May 2022 Updates

by Charles J Vella, PhD

Sir Paul Mellars (1939-2022): Great European Anthropologist

Paul Mellars

- His research focused chiefly on the study of behavior and archaeology of Neanderthal populations in Europe, and the ways in which the Neanderthals were eventually replaced by biologically and behaviorally 'modern' populations *(Homo sapiens)* around 40,000 years ago.
- A major focus of his work was to integrate the archaeological evidence for human behavior with the rapidly emerging evidence from recent DNA research into the African origins and subsequent dispersal of our own species.
- He authored or edited several books in this field, including: *The Human Revolution* (1989), *The Emergence of Modern Humans* (1990), *The Origins of Modern Humans* and the Impact of Chronometric Dating (1992), and *The Neanderthal Legacy* (1996).

Why did modern human populations disperse from Africa *ca.* 60,000 years ago? A new model - Paul Mellars - 2006

- Recent research has provided increasing support for the origins of anatomically and genetically “modern” human populations in Africa between 150,000 and 200,000 years ago, followed by a major dispersal of these populations to both Asia and Europe sometime after *ca.* 65,000 before present.
- However, the central question of why it took these populations ≈100,000 years to disperse from Africa to other regions of the world has never been clearly resolved.
- Studies of both the mitochondrial DNA (mtDNA) mismatch patterns in modern African populations and related mtDNA lineage-analysis patterns point to a major demographic expansion centered broadly within the time range from 80 to 60 Ka, probably deriving from a small geographical region of Africa.

Mellars

- Recent archaeological discoveries in southern and eastern Africa suggest that, at approximately the same time, there was a major increase in the complexity of the technological, economic, social, and cognitive behavior of certain African groups, which could have led to a major demographic expansion of these groups in competition with other, adjacent groups.
- It is suggested that this complex of behavioral changes (possibly triggered by the rapid environmental changes around the transition from oxygen isotope stage 5 to stage 4) could have led not only to the expansion of the L2 and L3 mitochondrial lineages over the whole of Africa but also to the ensuing dispersal of these modern populations over most regions of Asia, Australasia, and Europe, and their replacement (with or without interbreeding) of the preceding “archaic” populations in these regions.

Cerebrospinal Fluid from Youngsters Boosts Memory in Old Mice

- The cerebrospinal fluid from young mice is awash with factors that keep the brain sharp.
- When injected into the brains of old mice, CSF from young mice, or young people, revved expression of a host of oligodendrocyte genes within the hippocampus, counteracting the slump in proliferation and function of the myelin-making cells that typically occurs with age.
- Due to effects to fibroblast growth factor 17 in the young CSF, which increased expression of serum response factor in oligodendrocytes
- Human umbilical cord blood, and plasma from people in their 20s or from 3-month-old mice, boosts neurogenesis, neuronal plasticity in the hippocampus, and memory in aged mice
- Importance of flagging oligodendrocyte function in age-related cognitive decline

CSF identification of Alzheimer's

- FDA issued its first approval for a fluid biomarker test, greenlighting Fujirebio's Lumipulse G cerebrospinal fluid Aβ42/40 assay. Needs lumbar puncture.
- Blood test: Quest Diagnostics will offer a plasma Aβ assay nationwide. Aβ42/40 ratios below a cutoff of 0.160 indicate the likelihood of AD. When combined with APOE genotype and age, the assay detected the presence of amyloid in the brain with about 90 percent accuracy. Use mass spec plasma Aβ tests.
- C2N Diagnostics' Precivity AD assay as the only blood tests certified for clinical use in the United States, though these tests are not yet FDA-approved or covered by insurance. $1250 per assay. Issue of comorbidities, i.e. BMI, ethnicity

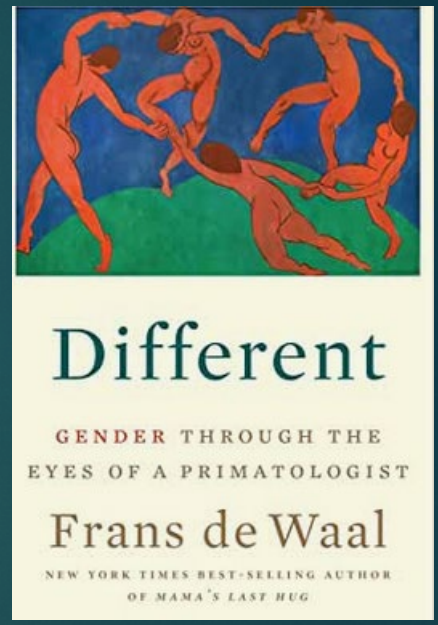
Biomarkers

- Less expensive than PET imaging test for BA and Tau proteins
- Can aid diagnosis but by themselves do not indicate the presence of disease; still need neuropsychological testing to verify dementia
- CSF and plasma tests should not be used in cognitively healthy people worried about their risk of AD. Because the disease has such a long preclinical phase, some older people who test positive will not develop symptoms in their lifetime.

Pterosaurs, at 250 Ma, had different colored feathers: developed long before flight (for insulation or signaling)

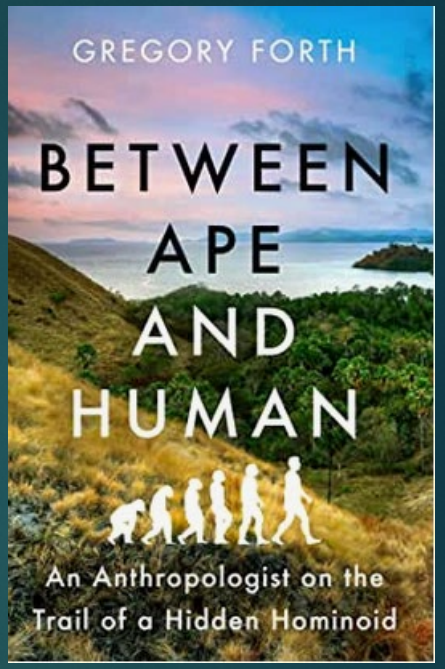
Primatologist Frans de Waal

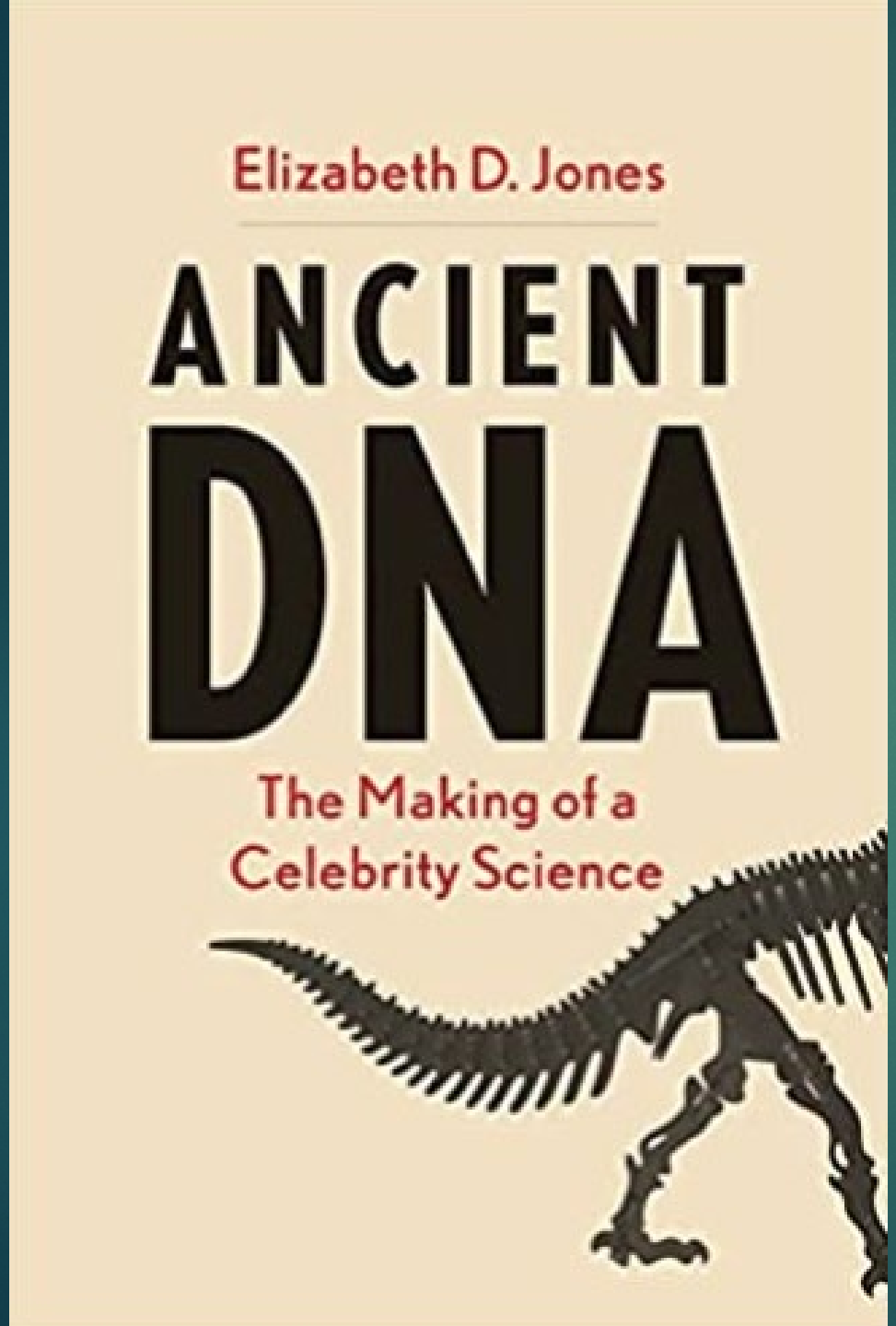
- Frans de Waal: He has shown that cooperation is at least as important as competition in explaining primate behavior and society. His work has revealed that the great apes might fight, but they also reconcile their differences. They have a capacity for empathy and a concept of fairness that de Waal proposes is the foundation of the human moral compass.
- He believes that chimps, bonobos and humans are simply different types of ape and that empathetic and cooperative behavior are continuous between these species.
- Males tend to be more physically violent than females. This is true for all the apes
- Bonobos are famously very sexual, having sex with each other all the time – males with males, females with females and males with females
- De Waal in his new book, *Different: Gender Through the Eyes of a Primatologist*, proposes that apes have gender identity



Hobbits of Flores – new book

- A professor of anthropology says a relic population of *Homo floresiensis* – nicknamed "hobbits" – believed extinct for 50,000 years, may still exist on the Indonesian island of Flores.
- Gregory Forth, University of Alberta in Canada, recorded 30 stories of encounters with hobbits given by members of the Lio people who live on the eastern portion of Flores, speaking directly with each eyewitness. He has compiled those accounts in a new book, *Between Ape and Human: An Anthropologist on the Trail of a Hidden Hominoid*,
- He concludes a small population of what he said he can only call an ape-man were seen by the more than two dozen members of the Lio; a non-*sapiens* hominin has survived on Flores to the present or very recent times.
- Like the Yeti?





1990s studies of dinosaur “DNA” + Jurassic Park

All four of the key DNA building blocks have been found in meteorites

- All four building blocks of DNA (ATCG) have been discovered in meteorite samples, suggesting that space rocks may have delivered the compounds to Earth, contributing to the origin of life
- Adenine and guanine, which belong to a group of chemical compounds called purines – were first detected in meteorites in the 1960s.
- Now, Yasuhiro Oba at Hokkaido University in Japan and his colleagues have discovered the remaining two DNA nucleobases, cytosine and thymine, known as pyrimidines, in several meteorites.
- The team found the nucleobases in about 2 grams of rock from three meteorites: the Murchison, Murray and Tagish Lake meteorites. The Murchison and Murray meteorites, which hit Earth in the mid-20th century, are thought to date to at least 5 billion years ago. Like Earth, the Tagish Lake meteorite probably formed 4.5 billion years ago, and it hit our planet about two decades ago.

Origin of life theory involving RNA

- New results point to an important part played by RNA at the origins of life, but without requiring RNA alone to self-replicate
- Structure that links amino acids suggests that early organisms could have been based on an RNA–protein mix.
- RNA molecules can link short chains of amino acids together.
- The 'RNA world' hypothesis, which proposes that before the evolution of DNA and the proteins it encodes, the first organisms were based on strands of RNA, a molecule that can both store genetic information — as sequences of the nucleosides A, C, G and U — and act as a catalyst for chemical reactions.

Origin of life theory involving RNA

- In an RNA world, the standard theory says, life could have existed as complex proto-RNA strands that were able to both copy themselves and compete with other strands.
- Later, these ‘RNA enzymes’ could have evolved the ability to build proteins and ultimately to transfer their genetic information into more-stable DNA.
- If the origins of RNA and the origins of protein are linked, and their emergence is not independent, then the math shifts radically in favor of an RNA–protein world and away from an RNA world

Periodic Table of Intelligence

- New project: a periodic table of intelligence: For intelligence – broadly defined as an organism's ability to flexibly respond to a changing environment
- Assume intelligence in the clever antics of whales and dolphins, chimpanzees and orangutans, with larger brains
- But what about wasps? Recognize human faces.
- Or crabs? They use stinging anemones to defend themselves against predators.
- Alligators that place sticks on their snouts to catch egrets looking for nesting material.

Animal IQ

- Mosquitoes: learn to avoid pesticides after a single taste.
- Plants: A parasitic vine called a dodder sniffs out its prey with remarkable discernment. i.e. tomato
- Slime molds: single cells organism can solve mazes, can learn and teach others; will find the shortest path to the food and retract all paths that don’t lead to these points
- Biofilms: collectives of bacteria – possess short-term memory and the ability to make decisions.
- Intelligence may not even require a brain: non-neural systems and self-organizing swarms have joined the club of cognitive agents.

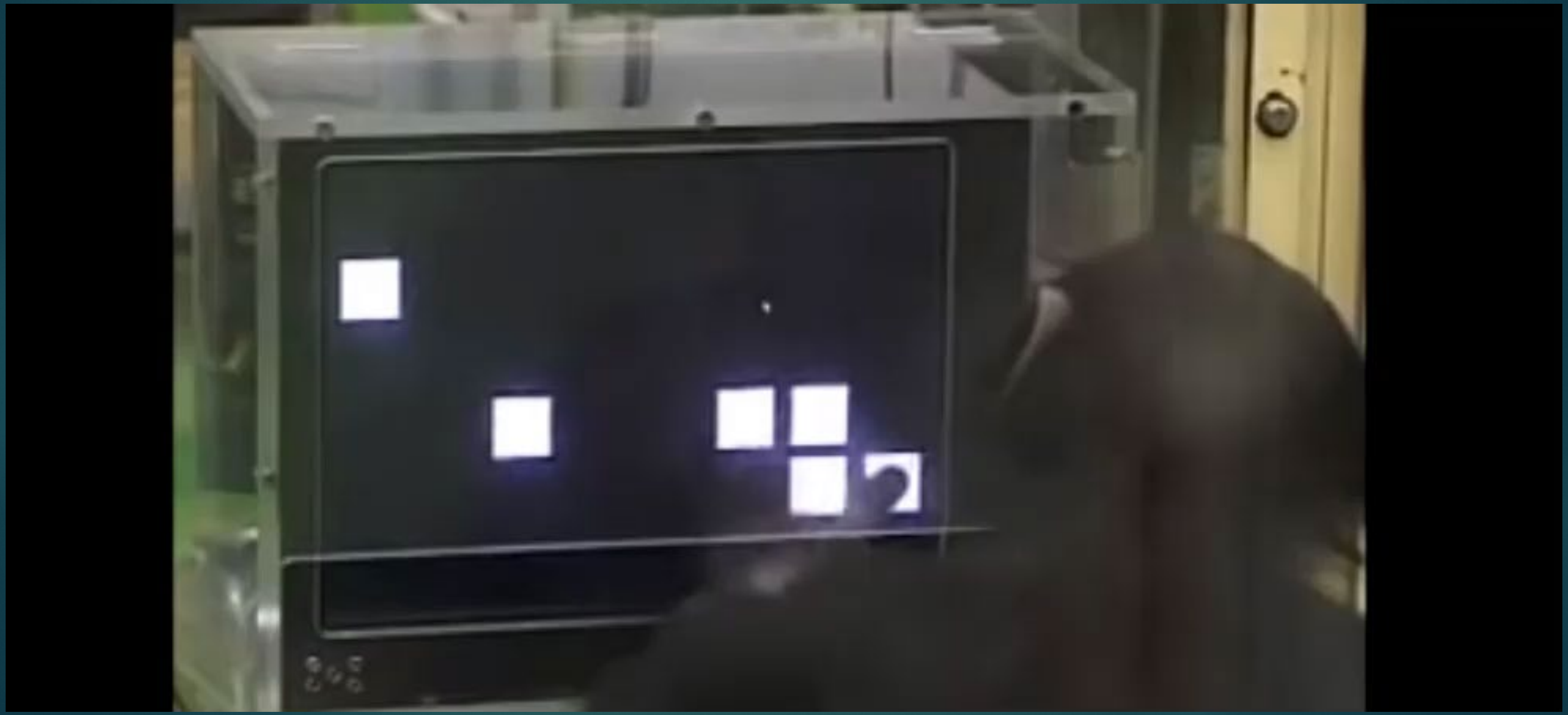
Animal IQ

- It certainly isn't brain size: Adult human brains weigh between 1.2 and 1.5 kilograms, contain about 86 billion neurons and make up about 2 per cent of our body weight. But a whale's brain can weigh 9 kilograms, an African elephant has some 257 billion neurons and the brain of a shrew – a small, mouse-like creature not renowned for its smarts – comprises about 10 per cent of its body mass.
- Honeybees: able to count up to 5 and grasp abstract concept of zero with a brain that is less than 2 cubic mms.
- Behavior might be a better way to categorize cleverness.
- Take the courting male cuttlefish that positions himself between a female and his rival and displays female colors on the side of his body facing his competitor and male ones on the side that the female can see.
- Or consider a rook. If this bird is presented with a treat floating in a water-filled vessel, it drops stones into the liquid until the level has risen high enough to bring the tasty morsel into reach.

Animal IQ

- Recognizing oneself in a mirror is seen as a sign of advanced cognition. Dolphins, magpies and manta rays can do it – but dogs typically can't.
- Does this reflect a lack of intelligence in canines or perhaps something else, such as their reliance more on smell than vision?
- Ayumu, a chimpanzee taught to remember random sequences of nine numbers that a screen flashes at him for only 60 milliseconds – less than the blink of an eye. But Ayumu easily types out the digits in the right order. Has beaten all humans.

Ayumu, a chimpanzee



Animal IQ

- An octopus possesses about 550 million neurons, of which around 160 million sit in its large optic lobes and 42 million inside a brain shaped like a doughnut because the esophagus runs through it.
- 350 million neurons are distributed among the animal's eight arms, which constantly explore the environment and process information, basically "thinking" independently.
- An octopus will easily open a jar – an object that hasn't been part of its evolution. And cuttlefish can resist the temptation to eat a treat to get rewarded with a better one a while later. In this version of the marshmallow test, they manage to delay gratification for up to 2 minutes, broadly similar to chimpanzees.

Periodic table of intelligence Project

- Cognition might be simple learning, influenced by the environment and limited by brain size and body type.
- They present five types of cognitive systems categorized by a type of information flow within them. Each transition consisted in changes to information flow in systems, opening up new capacities while transforming the scope of existing cognitive functions.

Contemporaneous Omo skulls: AMH = Omo 1; but Omo 2 is more primitives

eplicas of Omo Kibish 2 (left) and reconstruction of Omo Kibish 1 by Day&Stringer (right). Credit: Chris Stringer

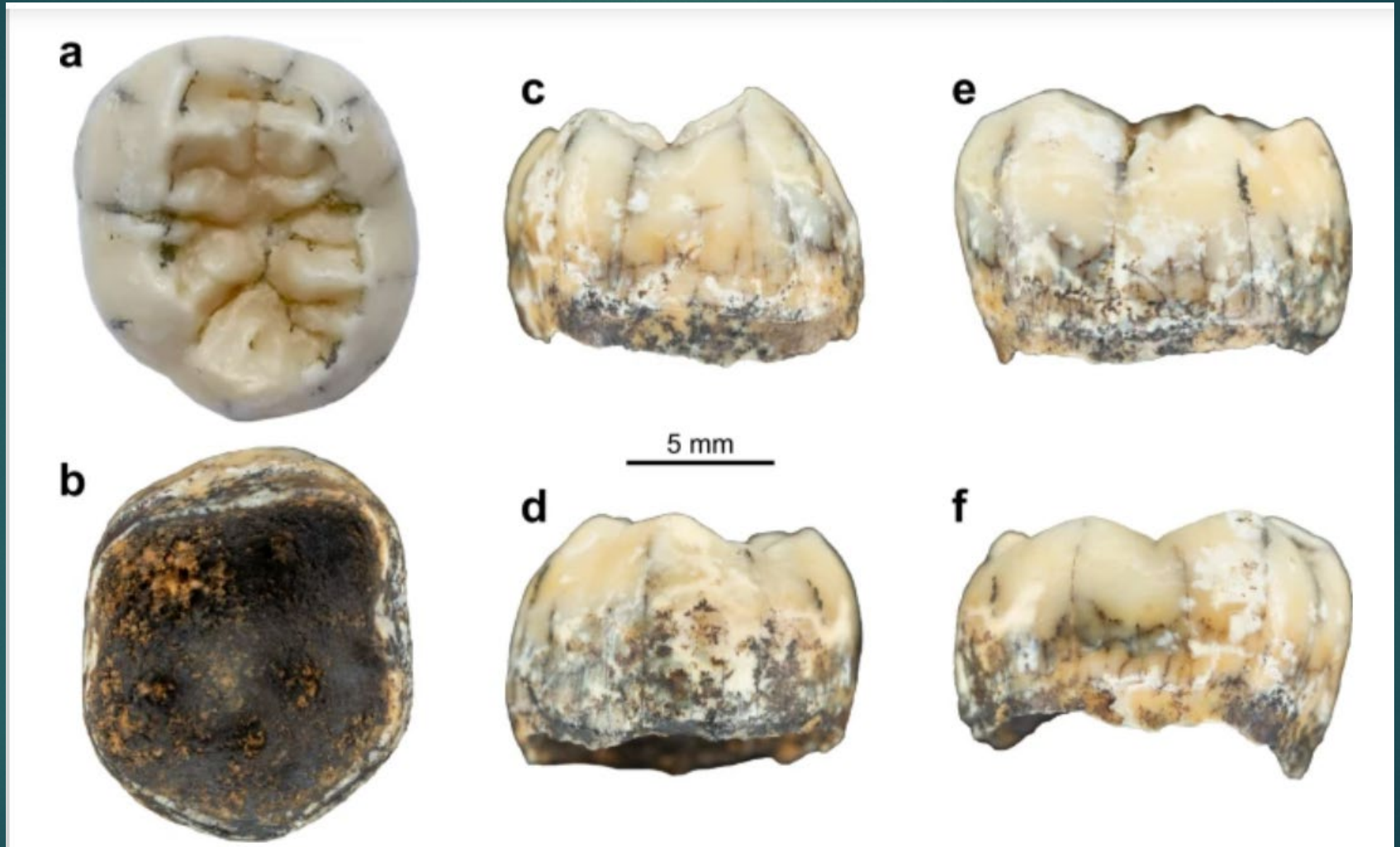
2013: TPL2 mandible, Laos, 63 Ka

Early modern human morphological diversity in Southeast Asia at Tam Pa Ling, Laos

- Tam Pa Ling (TPL), a cave site in northern Laos, is the source of early modern human fossils – a partial cranium (TPL1) and a complete mandible (TPL2) – that represent the earliest anatomically modern humans in continental Southeast Asia and introduce new migration routes into the region during MIS 3.
- A new partial mandible from the site, TPL 3; mixture of archaic and derived traits, with a chin; an age range of 70 ± 8–48 ± 5 ka
- Among multiple mammal fossils, brought into cave by porcupines
- Demonstrates the presence of modern humans in Southeast Asia from at least 70 Ka. Additionally, as Tam Pa Ling lies a thousand miles inland, the finds challenged previous assumptions that humans migrated out of Africa by following coastlines. They suggest that the migration may also have proceeded along river valleys, which served as natural corridors through the continent.

L. Shackleford, et al. 2018

Denisovan tooth from Laos?



Pictures of TNH2-1 in occlusal (**a**), inferior (**b**), mesial (**c**), distal (**d**), buccal (**e**) and lingual (**f**) views.

A Middle Pleistocene Denisovan molar from the Annamite Chain of northern Laos

- A tooth (TNH2-1) found in 2018 in the Tam Ngu Hao 2 cave (it would translate as Cobra Cave), in the Annamite Mountains, Laos.
- It is a lower molar (M1 or M2) dated at 164-131 ka, a chronology corresponding to the range of the oldest Denisovan remains known at the moment.
- TNH2-1 has a large crown and complex occlusal surface, which makes it different from the smaller and morphologically simpler teeth of *Homo floresiensis*, *H. luzonensis*, and *H. sapiens*, and close to larger Neanderthal and Denisovan molars.
- It has hardly any wear, which places the age of death of its owner between 3.5 and 8.5 years. Protein analysis indicates it is from a female individual, It lacked a specific enamel protein encoded by a gene on the Y chromosome, which is only carried by males.

Fabrice Demeter, et al., 2022

Denisovan? tooth

- Tooth is from the genus *Homo*, although distinguishing whether she was a Neanderthal or a Denisovan is difficult.

- It cannot be ruled out that it is Neanderthal, but this would astonishingly expand the range of this human species by about 4000 km southeast of Denisova Cave. It seems like a less likely idea.

- Compared it to 400 molars from living and extinct humans. Of those teeth, the Cobra Cave specimen most closely resembled a molar lodged in the Denisovan jaw from Tibet.

Denisovan Tooth

- The close morphological affinities with the Xiahe specimen from Tibet indicate that they belong to the same taxon and that Tam Ngu Hao 2 most likely represents a Denisovan. Denisovans have absolutely gigantic teeth.

- The discovery of Denisovans in Laos shows that they were exactly where they needed to be to interbreed with modern humans who arrived in Southeast Asia thousands of years later.

- Only the second Denisovan fossil to be found outside Siberia. Its presence in Laos supports the idea that the species had a much broader geographic range than the fossil record previously indicated.

- And some ancient teeth that were already discovered in China and Taiwan seem now like they might have a Denisovan shape, warranting a fresh look.

No sustained increase in zooarchaeological evidence for carnivory after the appearance of *Homo erectus*

- Larger brains first appear in *Homo erectus*.
- The evolution of these traits is commonly linked to a major dietary shift involving increased consumption of meat.
- Early archaeological sites preserving evidence of carnivory predate the appearance of *H. erectus*, but larger, well-preserved sites only appear after the arrival of *H. erectus*.
- This qualitative pattern is a key tenet of the "meat made us human" viewpoint,
- Data from sites across eastern Africa have not been quantitatively synthesized to test this hypothesis.
- New analysis shows no sustained increase in the relative amount of evidence for carnivory after the appearance of *H. erectus*, calling into question the primacy of carnivory in shaping its evolutionary history.

W. Andrew Barr, et al. 2022

Carnivory sampling error

- New Analysis: a quantitative synthesis of the zooarchaeological record of eastern Africa from 2.6 to 1.2 Ma.
- Sampling error: The prevalence of hominin carnivory are all strongly related to how well the fossil record has been sampled
- When correcting for sampling effort, there is no sustained increase in the amount of evidence for hominin carnivory between 2.6 and 1.2 Ma.
- These findings undercut evolutionary narratives linking anatomical and behavioral traits to increased meat consumption in *H. erectus*, suggesting that other factors are likely responsible for the appearance of its human-like traits.

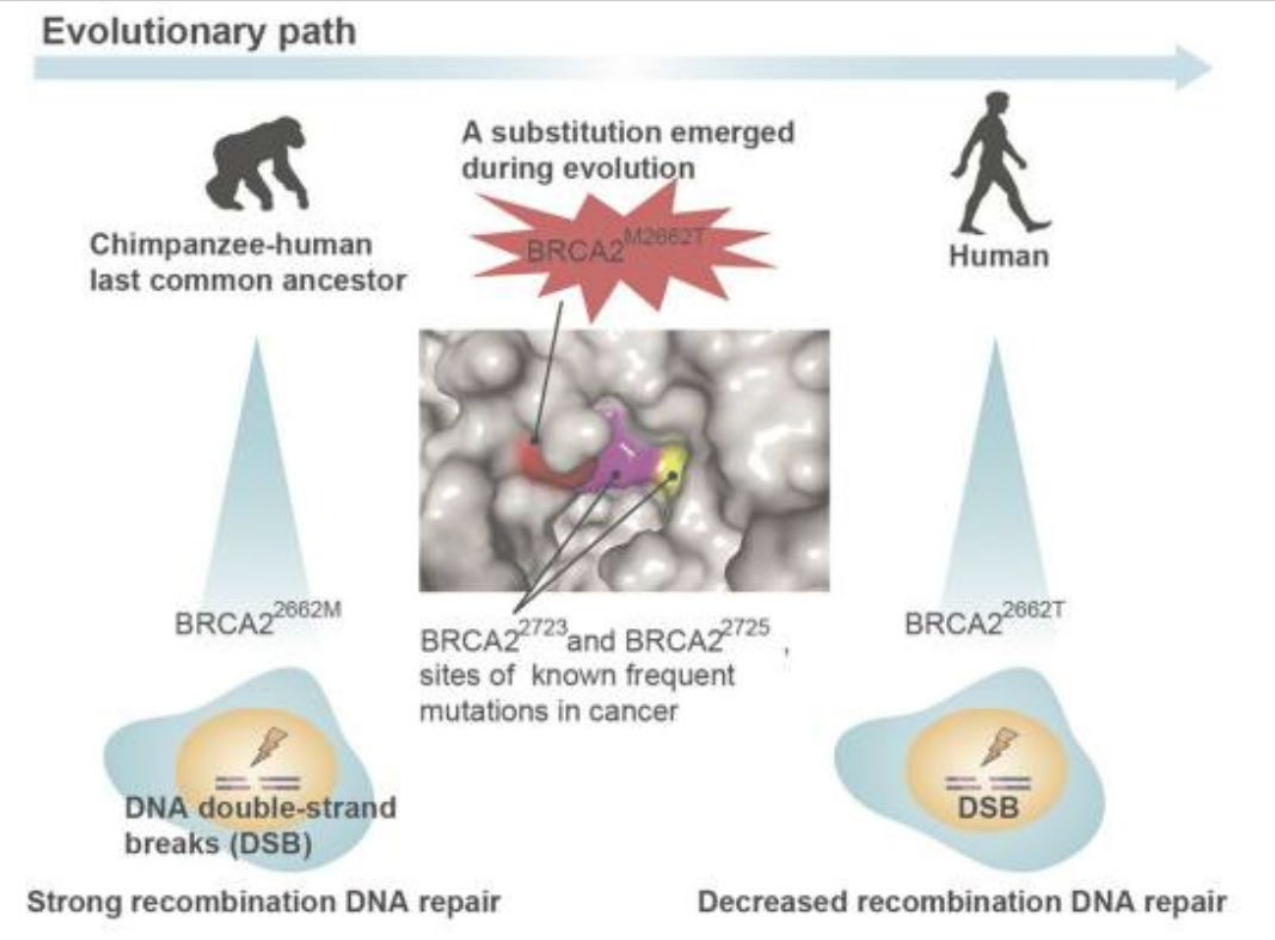
Use of tools rather than cooking

- Study favors the most classical view suggesting that early hominins increased their foraging efficiency by including new sources of food in their diet, especially seeds and meat.
- Also, the use of tools is well documented and strongly correlates with the increase in brain size during human evolution
- Use of Lower Paleolithic technologies to process meat and tubers reduced the number of chewing cycles and the total masticatory force, explaining the increased foraging efficiency of early hominins at the onset of brain expansion.
- Therefore, the rise in the use of tools, rather than cooking, is more likely to explain how early hominins increased their daily energetic intake.

1 – Antecessor, 800 Ka; 2 – Sima N, 430 Ka; 3 – Jebel Irhoud, 315 Ka; 4 – Florisbad, 260 Ka

5 – Omo 1, 233 Ka; 6 – Herto, 160 Ka; 7 – Laetoli, 120 Ka; 8 - Modern

Early *H. sapiens* is less a species than a clade: a group of organisms of various taxonomic groups, descended from a common ancestor and sharing many features, but also with a lot of physical variation.



Women with a BRCA2 variant that makes them more susceptible to developing cancer can more easily become pregnant.

- **DNA change made humans more susceptible to cancer**
- Humans develop more cancer than any other primate
- Found a small difference in the BRCA2 gene (tumor suppression due to coding for DNA repair.)
- Single letter change lessened its effectiveness at coding for DNA repair by 20%
- Why humans evolved to have a BRCA2 gene that increases the risk of developing cancer?
- A tradeoff between an increased risk of cancer and an increase in fertility rates.

The non-human living inside of you

- Half of your genome started out as an infection
- Eight percent of our DNA consists of remnants of ancient viruses, and another 40 percent is made up of repetitive strings of genetic letters that is also thought to have a viral origin
- They may be deeply involved with a wide range of diseases including multiple sclerosis, hemophilia, and amyotrophic lateral sclerosis (ALS), along with certain types of dementia and cancer.

Retrotransposons = jumping genes

- Retrotransposons, a subset of transposable elements (TEs), are genomic parasites capable of inserting new copies of themselves throughout the genome by a process called retrotransposition.
- Previous work has shown that TDP-43 (central to Frontal Temporal dementia) represses retrotransposon transcripts at the RNA level in animal models of TDP-43 pathology
- TDP-43 protein is highly adept at latching onto and hiding stretches of DNA. HIV pts with ALS sxs: HIV meds suppressed the virus-like activity from jumping genes, and improved their ALS sxs.
- Ancient viruses in question interacts strongly with TDP-43. Faulty form of the protein might no longer be able to hold back critical nerve-killing jumping genes. Normal form of TDP-43 suppresses harmful activity from jumping genes in mice and humans

Jumping genes

- An early clue came from the pioneering geneticist Barbara McClintock. In the 1940s, long before the decoding of the human genome, she realized that some stretches of our DNA behave like infectious invaders.
- These DNA chunks can move around through the genome, copying and pasting themselves wherever they see fit, which inspired McClintock to call them “jumping genes.”
- Her once-controversial idea earned her a Nobel Prize in 1983.
- Jumping genes originate in the viral portion of the genome.

Paleogenetics, Part 7

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

by
Charles J Vella, PhD, 2022

Adaptive introgression

- A gene variant will alter a phenotype (your observable features) if gene frequency increases because it proves beneficial for individual. If more born and survive survive with that trait.

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

- Some may just have hitched a ride along with some beneficial DNA

Genetic Introgression between hominins

- Introgression, also known as introgressive hybridization, in genetics = 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:
  - introgression occurs between two populations of different species
  - Gene flow - between 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.

- Neandertal DNA:
  - 1.8–2.6% of modern genomes for people outside Sub-Saharan Africa,
  - up to 0.3% for those in Africa.
  - Above are averages for whole MH genome; some specific genomic areas are 62% N DNA

- 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 MHs 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)

- Estimated that the last Neanderthal gene flow into early ancestors of Europeans occurred 47,000–65,000 years BP.

- The N-MH gene flow 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:
  - 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

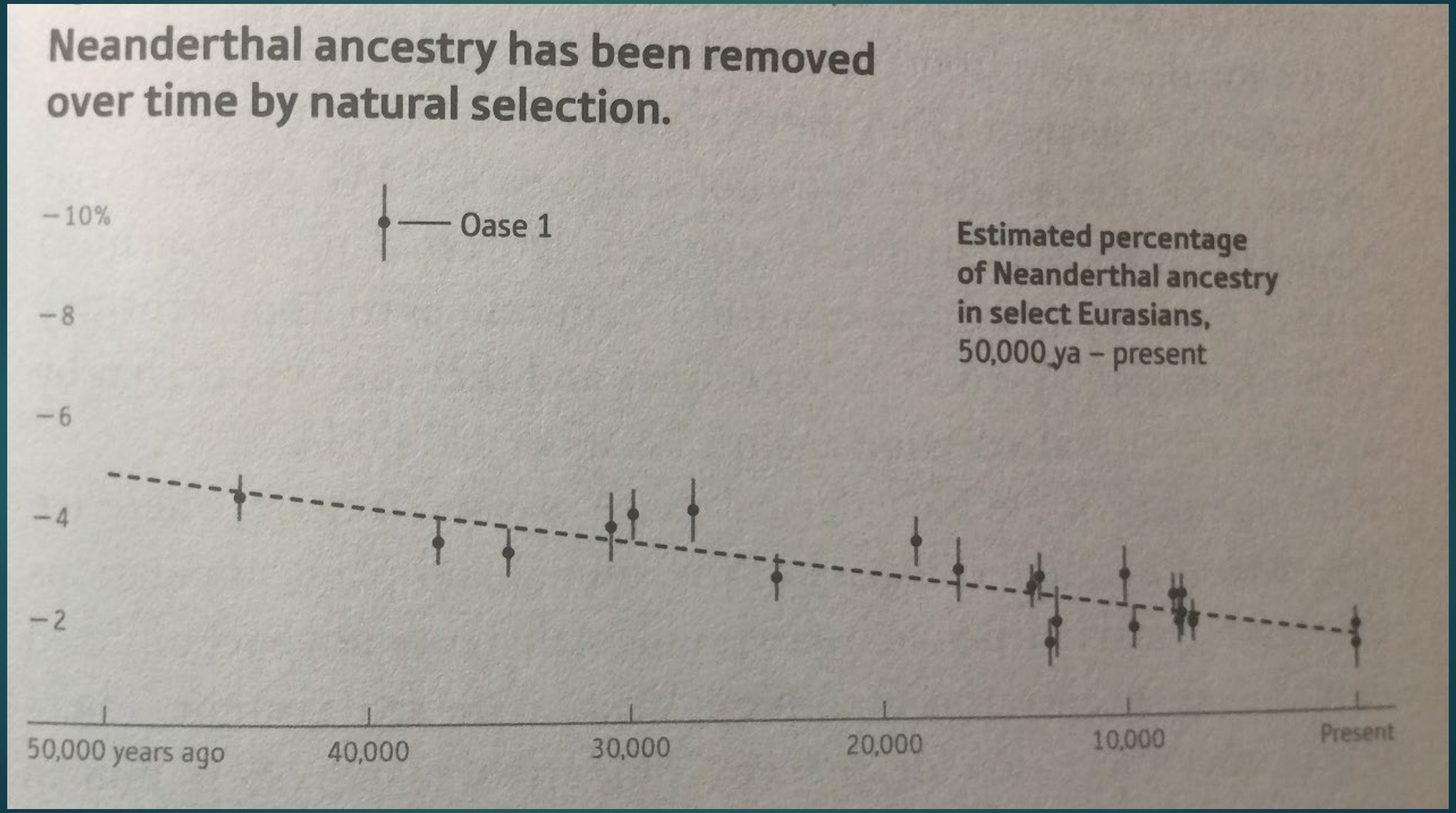
Negative Selection

- 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

Functional Archaic Admixture

- There are three lines of evidence for this selection against archaic ancestry:
  - archaic haplotypes have decreased in frequency over time (10% to 2%)
  - 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.

Negative selection for N DNA



Functionality of N genes in MHs

- No one has actually shown yet in a culture that a human and Neanderthal allele have a different physiological function

- In their 2014 study, Vernot and Akey found several sequences of Neanderthal origin that were present in more than 50% of the genomes from living humans.

N, D DNA in MHs

- 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. It is currently unknown who these archaic African hominins were.

Benefits of adaptive introgression (interbreeding with an adapted species)

- Species can adapt through traditional natural selection, in which spontaneous mutations that happen to be helpful gradually spread through the population. But such mutations strike rarely, making it a very slow process.
- A more expedient option is to mate with species that have already adapted to the region (cold climate, weak sun and local microbes) and co-opt some of their helpful DNA.
- The Neanderthal and Denisovan genes with the greatest signs of selection in the modern human genome largely have to do with how humans interact with the environment.

Genes that our ancestors lifted from archaic humans.

- Interactions with Neandertals and Denisovans helped our ancestors survive. Such “adaptive introgression” has been well documented in plants and bacteria
- To find these adaptive segments, the genomes of contemporary humans are searched for regions of archaic DNA that are either more common or longer than expected. Over time, useless pieces of Neanderthal DNA — those that don’t help the carrier — are likely to be lost. And long sections of archaic DNA are likely to be split into smaller segments unless there is selective pressure to keep them intact.

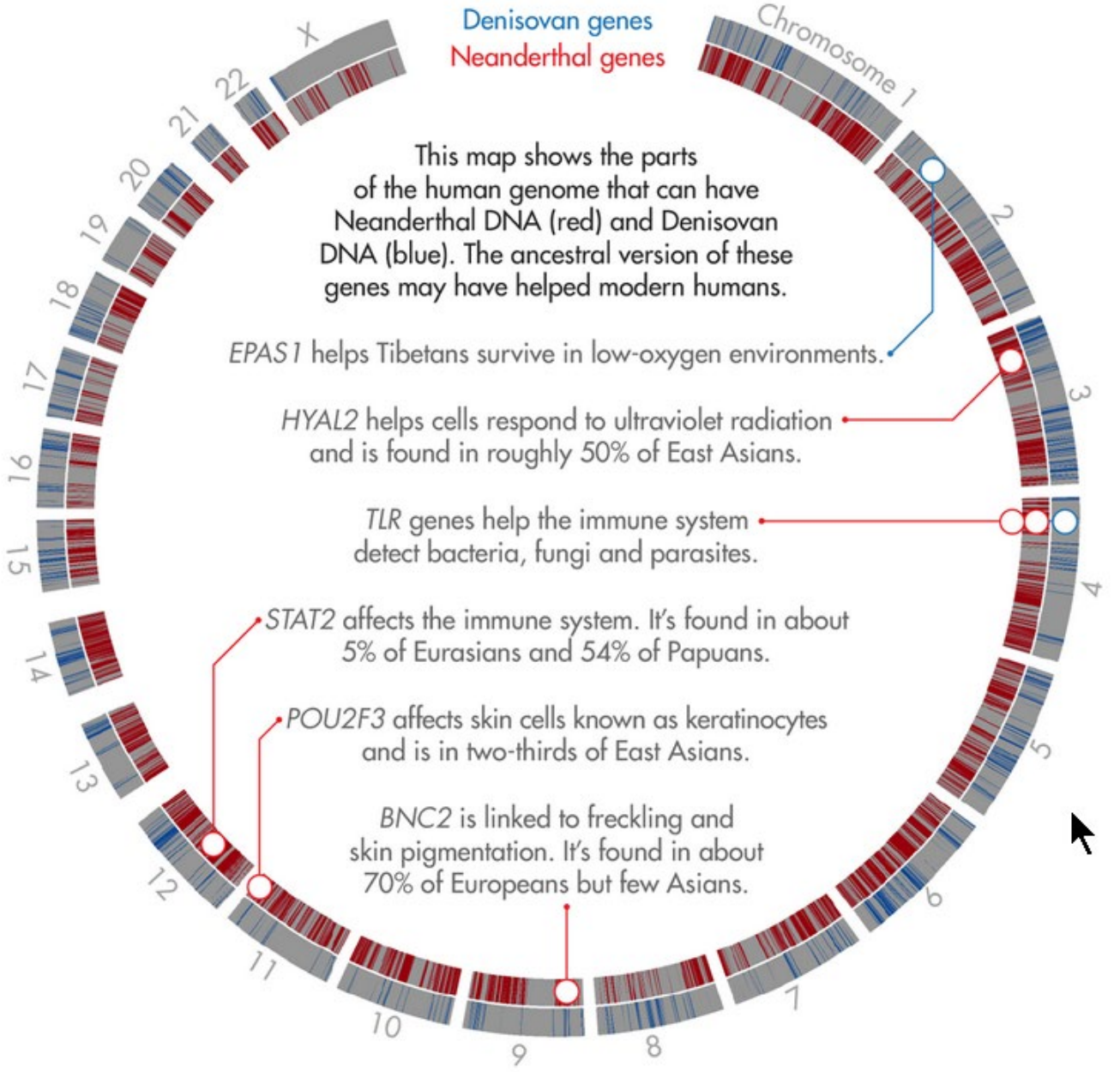
Akey

- When modern humans started dispersing around the globe, they encountered unique pathogens that archaic humans were better adapted to.
- Luckily for modern humans, they picked up some immune genes from Neandertals, such as a version of *STAT2*, a gene involved in the interferon response that fights viral infections; moderns also acquired different types of human leukocyte antigen genes, which help the immune system detect foreign invaders.
- The DNA record shows that these genes spread rapidly through Europeans and Asians.
- Neandertals, whose ancestors had at least 400,000 years to adapt to Europe's gray skies and frigid winters, also bequeathed some skin genes to the modern humans they encountered, including a gene called *BNC2*, which is associated with light skin in Europeans and allows skin to synthesize more vitamin D.

But N DNA also helped MHs

- Certain Neanderthal and Denisovan genes seem to have swept through the modern human population — one variant, for example, is present in 70 percent of Europeans — suggesting that these genes brought great advantage to their bearers and spread rapidly.
- In some spots of our genome, we are more Neanderthal than human. It seems pretty clear that at least some of the sequences we inherited from archaic hominins were adaptive, that they helped us survive and reproduce.
- Some of these genes are tied to our immune system, to our skin and hair, and perhaps to our metabolism and tolerance for cold weather, all of which might have helped emigrating humans survive in new lands.

A MAP OF ANCIENT GENES



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

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

What do we know of functionality of genes

- ENCODE project, 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, a 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: 1 %

- A little over 1% of human DNA (~19,000 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
- ENCODE project aims to identify all functional elements in the human genome, based on biochemical effects

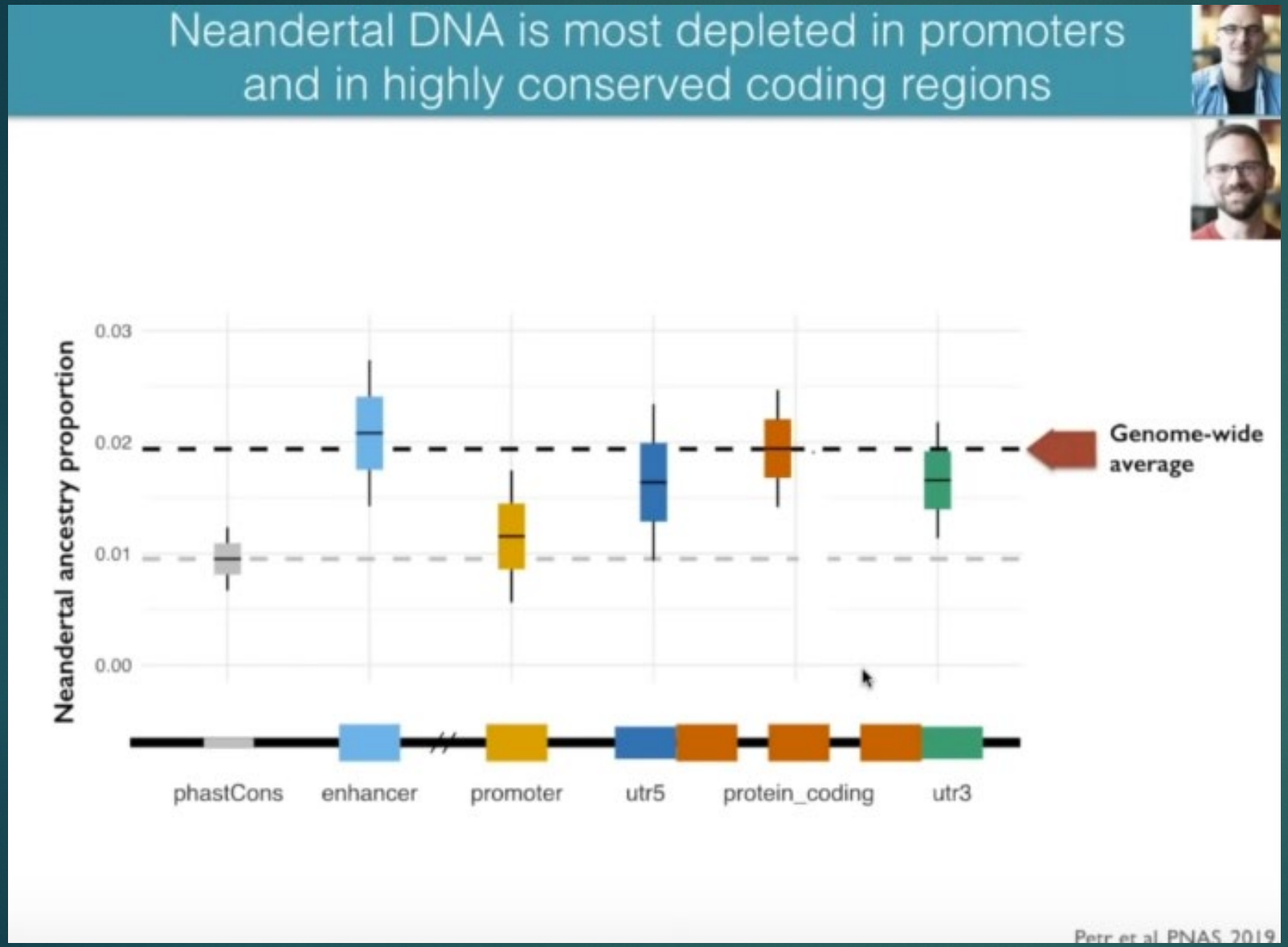
Non-protein coding DNA is not “Junk” DNA

- DNA outside protein producing areas are really important; not “junk”; constitutes 98% of Genome
- 5-10% of the human genome is highly conserved across mammals, implying it is highly functional
- But only ~2% code for proteins
- Most of the non-coding areas are non-coding in function, but are regulatory, control what genes do

N gene regulatory impact

- Neanderthal-inherited sequences are not silent remnants of ancient interbreeding but have measurable impacts on gene expression that contribute to variation in modern human phenotypes.
- Pervasive *cis*-regulatory impacts of N introgression;
  - Cis regulation: regions of non-coding DNA which regulate the transcription (DNA to RNA) of neighboring genes
- One-quarter of Neanderthal-introgressed haplotypes show *cis*-regulatory effects
- Demonstrates that many of these N sequences are functionally significant, contributing to genome complexity and patterns of gene expression variation in modern humans

Rajiv C. McCoy, et al., 2017



Protein coding gene regions are depleted of N DNA

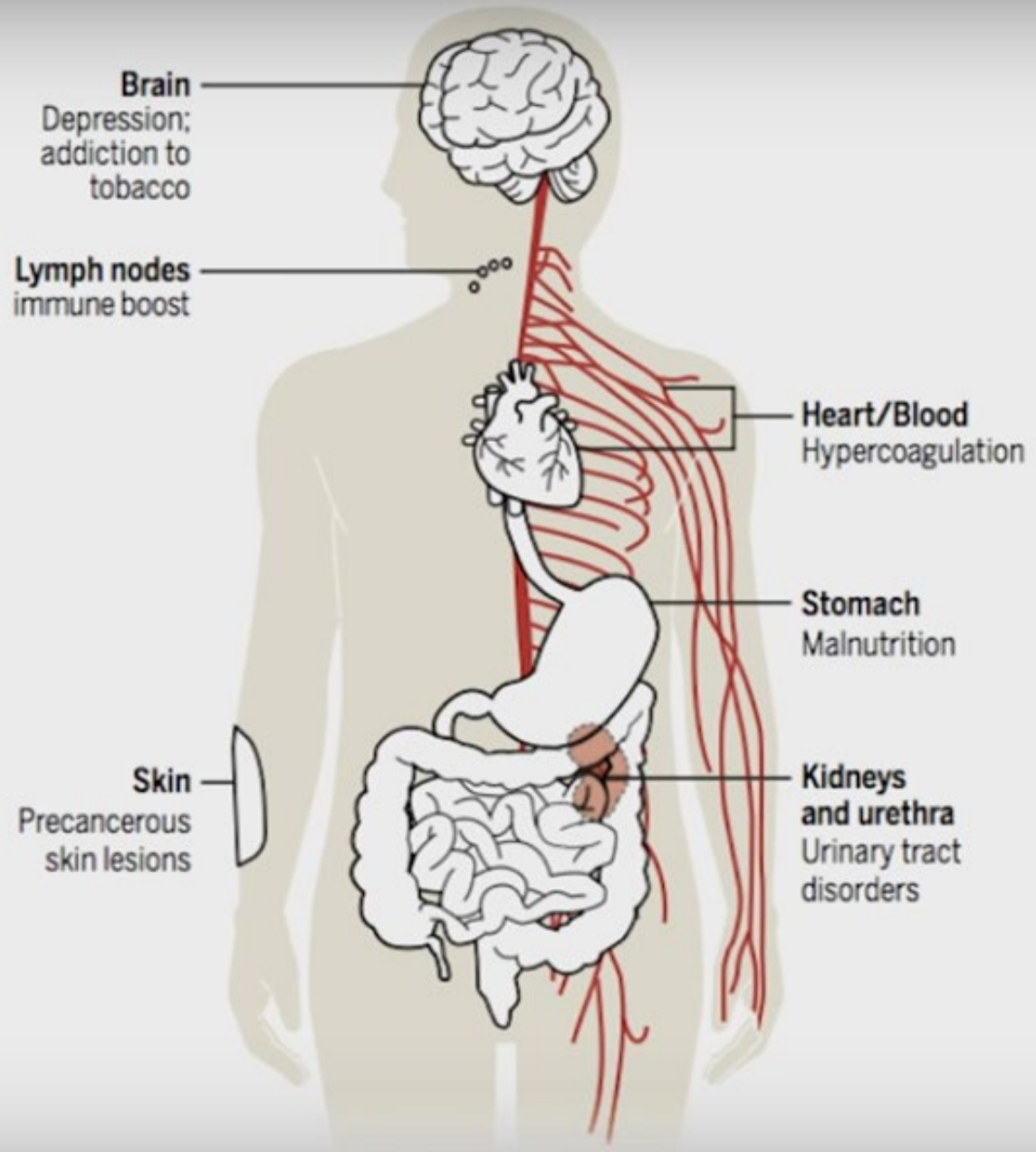
N DNA is in regulatory regions

N DNA is most depleted in promotors and in highly conserved coding regions

What was not contributed by N

- Less N in gene coding regions of MH genome, indicating that N genes are typically bad for survival functions in MHs
- Where do you not find D or N contributions: unique functions of MHs, which select vs these other groups

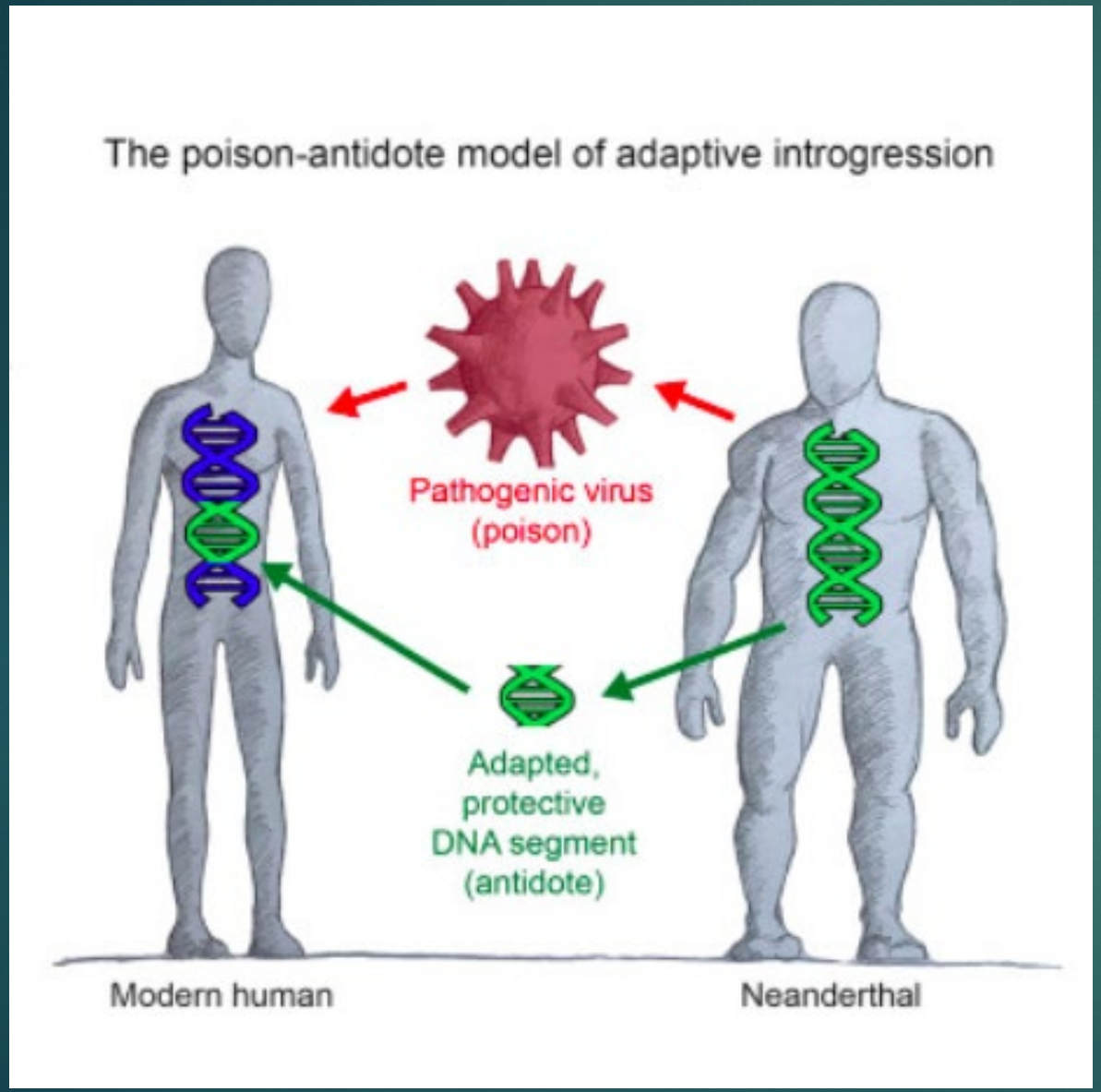
Neanderthal Legacy in Modern Humans



N allele variants

- Natural selection has efficiently weeded out harmful variants; most N variants are gone
- UK Biobank (UKB), a large database that holds genetic and health records for 500 K British volunteers
- Number of N variants = 112,000
- Sriram Sankararaman: 6000 relatively rare alleles likely to come from Neanderthals
- Some Neanderthal gene variants may have been optimal for active lives outdoors in prehistoric Europe, they may be problematic for people now, who live mostly indoors in artificial light and get less exercise.

Poison-antidote model of adaptive introgression



- Study hypothesized that interbreeding between Neanderthals and modern humans led to
- (1) Poison = the exposure of each species to novel viruses
- (2) Antidote = the exchange of adaptive alleles that provided resistance against these viruses.

David Enard & Dmitri A. Petrov, 2018

“Poison-antidote” model of N-MH gene swapping

- Enard and Petrov study: “poison-antidote” model of gene swapping.
- Ns and MHs infected each other with the pathogens from their respective environments. That’s the poison part.
- The antidote, meanwhile, was the result of their hybridization.
- These viruses were old news to Neanderthals, but were a new sudden challenge for modern humans. Then, modern humans took the fast-track route for adaptation against these new viruses simply by borrowing the pre-adapted genetic material from Neanderthals.

Poison-antidote model of adaptive introgression

- Most introgressed DNA segments from Neanderthals to modern humans were removed by purifying selection,
- Less is known about the adaptive nature of introgressed sequences that were retained.
- Study: interbreeding between Neanderthals and modern humans led to
  - (1) the exposure of each species to novel viruses and
  - (2) the exchange of adaptive alleles that provided resistance against these viruses.

And the other way…Infections from MHs to Ns

- Tropical infections were likely to have passed from humans to Neanderthals -- such as tapeworm, tuberculosis, stomach ulcers and types of herpes -- chronic diseases that would have weakened the hunter-gathering Neanderthals

- *Helicobacter pylori*, a bacterium that causes stomach ulcers, as a prime candidate for a disease that humans may have passed to Neanderthals
- Herpes simplex 2

Charlotte Houldcroft, 2016

Poison-antidote model of adaptive introgression

- Long, frequent—and more likely adaptive—segments of Neanderthal ancestry in modern humans are enriched for proteins that interact with viruses.

- These proteins which interacted specifically with RNA viruses were more likely to belong to introgressed segments in modern Europeans.

- Retained segments of Neanderthal ancestry can be used to detect ancient epidemics.

N DNA that was beneficial

- It's likely that most Neanderthal genes were bad for our health or reduced our fertility, and therefore were lost in modern humans.

- But certain Neanderthal genes became more common, probably because they provided some kind of evolutionary advantage.

Resistance to RNA viruses

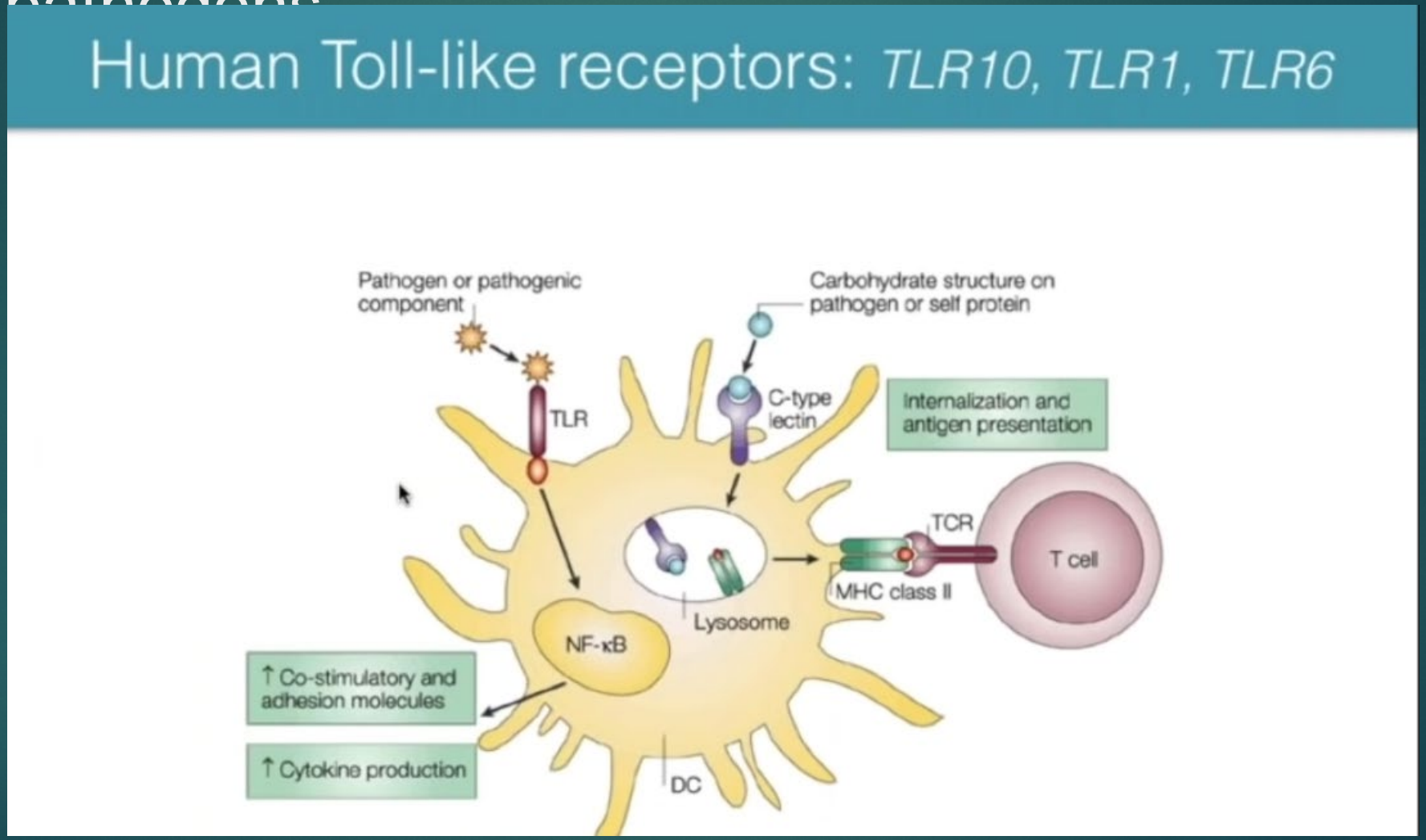
- Neanderthal DNA-based adaptation was particularly strong against RNA viruses in Europeans:

- The Neandertal-like splice acceptor variant has been associated with protection against West Nile Virus (rs10774671)

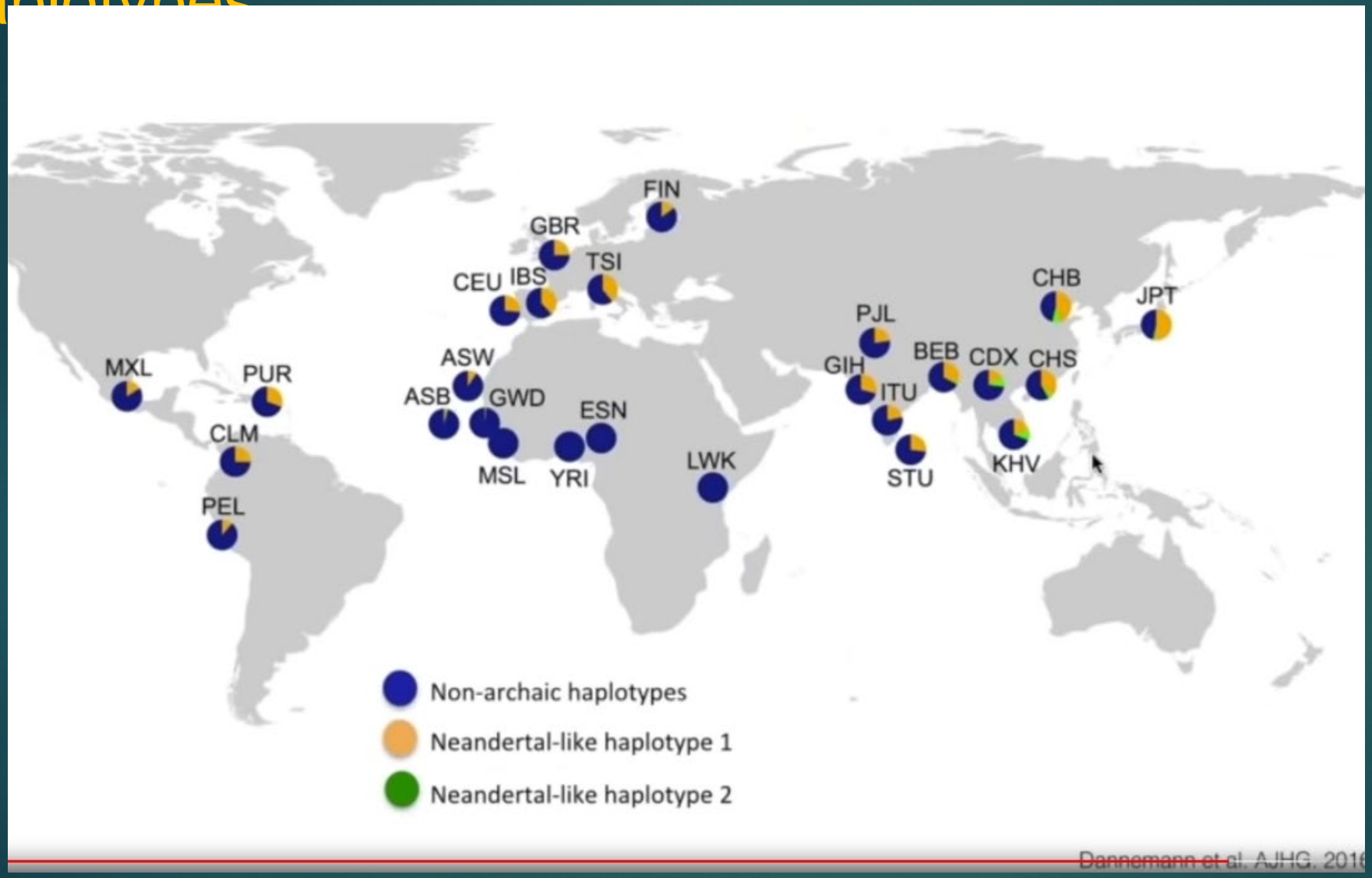
- Neandertal-like haplotype has been associated with increased resistance to hepatitis C infections.

- Notably, the Neandertal missense variant in OAS1 (rs2660) has been shown to be associated with moderate to strong protection against SARS-CoV

N innate immune variants: inflammatory antimicrobial responses – first line of defense vs bacterial pathogens



Geographic distribution of N introgressed *TLR* haplotypes



N immune variants that identify invaders and trigger adaptive immune response

N variant has spread world wide

Immunity: toll-like receptors

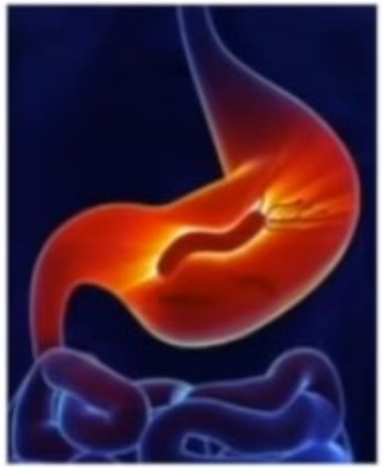
- Pathogens are one of the strongest selective forces out there. New lands have novel infectious diseases for which newcomers have no immunity.
- Janet Kelso et al. identified a large stretch of Neanderthal DNA — 143,000 DNA base-pairs long.
- The region spans three different genes that are part of the innate immune system.
- These genes produce proteins called toll-like receptors, which help immune cells detect foreign invaders and trigger the immune system to attack. Modern humans can have several different versions of this stretch of DNA.
- But at least three of the variants appear to have come from archaic humans — two from Neanderthals and one from Denisovans.

Neandertal Immunity Genes

- MH inherited some of their immunity genes (Toll-like receptor genes *TLR1*, *TLR6* and *TLR10)* from Ns
- Spending a night or two with a Neandertal was a small price to pay for getting thousands of years of genetic adaptation.
- This didn't change the *TLR* genes themselves but it changed the activity of the genes.
- Those people are less likely to get infected with the ulcer-causing *Helicobacter pylori* bacterium.
- But the advantage comes with a cost: Those people are more prone to allergies

K. Harris and R. Nielsen, 2015

Evolutionary tradeoffs: enhanced innate immunity surveillance, increased reactivity to pathogens and to nonpathogenic allergens



Introgressed alleles associated with

- reduced *H. pylori* infection
- increased allergic susceptibility

Immunity: double edged sword

- This added resistance came at a price. The trade-off for that was a more sensitive immune system that was more sensitive to nonpathogenic allergens.

- Most of the Neanderthal and Denisovan genes found in the modern genome have unknown functions.

Archaic Admixture Informs Demographic Models of Human History

- Green, et al. 2010: all non-African populations had approximately the same levels of Neanderthal ancestry.

- Original Theory = hybridization occurred once in the ancestral population to all present day non-Africans, likely in the Levant shortly after the dispersal of modern humans out of Africa.

- Next data: East Asians were found to have on average 20% (now 8%) more Neanderthal sequence than European individuals

Vattathil & Akey, 2015

East Asians

- The observation of higher Neanderthal ancestry in East Asians prompted reconsideration of the single-pulse model, and new models suggest at least two distinct admixture events—
  - an initial pulse of admixture into the common ancestor of all present day non-African populations and
  - an additional pulse of admixture into the ancestors of East Asians after their divergence from European populations

East Asians

- An alternative explanation that has been proposed is a single pulse of admixture followed by less efficient purging of deleterious Neanderthal sequence in East Asians, given their smaller effective population sizes.

- But more recent analyses found that the two-pulse model better explained the data.

Denisovans

- Much less is known about Denisovan admixture with modern humans,
- Papua New Guineans carry the highest level of Denisovan ancestry (4%–6% of the genome) among all populations studied to date,
- Modern humans peopled Asia in at least two distinct waves, with one wave taking a southern route and acquiring Denisovan ancestry and a separate wave responsible for colonization of East Asia and Indonesia

Genetic purging via negative selection

- Widespread purging of Neanderthal sequence in MHs:

- The amount of surviving Neanderthal sequence varies considerably across the genome.

- Such marked heterogeneity suggests that
  - there may have been fitness consequences to hybridization and
  - some N sequences were deleterious to MHs.

Genetic purging via negative selection

- Consistent with this hypothesis,
  - If a MH allele is important, it is not N:
    - the frequency of Neanderthal alleles is negatively correlated with inferred functional importance.
  - The more MH specific a sequence is, the less N sequence is present: odds of observing a Neanderthal sequence in a region is inversely proportional to the amount of sequence divergence between the modern human and Neanderthal genome
- Both of these signatures are expected if introgressed Neanderthal sequence experienced widespread purifying selection in modern humans.

Negative selection from N sex genes

- X chromosome is significantly depleted of Neanderthal sequence, with an approximate 5-fold reduction in Neanderthal ancestry compared to the autosomes (other 22 chromosomes), suggesting reduced fitness in male hybrid offspring (and perhaps male hybrid sterility).

- Testes-specific genes are also significantly depleted of Neanderthal DNA, further supporting the inference of reduced fitness in male hybrid offspring.

Modern Males Lack Neanderthal Y Chromosome Genes

- All the first N genomes analyzed were female. We only have female N sexual DNA
- No information on N's Y chromosome
- Neanderthal Y chromosome DNA has never been observed in any human sample ever tested
- If females consistently miscarried male babies carrying Neanderthal Y chromosomes, that would explain its absence in modern humans. Male fetuses conceived through sex with Neanderthal males would have miscarried.

N Hybrid viability

- 2016 research indicates some Neanderthal males might not have had viable male offspring with some AMH females.

- This could explain the reason why no modern man has a Neanderthal Y chromosome.

Linkage disequilibrium: evidence for selective genetic sweeps

- How do we know a gene has had a positive selective sweep in a population?

- Linkage disequilibrium is the non-random association of alleles at a pair of genetic loci.
- It is the correlation between nearby variants such that the alleles at neighboring polymorphisms (observed on the same chromosome) are statistically associated within a population more often than if they were unlinked.

Linkage disequilibrium

- It manifests as a deviation of observed haplotype frequencies from the frequencies expected under the assumption that alleles at the 2 loci associate independently.

- It is a fundamental concept in population genetics; important in genetic association mapping and detection of natural selection.

Adaptive introgression

- High local LD can indicate an allele that has recently increased to high frequency under strong selection

- A telltale signature of adaptive introgression is the presence of mutations in strong Linkage Disequilibrium that exist at high frequency in a particular population and that are only present in the archaic source population, while absent or at very low frequencies in other present-day human populations.

- For example, a set of 5 such mutations cluster tightly together in the *EPAS1* (endothelial PAS domain protein 1) region in Tibetans, suggesting archaic adaptive introgression has occurred

Adaptive introgression

- If an introgressed variant is associated with a phenotype known to confer an advantage to a particular population, the variant may have undergone selection in that population.

- For example, the introgressed *EPAS1* gene in Tibetans contains SNP variants associated with statistically significantly reduced hemoglobin levels, which served as an adaptation to high-altitude hypoxia

Modern humans lost DNA when they left Africa—but mating with Neandertals brought some back to them

- When Neandertals mated with modern humans, they shared more than an intimate moment and their own DNA.

- They also gave back to MHs thousands of ancient African gene variants that Eurasians had lost when their ancestors swept out of Africa in small bands, perhaps 60,000 to 80,000 years ago.

Ann Gibbons, 2017

African DNA brought by N DNA into MHs

- The ancient African variants were found when the genomes of more than 20,000 people in the 1000 Genomes Project and Vanderbilt's BioVU data bank of electronic health records.

- They soon noticed a strange pattern: Stretches of chromosomes inherited from Neandertals also carried ancient alleles, or mutations, found in all the Africans they studied, including the Yoruba, Esan, and Mende peoples.

- The researchers found 47,261 of these single-base changes across the genomes of Europeans and 56,497 in Asians.

African DNA brought by N DNA into MHs

- In Eurasians these alleles are only found next to Neandertal genes, suggesting all this DNA was inherited at the same time, when the ancestors of today's Eurasians mated with Neandertals roughly 50,000 years ago.

- The most parsimonious explanation is that these alleles represent the ancestral human condition, inherited by both Neandertals and modern humans in Africa from their common ancestor.

African ancestral DNA

- When MHs migrated out of Africa, their small numbers resulted in a bottleneck, in which they lost many alleles that remained in larger populations in Africa.

- Later, the Neandertals reintroduced these alleles—along with distinct Neandertal genes—to the ancestors of Eurasians.

- Neandertals brought back some of the lost ancestral genetic variance to modern humans

N vs MH genes

- Geneticist Joshua Akey examined gene activity of more than 700 genes in which at least one person carried a MH and a Neandertal version of the gene.

- Human versions of some genes are more active than Neandertal versions, especially in the brain and testes. In other tissues, some Neandertal versions of genes were more active than their human counterparts.

- In the brain, human versions were favored over Neandertal variants in the cerebellum and basal ganglia. That finding may help explain why Neandertals had proportionally smaller cerebellums than humans do.

R.C. McCoy et al. *Cell*. Vol. 168, 2017,

N vs MH genes

- Neandertal versions of genes in the testes, including some needed for sperm function, were less active than human varieties.
- That finding is consistent with earlier studies that suggested male human-Neandertal hybrids may have been infertile.

- But Neandertal genes don't always lose. In particular, the Neandertal version of an immunity gene called *TLR1* is more active than the human version.

- Lopsided gene activity may help explain why carrying Neandertal versions of some genes has been linked to human diseases

Candidates for adaptive introgression of N genes

- Immunity genes
- Pigmentation
- Keratin
- Metabolism
- Height
- Denisovan - Altitude adaptation

Peaks of archaic ancestry

- *HYAL2* helps cells respond to ultraviolet radiation and is found in roughly 50% of East Asians. = N
- *TLR* genes help the immune system detect bacteria, fungi and parasites. = N, D
- *STAT2* affects the immune system. It's found in about 5% of Eurasians and 54% of Papuans. = N
- *POU2F3* affects skin cells known as kératinocytes and is in two-thirds of East Asians. = N
- *BNC2* is linked to freckling and skin pigmentation. It's found in about 70% of Europeans but few Asians. = N; at 30 K, only 2% carried it
- *EPAS1* helps Tibetans survive in low-oxygen environments = D

Immunity

- Viral challenges, bacterial challenges are among the strongest selective forces out there.

- Unlike changes in other environmental conditions such as daylight patterns and UV exposure, pathogens can kill you in one generation.

- Certain human leukocyte antigen (HLA) alleles, key players in pathogen recognition, held signs of archaic ancestry—from Neanderthals, and from the Denisovans

Immunity contribution

- Regions of our genome involving our bodies' interaction with the environment, such as the immune system, are the most likely targets of adaptive introgression

- Neanderthals were better adapted to the pathogens present in non-African environments than anatomically modern humans that had newly moved into these regions.

- Immunity genes: MHs had many rare variations of HLA genes; N HLA genes added more diversity to immune system

Kay Prüfer, et al., *Nature, 2013*

N Immunity genes

- Possibility that introgressed Neanderthal alleles may have contributed to the Denisovan functional variation at the HLA and the CRISP cluster, which are involved in immunity and sperm function, respectively.
- HLA alleles from Neanderthals and Denisovans have been of functional relevance in modern humans.
- N defense against pathogens
  - STAT2 is an innate immune gene that is involved in interferon response after viral infection from Ns
  - The highly polymorphic human leukocyte antigen (*HLA*) region in chromosome 6

Neandertal HLA

- It has been found that a variety of genes (HLA-A*02, A*26/*66, B*07, B*51, C*07:02, & C*16:02) of the immune system were contributed from Neanderthals to modern humans.

- Archaic alleles contribute proportionally more to variation in expression than nonarchaic alleles.

- Neanderthal alleles affect expression of the immunologically genes OAS1/2/3 and TLR1/6/10

Ns gave us innate immune genes via natural selection

- The oligoadenylate synthetase (OAS) locus, which consists of three genes—*OAS1, OAS2,* and *OAS3*—that encode enzymes involved in the innate immune response against viruses.

- Neandertal haplotype at the OAS locus was subjected to positive selection in the human population.

- Neandertal-introgressed haplotype likely reintroduced an ancestral variant of *OAS1* encoding a more active protein.

A. Sams, et al., 2016

N immune genes in MHs

- *OAS* Neanderthal allele is found in about 60 percent of individuals in Africa.

- Outside of Africa, it is only found in individuals that harbor the Neanderthal haplotype.

- This allele was lost during the out-of-Africa migration and that the Neanderthal haplotype resurrected this allele after the bottleneck following the human migration out of Africa.

Denisovan DNA: Toll receptors, adipose genes

- Regions of MH DNA that are significantly depleted of Denisovan DNA; these “deserts” were the same ones that lacked Neanderthal sequences—indications of selection against deleterious variants
- Denisovan DNA has toll-like receptors, similar to those found with Neanderthal variants.
- Denisovan variants in the genomes of Greenland Inuits that include genes involved in the development and distribution of adipose tissue, perhaps pointing to advantages in cold tolerance and metabolism.

N DNA in MHs

- Neanderthal variants alter expression levels of genes encoding toll-like receptors (TLRs) = key players in innate immune responses.
- Both response to pathogens and susceptibility to developing allergies are associated with Neanderthal TLR production.
- One-third of Neanderthal variants, under positive selection, are linked to genes encoding proteins that interact with viruses

N DNA and Covid

- N genomic regions associated both with increased risk and also protection against severe COVID-19

- The major genetic risk factor associated with becoming severely ill with COVID-19 when infected by severe acute respiratory syndrome SARS-CoV-2 is inherited from Neandertals.

Hugo Zeberg and Svante Pääbo, 2022

Covid-19

- After age, N variant is strongest risk factor for severe response to COVID-19 = 10% of deaths

- A Neandertal haplotype in a region on chromosome 3 is associated with becoming critically ill upon infection with Covid 19. Each copy of this haplotype approximately doubles the risk of its carriers requiring intensive care.

N Covid variant (rs35044562): positively selected for only in SE Asia, where it had some unknown positive ef

Protection vs Covid via N haplotype

- New data: A 75-kb Neandertal haplotype is protective against severe disease.
- Occurs at substantial frequencies in all regions of the world outside Africa.
- The frequency of the protective Neandertal haplotype may have increased between 20,000 and 10,000 y ago and again during the past 1,000 yrs.
- This is a N OAS haplotype on chromosome 12 (rs10735079), which is associated with a ~22% reduction in relative risk of becoming severely ill with COVID-19 when infected by SARS-CoV-2

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

- Some introgression 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.

Hugo Zeberg, 2022

N genes = double-edged sword

- 2 - The major genetic risk factor for severe COVID-19 is also associated with protection against HIV -- can reduce the chances of infection by the HIV virus by 27%
  - this genetic variant has had tragic consequences during the last 2 y in the COVID-19 pandemic,
  - offered considerable protection against HIV during the last 40 years. Its role in past and future pandemics remains to be seen.

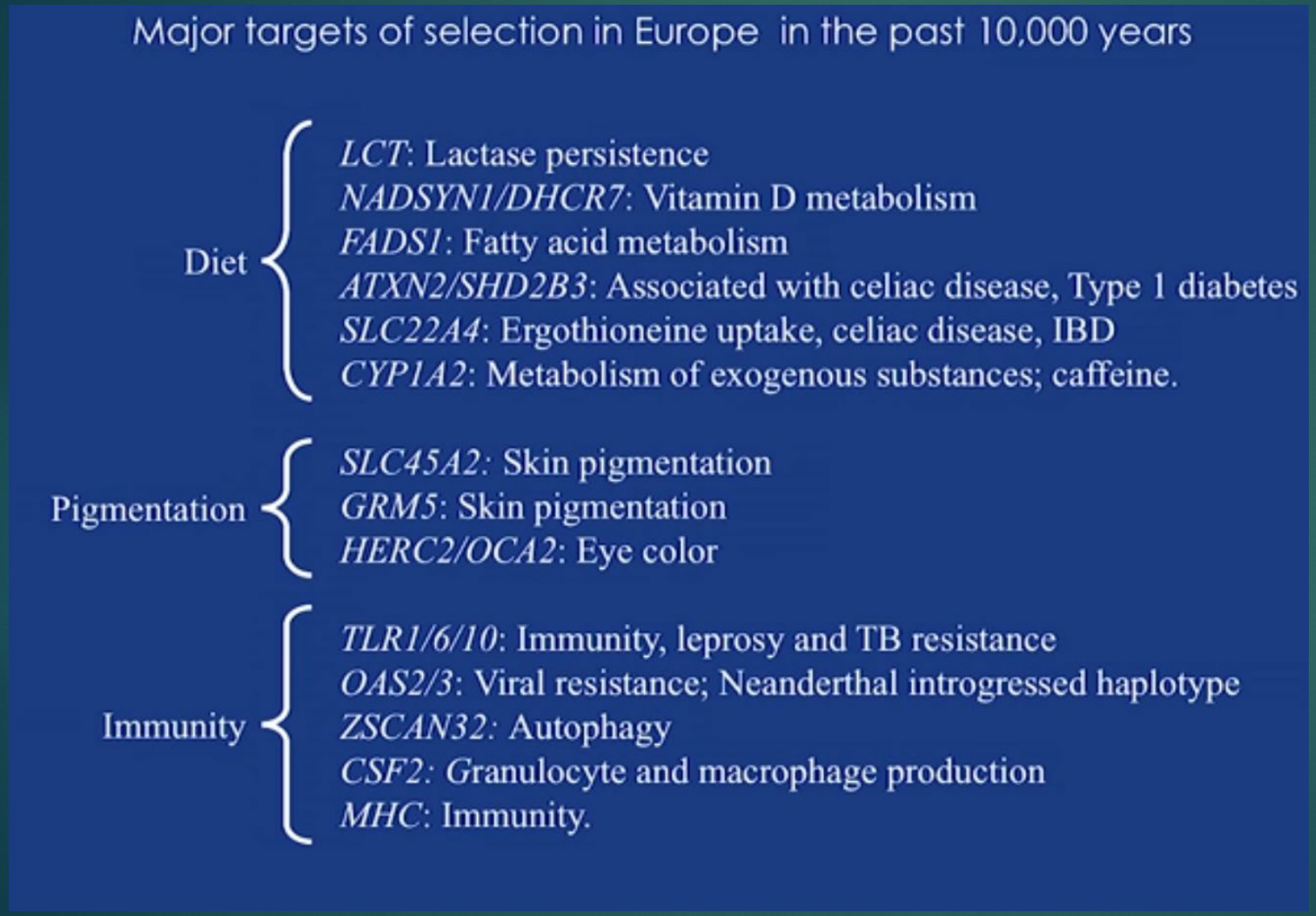
N OAS haplotype: anti-RNA viruses

- A Neandertal haplotype on chromosome 12 is protective for severe disease in the current SARS-CoV-2 pandemic.
  - present in populations in Eurasia and the Americas at carrier frequencies that reach 50%.

- The ancestral Neandertal OAS locus variants may thus have been advantageous to modern humans throughout Eurasia, perhaps due to one or many epidemics involving RNA viruses,

- Neandertal haplotype has been found to be protective for at least three RNA viruses (West Nile virus, hepatitis C virus, SARS-CoV).

3 main groupings of selected genes in Europe in last 10 K years



- Diet = Related to new agriculture usage
- Pigmentation = Movement to more northern latitudes
- Immunity = Movement into denser populations, closer exposure to domesticated animals

Genetic adaptation took awhile

- Neanderthal introgression contributed to adaptive immune variants in MHs

- These N adaptive immune variants were only selected 10 K ago not when introgressed 40 Ka

- Immunity:
- *TLR1/6/10:* Immunity, leprosy and TB resistance
- *OAS2/3*: Viral resistance; Neanderthal introgressed haplotype

Microcephalin and Archaic Hominins: Did Ns contribute this gene to MHS

Microcephalin and Archaic Hominins

- The microcephalin gene relates to brain size during development.
- A mutation in the microcephalin gene, MCPH1, is a common cause of microcephaly. Mutations in microcephalin cause the brain to be 3 to 4 times smaller in size.
- A variant of MCPH1, haplogroup D, may have been positively selected for in modern humans – and may also have come from an interbreeding event with an archaic population.
- All of the haplogroup D variants come from a single copy that appeared in modern humans around 37,000 years ago.
- However, haplogroup D itself came from a lineage that had diverged from the lineage that led to modern humans around 1.1 million years ago.

Microcephalin: example of difficulty of sourcing origination

- Evans et al. (2006) had previously suggested that a group of alleles collectively known as haplogroup D of microcephalin, a critical regulatory gene for brain volume, originated from an archaic human population.
- The high frequency of the D haplogroup (70%) suggest that it was positively selected for in modern humans.
- The distribution of the D allele of microcephalin is high outside Africa but low in sub-Saharan Africa, which further suggest that the admixture event happened in archaic Eurasian populations.
- There was speculation that the Neanderthals were the source of the microcephalin haplogroup D (Evans et al. 2006),

Microcephalin

- Distribution difference between Africa and Eurasia suggests that the D allele originated from Neanderthals, but they found that a Neanderthal individual from the Mezzena Rockshelter (Monti Lessini, Italy) was homozygous for an ancestral allele of microcephalin, thus providing no support that Neanderthals contributed the D allele to modern humans and also not excluding the possibility of a Neanderthal origin of the D allele.
- Green et al. (2010), having analyzed the Vindija Neanderthals, also could not confirm a Neanderthal origin of haplogroup D of the microcephalin gene.

Chromosome 8: microencepalin gene, not N

- Old gene: originating 1.1 Ma; found mostly out of Africa

*** Pigmentation & Skin

Skin – Nina Jablonski

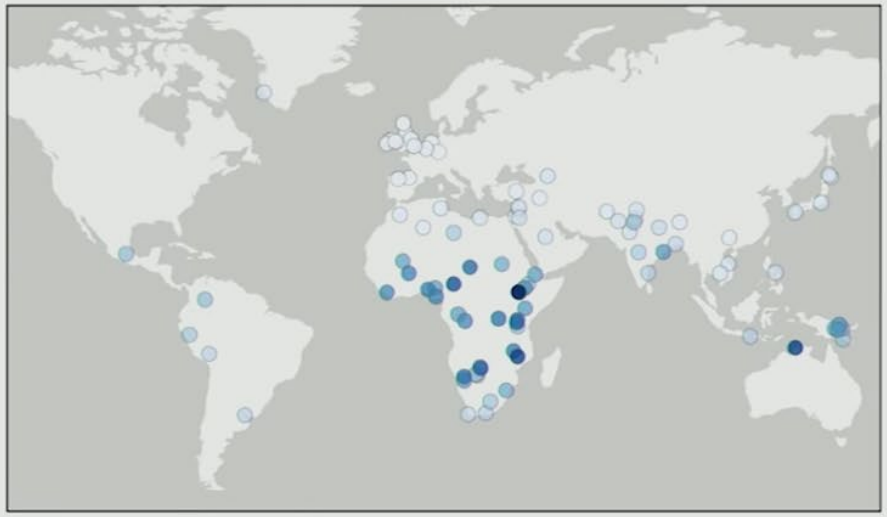
- Naked skin is hallmark of *Homo*, as is sweat to liberate heat
- Naked skin in *Homo* from 2 M years
- Genome indicates most difference between chimps and us is in epidermis of our skin

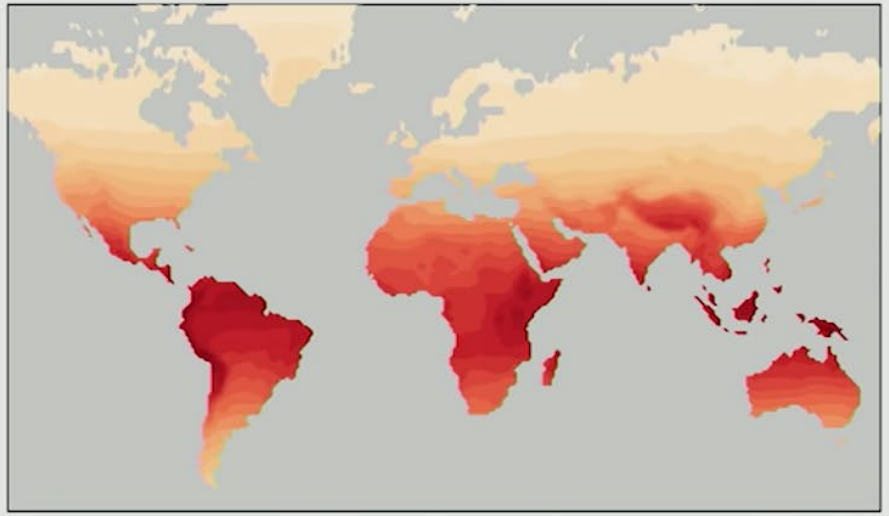
- Common ancestor had lightly pigmented skin & dark hair
- At 2 Ma, less hair & darker pigmentation

Living Color: The Biological and Social Meaning of Skin Color by Nina G. Jablonski

When the genus Homo moved from the trees to the savannah there would have been selectio
to become darkly pigmented

Skin Color is an Adaptive Trait





- **High Latitudes** – Pale Skin – Vitamin D
- **Low Latitudes** – Dark Skin – Cancer, Folate
- The majority of genetic studies are in European populations
- Little is known about the genetics of skin color in African populations

Skin Color: not march of progress, not racial

- The history of human skin color clearly illustrates that evolution is not a march of "progress" towards any particular end.
- Our earliest human ancestors in Africa probably had light skin (just as chimpanzees do underneath their fur).
- As these ancestors moved from forests to the open savannah and evolved reduced hair covering, natural selection favored gene variants for darker skin and protection from sun damage — but this was not a uniform process purging all "light" gene versions out of existence.
- This ancestral population still had a lot of genetic variation for a range of skin tones, even if the ones producing darker skin were more common.

Skin color

- Different gene versions rose to high frequency in different populations according to the balance between selection favoring UV protection and selection favoring vitamin D production.

- Several different groups evolved lighter skin as ancient gene versions for this trait were favored (e.g., in Europeans) — at least one of these gene versions made it *back* to Africa where it became common among the KhoeSan.

Multicolored skin species

- Sun protection: dark skin at equator – very high levels of UVR in Africa; dark skin (melanin/eumelanin pigment as sunscreen) as protection
- All MHs at 80-10 KA were dark skinned
- But with migration to higher altitudes, need Vitamin D from UVB; evolutionary compromise of skin depigmentation
- Multiple genes that contribute to same dark phenotype
- Skin color developed independent of other phenotype characteristics; not a unique marker of group or racial identity

Loci associated with skin pigmentation identified in African populations, N. Crawford, et al., 2017

- Variation in pigmentation among human populations may reflect local adaptation to regional light environments, because
  - dark skin is more photoprotective,
  - whereas pale skin aids the production of vitamin D.

- Populations at lower latitudes have darker pigmentation than those at higher latitudes, suggesting that skin pigmentation is an adaptation to differing levels of ultraviolet radiation (UVR).

Pigmentation

- Because equatorial regions receive more UVR than temperate regions, populations from these regions (including sub-Saharan Africans, South Asians, and Australo-Melanesians) have darker pigmentation, which likely mitigates the negative impact of high UVR exposure, such as skin cancer and folate degradation.
- In contrast, the synthesis of vitamin D3 in response to UVR, needed to prevent rickets, may drive selection for light pigmentation at high latitudes.

Skin color of Europeans

- The original hunter-gatherers, descendants of people who had come from Africa, had dark skin as recently as 9,000 years ago.
- Farmers arriving from Anatolia were lighter, and this trait spread through Europe.
- Later, a new gene variant emerged that lightened European skin even more.

Iain Mathieson, et al., 2015

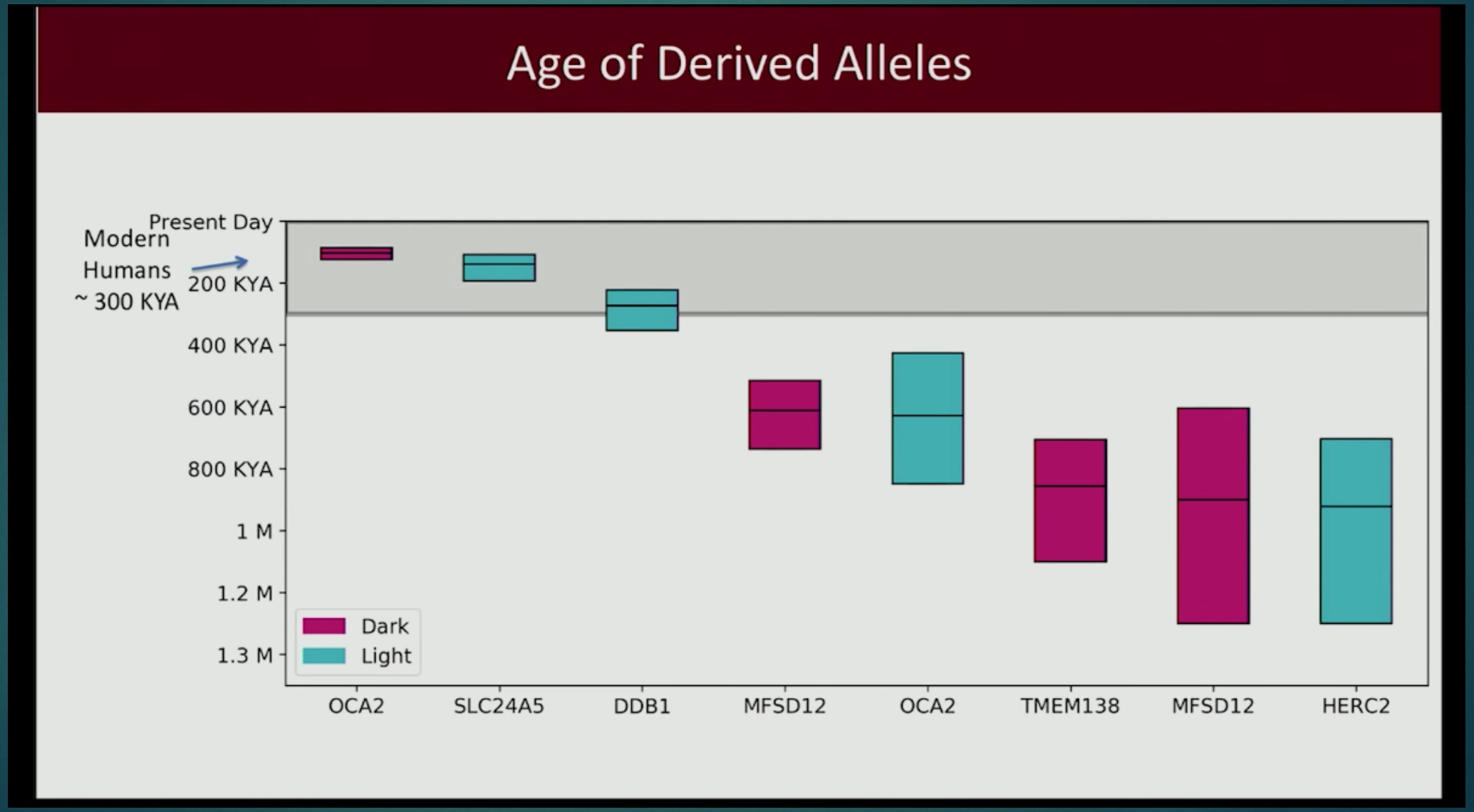
Skin

- Why? Scientists have long thought that light skin helped capture more vitamin D in sunlight at high latitudes.

- But early hunter-gatherers managed well with dark skin. Dr. Reich suggests that they got enough vitamin D in the meat they caught.

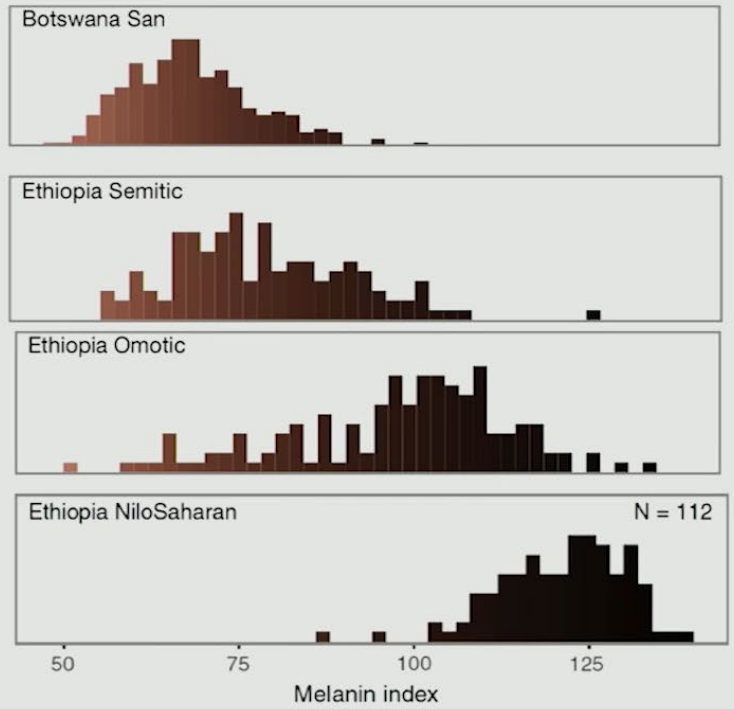
- He hypothesizes that it was the shift to agriculture, which reduced the intake of vitamin D, that may have triggered a change in skin color.

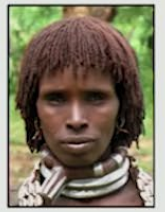
Light genes are ancestral in Africa; there are both light and dark genes in African; chimps skin is light



Oldest genetic San are the lightest pigmented in Africa; darkest are pastoralists who originated from South Sudan

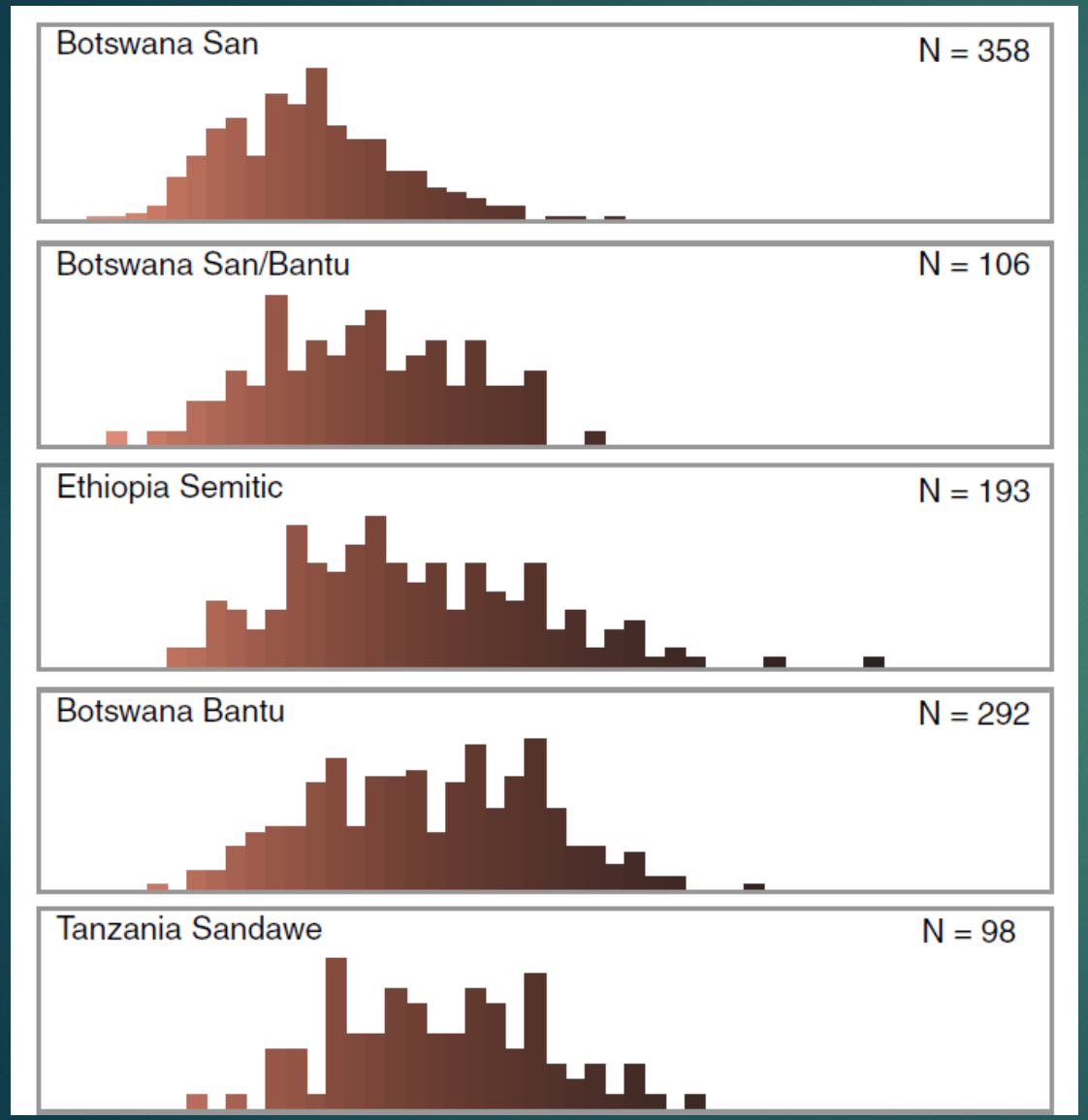
Field Work and Phenotyping

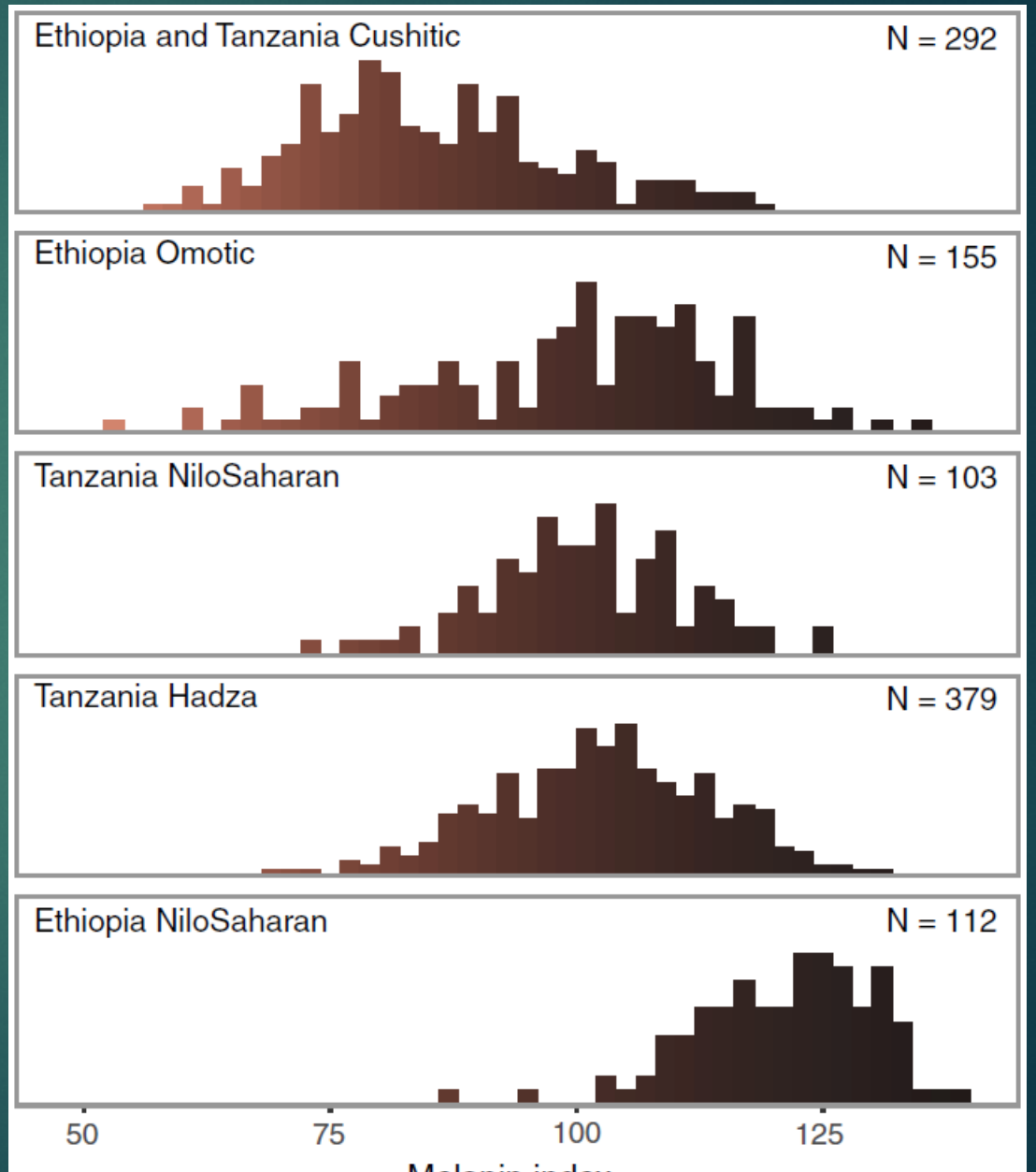




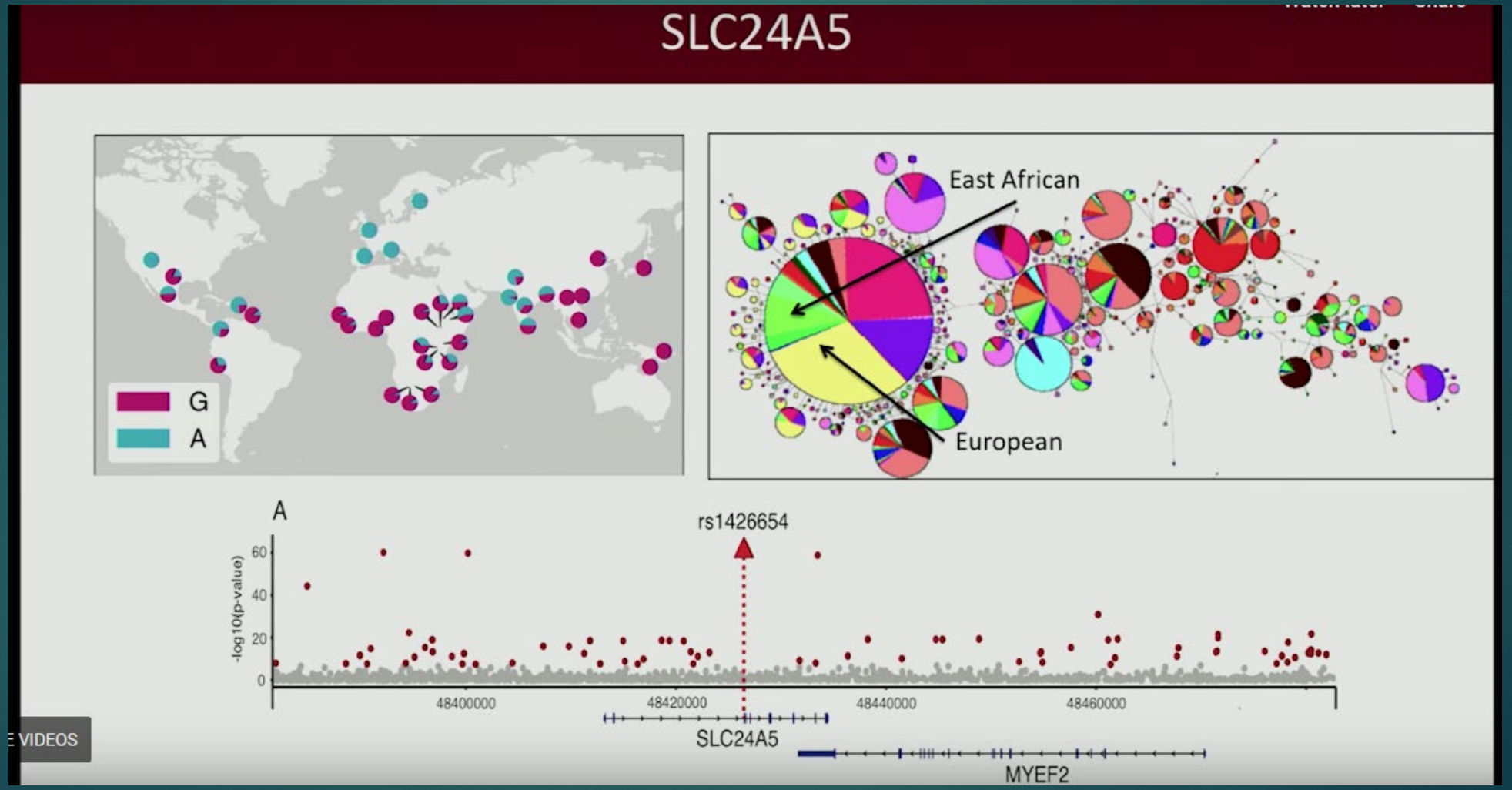
Crawford et al., *Science*, 2017

Melanin distribution in Africa: Many colors

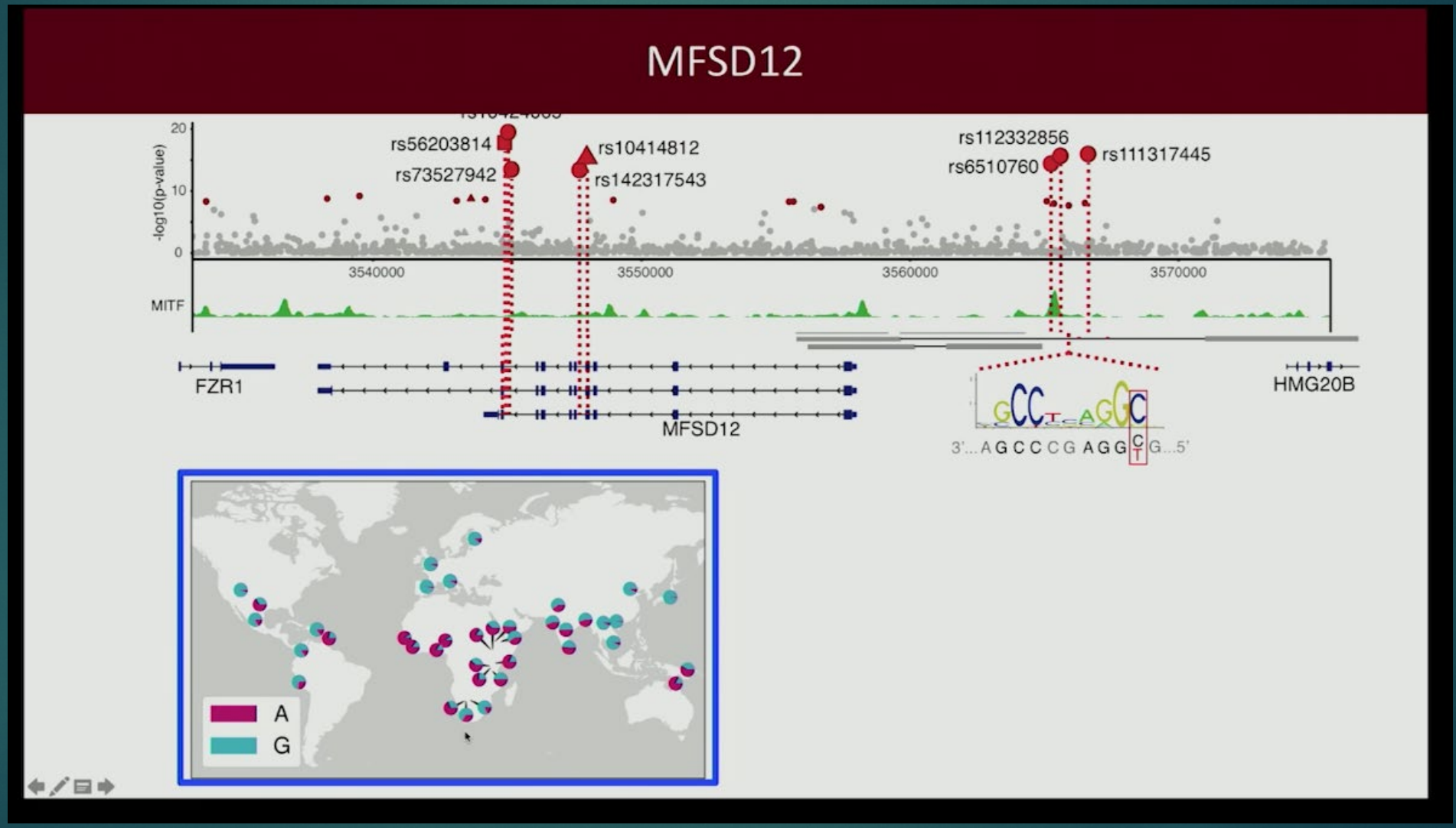




SLC24A5: number 1 gene for light skin coloration; dominant in Europe; in East Africa via introduction from Europe



MFSD12: 2nd most powerful light skin gene: 100% dominance in Europe, East Asia, and in San



Pigmentation

- The newer *SLC24A5* allele was introduced to Europe at high frequency by the Anatolian Neolithic migration, while the newer *SLC45A2* allele was introduced at lower frequency and subsequently selected.

- Both of these alleles are now virtually fixed in Europe.

Pigmentation: lighter in last 5 Ka

- Specific combination of pigmentation alleles that is common in western Europe today is relatively recent and reached its current high frequency only within the past 5,000 years.

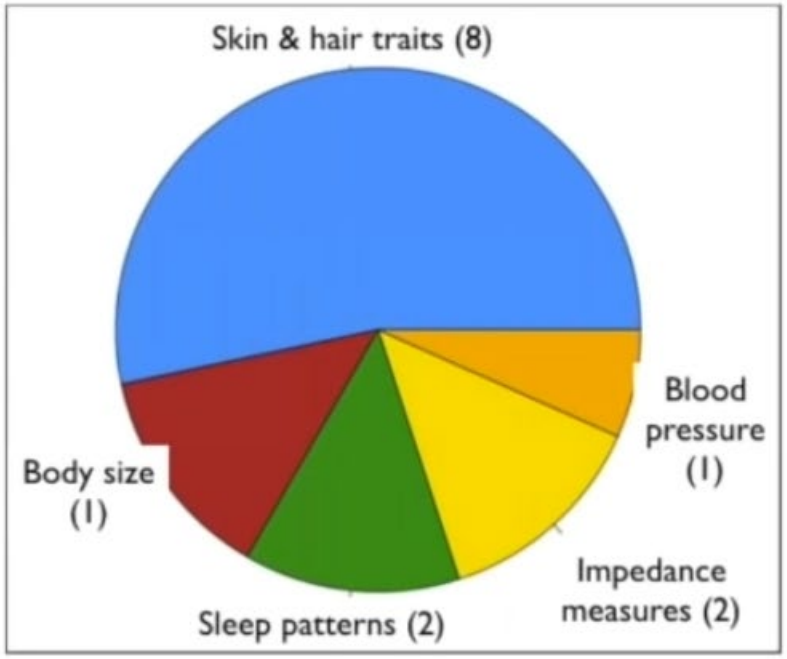
- Similarly, signals of selection in southern Africa in the past 2,000 years may also be linked to relatively recent changes in pigmentation.

Pigmentation: light eye color

- The derived light eye color allele is first seen in hunter–gatherers from present-day Italy and Georgia around 13 to 14 Ka and appears to have become almost fixed in parts of northern and western Europe by around 8 Ka.

- This rapid increase in frequency seems likely to have been driven by selection.

Traits associated with introgressed N variants



Phenotype	Overlapping gene(s)	Association P-value
Natural hair color	*SPIRE2, TCF25, MC1R, TUBB3, FANCA*	4E-202
Skin color	*RUNX2*	4E-30
Ease of skin tanning	*BNC2*	2E-22
Natural hair color	*SLC24A4*	5E-21
Skin color	*BNC2**	2E-14
Comparative height at age 10	*ZNF536*	4E-14
Pulse rate, automated reading	*GJA1**	6E-14
Morning/evening person	*ASB1*	4E-10
Skin color	*CHORDC1**	6E-10
Impedance of leg (left)	*ADAMTSL3, GOLGA6L4*	1E-09
Childhood sunburn occasions	*BNC2*	1E-09
Sitting height	*PBLD*	2E-09
Natural hair color	*EXOC2*	3E-09
Daytime dozing / sleeping	*EXOC6*	4E-09
Impedance of leg (right)	*ADAMTSL3, GOLGA6L4*	6E-09

50% of N variants = Skin & hair traits, esp. pigmentation

N variants and MH phenotype traits: skin, hair,

- Phenotype Overlapping gene(s)
- Natural hair color *SPIRE2. TCF25. UC1R TUBQ3. FANCA*
- Skin color *RUNX2*
- Skin tanning *BNC2*
- Natural hair color *SIC 24 A 4*
- Skin color *BNC2-*
- Height at age 10 *ZNF536*
- Pulse rate, *GJAV*
- Morning/evening person *ASB1*

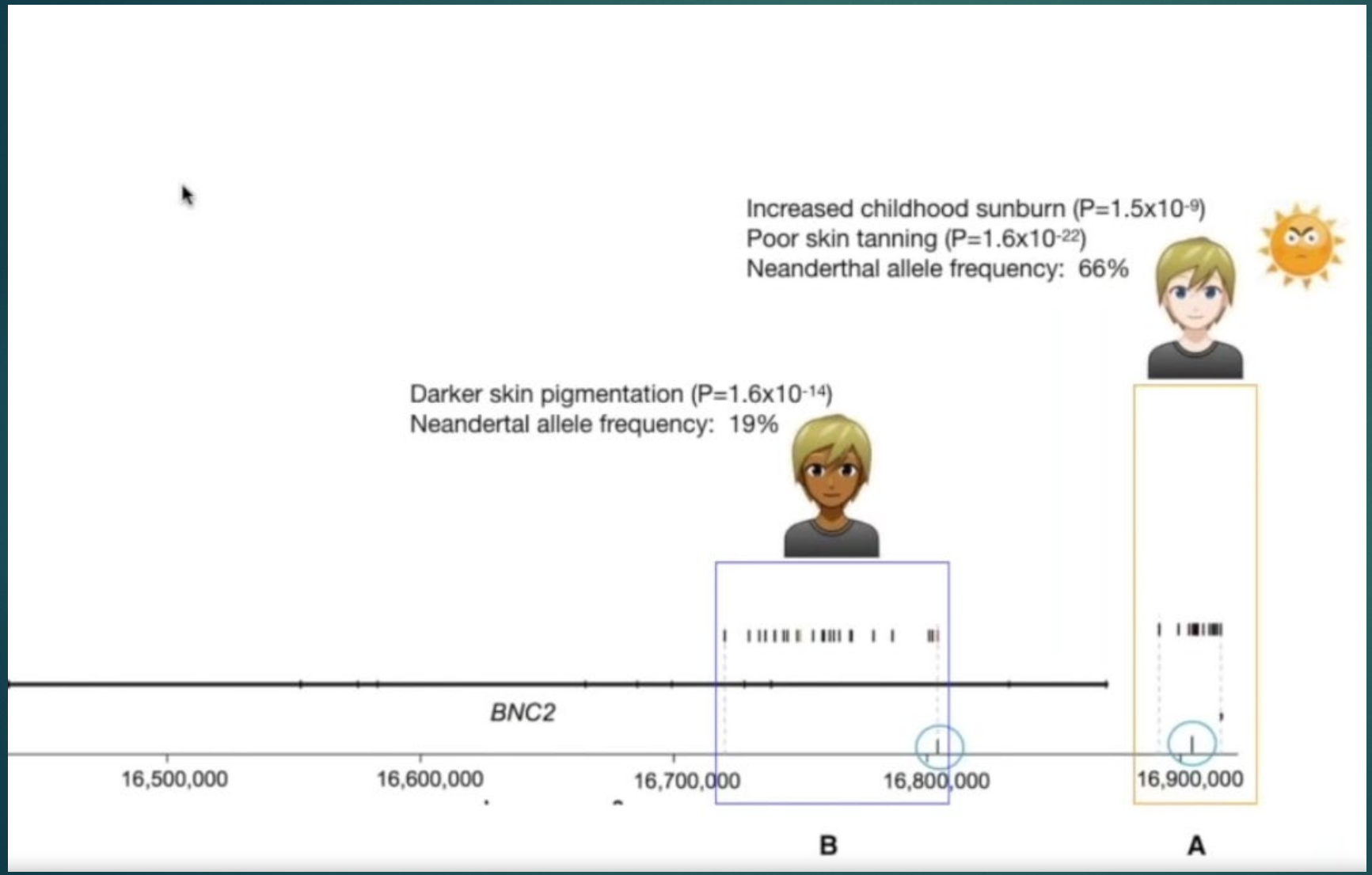
Phenotype	Overlapping gene(s)
Skin color	*CHORDCV*
Impedance of leg (left)	*ADAMTSL3, GOLGA6L4*
Childhood sunburn occasions	*BNC2*
Sitting height	*PBLD*
Natural hair color	*EXOC2*
Daytime dozing / sleeping	*EXOC6*
Impedance of leg (right)	*ADAMTSL3, GOLGA6L4*

N genetic inheritance: fair skin, straight hair

Candidates for adaptive introgression

On chromosome 3, there is a 200kb haplotype of Neanderthal origin that has a high frequency (> 49%) in the East Asian; *HYAL2*, involved in the cellular response to ultraviolet radiation; adaptive response to ultraviolet radiation as modern humans expanded throughout Asia

2 Archaic haplotypes at BNC2 influence skin color and the effects of sun exposure



1 N fair skin variant, is among highest N allele present in modern Europeans, at 66%; but absent in Asians:

Produce more sunburn, poor tanning, skin keratin lesions to sun exposure

2 N olive skin variant = 20 %

N functional variants: hair and skin

- Three N genes in the small set of adaptively introgressed loci that play important roles in hair and skin biology.

- One of these genes, BNC2, from Ns. is associated with skin pigmentation and freckling in Europeans, and this archaic haplotype is present at 70% frequency in Europeans, while it is absent in Asians

- People who carried Neanderthal DNA there tended to have pale skin that burned instead of tanned.

Red-haired Neandertals?

Red Hair color

- Original theory: Ancient DNA Reveals Neandertals With Red Hair, Fair Complexions
- A pigmentation gene from the bones of two Neandertals, indicates that at least some Neandertals had pale skin and red hair, similar to some of the *Homo sapiens* who today inhabit their European homeland.

Red Headed Neandertals

- Original 2007 theory: aDNA reveals Neandertals with red hair, fair complexions

- A fragment of the gene for the melanocortin 1 receptor (MRC1) was sequenced using DNA from two Neanderthal specimens from Spain and Italy, El Sidrón 1252 and Monte Lessini

- Modern humans have other MCR1 variants that are also less active resulting in red hair and pale skin. The less active Neanderthal mutation probably also resulted in red hair and pale skin, as in modern humans.

(Lalueza-Fox et al. 2007).

What did we get from Ns

- Red hair:
- MH MC1R gene for red hair in MHs.

- Gene *MC1R* encodes a melanocyte stimulating hormone receptor. This gene is known to affect hair color and is associated with red hair, freckles and fair skin type in MHs

- Ns have different red hair MC1R gene; none of the dozen light pigmentation genes in MH (developed in last 20K) are N

Red hair

- No modern human has the exact mutation that Neanderthals had, which means that both Neanderthals and humans evolved this phenotype independent of each other.

- Most modern redheads are from more recent genetic mutations; but a few modern redheads do have the rare N genes for this

N variants

- The genetic variant of the MC1R gene which was originally linked to red hair in Neanderthals is not found in Europeans but in Taiwanese Aborigines at 70% frequency and at somewhat high frequencies in East Asians;

- There is actually no evidence that Neanderthals had red hair.

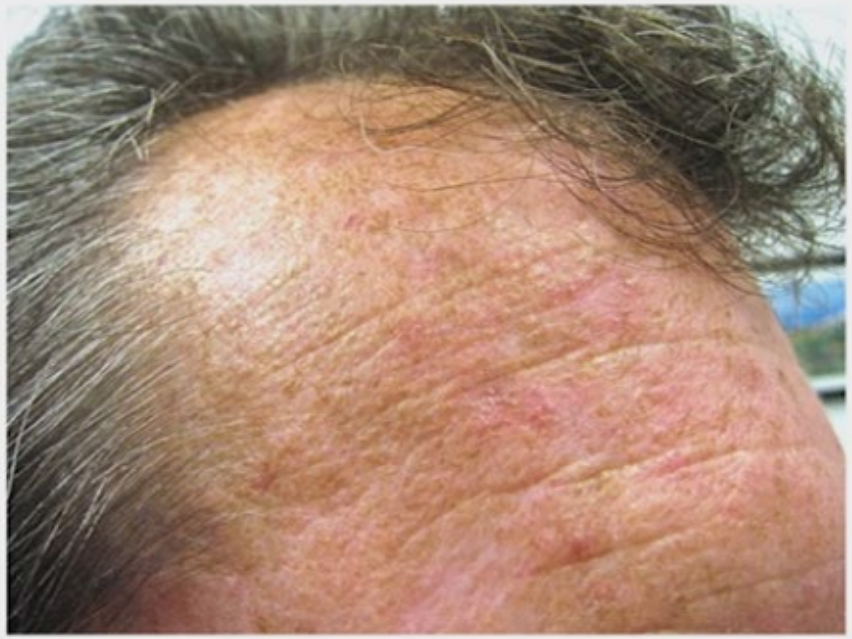
Skin: Keratin

- Adaptive introgression signal in a cluster of keratin genes on chromosome 12 in both Asians and Europeans: some skin conditions (variation in Keratin in skin & hair (several alleles); skin lesions resulting from sun exposure (actinic keratosis)

- Association between Neanderthal ancestry and two types of noncancerous skin growths associated with dysfunctional keratinocyte biology—supporting the idea that the Neanderthal DNA was at one point selected for its effects on skin.

- Keratin filaments: hair type variety; N Keratin genes are more common in MHs; do not know how connected to phenotype

Actinic Keratosis



- Caused by malfunctioning keratinocytes
- Keratinocytes protect skin from UV radiation
- Involved in early immune system response

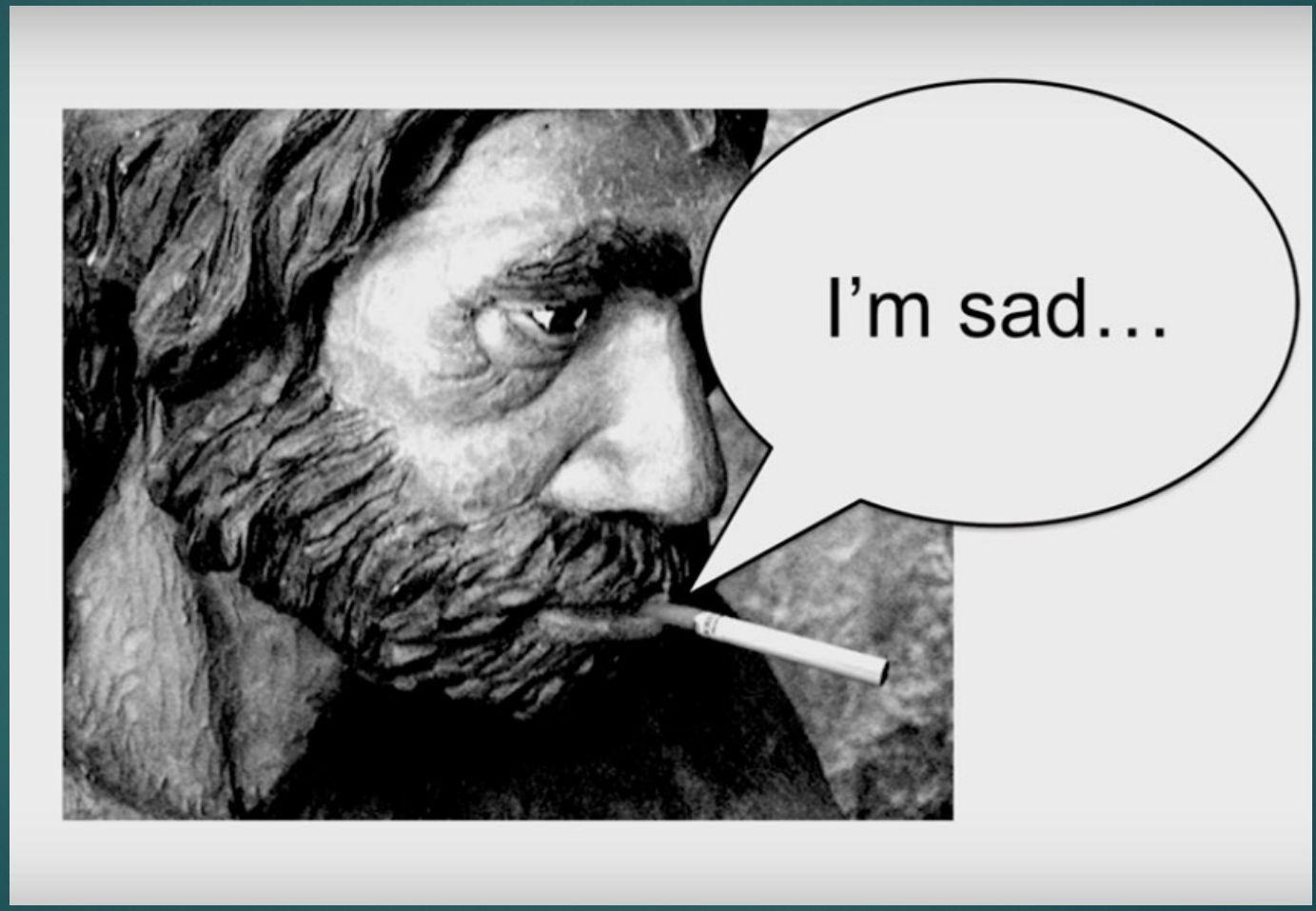
Neanderthal DNA collectively influences clinical traits

Phenotype	System	Risk Explained
Actinic keratosis	Skin	~2.0%
Depression	Brain	~1.5%
Obesity	Metabolism	~0.9%
Seborrheic keratosis	Skin	~0.7%

Why?

We don’t know

Ns did not smoke. Depression?



Autism: a hanger-on

- Stretches of duplicated DNA, called copy-number variants.
- A deletion, which causes the loss of the segment's 28 genes, results in autism.
- Located at a region on chromosome 16 designated 16p11.2, first appeared in our ancestral genome about 280,000 years ago.
- This organization is not seen in any other primate – not chimps, gorillas, orangutans, nor in N or D genomes.
- Yet today it is found in genomes of humans the world over.

Autism

- A deletion, which causes the loss of the segment's 28 genes results in autism.
- The wide and rapid distribution of these copy-number variants suggests the genes within the repetitive sections confer benefit that outweigh the disadvantages that come with the increased risk of autism in some offspring, should deletion occur.
- Not in N DNA

Bitter Taste Gene

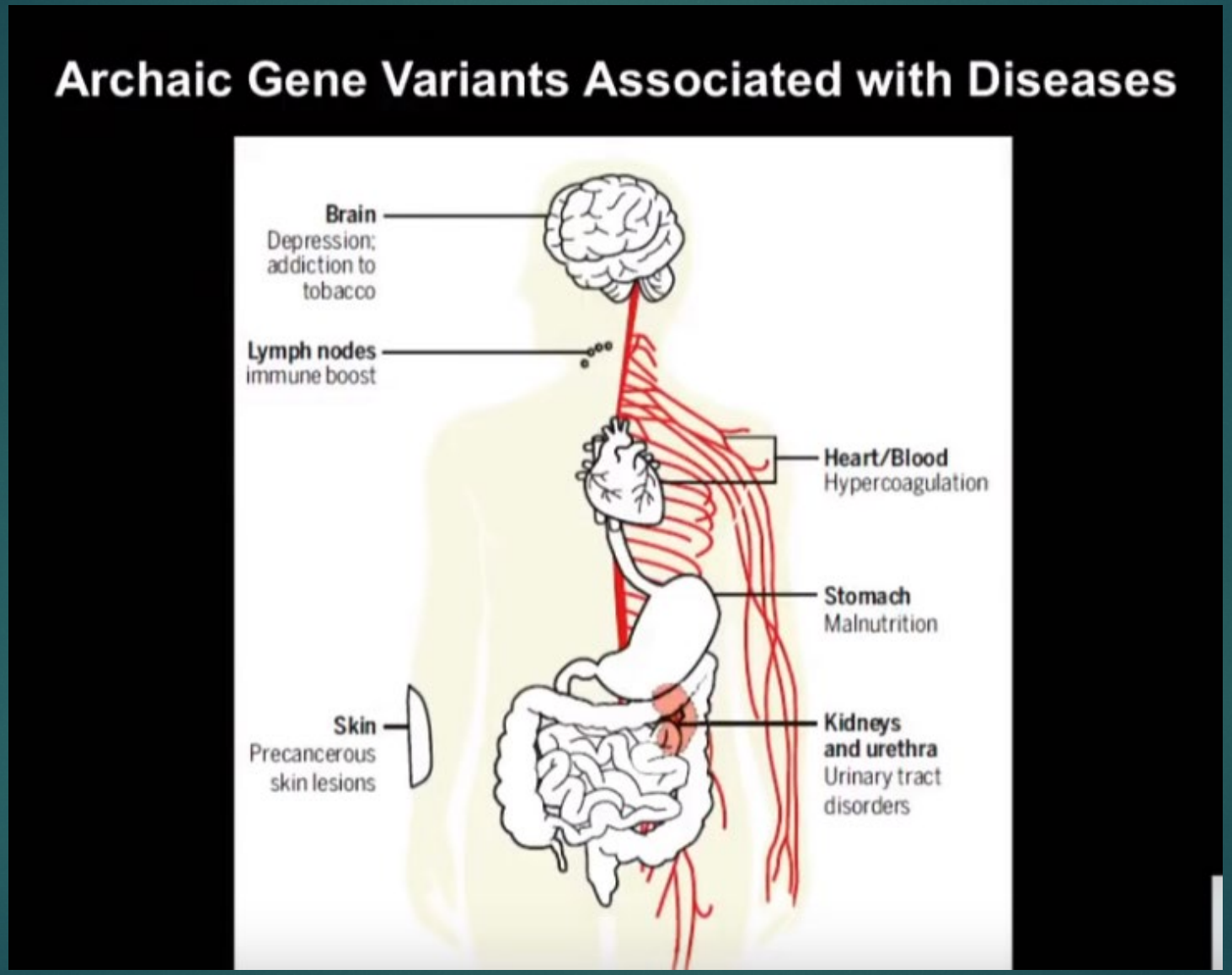
- MHs, Ns, Ds: lost two bitter taste genes, *TAS2R62* and *TAS2R64*, that are still present in chimpanzees; , so they were presumably able to eat a wider range of tuberous plants.

- Two million years ago, *Australopithecus* or early *Homo* likely found wild yams and other tubers bitter.

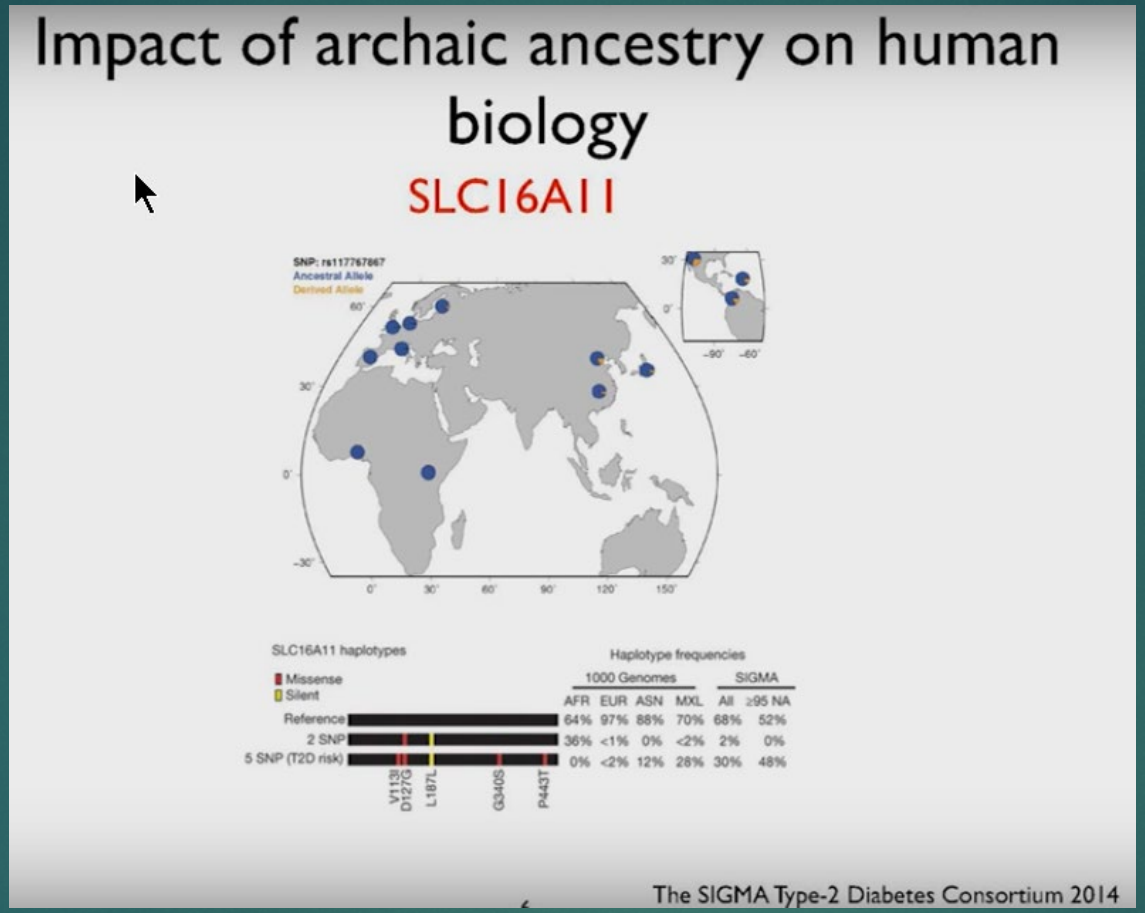
- Modern humans, Neandertals, and Denisovans all lost the ability to detect the bitter flavor in some wild plants and eventually modern humans bred varieties of squashes, gourds, and yams that are less bitter than the wild types.

**Neandertal genes are mostly disease related

Most N variants associated with diseases

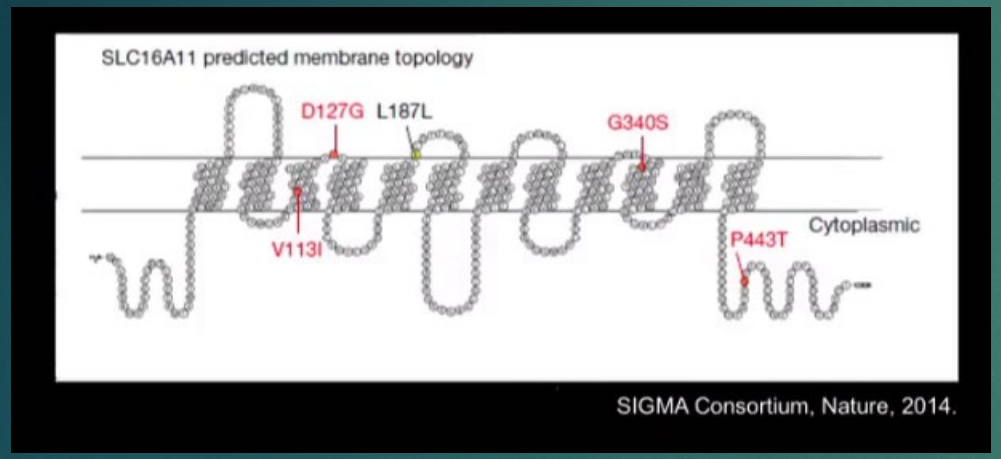


Type II DM in Mexican Americans: GWA study



Unique variance in SLC16A11 gene with unique distribution (high frequency in Americas, largely absent in Africa, and low frequency everywhere else; the DM variant originated in Ns

N functional contribution to MHs: Lipid Transport



- Lipid transport into cells: N variant associated with Type 2 Diabetes risk;
- In Ns, good during starvation; but bad if lot of food available;
- so likely a N adaptation to starvation

Akey: N and Diabetes

- Not all such archaic genes are beneficial:
  - Mayas in Mexico, some Native Americans, and about 25% of Asians
  - retain an allele from Neandertals that boosts their risk for Type 2 diabetes.

- Genes involved in fat synthesis (lipid catabolism, the breakdown of fats to release energy) held more than three times as many Neandertal sequences

- N Risk variant for Type 2 Diabetes: lipid transportation; Today, though, these fatty acids are also implicated in diseases that are part of the so-called "metabolic syndrome"

Lipid catabolism

- Don't see the same alleles in the Denisovans

- In Ns, good during starvation; better energy conservation; but bad if lot of food available; so likely a N adaptation to starvation

- Neanderthal DNA at various sites in the genome influences obesity and malnutrition, pointing to potential metabolic effects

2017: living footprint of *H. neanderthalensis:* N neural inheritance

- Amount of Neanderthal-originating polymorphism carried in living humans is related to cranial and brain morphology.

- Neanderthal skull morphology: N genetic load is biologically functional in modern-day humans.
  - The more a person's genome carries genetic vestiges of Neanderthals, the more certain parts of his or her brain and skull resemble those of N

Michael D. Gregory, et al., 2017

N allele variants

- Elongated vs round skulls: two Neanderthal gene variants linked to slightly less globular head shape in living people.

- MH infants start life with elongated skulls, somewhat like Neanderthals. It's only when the modern human brain nearly doubles in size in the first year of life that the skull becomes globular

NeanderScore

- A greater load of Neanderthal-derived genetic variants (higher "NeanderScore" = d statistic in genetics for admixture) is associated with skull shapes resembling those of known Neanderthal cranial remains, particularly in occipital and parietal bones.
- Anterior-posterior cranial length: significantly correlates with NeanderScore.
- NeanderScore positively correlated with an increase in sulcal depth in the right intraparietal sulcus;
- Greater Neanderthal SNP load correlated with more gray and white matter volume.

MH brain with N DNA

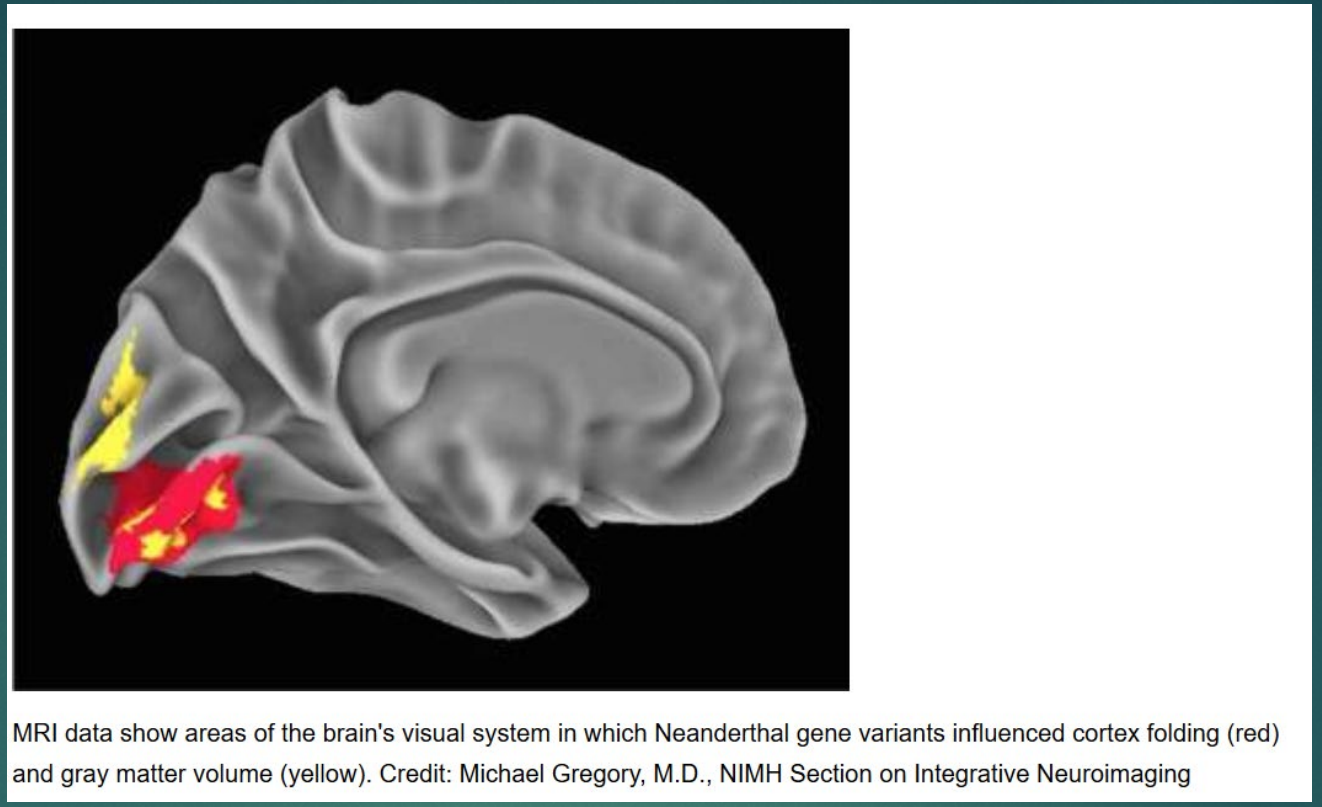
- Neanderthal admixture is associated with an expansion of the posterolateral area of the modern human skull, extending from the occipital and inferior parietal bones to bilateral temporal locales.

- Neanderthal admixture is positively correlated with an increase in sulcal depth for the right intraparietal sulcus and an increase in cortical complexity for the early visual cortex of the left hemisphere.

NeanderScore

- N score: increase in white and gray matter volume localized to the right parietal region adjacent to the right intraparietal sulcus.
- In the area overlapping the primary visual cortex gyrification in the left hemisphere, Neanderthal admixture is positively correlated with gray matter volume.
- The results also show evidence for a negative correlation between Neanderthal admixture and white matter volume in the orbitofrontal cortex.
- In Papuans, Neanderthal DNA is found in highest frequency in genes expressed in the brain, whereas Denisovan DNA has the highest frequency in genes expressed in bones and other tissues

N visual areas



MRI data show areas of the brain's visual system in which Neanderthal gene variants influenced cortex folding (red) and gray matter volume (yellow). Credit: Michael Gregory, M.D., NIMH Section on Integrative Neuroimaging

Increased gyrification in N visual areas

Neanderthals had more prominent visual systems than modern humans. It's been proposed that Neanderthals depended on visual-spatial abilities and toolmaking, for survival, more so than on the social affiliation and group activities that typify the success of modern humans—and that Neanderthal brains evolved to preferentially support these visuospatial functions. The new MRI evidence points to a gene variant shared by modern-day humans and Neanderthals that is likely involved in development of the brain's visual system.

** N variants and phenotypic effects

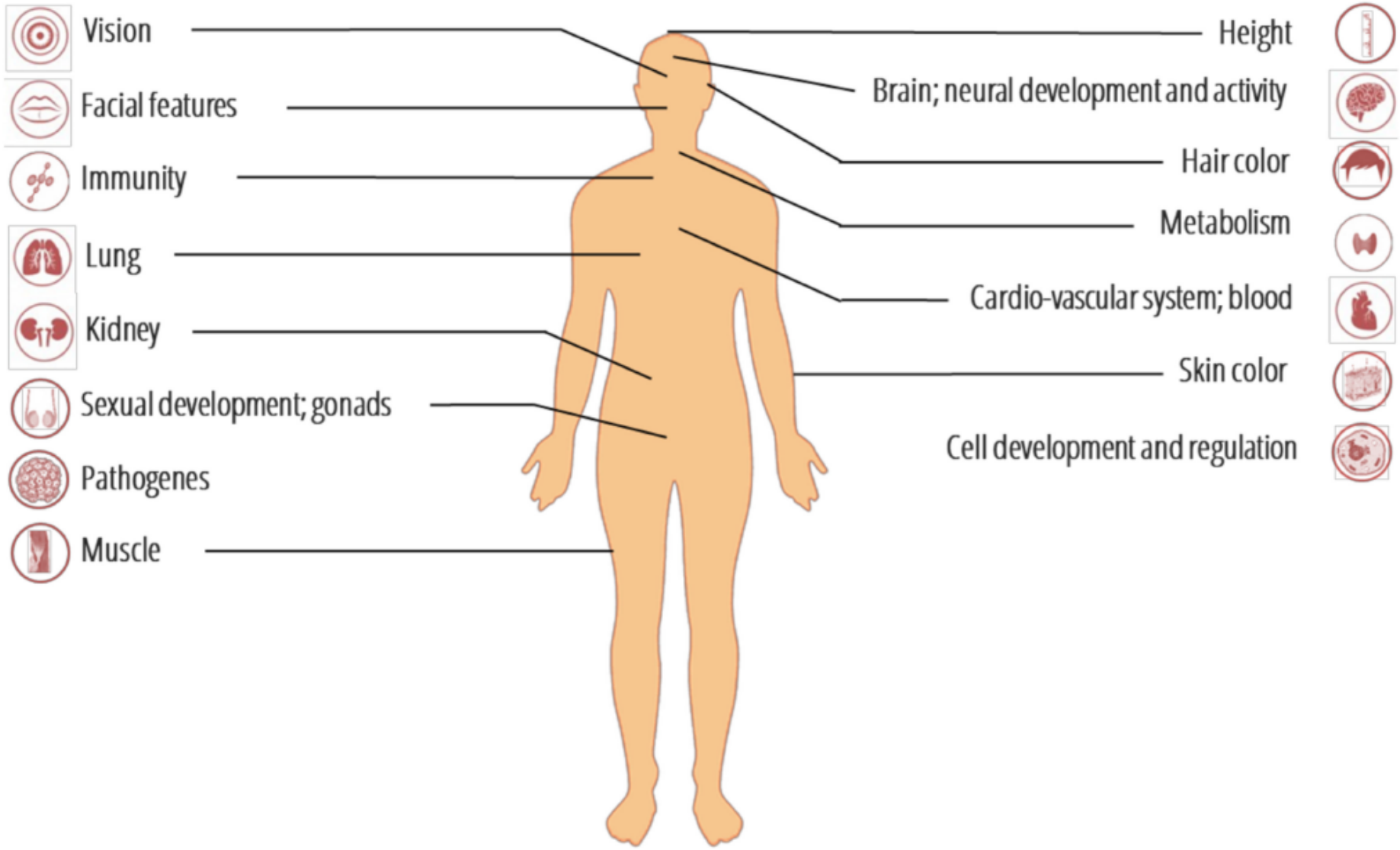


Figure 2. The modern human organs and systems affected by introgressed variants from ancient genomes (see Table S1 for details).

What part of modern genome is N?

- ABO blood group – ABO gene with 3 variants
  - N had A and O alleles (no B yet)– shared these with MH from LCA
  - Type A is original; B evolved 2.5 MYA
- FoxP2 present in both N and MH - from LCA
- HAR1 (Human Accelerated Region) - brain development gene; not present in primates; Denisovans have 2 differences not present in MH; 1 difference from N; HAR1 evolved during differentiation of these 3 groups

N Phenotypic traits

- There are several less-easily explainable phenotypic associations with Neanderthal introgression.
- Neanderthal variants associated with chronotype—whether people identify as early birds or night owls—as well as links with susceptibility to feelings of loneliness or isolation and low enthusiasm or interest.
- Being a self-described night owl and being prone to daytime napping were both traits positively influenced by Neanderthal variants

N DNA

- Genetic loci associated with having red hair were found to be devoid of Neanderthal variants, suggesting red-headed Neanderthals were either rare or non-existent.

- Neanderthal variants are associated with
  - sun-induced skin lesions
  - loneliness,
  - low mood, and
  - smoking.

- Determining how the effects seen in present-day people might once have affected Neanderthals themselves “is one of our crucial challenges. i.e. Neanderthals did not smoke.”

N DNA

- Neanderthal variants linked to risks for depression and addiction
- Kelso suspects that light might be a unifying factor, with both changes in day-length patterns, lesser light, and UV exposure reductions as they moved to more-northern latitudes.

Kelso and Dannemann, 2017

Increased fertility for women with Neanderthal gene

Neanderthal progesterone gene in modern women

- The hormone progesterone is important for preparing the uterine lining for egg implantation and for maintaining the early stages of pregnancy.
- 30% of European women inherited the PGR receptor for progesterone from Neanderthals -- a gene variant associated with increased fertility, fewer bleedings during early pregnancy, fewer miscarriages, and had more children.
- N = 244 K women: 29 % carry 1 copy of the Neandertal receptor and 3 % have 2 copies. These women produce more progesterone receptors in their cells

Hugo Zeberg , Janet Kelso, and Svante Pääbo, 2020

The phenotypic legacy of admixture between MHs & Ns –

- Analysis of the contribution of common Neanderthal variants to over 1,000 electronic health record (EHR)-derived phenotypes in ~28,000 adults of European ancestry.
- Found associations of Neanderthal alleles with neurological, psychiatric, immunological, and dermatological phenotypes.
- Neanderthal alleles together explain a significant fraction of the variation in risk for:
  - depression – both for risk for and reduction of sxs
  - skin lesions resulting from sun exposure (actinic keratosis
  - hypercoagulation
  - tobacco use.

Corinne N. Simonti,, et al., 2016

Corinne N. Simonti, et al., 2016

Clotting, Depression, & Circadian rhythms

- Neandertal variants don't usually fall within genes, instead affecting DNA that influences where, when and how strongly genes are activated.
- The Neandertal variants most strongly associated with depression were located near circadian clock genes
- Since it is unlikely that Neanderthals experienced such disturbances to their natural sleep cycles, they may never have expressed this gene, but in modern humans who can control our climate and for whom our lifestyle often disrupts our circadian rhythms, this gene is expressed more frequently.

N gene alleles in MH genome: Conditions associated with N alleles

- Variation in interleukin-18 levels (associated with inflammatory disease)
- Innate immunity genes (Toll-like receptor (TLR) genes--TLR1, TLR6, and TLR10)
- Variation in optic disc size
- Variation in smoking behavior
- FOXP2 (language)

B. Vernot & J. Akey, 2014

Neandertal DNA is slightly detrimental to modern humans, making some people more prone to certain diseases,

- Increased disease risk associated with Neandertal alleles:
  - Lupus
  - Primary biliary cirrhosis
  - Crohn's disease (2 alleles)
  - Type 2 diabetes
  - Covid-19
  - More allergies
  - Cystic fibrosis lung function
  - Cholesterol levels

B. Vernot and J. M. Akey, Science; Sankaraman et al., Nature, 2014; Corinne N. Simonti, et al., 2016

The phenotypic legacy of admixture between modern humans and Neanderthals

- Actinie keratosis
- Mood disorders
- Depression
- Obesity
- Seborrheic keratosis
- Acute upper respiratory infections
- Coronary atherosclerosis

Corinne N. Simonti, et al., 2016

N genes and disease

- Human papillomavirus HPV16 strain from N or D
- Propensity to sneeze after eating dark chocolate.
- Propensity to get scaly lesions after extreme sun exposure
- Both increased and decreased risk for depression (1-2%).
- Trait for faster blood clotting. In the modern world, however, this trait means greater risk for stroke and pregnancy complications.
- Lower risk of schizophrenia
- Response to antipsychotic drugs

Simonti et al., 2016; Rajiv C. McCoy, et al., 2017

N Gene association

- Slightly increased height on average
- Accumulation of belly fat
- Risk of developing eating disorders
- Rheumatoid arthritis
- Genital warts
- Slightly increased risk of heart attack
- More corns and callouses
- More bladder pain and incontinence

N and smoke/smoking

- In 2016, a gene in both modern humans and Neanderthals that controls the body's response to carcinogenic hydrocarbons.

- They found that Neanderthals were up to 1,000 percent more sensitive to these carcinogens than humans but had more genetic variants that better neutralized the harmful effects.

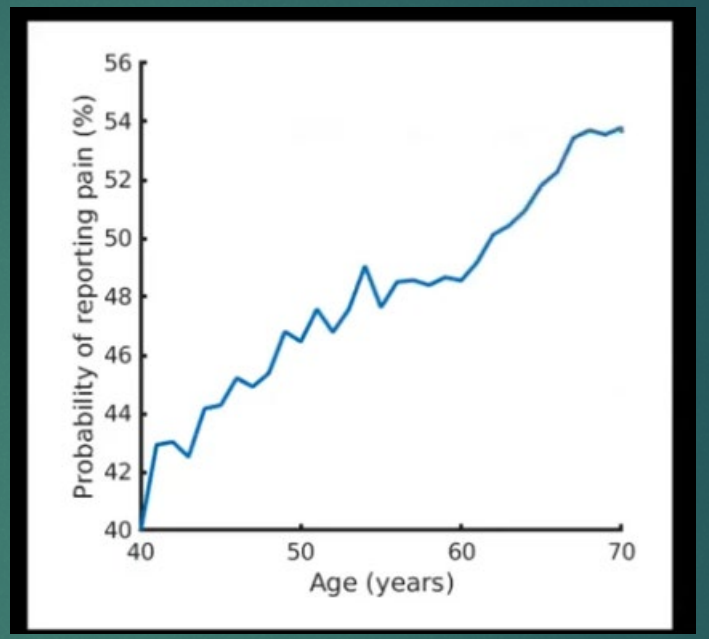
- Maybe this was an adaptation that occurred as the result of early fire use as our hominin ancestors started to inhale carcinogenic smoke. That is still unclear.

UK BioBank: 0.4% carry N variant: Neanderthal sodium channel increases pain sensitivity in present-day humans

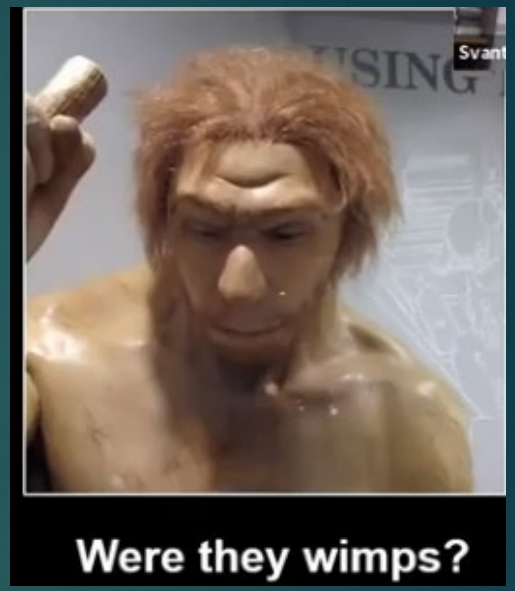
UK BioBank

362,944 individual, 1,337 (0.4%) carry the Neandertal allele

Specific pain phenotypes
Chest pain due to walking ceases when standing still
Knee pain for 3 months
Facial pains for 3 months
Neck/shoulder pain for 3 months
General pain for 3 months
Chest pain or discomfort
Back pain for 3 months
Chest pain or discomfort when walking uphill or hurrying
Chest pain or discomfort walking normally
Leg pain when walking normally
Leg pain on walking
Stomach/abdominal pain for 3 months
Leg pain when standing still or sitting
Hip pain for 3 months
Chest pain felt outside physical activity
Leg pain when walking uphill or hurrying
Leg pain in calf/calves
Leg pain when walking ever disappears while walking
Chest pain felt during physical activity

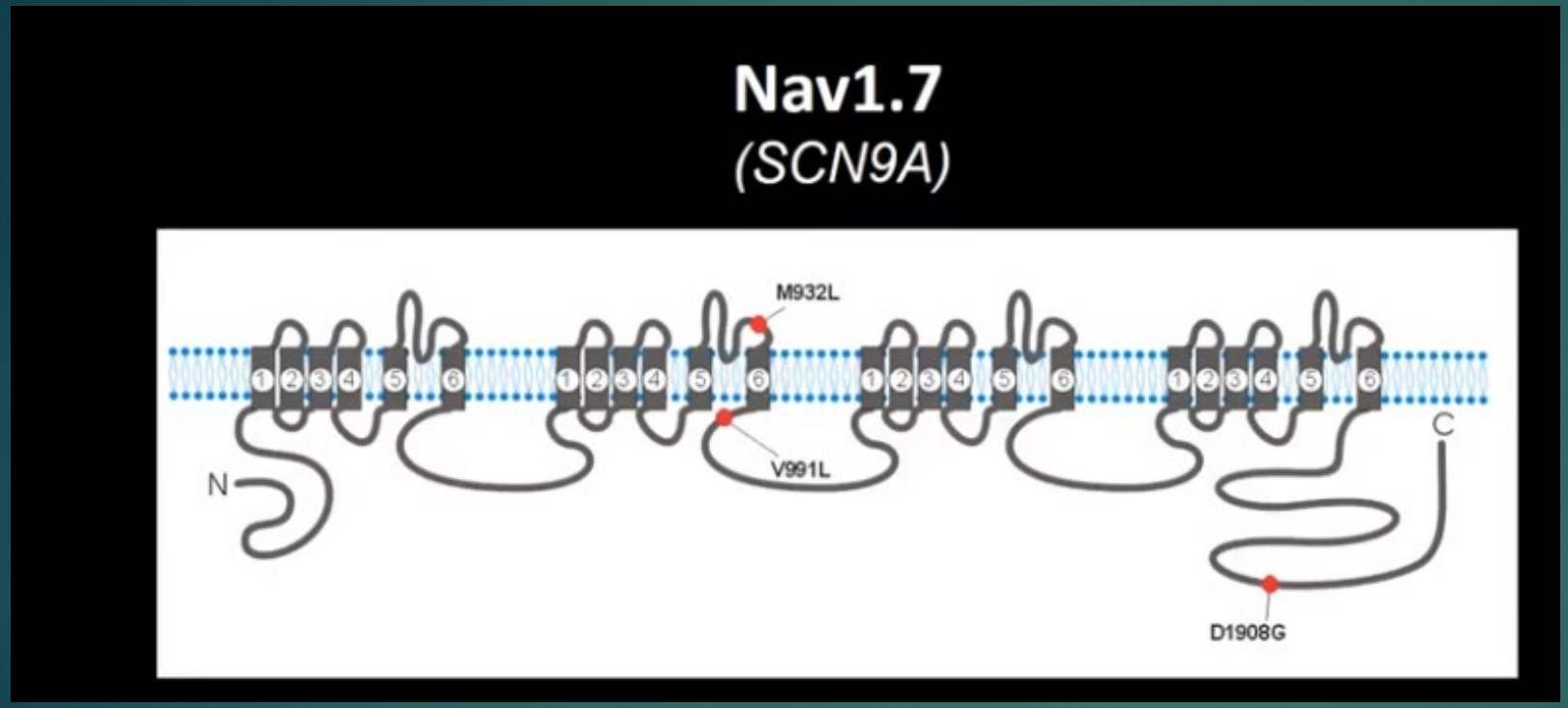


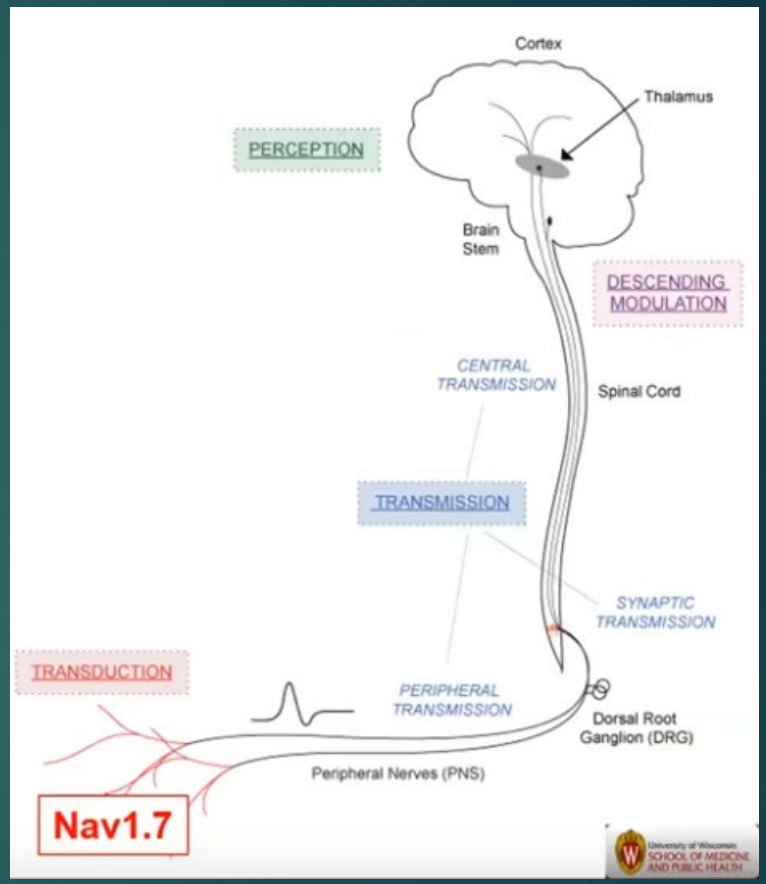
More pain reports with age



Those who carry N variant report more pain;
equivalent of 8 years older in pain report

Nav1.7 gene: pain perception in Ns was more sensitive





Ion channel controller

A Neanderthal Sodium Channel Increases Pain Sensitivity in Present-Day Humans – H. Zeberg, et al., 2022

- Neanderthal variant of the sodium channel Nav1.7, which is crucial for the initiation of the pain signals, occurs in some humans today.
- The Neanderthal variant is associated with increased sensitivity to pain.
- The Neanderthal variant carries three amino acid differences to the common variant. The Neanderthal channel is more likely to be in a ready-to-open state. Carriers of the Neanderthal variant experience more pain. A leading cause of idiopathic small-fiber neuropathy
- Would have allowed Neanderthals to be more sensitive to stimuli

Epigenetics In Neandertal

- 99% of epigenome of Neandertals, Denisovans, and Modern Humans is identical.
- 700 areas varied; in 200 areas, N and D shared the same methylation pattern, while humans had opposite (key to uniquely human traits).
- Genes in these regions play roles in immunity, metabolism, and disease.
- More than half of these disease-linked genes are associated with psych and neuro conditions.
- Limits: methylation in bone, not brain; may not be representative

Liran Carmel & S. Pääbo, et al., 2013 & Gokhman D,, et al., 2014

Epigenetics In Neandertal and Denisovan

- In April 2014, a first glimpse into the epigenetics of the Denisovan was gained with the publication of the full DNA methylation of the Denisovan and the Neanderthal.

- The reconstructed DNA methylation map allowed researchers to assess gene activity levels throughout the Denisovan genome and compare them to modern humans and to the Neanderthal.

- The study found ≈200 genes that show distinct regulatory patterns in the Denisovan.

Epigenetics

- One of the major findings focused on the limb morphology of Neanderthals.

- Gokhman et al. found that changes in the activity levels of the HOX cluster of genes were behind many of the morphological differences between Neanderthals and modern humans, including shorter limbs, curved bones and more.

Stem Cells: N in a petri dish

- Particular type of stem cell, called induced pluripotent stem (iPS) cells. These are made by reprogramming adult cells, and can then be transformed into any kind of cell.

- Camp wants to systematically explore how Neanderthal DNA behaves in different tissues.

Michael Dannemann, et al., 2018

Stem Cells: N in a petri dish

- A large repository of human induced pluripotent stem cells (iPSCs) harbors extensive Neandertal DNA, including most known functionally relevant Neandertal alleles present in modern humans.

- This resource contains Neandertal DNA that contributes to human phenotypes and diseases, encodes hundreds of amino acid changes, and alters gene expression in specific tissues.

- That means we could discover why some chunks of Neanderthal DNA seem to be beneficial to living humans.

Why did a Neanderthal-human hybrid not prevail?

- Two recent studies converge on an explanation.
- They suggest the answer comes down to different population sizes between Neandertals and modern humans, and this principle of population genetics: In small populations, natural selection is less effective.
- Neanderthals were more inbred than modern humans and accumulated more mutations that have a slightly adverse effect.
- Natural selection in the larger human population started purging those mutations

Why did a Neanderthal-human hybrid not prevail?

- David Reich, 2014: Neanderthal DNA tended to be located far away from important genes in the human genome.

- Attributed some of the finding to possible infertility in Neanderthal-human hybrids

- Juric & Coop, 2016: a pattern of weak natural selection because of population size differences between Neanderthals and humans could account for the distance between Neanderthal DNA and genes in the human genome today. Early hybrids would have been much less fit than pure humans.

Capra: Correlated N haplotypes

- Those data will likely yield some surprises. Capra has found evidence, for example, that some of the Neanderthal segments that correlated with modern phenotypes may not affect those phenotypes directly.

- His work has uncovered cases in which the correlation was driven by sequences close enough in the MH genome to Neanderthal variants that the two always appear together.

- These sequences were carried by the common ancestor of Neanderthals and modern humans but were missing from the group of humans who founded the modern Eurasian population.

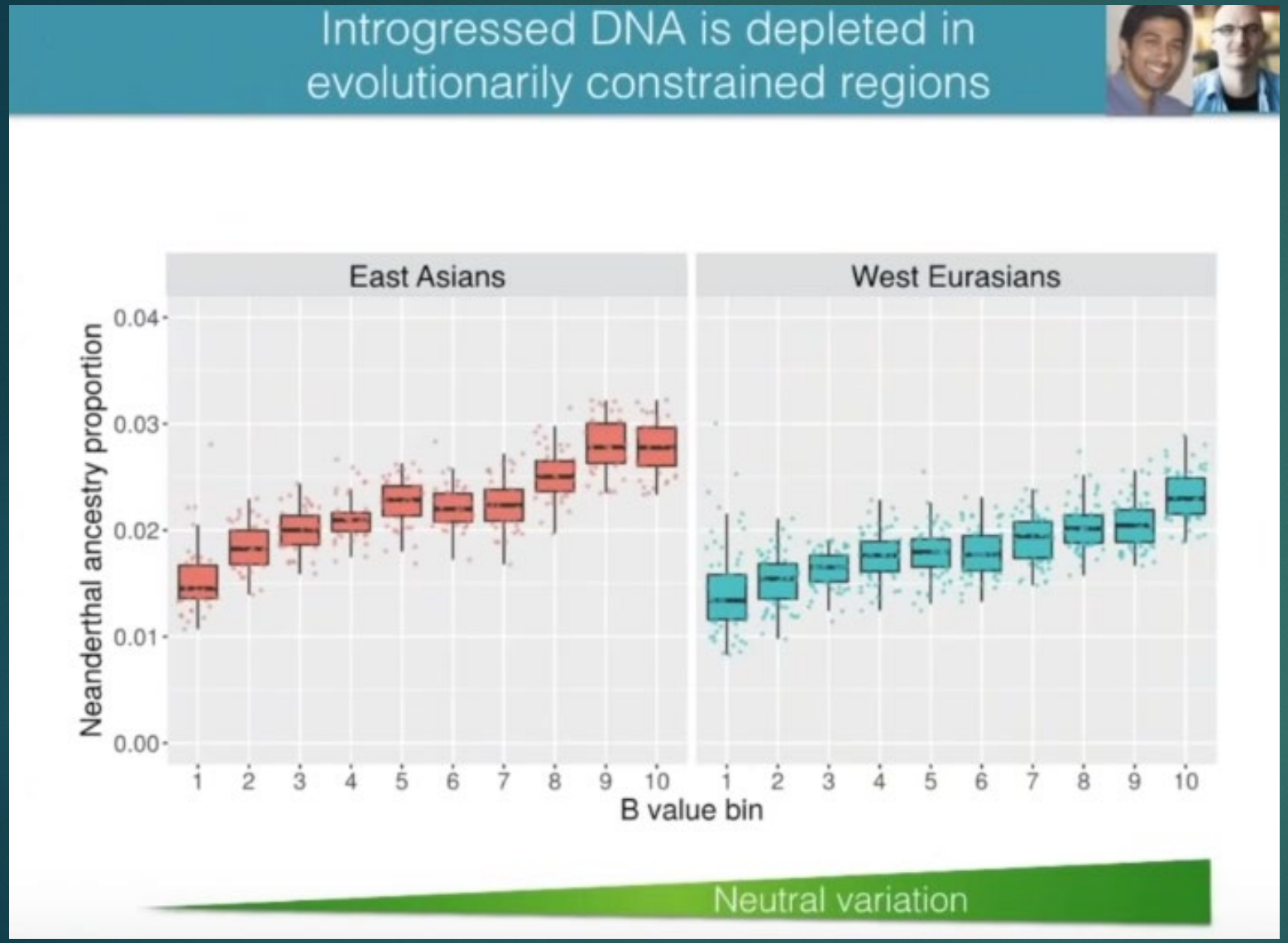
N DNA

- These variants, which had been retained by Neanderthals, were then reintroduced to the ancestors of modern non-Africans

- 17 million base pairs of African genomes are Neanderthal; =.3 percent of genome; a third of the amount the team found in Europeans and Asians

- European genomes contain 51 million base pairs of Neanderthal DNA and Asian populations with 55 million.

** Negative Selection of N genes:
Genetic Deserts



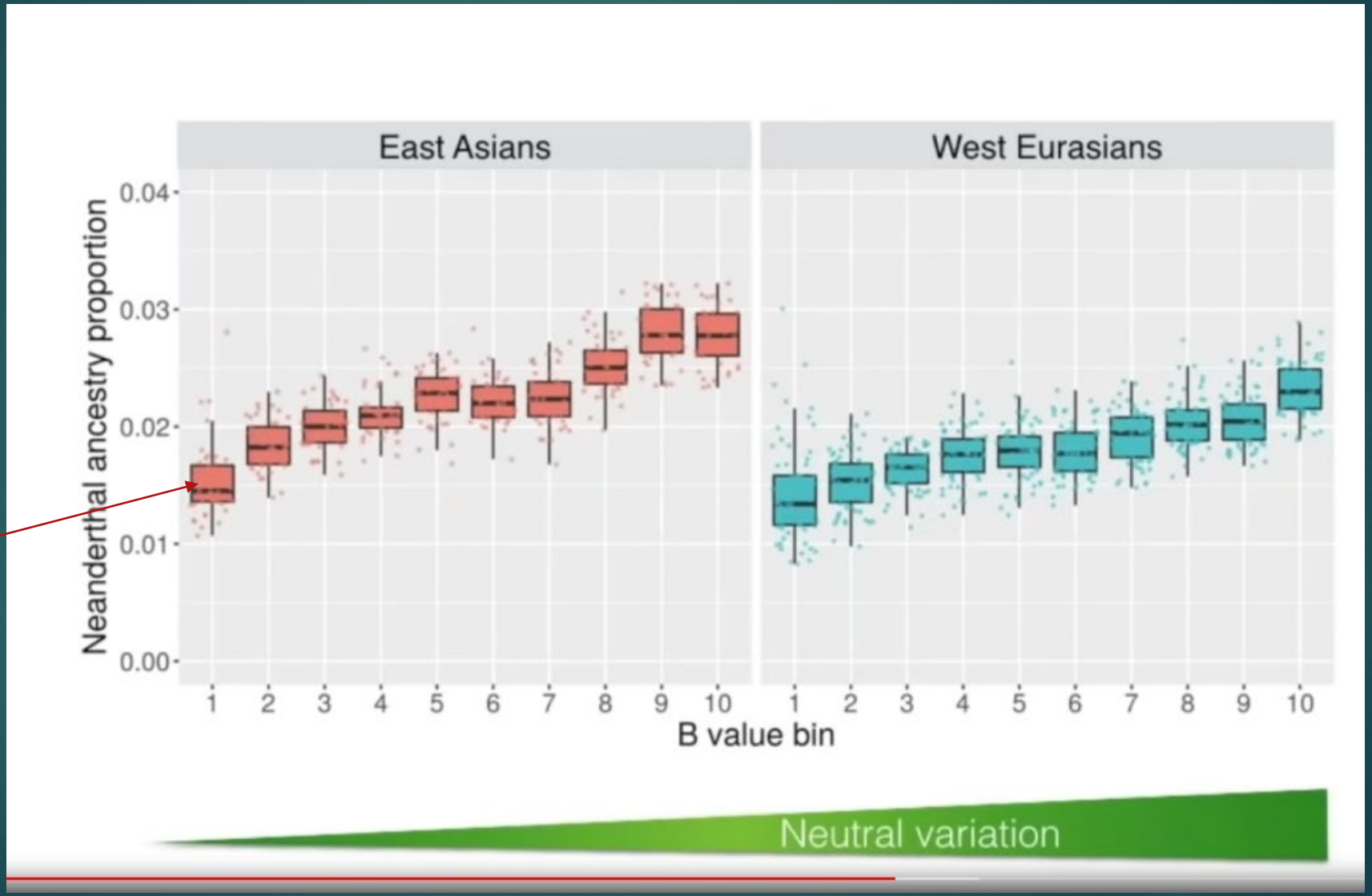
N Dna is not located in areas that are now functionally important

Purifying selection has acted to remove N DNA from areas of functional MH DNA

Implies that a substantial proportion of N DNA was deleterious in MH; and of possible hybrid incompatibility between N and MHs

Neanderthal DNA is depleted around functional genomic regions; depleted in evolutionarily constrained regions

More functional areas have less N DNA



Purifying selection is actively removing more deleterious N DNA

N and H sapiens: Not a good mix

- The DNA of *Homo Sapiens* and Neanderthals didn't mix very well. Long, long stretches of human DNA have no Neanderthal gene input at all.
- This indicates that genetic modifications in these regions proved negative for survival. For example, the MH FOXP2 gene for motor coordination and language and speech has no Neanderthal input.

- Neanderthal input is entirely absent from large sections of human DNA. Human male X chromosomes are particularly lacking in Neanderthal input, meaning there's a good chance that male children of a Human-Neanderthal union had lower fertility than average. It would be the women hybrids which passed on N DNA.

Genetic Deserts

- The genomes of non-African humans have sequences devoid of introgressed variation (“deserts”) from Neanderthals and Denisovans, possibly driven by selection against introgression.

- Introgression deserts of Neanderthal and Denisovan DNA in modern humans are largely overlapping.

- Of particular interest is a significant reduction in admixture associated with genes showing testes-specific expression, suggesting that admixture may have led to reduced male fertility and supporting evidence of reduced introgression on sex chromosomes

Unique MH DNA & N DNA deserts

- There has been strong selection against archaic introgression among protein-coding genes,

- Can identify functional regions contributing to the uniqueness of some modern human traits by fact that they are strongly depleted of archaic ancestry.

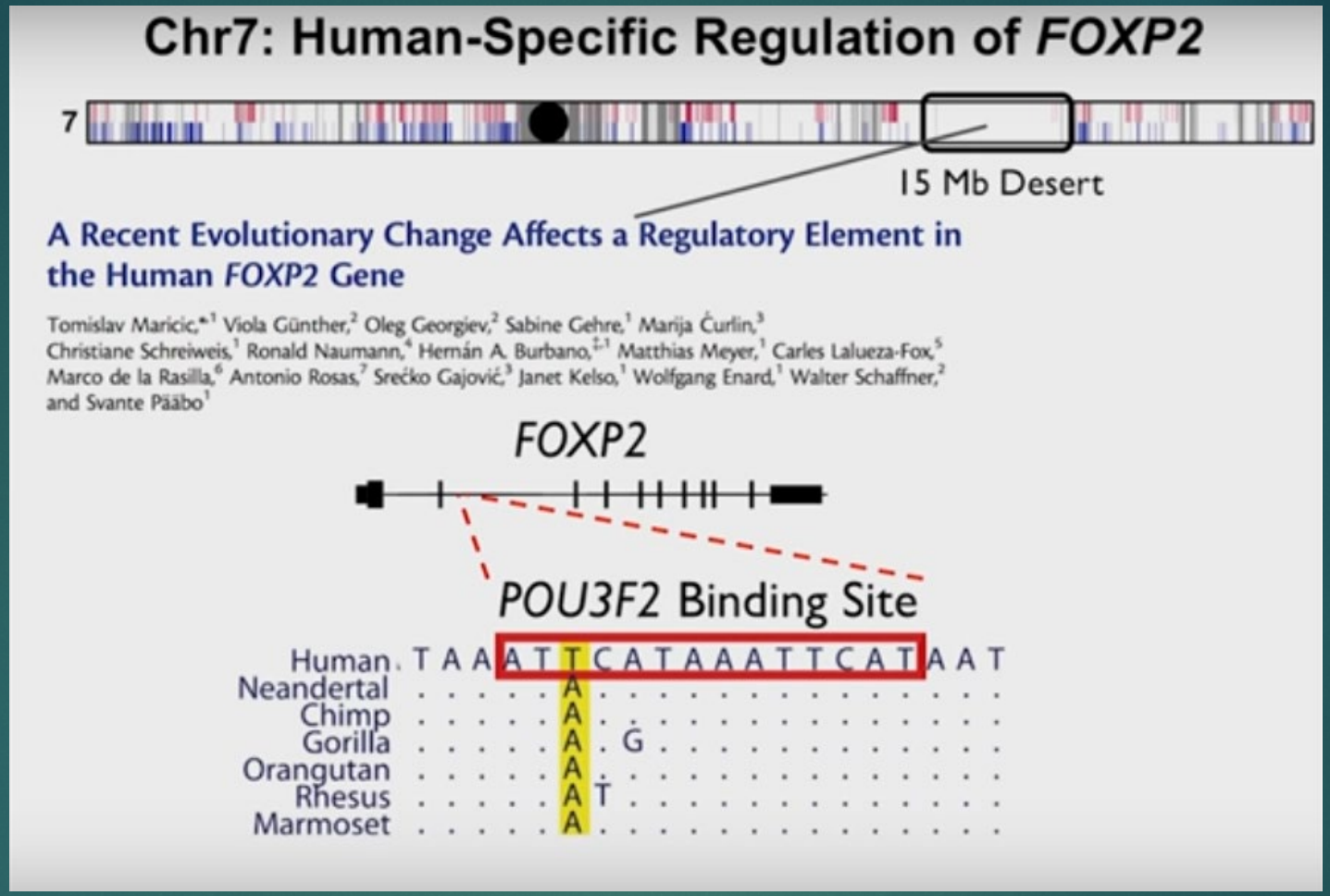
- For example, no Neanderthal ancestry has been detected around the forkhead box protein P2 (*FOXP2*) gene, mutations of which are associated with language disorders.

Unique MH DNA & N DNA deserts

- Similarly, Neanderthals and Denisovans carry a single copy of *AMY1* gene, encoding an amylase enzyme responsible for starch digestion.

- In contrast, MHs carry multiple copies of the gene and there is no evidence of Neanderthal introgression.

- This has been interpreted as an evidence that the production of larger amounts of salivary amylase for starch digestion has been under positive selection in modern humans compared to archaic species.



Largest area of depletion is on Chromosome 7; a 15 Mb (100 gene) desert;
Area contains FOXP2, a speech and language gene
Deserts of N DNA can help us identify areas that are important to evolution of MHs

Deleterious DNA

- Moreover, regions depleted of both Neanderthal and Denisova ancestry are enriched for genes expressed in specific brain regions (e.g., the ventral frontal cortex-ventrolateral prefrontal cortex in infants and the striatum in adulthood).

- There are large genomic regions devoid of Denisovan-derived ancestry, partly explained by infertility of male hybrids, as suggested by the lower proportion of Denisovan-derived ancestry on X chromosomes and in genes that are expressed in the testes of modern humans.

Purifying selection

- An introgressed deletion associated with a decrease in the time to menarche may constitute an example of a former Neanderthal-specific trait contributing to modern human phenotypic diversity

- Further evidence of the deleterious effect of Neanderthal introgression can be identified at the expression level.

- Analysis of gene expression of Neanderthal alleles in current individuals shows a significant downregulation in the testes and brain compared to other tissues

Adaptive introgression of Haplotypes

- Adaptive introgression could bring variants at a higher frequency than de novo mutations, providing linked blocks of sequence with multiple functional mutations, potentially including co-adapted alleles.
- For example, genes involved in functions related to keratin filaments, sugar metabolism, muscle contraction, body fat distribution, enamel thickness, brain size and functioning have been targeted by adaptive introgression from Neanderthals in different non-African genomes.

** N Genomic Deserts

Preface

- It is important to remember that Neanderthals:
  - were a heavily inbred population (the Altai Neandertal's parents were related as half-siblings)
  - with very low effective population sizes (possibly by an order of magnitude lower than the early AMH's),
  - which may have lowered their genetic fitness (capacity to survive and reproduce) by as much as 40%

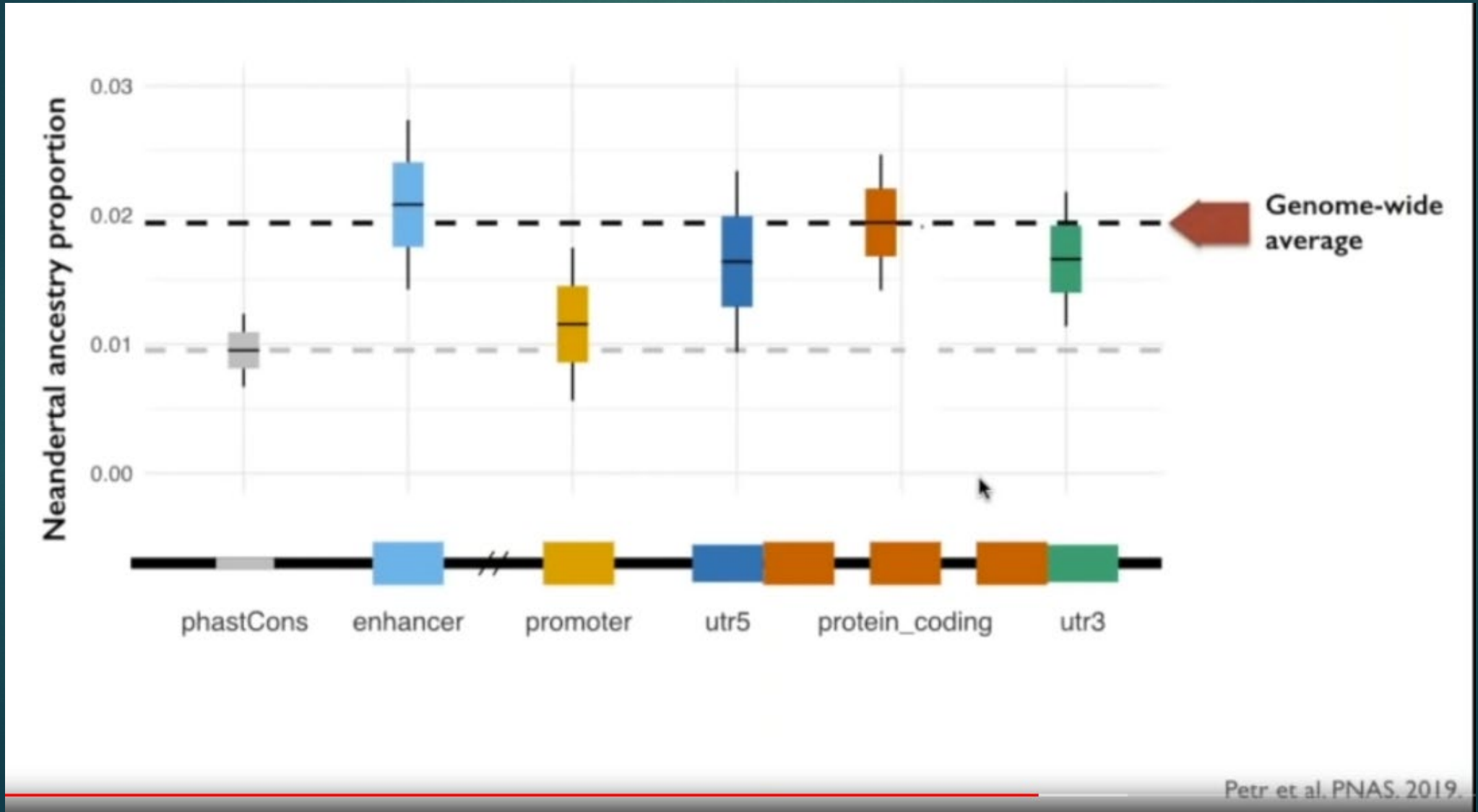
Neandertal effective population sizes

- K Prüfer, et al. 2014: Ne = 1,000–5,000; a shorter common branch for the Neandertal–Denisovan ancestor (300 generations).
- Rogers et al., 2017: estimate that the effective population size (Ne) of Neandertals was n = ~15,000; a longer common branch for the Neandertal–Denisovan ancestor (5,000–10,000 generations).
- Fabrizio Mafessoni & Kay Prüfer, 2017: Rogers et al. model predicts a large Ne for Neandertals that is at odds with the low heterozygosity in the Altai Neandertal. A relatively small effective population size for Neandertals and a longer shared branch for Neandertals and Denisova remain better supported.

Deserts

- Most Neanderthal genes survive in *H. sapiens* in regions of non-coding DNA. The regions that are most important for function—the protein-coding genes—are depleted of Neanderthal DNA.
- These 'genomic deserts' from which archaic DNA seems to have been eliminated are
  - mostly non-coding regions located preferentially near protein-coding genes,
  - evolutionarily conserved genes involved in brain development, including FOXP2
  - Neanderthal ancestry has been selected against in conserved biological pathways, such as RNA processing
  - Genes expressed in the testes and in meiotic germ cells -- potentially relevant for male hybrid sterility.
  - The most plausible explanation for this loss of archaic DNA is negative selection

Neandertal DNA is most depleted in transcription promoters and in highly conserved coding regions; N DNA mostly in non-coding regulatory regions



N 2%

Less N %

Gene enhancers in non-coding DNA

- In genetics, an **enhancer** is a short (50–1500 bp) region of DNA that can be bound by proteins (activators) to increase the likelihood that transcription of a particular gene will occur.
- These proteins are usually referred to as transcription factors. Enhancers are *cis*-acting (regions of non-coding DNA which regulate the transcription of neighboring genes.)
- They can be located up to 1 Mbp (1,000,000 bp) away from the gene, upstream or downstream from the start site. There are hundreds of thousands of enhancers in the human genome

Selection against archaic DNA in human regulatory regions

- N & D DNA in MHs has been systematically depleted from the most functionally important regions of the human genome.
- N DNA is more common in nonfunctional and regulatory regions of the genome than in coding regions.
- This depletion suggests that many Neanderthal and Denisovan alleles had harmful effects on the genes of hybrid individuals
- Neanderthal depletion is highly correlated with Denisovan depletion across sets of enhancers active in particular tissues

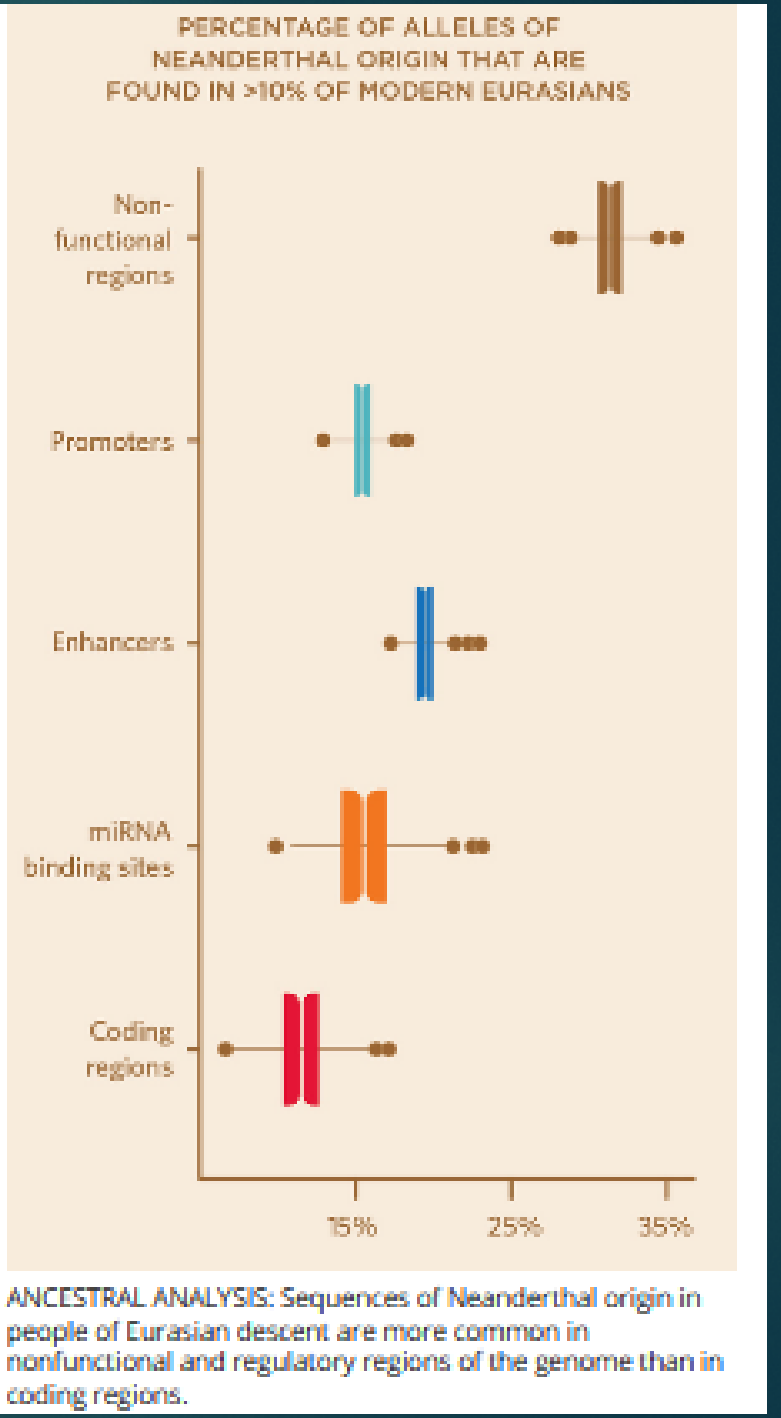
Natalie Telis, et al., 2019

David Reich & Joshua Akey: Neanderthal variants do not appear in coding regions.

French Study: Neanderthal ancestry was enriched in areas tied to gene regulation (*Cell*, 167:643–56.e17, 2016).

The implication was that sequences that originated in Neanderthals tend to have "less impact through protein and more impact through gene expression.

A quarter of the stretches of Neanderthal DNA in human genomes affect the regulation of genes



ANCESTRAL ANALYSIS: Sequences of Neanderthal origin in people of Eurasian descent are more common in nonfunctional and regulatory regions of the genome than in coding regions.

Strong depletion of Neanderthal variants in coding portions of genes

- Neanderthal sequences make significant contribution to gene expression variability.

- Rotival et al.: strong depletion of Neanderthal variants in coding portions of genes, and a slight enrichment of the archaic sequences in regulatory regions

- Desert areas harbor genetic changes that are very important to MH phenotype

N DNA in Regulatory regions, not gene coding areas

- Archaic sequences affect gene expression.

- N DNA tends to have "less impact through protein and more impact through gene expression"

- .

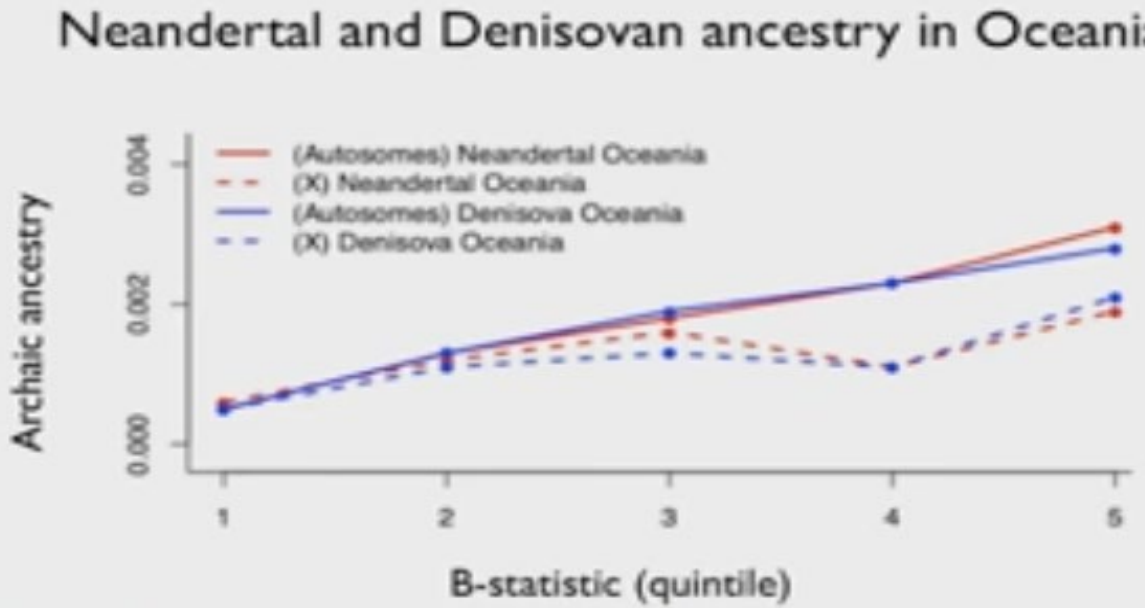
N DNA functionality: brain organoids

- As a postdoc in Pääbo's lab in Germany, Camp, along with Vernot, Kelso, and Dannemann, established a handful of brain organoids from induced pluripotent stem cell lines of modern Europeans who vary in their Neanderthal-derived genetics, and tracked single-cell transcriptomes as the cultured cells matured.
- The early data suggest that the Neanderthal variants affect gene regulation

Neandertal DNA

- Average Neandertal at least 40 percent less evolutionary fit than the average early modern human fresh from Africa
- Due to dwindling population size, N built up more weakly harmful mutations.
- When humans and Neandertals interbred, the MHs larger population size allowed evolution to weed out the slightly bad variants

Purifying selection on archaic alleles



Stronger selective pressure

Possible selection pressures ?

Deleterious archaic alleles (Juric et al. 2015, Harris and Nielsen 2015)

Hybrid sterility (Sankararaman et al. 2016)

Archaic DNA declines in areas that are strongly selected in MHs; There is a purifying selection process on archaic alleles; 2 possibilities:1- there are deleterious archaic alleles, which do not survive 2 – Hybrid sterility (genetic incompatibilities)

N fitness: Neanderthal DNA is conspicuously low in regions of the X chromosome and testes-specific genes.

- Neanderthals suffered a high load of weakly deleterious mutations accumulated during extended population bottlenecks
- Assuming additive fitness effects, this mutational burden was estimated to have reduced Neanderthal fitness by at least 40% compared to modern humans
- Deleterious haplotypes introgressed into larger modern human populations would have been subject to strong selection during the first ~20 generations after hybridization—a prediction with growing empirical support from genetic data
- Downregulation of Neanderthal alleles in the brain and testes; consistent with the hypothesis that male hybrid individuals may have incurred reduced fertility

(Juric et al., 2016, Harris and Nielsen, 2016).

N Fitness

- Study: potential fitness effects of Neanderthal alleles in human genomes:
- Neanderthals harbored a large number of weakly deleterious alleles due to genetic drift in their extremely small effective population size, and that introgression of Neanderthal alleles into larger, human populations resulted in selection effects strong enough to account for the depletion of Neanderthal alleles throughout the human genome.
- It is therefore unnecessary to invoke hybrid incompatibility to explain the selection against Neanderthal alleles.

An Alternative theory: Fitness, not hybrid incompatibility

- Neanderthals were subdivided into small populations with little genetic exchange.
- Inbreeding within these small populations imbued Ns & Ds with a higher fraction of deleterious mutations than living people.
- The fitness cost of this mutation load may explain the introgression bias against functional regions in the Neanderthal genome into modern human populations.

N fitness

- Hypothesize that stronger purifying selection on the X chromosome as well as sex-biased matings between Neanderthal males and human females could account for the reduced level of Neanderthal-derived ancestry seen on that chromosome.
- Selection against deleterious alleles, rather than hybrid incompatibilities, most likely accounts for patterns of Neanderthal ancestry in modern human populations.
- Jurich *et al*. and Harris and Kelley estimate an average F1 hybrid individual would carry somewhere between an astonishing 40 to 94% reduction in fitness compared to modern humans.

Don’t need hybrid incompatibility idea

- Both research groups also found that the patterns of Neanderthal ancestry in contemporary human populations were not explained by hybrid incompatibility.
- The implication of this result, of course, is that it weakens the argument that humans and Neanderthals were separate species.
- Harris K and Nielsen R. The genetic cost of Neanderthal introgression. 2016, Genetics
- Juric I, Aeschbacher S, Coop G. The strength of selection against Neanderthal introgression. 2017

Negative selection

- N & D DNA was glaringly absent from several regions of the modern human genome.
- That absence may signal that these stretches of the genome are instrumental in making modern humans unique.
- Regions depleted of archaic lineages are significantly enriched for genes expressed in specific brain regions, particularly in the developing cortex and adult striatum.

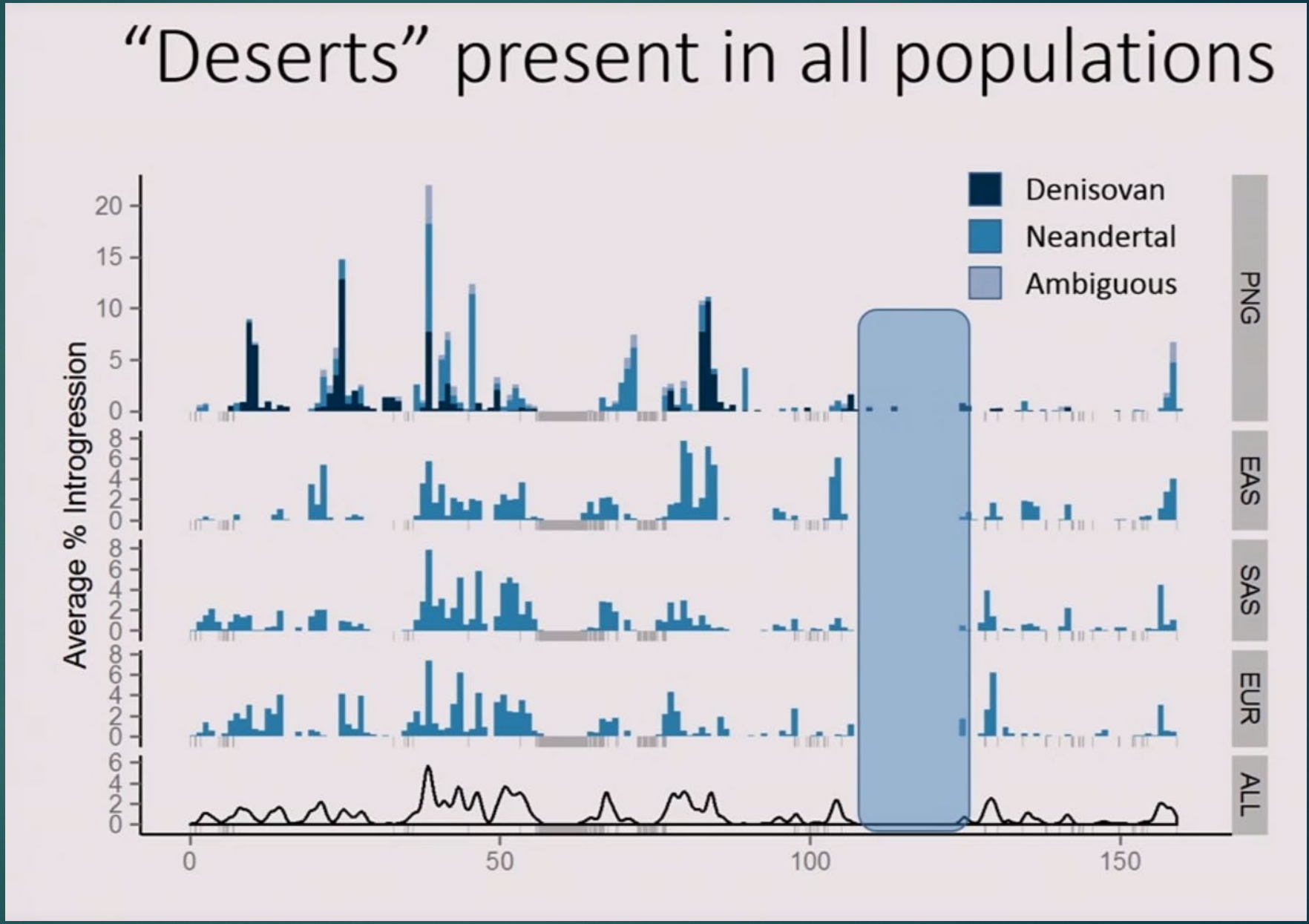
Negative Selection

- A large region depleted of archaic sequence contains the FOXP2 gene, which has been associated with speech and language.

- This region is also significantly enriched for genes associated with autism spectrum disorder (there is a correlation between genes in prodigies and in autism.)

- No sign of Neandertal or Denisovan DNA appears in areas of Melanesians' genomes involved in brain development

Deserts = Areas uniquely important functions for MH



The Strength of Selection against Neanderthal Introgression

- Bulk of purifying selection against Neanderthal ancestry is best understood as acting on many weakly deleterious alleles.

- We propose that the majority of these alleles were effectively neutral—and segregating at high frequency—in Neanderthals, but became selected against after entering human populations of much larger effective size.

- While individually of small effect, these alleles potentially imposed a heavy genetic load on the early-generation human–Neanderthal hybrids.

Juric et al., 2016

The Strength of Selection against Neanderthal Introgression

- On average, selection against individual Neanderthal alleles is very weak.

- This is consistent with the idea that Neanderthals over time accumulated many weakly deleterious alleles that in their small population were effectively neutral.

- After introgressing into larger human populations, those alleles became exposed to purifying selection.

Wolf & Akey, 2018: genome deserts

- **What caused deserts of archaic sequence to form?**

- While introgressed sequence tends to be widespread across the N & D genomes, covering all 22 autosomes and the 2 sex chromosomes, it was a striking discovery to find that there also exist large depletions – “deserts” - of archaic ancestry. On the autosomes, the largest deserts span multiple megabases, with a handful extending up to 10 Mb in length.

- One proposed explanation for autosomal deserts is that they resulted from intense bottlenecks in the human population.

Genome deserts: Haplotypes

- Alternatively, selection against Neanderthal haplotypes at desert loci might also generate large depletions of archaic sequence.

- Selection against specific deleterious Neanderthal alleles in the admixed population could remove large swaths of linked archaic sequence.

End: Part 7