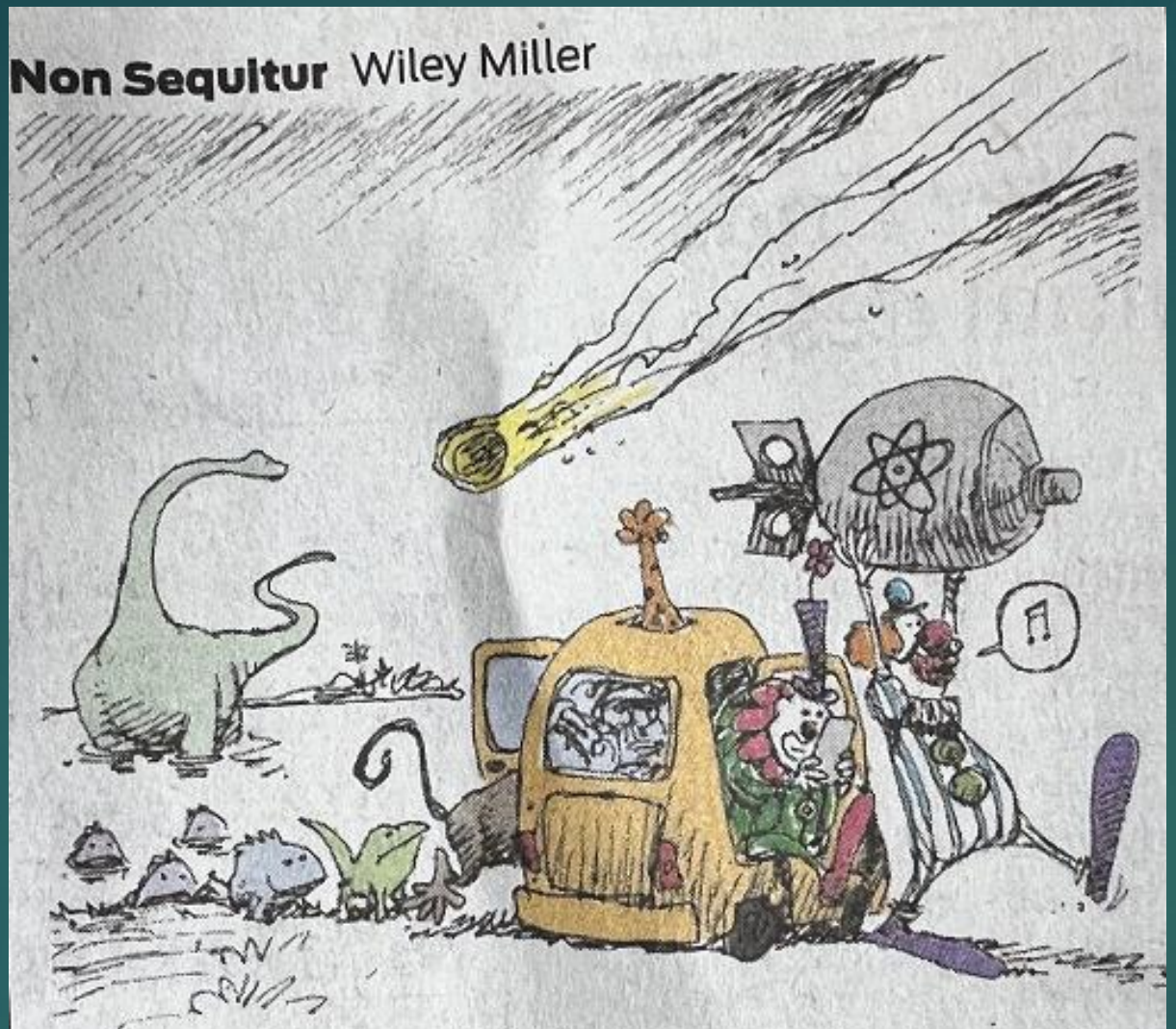
Paleogenetics, Part 7

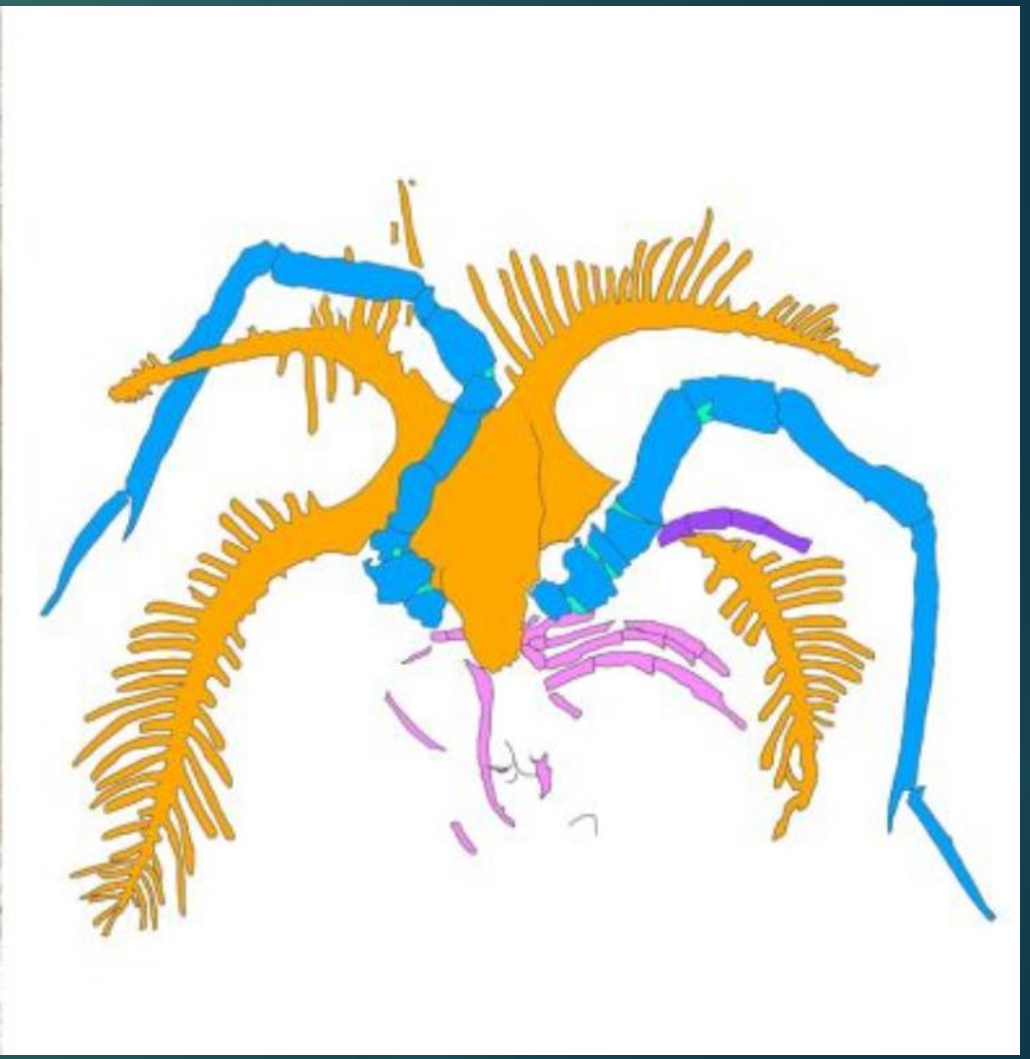
CHARLES J VELLA, PHD, 2022

April 2022 Updates

Non Sequitur Wiley Miller



Burgess Shale: *Tomlinsonus dimitrii* – 450 Ma, Ordovian period, 2 inches long



What has no eyes, walked on stilts and died in 'Paleo Pompeii'? This ancient weirdo.

Leading cause of death among children = guns

- Firearm injuries are now the leading cause of death among children under 19.
- Gun-related deaths in children surpassed deaths caused by motor vehicle collisions beginning in 2019. And while the death rate due to car accidents has steadily declined since 2001, the firearm death rate has continued to climb, with increased homicide and suicide rates driving a 14% total increase over the last two decades.
- Overall firearm-related death rate was more than four times higher for black children than for white children, and the homicide rate was over 14 times higher for black children. For decades gun injuries already have been the leading cause of death for black children in this country.
- Need for secure firearm storage

Having a gun in your house

- A handgun at home doubles risk of homicide. Gun ownership does not increase safety.
- Stanford Univ. Study, 2022: 12 year study; 1 in 3 homes in US have a gun
- People who live with a handgun owner are 7 x more likely to be shot to death by a spouse or partner; 84% of the victims are women
- People who live with a handgun owner are more than twice as likely to be killed by a firearm than those in a home with no gun.
- Living with a gun owner does not protect you from being killed by a stranger
- Those killed in a home with a gun were 4 times more likely to die by gunfire

Real mass shootings – unlike what you see on TV

- The majority (57%) of mass shootings in the U.S. take place in private.
- Occur at home (70%), and the victims are predominantly women and children (64%).

- The untold story of mass shootings in America is one of domestic violence.
  - one of men killing their wives or ex-girlfriends or families.
  - The victims are intimately familiar to the shooters, not random strangers.
  - Every month, 50 women are shot to death by intimate partners in the U.S.

Negative associations of disbelief in human evolution – S. Syropoulos, et al., 2022

- Researchers theorized that belief in evolution would tend to increase people's identification with all humanity, due to the common ancestry, and would lead to fewer prejudicial attitudes.
- People who perceive themselves as more similar to animals are also people who tend to have more pro-social or positive attitudes toward outgroup members or people from stigmatized and marginalized backgrounds
- Darwin's 19th century theory of evolution has been cited to perpetrate racism, prejudice and homophobia, in part through the phrase, "survival of the fittest," used to describe the process of natural selection.

Belief in Evolution

- Eight studies involving different areas of the world; accounted for education, political ideology, religiosity, cultural identity and scientific knowledge; based on surveys from 1993, 1994, 2000, 2006, 2008, 2010, 2012, 2014, 2016 and 2018
- A disbelief in human evolution was associated with higher levels of prejudice, racist attitudes and support of discriminatory behavior against Blacks, immigrants and the LGBTQ community in the U.S.
- Similarly, across the globe—in 19 Eastern European countries, 25 Muslim countries and in Israel—low belief in evolution was linked to higher biases within a person's group, prejudicial attitudes toward people in different groups and less support for conflict resolution
- Belief in evolution relates to less prejudice, regardless of the group you're in, and controlling for all of these alternative explanations; belief in evolution relates to less prejudice independently from belief, or lack thereof, in God or any particular religion

Belief in evolution means you are less prejudiced

- The data analysis showed unfailingly "that the disbelief in human evolution is the driving factor and most consistent predictor of prejudice in comparison to other relevant constructs”
- In multiple countries: In Israel, people with a higher belief in evolution were more likely to support peace among Palestinians, Arabs and Jews. In countries in the Islamic world, belief in evolution was associated with less prejudice toward Christians and Jews. In Eastern Europe, where Orthodox Christians are the majority, a belief in evolution was linked with less prejudice toward gypsies, Jews and Muslims.

Ancient cartoons/moving pictures

- The world's oldest moving pictures Pictures of ancient animals carved onto flat stones tens of thousands of years ago were deliberately placed around fires so they would look animated in the flickering firelight, a new study suggests.

  Creating such animated carvings might have been a popular prehistoric activity as a family group sat around a fire. And at least some of the wall paintings and carvings found in ancient caves might also have been influenced by their appearance in the moving light and shadows of flames.

Ethnicity & Dementia in US Veterans

- K. Yaffe, UCSF & Veterans Admin: study of 1.87 M vets: average age was 69, 89% were white, 10% were Black, 1% Hispanic, 0.5% Asian and 0.4% Native American. 2.3% were female
- Age-adjusted incidence of dementia per 1000 person-years over a mean follow-up of 10 years was
  - 11.5 for White participants.
  - 12.4 for Asian participants,
  - 14.2 for Native Americans
  - 19.4 for Black participants,
  - 20.7 for Hispanic participants,
- 13% diagnosed with dementia over 10-year study, rates were markedly higher for Hispanic and Black veterans (99%) than they were for whites (55%); Asian (24%), Native Americans (8%)
- Vets, because of military-related risk factors, are at higher risk for dementia, due to TBI, PTSD, poor cardiovascular health

Erica Kornblith, et al., 202

Brain-wide mapping reveals that engrams for a single memory are distributed across multiple brain regions

- Most comprehensive and rigorous evidence yet that the mammalian brain stores a single memory across a widely distributed, functionally connected complex spanning many brain regions, rather than in just one or even a few places.

- A memory is stored not just in a single engram cell ensemble but in learning-induced enduring changes in multiple functionally connected neuronal ensembles was suggested by Richard Semon (“unified engram complex”)1 and Donald Hebb (“neurons that fire together wire together”)

- Memory recall becomes more behaviorally powerful when multiple memory-storing regions are reactivated, rather than just one.

- It basically provides the first rank-ordered list for high-probability engram regions.

Functions of engram areas

- Memory engram within an individual brain region may contribute a subset of the overall memory information.
- Hippocampal engrams are thought to primarily contribute contextual information by acting as an index for cortical memories of various sensory modalities
- Amygdala engrams hold valence information for a given experience.
- Cortical engrams such as those in the retrosplenial and prefrontal cortices may support spatial navigation and top-down control of memory retrieval, respectively.
- Engrams in auditory and olfactory cortices may support auditory recognition memory and odor-induced learned behaviors, respectively.

Fear memory

- This study = contextual fear conditioning memory in mice: Analysis of more than 247 brain regions in mice who were taken from their home cage to another cage where they felt a small but memorable electrical zap. In one group of mice their neurons were engineered to become fluorescent when they expressed a gene required for memory encoding. In another group, cells activated by naturally recalling the zap memory (e.g. when the mice returned to the scene of the zap) were fluorescently labeled instead
- By using a computer to count fluorescing cells in each sample, the team produced brain-wide maps of regions with apparently significant memory encoding or recall activity.
- Calculated an "engram index" to rank order 117 brain regions with a significant likelihood of being involved in the memory engram complex

Memory

- Memory engrams are held by neuronal ensembles that are activated by learning and are reactivated to support recall
- These experiments not only revealed significant engram reactivation in known hippocampal and amygdala regions, but also showed reactivation in many thalamic, cortical, midbrain and brainstem structures
- Many brain regions found likely to be involved in encoding a memory were also found to be involved in recall upon reactivation (freeze behavior)
- Stimulating up to three involved regions simultaneously produced more robust freezing behavior than stimulating just one or two.

Rank-ordered list of 117 brain regions for memory encoding

- 1.59 Midbrain reticular nucleus
- 1.38 Laterodorsal tegmental nucleus
- 1.36 Presubiculum
- 1.33 Fields of Forel
- 1.25 Cuneiform nucleus
- 1.02 Basolateral amygdalar nucleus, anterior part
- 0.97 Substantia innominata
- 0.95 Nucleus of the lateral olfactory tract, body
- 0.95 Nucleus of the lateral olfactory tract , medial
- 0.87 Medial pretectal area
- 0.84 Tegmental reticular nucleus
- 0.82 Nucleus of the lateral lemniscus
- 0.76 Dentate gyrus
- 0.74 Ectorhinal area

0.71 Tuberomammillary nucleus, ventral part
0.69 Olivary pretectal nucleus
0.65 Superior colliculus, deep white layer
0.65 Paraventricular hypothalamic nucleus
0.65 Supraoptic nucleus
0.61 Basomedial amygdalar nucleus
0.56 Field CA3
0.55 Magnocellular reticular nucleus
0.54 Basolateral amygdalar nucleus
0.52 Claustrum
0.51 Lateral habenula
0.50 Tuberomammillary nucleus
0.49 Field CA1
0.49 Frontal pole, layer 6a
0.48 Lateral hypothäamic area
0.47 Inferior colliculus

Memory reactivation

- 34.85 Laterodorsal tegmental nucleus
- 34.26 Tuberomammillary nucleus, ventral part
- 33.17 Magnocellular nucleus
- 33.15 Supraoptic nucleus
- 31.87 Superior colliculus, deep white layer
- 30.91 Paraventricular hypothalamic nucleus
- 29.02 Trapezoid body
- 28.33 Ventral premammillary nucleus
- 27.05 Subparafascicular nucleus
- 27.05 Medial septal nucleus
- 27.02 Anterior hypothalamic nucleus
- 26.86 Diagonal band nucleus
- 24.88 Superior central nucleus raphe

24.75 Paraventricular hypothalamic nucleus
24.68 Nucleus of the lateral olfactory tract,
22.43 Interanterodorsal nucleus of the thalamus
22.26 Nucleus of reuniens
22.17 Frontal pole, layer 6a
21.97 Medial pretectal area
21.56 Agranular insular area, ventral part
21.01 Posterior hypothalamic nucleus
20.90 Basolateral amygdalar nucleus, ventral part
20.90 Hippocampo-amygdalar transition area
20.88 Magnocellular reticular nucleus
20.68 Claustrum
20.56 Nucleus of the lateral olfactory tract, body

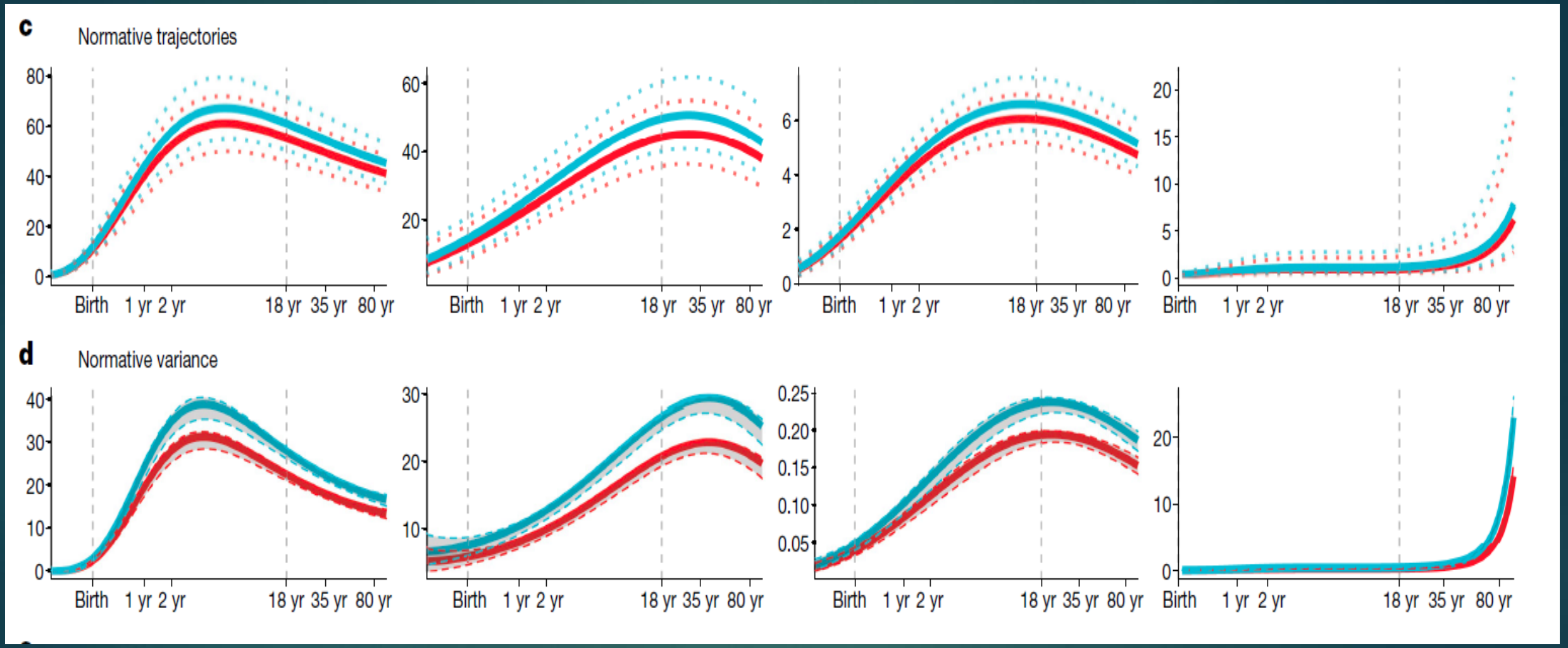
Discovery of mechanism behind the chemically-induced suppression of fearful memories

- KNT-127, a selective agonist of the d-opioid receptor or DOP, facilitates contextual fear extinction in mice.
- Administered KNT-127 to specific brain regions and identified the brain regions involved in promoting fear extinction via delta receptor activation
- KNT-127 administered to basolateral nucleus of the amygdala and infralimbic subregions (IL) of the medial prefrontal cortex significantly reduced the freezing response during re-exposure
- Currently, serotonin reuptake inhibitors and benzodiazepines are prescribed during therapy for fear responses

New brain growth charts based on 124,000 MRIs

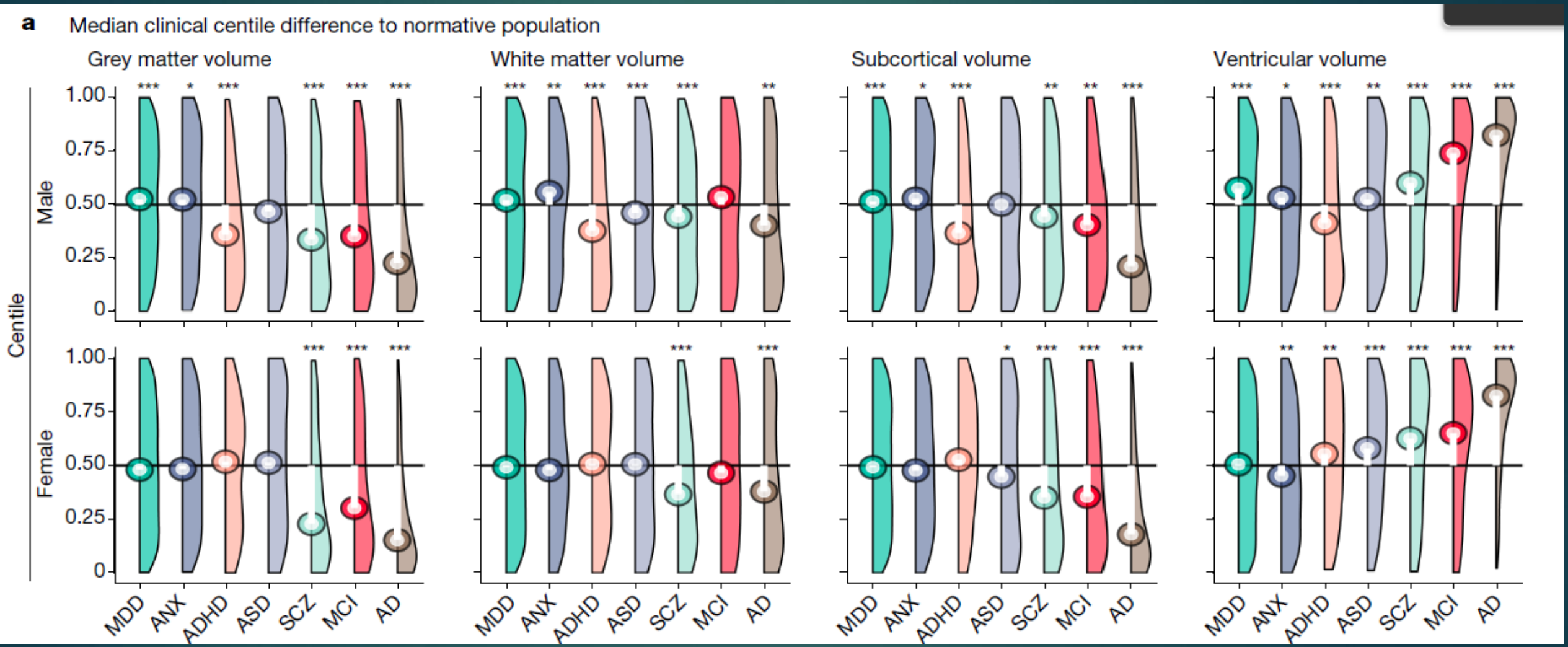
- Like childhood height & weight charts, new brain charts measure: based on 101,457 human participants between 115 days post-conception to 100 years of age
- Reveal atypical brain development, neurodegenerative diseases, preterm birth and neurogenetic disorders, mental illness
- Four main tissue volumes of the cerebrum (total cortical grey matter volume (GMV), total white matter volume (WMV), total subcortical grey matter volume (sGMV) and total ventricular cerebrospinal fluid volume (ventricles or CSF)).

Normative trajectories & variance (blue = male)



Increase in GMV, peaking a 5.9 years, then near-linear decrease; white matter, 29 years, decline after 50; subcortical peak at 14; CSF peaks at age 2, then plateau until age 30, then a slow linear increase, with exponential increase in 60s

Atrophy by Disorder by sex – note Schiz



Schizophrenia study

- Landmark genetic study: 121,000 people, an international consortium called SCHEMA, led by researchers at the Broad Institute of MIT and Harvard, has identified extremely rare protein-disrupting mutations in 10 genes that strongly increase an individual's risk of developing schizophrenia—mutations in these genes drive a 20- to 52-fold increase in risk.
- A second, complementary study in a larger but overlapping group of 320,400 people, brings to 287 the number of regions of the genome associated with schizophrenia risk, including ones containing genes identified by SCHEMA.
- These studies underscore an emerging view of schizophrenia as a breakdown in communication at the synapse

Schizophrenia

- Genomic regions they implicated are largely active only in neurons, only in the brain, and affect mechanisms that directly impact neuron function, such as synaptic structure and organization.
- 320,400 people from collections across the world, including people of European, Finnish, African American, LatinX, East Asian, and Ashkenazi Jewish descent.
- The SCHEMA (SCHizophrenia Exome Meta-Analysis) Consortium—which came together in 2017—focuses on the exome, the nearly two-percent of the genome that encodes proteins. Specifically, the SCHEMA Consortium looked for variants that would either knock out or markedly alter a gene's ability to produce functioning proteins.

Schizophrenia

- By sequencing whole exomes from 24,248 people with schizophrenia and 97,322 without, the SCHEMA team identified ultra-rare variants in 10 genes that dramatically increased a person's risk of developing schizophrenia. These variants, called PTVs for "protein truncating variants," prevent cells from producing a gene's full-length functional protein.
- In general, any given person has a roughly one percent chance of developing schizophrenia in their lifetime, but if you have one of these mutations, it becomes a 10, 20, even 50 percent chance; hint at an additional 22 genes that also likely influence schizophrenia risk,

Schizophrenia: a synaptic disorder

- Together, these genes point to dysfunction at the synapse -- where neurons connect and communicate with each other -- as a possible cause of schizophrenia.
- 2016 study: described for the first time how variations in a single gene -- complement component 4, or C4 -- raises schizophrenia risk by triggering excessive "pruning" of synapses.
- Insights into two of the 10 genes from the SCHEMA study, *GRIN2A* and *GRIA3*, further implicate the synapse as a key part of schizophrenia's mechanistic roots. These two genes encode portions of the glutamate receptor.
- SCHEMA study provides the first solid genetic evidence of that glutamate signaling is involved in schizophrenia. Additionally, *GRIN2A* activity in the brain peaks during adolescence, around the time people suffering schizophrenia begin to experience symptoms.

Bipolar Disorder

- In a separate study published in *Nature Genetics*, members of the international Bipolar Exome Consortium (BipEx), including Neale, report how comparisons of SCHEMA and BipEx data have helped reveal rare PTVs in the gene *AKAP11* gene that raise the risk of bipolar disorder several-fold, making it the strongest genetic risk factor found for bipolar disorder to date.

An estimation of the absolute number of axons indicates that human cortical areas are sparsely connected

- Despite the functional importance of connections between far-reaching regions of the brain, the actual number of these connections is low.
- The analysis indicated that there are almost 2.5 billion long-range axons traversing the cerebral cortex.
- However, despite this large number, they found that the numbers connecting different functional brain regions were quite low.
- For example, among the estimated 130 million axons in the arcuate fasciculus tract, only about 1 to 2 million (less than 2%) directly connected Broca's and Wernicke's areas, a connection that is necessary for normal language ability.
- The model predicts that other long connections, like those from the hippocampus to the frontal cortex that are needed for memory retrieval, are actually made in multiple steps.

Number of long range axons

- Estimate the absolute number of axons linking cortical areas from a whole-cortex diffusion MRI (dMRI) connectome, calibrated using the histologically measured callosal fiber density.
- Median connectivity is estimated as approximately 6,200 axons between cortical areas within hemisphere and approximately 1,300 axons interhemispherically, with axons connecting functionally related areas surprisingly sparse.
- For example, we estimate that <5% of the axons in the trunk of the arcuate and superior longitudinal fasciculi connect Wernicke's and Broca's areas.
- These results suggest that detailed information is transmitted between cortical areas either via linkage of the dense local connections or via rare, extraordinarily privileged long-range connections.

Neuropathology and virus in brain of SARS-CoV-2 infected non-human primates: Significant role for brain hypoxia

- Researchers at Tulane University have shown in detail how COVID-19 affects the central nervous system. The findings are the first comprehensive assessment of neuropathology associated with SARS-CoV-2 infection in a nonhuman primate model.
- Brain shows neuroinflammation, microhemorrhages, brain hypoxia, and neuropathology that is consistent with hypoxic-ischemic injury in SARS-CoV-2 infected non-human primates, including evidence of neuron degeneration and apoptosis.
- The research team found severe brain inflammation and injury consistent with reduced blood flow or oxygen to the brain, including neuron damage and death. Microhemorrhages, or small bleeds in the brain, were also present, but without substantial virus detection in brain. Surprisingly, these findings were seen in subjects that did not experience severe respiratory disease from the virus.

Ibolya Rutkai, et al., 2022

Covid in brain

- Neurological complications are often among the first symptoms of SARS-CoV-2 infection and can be the most severe and persistent
- Findings of hypoxic-ischemic injury in brain are also in agreement with autopsy studies of brain from human subjects.
- This may arise from chronic, peripheral hypoxemia, as well as reduced cerebral blood flow due to acute microhemorrhages.

Covid causes hypoxia: Low oxygenation as major factor

- The brain is a highly metabolic organ and requires aerobic metabolism of glucose. Any prolonged or chronic intermittent reductions of blood O_2 may contribute to localized CNS hypoxia and energy failure.
- Neuronal injury did not appear to be a direct consequence of virus infection, as only limited virus was convincingly detected in brain vasculature
- Neuronal injury and death most likely occur as a result of energy failure, which is an early consequence of hypoxic-ischemic events. Multiple microhemorrhages, microinfarcts, and hypoxemia appear to play a role in neuronal injury and death

2016 study: 1,500 scientists lift the lid on reproducibility

- More than 70% of researchers have tried and failed to reproduce another scientist's experiments, and more than half have failed to reproduce their own experiments. Those are some of the telling figures that emerged from *Nature*'s survey of 1,576 researchers who took a brief online questionnaire on reproducibility in research.
- The data reveal sometimes-contradictory attitudes towards reproducibility. Although 52% of those surveyed agree that there is a significant 'crisis' of reproducibility, less than 31% think that failure to reproduce published results means that the result is probably wrong, and most say that they still trust the published literature.

Neuroscience studies of behavior are unreliable

- Statistical Power Shortages Dim Results of Many Neuroimaging Studies -- Low study numbers render the results of many studies based on brain scans unreliable
- Now, in a bombshell 16 March *Nature* study[1], Marek and his colleagues show that even large brain-imaging studies, such as his, are still too small to reliably detect most links between brain function and behavior.
- As a result, the conclusions of most published 'brain-wide association studies' — typically involving dozens to hundreds of participants — might be wrong.
- 1000 of most cited studies used average of 12 subjects; The median current neuroimaging study sample size is about 25.

S. Marek, et al., 2022

Neuroimaging studies

- Such studies link variations in brain structure and activity to differences in cognitive ability, mental health and other behavioral traits.
- Most neuroimaging studies have too few participants to reliably link complex behaviors to variations in brain structure or function.
- These small studies result in statistically underpowered studies, inflated effect sizes and replication failures.
- As sample sizes grew into the thousands, replication rates began to improve and effect size inflation decreased.

Replicability in neuroscience

- The results point to the importance of large, multisite collaborations and data-sharing to ensure that imaging studies have enough statistical power to detect real associations. To yield reproducible data requires thousands of participants.
- Datasets of fewer than 1,000 participants produced a wide range of results, including some that appeared to be significant.
- Some experiments run with 25 participants, for example, identified a strong positive link between resting-state functional connectivity and cognitive ability. Others of the same size, however, resulted in strong negative correlations between those same measures, and some found no link.

Neuroscience studies

- Because of publishing biases, the experiments that happen to result in strong correlations are those that end up getting published, whereas the more commonly found non-significant results “don’t see the light of day.” = publication bias
- And this bias leads to an inflated effect size in the literature: The smallest studies have the potential to falsely report the strongest connections.
- Any experiment that relies on correlational analyses will run into similar issues if the sample sizes are too small—just as genetics studies did in previous years,

Replicability & reliability of behavioral neuroscience

- Analyzed magnetic resonance imaging (MRI) brain scans and Behavioural data from 50,000 participants in several large brain-imaging efforts, such as the UK Biobank's collection of brain scans.
- The researchers then used subsets drawn from these large databases to simulate billions of smaller studies. These analyses looked for associations between MRI scans and various cognitive, behavioral and demographic traits, in samples ranging from 25 people to more than 32,000.

Replicability

- Found associations that they could replicate in different subsets of the data. However, these links tended to be much weaker than those typically reported by most other studies.
- The strongest reliable correlations found had an *r* of 0.16, and the median was 0.01. In published studies, *r* values above 0.2 are not uncommon.
- Even associations identified in a study of 2,000 participants — large by current standards — had only a 25% chance of being replicated. More typical studies, with 500 or fewer participants, produced reliable associations around just 5% of the time.
- But it suggests that high *r* values common in the literature are almost certainly a fluke, and not likely to be replicated.

Replicability

- Factors that hinder reproducibility in other fields, such as the tendency to publish only statistically significant results with large effect sizes, means that these spurious brain–behavior associations fill the literature. “People are only publishing things that have a strong enough effect size. You can find those, but those are the ones that are most wrong.”
- To make such studies more reliable, brain-imaging studies need to get much bigger. Studies need to have n in thousands to replicate reliably.
- Genetics research was plagued by false positives until researchers, and their funders, started looking for associations in very large numbers of people. The largest genome-wide association studies (GWAS) now involve millions of participants.
- Studies of neuroimaging that show within individual changes with few subjects are reliable. Can conclude that a mental function correlates to a brain area.

Drosophila melanogaster

Charlie got his only A+++ grade on a biology paper as a college sophomore for his study of the effect of radiation on fruit flies, repeating Herman Mueller's 1920 studies.

Found that UV exposure did not produce next generation phenotypic mutations (i.e. eye color, wing shape, body distortion).

Had to ask his dentist to use his X-ray machine to successfully induce such changes.

Fruit Flies Evolve in Time with the Seasons

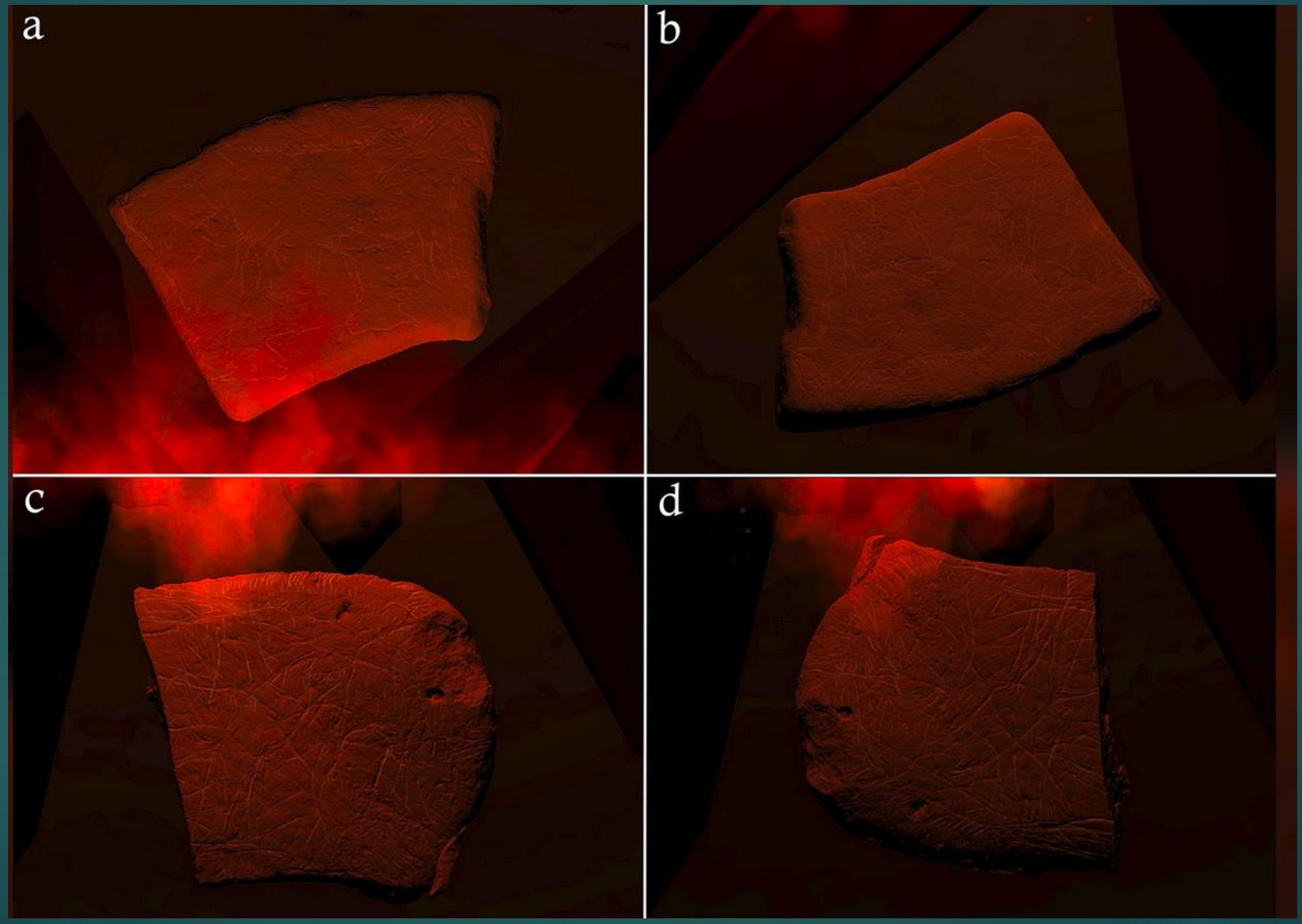
- Evolution is generally thought to move slowly, punctuated only by significant ecological disturbances like pollution or habitat destruction.
- Evolution can operate on extraordinarily fast timescales

- New study finds that evolution may in fact happen fast enough to enable adaptation to seasonal changes that happen each year—at least in fruit flies (*Drosophila melanogaster*).
- In a large-scale controlled field experiment lasting four months, scientists documented changes to 60 percent of the flies' genes. The researchers also observed pronounced, rapid changes to six physical characteristics related to survival from July to November.

Fruit flies

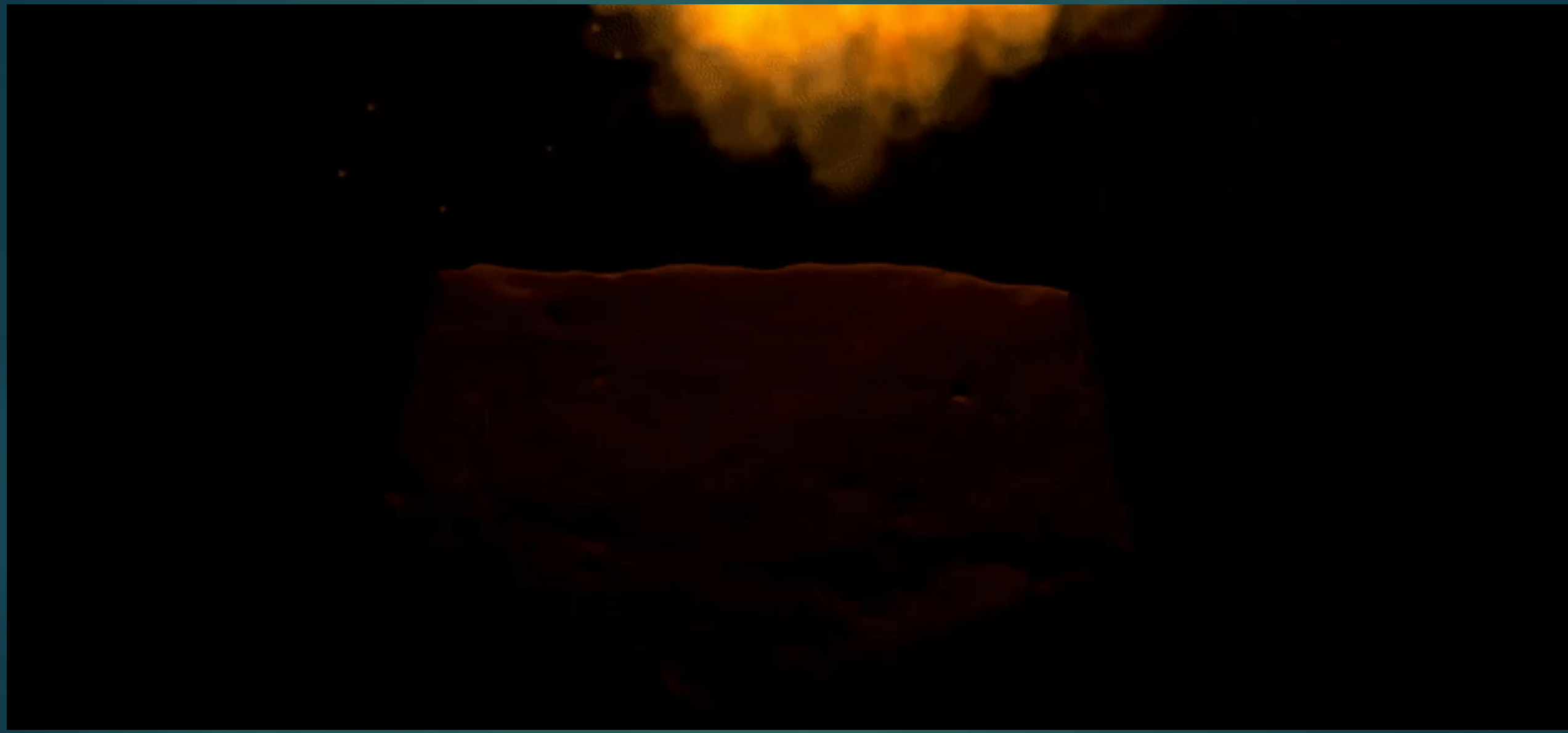
- Adaptation is a foundational process in evolutionary biology that is central to human health and the conservation of biodiversity.
- Adaptive tracking, defined as continuous adaptation in response to rapid environmental change, is a potentially critical mechanism by which populations persist in changing environments.
- Ecosystems can experience rapid environmental change but whether populations can continuously adapt to those changes is unknown.
- Rudman *et al*. observed rapid parallel evolution in 10 *Drosophila melanogaster* populations over 4 months of seasonal change (from summer to autumn) in Pennsylvania

Paleolithic TV



Ancient TV

- Study of 50 limestone “plaquettes” – flat, carved rocks – that were excavated in the mid-19th century at the Montastruc rock shelter in southern France; they are now held at the British Museum in London. Together, the plaquettes are covered with 77 naturalistic carvings of wild animals, including horses, chamois, reindeer, and bison. Made during the Magdalenian epoch of the Late Upper Paleolithic period, between 12,000 and 16,000 years ago.
- Many of the carved plaquettes were damaged by fire – some were covered by layers of white ash, while others were scorched or cracked by heat. And many of the animal engravings were superimposed on each other.
- Similar practices may also have influenced some of the ancient paintings on the walls of caves – such as at the stunning Chauvet Cave in southeastern France, where many of the animal portraits are similarly overlaid on each other and some seem to show signs of being heated by fires underneath them



Oldest life on earth: 3.8 to 4.3 Ba

- On an outcrop of exposed volcanic and sedimentary rock on the eastern shores of Hudson Bay in northern Quebec, researchers have unearthed what may be the earliest fossilized life forms ever discovered.
- These microbial ancestors lived between 3.75 and 4.28 billion years ago, only 300 million years after the Earth formed.
- If life developed this rapidly on Earth, it suggests that abiogenesis—the process by which non-living matter becomes a living organism—is potentially “easy” to achieve, and life in the universe may be more common than we thought.

Oldest life on earth: 3.8 to 4.3 Ba

- Filaments on rocks once deep under the ocean close to a system of hydrothermal vents: microbes lived off iron, sulfur, and maybe carbon dioxide and light—a form of photosynthesis without oxygen.
- Study strongly suggests a number of different types of bacteria existed on Earth between 3.75 and 4.28 billion years ago,
- Previous to this study, the oldest fossils ever found, from a rock formation in Western Australia, were claimed to be 3.46 billion years.

Chris Stringer on Alternatives for “modern” and “archaic” humans

- “We need to overcome one of the most difficult problems in discussing our origins - the terminology around ‘archaic' and ‘modem' humans. I have long used the latter term to represent the ‘anatomically modem' morphology of recent and extant *H sapiens*. who share distinctive traits in the cranium and the rest of the skeleton.

- However, this usage is often conflated and confused with the similarly problematic term for ‘modem' behavior, and so I would like to untangle this by reverting to the term *apomorphic* from cladistics. replacing anatomically modem *H. sapiens* by apomorphic *H. sapiens*.

Stringer

- Apomorphic means having specialized traits that are unique to a group or species, thus showing characters not present in an ancestral form.
- The opposite of apomorphic is plesiomorphic - having ancestral traits - and in future I am going to use this term for what I have previously called ‘archaic’ or ‘primitive’ *H. sapiens*. both of which terms also come with then own unfortunate social baggage.

Twitter debate: Chris Stringer on Apomorphic vs plesiomorphic

- Thus I would now say that fossils like Jebel Irhoud 1 and Omo Kibish 2 represent probable plesiomorphic *H sapiens* (pHs), while I would describe Omo Kibish 1 as a probable apomorphic *H sapiens* (aHs).
- This also means that we can move away from the confusing situation where a Neanderthal is described as an 'archaic' human (because it is not a 'modem' human), even though it has numerous derived traits compared with more plesiomorphic humans like *H erectus.* such as a larger brain and a projecting midface.

Stringer: apomorphic *H sapiens* (aHs).

- In future I will describe early members of the Neanderthal lineage such as those from the Sima de los Huesos as plesiomorphic Neanderthals (pHs). while I will term fossils like La Ferrassie 1 and Forbes' Quarry as apomorphic Neanderthals (aHs).
- In such a case ‘apomorphic' for a Neanderthal does not necessarily mean the same as ‘apomorphic' for a *H. sapiens* (unless these are synapomorphies - shared derived traits), so the lineage or species names need to be included as well, to avoid confusion.
- And instead of talking vaguely about ‘archaic’ introgression. this should be more specific, such as Neanderthal-lineage introgression. Denisovan-lineage introgression. or non-aHs lineage introgression.”

But reaction to proposal – Basal vs derived

- However, several people pointed out that plesiomorphic and apomorphic should apply to *Traits* and not groups or species.
- Some suggested just using early and late, but many fossils are undated or have disputed dating, and moreover the age of a fossil doesn't necessarily indicate how plesiomorphous or apomorphous it is
- Mike Plavcan made the alternative suggestion of simply using the terms 'basal' (meaning near the ancestral position on a tree or phylogeny) and derived'(meaning having specialized, non-ancestral traits), and I think that works well.
- Fossils like Jebel Irhoud 1 and Omo Kibish *2* represent basal *H. sapiens* (bHs), while on Omo Kibish 1 as a derived *H sapiens* (dHs).
- Early members of the Neanderthal lineage such as those from the Sima de los Huesos basal Neanderthals (bHn). while fossils like La Ferrassie 1 and Forbes' Quarry would be derived Neanderthals (dHn).

Chimpanzee nut cracking = social learning

- Field experiments at Seringbara (Nimba Mountains, Guinea) to test whether chimpanzee nut cracking can be individually (re-)innovated.
- We provided: (1) palm nuts and stones, (2) palm fruit bunch, (3) cracked palm nuts and (4) *Coula* nuts and stones.
- Chimpanzee parties visited ($n = 35$) and explored ($n = 11$) the experiments but no nut cracking occurred.
- In these experiments, chimpanzees did not individually (re-)innovate nut cracking under ecologically valid conditions.
- Our null results are consistent with the hypothesis that chimpanzee nut cracking is a product of social learning.

Climate

- During the past 5 million years (Ma), a gradual transition in climate conditions has occurred from the warmer and wetter Pliocene (5.3–2.6 Ma) to the colder and drier Pleistocene (2.6–0.011 Ma).
- During this time, tropical savannahs and open grasslands expanded in central–eastern Africa, which, according to the savannah hypothesis, contributed to the early evolution of our human ancestors.
- Milankovitch cycles in solar insolation and climate, particularly the eccentricity-modulated precessional cycle, further created multiple human migration corridors from sub-Saharan Africa into northern Africa, the Arabian Peninsula and Eurasia.

New Climate cycle model study

- The push and pull of other planets alters Earth's climate by changing both the planet's tilt, and the shape of its orbit.
- Over 41,000-year cycles, Earth's tilt oscillates, affecting the intensity of seasons and changing how much rain falls over the tropics.
- And over 100,000-year cycles, Earth goes from having a more circular orbit — which brings more sunlight and longer summers — to having a more elliptical orbit, which reduces sunlight and can lead to periods of glacial formation.

A. Timmermann, et al., 2022

Climate and human evolution

- Prior research:
  - Climatic links with different events in human evolution:
  - the origin of our genus *Homo*,
  - the first movements of *Homo erectus* out of Africa,
  - the presence of hominins at different times in the Arabian Peninsula,
  - the appearance of our species *Homo sapiens* and its moments of strongest expansion, etc.

- Recurring climate changes may have orchestrated where *Homo* species lived over the last 2 million years and how humankind evolved.

Two Decade study of 2 M years of climate and human migration

- Ups and downs in temperature, rainfall and plant growth promoted ancient hominid migrations within and out of Africa that fostered an ability to survive in unfamiliar environments
- The new scenario derives from a computer simulation of the probable climate over the last 2 million years, in 1,000-year intervals, across Africa, Asia and Europe.
- They ran a single Korean supercomputer for 6 months to create data. Examined the relationship between simulated predictions of what ancient habitats were like in those regions and the dates of known hominid fossil and archaeological sites, ranging in age from around 2 million to 30,000 years old.

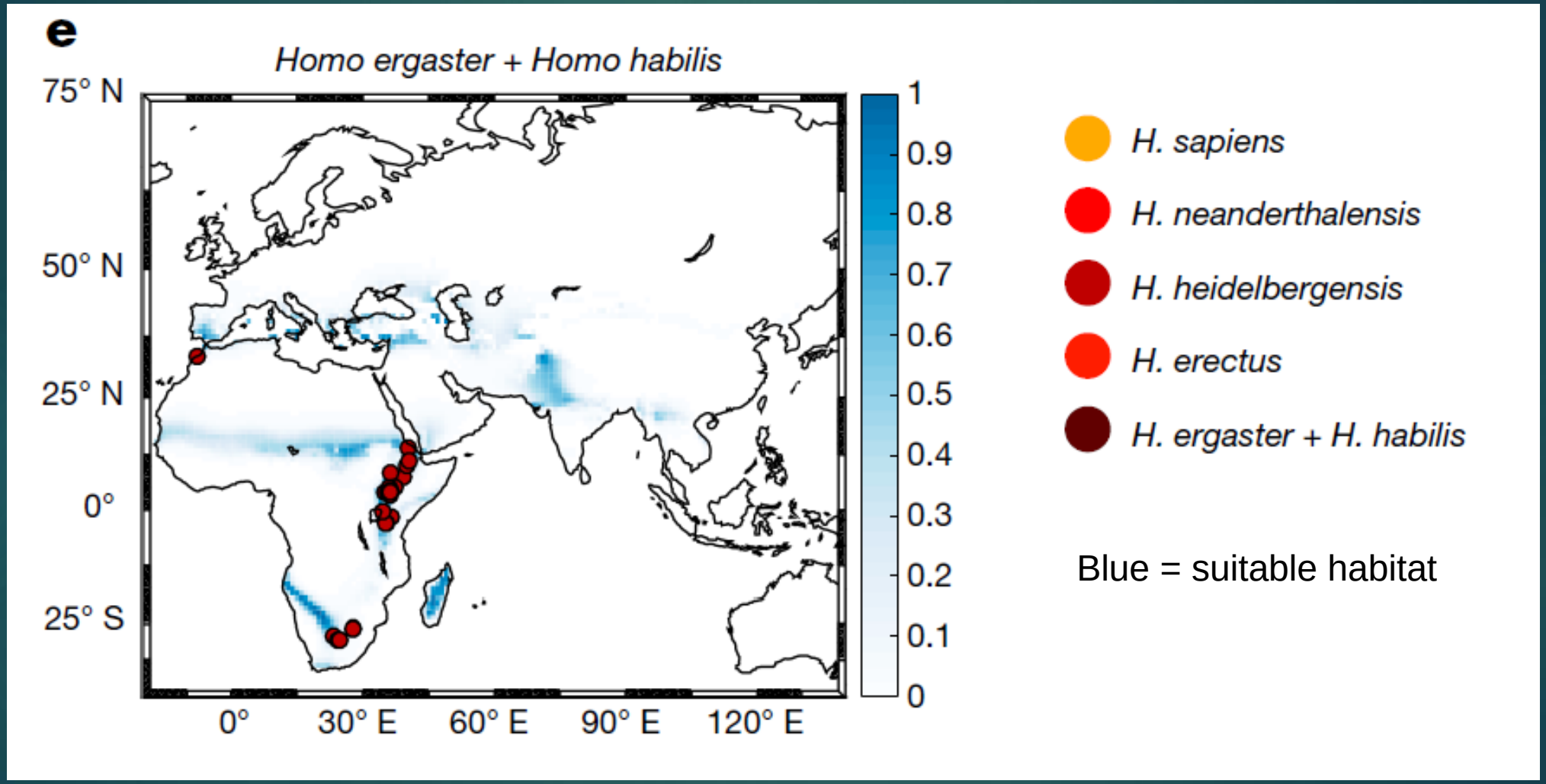
Timmermann, A., Yun, KS., Raia, P. et al. (2022)

Climate as a great engine of human evolution

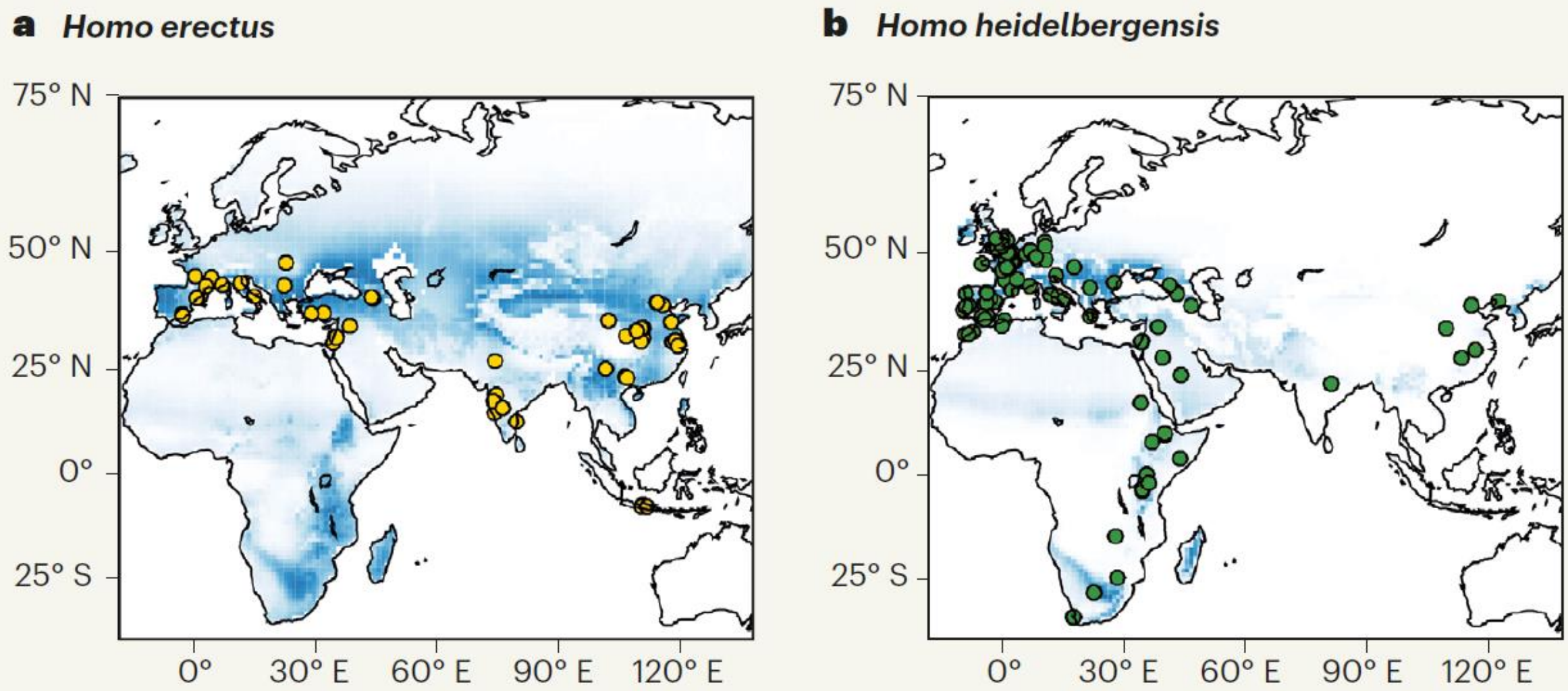
- New modeling study: based on a "supermodel" that allows
  - the simulation of the Milankovitch cycles and their climatic and environmental impacts at any point on the planet (temperature, rainfall, vegetation...),
  - and put it in relation to a database of 3,200 records of human presence in different locations, made up of fossil and, above all, archaeological materials, which are distributed
  - among five “species”: *H. erectus* , *H. heidelbergensis* , *H. neanderthalensis* , *H. sapiens* , and early *Homo* Africans (which includes *H. habilis* and *H. ergaster*).
  - (Denisovans, *Homo naledi*, *Homo floresiensis* and *Homo luzonensis were excluded* – too little data)
- Climatic shifts over the past two million years shaped hominin habitats, dispersal patterns and species diversity

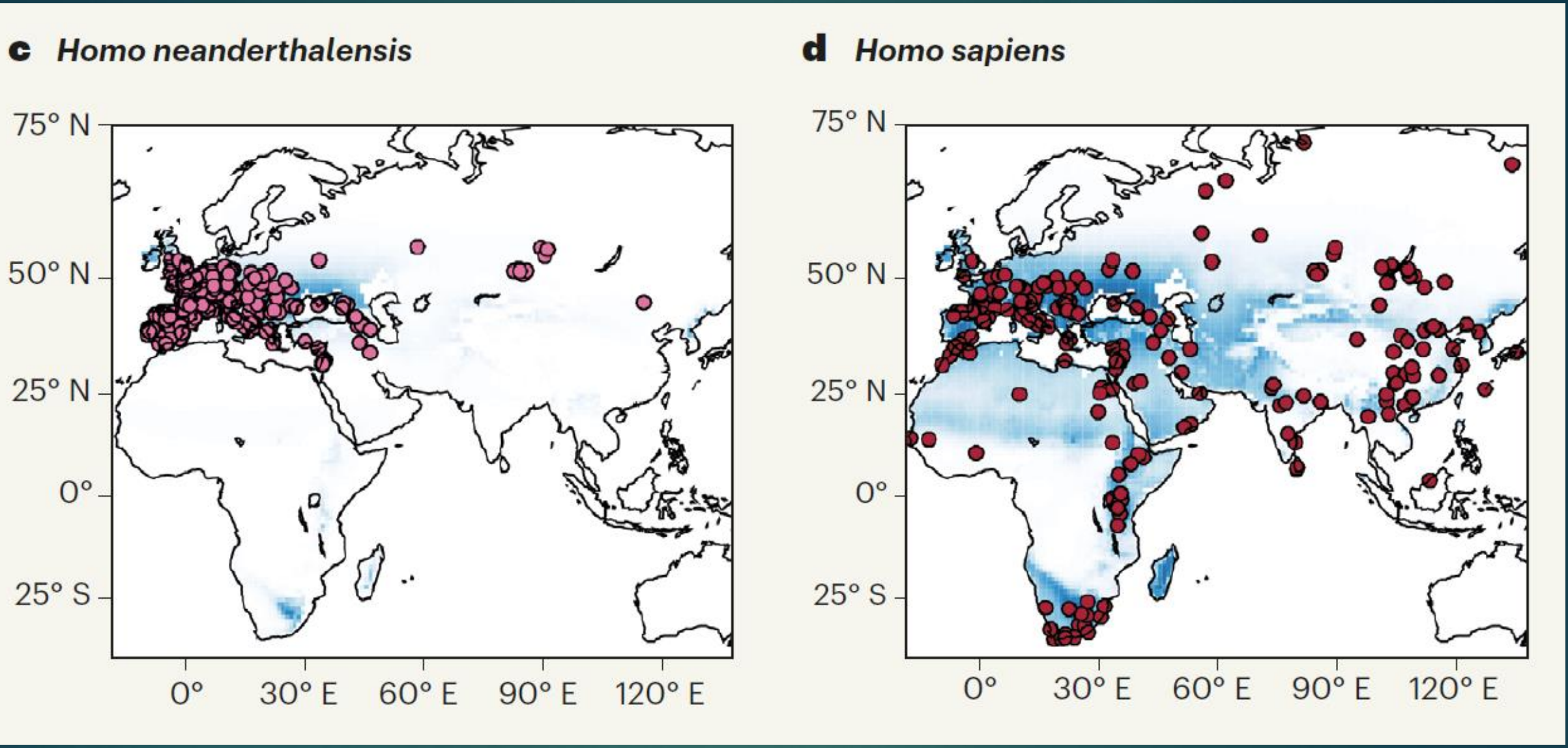
Timmermann *et al.*, 2022

Habitat suitability and the distribution of early humans and our close relatives



Habitat suitability and the distribution of early humans and our close relatives





Note: species presence based on lithics tools, in absence of hominin fossils. More than one species can be responsible for producing similar types of stone tool.

3 major Climate factors

- Eccentricity: The Earth's orbit is an ellipse whose eccentricity varies between 0.0034 (that is, a nearly circular shape) and 0.06 over two superimposed cycles: a main one every 413,000 years and others with a frequency of 100,000 years. It affects the total amount of solar radiation received: maximum at perihelion (maximum distance from the Sun, 151 million km) and minimum at aphelion (minimum, 146 million km). With maximum eccentricity, the difference in insolation between perihelion and aphelion reaches 30% (currently it is 3.5%).
- Precession: it is the circumference that the axis between the two terrestrial poles draws (like a spinning top when it stops) every 25,771 years. It impacts by reversing the situations of summer and winter in aphelion or perihelion.

3 major Climate factors

- Milankovitch cycles:. A century ago, the Serbian scientist Milutin Milankovitch developed mathematical models that relate the orbital variation of the Earth, motivated by gravitational interactions with the Sun, the Moon and the rest of the planets, with the distribution and seasonality of solar irradiation
- Three major orbital movements that condition the climate of the planet:
- Obliquity: it is a slight variation of the angle formed by the ecliptic (plane of the Earth's orbit) and the plane of the equator, and which oscillates between 21.5º and 24.5º every 41,000 years. When this angle increases, the seasonality is greater.

Current climate

- We are currently in an interglacial period with low (0.018) and decreasing eccentricity, medium (23.4º) and decreasing obliquity, and perihelion occurs during the austral summer. We have well contrasted seasons, and the northern hemisphere is tilted towards the Sun at aphelion (boreal summer), which softens summer temperatures (less extreme variation), and the opposite in the southern hemisphere (more extreme variation).
- The combination of these factors and their different degree of impact on the climate is highly complex. For example, from a million years ago to now, eccentricity-related 100-ka climate cycles predominate, but prior to that million-year threshold, predominant cycles were 41 ka due to eccentricity. obliquity.
- Different paleoecological studies have been able to verify Milankovitch's predictions based on the irradiation measured on sediment samples from different parts of the planet (ice cores, oceanic sediments, stalagmites...), also taking into account other possible local effects that alter the climate.

Climate and human migrations

- The main conclusion is that the global distribution of fossils and industry is not random, but follows a certain pattern that overlaps with climate changes caused by the movements of the Earth. Some particular conclusions are the following:

- Early *Homo* lived in a narrow range of conditions, with predominantly static populations inhabiting areas without large climatic variations.
- *Homo erectus* occupied very diverse habitats, indicating their generalist and adaptable nature for more than a million years, probably linked to their cultural development (fire, more advanced tools), which allowed them to explore and occupy new territories and environments.

Homo habilis and erectus

- For early African *Homo*, the results point to narrow corridors of suitable habitats across southern Africa and the East African rift valley, characterized by high spatial and temporal variability (small areas of suitable habitat varies and the habitats' change over time), consistent with the environmental specialization (restricted habitat range) of *H. habilis* and *H. ergaster.*
- The habitat data for Eurasian *H. erectus* is spatially extensive in comparison with that of the other species examined, consistent with the argument that this species was a flexible generalist that inhabited widely different environments.
- Habitat-suitability patterns for *H. heidelbergensis* and the Neanderthals were both overlapping and more restricted. Europe = birthplace of Neandertals
- *H. sapiens* contrasts with all other hominin species with respect to a widening of the presence of our species into generally drier landscapes.

H. erectus in Africa

- At 2 Ma, *Homo erectus* had already begun to roam outside Africa, while an East African species called *H. ergaster* stuck close to its home region. *H. ergaster* probably evolved into a disputed East African species called *H. heidelbergensis,* which split into southern and northern branches between 850,000 and 600,000 years ago.
- These migrations coincided with warmer, survival-enhancing climate shifts that occur every 20,000 to 100,000 years due to variations in Earth's orbit and tilt that modify how much sunlight reaches the planet.

H. heidelbergensis in Africa

- Using the model, the authors suggest that South African populations of *H. heidelbergensis* endured two periods (360,000 to 415,000 years ago and 310,000 to 340,000 years ago) in which their habitat suitability was greatly reduced.
- The return of high value habitats, from 200,000 to 310,000 years ago corresponds with the disappearance of that species and the emergence of *Homo sapiens*.
- Fossil and archaeological overlap and high habitat suitability is consistent with the idea that *H. heidelbergensis* evolved into *H. sapiens*.
- Evidence for this longstanding transition theory can be seen in the record of increasingly modern skulls like Kabwe 1 (300 Ka), Florisbad (260 Ka), and Herto (233 Ka).

Climate and human migrations

- If *H. Heidelbergensis* was ancestral to ourselves, and we arose during a speciation period between 200,000 and 300,000 years ago, the conditions favored by both species must have overlapped during that era. That's exactly what the climate model suggests occurred in South Africa.
- Climatic events produced strong environmental transformations and of available resources, and consequent genetic bottlenecks in which some surviving groups with certain advantages were the protagonists of the transitions from one human species to another in Africa and Europe.
- The *H. heidelbergensis* group had an East African origin from *H. ergaster*, and was also a highly mobile group, splitting into two branches 850-600 ka ago, with the northern branch spreading across North Africa and Eurasia.

Southern H. heidelbergensis

- Northern H. heidelbergensis migration at 680-580 ka ago, due to a more elliptical orbit that generated better climatic conditions.
- In southern Africa between 310,000 and 200,000 years ago, increasingly harsh environmental conditions accompanied a transition from *H. heidelbergensis* to *H. sapiens*, who later moved out of Africa.
- *Heidelbergensis* populations in southern Africa experienced two periods of habitat deterioration in which the
  - climate became much drier (415-360 ka and 340-310 ka),
  - while with a subsequent habitat improvement (310-200 ka) it coincided with the disappearance of that group and the appearance of our species *H. sapiens*.

H. Heidelbergensis & H. sapiens in Africa

- *Homo heidelbergensis*, started expanding its habitat around 700,000 years ago
- Distribution of *H. heidelbergensis* across the globe was possible because a more elliptical orbit created wetter climate conditions that allowed the species to migrate more widely..
- Timmermann and his colleagues say that their climate reconstruction favors the single-evolutionary-path hypothesis. The model suggests that our species evolved when *H. heidelbergensis* in southern Africa started losing liveable habitat during an unusually warm period. This population could have evolved into *H. sapiens* by adapting to the hotter, drier conditions.

European Climate & emergence of Neandertals

- Similarly, a similar convergence of favorable habitats occurred in Europe 400 ka ago, triggering a transition between *heidelbergensis* and *H. neanderthalensis*.
- *The* austral summer at perihelion 210-200 ka ago posed a new climatic stress on *sapiens*, which would have caused their dispersal and genetic diversification.
- The new habitat simulations also indicate that *H. sapiens* was particularly good at adjusting to hot, dry regions, such as northeastern Africa and the Arabian Peninsula.

Europe

- Then, after traveling north to Eurasia, *H. heidelbergensis* possibly gave rise to Denisovans around 430,000 years ago. And in central Europe, harsh habitats created by recurring ice ages spurred the evolution of *H. heidelbergensis* into Neandertals between 400,000 and 300,000 years ago.
- A similar convergence of suitable habitats, in Europe, lends support to the hypothesis that another species transition took place there between the European *H. heidelbergensis* and Neanderthals some 400,000 years ago.
- Ultimately it's not climate so much as the ecological conditions in any given place, like what kind of food and water were available, and the range of plant and animals species present, that determine which human species could have survived and how they must have adapted over time.

Critique: multiregionalism in Africa

- An alternative view to the newly proposed scenario of a Southern "homeland" of *H. sapiens*, suggests that, during the time that *H. heidelbergensis* allegedly lived, closely related *Homo* populations periodically split up, reorganized and bred with outsiders, without necessarily operating as distinct biological species.
- In this view, mating among *H. sapiens* groups across Africa starting as early as 500,000 years ago eventually produced a physical makeup typical of people today.
- If so, that would undermine the validity of a neatly branching evolutionary tree of *Homo* species leading up to *H. sapiens*, as proposed by Timmermann's group.

Rick Potts: Variability selection theory

- Paleoanthropologist Rick Potts of the Smithsonian Institution in Washington, D.C., has previously developed another influential theory about how climate fluctuations influenced human evolution that's still open to debate.
- Variability selection hypothesis: posits that early hominin evolution, selection and speciation were influenced by alternating periods of high and low variability in climate and resources.
- A series of climate-driven booms and busts in resource availability, starting around 400,000 years ago in East Africa, resulted in *H. sapiens* evolving as a species with a keen ability to survive in unpredictably shifting environments,
- But the new model indicates that ancient *H. sapiens* often migrated into novel but relatively stable environments, Timmermann says, undermining support for Potts' hypothesis, known as variability selection.

Critiques of new model

- It seems to indicate a specific origin of *Homo sapiens* in southern Africa, while paleogenomic studies in recent years have been pointing to a multiple origin, a "genetic soup" that emerged in central-southern Africa.
- This discrepancy may be due, on the one hand, to the bias of the study regarding the number of African records it contains, and 86% of the fossils included in the study are from Neanderthals and *Sapiens,* and on the other hand, because most of the records in the database refer to lithic industry without the presence of fossils, where the assignment of authorship to a human species is not clear.

Critiques

- The classification made into five species is debatable, for example: there is no general consensus on what *Homo heidelbergensis* is (this grouping may actually contain several species), its position as the last common ancestor of Neanderthals and *sapiens* has become obsolete, there is no consensus about the difference between *H. ergaster* and the remains of *H. erectus* in Africa, with an older presence than previously thought, etc.
- Although that is not the main focus of the work, the five classifications should be considered general groupings of human populations rather than species.

Purpose in Life

- Higher purpose or meaning in life was significantly associated with a reduced risk of multiple cognitive impairment outcomes, including dementia and mild cognitive impairment
- A sense of purpose is associated with a 19% reduced rate of clinically significant cognitive impairment
- Purpose in life may hold benefits to recovering from stressful evidence and is associated with reduced inflammation in the brain, both of which may be associated with reduced risk of dementia.
- Further, people with a higher sense of purpose in life may also be more likely to engage in activities such as exercise and social involvement, which may protect against dementia risk.
- Increase purpose and meaning to people's lives, rather than just hedonistic activities that might increase positive mood states.
- Studies also suggest that appreciating beauty in the everyday may be just as powerful as a sense of overarching purpose

Georgia Bell, et al., 2022

Archaeological dig in Indonesia where the Java Man fossils were found

Java Man, *Homo erectus* – 1890s

- New analysis of the original unpublished Trinil records of Eugène Dubois : animals in the fossil bed may all have perished in a single cataclysm, probably a volcanic eruption. Later, a volcanic mudslide swept all their bones down the valley to a single site.
- Discovered a molar tooth, a skullcap and a controversial femur; multiple mammal bones (stegodon, deer); many of the animal bones are broken, but don't have much surface damage (animals experienced something catastrophic)
- Dubois ran a careful excavation: one of the first to divide a site into meter-by-meter squares, ensuring each discovery could be precisely localized. This rigorous approach suggests the femur really is *H. erectus.*
- They may have died from breathing toxic fumes, he says. Afterwards, there was a lahar, a mudflow filled with rocks ejected from the volcano. The lahar swept the bones to the same site and entombed them in mud.

Tropical birds are more colorful—and why color helps them survive

- Study of 4500 birds: Bird colorfulness is generally highest at the Equator and decreases with increasing latitude towards the poles—specifically, their plumages displayed around 20%-30% more colors than birds living at higher latitudes outside of the tropics, whether north or south.
- Interestingly, this was true for both male and female birds, even though they can sometimes look very different from one another.
- Proved Darwin's observations correct—on the "rich variety of colors" found in the tropics

Bird Color

- Color diversity was highest in birds from dense, closed forest habitats such as rainforests, and also in those who eat fruits and floral nectar.
- Both of those traits are more common at tropical latitudes
- The average number of songbird species living together in the same location increases dramatically towards the Equator, so this enhanced colorfulness may help them to distinguish themselves from all the other birds in their rich tropical communities

New aDNA extraction method

- Methodological and technological improvements are continually revolutionizing the field of ancient DNA. Most ancient DNA extraction methods require the partial (or complete) destruction of finite museum specimens, which disproportionately impacts small or fragmentary subfossil remains, and future analyses.
- Most of these studies utilize polymerase chain reaction (PCR)-based amplification of short mitochondrial DNA fragments, primarily for use in species identification
- We present a minimally destructive ancient DNA extraction method optimized for small vertebrate remains.

New method

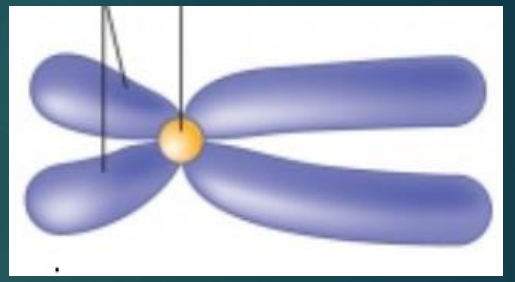
- For subfossil bones, an adapted minimally destructive aDNA extraction protocol (Tennyson et al., 2015) was optimized for reducing osteological damage to small vertebrate remains. Specifically, subfossil bones were immersed in a digestion buffer then removed (using forceps), soaked in dH_2O for 24 h and dried at room temperature to prevent further digestion. Suspended sediment particles (released from the bone exterior during digestion) were pelleted by centrifugation

Darwin’s notebooks

- Two of Charles Darwin’s 1837 notebooks containing his pioneering ideas on evolution and his famous "Tree of Life" sketch have been returned anonymously after going missing for 21 years, Cambridge University Library said on Tuesday.

- The prized documents were left on the floor in a public area of the British university's library in a pink gift bag, with a typed note wishing a Happy Easter to the librarian.

Human Genome Project: 2001



- First genome reference version
- It lacked 15% of the human DNA sequence into the picture.
- Most of the unmapped regions were concentrated around telomeres (the caps on the ends of chromosomes) and centromeres (the chromosomes' densely packed middle sections).
- In 2013, researchers narrowed this gap to just 8%, but they still couldn't place 200 million base pairs — the equivalent of an entire chromosome.

The map of our DNA is finally complete

- The T2T Consortium included 114 scientists at 33 institutions
- Published six papers in the journal *Science:* Scientists are finally done mapping the human genome,
- In the initial reference map, 3 billion basepairs. But sections of five chromosomes were missing, mainly areas that contained a lot of repeated genetic letters.
- Of the 20,000 genes in the human genome, about 950 originate in these reduplicative areas.

First complete, gapless sequence of a human genome

- With the original Human Genome Project, researchers could only map about 500 pairs of letters at a time; now can read up to about 100,000 pairs and so detect those repetitions.
- New reference version:
  - 3.055 billion base pairs;
  - 19,969 genes
- Telomere to Telomere group added 200 million new bps
- 180 "new" protein-coding genes, almost all of which mapped to segmental duplications (repetitive segments).

The map of our DNA is finally complete

- About 90 percent of the new sequence comes from the centromeres of chromosomes;
- First description of centromeres – dense middle of chromosomes, and telomeres at end of chromosomes
- New areas contained some of the most genetically diverse bps
- Research was done on a rare type of tumor (hydatidiform mole), a nonviable embryo made up only of paternal DNA from a sperm cell; sperm from a person of European descent; only an X chromosome; need to do a dual parent genome

The map of our DNA is finally complete

- Prior difficulty in mapping gaps due to extremely long strands of repetitive DNA that were impossible to place, until use of long read sequencing that used lasers to scan 20,000 to 1 million base pairs at a time.

- Still to do:
  - around 0.3% of the genome could contain errors;
  - need to do a Y chromosome

- Next step is Pangenomic Project

Human Pangenome Project

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

Human Pangenome Project

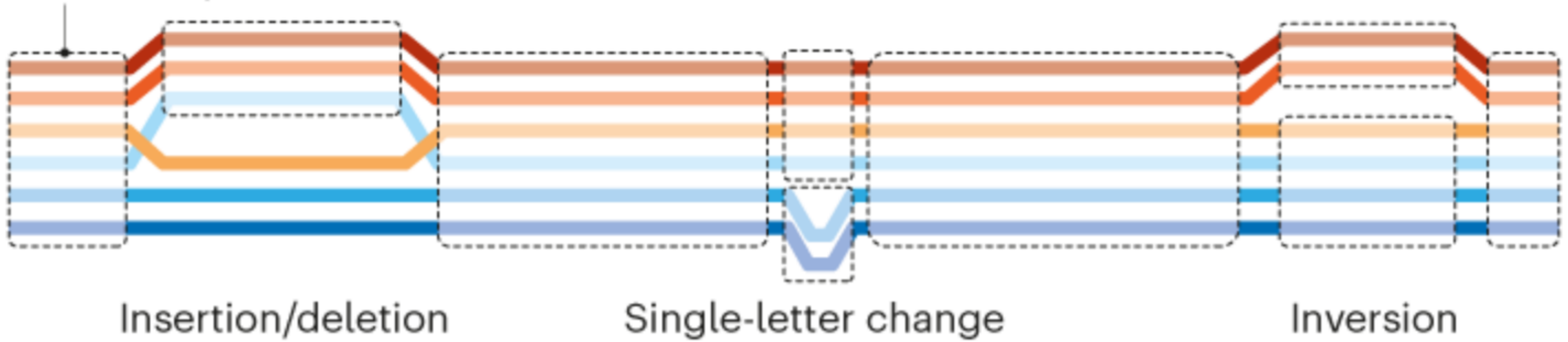
- Human Pangenome Project: New attempt to capture almost all human genetic variability; would represent the varieties of sequence that can be found in different populations; currently evaluating 350 genomes

- Using ‘long-read sequencing’, which analyses bigger stretches of DNA at a time.

Human Pangenome Project: population genetic variations

Exploring the pangenome

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



History of gene studies: Gene stars come and go

- Before the mid-1980s, for example, much genetic research centered on hemoglobin, the oxygen-carrying molecule found in red blood cells. More than 10% of all studies on human genetics before 1985 were about hemoglobin in some way.
- *HBB* Hemoglobin subunit beta and related genes were among the first to be linked to hereditary diseases such as sickle-cell anemia.
- *CD4* This T-cell receptor protein became in vogue owing to its role in HIV infection.
- *GRB2* Growth factor receptor-bound protein 2 helped launch the field of signal transduction (cellular communication).

Gene studies

- *TP53 A cancer repressor, t*he ‘guardian of the genome' is the most studied gene (and protein) of all time.
- *APOE* Apolipoprotein E briefly interrupted TP53’s reign owing to its role in cholesterol metabolism and Alzheimer's disease.
- Current gene interest responds to current disease importance.

Historical focus on just a few genes

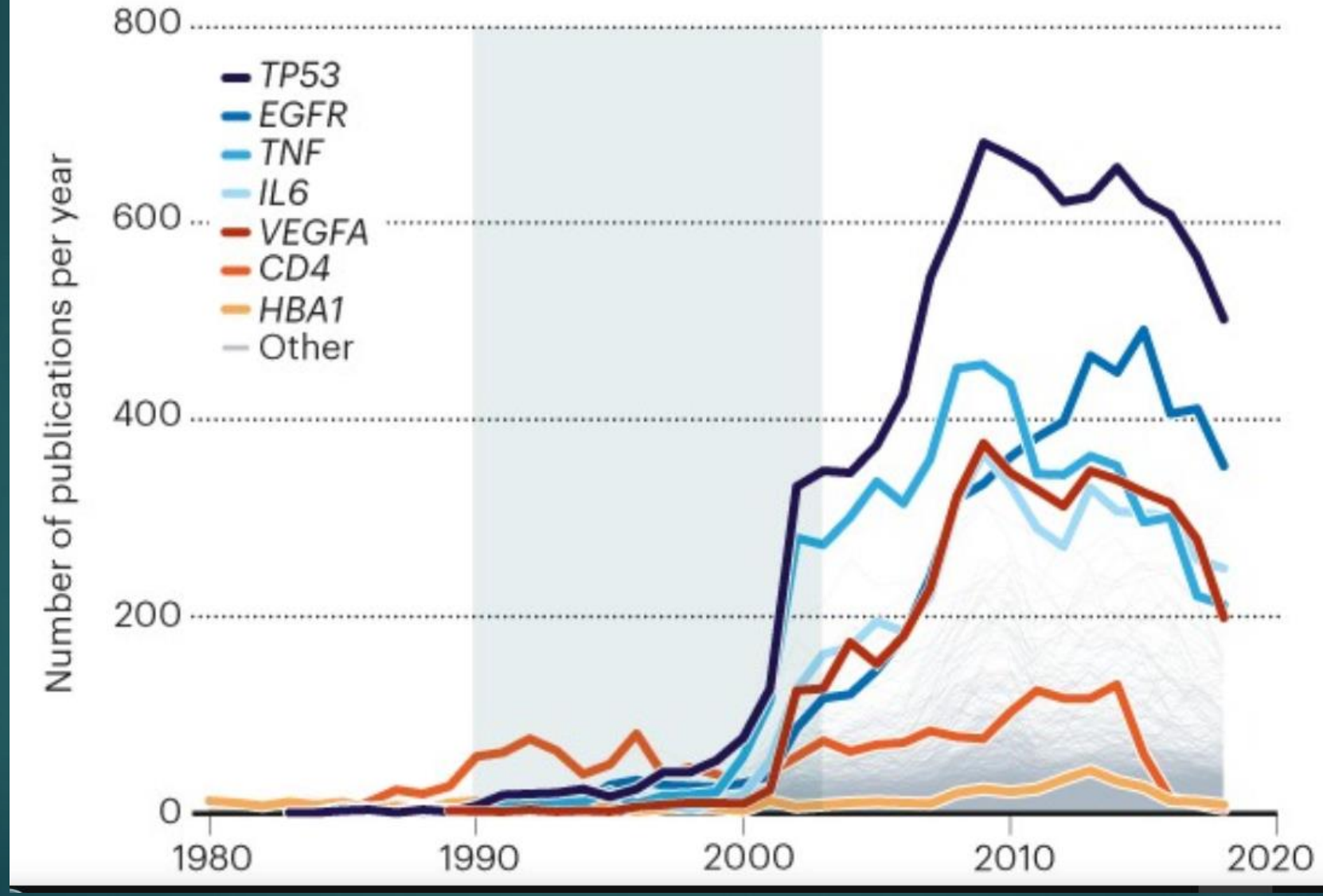
- Interest has focused largely on just a few genes.
- Before 1990, *HBA1* was the most studied because it encodes one of the proteins in adult hemoglobin, and involved in sickle cell disease.
- From 1990, attention then shifted to *CD4* (based on the cumulative number of publications) given the protein's involvement in T-cell immunity and as the cell receptor for HIV.

A few genes

- Yet the interest in these two genes pales next to the explosion of attention on individual genes following the draft 2001 HGP sequence.
- Some superstar genes, including *TP53*, *TNF* and *EGFR*, became the subject of hundreds of publications a year, with most other genes receiving scant attention
- We find that, by 2017, 22% of gene-related publications referenced just 1% of genes.

Star genes

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



The ten most studied genes of all time = 40,000 papers – 6 of 10 related to cancer research

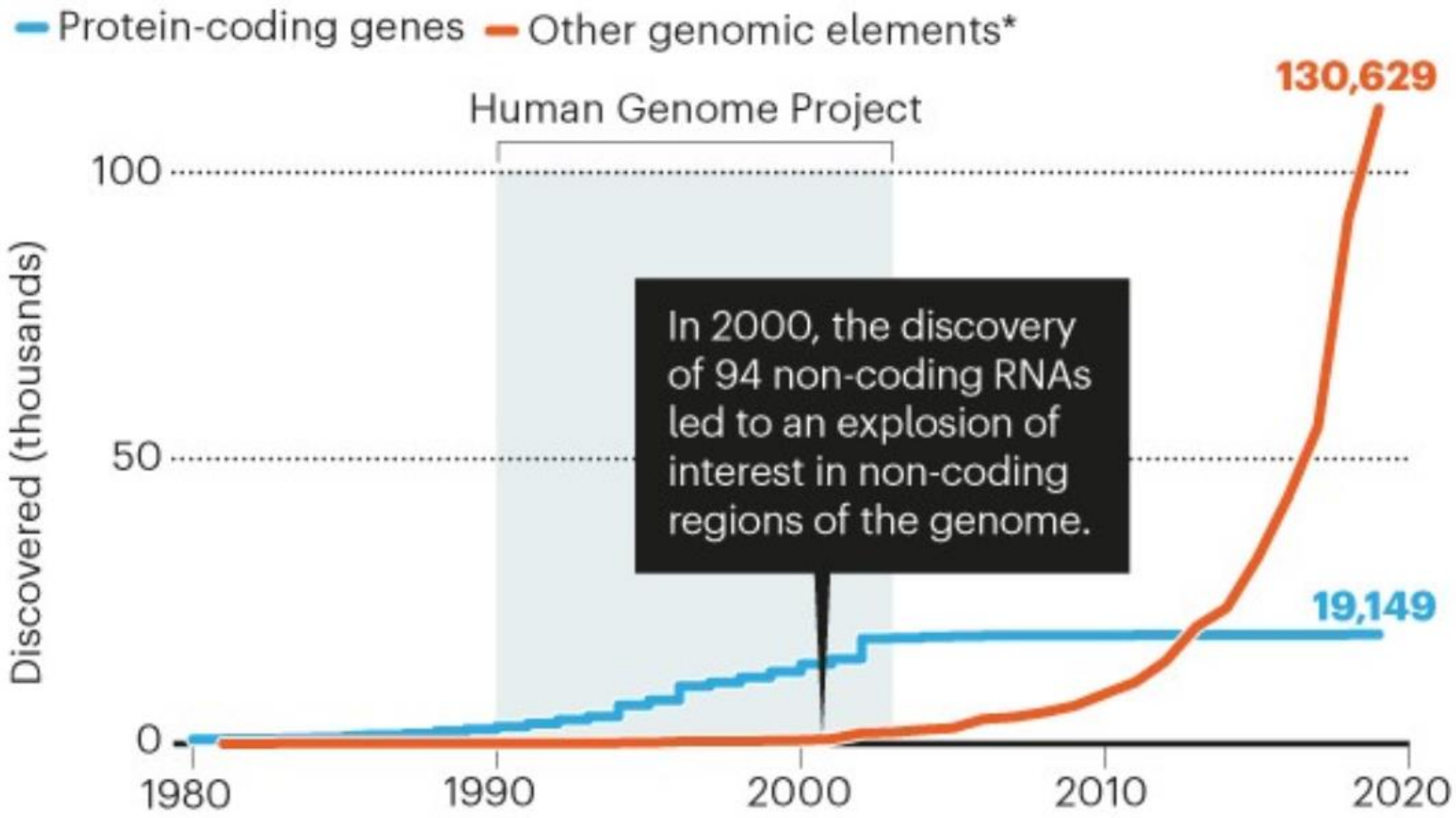
TP53	9,232 papers	Tumor suppressor; mutated in 50% of cancers
TNF	5,314	Tumor necrosis factor
EGFR	4,583	Epidermal growth factor mutated in drug-resistant cancers.
VEGFA	4,059	Vascular endothelial growth factor (cancer growth)
APOE	3,977	Cholesterol metabolism – Alzheimer's
IL6	3,930	Interleukin 6 --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

Genes: only select few are studied

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

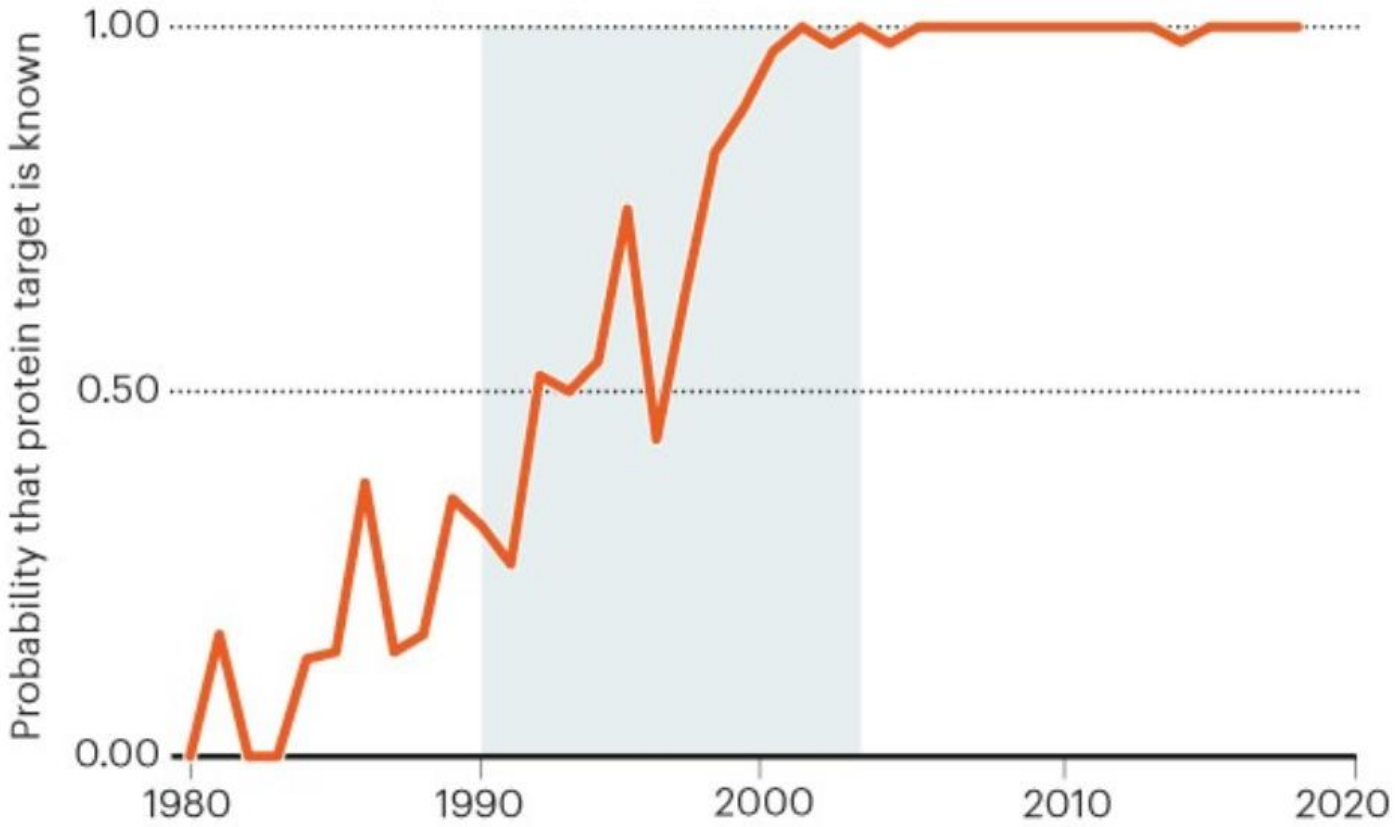
Non-coding elements

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



Drug targets

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



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

Drug targets

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

- That leaves 90% of the proteome untouched by pharmacology

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

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

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

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

Fruit fly evolution

- Combining a field experiment with laboratory common garden experiments, they observed changes in six phenotypes related to reproductive output or stress tolerance underlain by rapid, genome-wide evolution.

- The direction of trait and genomic shifts changed over months, in accordance with environmental changes.

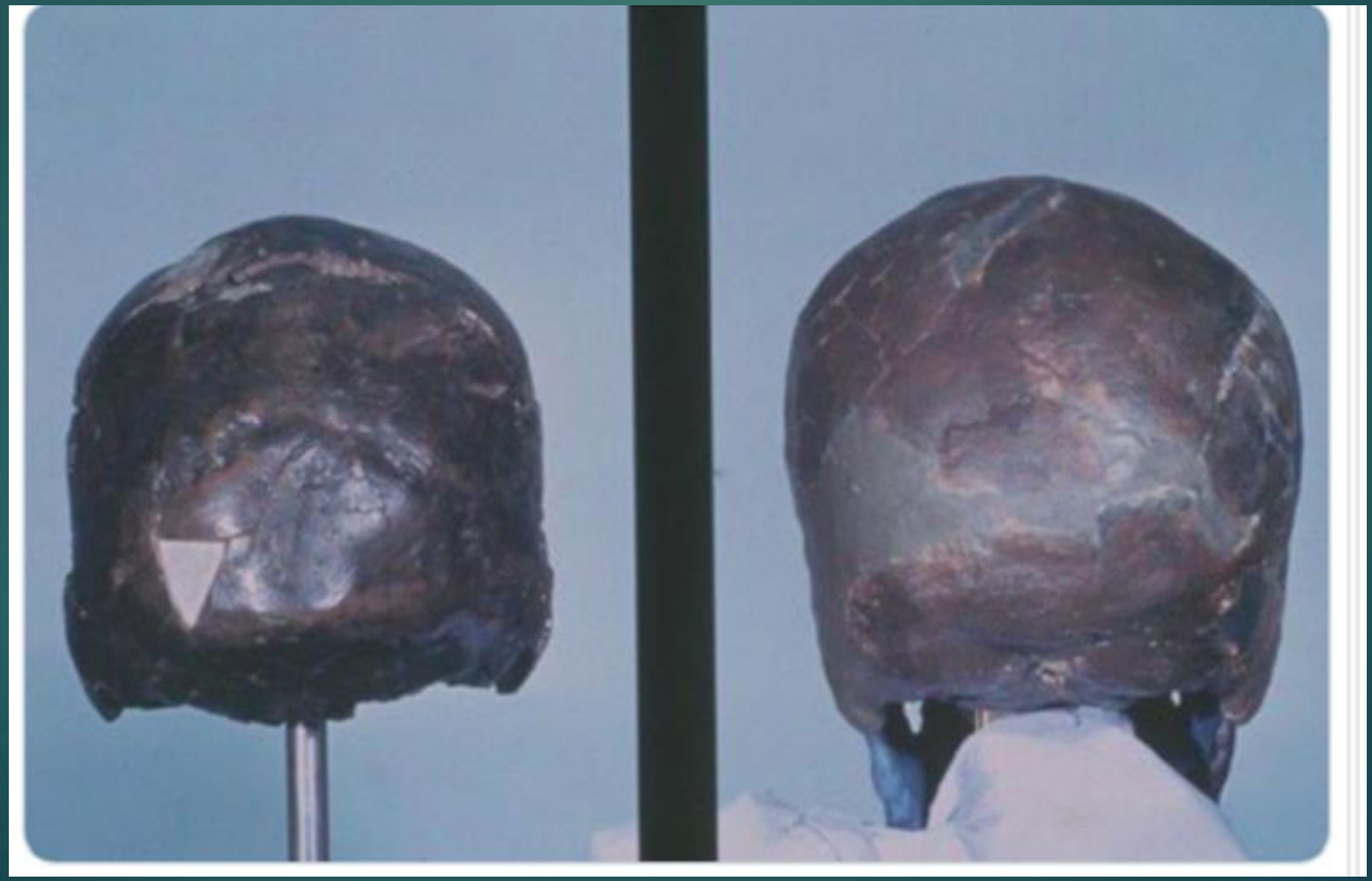
- This study demonstrates the potential for rapid, continuous evolution to changing environmental conditions

Fast evolution

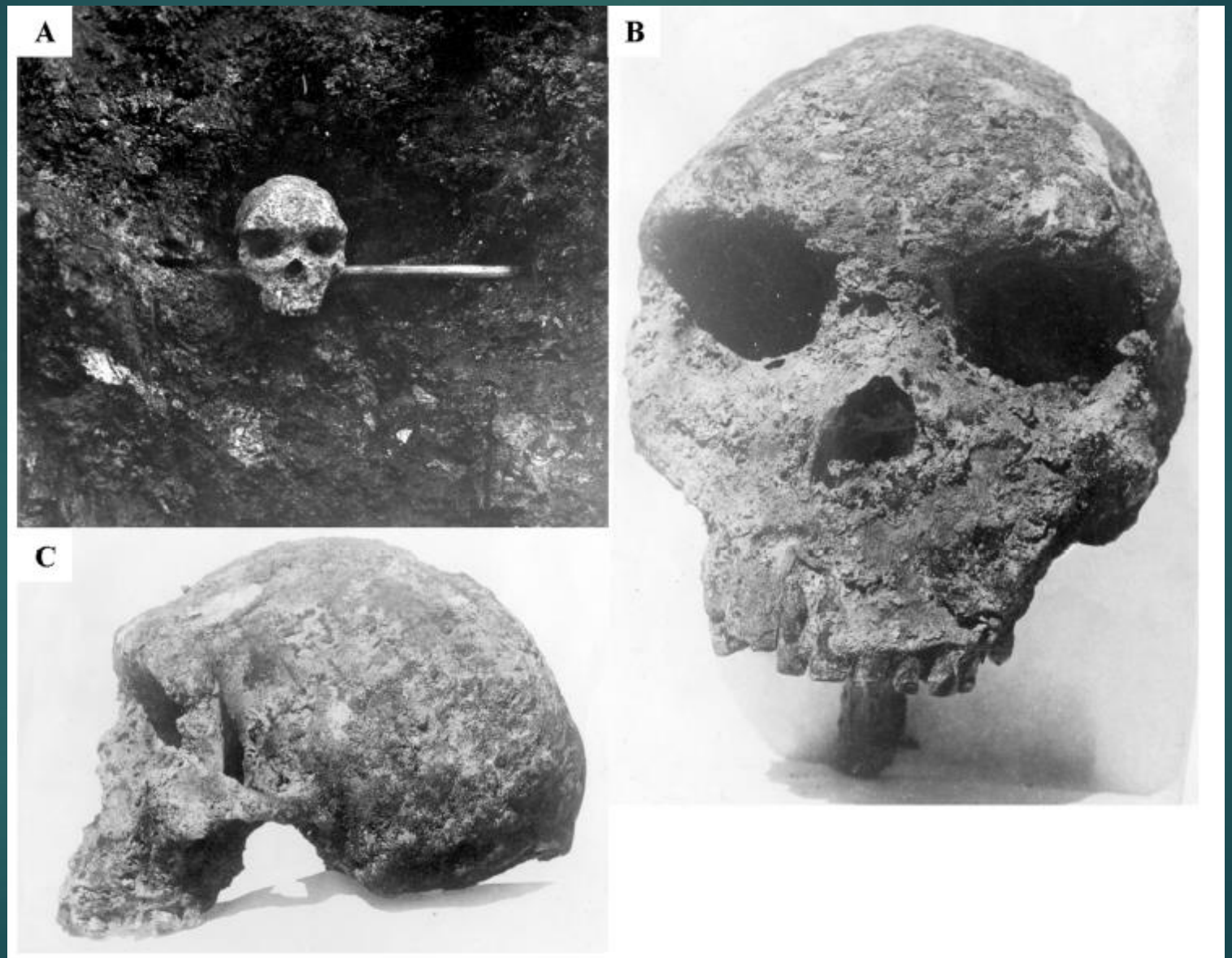
- Fruit flies are already known to evolve at a speedy pace. In laboratory studies, the insects evolve resistance to stressors like dry environments and cold temperatures within 8 to 9 generations.
- In contrast, the new study documented changes in flies' physical characteristics on shorter timescales—within 3 to 4 generations, each of which can last a month or more.
- This study builds on the group's previous field experiments, in which they found that the physical characteristics of fruit flies—from dehydration tolerance to coloration—change dramatically over the course of a year
- Taken together, these data underscore that natural selection is capable of driving evolution in multiple fitness-related phenotypes and much of the genome even over short time scales.

The dating of the Omo 1 skull (Ethiopia) has been revised : it is now at least 233 ka (previously 197 ka), which reinforces idea that the origin of our species is much older than previously thought.

Replicas of Omo Kibish 2 (left) and Day+Stringer recon. of 1 (right).
Both sapiens lineage from Ethiopia and dated 233 Ka, but Omo 1 (which has been directly dated) shows much clearer modern sapiens features

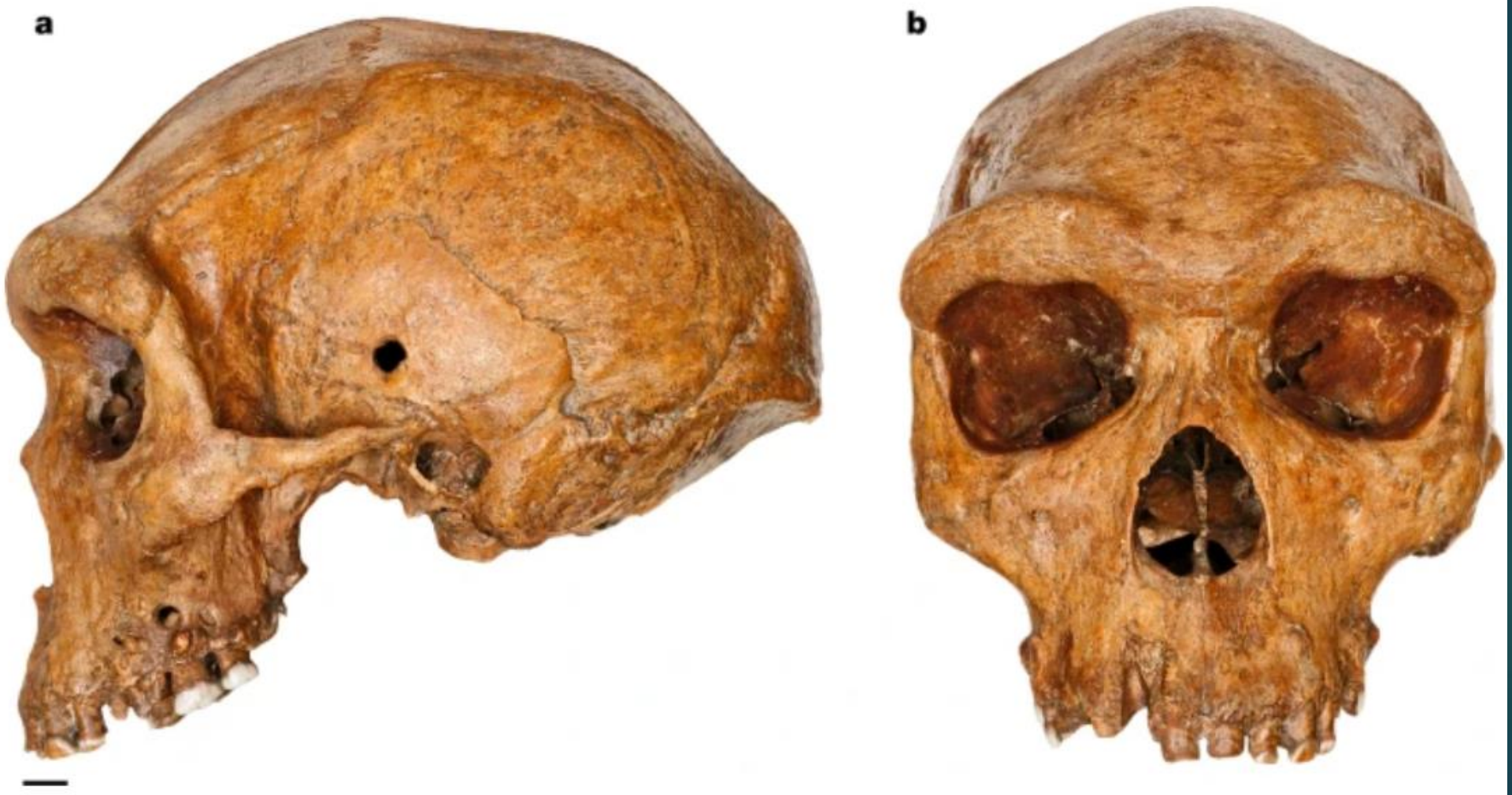


Broken Hill, Zambia 1921



Extended Data Fig. 1 | Photos of the skull shortly after its discovery. a, The cranium at the location in which it was found[34]. © Illustrated London News Ltd/Mary Evans. **b**, **c**, Frontal view (**b**) and lateral view (**c**) before the matrix was removed. Images from the Archive of the Natural History Museum.

Fig. 1: The Broken Hill cranium (E686), discovered at the Broken Hill mine, Zambia, in 1921.



Rainer Grün, et al., 2019

Broken Hill human fossils: a, Partial os coxa (E719). b, Femoral fragment (E907). c, Femoral midshaft (EM793). d, Tibia (E691).

Broken Hill/Kabwe skull new dating = 299 ± 25 Ka

- The cranium from Broken Hill (Kabwe) was recovered from cave deposits in 1921, during metal ore mining in what is now Zambia.
- It is one of the best-preserved skulls of a fossil hominin and was initially designated as the type specimen of *Homo rhodesiensis*, but now has often been included in the taxon *Homo heidelbergensis*.
- However, the original site has since been completely quarried away, and—although the cranium is often estimated to be around 500 thousand years old—its unsystematic recovery impedes its accurate dating and placement in human evolution.
- New analyses directly on the skull and found a best age estimate of 299 ± 25 thousand years (mean ± 2σ).

Broken Hill: same date as Jebel Irhoud

- Later Middle Pleistocene Africa contained multiple contemporaneous hominin lineages (that is, *Homo sapiens*, *H. heidelbergensis*/*H. rhodesiensis* and *Homo naledi*), similar to Eurasia, where *Homo neanderthalensis*, the Denisovans, *Homo floresiensis*, *Homo luzonensis* and perhaps also *Homo heidelbergensis* and *Homo erectus* were found contemporaneously.
- The age estimate also raises further questions about the mode of evolution of *H. sapiens* in Africa and whether *H. heidelbergensis*/*H. rhodesiensis* was a direct ancestor of our species.

Implications of the new age estimate

- The result of 299 ± 25 kyr for the age of the skull (E686) has major implications for reconstructions of human evolution in Africa.
- New dating of Broken Hill skull suggests caution about inferring the presence of modern humans from the presence of early Middle Stone Age artefacts, both because such archaeological material has been recovered from Broken Hill, and because the newly estimated ages of the Broken Hill human fossils are within the time range of the early Middle Stone Age. Thus, we can no longer assume that only *H. sapiens* produced stone tools assigned to the African Middle Stone Age.

Broken Hill

- The implications are even more profound for studies of human evolution.
- The skull (E686) has been seen by many researchers as part of a relatively gradual and widespread evolutionary sequence in Africa from archaic humans (*H. heidelbergensis*/*H. rhodesiensis*) to modern *H. sapiens*, when its age was estimated as a much older age at around 500 ka.

Broken Hill

- No evidence of expected African hominin evolutionary succession: Given that fossil material from Omo Kibish and Herto (Ethiopia) assigned to anatomically modern *H. sapiens* has been dated to at 233 ka, the fossil record would thus be expected to show a succession of fossils ranging from more archaic at around 500 ka ago to more modern-looking by about 200 ka.
- Although the new age determination for the Broken Hill skull lies at a time when an intermediate morphology might be expected, the skull shows no derived traits characteristic of anatomically modern humans.
- More pleisomorphic than Jebel Irhoud

Implications of Broken Hill: possible multiregionalism

- Roots of *H. sapiens* are much older than the age estimates for Omo Kibish 1 (233 ka) and Herto, which is supported by age estimates of more than 200 ka for the fossils from Florisbad (South Africa) and Guomde (Kenya), and of around 300 ka for the Jebel Irhoud (Morocco) material, all of which display more ‘modern’ traits than the skull (E686).
- In this model, Africa contained considerable, perhaps even multispecies, skeletal variation around 300 ka ago, something that is also suggested by age estimates of around 285 ka for the morphologically primitive *H. naledi* material from South Africa.

Broken Hill: co-existence of multiple African lineages

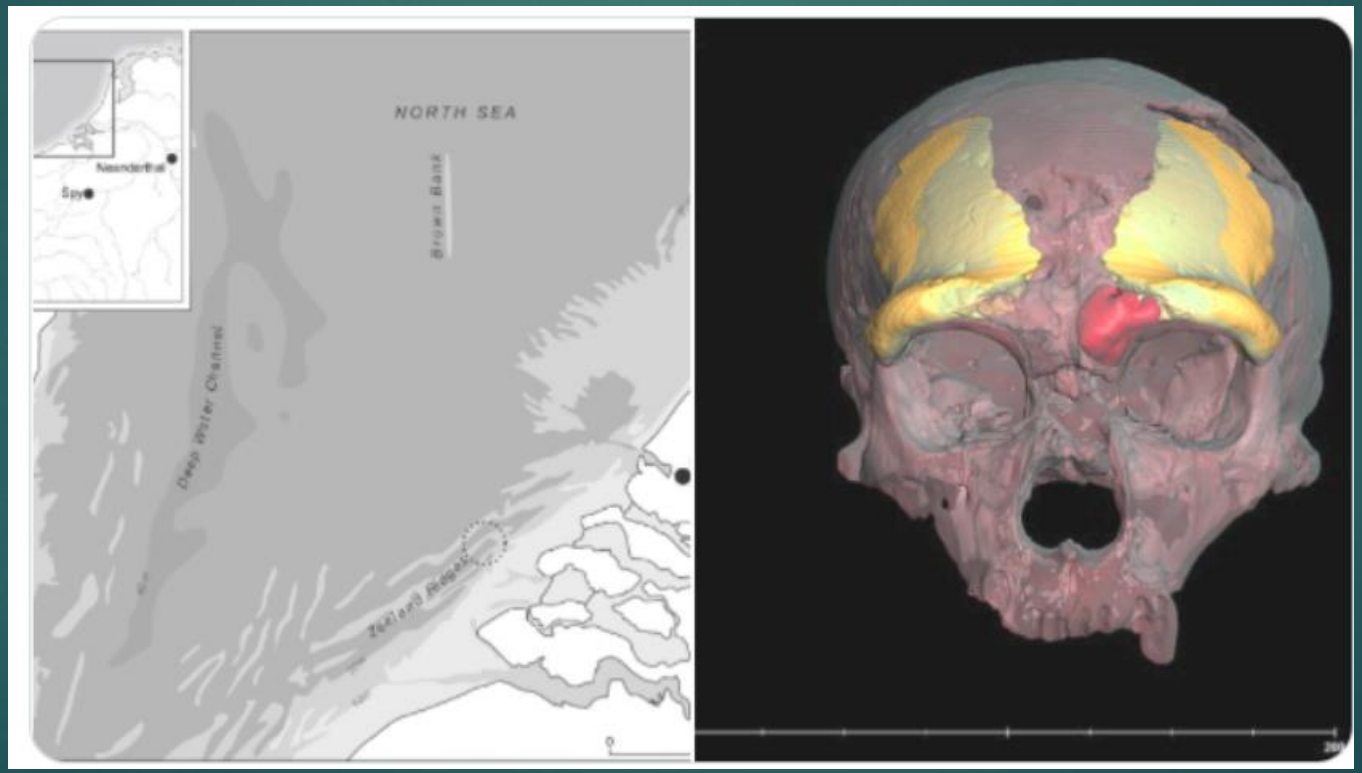
- This diversity is consistent with ideas that the evolution of *H. sapiens* was pan-African, taking place through intermittent genetic connections between subdivided populations in different areas of the continent.
- Such diversity might even have included gene flow between populations that would normally be considered distinct species. Hence, late-surviving populations of *H. heidelbergensis*/*H. rhodesiensis* could have been a source of 'ghost' introgressions.
- Therefore, just as Eurasia in the later Middle Pleistocene contained the multiple evolving lineages of *H. neanderthalensis*, Denisovans, *H. floresiensis*, *H. luzonensis* and perhaps also *H. heidelbergensis* and *H. erectus*, different human lineages and/or species also co-existed across Africa.

Broken Hill: not one of our LCA

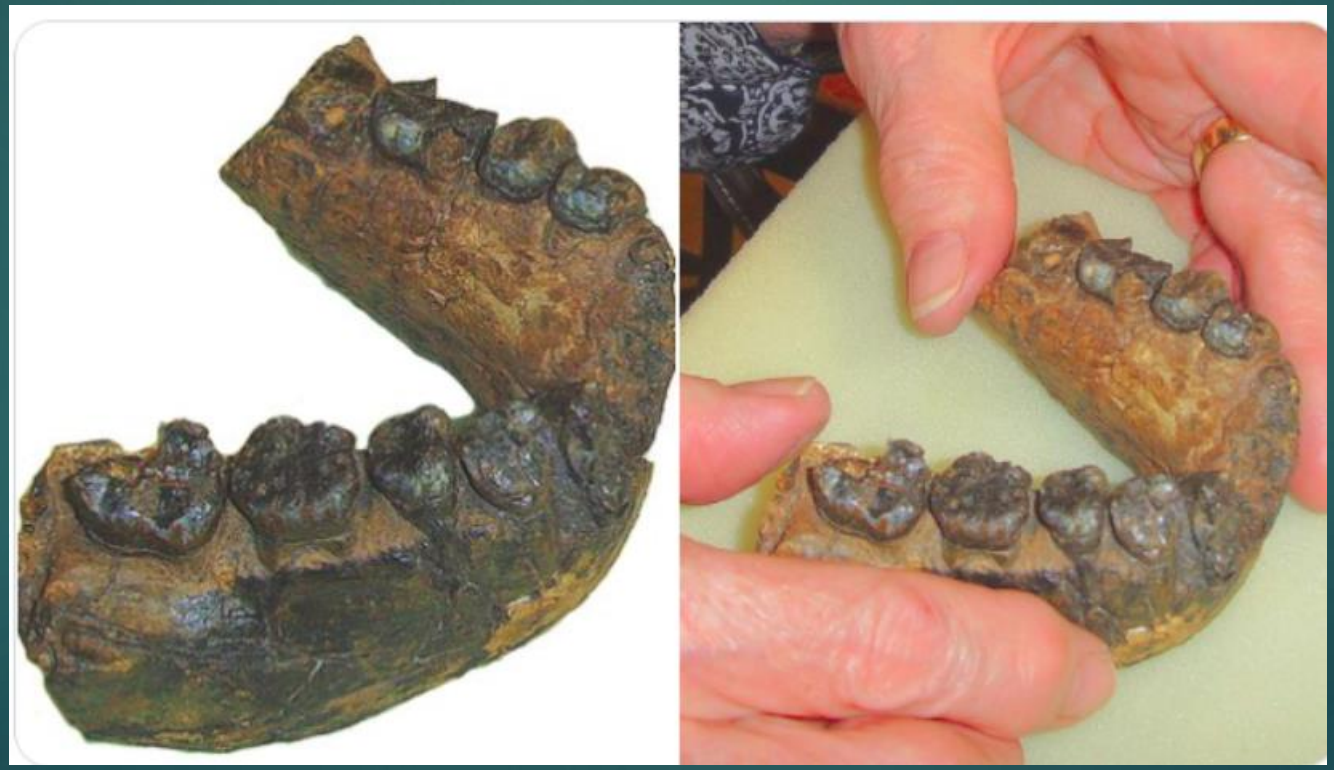
- The supposed status of *H. heidelbergensis*/*H. rhodesiensis* as an ancestral species for *H. sapiens* must also be reconsidered in the light of recent studies of the Sima de los Huesos material from Atapuerca, Spain.
- This sample, which displays clear Neanderthal affinities in both morphology and ancient DNA, has been dated to around 430 ka, suggesting that the evolutionary divergence of *H. neanderthalensis* and *H. sapiens* took place at a much earlier date.
- Moreover, new studies of facial evolution also suggest that *H. heidelbergensis*/*H. rhodesiensis* does not represent the most parsimonious last common ancestor.

Neandertal foot in matrix: El Sidròn, Spain

The Zeeland Ridge Neanderthal was discovered in sediments extracted from the bottom of the North Sea.
This is the first Pleistocene fossil hominin found under seawater.
The partial frontal bone shows a lesion caused by an epidermoid cyst.

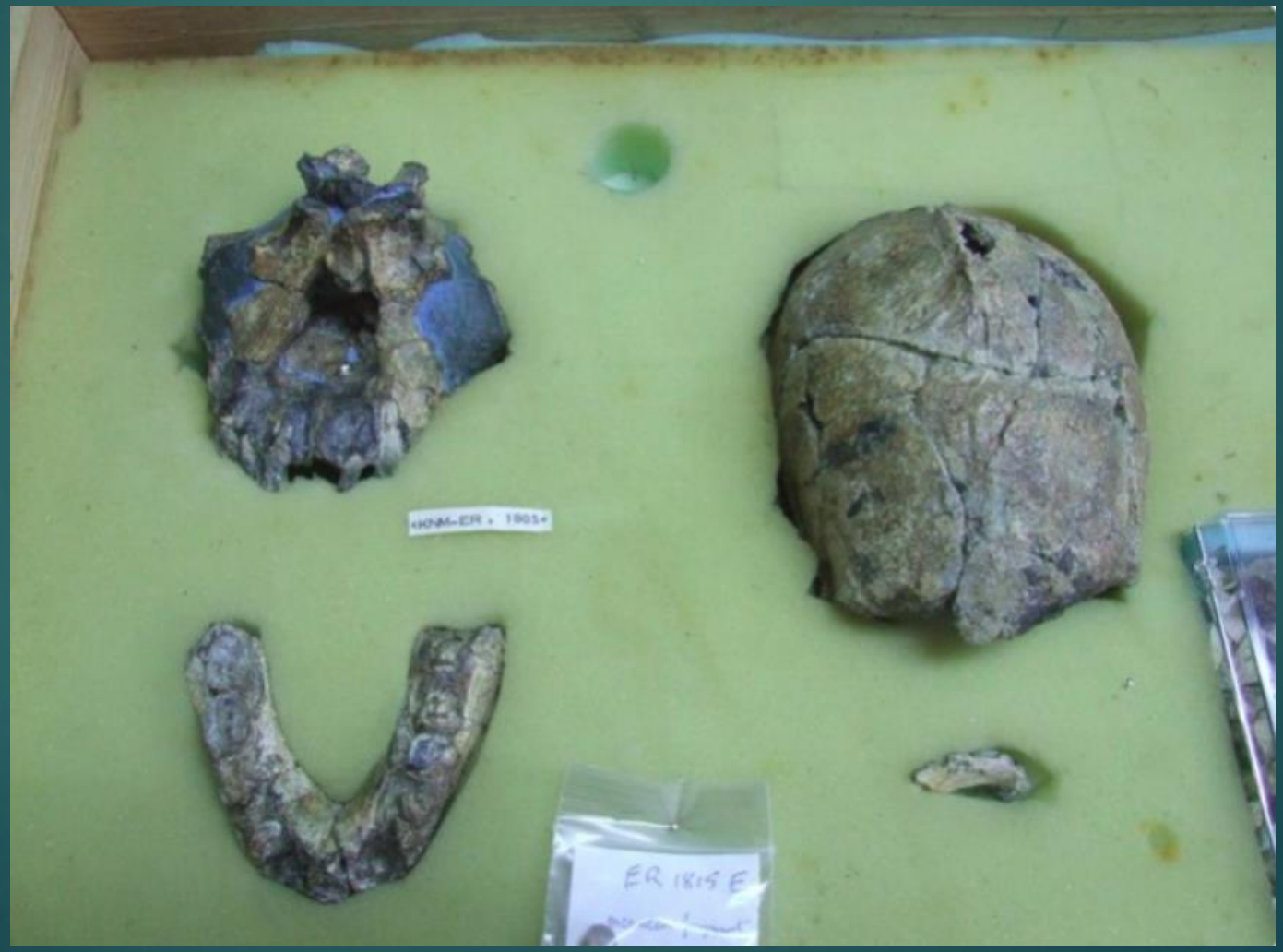


UR-501, aka the Uraha Jawbone, belongs to a Plio-Pleistocene hominid speculated to be *H. rudolfensis*.
The thickness of the lateral enamel in the premolars is similar to early homo, yet in the molars, the enamel is as thick as East Turkana's robust australopiths.



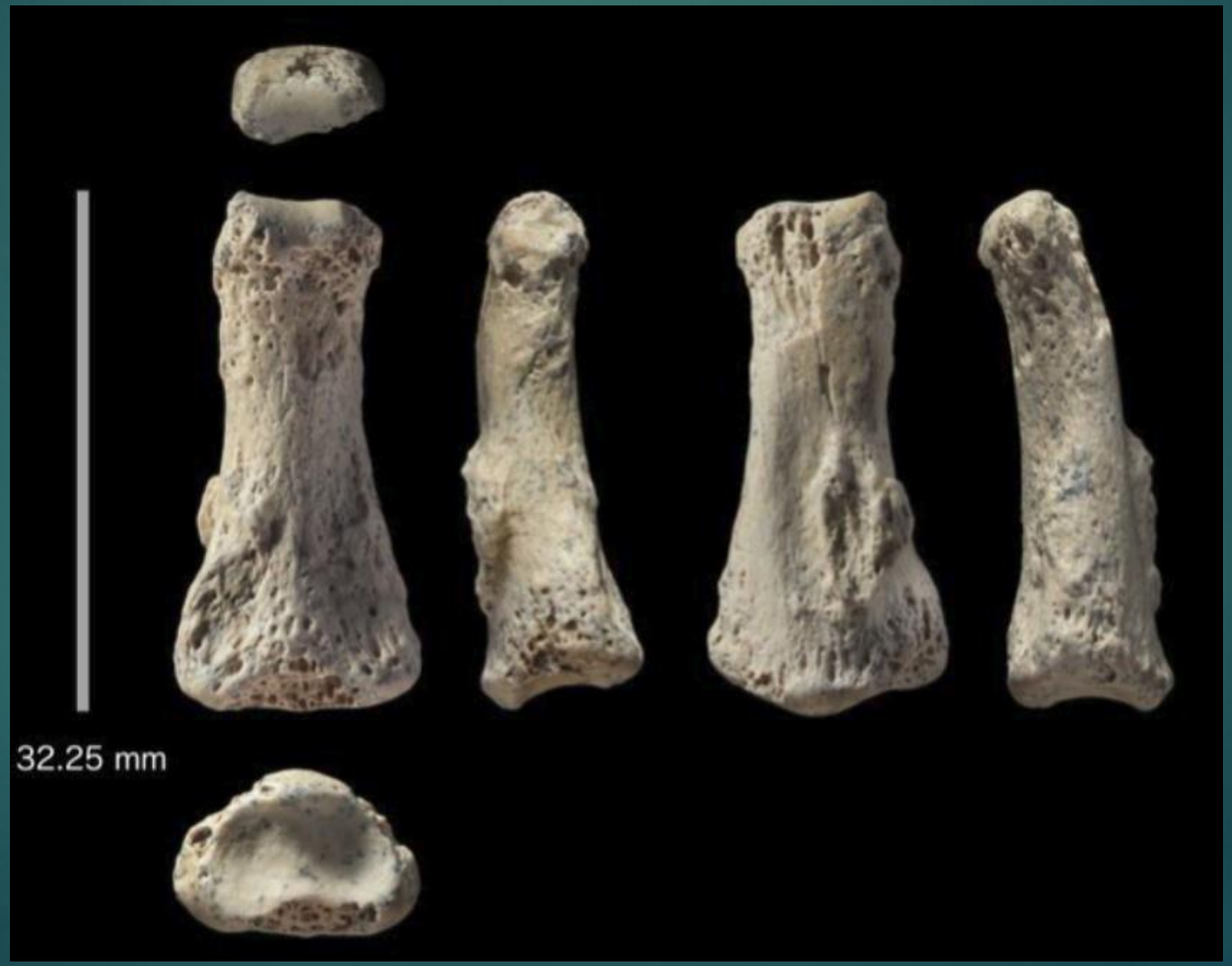
Neandertal-like occipitals La Chaise+Swanscombe (original) top, with a central suprainiac depression, and non Neandertal-like Vertesszollos (heidelbergensis?) and Zhoukoudian (erectus) bottom, angled with a continuous occipital ridge

The ~1.74 million year old KNM-ER 1805 skull found at Koobi Fora in Kenya in 1974. Once defined as *Homo erectus*, but now generally defined as *Homo habilis*



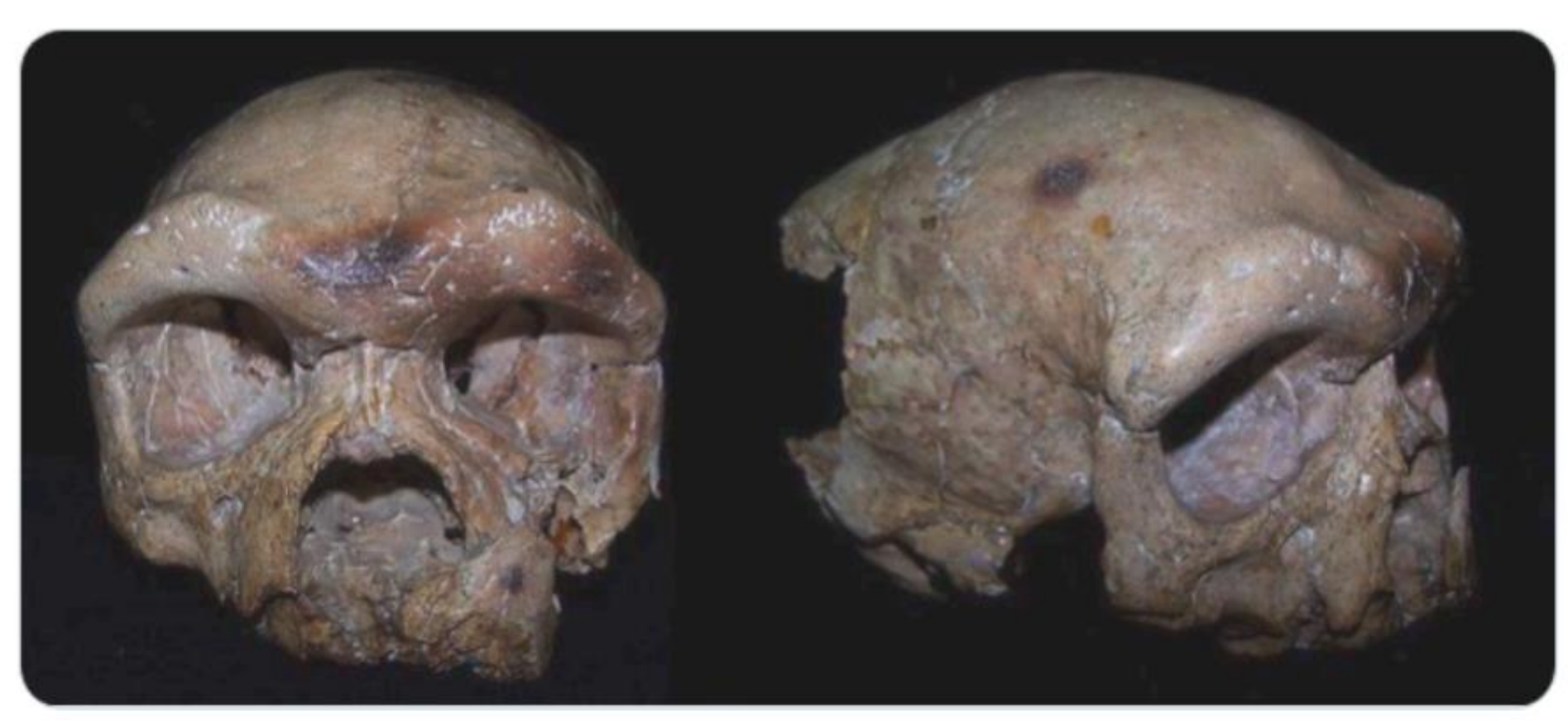
MRD Cranium (MRD-VP-1/1): An *eureka* moment, finding first cranium for *Australopithecus anamensis*

Al Wusta-1 Homo sapiens phalanx from Arabia. The oldest directly dated fossil of our species beyond Africa and the adjacent Mediterranean basin.



Piltdown Man casts from Danish collection. Skull acquired in 1931, lower jaw in 1932.

260 ka Dali skull discovered in China's Shaanxi Province in 1978. Denisovan???



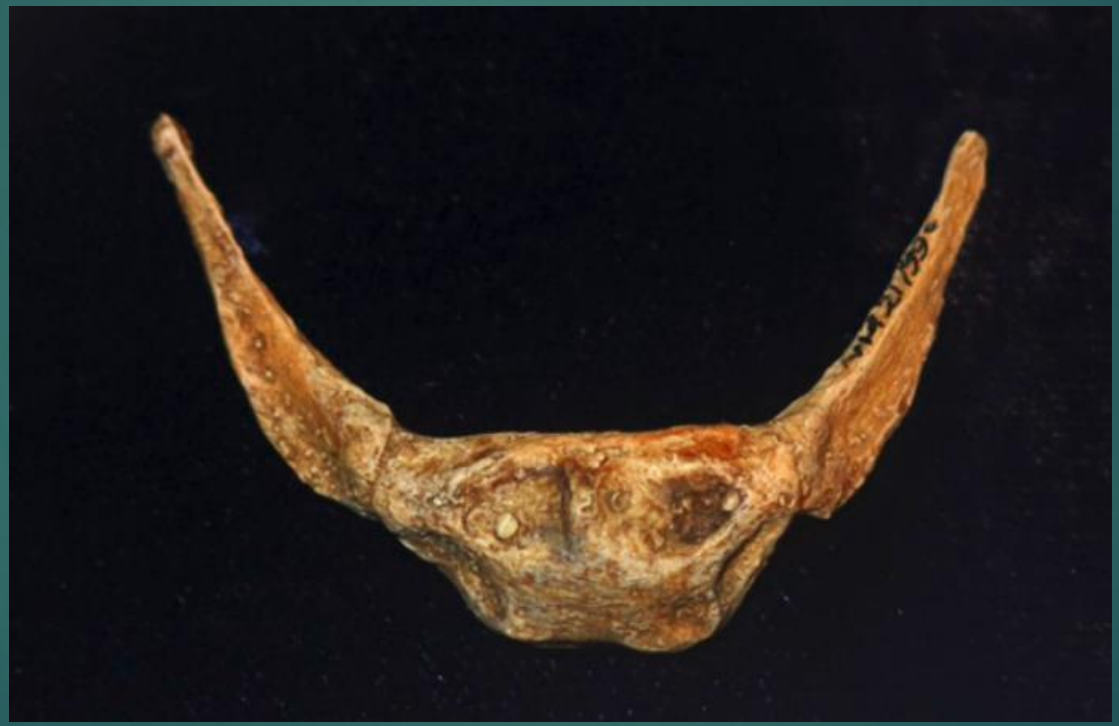
The Dali skull and other candidates to be Denisovan

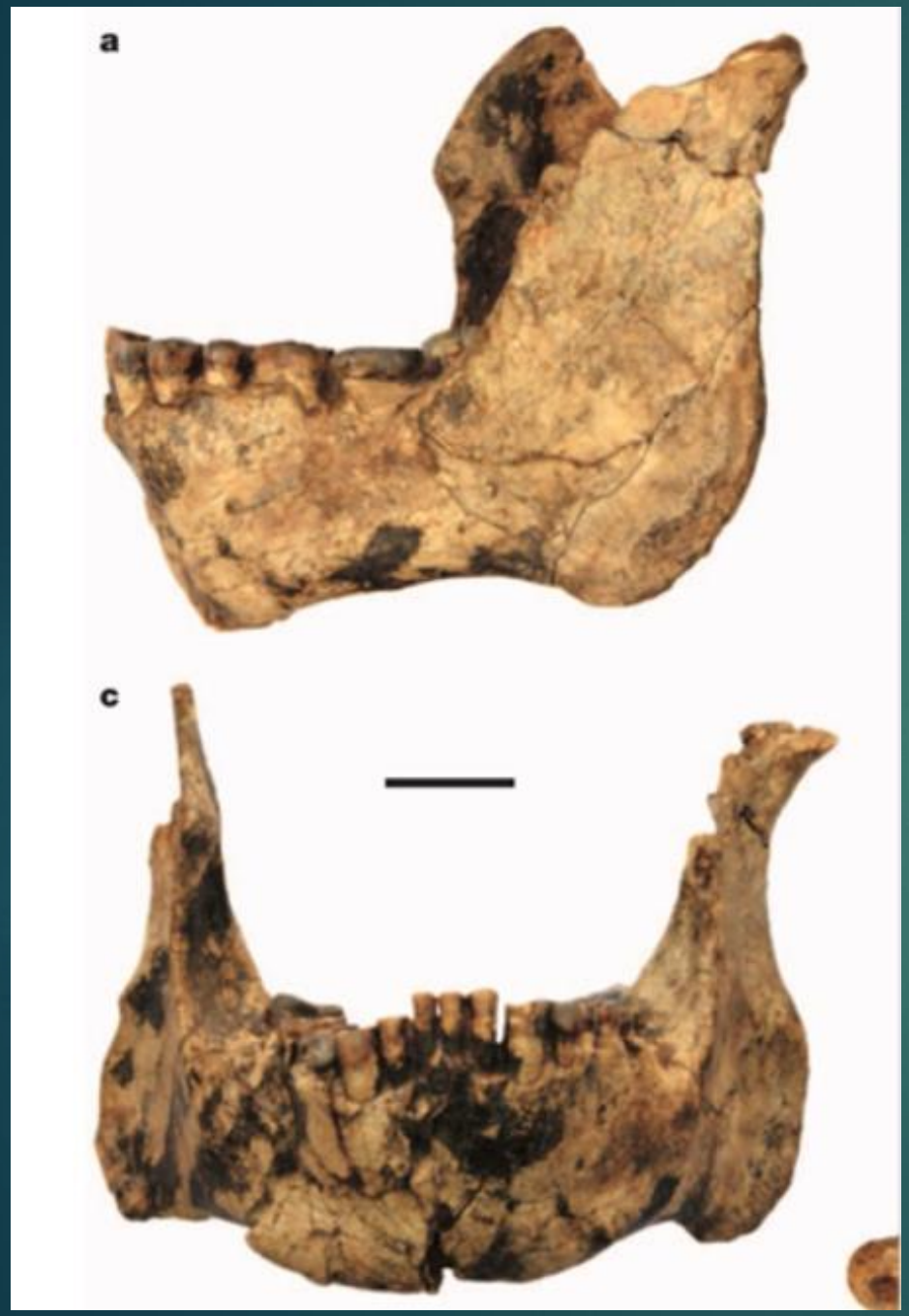
The classic Neanderthal 'en bombe' shape in La Chapelle (L) + La Ferrassie (R)

One of Ralph von Koenigswald's collectors found this *H. erectus* skull in 1937, but unfortunately he did not appreciate its value for he smashed it into 40 pieces in order to get compensated (10 cents for each separate fragment). Sangiran 2 was later re-assembled.

Simply beautiful, the Petralona skull.

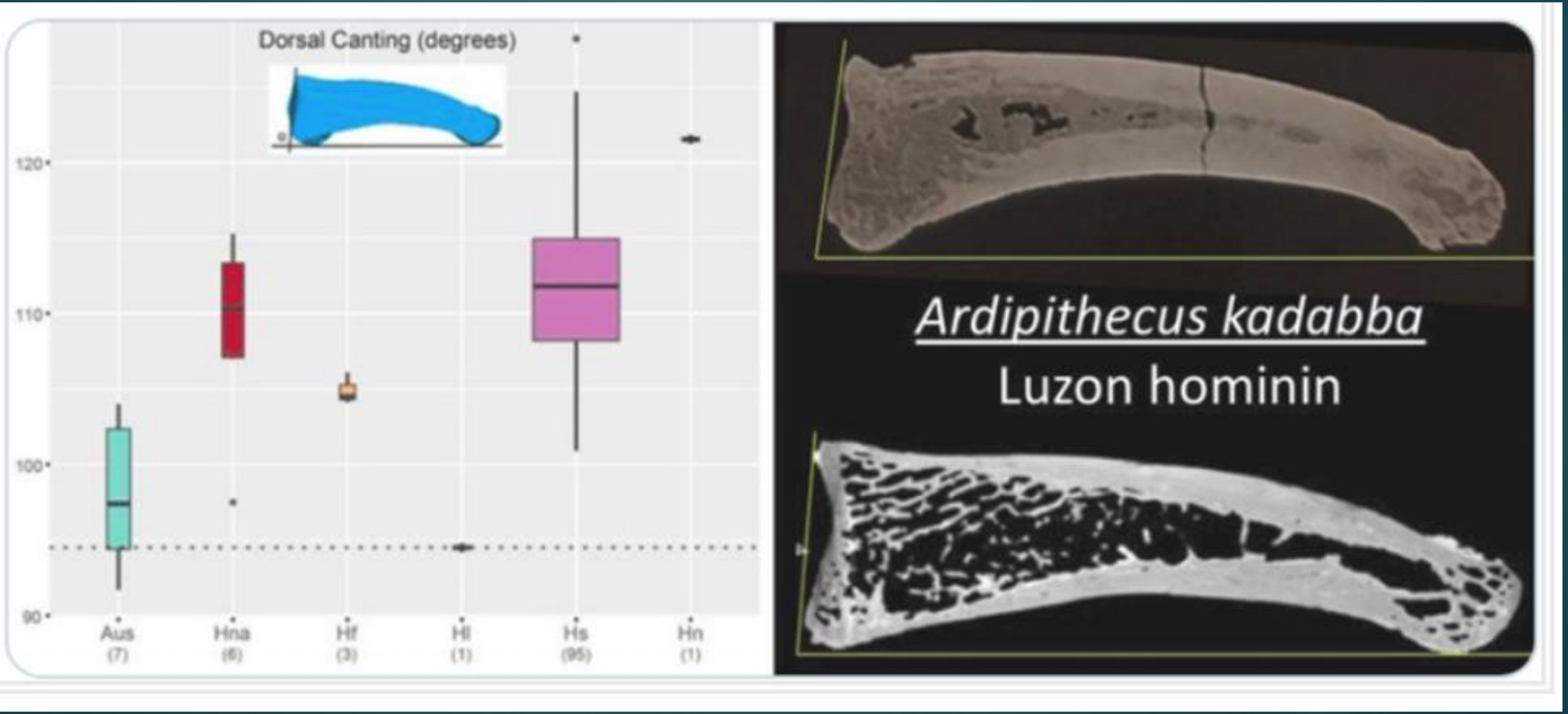
The hyoid from Kebara 2 Neanderthal skeleton. This is virtually identical to a modern hyoid and lends support to the theory that Neanderthals has modern patterns of speech



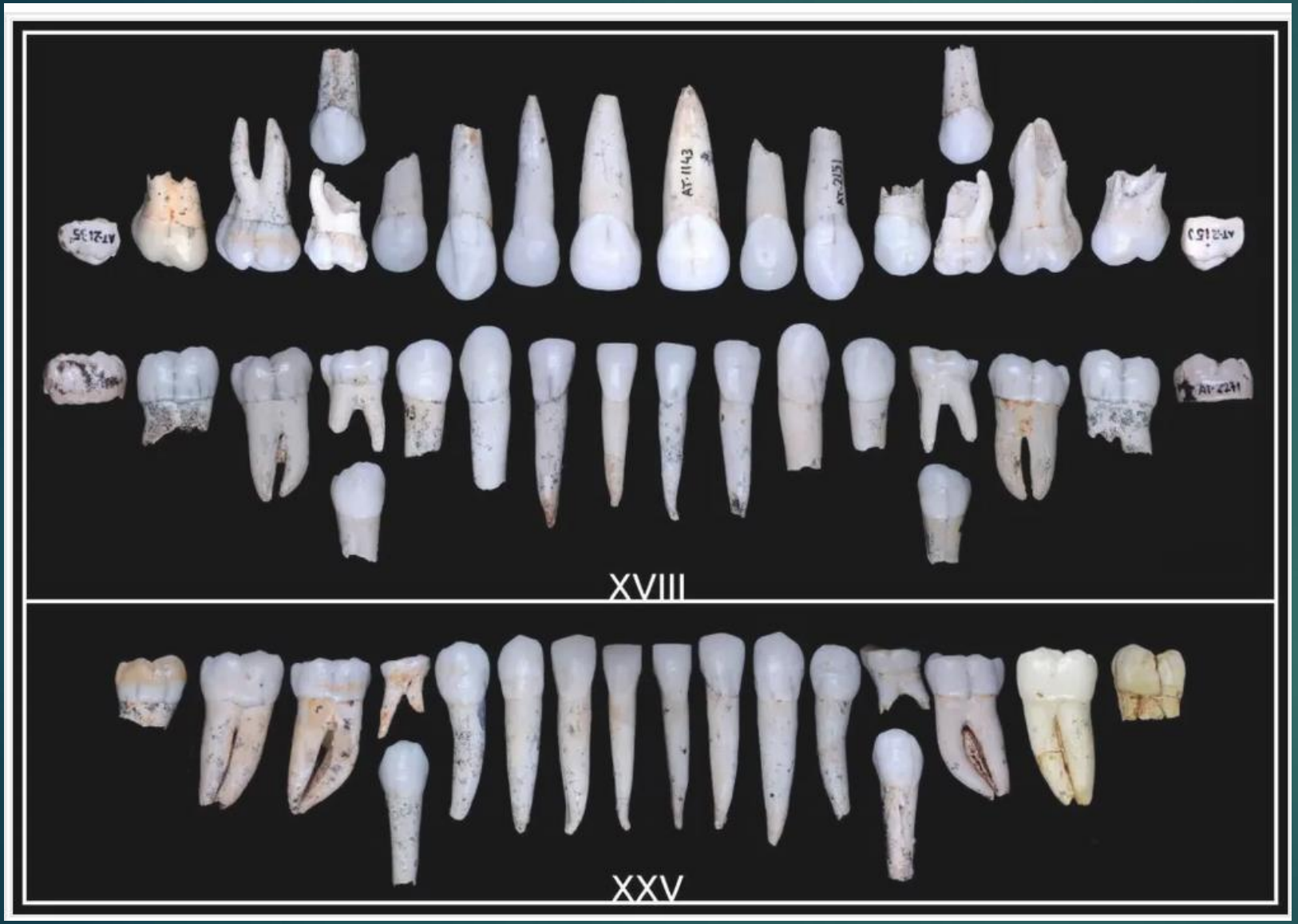


KMN-ER 60000, best mandible ever found for *Homo rudolfensis*.
Specimen from Koobi Fora.
Show little anterior projection beyond the bicanine line.
Estimated geological age of 1.78 to 1.87 Myr old

5+ million yr old Ardipithecus kadabba is thought to be bipedal since the toe joint is almost as angled as humans'.
How were these 50 thousand yr old Luzon hominins walking?

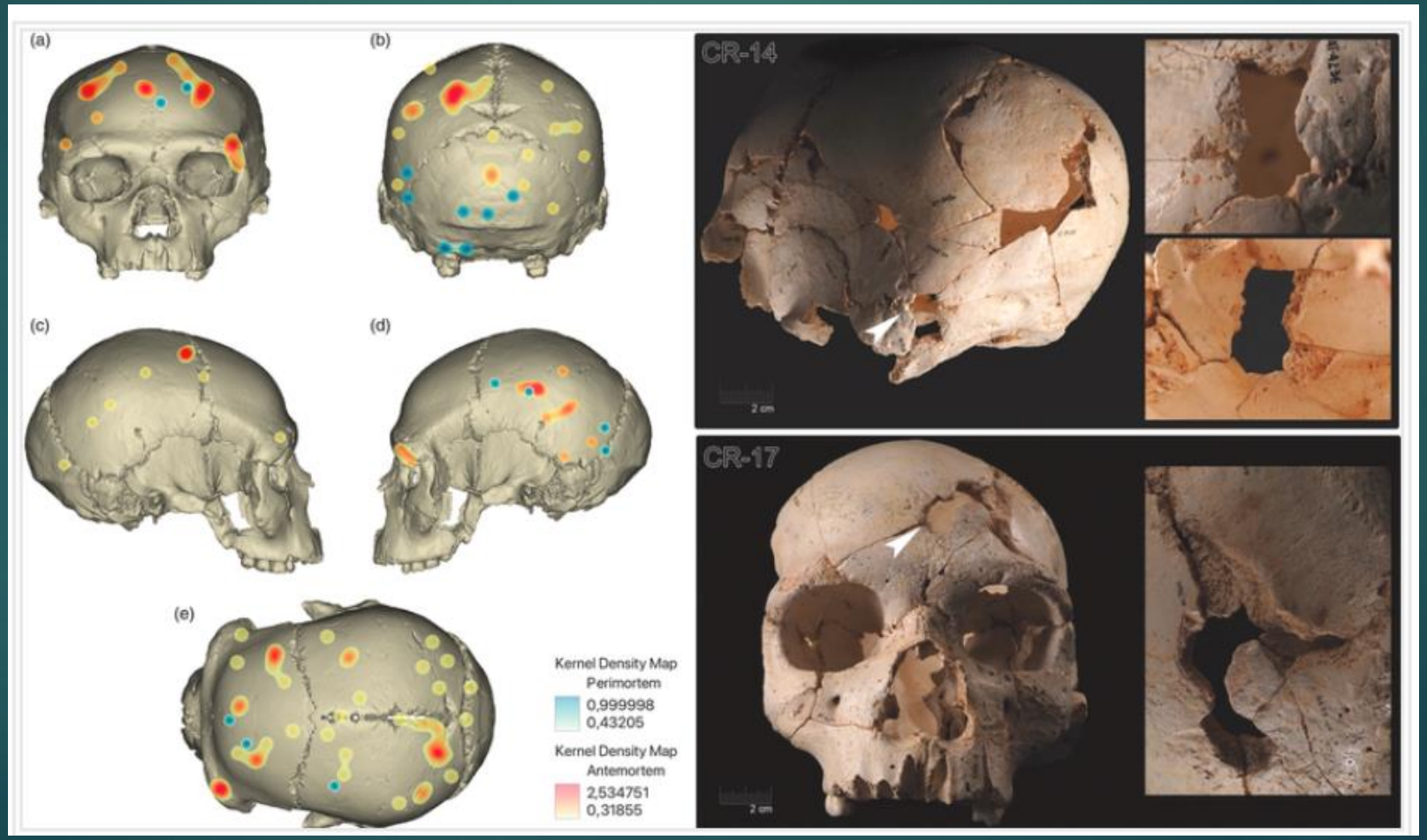


Neandertal family group from El Sidrôn, Spain at 49 Ka, with genetic and skeletal evidence of inbreeding, could be representative of the beginning of the demographic collapse of this hominin phenotype.



The pattern of dental development of two populations of hominins from Atapuerca, that of *Homo antecessor* from Gran Dolina (860 ka) and that of Sima de los Huesos (430 ka), indicates a relative growth of the molars faster than that of modern humans, and a development of the second molar in those of SH more advanced with respect to the first molar of *Homo antecessor* . Together with other previous work that showed enamel growth 27% faster than that of modern humans,
the combination of both studies suggests that hominins from both populations reached adulthood at around 14-15 years of age

The re-evaluation of the exceptional collection of skulls from the Sima de los Huesos (Atapuerca) shows that practically all of them (of all ages and of both sexes) have minor healed fractures, indicative of a complicated way of life, and that 9 of the 20 have *perimortem (near time of death)* fractures that seem to have their origin in violent actions between individuals



Where to locate fire in your cave.

- In Paleolithic caves, the hearth was a focal point of group activity, but its location had to be carefully chosen due to the harmful effects of smoke dispersal on the inhabitants
- Analysis of the influence of hearth location and smoke dispersal on potential activity areas at Lower Paleolithic Lazaret Cave, France.
- Simulated smoke dispersal from 16 hypothetical hearth locations and analyzed their effect on potential working spaces. Four activity zones were defined, according to the average smoke exposure recommendations from the *WHO* and *EPA*.
- Found that the size of the low smoke density area and its distance from the hearth are the main parameters for choosing hearth location. The simulation results show an optimal hearth location zone of about $5 \times 5 m^2$, and it is precisely in this zone that the Lower Paleolithic humans of Lazaret Cave placed their hearth.
- Our simulations of smoke density at Lazaret Cave clearly show that Lower Paleolithic humans in this cave were able to choose the perfect locations for their hearths.

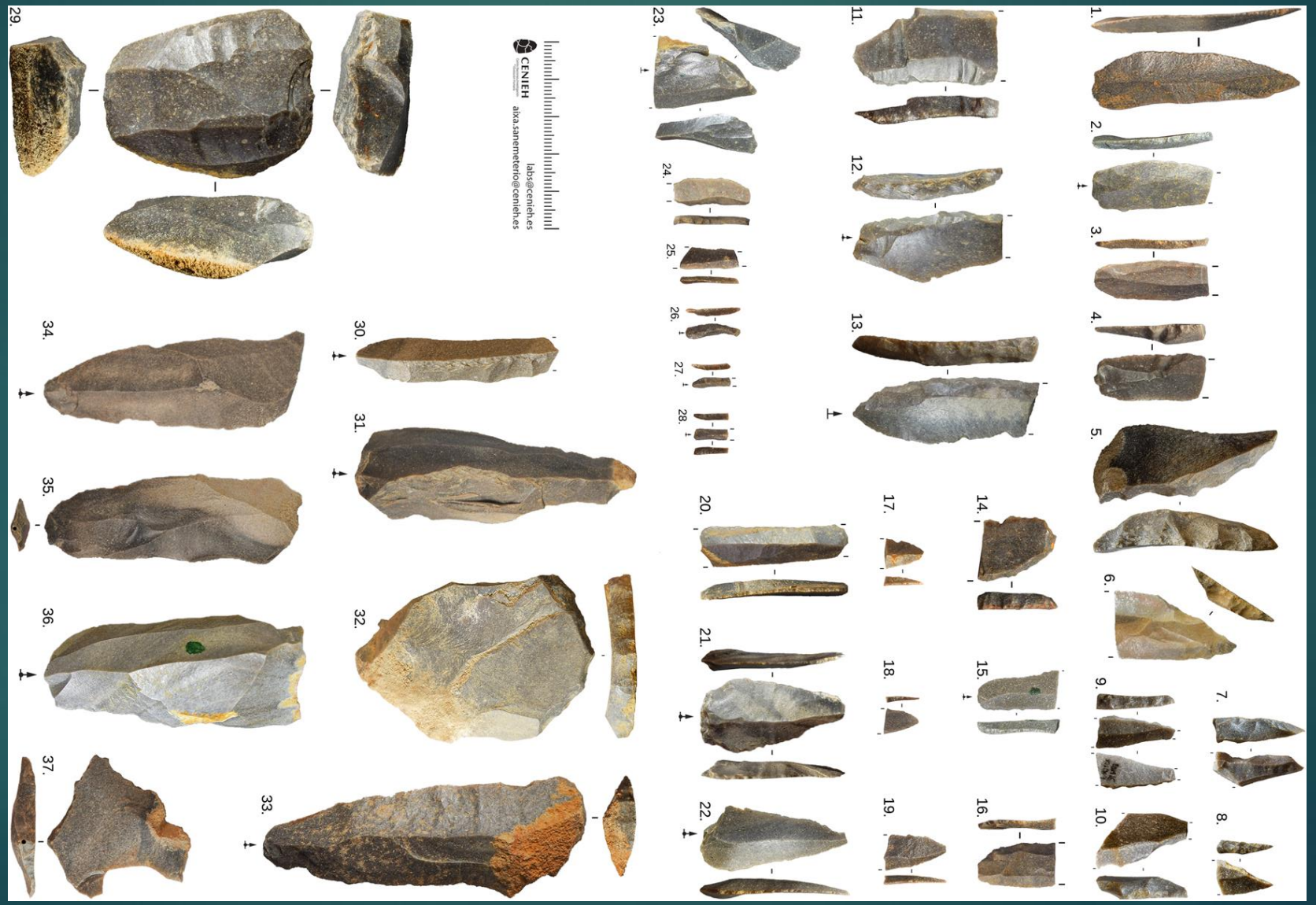
Hunter gatherer source populations

- Searching for the genetic footprint of current hunter-gatherers in central and southern Africa, from six individuals covering 18 ka
- Three parent populations have been found that interacted between 80 and 20 ka ago, coming from deeply divergent lineages from the East and southern Africa

Châtelperronian in Spain

- The Chatelperronian industry of Aranbaltza II (Spain), made up of almost 6000 lithic artifacts of different types, shows a Neanderthal presence in the place some 43.5 ka ago, which is after the disappearance of the classic Neanderthals of the final Mousterian (with a very different, and that used the discoid, Levallois and Quina techniques).
- While the classic Neanderthals inhabited the Cantabrian region until 45 ka ago, these Neanderthals appeared in the region before the arrival of modern humans, brought the Chatelperronian developed probably in the south of France and, in turn, were replaced by *Homo sapiens*.

Châtelperronian in Spain



Châtelperronian in Spain

- The Châtelperronian lithics, which extends from the Paris Basin to the Northern Iberian Peninsula between 44–39 Ka.
- First study of open-air Châtelperronian site in the Northern Iberian Peninsula, Aranbaltza II.
- The technological features of its stone tool assemblage show no links with previous Middle Paleolithic technology in the region, and chronological modeling reveals a gap between the latest Middle Paleolithic and the Châtelperronian in this area.
- Evidence of local Neandertal extinction and replacement by other Neandertal groups coming from southern France, illustrating how local extinction episodes could have played a role in the process of disappearance of Neandertals.

Homo luzonensis

- *Homo luzonensis:* Dental and postcranial elements found at Callao Cave (Northern Luzon, Philippines) and dated to at least 50–67 ka.

- Seven postcanine maxillary teeth are attributed to this taxon, five of them belonging to the same individual (CCH6) and representing the holotype of *H. luzonensis*, whereas the isolated upper premolar CCH8 and the upper third molar CCH9 are paratypes of the species.

- A new analysis of the structural organization of the teeth of *Homo luzonensis* (from about 50 ka) finds affinities of the external features with those of *H. erectus* more than with those of *H. habilis/H. rudolfensis* , and of interior features with *H. erectus* and *H. floresiensis* more than with those of Neanderthals and modern humans

H. luzonensis: mixed features

- Postcranial bones of the hands and feet of *H. luzonensis* and *H. floresiensis* show *Homo habilis*–like or australopith-like features, whereas cranial and dental morphology are more consistent with the Asian *Homo erectus* morphology.
- Due to this mosaic morphology, the origin and phylogenetic relationships of both *H. luzonensis* and *H. floresiensis* are still debated.
- To test the hypotheses that *H. luzonensis* derives from *H. erectus* or from an earlier small-brained hominin, we analyzed the µCT scans of the teeth. We investigated both external and internal tooth structure using morphometric methods including: crown outline shape, tooth crown tissue proportions, enamel-dentine junction shape, and pulp morphology.
- *Homo luzonensis* external crown morphology aligns more with *H. erectus* than with *H. habilis/H. rudolfensis*.

H. Luzonensis = evolved from H. erectus

- The internal structural organization of *H. luzonensis* teeth exhibits more affinities with that of *H. erectus* and *H. floresiensis* than with Neanderthals and modern humans.
- Results suggest that both *H. floresiensis* and *H. luzonensis* likely evolved
  - from some *H. erectus* groups that dispersed in the various islands of this region and
  - became isolated until endemic speciation events occurred at least twice during the Pleistocene in insular environments.

Microstratigraphic preservation of ancient faunal and hominin DNA in Pleistocene cave sediments

- DNA preserved in sediments has emerged as an important source of information about past ecosystems, independent of the discovery of skeletal remains.

- Little is known about the sources of sediment DNA, the factors affecting its long-term preservation, and the extent to which it may be translocated after deposition.

DNA preservation

- Impregnated blocks of intact sediment are excellent archives of DNA. DNA distribution is highly heterogeneous at the microscale in the cave sediment, suggesting that postdepositional movement of DNA is unlikely to be a common phenomenon in cases where the stratigraphy is undisturbed.
- Combining micromorphological analysis with microstratigraphic retrieval of ancient DNA therefore allows genetic information to be associated with the detailed archaeological and ecological record preserved in sediments.

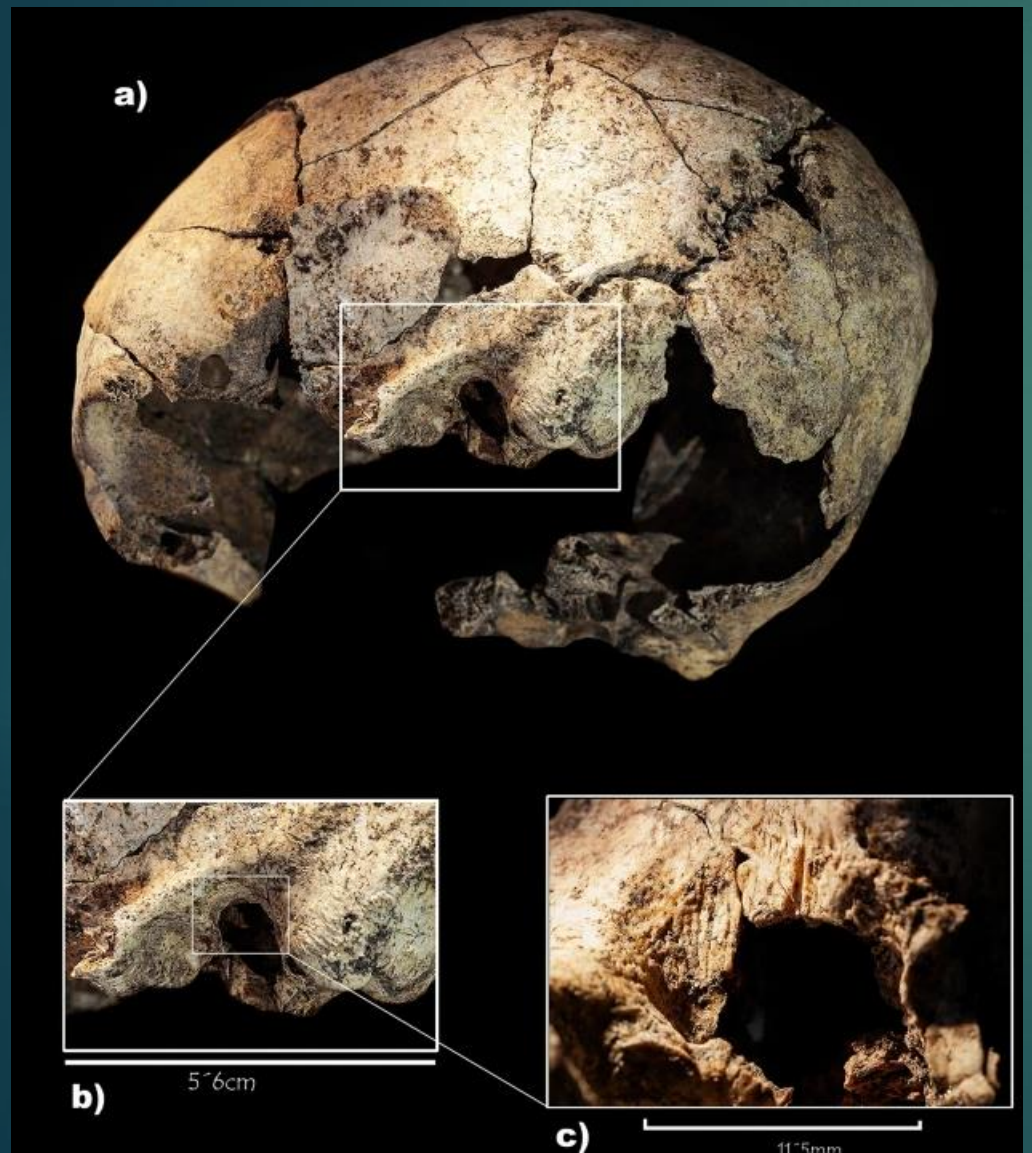
N DNA in soil of Denisova Cave

- 47 blocks of resin-impregnated archaeological sediment collected over the last four decades for micromorphological analyses at 13 prehistoric sites in Europe, Asia, Africa, and North America and show that such blocks can preserve DNA of hominins and other mammals.
- Extensive microsampling of sediment blocks from Denisova Cave in the Altai Mountains reveals that the taxonomic composition of mammalian DNA differs drastically at the millimeter-scale and that DNA is concentrated in small particles, especially in fragments of bone and feces (coprolites), suggesting that these are substantial sources of DNA in sediments.
- Three microsamples taken in close proximity in one of the blocks yielded Neanderthal DNA from at least two male individuals closely related to *Denisova 5*, a Neanderthal toe bone previously recovered from the same layer.

Handprints in Spanish Caves = a family affair

- Palaeolithic hand stencils corpus is formed by over 750 representations distributed in France, UK, Spain and Italy.
- A review of the 150 representations of painted hands in the Spanish caves of El Castillo, La Garma, La Fuente del Salín, Maltravieso and Fuente del Trucho, has shown that 20-25% of them were possibly painted by children between the ages of 2 and 12 years old. Therefore, this activity does not seem to be exclusive to one sex, age or specific roles linked to subsistence, but rather it would be a cohesive element of the group.
- Our morphometrical hand study suggest infants, children and juveniles' participation in graphic production.
- This result presents rock art as a collective action in which different strata of society took part.

The first otologic surgery in a skull from El Pendón site (Reinoso, Northern Spain): 6 Ka



Discovery of a skull with two bilateral perforations on both mastoid bones. These evidences point to a mastoidectomy, a surgical procedure possibly performed to relieve the pain this prehistoric individual may have suffered as a result of otitis media and mastoiditis.

The hypothesis of surgical intervention is also supported by the presence of cut marks at the anterior edge of the trepanation made in the left ear. Furthermore, the results demonstrate the survival of the individual to both interventions. Given the chronology of this dolmen, this find would be the earliest surgical ear intervention in the history of mankind.

N genes: double edged sword -- Covid-19 & HIV

- Gene flow from Neandertals was a double-edged sword.
- 1 - The major genetic risk factor for severe COIVD-19 resides on chromosome 3 and is inherited from Neandertals.
- The 40 ka Neanderthal genome from Vindija (Croatia) left a trace in 6 genes on chromosome 3 that is implicated in an increased risk of severe COVID-19. Reached carrier frequencies of 16% and 50% in Europe and South Asia, respectively

Hugo Zeberg, 2022

N genes = double-edged sword

- 2 - The major genetic risk factor for severe COVID-19 is associated with protection against HIV -- can reduce the chances of infection by the HIV virus by 27%

- Whereas this genetic variant has had tragic consequences during the last 2 y in the COVID-19 pandemic, it appears to have offered considerable protection against HIV during the last 40 years. Its role in past and future pandemics remains to be seen.

Ancient Britons rapidly evolved to cope with lack of sunlight

- Terhorst and Mathieson have now used the new technique to examine DNA from 529 ancient Britons from the past 4500 years, enhanced with genetic data from 98 present-day individuals.
- They found seven regions of the genome with strong evidence of selection.
- All these genes that are under selection can plausibly be linked to natural selection for increased vitamin D and calcium
- Our bodies make vitamin D when our skin is exposed to ultraviolet radiation in sunlight. When humans first evolved in Africa, there was no shortage of sunlight. However, when people migrated away from the tropics, they found themselves in places where the sunlight reaching them is less intense and the days can be shorter. Britain's cloudy skies didn't help either.

Britons

- Unable to produce enough vitamin D, Bronze Age Britons adapted.
- One shift was towards lighter skin.
- Skin pigmentation protects against UV, which is good in the tropics as it guards against skin cancer, but can limit vitamin D production in Britain.

Vitamin D

- The earlier inhabitants of Britons were hunter-gatherers who could get vitamin D by eating oily fish.
- Cheddar Man, who lived in Britain about 10,000 years ago, had very dark skin, and some Irish people from about 5000 years ago had moderately dark skin.
- Natural selection for paler skin only really kicked in when people started getting most of their food from crop farming, leaving them prone to vitamin D deficiency
- In Bronze Age Britain there was strong selection for producing lactase (another source of vitamin D) even into adulthood, allowing people to drink milk throughout their lives

Reptiles are the Real Bird Brains

- A research group argues that a species' number of neurons, rather than brain volume, should serve as indicator of cognitive capacity when studying brain evolution
- Mammals and birds have dramatically more neurons in their forebrain and cerebellum than reptiles, and neuron numbers have scaled up significantly only four times in more than 300 million years of brain evolution in the clade that includes reptiles, birds, and mammals,
- Instead of brain volume, which has long been used as a proxy for brain complexity, study used the number of neurons typically found in species' brains as an indicator of smarts.

Number of neurons

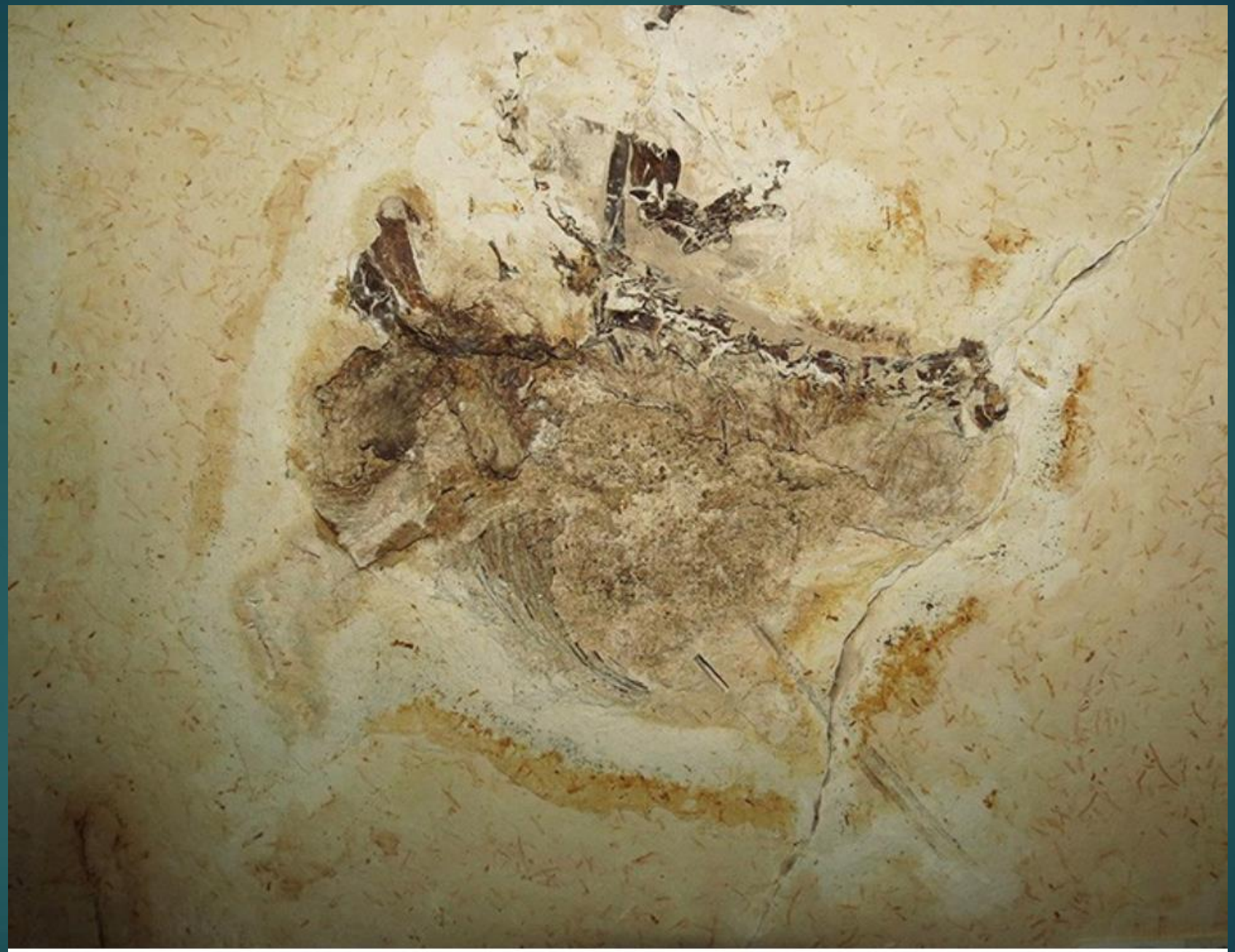
- In the study, the researchers used the isotopic fractionator, a method developed by Suzana Herculano-Houzel in 2005 that quantifies neuron number quickly and cheaply by homogenizing brain structures and labelling intact nuclei. Counted neurons in the forebrain, cerebellum, and “rest of brain” in bird and reptile species, and compared them to the same measures of neuron numbers in mammalian brain
- Birds have high neuronal densities; have just as many neurons as mammals,
- Reptiles have very low neuronal densities, with an average neuron number 20 times lower than that of birds or mammals of similar body size.
- Relationship between neuron number and brain size changed in a major way only four times in the evolution of land vertebrates. “With the appearance of birds and mammals, brains not only enlarged, but also density increased a lot,

Neuron count does not reveal brain functions

- Within mammals, previous studies had established that primates have higher neuronal density.
- Within birds, so-called core land birds, a group that includes woodpeckers, falcons, and parrots, also have relatively large brain sizes and densities in the brain.
- But the cortex is less neuron-dense than the cerebellum, but has a range of functions, which suggests shows that counting neurons gives an incomplete picture of cognition

Archaeological sites that have yielded genetic data and/or IUP assemblages.

1, Bacho Kiro Cave; 2, Ust'Ishim; 3, Peştera cu Oase; 4, Tianyuan Cave; 5, 6, Kostenki14 (Markina Gora) and Kostenki12 (Vokovskaya); 7, Troisème Caverne of Goyet; 8, Sunghir; 9, Peştera Muierilor; 10, Grotta Paglicci; 11, Peştera Cioclovina Uscată; 12, Krems Wachtberg; 13, Yana RHS; 14, 15, Dolní Věstonice and Pavlov; 16, Grotta del Cavallo; 17, Kents Cavern; 18, Grotta di Fumane; 19, Brno-Bohunice; 20, Stánska Skála III; 21, Temnata; 22, Kulychivka; 23, Korolevo 1 and 2; 24, Shlyakh; 25, 26, Üçagizli and Kanal Cave; 27, Um el'Tlel; 28, Jerf Ajlah; 29, Yabrud II; 30–32, Antelias; Abou Halka and Ksar Akil; 33–35, Emireh, El Wad and Raqefet; 36, Boker Tachtit; 37, Denisova Cave; 38, Kara-Bom; 39, Ust-Karakol 1; 40, Kara-Tenesh; 41, Makarvo IV; 42, Kamenka A–C; 43, Khotyk; 44, Podzvonkaya; 45, 46, Tolbor4 and Tolbor16; 47, Tsangan-Agui; 48–50, Suindonggou1, 2 and 9



The *Ubirajara jubatus* fossil sparked outrage among Brazilian palaeontologists

How a Brazilian dinosaur sparked a movement to decolonize fossil science

- In December 2020, paleontologists described an exciting new species: *Ubirajara jubatus*, the first dinosaur found in the Southern Hemisphere to display what were probably precursors to modern feathers. The paper prompted outrage among Brazilian researchers. The fossil had been found in Brazil, but they had never heard of it; it had been removed from the country and analyzed abroad.
- The publication was eventually withdrawn. The controversy sparked a movement in fossil-rich countries from Latin America to Mongolia to ensure that their scientific natural resources benefit their own people, including by inspiring future researchers. discovery of the species set off a Latin American movement to stop colonial paleontology.
- It was the latest instance of what some researchers now call palaeontological colonialism, in which scientists from wealthy nations obtain specimens from low- and middle-income countries without involving local researchers, and then store the fossils abroad.

Palaeontological colonialism

- Reviewed decades of papers describing fossils from Mexico and Brazil. The authors analyzed almost 200 studies published between 1990 and 2021, and found that more than half did not include local researchers. Of the Brazilian fossils described, 88% were stored outside Brazil.
- None of the studies they reviewed reported having permits for taking the fossils abroad

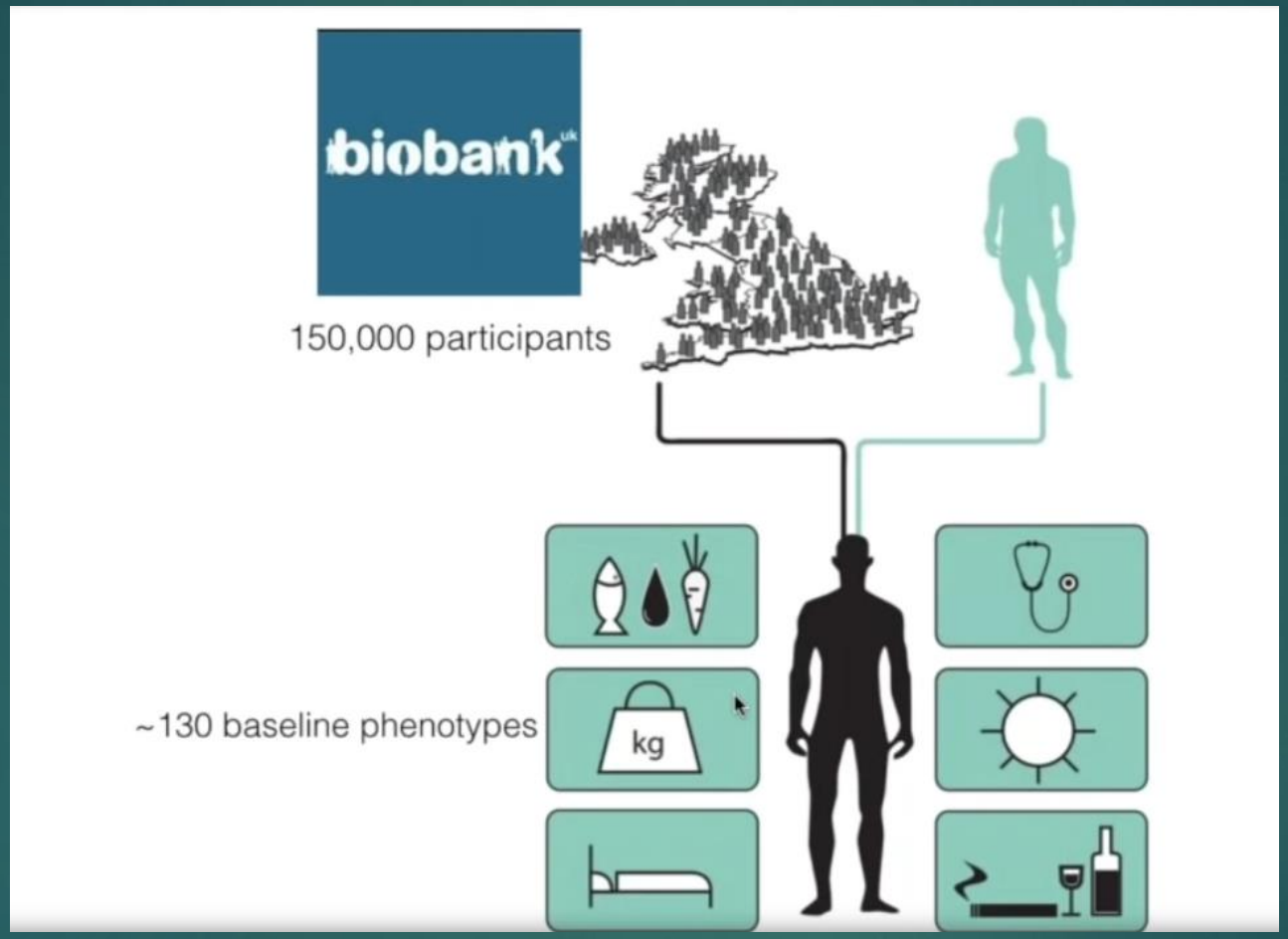
Paleogenetics, Part 7

Modern Functional Consequences of Ancient Genetic Introgressions into Modern Humans

Ancient genomes are a rich resource for variety of studies

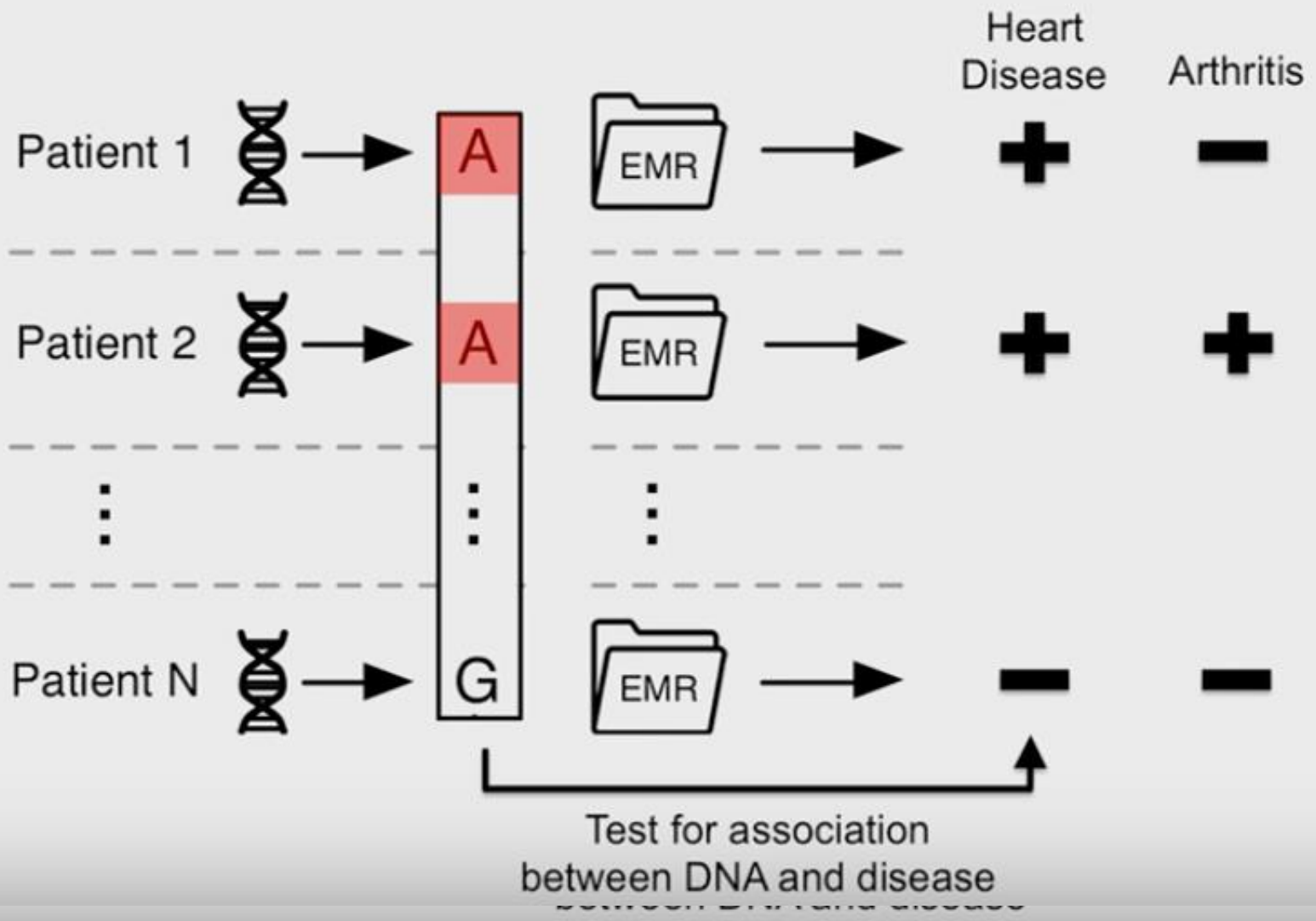
- Ancient genomes:
- For studying both ancient and modern human population histories.
- For identifying recent modern-human specific variants for functional evaluation
- Admixture traces human movements and interactions
- Introgressed alleles offer a view on recent selective pressures on modern humans
- Large biobanks with normal and disease phenotypes are an important resource for understanding recent human evolution

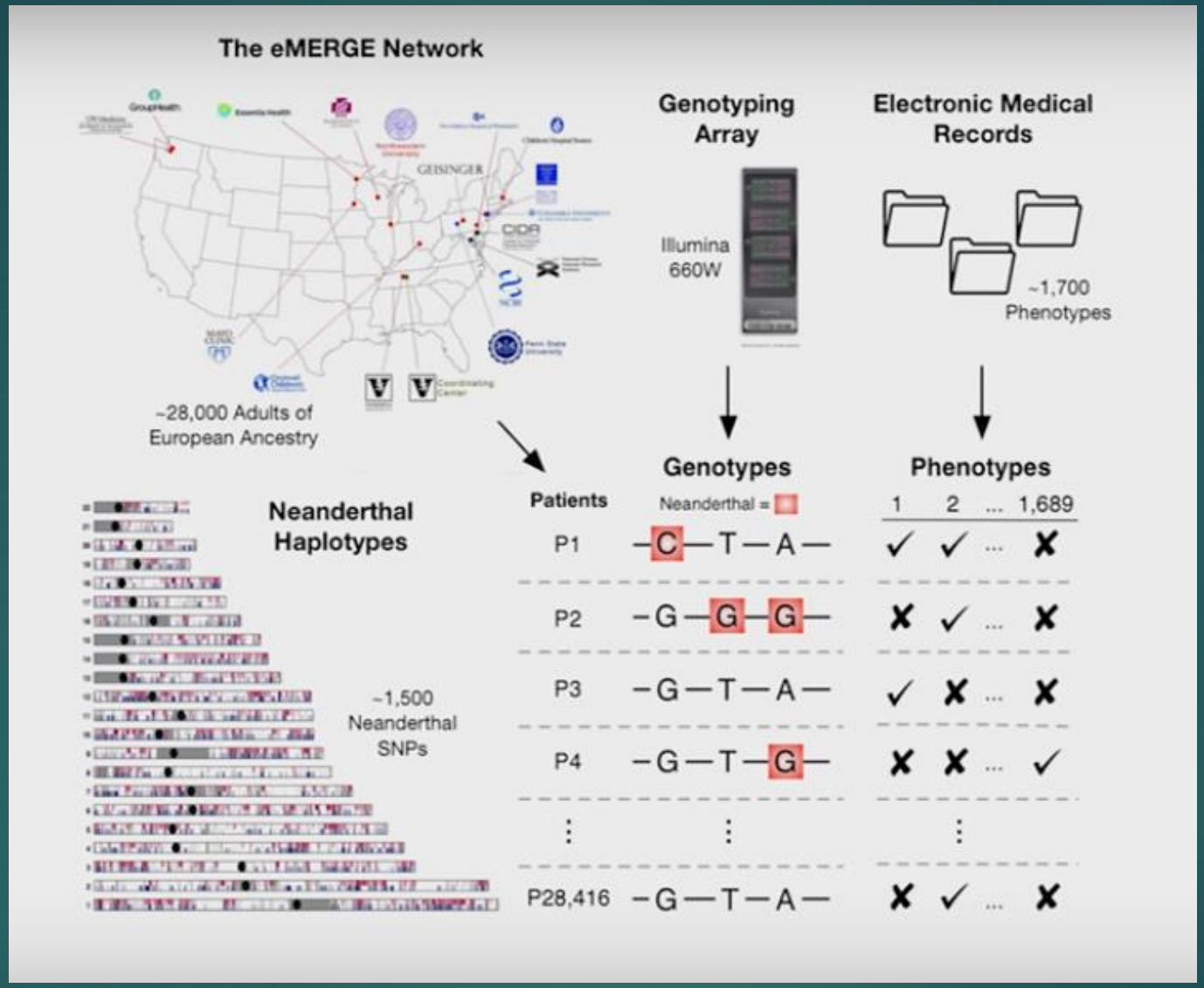
UK Biobank: 150 K pts - - combination of genotype & phenotype data



Large medical biobanks are a powerful resource for exploring genetics and human evolution.

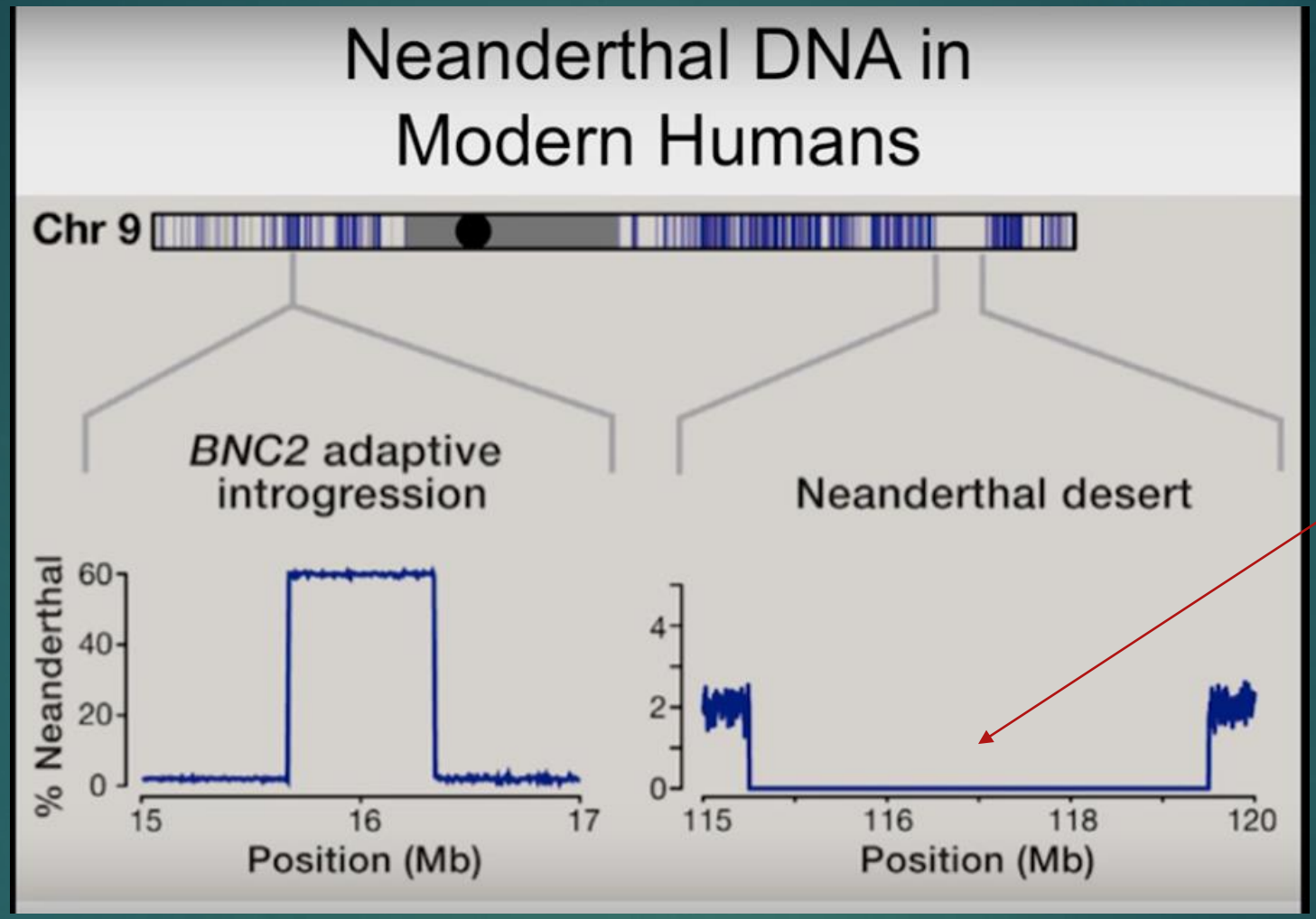
Genetic Association Testing





Effects of N DNA on current diseases: Used medical data of 28 K pts; got 600K genetic data points; compared to N data to 1700 phenotypic traits

60% of Europeans have N BNC2 in this location

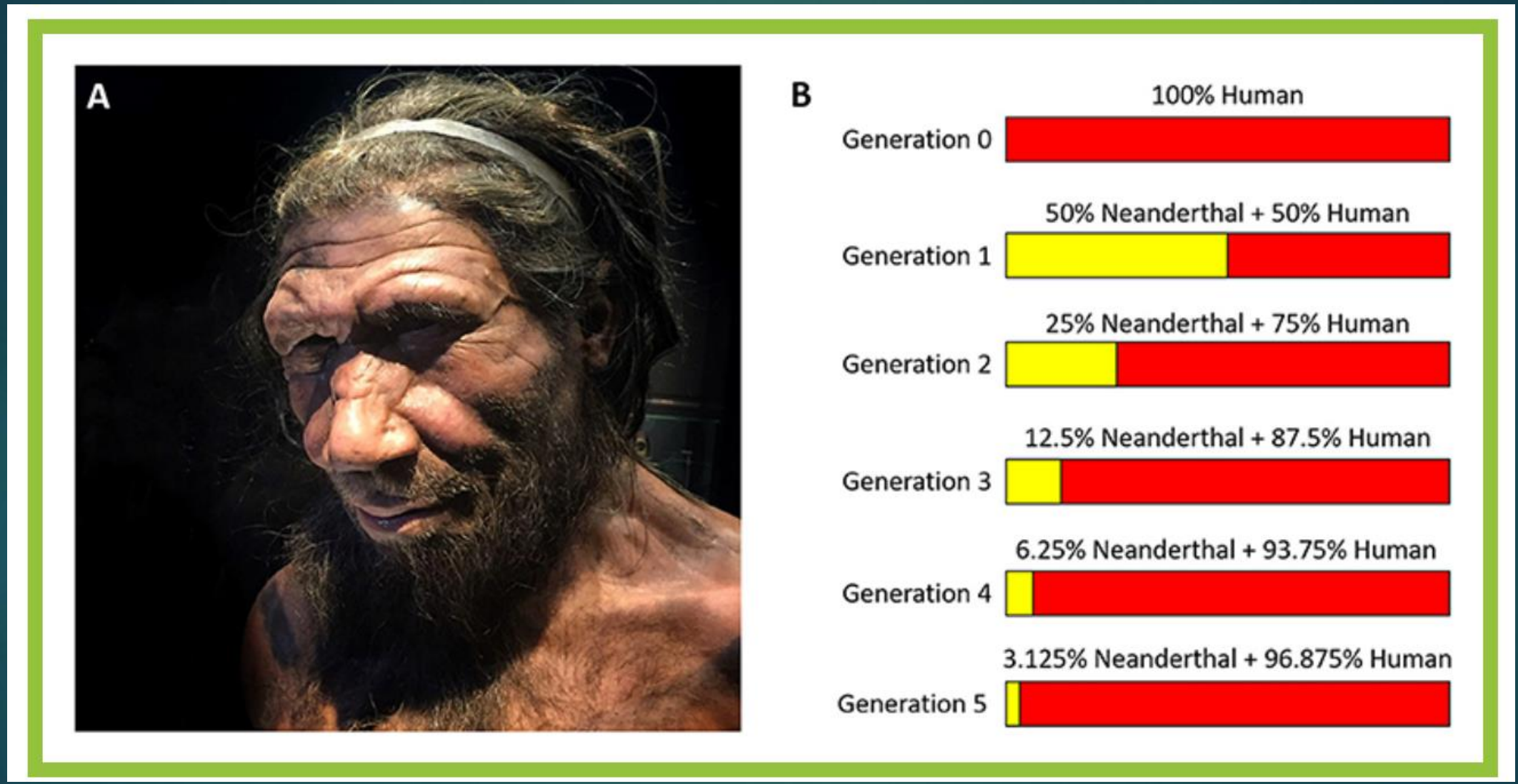


Never observed N DNA In this region in MHs

Reminder: Ns had less genetic diversity

- The Neanderthal genes suggest that sometime after 500,000 years ago, Neandertal numbers decreased and the population stayed small; less power to weed out bad mutations.
- [Neanderthals] had even less [genetic] variation than present-day humans
- Genetic diversity among Neanderthals was about one-fourth as much as is seen among modern Africans, and one-third that of modern Europeans or Asians.
- Less genetic diversity = more deleterious mutations & genes

N and MH Hybridization: why 2% N DNA today?

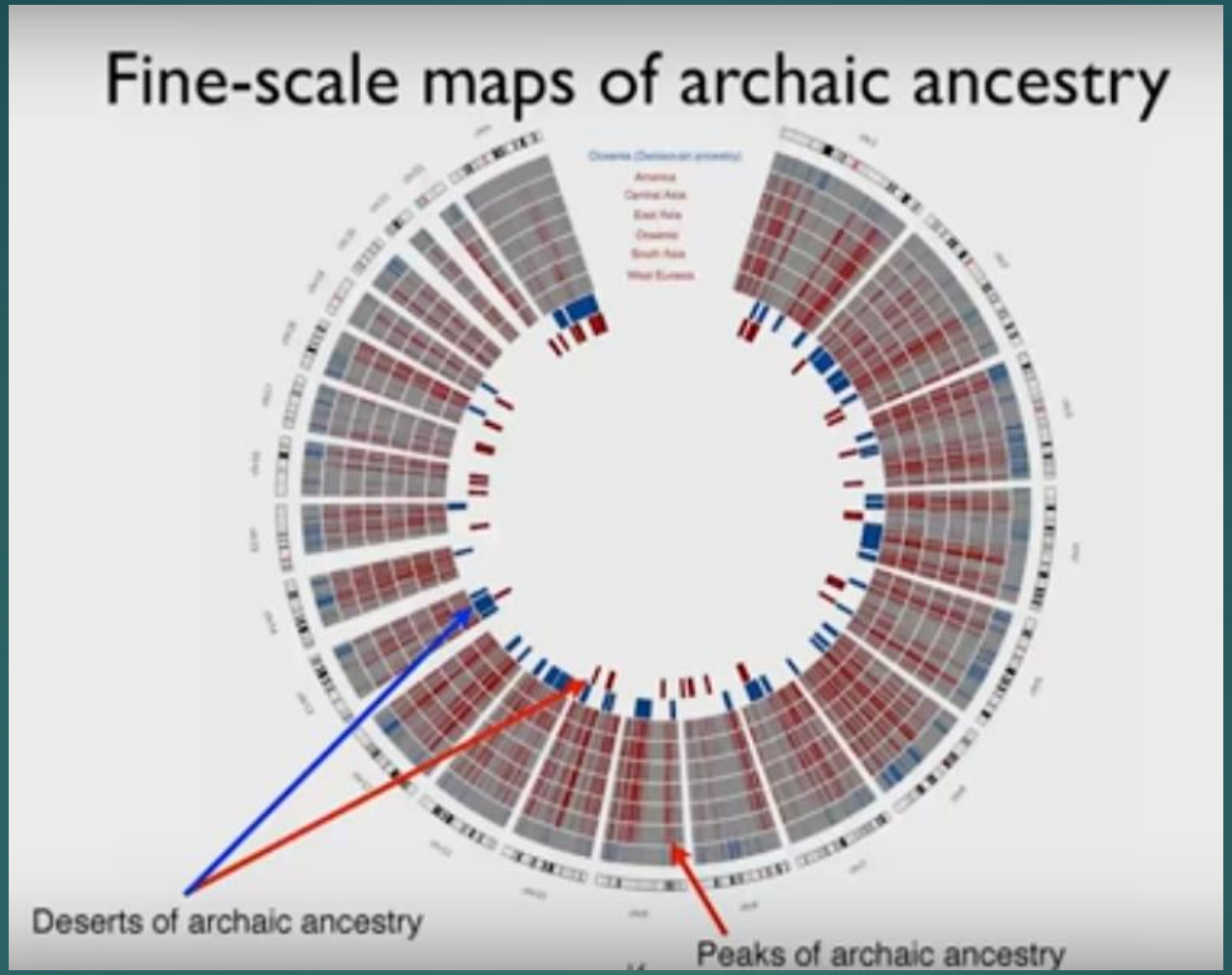


3% within 120 years; why is there not less N DNA in us

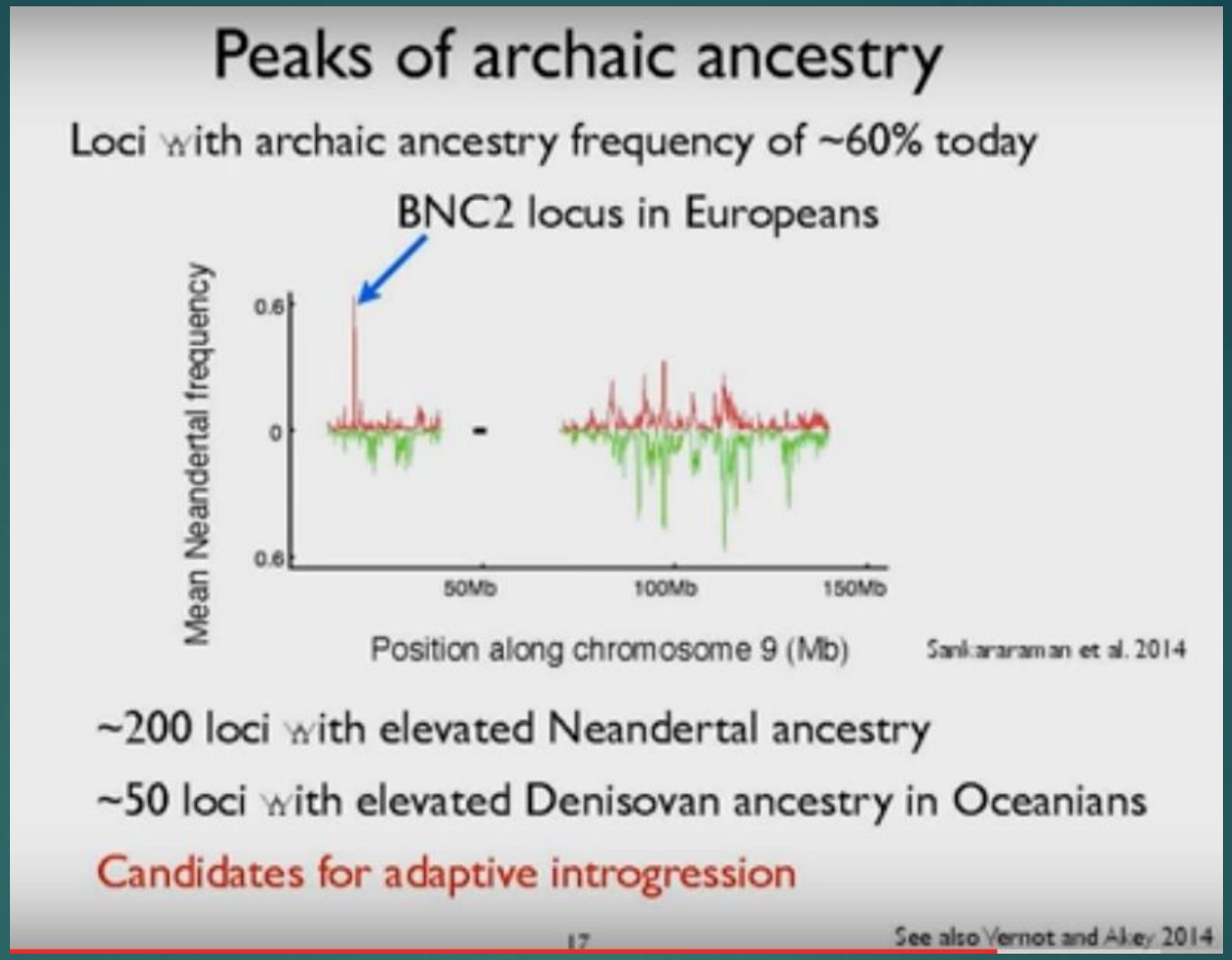
Answer: Adaptive introgression

- A gene variant will alter a phenotype if gene frequency increases because it proves beneficial for individual. If more babies survive with that trait.

- Some introgressed N DNA turned out to be helpful for humans and did not disappear from the human DNA.



Archaic ancestry in modern individuals are not randomly placed; there are hot spots – peaks and deserts of archaic ancestry



60% of Europeans carry N variant of BNC2 gene (compared with 2% who carried it 50 Ka ago); 200 similar loci with high N variant (and 50 loci in Oceanians); these are candidates for adaptive introgression, in which archaic allele provided adaptive benefit, which is why it goes up in frequency

Negative genes

- Research hints that a lot of Neanderthal DNA was maladaptive for us, and that natural selection has weeded many sequences out of the human genome.
- The reason we (*Homo sapiens*) ditched so much of it may simply be that Neanderthals were a small population with significant levels of inbreeding, which tends to lead to a buildup of harmful mutations.

MH and N genomes

- Reference human genome sequence share a most recent common ancestor ~706,000 years ago, and that the human and Neanderthal ancestral populations split ~370,000 years ago, before the emergence of anatomically modern humans.
- The Neanderthal and human genomes are at least 99.84% identical; = 4.8 M N bps
- 23andme: 135,171 Neandertal SNPs in human genome (of normal 4-5 Million SNPs) (.005% of 3 Billion variants)
- Akey - 2,504 genomes: Europeans on average had 51 M N bps , and East Asians had 55 M N bps; Africans = 17 M N bps

Genetic Introgression between hominins

- Introgression, also known as introgressive hybridization, in genetics is the transfer of genetic material from one species into the gene pool of another
- Introgression is a long-term process.
- This process is distinct from most forms of gene flow in that it occurs between two populations of different species, rather than two populations of the same species.
- There is strong evidence for the introgression of Neanderthal genes and Denisovan genes, as well as several unidentified hominins, into parts of the modern human gene pool

N DNA in MHs

- Neanderthal-derived DNA has been found in the genomes of most or possibly all contemporary populations, varying noticeably by region.

- N DNA for 1.8–2.6% of modern genomes for people outside Sub-Saharan Africa, and up to 0.3% for those in Africa.

- Prüfer et al. (2017): East Asians carry more Neanderthal DNA (2.3–2.6%) than Western Eurasians (1.8–2.4%).
- Chen et al. (2020): East Asians have 8% (not prior 20 %) more Neanderthal ancestry than Europeans

Not many sexual encounters

- Neves and Serva (2012): Amount of Neanderthal admixture in modern humans may have been caused by a very low rate of interbreeding between modern humans and Neanderthals, with the exchange of one pair of individuals between the two populations in about every 77 generations (2000 years)
- From the extent of linkage disequilibrium, it was estimated that the last Neanderthal gene flow into early ancestors of Europeans occurred 47,000–65,000 years BP. In conjunction with archaeological and fossil evidence, the gene flow is thought likely to have occurred somewhere in Western Eurasia, possibly the Middle East.

N, D DNA in MHs

- It is highest in East Asians, intermediate in Europeans, and lower in Southeast Asians.

- Denisovan-derived ancestry is largely absent from modern populations in Africa and Western Eurasia.

- The highest rates of Denisovan admixture have been found in Oceanian and some Southeast Asian populations. It is present in 4–6% of the genome of modern Melanesians; the highest amounts found in the Negrito populations of the Philippines. The date of Denisovan admixture was 44,000–54,000 years ago

N, D DNA in MHs

- In addition, low traces of Denisovan-derived ancestry have been found in mainland Asia, with an elevated Denisovan ancestry in South Asian populations compared to other mainland populations.
- Mainland Asian and Native American populations may have a 0.2% Denisovan contribution
- In Africa, archaic alleles consistent with several independent archaic admixture events in the subcontinent have been found. It is currently unknown who these archaic African hominins were.

Africa

- Roughly 2% of the genetic material found in the Biaka Pygmies and San was inserted into the human genome approximately 35,000 years ago from archaic hominins that separated from the ancestors of the modern human lineage around 700,000 years ago.
- A survey for the introgressive haplotypes across many Sub-Saharan populations suggest that this admixture event happened with archaic hominins who once inhabited Central Africa.

Africa

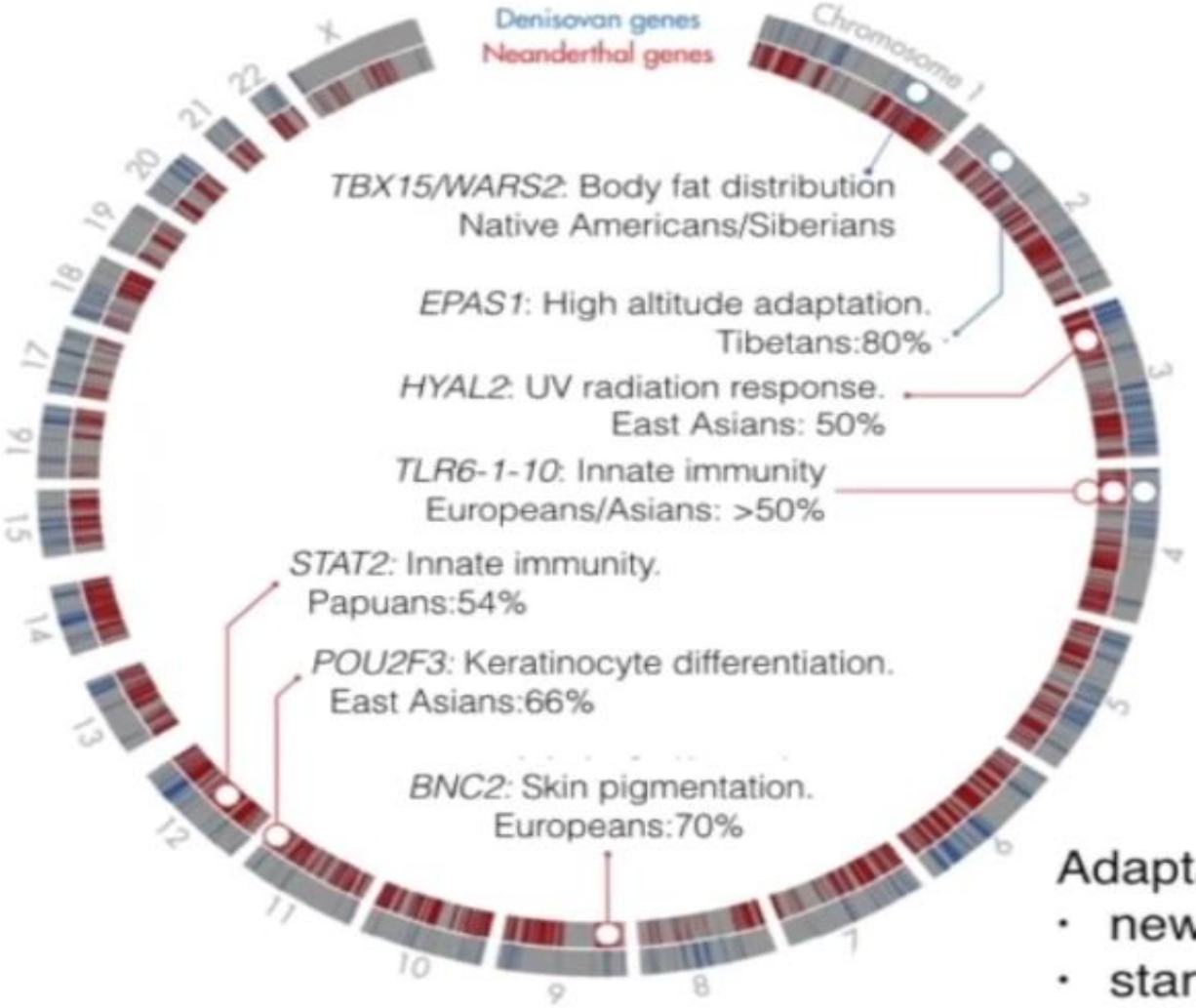
- Sequences of fifteen Sub-Saharan hunter-gatherer males from three groups—five Pygmies, five Hadza from Tanzania, and five Sandawe from Tanzania—there are signs that the ancestors of the hunter-gatherers interbred with one or more archaic human populations, probably over 40,000 years ago. Analysis of putative introgressive haplotypes in the fifteen hunter-gatherer samples suggests that the archaic African population and modern humans diverged around 1.2 to 1.3 million years ago

- 2% to 19% of the DNA of four West African populations may have come from an unknown archaic hominin which split from the ancestor of humans and Neanderthals between 360 kya to 1.02 mya.

Negative Selection

- No evidence of Neanderthal mitochondrial DNA has been found in modern humans. This suggests that successful Neanderthal admixture happened in pairings with Neanderthal males and modern human females
- There is a presence of large genomic regions in MHs with strongly reduced Neanderthal DNA due to negative selection, partly caused by hybrid male infertility.
- These large regions of low Neanderthal DNA were most-pronounced on the X chromosome and testes

Adaptation through Introgression



Adaptation of early modern humans

- new mutations
- standing variation
- introgression

Is our N genetic heritage important?

- 2% of Non-African DNA is N
- Did we get anything useful from our N DNA?
- Maternal mitochondrial DNA: dozen N samples
  - Limited mitochondrial distribution since 150 Ka
  - But no MH has N mitochondrial DNA

Does it matter?
Is it currently genetically functional?

Functional Archaic Admixture or non-aHs lineage introgression

- Admixture from archaic humans may have helped modern humans expanding outside of Africa and to adapt to the unfamiliar environments of Eurasia.

- Ns, who inhabited Eurasia for 400 ky before MHs, would have been a source of advantageous genetic variants pre-adapted to local environmental features, such as colder climates, lower ultraviolet (UV) exposure, and endemic pathogens.

- However, most archaic human ancestry is not adaptive but appears to have been deleted by negative selection.

Functional Archaic Admixture

- There are three lines of evidence for this selection against archaic ancestry:
  - archaic haplotypes have decreased in frequency over time,
  - archaic haplotypes are depleted in more conserved parts of the genome (those that are survival related)
  - archaic variants are less likely to have functional consequences.

Neandertal DNA in Modern Humans

- Living Europeans have inherited around 1.2% and East Asians about 1.4% of their DNA from our Neandertal cousins.
- Upside: helped our ancestors survive in prehistoric Europe. Neanderthals are believed to have lived out of Africa long enough to adapt to the unique colder climatic, dietary, and pathogenic landscapes found at higher latitudes. When humans migrated into Eurasia, they encountered unfamiliar hazards and pathogens. By mating with Neanderthals, they gave their offspring needed immunities, defenses and advantages.
- N immune system-related genes, likely conferred adaptive advantages against infectious microorganisms in new environments.

Functional Archaic Admixture

- Within European-ancestry populations, there is some evidence that archaic variants contribute significantly but with a small effect size to several phenotypes, including skin and hair structure, and height.

- Proportions of Neanderthal ancestry vary by only a small amount within Eurasia [~2.2% in Europe compared with ~2.4% in East Asia] and this ancestry probably derives from the same Neanderthal population

Functional Variation & Phenotypes

- Ancient DNA can illuminate the evolutionary history of human phenotypic (observable characteristics of an individual) diversity

- In particular, ancient DNA should be valuable for identifying and quantifying the contribution of natural selection to phenotypic variation

- Ancient DNA allows us to directly detect rapid changes in allele frequencies over time = the immediate results of natural selection.

Medical opinion on aDNA

- According to the U.S. National Library of Medicine, such [aDNA] data points “do not provide practical information about a person’s current health or chances of developing particular diseases. Having more or less DNA in common with archaic humans says nothing about how ‘evolved’ a person is, nor does it give any indication of strength or intelligence.”

What do we know of functionality of genes

- Oxford University group: Only 8.2 percent of human DNA is likely to be doing something important -- is 'functional'
- Identified how much of our genome has avoided accumulating changes over 100 million years of mammalian evolution -- a clear indication that this DNA matters, it has some important function that needs to be retained.
- Looked at where insertions and deletions of chunks of DNA appeared in the mammals' genomes. These could be expected to fall approximately randomly in the sequence -- except where natural selection was acting to preserve functional DNA, where insertions and deletions would then lie further apart.

Functional genes

- A little over 1% of human DNA (genes) accounts for the proteins that carry out almost all of the critical biological processes in the body.
- The other 7% is thought to be involved in the switching on and off of genes that encode proteins
- Every mammal has approximately the same amount of functional DNA, and approximately the same distribution of functional DNA that is highly important and less important
- ENCODE project aims to identify all functional elements in the human genome, based on biochemical effects

Adaptation through Introgression: adaptation to new European environment, pathogen defense

- Chrom 1: Denisovan in Native Americans/Siberians: *TBX15/WARS2* Body fat distribution
- Chrom 2: Denisovan in Tibetans (80%): *EPAS1* High altitude adaptation
- Chrom 3: Neandertal in East Asians 50%: *HYAL2.* UV radiation response
- Chrom 4: Neandertal/Denisovan: >50%: *TLR6-1-10.* Innate immunity
- Chrom 9: Neandertal: Europeans 70%: *BNC2* Skin pigmentation.
- Chrom 11: Neandertal: East Asians 66%: *POU2F3* Kératinocyte differentiation
- Chrom 12: Neandertal: Papuans 54%: *STAT2:* Innate immunity

Icelandic study: little effect of N genes in MHs

Skov, L., Coll Macià, M., Sveinbjörnsson, G. et al.
The nature of Neanderthal introgression revealed by 27,566 Icelandic genomes.
Nature (2020). https://doi.org/10.1038/s41586-020-2225-9

The nature of Neanderthal introgression revealed by 27,566 Icelandic genomes - Laurits Skov, et al., 2020

- Most humans outside of Africa trace about 2% of their genomes to admixture from Neanderthals, which occurred 50–60 thousand years ago.

- Here we examine the effect of this event using 14.4 million archaic chromosome fragments that were detected in fully phased whole-genome sequences from 27,566 Icelanders, corresponding to a range of 56,388–112,709 unique archaic fragments that cover 38.0–48.2% of the callable genome.

- 85% of fragments are from Altai or Vindija Neanderthal and 3% from Denisovan origin; 12.2% of fragments are of unknown origin.

N gene effects in Iceland MHs

- 2020 Icelandic study: a study of tens of thousands of Icelanders finds their Neanderthal legacy had little or no impact on most of their physical traits or disease risk.
- Full genomes of 27,566 Icelanders in a database at deCODE Genetics in Iceland, seeking unusual archaic gene variants. The researchers ended up with a large catalog of 56,000 to 112,000 potentially archaic variants
- Team analyzed a further 286 genomes representing individuals from sub-Saharan Africa to serve as a comparative baseline, assuming that their own DNA would contain little, if any, intruding Neanderthal or Denisovan genes. Discovered tens of thousands of ancient fragments.

Skov, L. et al.,2020. "The nature of Neanderthal introgression revealed by 27,566 Icelandic genomes".

2020 Icelandic study

- Icelanders had inherited 3.3% of their archaic DNA from Denisovans and 12.2% from unknown sources.
- Calculated the association of the Neanderthal and Denisovan DNA with 271 traits. Unlike most previous studies, the team examined whole genomes, which allowed them to evaluate whether modern human genes were also influencing traits.
- They found that most traits were better explained by association with modern gene variants. Only five traits were notably influenced by archaic DNA
- Men with one archaic variant had a slightly reduced chance of prostate cancer, and both men and women carrying two other variants may have reduced height and accelerated blood clotting,

Skov, 2020: Icelandic DNA: Ancient DNA has little current effect

- Archaic introgression has a relatively minor effect on phenotypic variation in contemporary humans.

- Assessed 271 phenotypes, report 5 associations driven by variants in archaic fragments and show that the majority of previously reported associations are better explained by non-archaic variants.

- Only validated the archaic origin of 3 out of 26 previously reported phenotype association findings attributed to archaic variants; archaic ancestry has—at most—a modest directional impact on contemporary human phenotype variation

Laurits Skov, et al., 2020

Skov summary

- Neanderthal DNA has no great importance for modern humans.
- We have previously thought that many of the Neanderthal variants previously been found in modern human DNA were associated with an increased risk of diseases.
- However, our study shows that the human gene variants located directly beside the Neanderthal genes are better explanations for the risk.

Icelandic DNA: more different N DNA

- Typically, archaic introgression into humans stems from a group of Neanderthals related to those which inhabited Vindija Cave, Croatia, as opposed to archaics related to Siberian Neanderthals and Denisovans: Vindija Neanderthal (50.8%), Altai Neanderthal (13.1%), Denisovan (3.3%),
- 13.1 and 3.3% of the archaic DNA in the modern Icelandic genome descends from these two latter groups, respectively, and such a high percentage could indicate a western Eurasian population of Denisovans which introgressed into either Vindija-related Neanderthals or immigrating modern humans.

Skov, 2020

- We find that Icelanders have more Denisovan-like fragments than expected through incomplete lineage sorting. This is best explained by Denisovan gene flow, either into ancestors of the introgressing Neanderthals or directly into humans.
- Fragments require Denisovan introgression, either directly into humans or into Neanderthals who later mixed with humans, which must have occurred soon after they migrated out of Africa. This raises the possibility that there were Denisovan-like groups west of the Altai mountains, where such gene flow into humans must have occurred
-

Skov summary

- Examined archaic variants for association with 271 phenotypes in Icelanders; identified only five archaic variants with genome-wide significant associations.
- 5 variants:
  - slightly lower risk of prostate cancer, - decreased levels of prostate specific antigen (PSA) and risk of prostate cancer;
  - 2 variants related to lower levels & mass of hemoglobin,
  - lower body length (one millimeter)
  - slightly faster blood plasma clotting.
- Neanderthal children had older mothers and younger fathers than the Homo-Sapiens children in Africa did at the time.

Skov, 2020

- Estimated the effective population sizes (*Ne*) of different archaic groups; find that Neanderthals had a relatively small *Ne* of 2,000–3,000 individuals
- Identification of genomic regions with very little or no archaic introgression (archaic deserts): found 282 distinct archaic deserts covering 570 Mb; the X chromosome is particularly devoid of archaic introgression;
- Indicates that non-deleterious archaic variants were more likely to be retained in the human gene pool when they could be uncoupled from deleterious archaic variants by recombination

Skov

- Findings support previous estimates that most people outside of Africa have approximately 2% archaic ancestry; more significant than expected genomic fragments from Denisovans

- Identified nearly 300 "archaic deserts" where there are no archaic fragments; these cover nearly 25% of the genome, including the entire X chromosome

Skov: Icelanders have D DNA

- So how did D genes end up in Islanders' DNA? And when?
- Either Neanderthals had children with Denisovans before they met the Homo Sapiens. This would mean that the Neanderthals with whom Homo Sapiens had children were already hybrids, who transferred both Neanderthal and Denisovan genes to the children
- Or Homo Sapiens met Denisovans long before they met Neanderthals

Skov: N genetics

- Contrary to previous studies, the researchers found no statistically significant association between archaic DNA and freckles, hair color, eye color, or autoimmune diseases like Crohn disease and lupus.

- They conclude that Neanderthal DNA only has small effects on complex traits such as height or depression, in which many genes interact.

- Did not examine immune function or cranial shape, for which there is strong evidence of Neanderthal influence.)

- Archaic DNA may have different effects in Icelanders than in other populations.