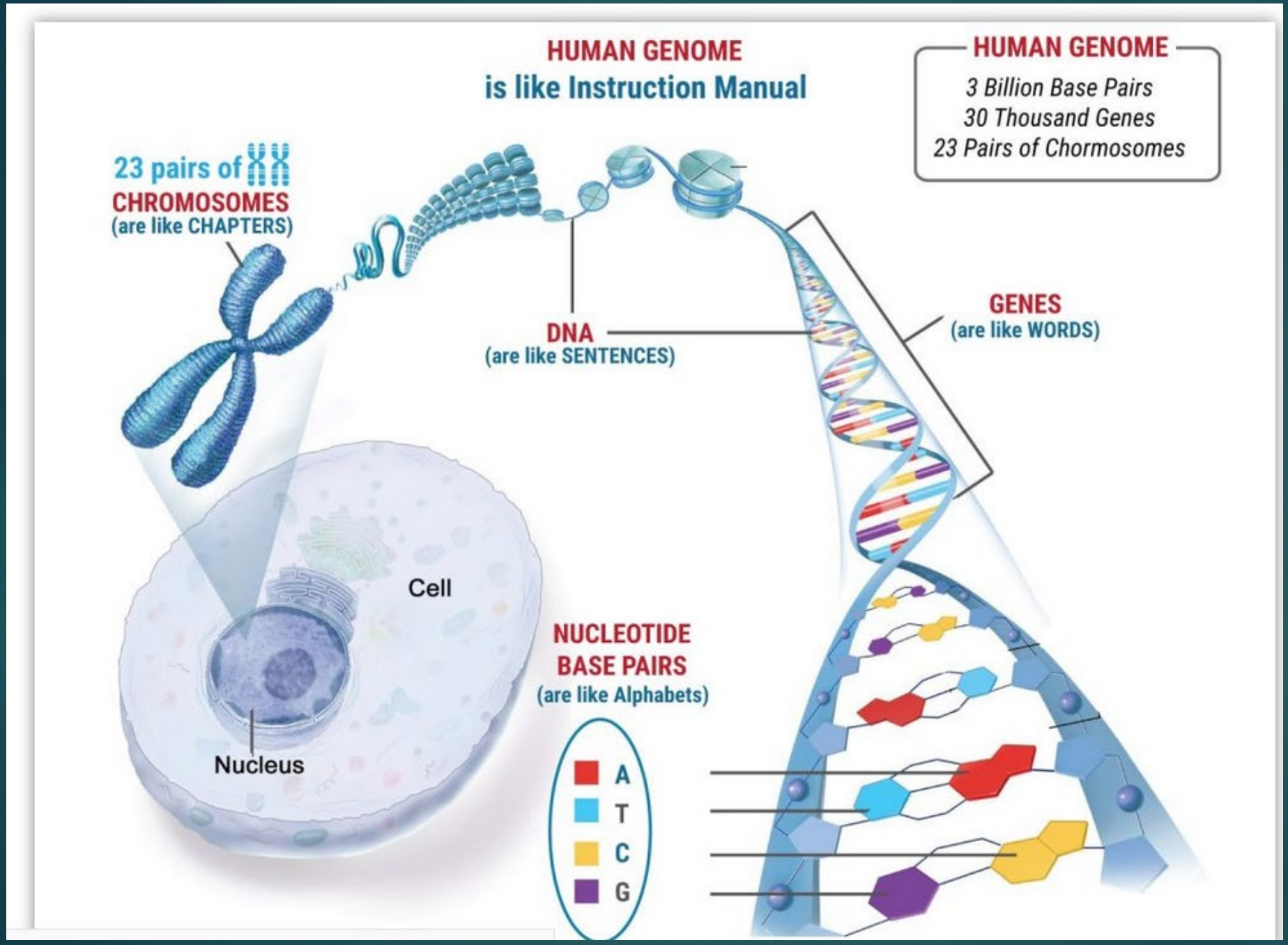
- Molecular biology arose as an attempt to answer the questions regarding the mechanisms of genetic inheritance and the structure of a gene. Proteins were the first study targets until it was discovered that a change in DNA could turn one strain of bacteria into another.
- In 1953, James Watson and Francis Crick published the double helical structure of DNA courtesy of the X-ray crystallography work done by Rosalind Franklin and Maurice Wilkins.
- The central dogma of molecular biology describes the process in which DNA is transcribed into RNA, which is then translated into protein.

- Definitive history: The Eighth Day of Creation: Makers of the Revolution in Biology, by Horace Freeland Judson, 1996
- The Double Helix by James Watson
- Life's Greatest Secret: The Race to Crack the Genetic Code by Matthew Cobb

** A Basic Review of Genetics

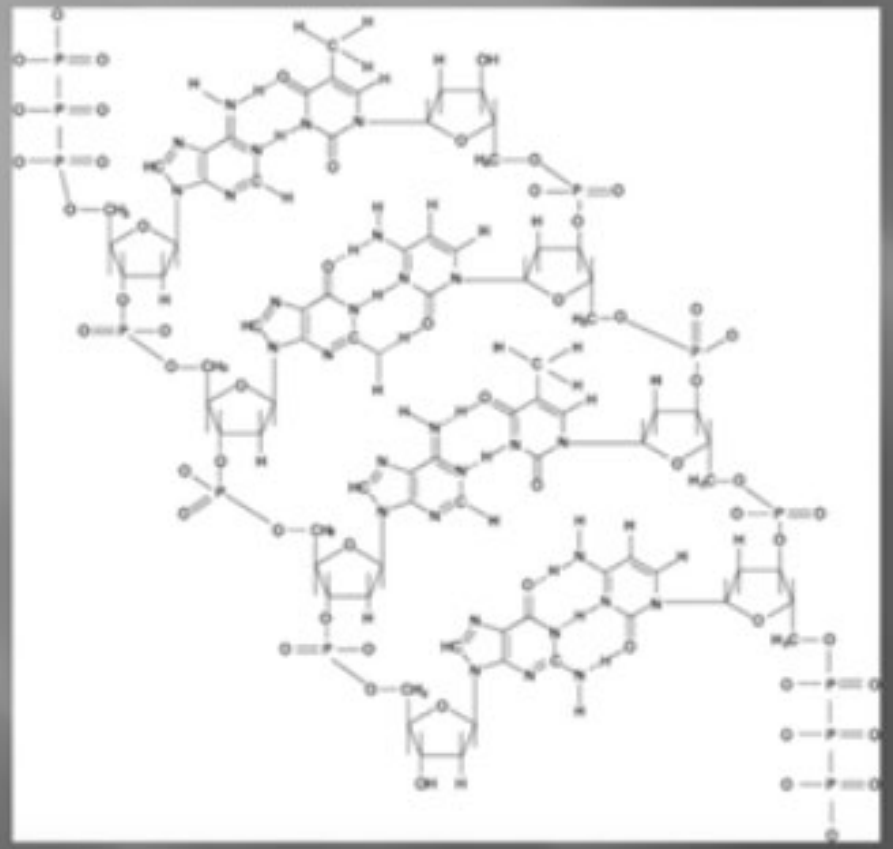

From DNA to protein - 3D
Play (k)
0:00 / 2:41

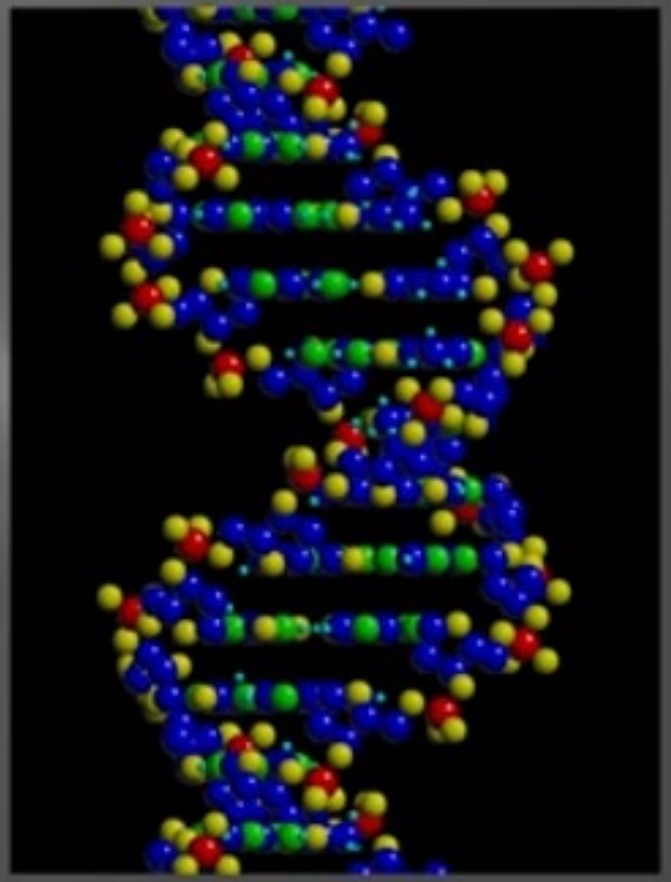
Basics of DNA


HUMAN GENOME
is like Instruction Manual
HUMAN GENOME
3 Billion Base Pairs
30 Thousand Genes
23 Pairs of Chormosomes
23 pairs of XX
CHROMOSOMES
(are like CHAPTERS)
DNA
(are like SENTENCES)
GENES
(are like WORDS)
Cell
Nucleus
NUCLEOTIDE
BASE PAIRS
(are like Alphabets)
A
T
C
G

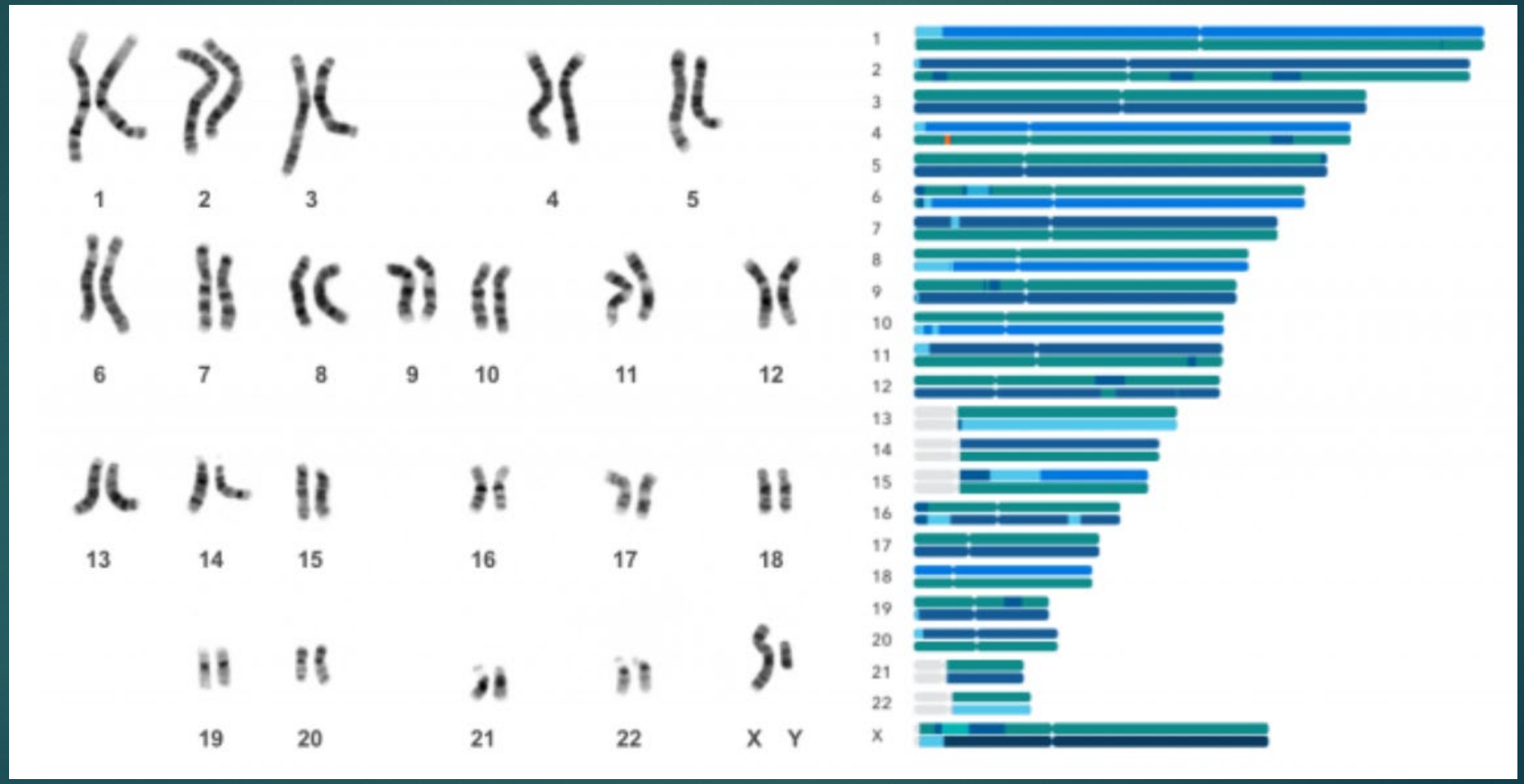
Human DNA: in all 32 trillion of your cells

What is DNA?

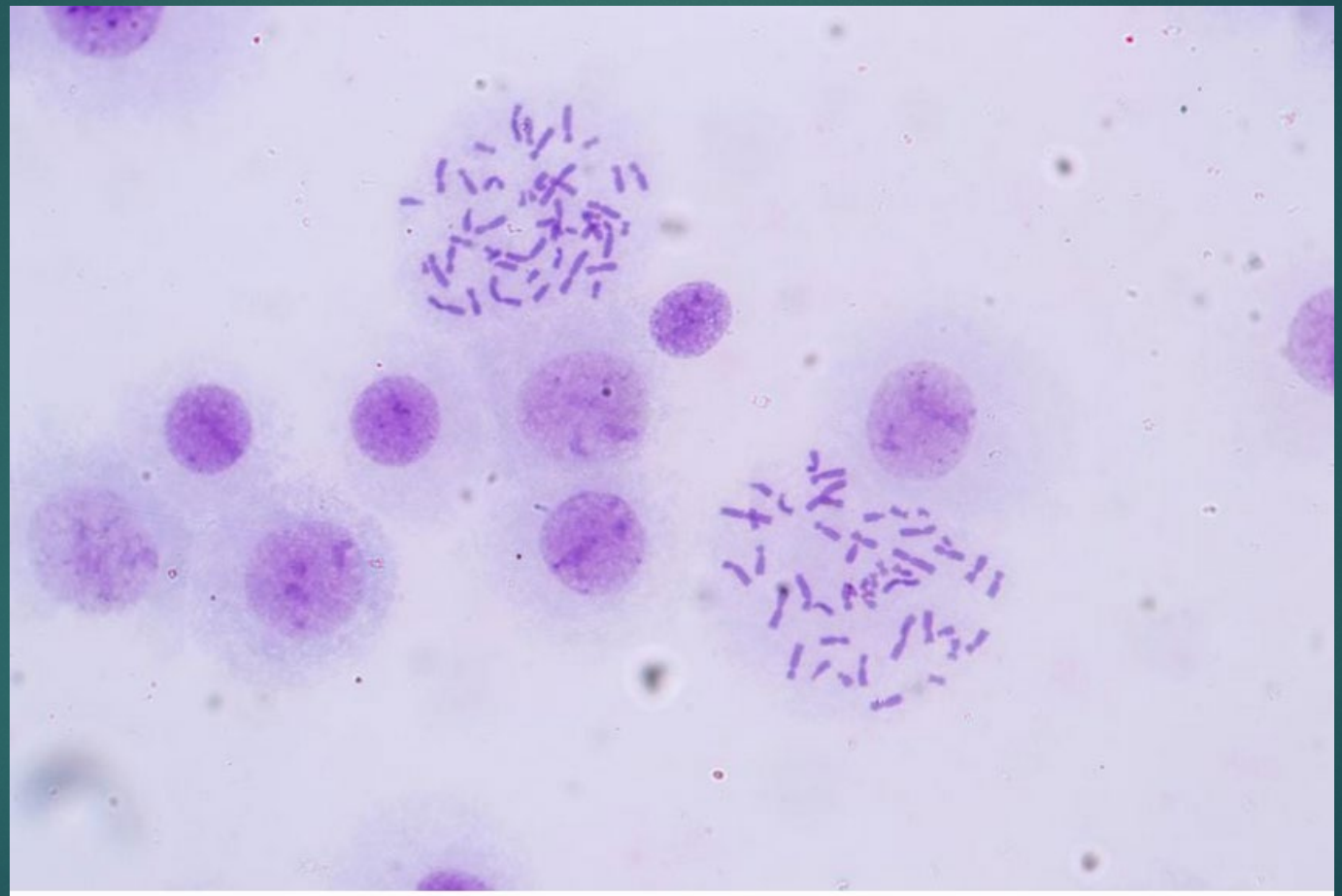




23 Chromosomes

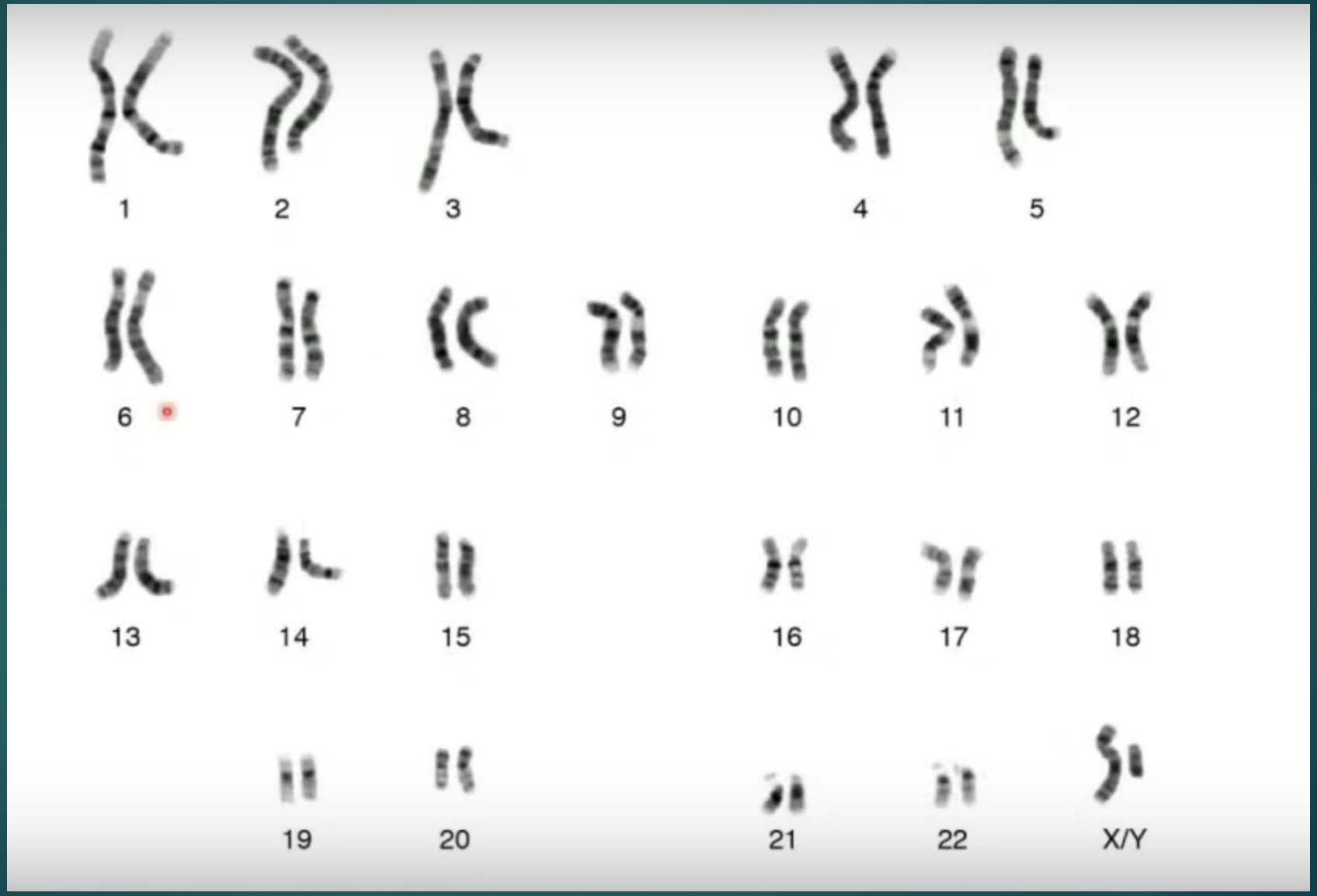


Chromosomes under a microscope

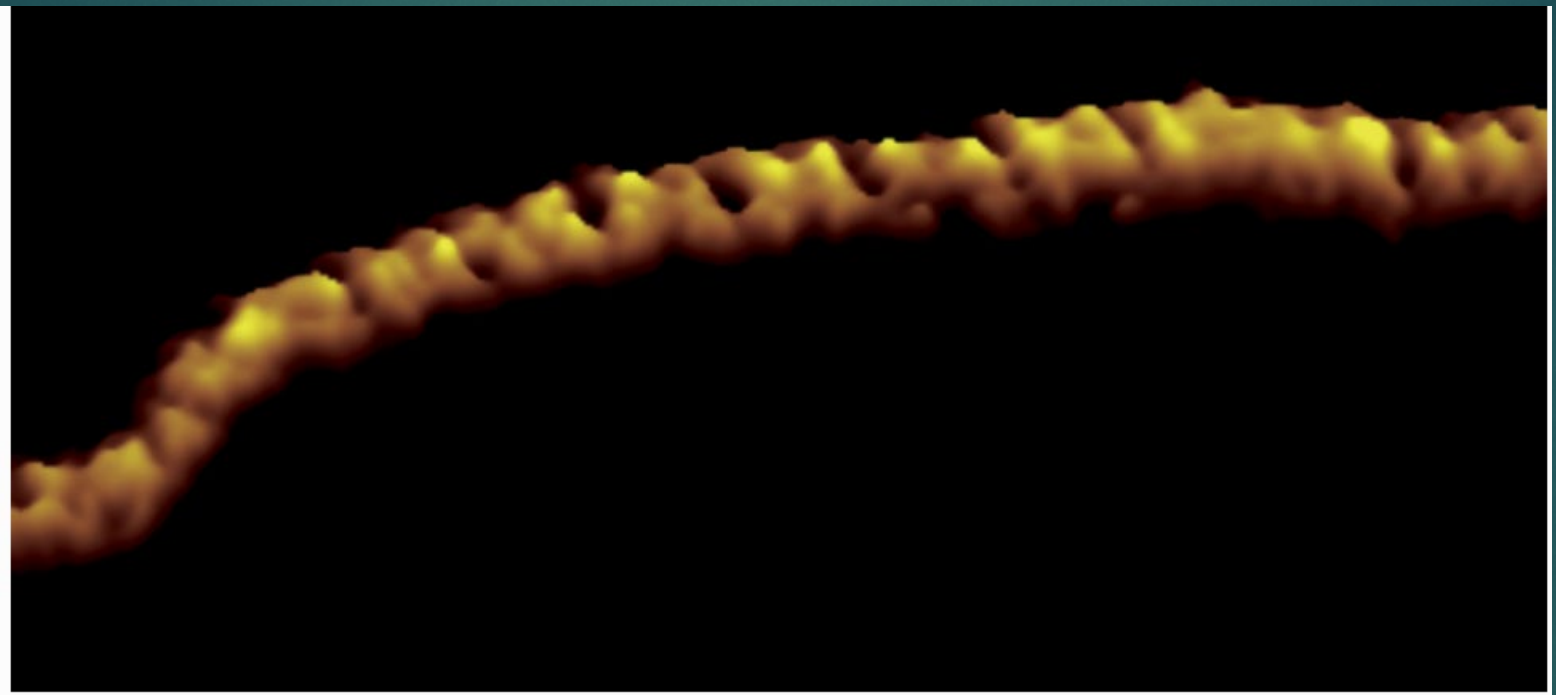


Human chromosomes visible in cells under the microscope.

DNA’s 3 Billion letters (twice) = 262,000 pages if printed out



DNA molecule



Visualisation of a single molecule of DNA using atomic force microscopy. Image from Pyne A, Thompson... [+] ALICE PYNE

Model a billion atoms of an entire gene

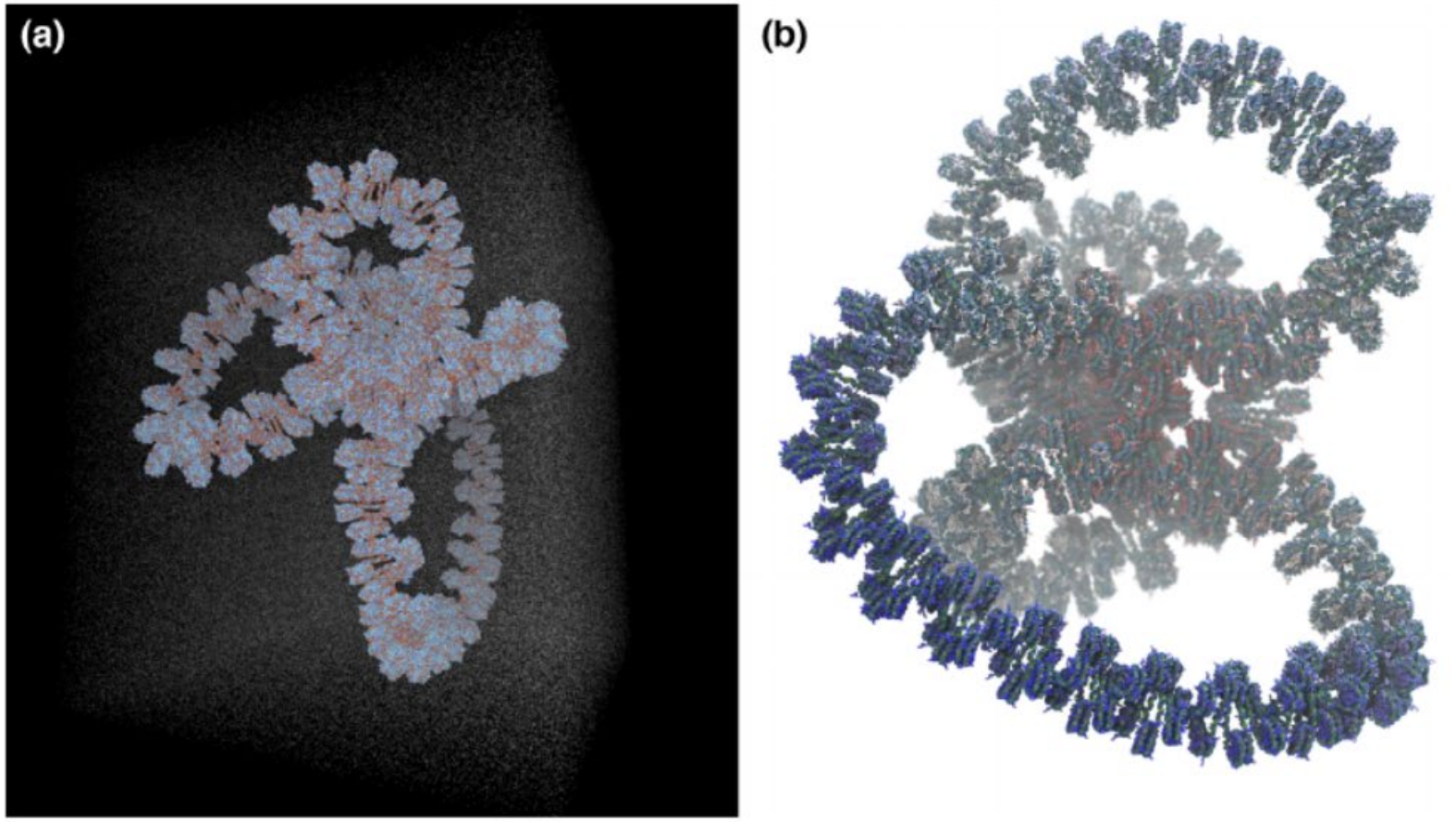
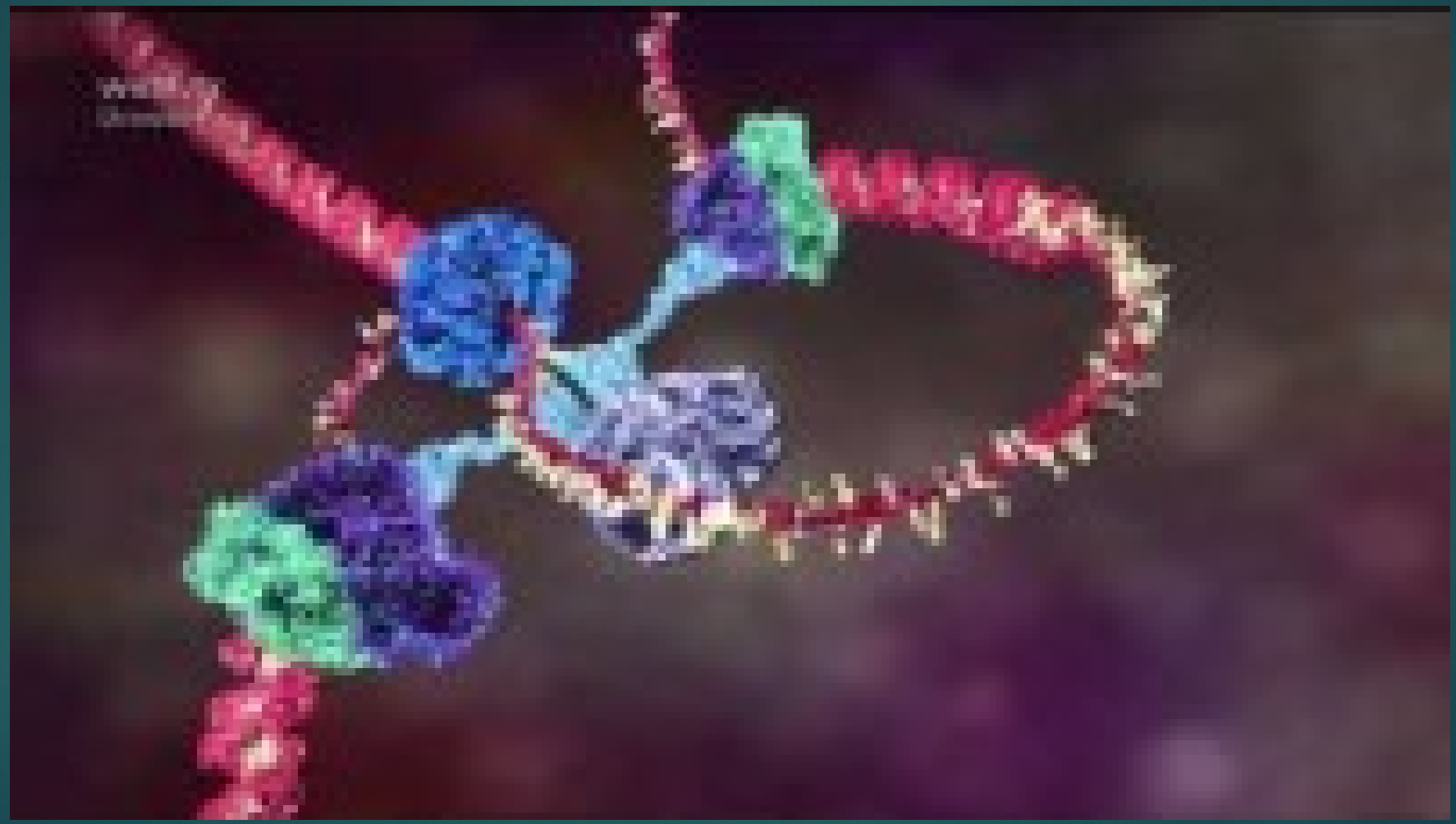
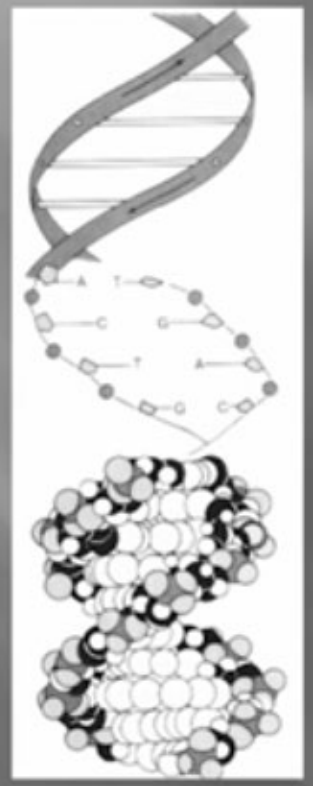


Figure 1. Explicit solvent simulations of GATA4 gene locus. a) Structure of fully solvated GATA4 gene in a periodic simulation cube, consisting of 83 kilobases of double-stranded helical DNA wrapped around 427 nucleosomes. b) A more detailed view of the gene structure. Protein tails used for programming gene expression protrude from each nucleosome. In a) and b), water molecules are not shown for image clarity. Ions are shown in a).

Most amazing 3D DNA visualization: Science-Art exhibition: https://www.youtube.com/watch?v=7Hk9jct2ozY



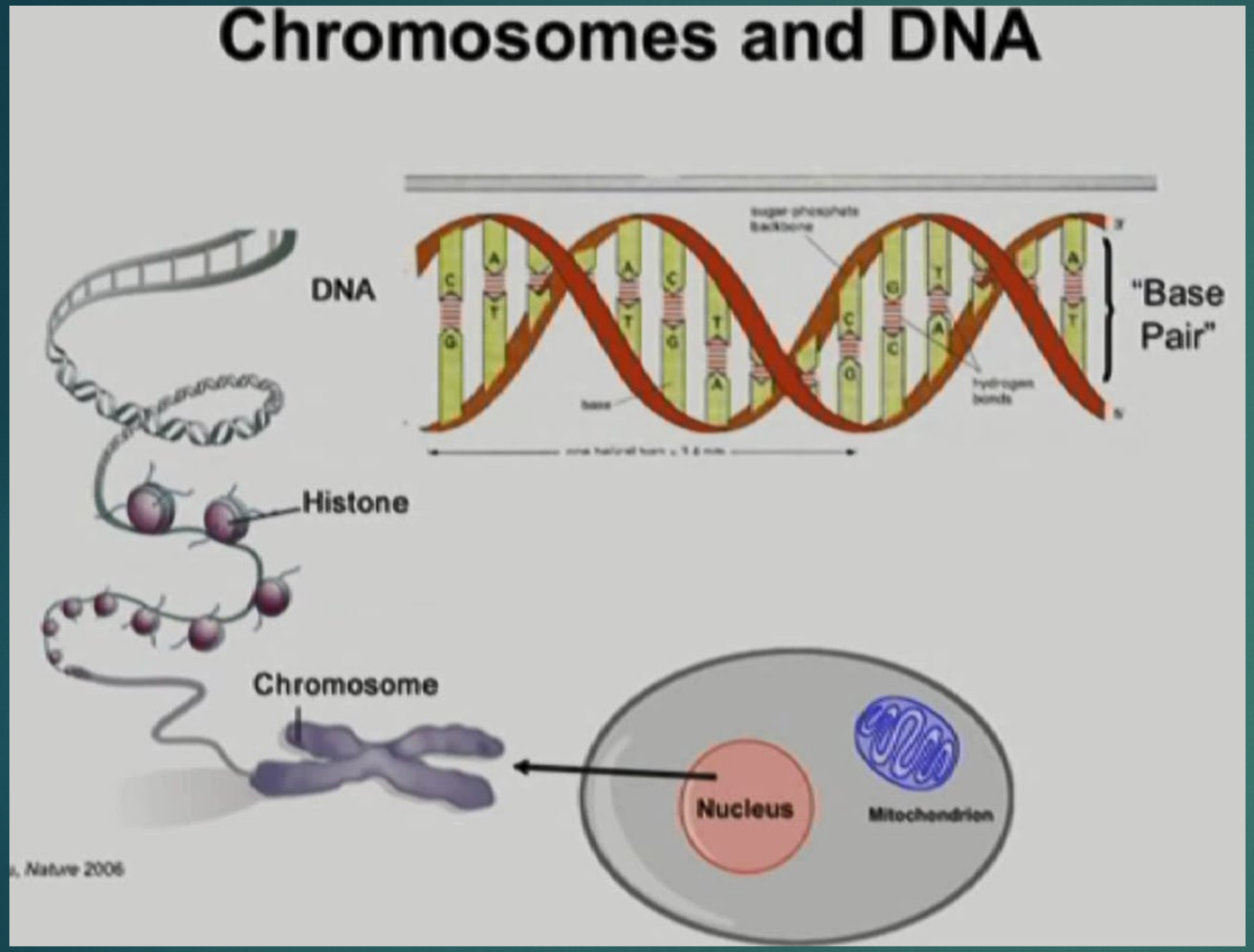
Simplicity of Nuclear DNA



6 Billion "rungs" in all nucleated cells.

3 Billion from Mom

3 Billion from Dad



DNA in chromosomes in every cell nucleus

Double helix (2 exact copies in opposite direction)

4 bases (ATCG); each 8-10 atoms wide

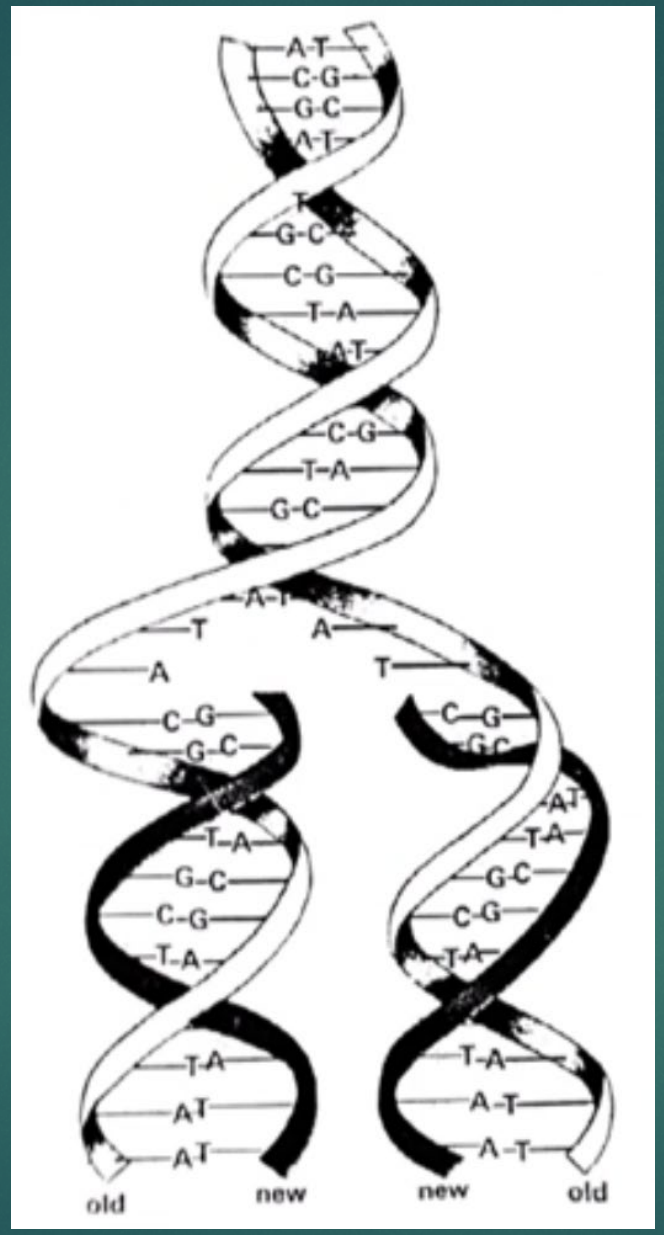
Form base pairs (A-T, C-G); bind together if exact opposite letter

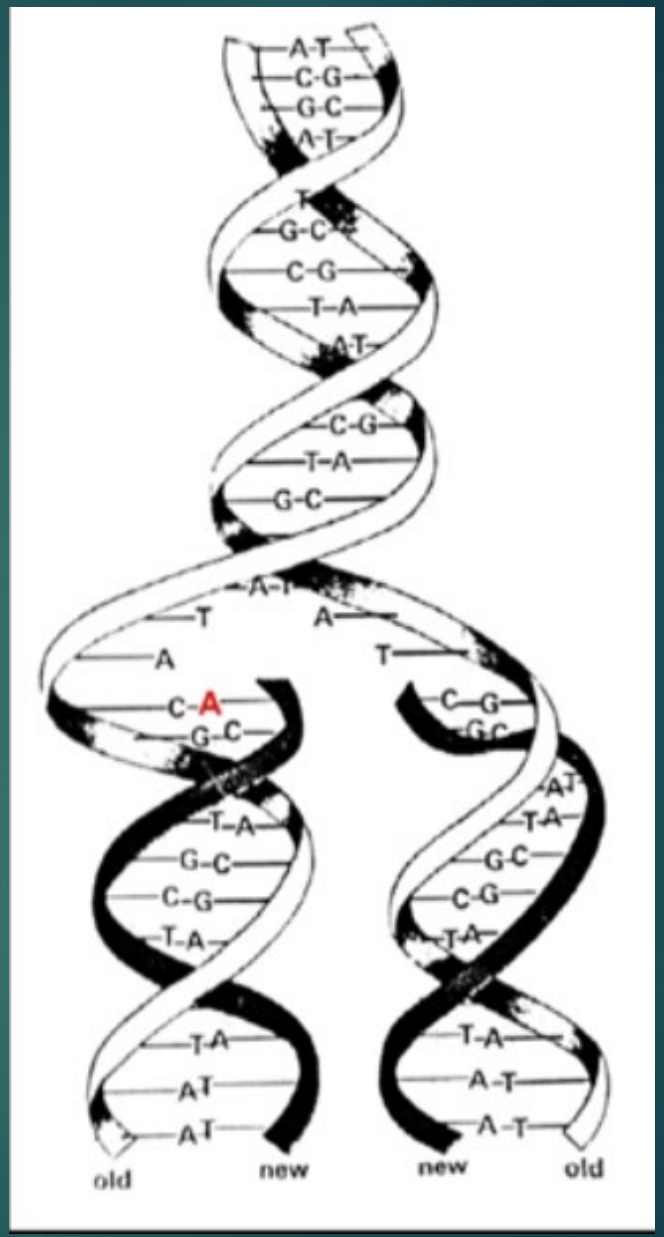
DNA

- DNA is composed of two strands of nucleotides coiled around each other, linked together by hydrogen bonds and running in opposite directions.
- Each strand is composed of four complementary nucleotides – adenine (A), cytosine (C), guanine (G) and thymine (T) – with an A on one strand always paired with T on the other, and C always paired with G.
- Such a structure allowed each complete strand to be used to reconstruct the other, an idea central to the passing on of hereditary information between generations.

Double Helix Molecule

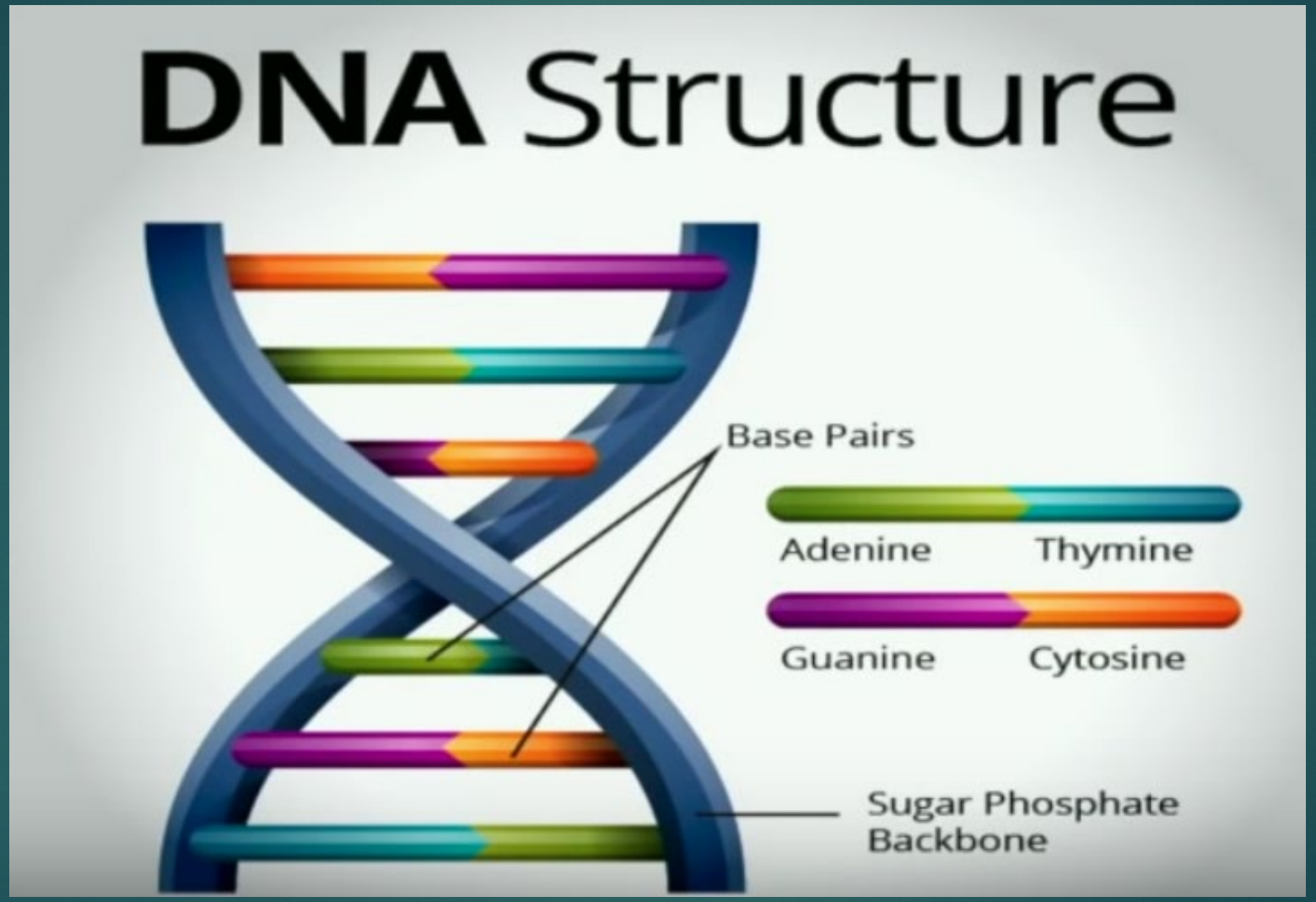
Information in sequence of 4 bases:
A –T – C - G





Information is there twice – once on each strand; come apart when new cells formed; new strands synthesized; use old ones as template; sometimes, error occurs

DNA: nucleotides = basepairs = ATGC



Basic terms in Genetics

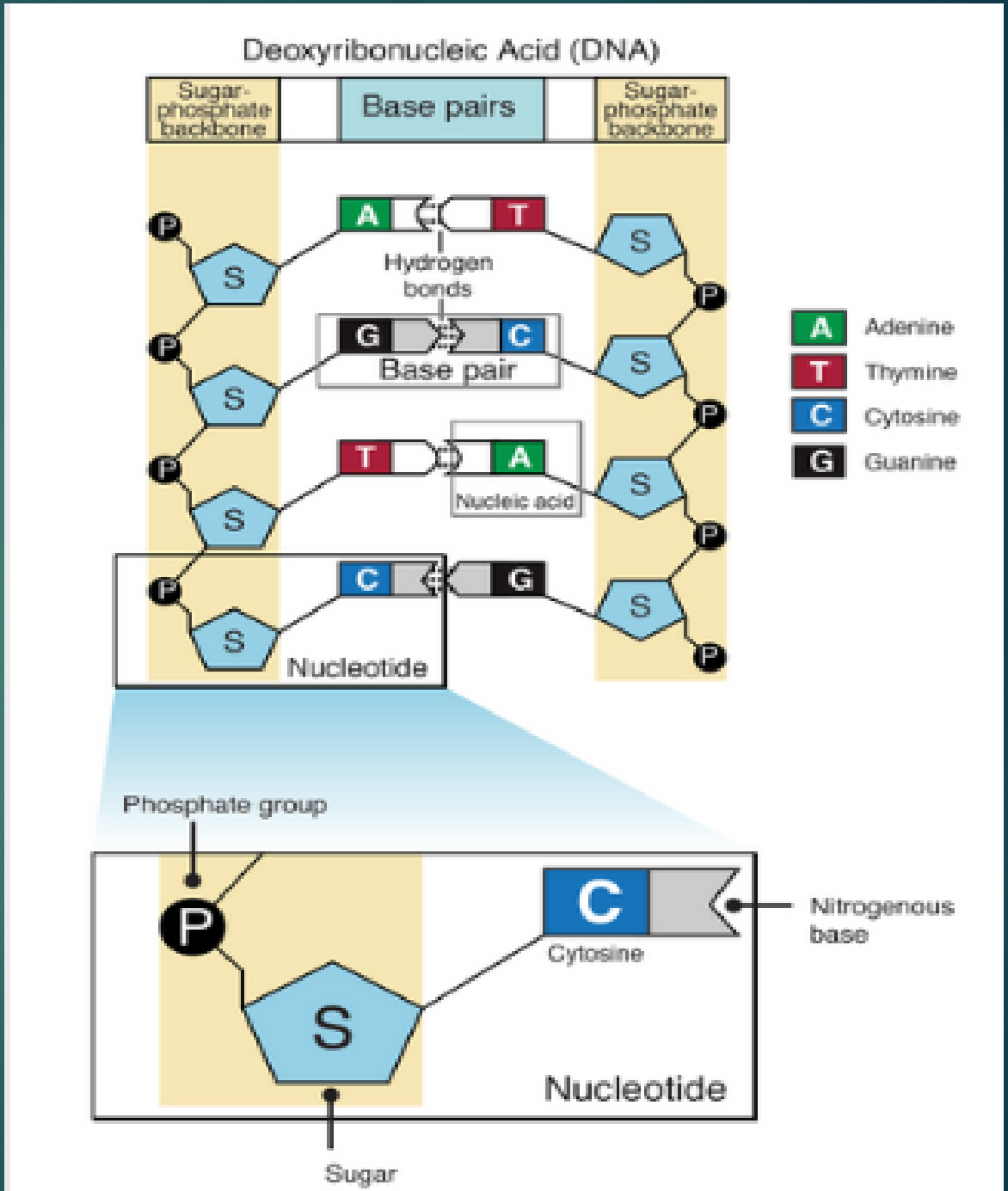
Nucleotide = the basic building block of DNA, made of nucleic acids. It consists of a sugar molecule (deoxyribose in DNA) attached to a phosphate group and a nitrogen-containing base. The bases used in DNA are adenine (A), cytosine (C), guanine (G), and thymine (T). In RNA, the base uracil (U) replaces thymine.

Gene = a sequence of nucleotides in DNA or RNA that can synthesize either RNA or a protein; During gene expression, the DNA is first copied into RNA. The RNA can be directly functional or be the intermediate template for a protein that performs a function.

Chromosome = a long DNA molecule with part or all of the genetic material of an organism.

Genome = all genetic material of an organism. It consists of DNA; includes both the genes (the coding regions) and the noncoding DNA, as well as mitochondrial DNA

- Nucleotide: the basic building block of nucleic acids.
- RNA and DNA are polymers made of long chains of nucleotides.
- A nucleotide consists of a sugar molecule (either ribose in RNA or deoxyribose in DNA) attached to a phosphate group and a nitrogen-

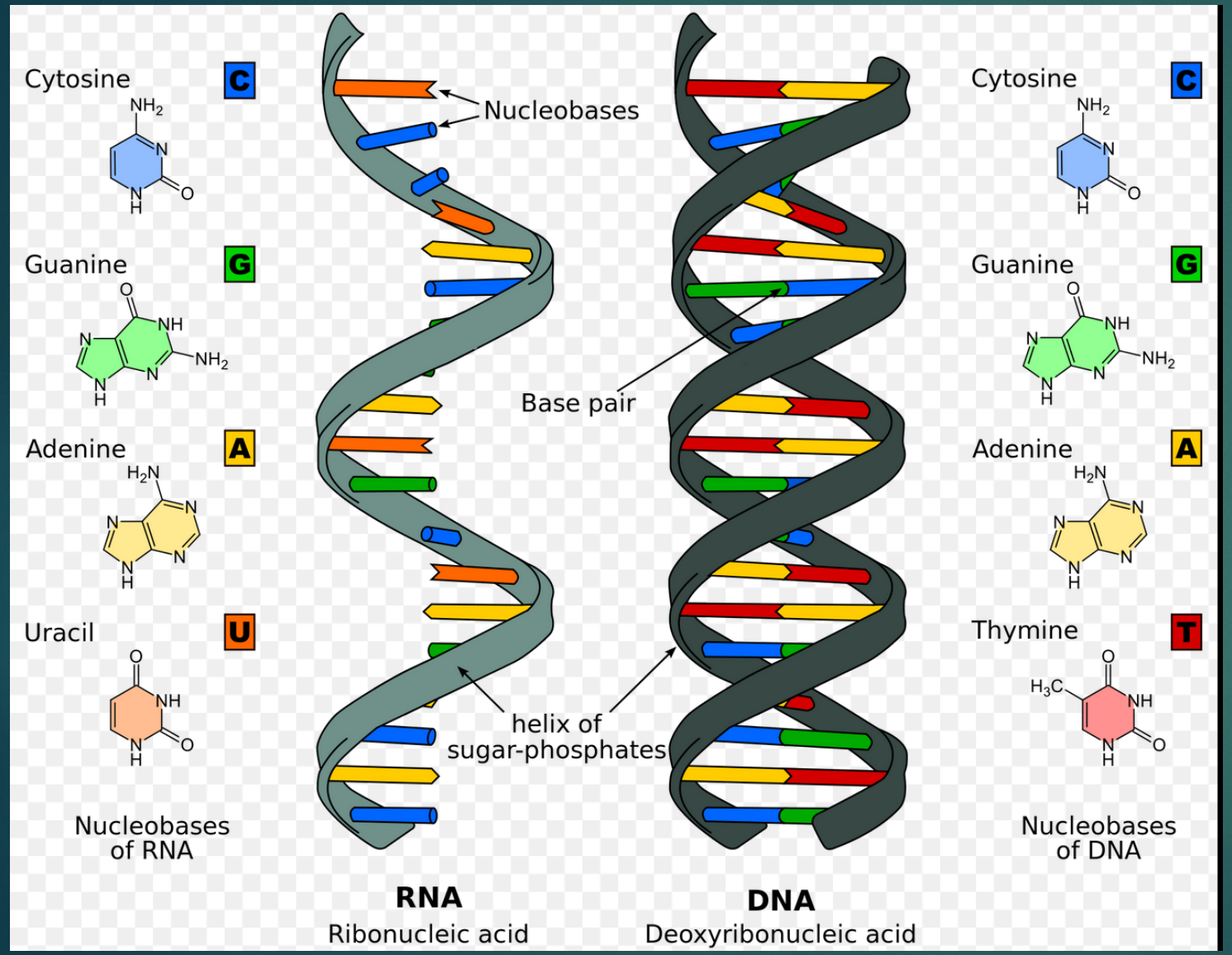


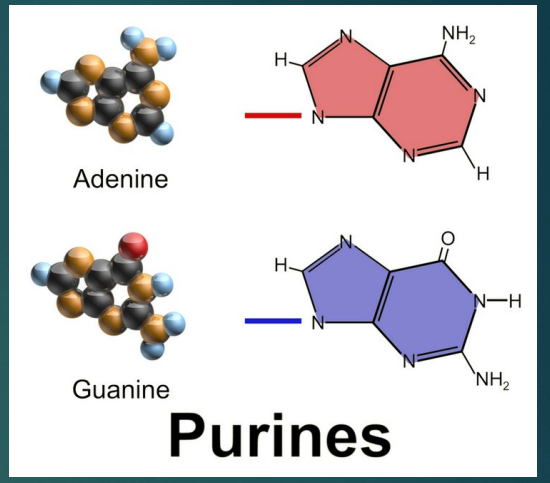
Nucleotide

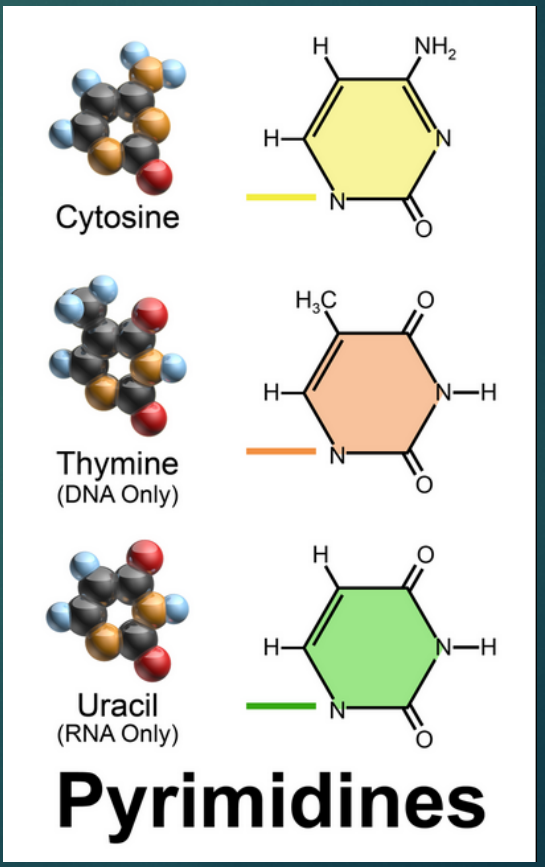
- **Nucleotide** is an organic molecule consisting of a nucleoside and a phosphate.
- They serve as units of the nucleic acid polymers –
  - deoxyribonucleic acid (DNA) and
  - ribonucleic acid (RNA),
  - both of which are essential biomolecules within all life-forms on Earth.
- Nucleotides are obtained in the diet and are also synthesized from common nutrients by the liver.
- Nucleotides are composed of three subunit molecules:
  - a nucleobase,
  - a five-carbon sugar (ribose or deoxyribose),
  - and a phosphate group consisting of one to three phosphates.

  - Four nucleobases in DNA are guanine, adenine, cytosine and thymine; in RNA, uracil is used in place of thymine.

Nucleobases: base pairs(A-T, C-G)







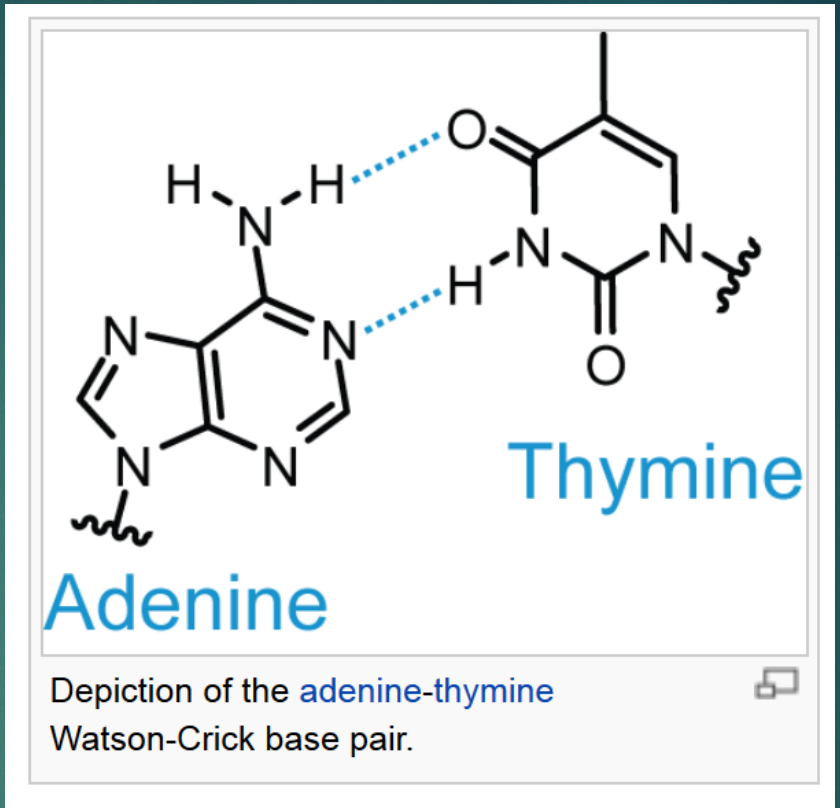
Nucleic Acids

Purines (large)
- Ademine (A)
- Guamine (G)

Pyrimadines (small)
- Thymine (T)
- Cytosine (C)

Depurination = loss of a purine (which is more common) or a pyrimidine in a basepair, leading to an abasic (no bp) site. Abasic sites are the most common modification in the genome in most organisms

Base Pair: Hydrogen Bond



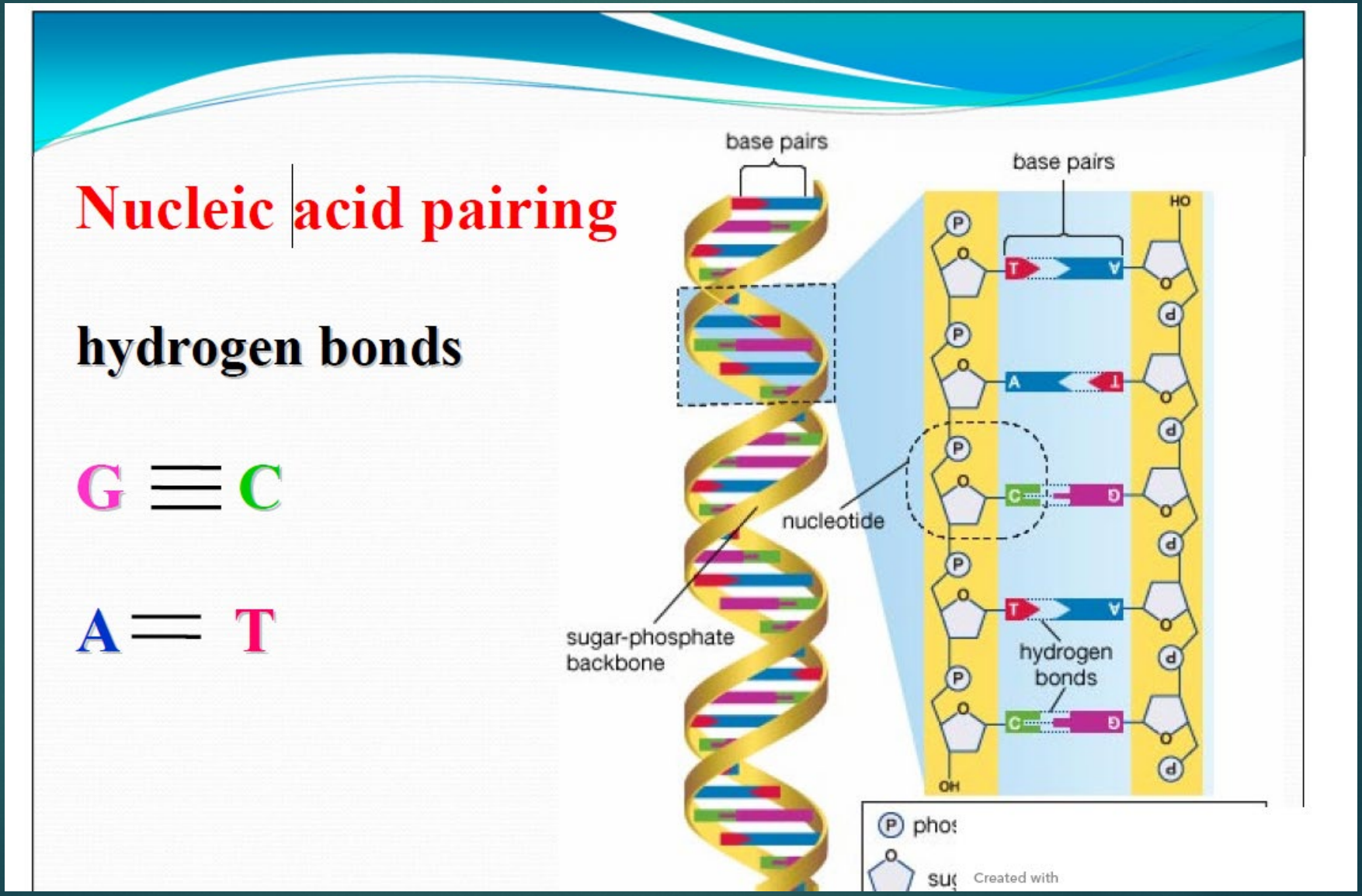
Depiction of the adenine-thymine Watson-Crick base pair.

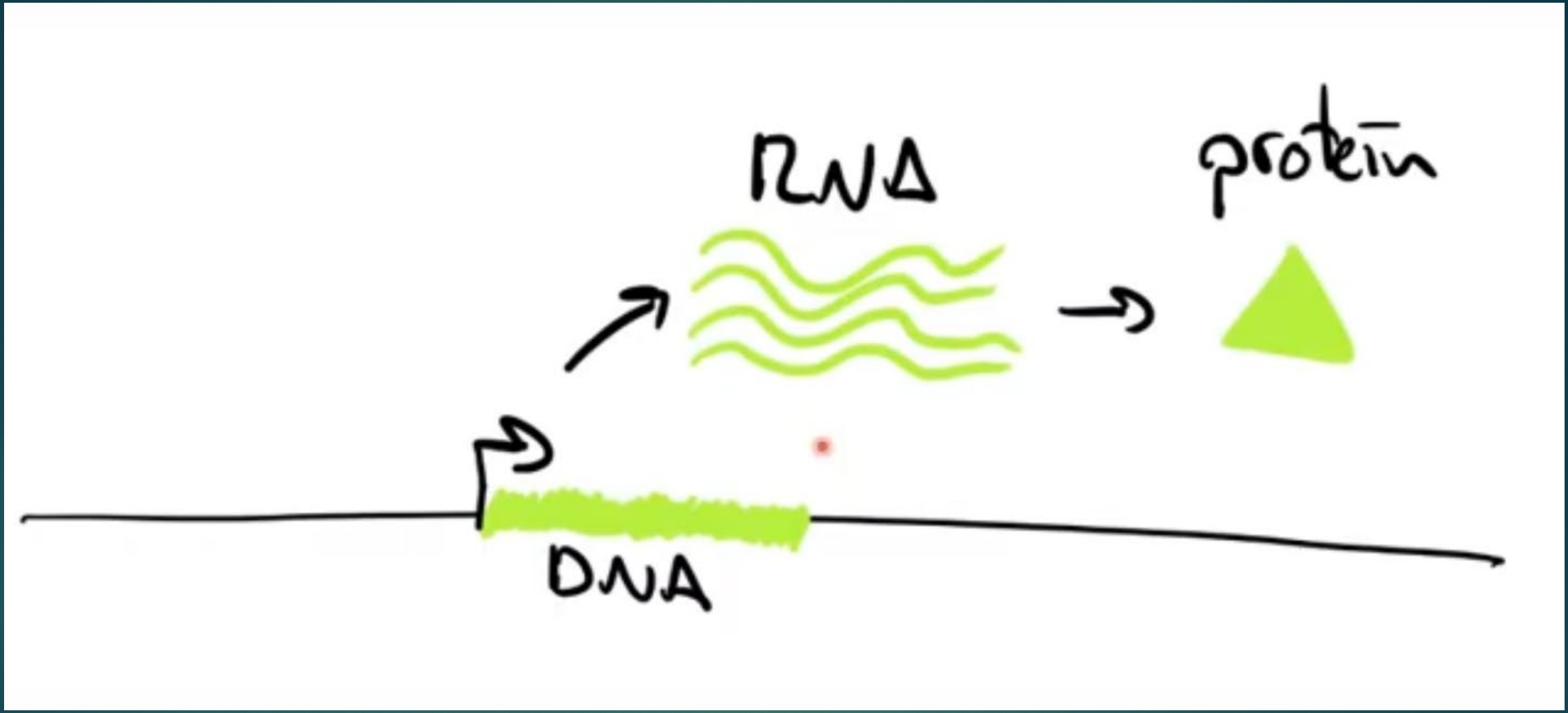
A base pair is the "rung in the ladder“ that makes a double strand in DNA.

A with T: the purine **adenine** (A) always pairs with the pyrimidine **thymine** (T)
C with G: the pyrimidine **cytosine** (C) always pairs with the purine **guanine** (G)

In RNA the thymine is replaced by uracil.

Nucleic acid pairing





DNA makes RNA copies of parts of itself (transcription), which in turn create proteins

DNA Pairing

Purine always pairs with Pyrimidine

Adenine always pairs with Thymine

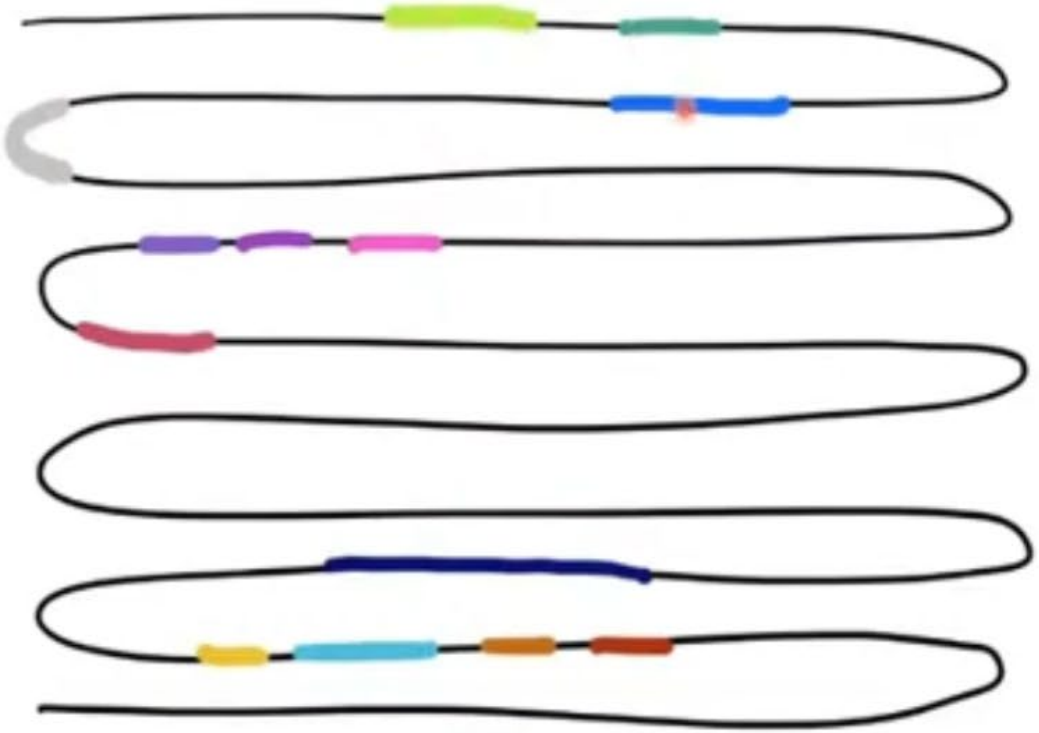
Guanine always pairs with Cytosine

When they don't, it is a mutation

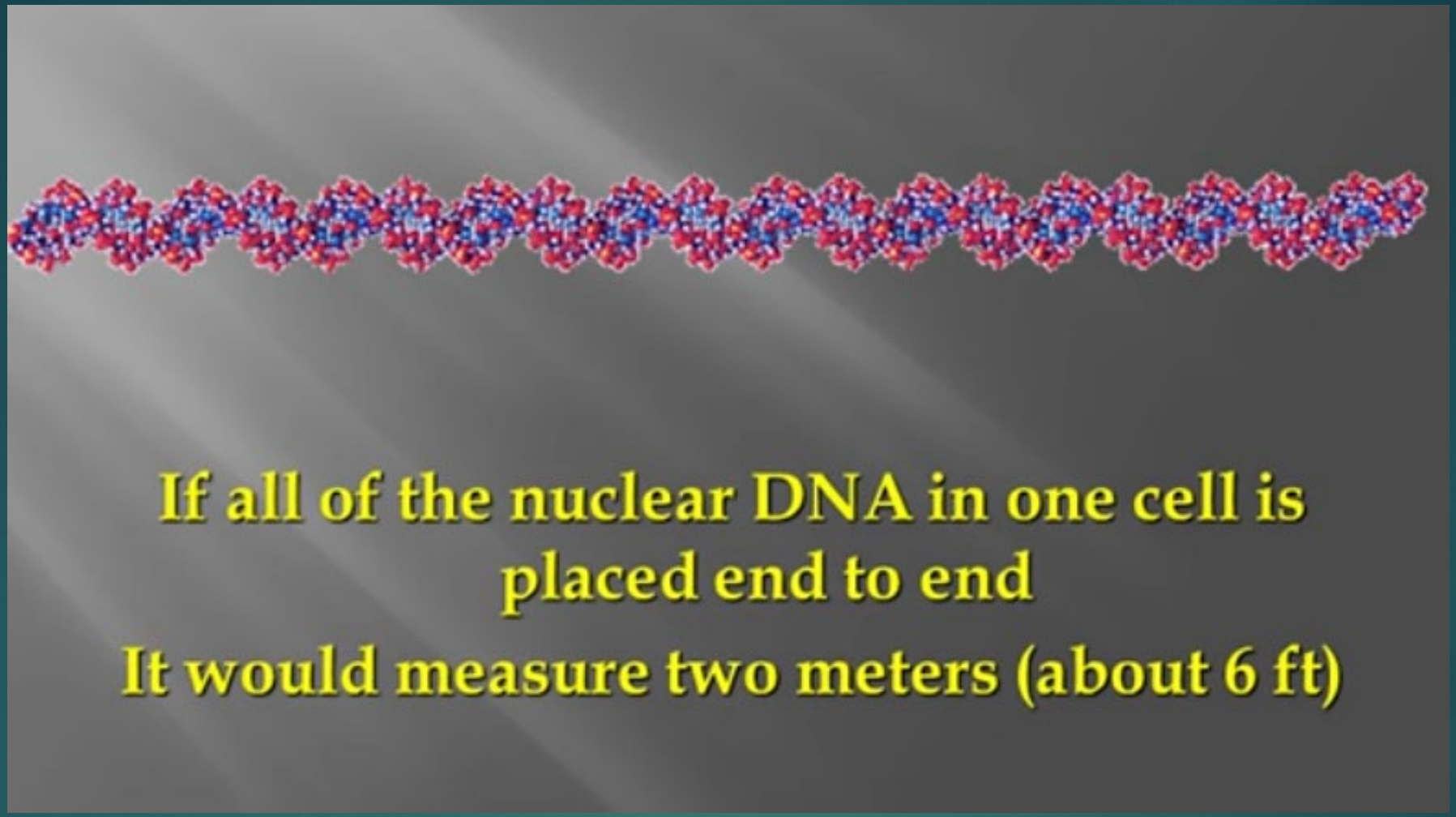
Most mutations have a neutral effect.

If mutations occur in coding regions, outcome is usually negative

23 chromosomes =
20 K genes

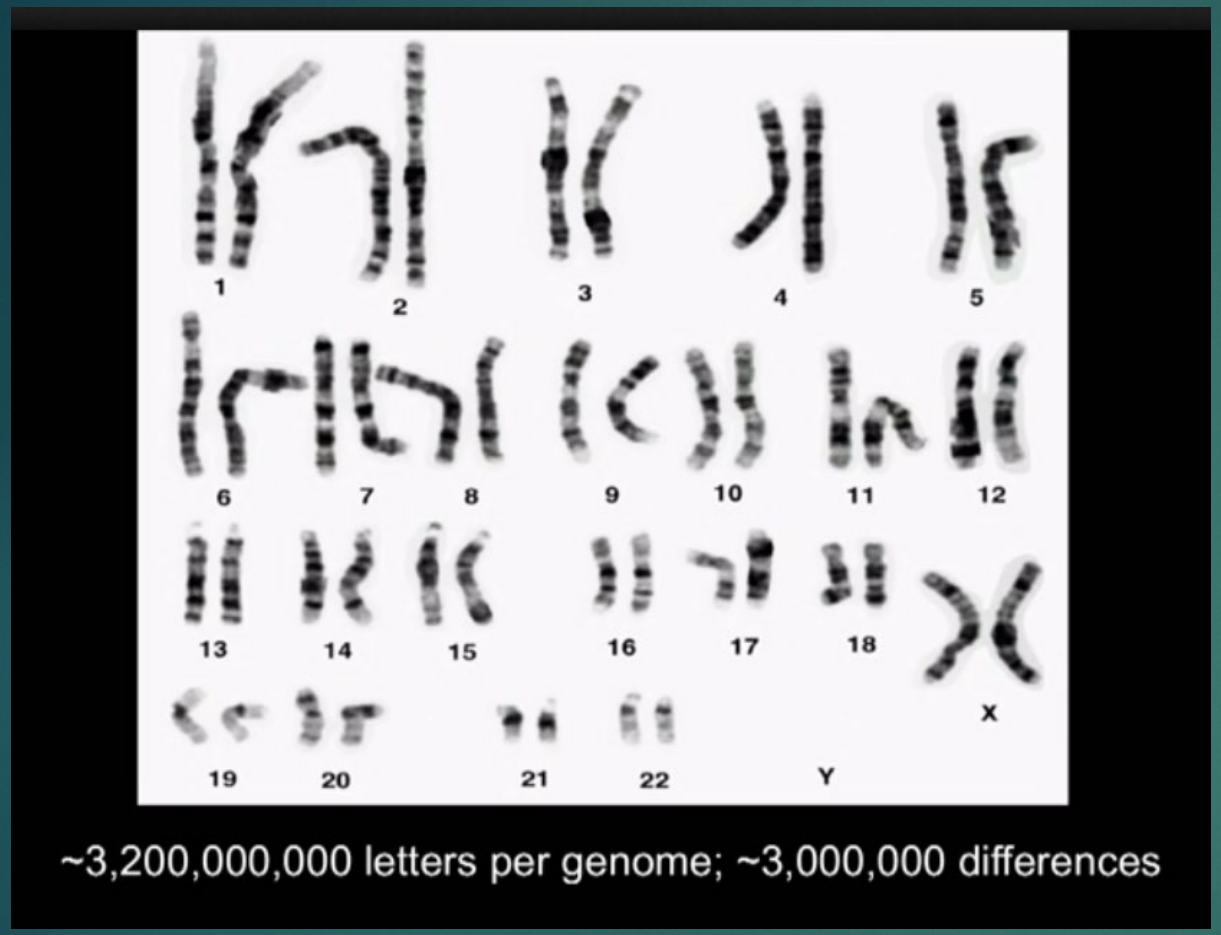


1 chromosome



DNA in every nucleus of every cell in body:
.000326 inches wide

3.2 Billion bases per genome



- 99.9% identical DNA between any 2 of us
- Every new baby has 100-200 new mutations
- Between any 2 humans, a mutation every 1200 bases (in every 100 bases in H vs Chimp)

- Each of us has 2 genomic strands; 6.4 billion nucleotides
- 3 million base pair differences between any 2 people (.1%)

Basic terms in Genetics

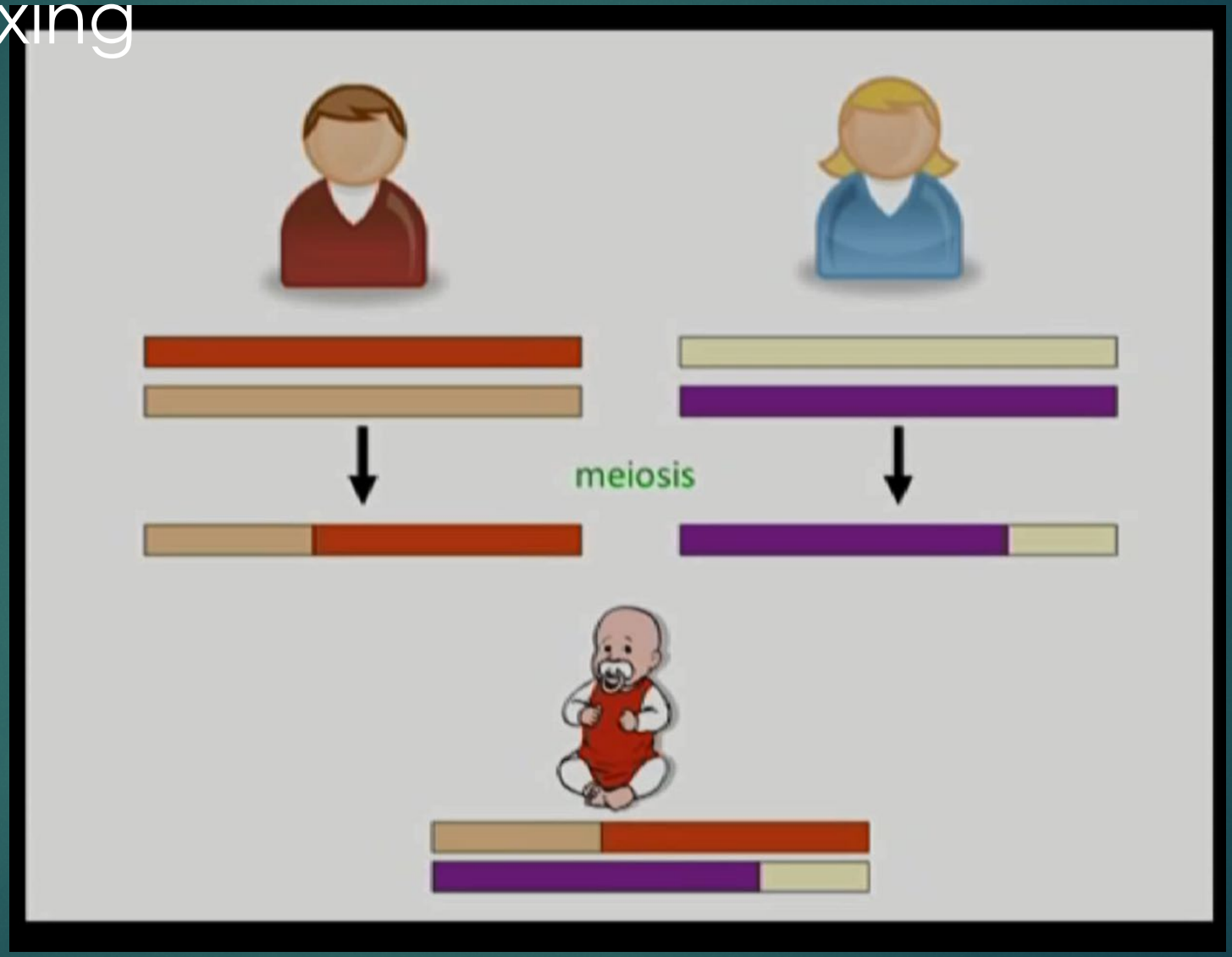
- Genetic Loci = a specific, fixed position on a chromosome where a particular gene is located
- Allele = 1 of 2 or more alternative forms of a gene that arise by mutation; found on same place on chromosome
- Haplotype = a combination of alleles at multiple loci that are transmitted together on same chromosome
- Recombination is a process during meiosis by which pieces of DNA are broken and recombined to produce new combinations of alleles

Recombination: Ancestral genetic mixing

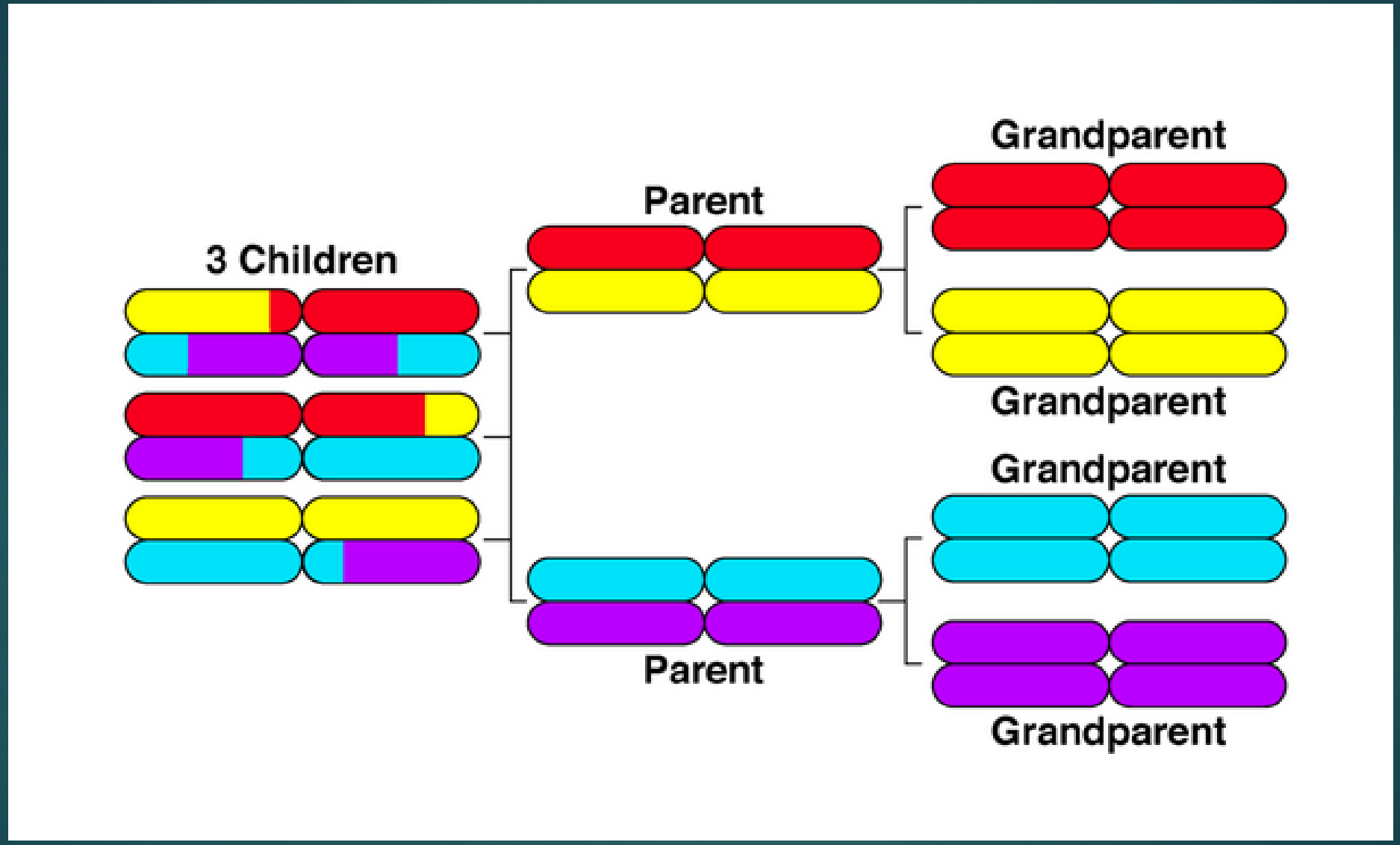
Gfather
Gmother

Father

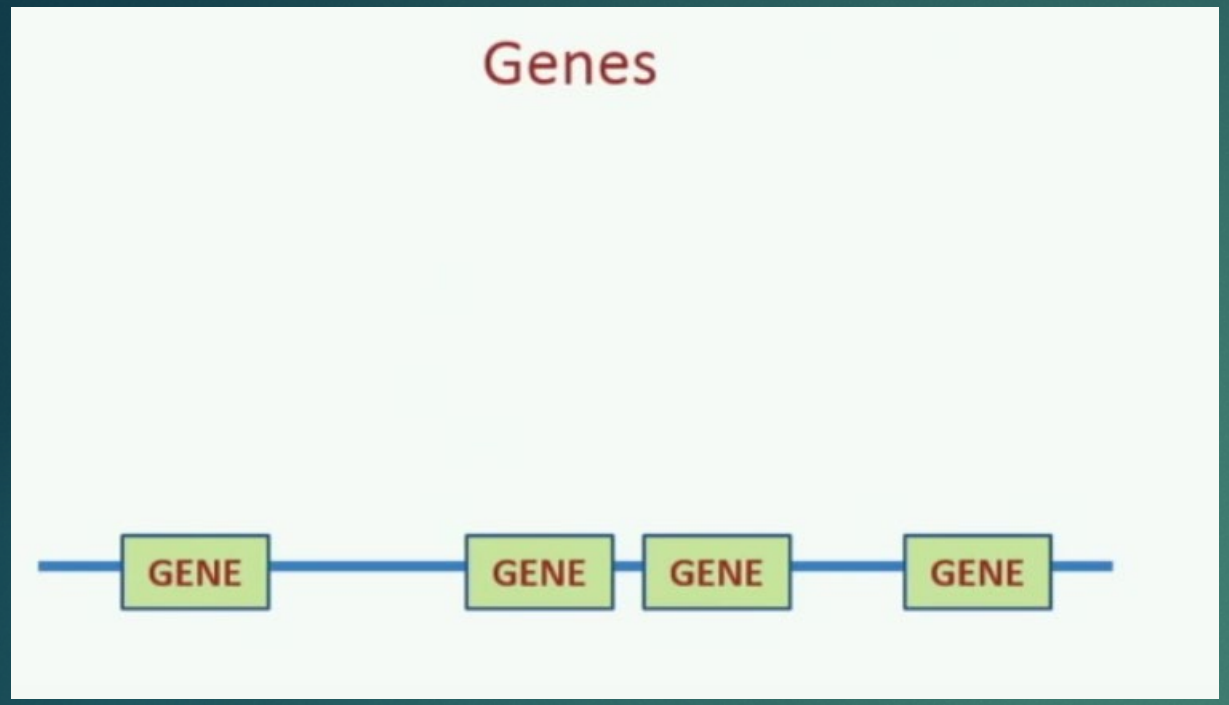
You

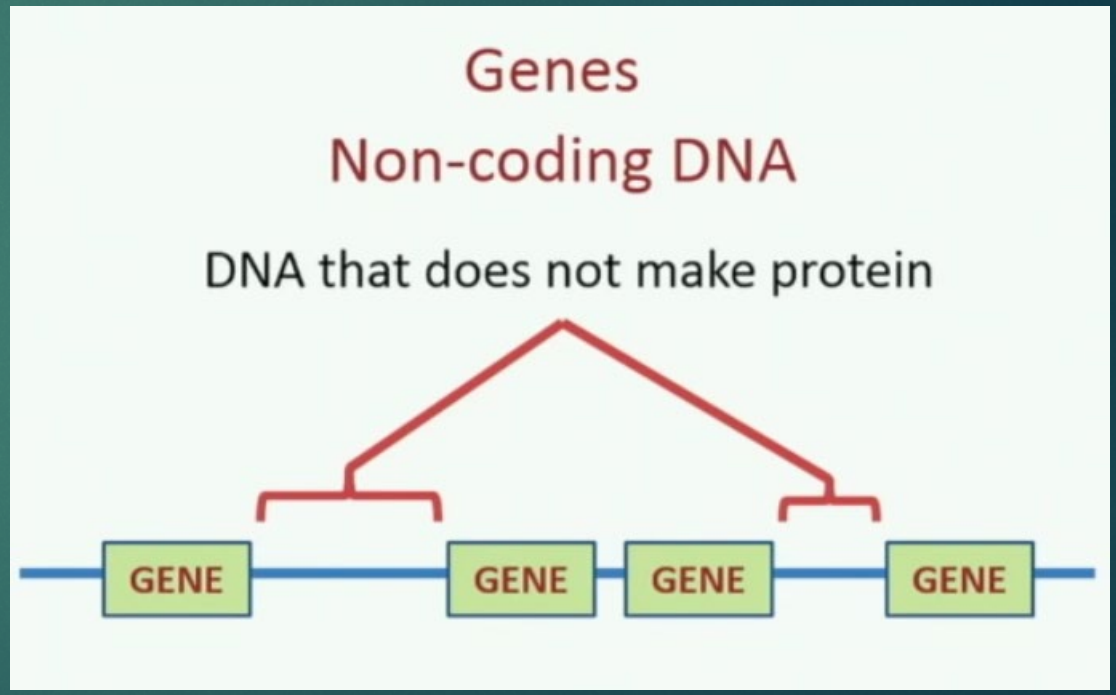


Recombination



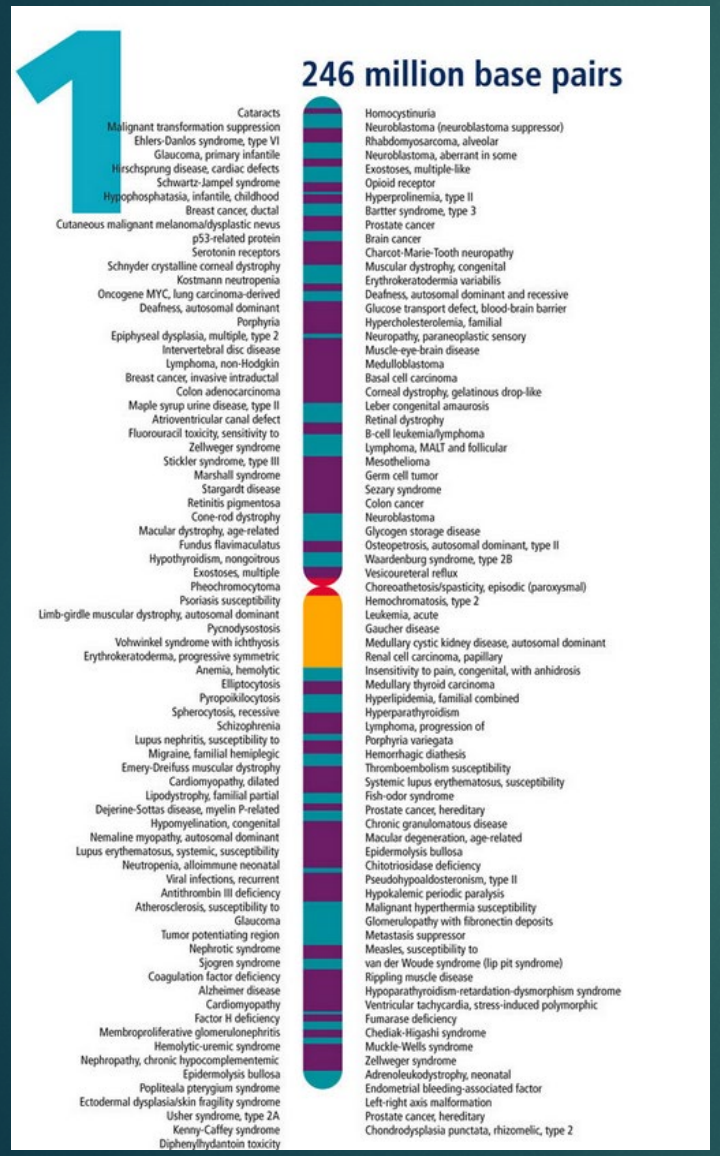
Genes: sections of DNA that code for proteins

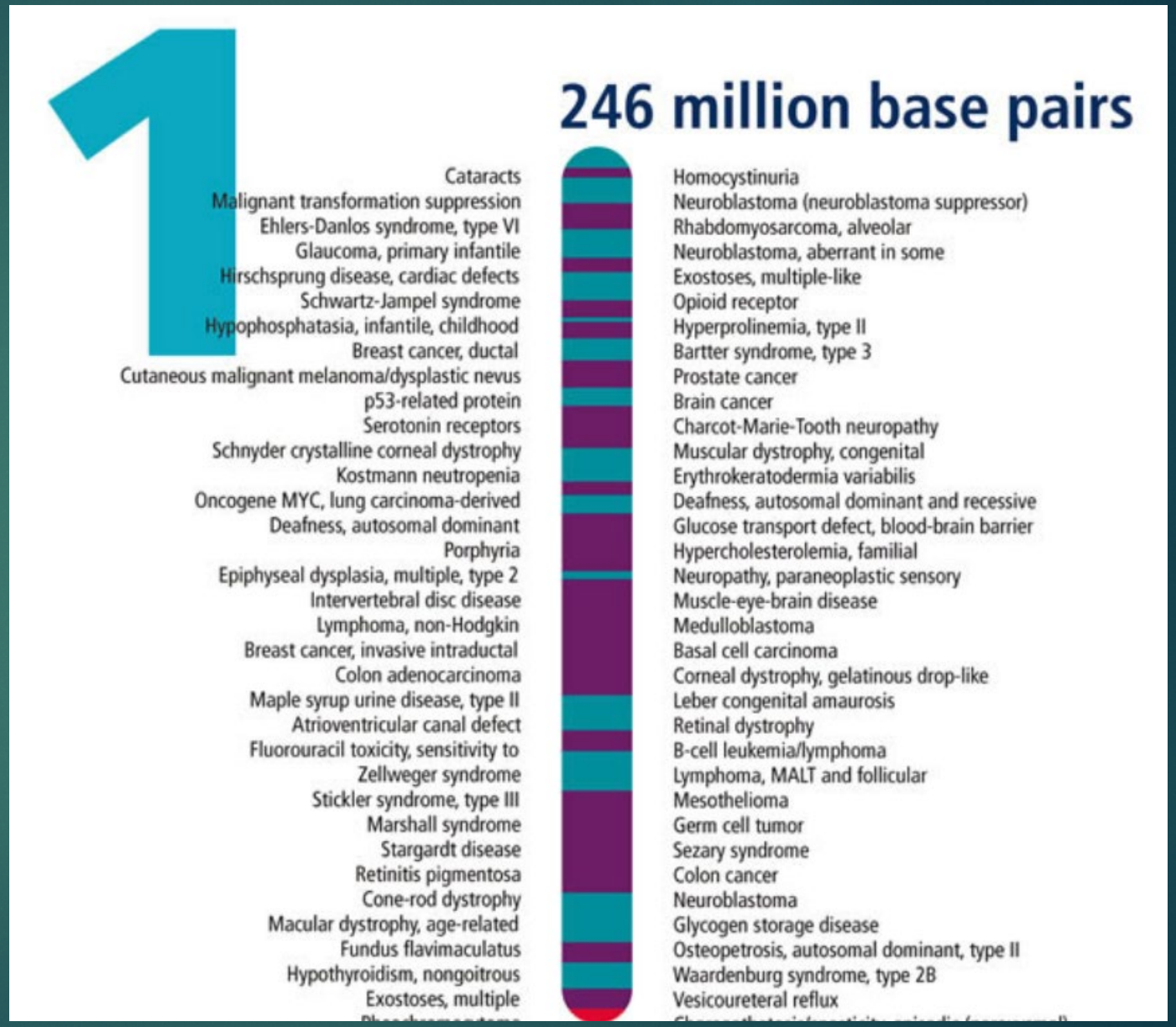


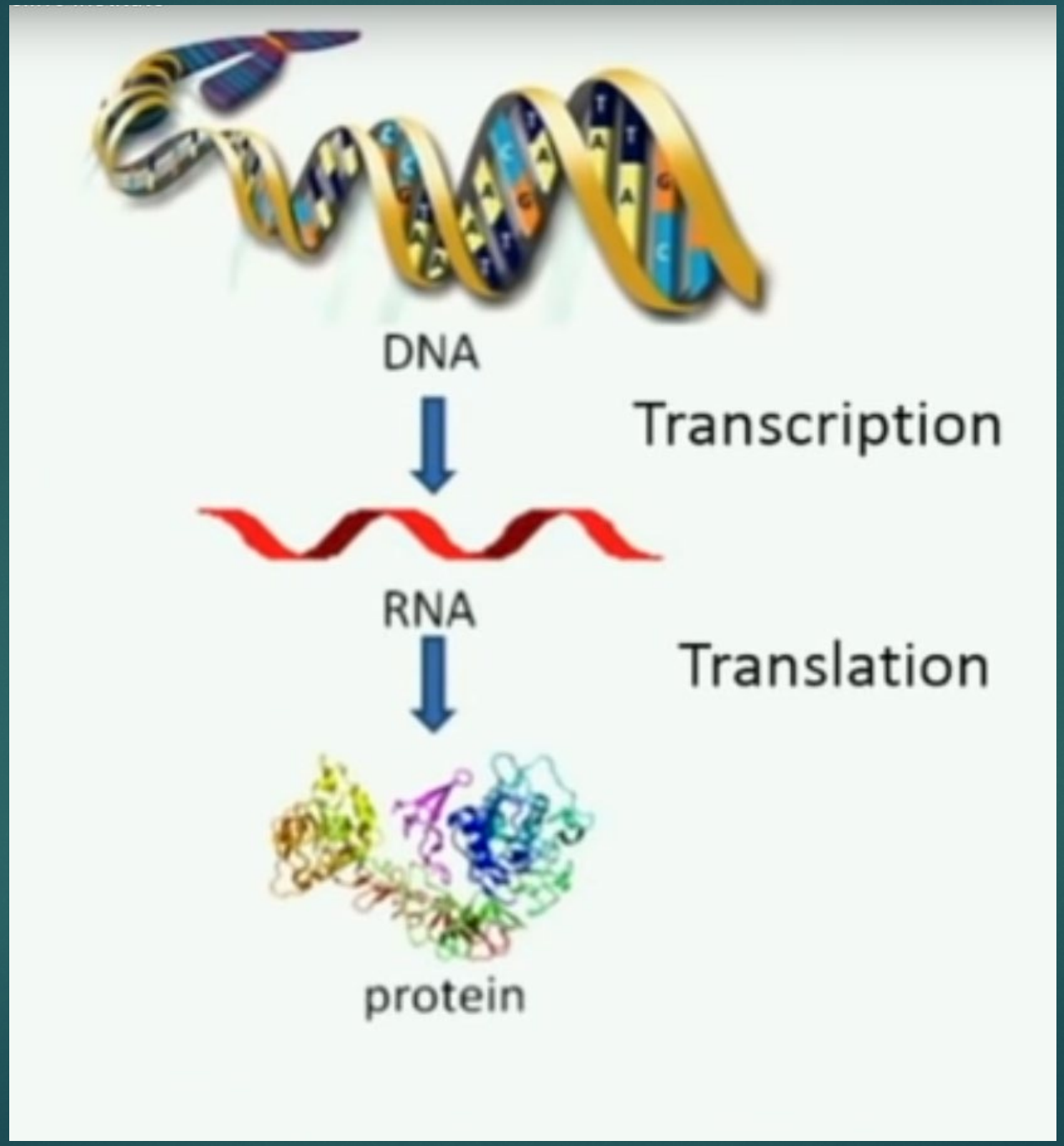


Junk DNA:
carry instructions for gene regulation

Genes on Chromosome 1



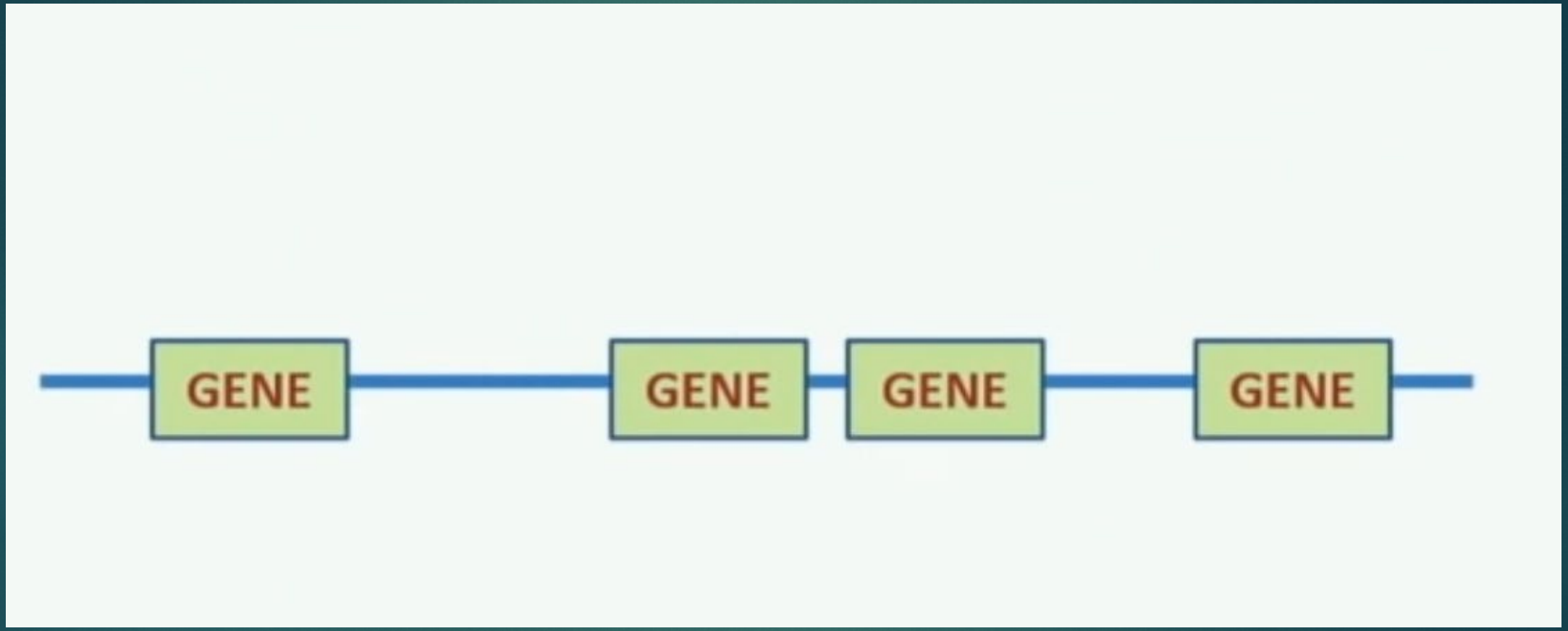




= RNA production

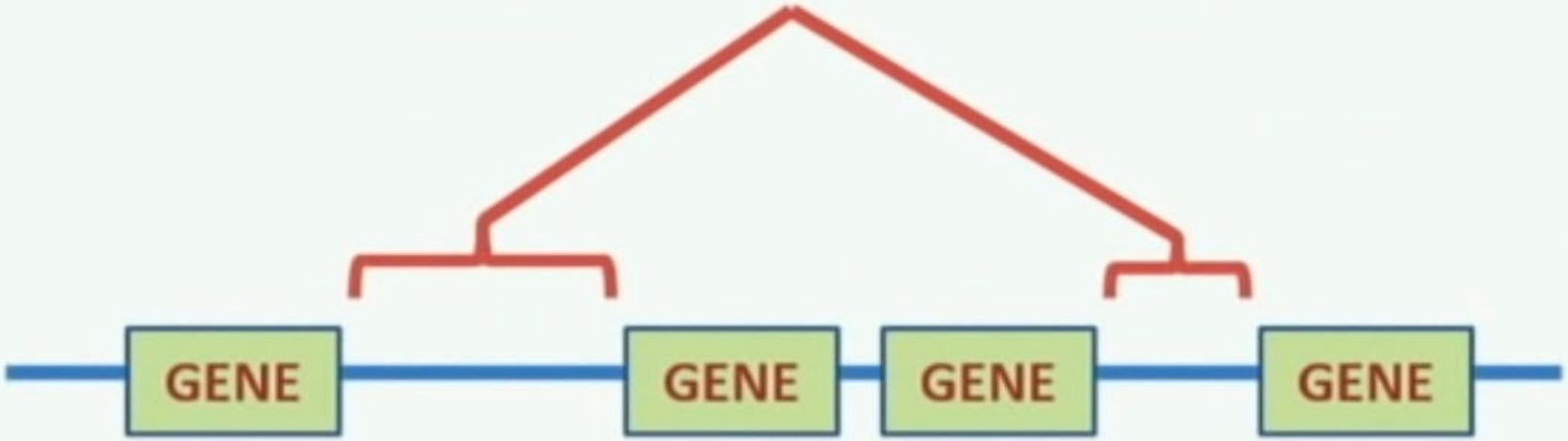
= Protein synthesis

Genes on a chromosome code for proteins

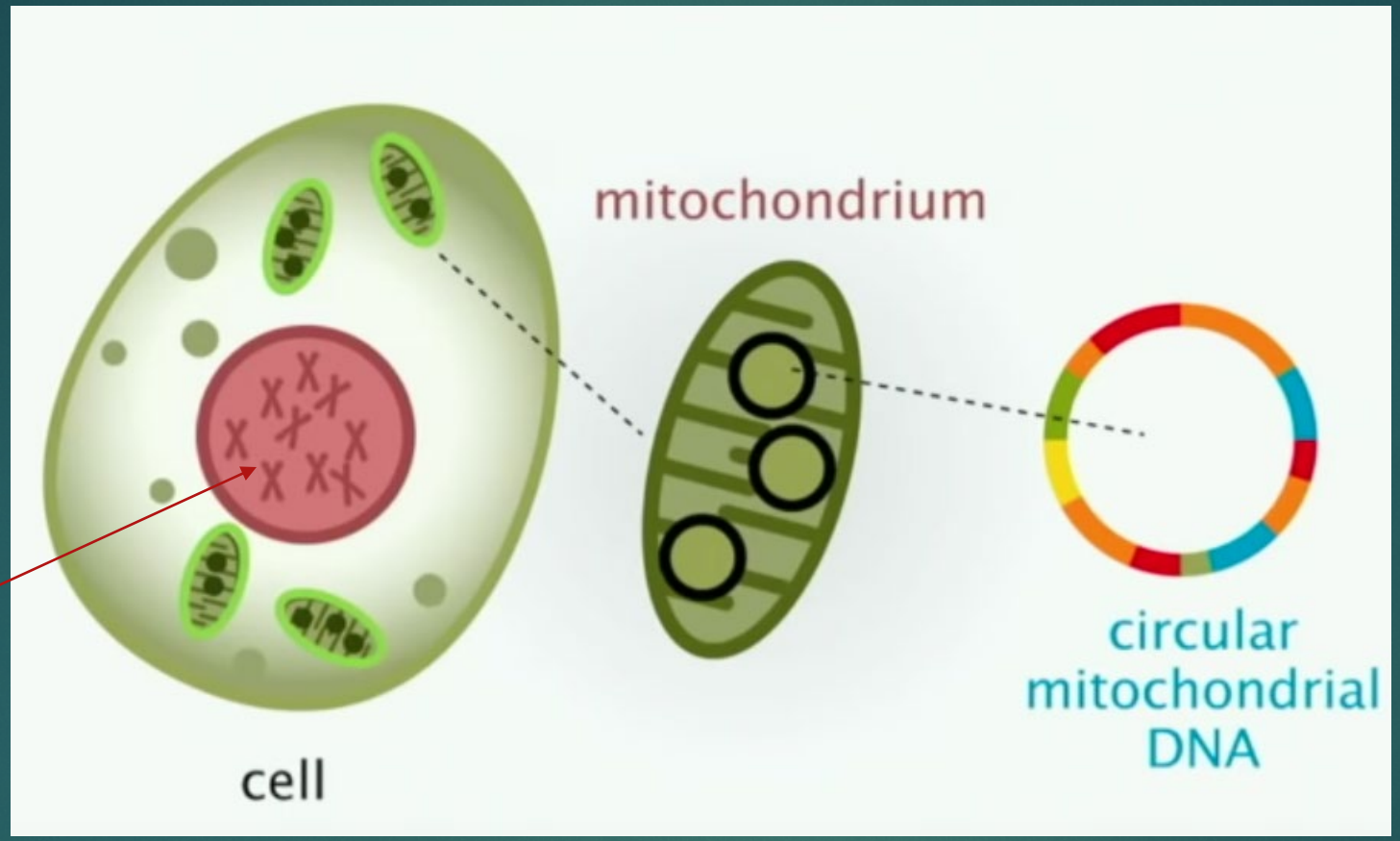


Non-coding DNA

DNA that does not make protein



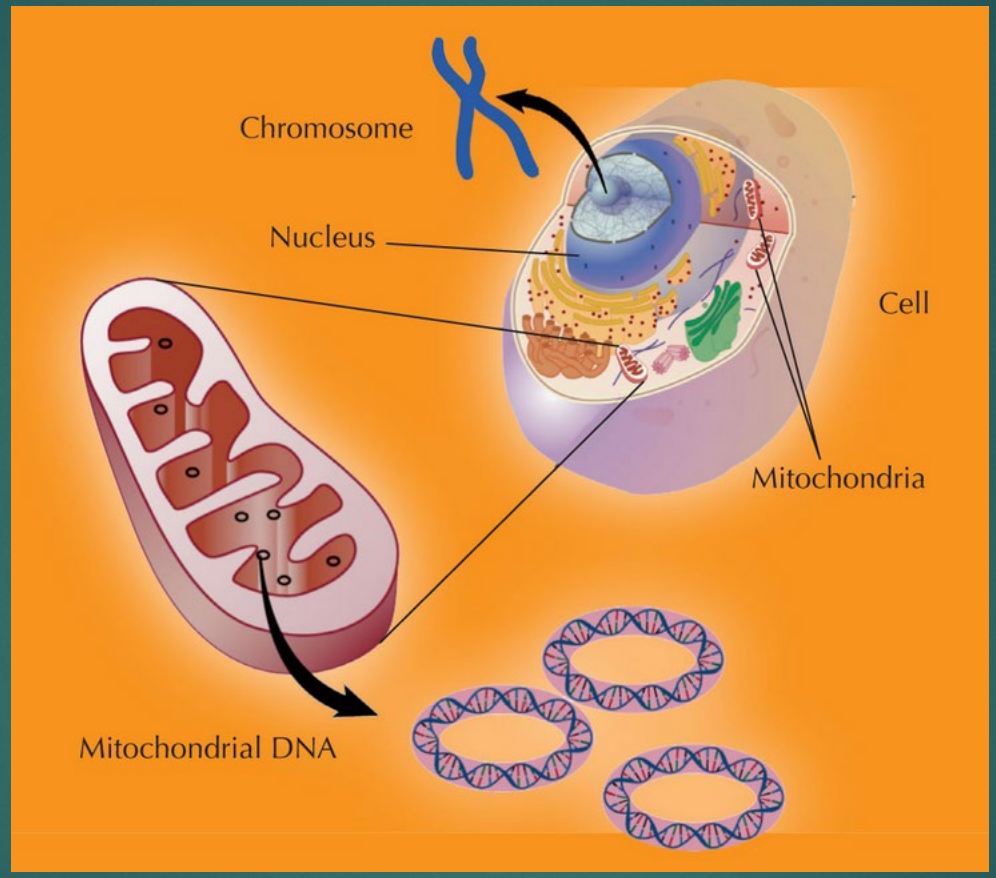
Mitochondria



Nuclear DNA

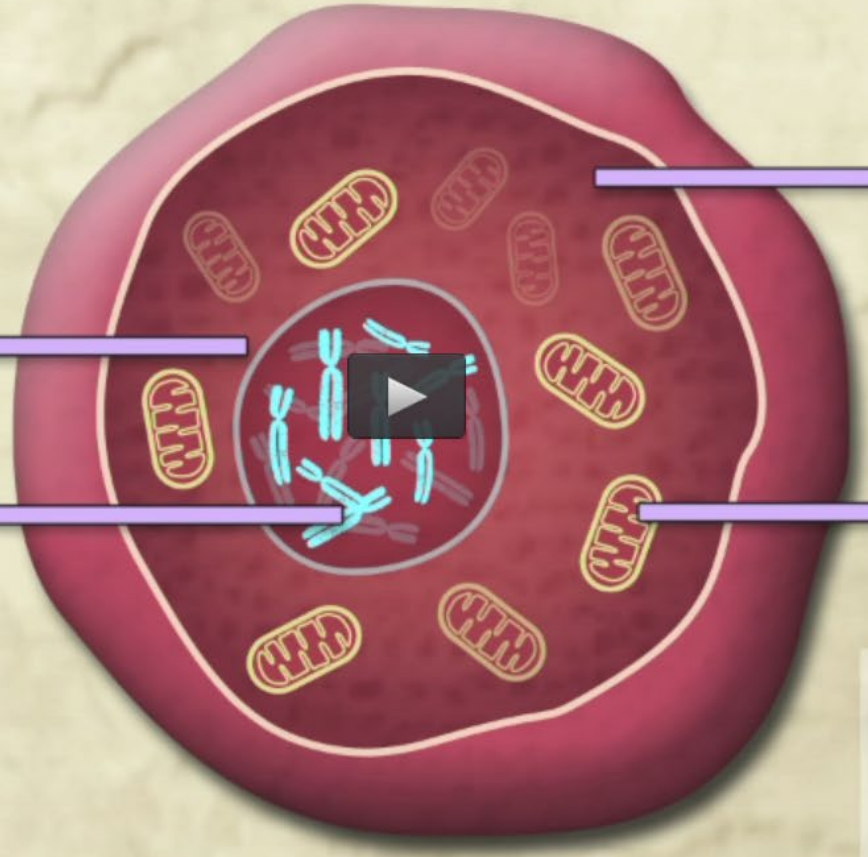
Energy producing Mitochondria live outside nucleus; primitive circular DNA inherited from bacteria

Mitochondrial DNA



0 (blood) to 2000 (liver) mitochondria in cells
2 M in neurons

Different Sources of DNA in a Human Cell



Cytoplasm

Nucleus

Chromosomes

Mitochondria

Nuclear DNA

Mitochondrial DNA (mtDNA)

Nuclear Versus Mitochondrial Genome

22 autosome pairs and sex chromosomes

3.4 billion bases

~20,000 genes

Circular double-stranded

16,600 bases

37 genes

Inherited from both parents

Extensive recombination

Large number of variable regions useful for studying diversity

Maternally inherited

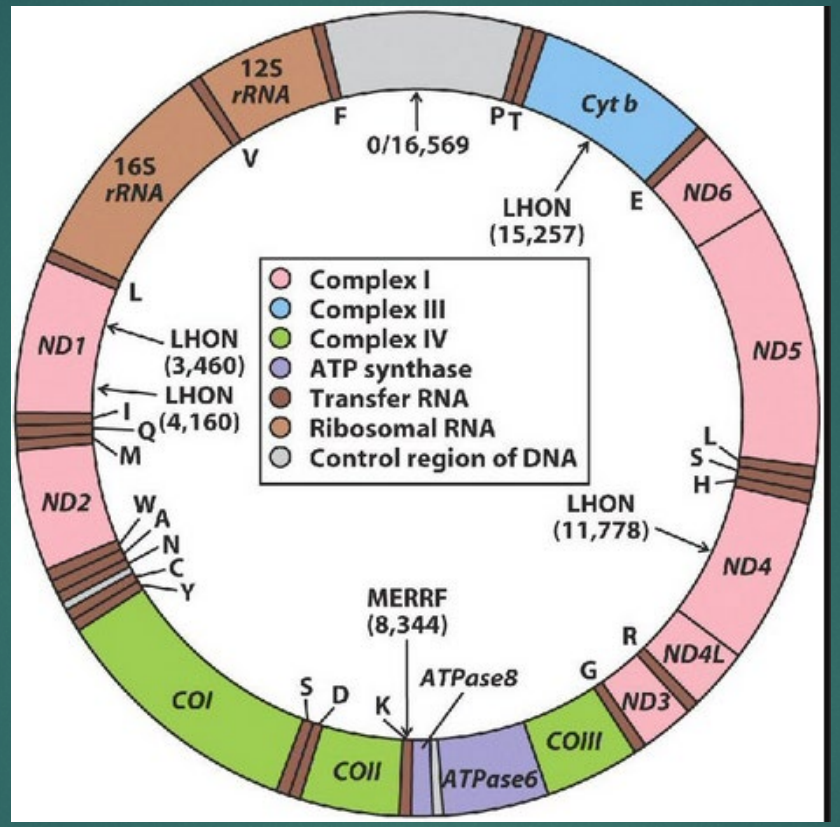
No recombination

Useful for tracing evolutionary history

High mutation rate

mtDNA

- Mitochondrial DNA (mtDNA):
- A separate DNA genome of the mitochondria, which are maternally inherited organelles found within every cell.

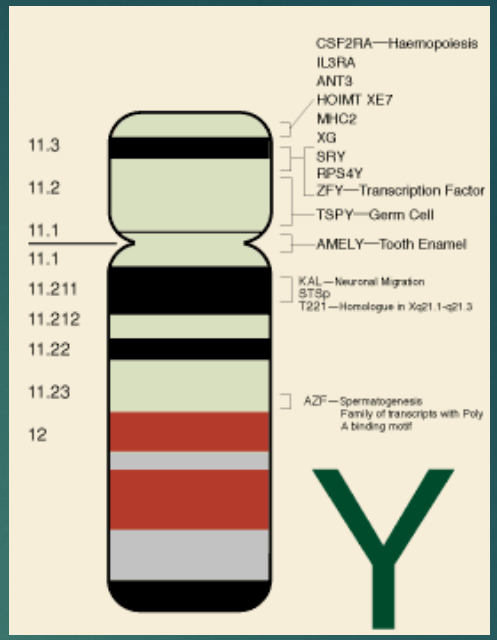


Circular;

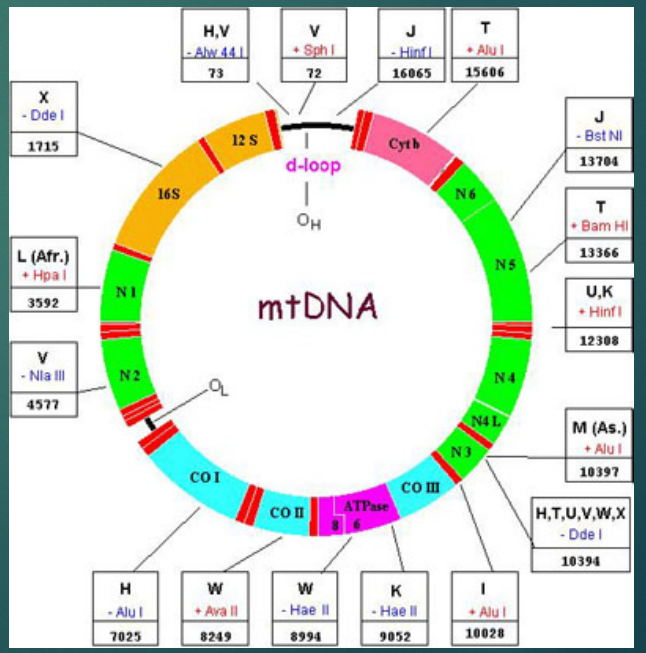
37 genes (13 protein encoding;
22 tRNA encoding, 2 rRNA),

16569 base pairs

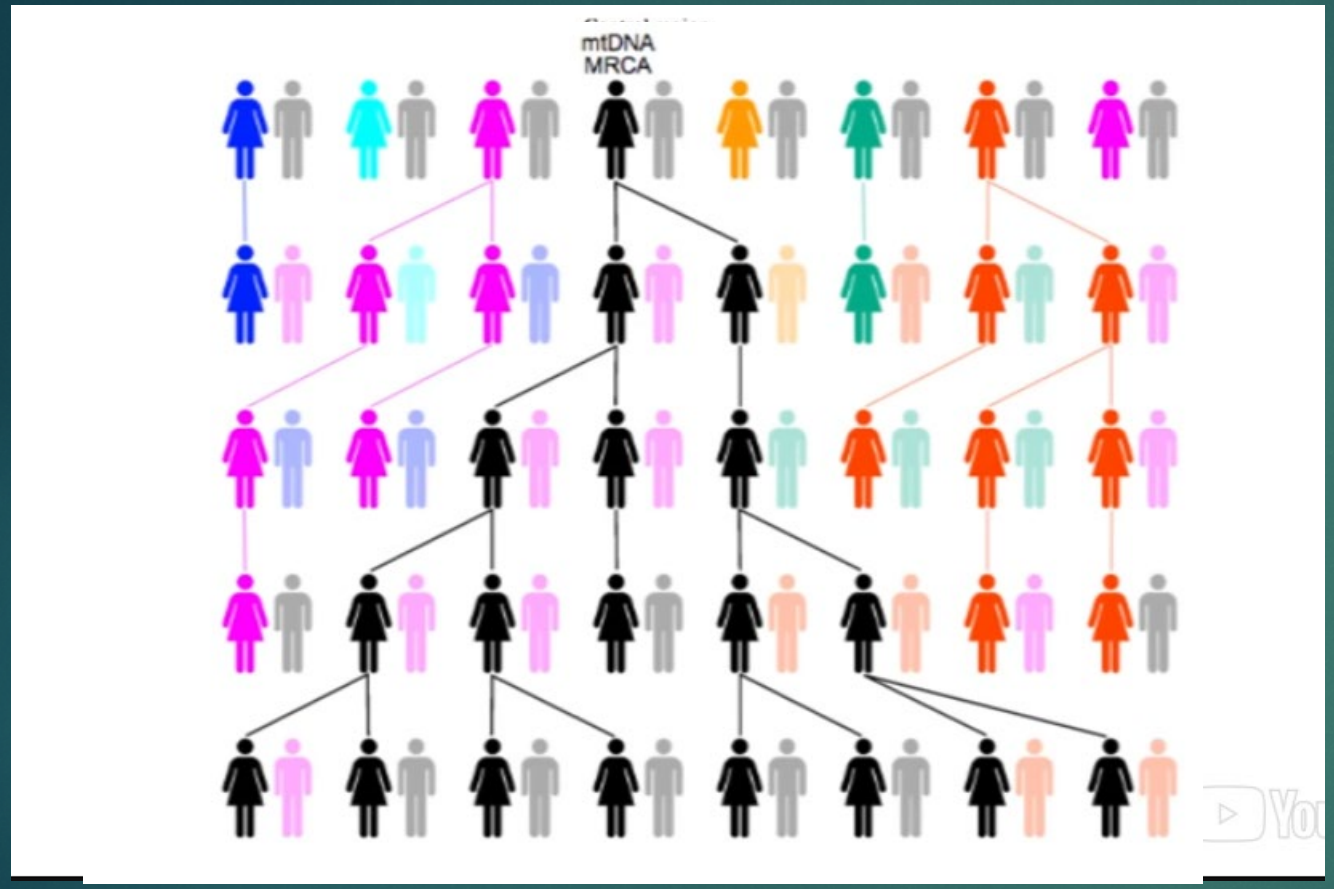
- Y chromosome data is used to trace paternal ancestry.



- mtDNA is used to trace maternal ancestry.



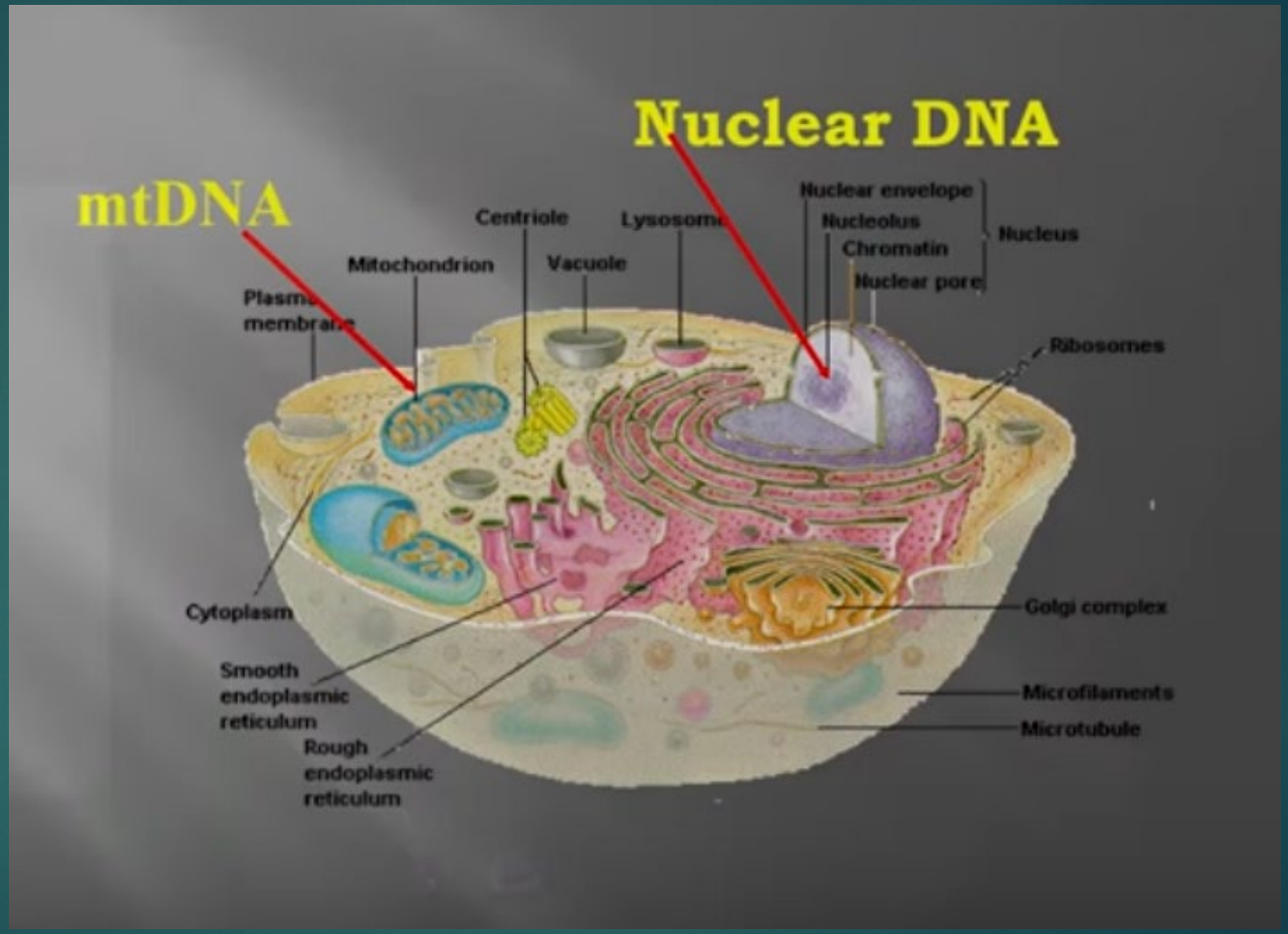
Mitochondrial DNA: maternal heritage, no recombination



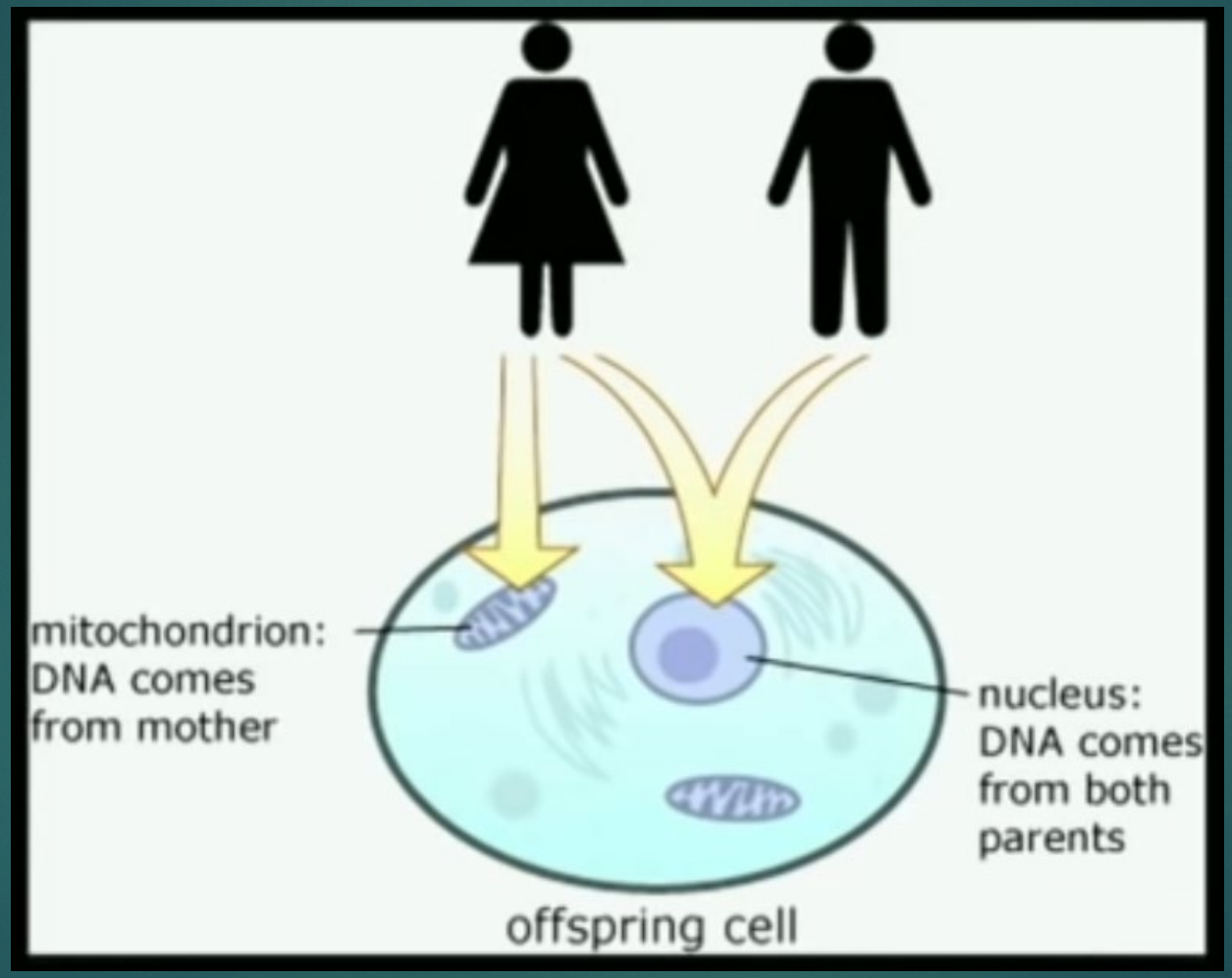
- Vital for function of cell; any mutations tend to be negative, and selected against;
- evolution coalesced recently in humans in Africa = Mitochondrial Eve, c. 150-200K;
- speciation event that occurred late in the Pleistocene.

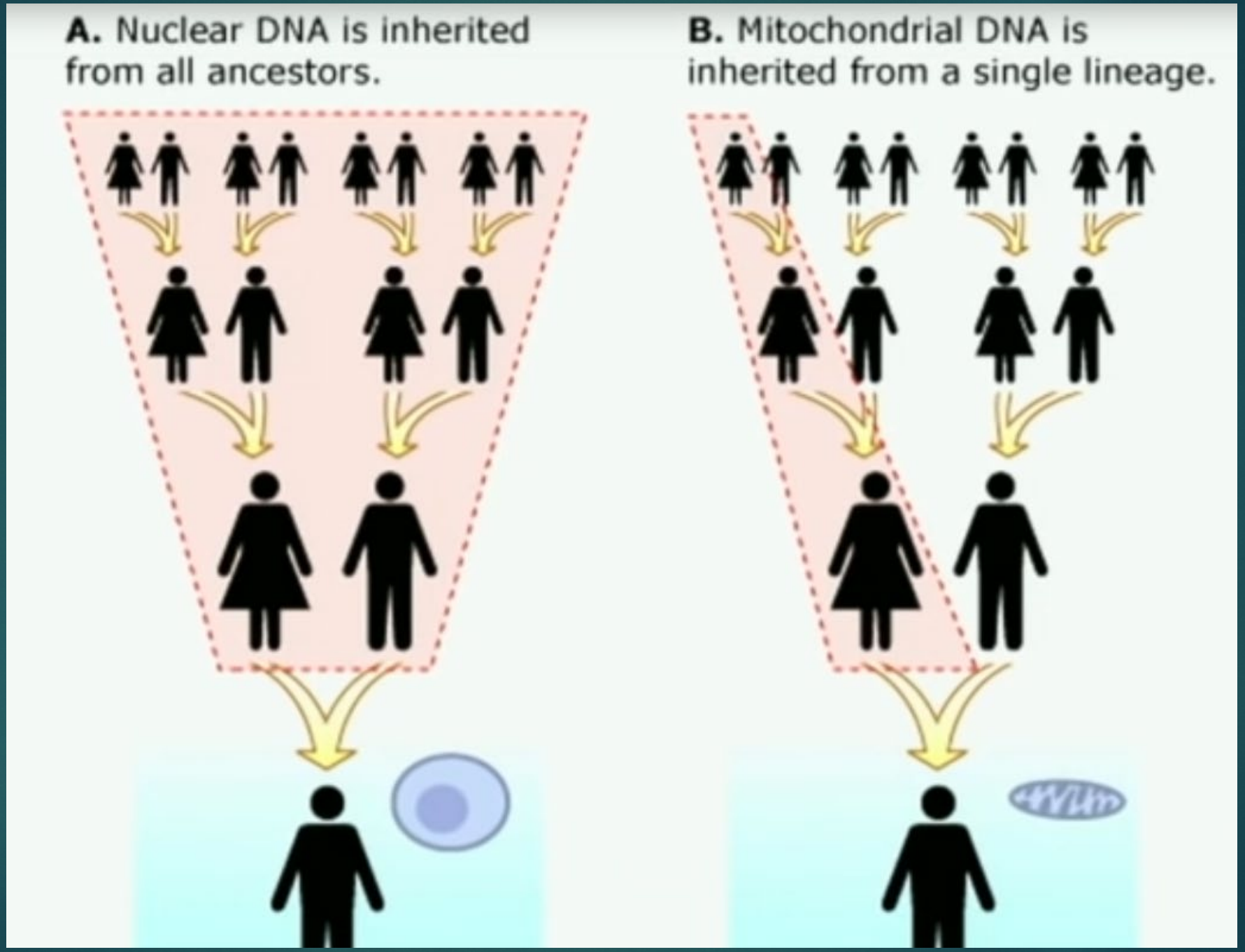
Mitochondria was a parasite that invaded cells (closer to bacterial than human genome)

# of mitochondria in a cell relates to amount of energy use via ATP; brain and heart cells have a lot

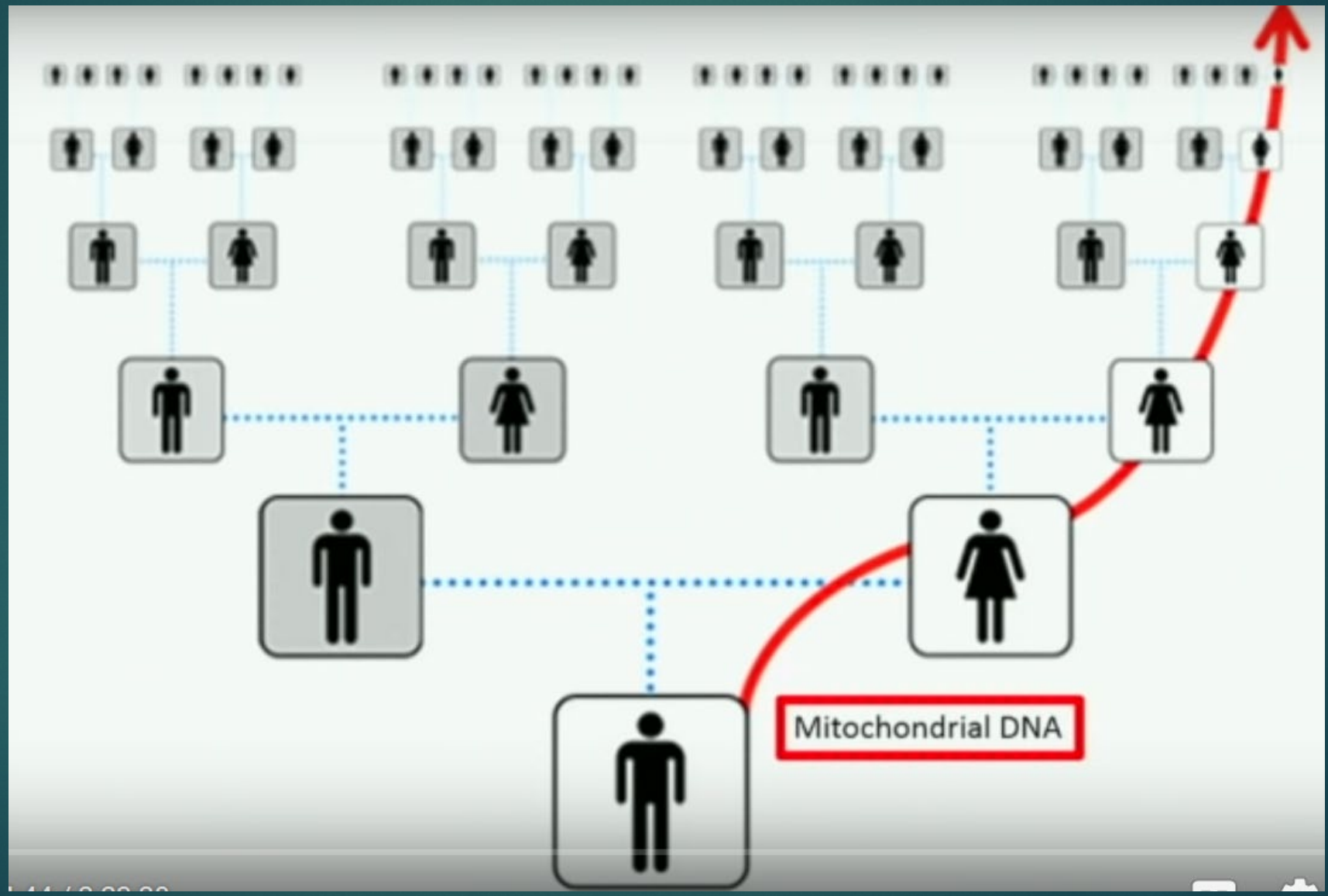


mtDNA = maternal; nuclear DNA = both parents

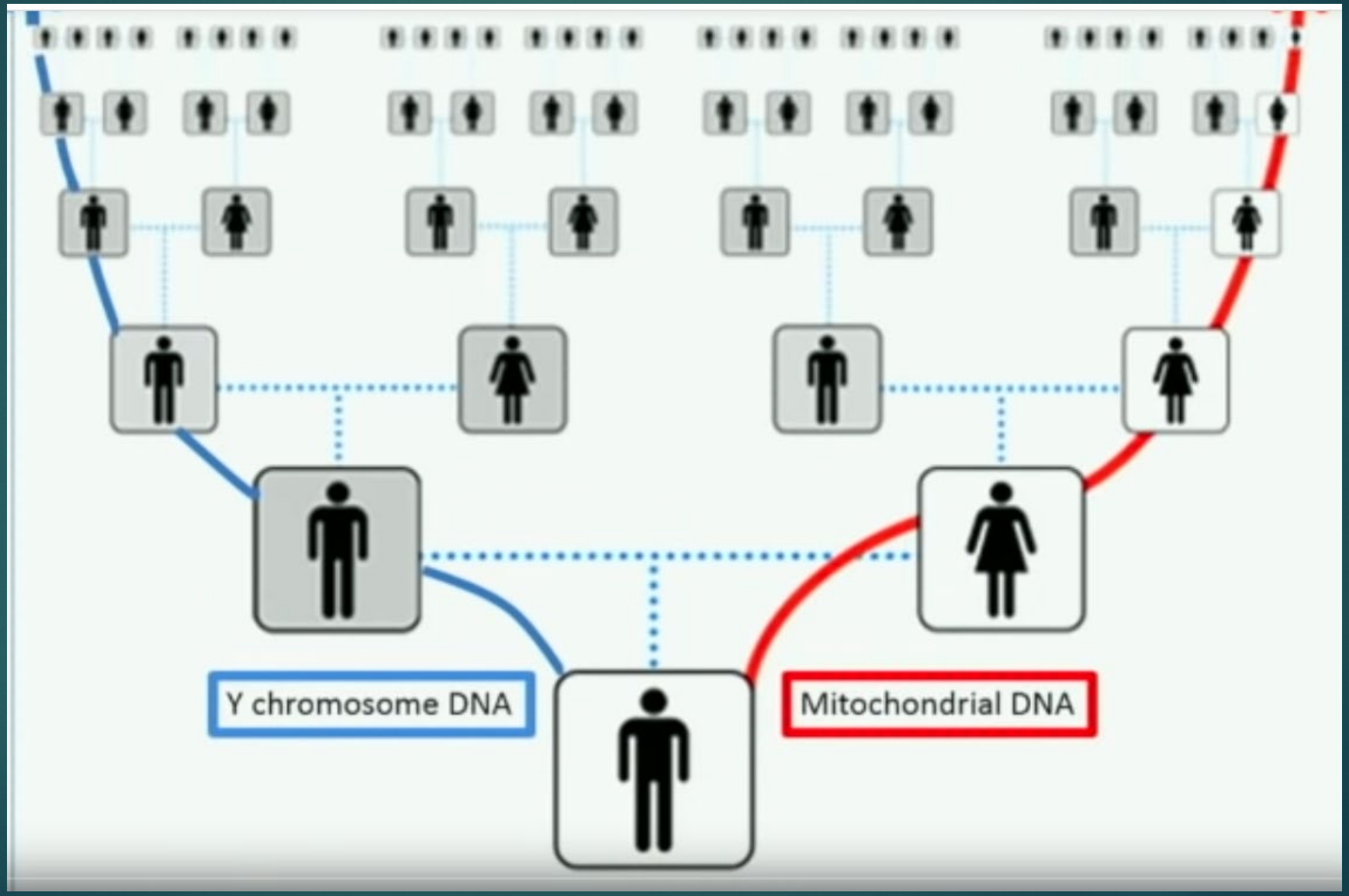



A. Nuclear DNA is inherited from all ancestors.
B. Mitochondrial DNA is inherited from a single lineage.

Mitochondrial DNA more prone to mutation; poorer repair mechanisms



Y chromosome = paternal ancestry



Can compare DNA Sequences

```
Human 1:     AGTTACCATGACTAGACTAGCTGAAGGGTA
Human 2:     AGTTACCATGACTAGACTAGCTGAAGGGTA

GATCCGATCGACTTTTACATTAGCTACGACTACGACTACGAT
GATCCAATCGACTTTTACATTAGCTACGACTACGACTACGAT

GATCGATTATGCTTATAAACTTACAGCATCGCATACGTCTAC
GATCGATTATGCTTATAAACTTACAGCATCGCATACGTCTAC
```

2 humans: 1 difference in every 1200-1300 letters

Mutations = letter change in nucleotide

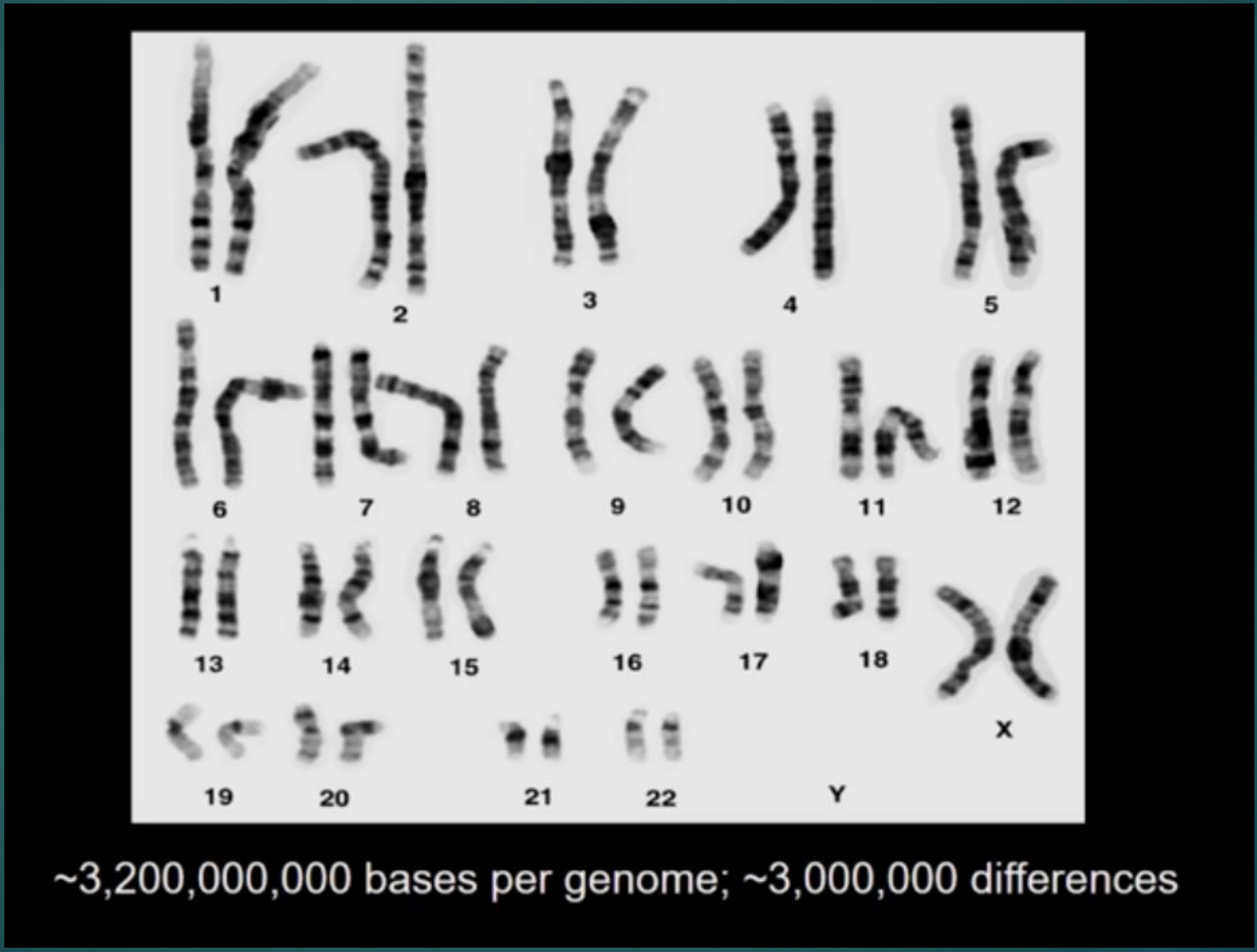
Mutations occur as a function of time

More differences in Chimpanzee

Chimps: 1 letter in a hundred different

~3,200,000,000 bases per genome;

~3 million differences between 2 people

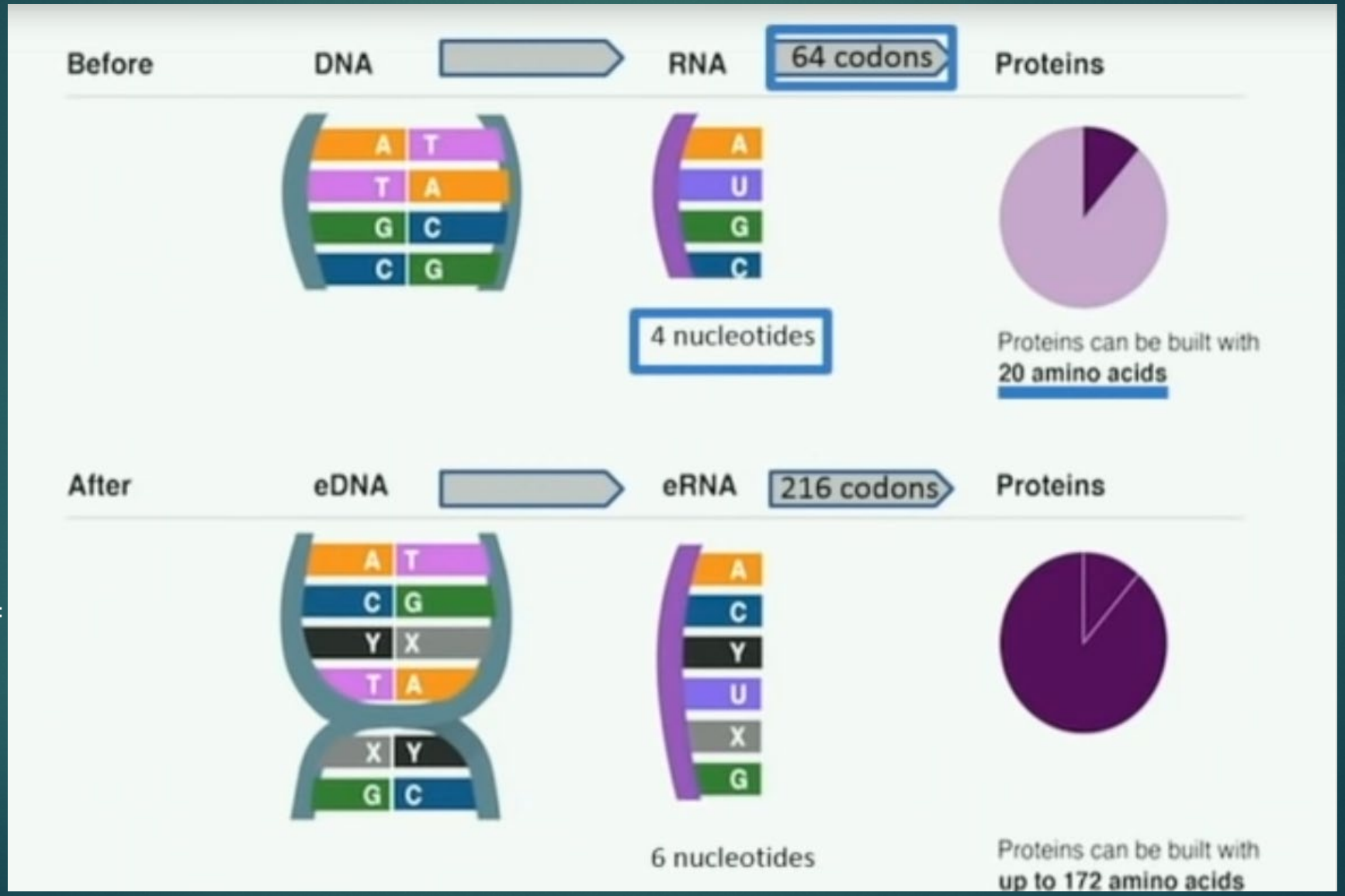


Creation of new types of DNA and amino acids:

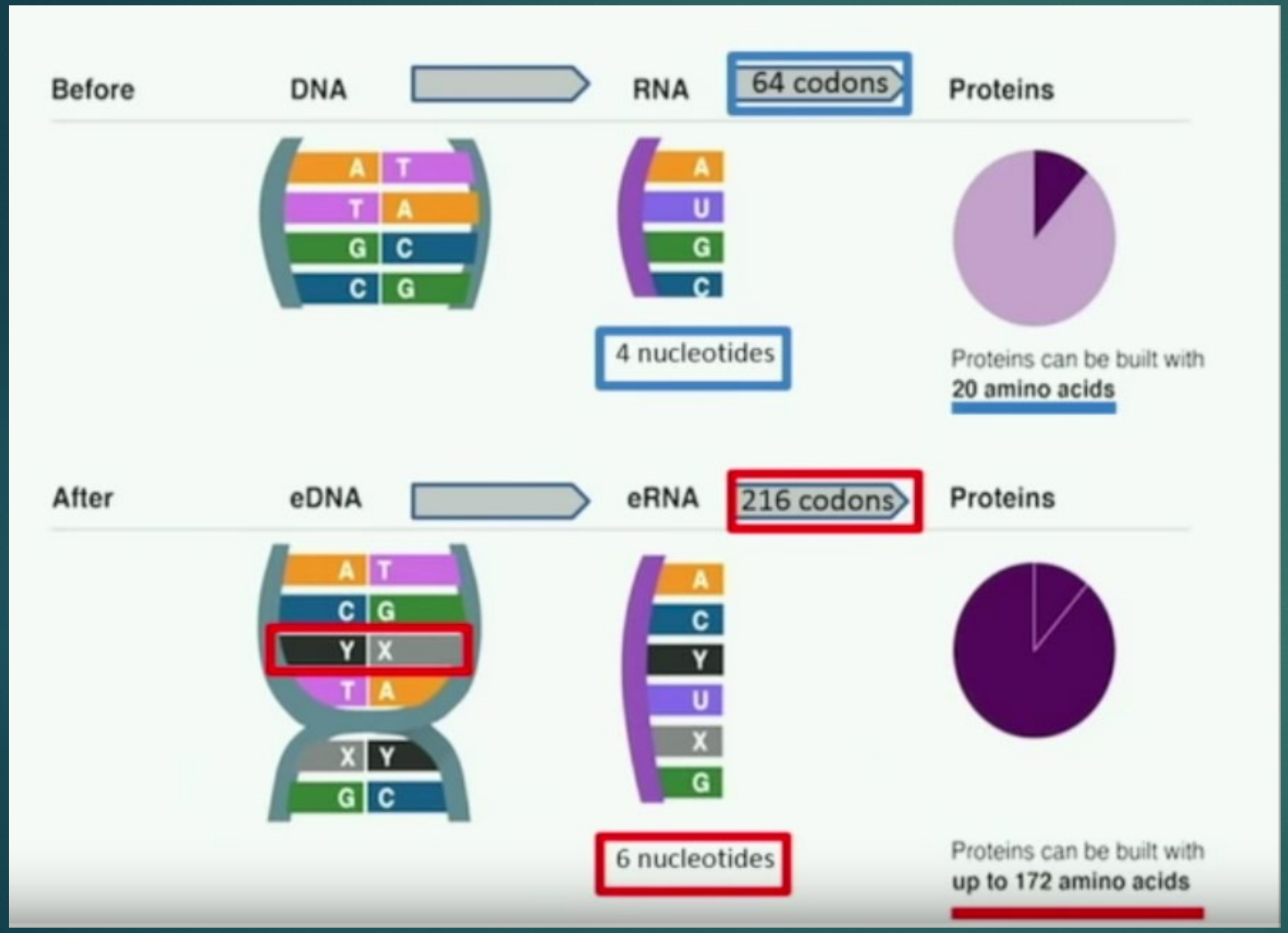
2 new letters (Y-K), 6 new nucleotides, 172 amino acids

In nature =

Man made =



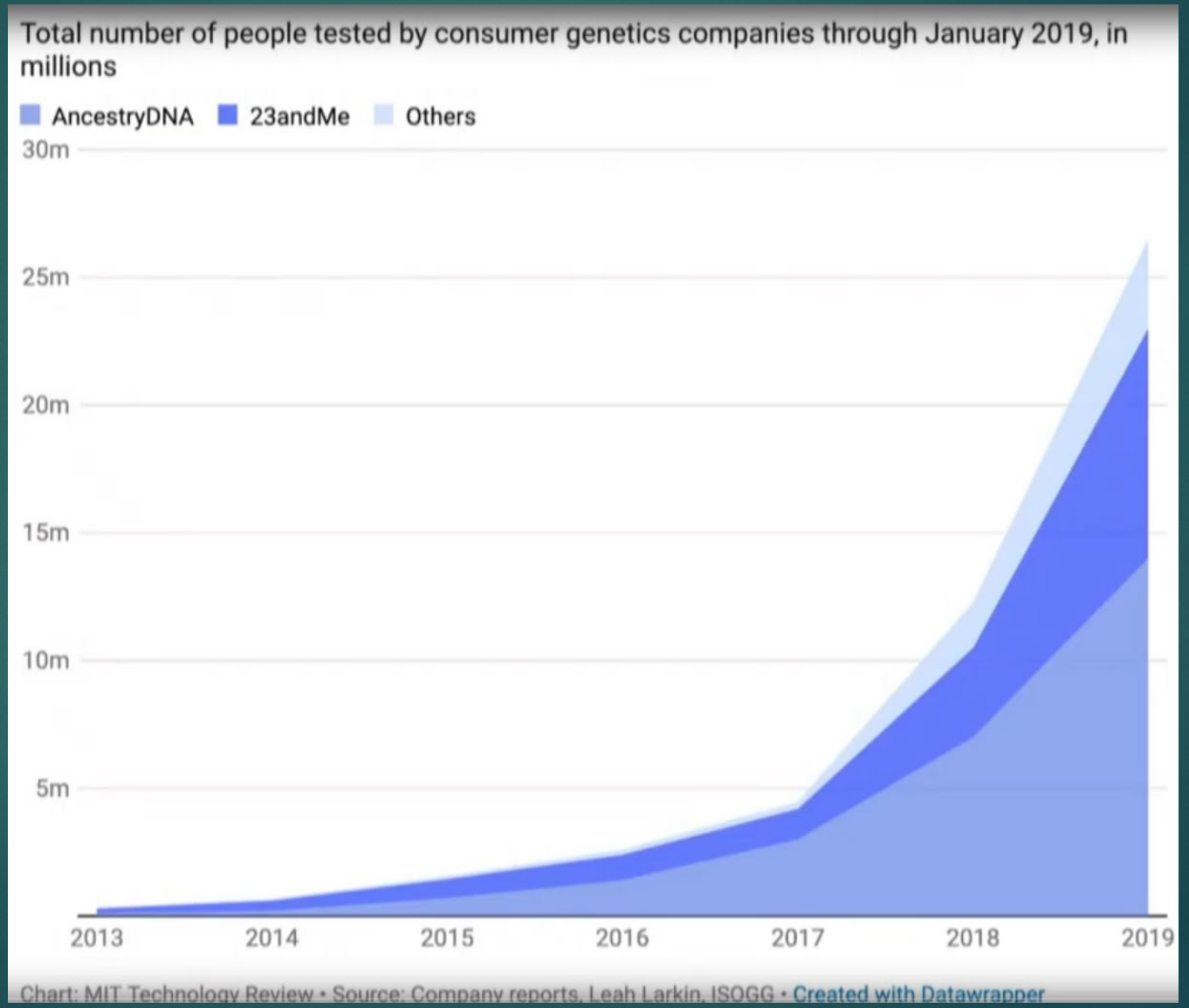
RNA, Codons (three nucleotides), Amino Acids



4 nucleotides produce
64 codons which produce
20 amino acids

Creation of extended DNA =
6 nucleotides which produce
216 codons which produce
172 amino acids

Personal genetics testing



Late-Onset Alzheimer's Disease

Alzheimer's disease is characterized by memory loss, cognitive decline, and personality changes. Late-onset Alzheimer's disease is the most common form of Alzheimer's disease, developing after age 65. Many factors, including genetics, can influence a person's chances of developing the condition. This test includes the most common genetic variant associated with late-onset Alzheimer's disease.

Jamie, you **do not have** the ε4 variant we tested.

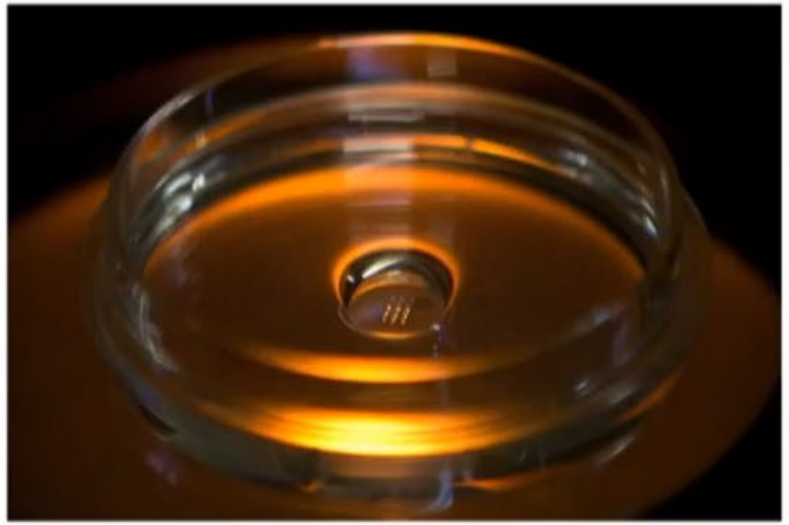
Your risk for Alzheimer's disease also depends on other factors, including lifestyle, environment, and genetic variants not covered by this test.

23andme.com/dna-reports-list/

The New York Times

Chinese Scientist Claims to Use Crispr to Make First Genetically Edited Babies

The researcher, He Jiankui, offered no evidence or data to back up his assertions. If true, some fear the feat could open the door to "designer babies."



A microplate from the Chinese scientist He Jiankui's lab containing embryos whose genes have been edited. Dr. He's announcement prompted a statement from a group of 122 scientists condemning his actions as "crazy." Mark Schiefelbein/Associated Press

By Gina Kolata, Sui-Lee Wee and Pam Belluck

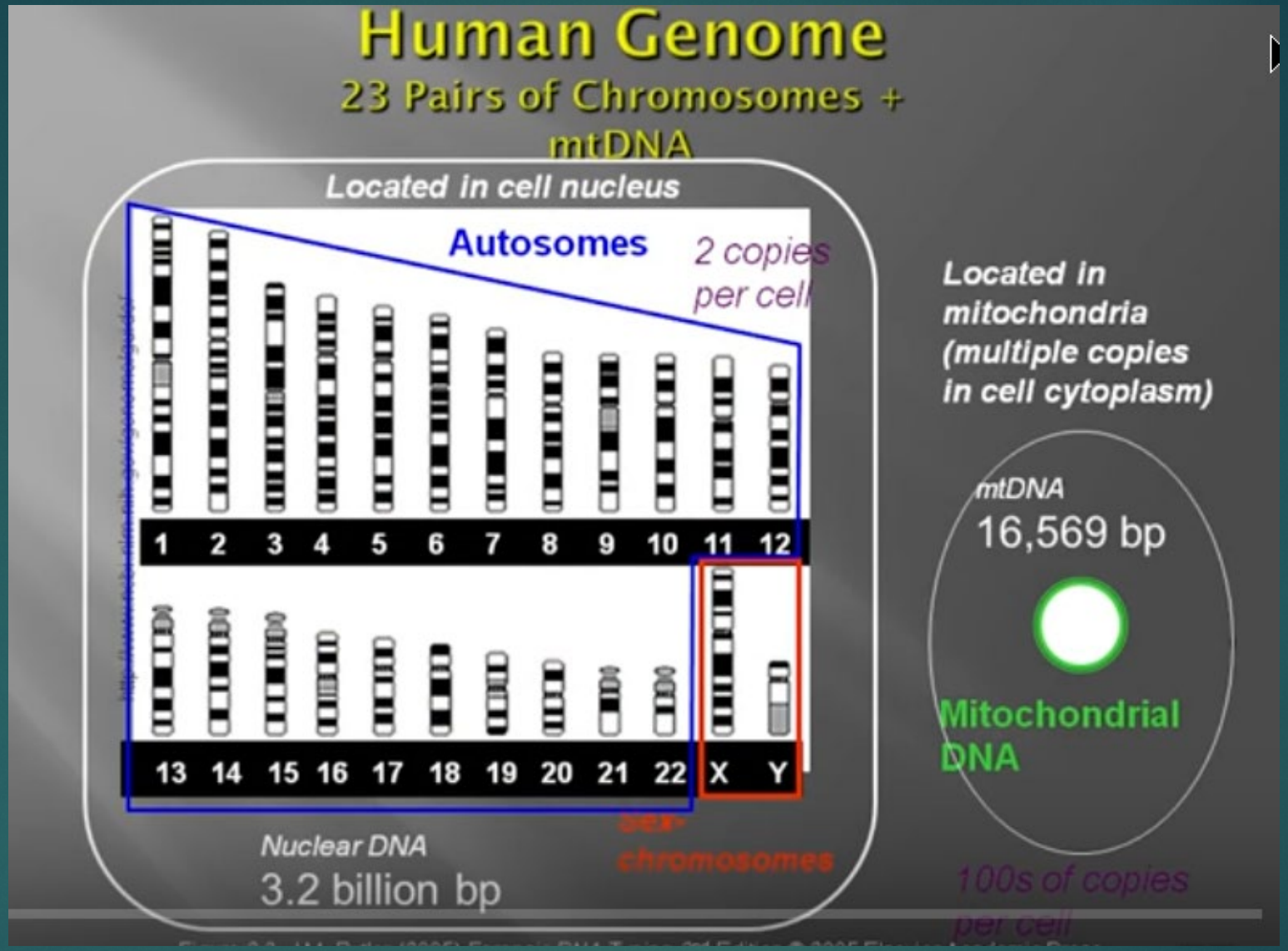
Nov. 26, 2018

Personal Genomics Companies: Ancestry, 23andMe

- Commercial DNA companies sample less than 1% of 1% difference between people.
- Chromosomes in sperm and egg are not identical to each chromosome in every other cell in each parent
- Go from 46 chromosomes in each cell to 23 chromosomes in sex cell; chromosomes in each pair swap some sections = recombination = single chromosome is unique mash up of each pair; recombination occurs uniquely in each sex cell
- 2 sister's cells are uniquely different blend of parents and from each other

Personal Genomics Companies

- Without recombination, 25% from each Grandparent; the further back your ancestry, the more likely your ancestors do not represent your DNA
- Without recombination, 1/64th of your DNA of each ancestor 6 generations back; with recombination, can be higher than that or zero
- Ancestry.com looks for match to today's DNA and locations; primarily European data
- Your 2% N is from the 1% difference; 1200 generations in 38 Ka



Chimps have 24 chromosomes; 2 fused in us
Humans: females have 2 Xs, males have X and Y