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Miguel Romero's comment is at the end of this document

Nobel Prize to Paleogenetics Rockstar Svante Pääbo Evokes Memories of Being Drawn to Science

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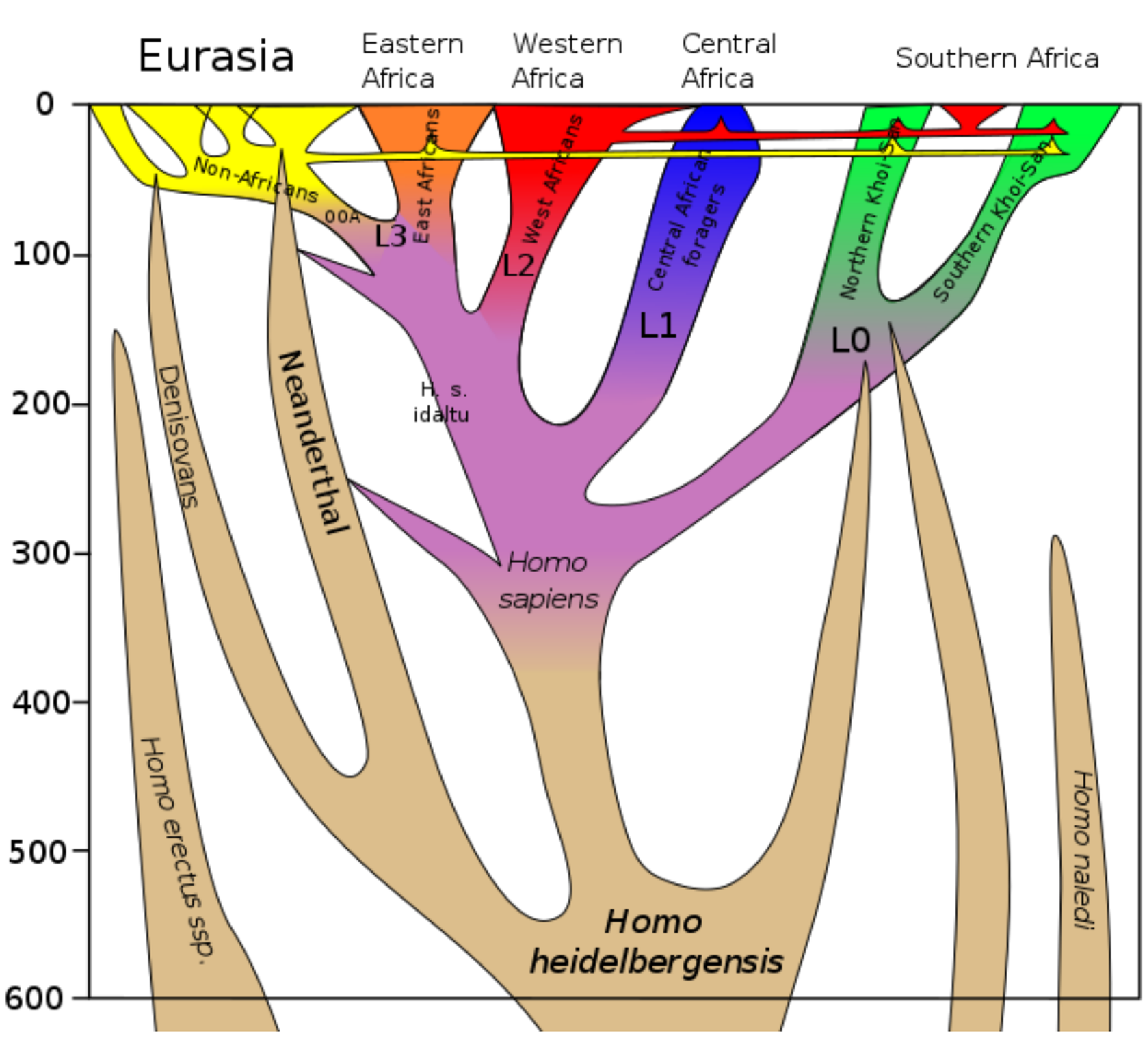

One of my favorite places as a child was the American Museum of Natural History. While most kids would rush to the towering dinosaur skeletons, I'd stand, transfixed, at a small glass-enclosed display of skulls and try to envision what their owners had looked like – australopithecines, Neanderthals, a few others. I remember that part of the museum as The Hall of Man; it's now the Hall of Human Origins.

Discovering My First Fossil

I loved the museum, but yearned to discover things myself. That happened when I was in the fourth grade, and my parents took my sister and me to the Baseball Hall of Fame in Cooperstown, NY. We couldn't have cared less about baseball. But behind the motel, we waded in a stream, where the angle of the sun on the wet rocks revealed striking patterns of stripes. I picked one up, and realized that it wasn't an ordinary rock.

It was a fossil. Edith and I spent the weekend collecting.

My mother, who let me adopt insects I found in produce and even crayfish when I couldn't find any tadpoles in the nearby Brooklyn Botanical Gardens, took me and my fossils up to the 8th floor of the dinosaur museum. We barged in on a paleontologist. The startled man kindly explained to me that yes, I'd discovered fossils, but they weren't evidence of ancient humans. They were worm borings. I wasn't disappointed though, and began reading about worms.

Soon after, when we had to write an essay on what we wanted to be when we grew up, I wrote invertebrate paleontologist. I still have the cigar box of fossils from that weekend.

By college, my interest had turned to genetics. But I never imagined that we'd be able to scrutinize the genes and genomes of ancient humans and their hominid ancestors, enabling reconstructions based on more than bones. The once separate roads of paleontology and genetics converged and then merged, fleshing out our forebears one gene and then one precious genome at a time.

So when my dear friend Barry Palevitz emailed me on Monday morning that paleogeneticist Svante Pääbo had won the 2022 Nobel Prize for Physiology or Medicine, I was jubilant. Dr. Pääbo has frequently made headlines for his work on Neanderthals (also spelled Neandertal) and the more-recently-discovered Denisovans, but his publication list includes much more.

Barry is a former botany professor from the University of Georgia, and I'm a former *Drosophila* geneticist, the plant guy and fly pusher united in our fascination with evolution. It explains everything in life science. The same undulating and intertwining forces of mutation, genetic drift, and natural selection that have molded the genomes of modern humanity are also at play in the ever-changing collection of viral variants of SARS-CoV-2.

I eagerly awaited the evening news on Monday. Although I expected coverage of the Nobel to be in the last millisecond, I was stunned that NBC Nightly News didn't report it at all, not even the famed image of Dr. Pääbo holding a Neanderthal skull. The news did, however, devote many minutes to the sad tale of Kim Kardashian's fine for tweeting about cryptocurrency. CNN ran the Nobel story at the very bottom of the online feed.

What?!? Haven't we just emerged from a two-year pandemic that, in addition to killing millions, revealed and continues to reveal rampant science illiteracy? Evolution is why COVID is here to stay. Politician's pronouncements won't stand up against the ever-present forces of evolutionary change.

I couldn't help but compare the coverage of Dr. Pääbo's Nobel to other awards. Chatter for entertainment awards begins weeks in advance. Sports and political competitions are breathlessly reported in minute-by-minute detail. Nobel prizes in science? Not so much.

Fortunately several outlets indeed reported the prize announcement with appropriate background, for science writers like me have been covering the work of Dr. Pääbo, director of the Max Planck Institute for Evolutionary Anthropology in Leipzig, for decades.

Like EGOT winners Mel Brooks, Whoopi Goldberg, and Rita Moreno – *E*mmy, *G*rammy, *O*scar, and *T*ony – Dr. Pääbo has won many awards. He and co-workers have probed the DNA sequences of a variety of species, from cichlid fish to prehistoric canines to ancient ground sloths and an array of marsupials. He's compared genome sequences of our immediate forebears to provide clues to reconstruct past migrations. They include the famous Tyrolean Ice Man; Egyptian mummies; and the west European hunter-gatherers, ancient north Eurasians, and early Near Eastern farmers who gave rise to modern Europeans.

Remembering a Key Lecture

Dr. Pääbo gave a riveting lecture at the 2008 annual meeting of the American Society of Human Genetics, two years before he analyzed the DNA of a child's finger bone that would lead to discovery of the Denisovans. The meeting, in San Diego, happened during violent storms and I recall the hotel elevators full of children clutching cats and belongings.

I found mention of the talk in Recollections from 60 ASHG Meetings, by Bronya J.B. Keats and Terry J. Hassold. Their essay is "a synthesis of the 'wow' moments that are fixed in the memories of some of those who have attended the ASHG meetings." Dr. Pääbo's presentation, "A Comparative Approach to Human Origins," was part of a symposium, Human Brain Evolution: What Makes Us Unique?" I sat in the front row.

Keats and Hassold quote one attendee:

"The exciting results in Dr. Pääbo's presentation on the FOXP2 humanized mouse made the hair on the back of my neck stand up—the likely evolutionary pathways to human speech changed the way I teach human evolution to medical students."

A year earlier, the team had reported finding that humans and Neanderthals have the same version of the gene *FOXP2*, involved in speech and language.

Since the 2008 meeting, the team has sequenced DNA from more Neanderthal remains that were collected from several geographical sites. And then the Denisovans joined the party.

Covering Dr. Pääbo's Work in my Human Genetics Textbook

I've written about the quest to fill-in-the-blanks of our knowledge of the Neanderthals and Denisovans in articles and books.

The Denisova Genome and Guys Banging Rocks, for Scientific American blogs, appeared in 2012, when only a few genes had been identified. In 2016 I posted From Denisovan DNA to Future Humanity here at *DNA Science*.
My favorite was The Cave Where it Happened: The Daughter of a Neanderthal Mom and a Denisovan Dad, from 2018.

Updates to my textbook *Human Genetics: Concepts and Applications* also provide a chronology of some of Dr. Pääbo's contributions to human paleogenetics. It's been exciting to revise the information as discoveries fill in the narrative, and images of fossils have been replaced with gene sequences.

Between the eleventh and twelfth editions – 2015 and 2018 – what we know of the human family tree exploded, in light of the discovery of the finger bone that opened the door to the Denisovans. "Denise" lived 32,000 to 50,000 years ago in the Denisova cave in the Altai mountains of southern Siberia. Figure 16.1 in my textbook, "Our place on the human family tree," circa 2015, depicts Denisovans and Neanderthals splitting off on the road towards *Homo sapiens sapiens* – us – within the last million years. The figure is in the Human Ancestry and Evolution chapter.

I kept the human family tree figure in the twelfth edition, but added a new more detailed one, entitled "Gene flow among archaic and anatomically modern humans." It has more branches.

The new figure depicts, at the base, a common ancestor, as all evolutionary trees do. The meme of chimps and gorillas leading to us is absurd, for evolution is not a straight line of one type of organism magically becoming another. Evolution continually diverges as DNA mutates and genes recombine, while natural selection keeps some changes and ditches others.

Denisovans and Neanderthals split from a shared ancestor about 400 million years ago. Then sometime between 200 and 125 million years ago, Neanderthals branched into at least four groups.

Paleogeneticists deduce plausible branching patterns using algorithms that compare DNA sequences from cells meticulously collected from tiny bits of fossilized bone. The more base sequence differences, the longer ago two types of organisms diverged from a shared ancestor, for mutations accumulate over time. "Molecular clocks" that impose estimated timescales are derived from known mutation rates of certain genes.

I developed the more highly branched figure new to the twelfth edition of my textbook after reading lots of papers and drawing trees with colored pencils, deploying my kindergarten-level art skills. The depiction is indeed complicated – yet it's only a glimpse of probable reality, for we don't know what we don't know.

My publisher won't allow me to post the figure, but here's the caption:

DNA sequence similarities indicate that genes flowed (individuals mated) from Denisovans to some groups of anatomically modern humans, from Siberian Neanderthals to Denisovans, from Spanish Neanderthals to Europeans, and from unknown anatomically modern humans to Siberian Neanderthals and to Denisovans.

In a nutshell, whatever differences separated what we call Neanderthals and Denisovans, they weren't enough to keep these human ancestors from mating!

I Have a Lot of Neanderthal DNA

Given my writing about Neanderthals, I was thrilled to learn, courtesy of 23andMe, that I have 76 percent more places in my genome where the DNA base is the one from Neanderthals compared to other modern humans. The estimate reflects percent ancestors, not percent of the genome as is often reported in the media. Of course the distinction isn't much, genomically speaking, between us and a Neanderthal or Denisovan. A mere million years from a shared ancestor is but a blink of evolutionary time.

Paleogenetics provides practical medical information too. A table in my textbook lists gene variants of Neanderthals retained in modern European genomes linked to human health conditions, as eclectic as too-fast blood clotting, tobacco use disorder, urinary incontinence, precancerous skin lesions, and even depression.

I'm happy that the Nobel committee has recognized the value of basic research, which spawns applications as well as reawakening childhood memories of fascination with the past of *Homo sapiens sapiens*.

DISCUSSION

Miguel Romero
October 27, 2022 at 2:52 pm
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An undergraduate project in 2014 investigated the use of DNA microarrays for detecting HIV infection. Mindful of specificity requirements numerous public databases were queried with the 9719 base-pair (K03455.1) and 9181 base-pair (NC_001802.1) full length HIV-1 genomes.1 HIV-1 sequences were found in numerous taxa, including the genome of a living male Homo sapiens published in Nature.2,3,4 A BLASTN search of Professor Pääbo's million base-pair DNA of the 38,000-year-old fossil Homo sapiens neanderthalens5 was also performed. This returned sequences homologous to DNA of HIV-1 proteins p10, p51and p66. TBLASTN, a sensitive bioinformatic tool for searching similarities, returned amino acid sequences with high identity positives to the p7, p24, p41, p51, p66 and p160 HIV-1 proteins.6 I attributed these findings to contamination, although it was not possible to determine how this occurred. Also, I was puzzled by failure to obtain similar findings following searches utilising "control" RNA viruses with similar length genomes to HIV.

Prompted by the 2022 Nobel prize announcement, I re-read Professor Pääbo's paper in which he said, "determination of ancient hominid sequences is fraught with special difficulties and pitfalls. In addition to degradation and chemical damage to the DNA that can cause any ancient DNA to be irretrievable or misread, contamination of specimens, laboratory reagents and instruments with traces of DNA from modern humans must be avoided…This problem is especially severe when Neanderthal remains are studied because Neanderthal and human are so closely related that one expects to find few or no differences between Neanderthals and modern humans within many regions, making it impossible to rely on the sequence information itself to distinguish endogenous from contaminating DNA sequences. A necessary first step for sequencing nuclear DNA from Neanderthals is therefore to identify a Neanderthal specimen that is free or almost free of modern human DNA"7 In other words, the paloegeneticist must be as fastidious as the geologist searching for microorganisms in extraterrestrial rocks. Given that (a) the age of Homo sapiens neanderthalens precludes an ancient HIV infection; (b) the "Vi-80 Neanderthal bone extract is largely free of contaminating modern human mtDNA"6 and; (c) Pääbo and his colleagues used the 454 sequencing platform because it "is extremely well suited for analyses of bulk DNA extracted from ancient remains"7, what explains the detection of HIV DNA in Homo sapiens neanderthalens?

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REPLY

Ricki Lewis, PhD
November 3, 2022 at 1:31 pm

Thank you Miguel. It is difficult to assess missing information. Perhaps the samples indeed were contaminated. Or, perhaps we do not know the sequences of viruses that led to HIV. Or, perhaps HIV arose more than once.