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GENOME SECRETS OF EXTINCT HOMINIDS, OR CAN PALEOGENOMICS ANSWER THE QUESTION: HUMANKIND, WHO WE ARE? NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2022

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The Nobel Prize in Physiology or Medicine 2022 was awarded to Professor Svante Pääbo, a Swedish paleogenetic researcher, specialist in the field of evolutionary genetics, Director of the Department of Evolutionary Genetics at the Max Planck Institute for Evolutionary Anthropology of Leipzig (Germany), for "discoveries concerning the genomes of extinct hominids and human evolution". Explaining the significance of S. Pääbo's work, the Nobel Committee noted that "he pioneered the methods to isolate and analyze DNA from archaic bone remains. In ancient bones, DNA has decayed, been chemically damaged and massively contaminated with DNA from bacteria and contemporary humans who work with the samples. Having utilized modern genetic methods, S. Pääbo created his own methods of sequencing the ancient DNA".

Keywords: Nobel Prize in Physiology or Medicine 2022, Svante Pääbo, human evolution, genome, hominids.

On October 3, 2022, the 121-st Nobel Week started in Stockholm. The Nobel Assembly at the Karolinska Medical Institute was traditionally the first to announce the names of the Nobel Prize laureates in physiology and medicine. A little earlier, the Clarivate Analytics company, the successor of the Institute for Scientific Information founded in 1956, had claimed the names of citation laureates who might be the most likely laureates for the Nobel Prize in Physiology or Medicine 2022 [1].

The most prominent laureates considered Masato Hasegawa, the Head of the Department of Brain and Neurosciences of the Tokyo Metropolitan Institute of Medical Sciences (Japan) and Virginia Man-Yee Lee, the Director of the Center for Neurodegenerative Diseases Research of the Department of Pathology and Laboratory Medicine of the University of Pennsylvania (USA), who made a significant contribution to the study of neurodegenerative diseases, in particular, they isolated a TDP-43 protein, the misfolded variant of which formed aggregates in neurons of patients suffering from such severe brain diseases as amyotrophic lateral sclerosis, frontotemporal dementia and Alzheimer's disease.

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Secondly, it is worth mentioning the American researcher Mary-Claire King, a professor of medicine and genomic sciences at the School of Medicine of the University of Washington (USA), who was named a probable laureate for discovering the role of mutations in the BRCA1 gene, which is respon-

sible for DNA repair in breast and ovarian cancer patients, and demonstration of hereditary predisposition to these diseases.

In the third place, we should name Stuart H. Orkin, an emeritus professor of pediatrics at Harvard Medical School and a researcher at the Howard Hughes Medical Institute (USA), who could get the Nobel Prize for research into the genetic basis of blood diseases with the aim of improving gene therapy of sickle cell anemia and beta-thalassemia.

As widely known, the predictions made by Clarivate Analytics usually come true in the course of time; therefore the scientists mentioned above have a good chance of receiving the Nobel Prize in the years to come.

But in 2022, Swedish researcher Svante Pääbo became the laureate of the 113-th Nobel Prize in Physiology or Medicine. Thomas Perlman, the Secretary-General of the Nobel Committee for Physiology and Medicine, announced the rationale for the award decision stating that the scientist was awarded this prestigious award for "his discoveries concerning the genomes of extinct hominids and human evolution". According to the official press release, the fundamental research of the scientist "gave rise to an entirely new scientific discipline; *paleogenomics*. By revealing genetic differences that distinguish all living humans from extinct hominids, his discoveries provide the basis for exploring what makes us uniquely human" [2].

The coronavirus pandemic caused the cancellation of the traditional Nobel Prize ceremony in Stockholm in 2020-2021. The organizers held only small ceremonies for the local public with online inclusions of laureates who received diplomas and medals in their native countries. This year, on the day of Alfred Nobel's death (December 10), the traditional official ceremony and the banquet have finally taken place in the concert hall of the Stockholm Philharmonic and the city hall, respectively. The Nobel Foundation decided to invite the 2020-2022 Nobel laureates to take part in the events, excluding the ambassadors of the Russian Federation and Belarus to Sweden in connection with the war of Russia against Ukraine. The Nobel Prize amount for 2022 was set at 10 million Swedish kronor, or $910,000.

So, what do we know about the life path and scientific achievements of the 2022 Nobel laureate in physiology and medicine?

67-year-old professor Svante Pääbo works as the director of the Department of Evolutionary Genetics of the Max Planck Institute for Evolutionary Anthropology in Leipzig (Germany). He was born on April 20, 1955 in Stockholm (Sweden). His mother, Karin Pääbo, moved to Sweden from Estonia after its occupation by the USSR in 1940, and worked as a chemist. She had an affair with the head of the laboratory and Svante's father, Sune Bergström, a member of the Board of the Nobel Foundation and a world-renowned biochemist who in 1982, together with the Swede Bengt Samuelsson and the American John Wayne, won the Nobel Prize in Physiology or Medicine for the discovery of prostaglandins and close biologically active substances. Sune Bergström was married and had a son, the same age as Svante, who learned about the existence of his half-brother only shortly before his father's death in 2004.

In his early childhood, Svante Pääbo was interested in archaeology, which caught his heart even more at the age of 14 after a trip to Egypt with his mother. He wanted to be like Indiana Jones, discovering mummies and other ancient hidden treasures. After returning to Sweden, Svante explored places where trees had fallen after severe storms searching for fragments of Stone Age pottery. Since 1975, Svante studied the Russian language at the school for interpreters of the Swedish Armed Forces, as well as Egyptology, Coptic language and the history of science at the Faculty of Humanities of Uppsala University (Sweden). After two years of studying at the university, he came to the conclusion that archeology was not as romantic as he had thought, and switched to studying biochemistry and medicine since then. His father played a certain role in choosing his future specialty, although Svante was seeing him only on Saturdays and did not maintain a close relationship with him.

After graduating from the Medical School of Uppsala University in 1980, S. Pääbo worked as a physician for some time, and in 1981 he returned to the university, where he entered postgraduate studies at the Department of Cell Research. In 1986, Svante Pääbo defended his thesis on molecular immunology, in which he investigated the effect of adenoviral protein E19 on the immune system. Later on, he worked for some time at the Institute of Molecular Biology of the University of Zurich, Switzerland, and at the Institute of Cancer Research, London. In 1987, S. Pääbo moved to the University of California, Berkeley (USA), where he embarked on the isolation of genetic material from fossils and animals that had become extinct in recent times. In 1990,

Svante Pääbo moved to Germany, where he worked as a professor of general biology at the University of Munich until 1997, and then became one of the five founding directors of the Max Planck Institute for Evolutionary Anthropology, Leipzig, where he headed the Department of Evolutionary Genetics. S. Pääbo also lectures at the Okinawa Institute of Science and Technology (Japan). In 2015, he was awarded the Doctor of Sciences degree.

Svante Pääbo is an academician with many scientific organizations, such as the Royal Swedish Academy of Sciences (since 2000), the European Academy (since 1998), the Berlin-Brandenburg Academy of Natural Sciences and Humanities (since 1999), the German National Academy of Sciences Leopoldina (since 2001) , the Saxon Academy of Sciences, the US National Academy of Sciences (since 2004), the American Academy of Arts and Sciences (since 2011), the French Academy of Sciences, and the Royal Society of London (since 2016).

Svante Pääbo is a laureate of a huge number of scientific honors, including the Leibniz Prize (1992); Max Delbrück Medal (1998); the Karus Prize of the Leopoldina Academy of Sciences (1999); the Rudbeck Prize (2000); the Leipzig Science Prize of the Saxon Academy of Sciences, Ernst Schering Prize (2003); the Virchow medal, the Louis-Jeantet Prize in the field of medicine (2005); the Golden Plate Award of the American Academy of Achievement (2008); the Darwin-Plakette of the Leopoldina Academy of Sciences, the Kistler Prize of the Foundation For the Future (2009); Theodore Bücher Medal for Outstanding Achievement in Biochemistry and Molecular Biology (2010); Newcomb Cleveland Prize, German Society of Clinical Chemistry and Laboratory Medicine Award for Biochemical Analytics (2011); Gruber Genetics Prize (2013); the Breakthrough Prize in the field of life sciences (2015); Keio Medical Science Prize (2016); Dan David Prize (2017); Nakasone Award, Princess of Asturias Award, Körber Prize, Nirenberg Prize (2018); the Wiley Prize in Biomedical Sciences, the Darwin-Wallace Medal (2019); the Japan Prize (2020); the International Fissen Foundation Prize, the Messri Award of the University of Southern California (2021) and many others. In 2007, S. Pääbo was added to the list of the 100 most influential people in the world according to the Time magazine.

Svante Pääbo remained single for a long time and admitted in his book "Neanderthal Man: In Search of Lost Genomes" (2014) to being bisexual,

but since 2008, he has been married to his colleague, American Linda Vigilant, with whom they have a common son and a daughter, and are raising two more children from Linda's first marriage [3].

At one of congresses held by the Federation of European Biochemical Societies, one of the authors of this article met Svante Pääbo and, sincerely admiring his "genetic archeology" and human evolution research, invited him to speak as an honorary lecturer in Kyiv at the Parnas Conference on Biochemistry and Molecular Biology 2018 and at the Ukrainian Biochemical Congress 2019 in Ternopil, but then Svante politely declined, citing his busy schedule, which we dwell upon below.

Svante Pääbo was awarded the Nobel Prize in Physiology or Medicine for discoveries related to the genomes of extinct hominids and human evolution. Who are hominids? And what did the scientist himself do for a deeper understanding of human evolution?

Hominids (*Hominidae*) is a family of human-like primates, which primarily includes humans and their extinct ancestors (and, according to the modern classification, also great apes: orangutan, gorilla, and chimpanzee). Scientists have always been interested in the question of how the evolution has led to the emergence of modern humans with their high intelligence, complex emotions, extensive social relations, and the ability to speak and learn about the environment, which ultimately brought them to domination on our planet, changing it to their needs and paving the way into space? The only source of information about human evolution is the paleontological findings of the extinct human ancestor remains. However, the comparative studies until recently only allowed us to make assumptions about the appearance and lifestyle of ancient hominids. Svante Pääbo made a breakthrough in this field, laying the foundations of a new science, the paleogenetics, which benefits from genetic methods in paleontological research [4]. Although the term "paleogenetics" was

proposed by Emil Zuckerkandl and chemist Linus Pauling well in 1965 [5], it was Svante Pääbo who became a godfather for the new discipline.

Is it possible to study genomes of extinct biological species? Can genes, which are organic polymers of deoxyribonucleic acid (DNA), easily destroyable under the influence of environmental factors, be preserved after thousands or millions of years? Of course, no, they cannot. However, Svante Pääbo really did the impossible thing. He invented a way to study the genomes of ancient creatures. How exactly did this happen?

S. Pääbo's passion for Egyptology played a big role in the discovery. Despite the fact that he left his intention to become an archeologist due to an excessive philological inclination in this specialty and his work at Uppsala University under the supervision of Per A. Peterson on a thesis of molecular immunology, he did not leave the idea to investigate the Egyptian mummy with the help of modern methods of genetics and molecular biology, which began to thrive in the 1980s. First of all, he convinced himself of the possibility of DNA isolation from a piece of oven-dried veal liver. Then, with the help of his professor of Egyptology, the young scientist obtained a tissue sample of an Egyptian mummy from the Swedish museum in Uppsala, but failed to sequence DNA. However, the next experiment with mummy samples from the German Bode Museum of East Berlin proved successful. Svante Pääbo worked at the laboratory in the evenings and on weekends secretly from his scientific supervisor, because he believed, with a good reason, that this initiative would not please him. S. Pääbo told him everything only after he managed to isolate the mummy's DNA. The supervisor was happy, and the results were published in 1984 in a small German magazine. A year later an article devoted to an extended study of 23 Egyptian mummies was published in Nature Journal [6].

The article in Nature was read (and impressed) by Allan C. Wilson, an evolutionary molecular biologist from the University of California at Berkeley, who studied the DNA of extinct animals and had just isolated the DNA of *Equus quagga quagga*, a zebra-like animal which became extinct in the 19-th century. Wilson asked Pääbo to leave his subordinates for some time off for joint research and was quite surprised when it turned out that Svante Pääbo was only a graduate student and did not have his own laboratory. After all, in 1987, Pääbo moved to the United States and began working at the Wilson's laboratory, who then conducted research on mitochondrial DNA of 147 people from five different geographical locations with the help of restriction enzymes and proved that they all originated from the same woman who lived probably 200 thousand years ago in Africa [7]. Scientists focused on the study of mitochondrial DNA because of its small size (16.5 thousand pairs of nucleotides) and a significant number of copies, although it was inherited only through the maternal line. Wilson's laboratory became the first academic laboratory to be equipped with a thermal cycler necessary for conducting the polymerase chain reaction (PCR), the newest technique at the time, for the discovery of which the American Kary B. Mullis later was awarded the Nobel Prize in Chemistry of 1993. Together with Wilson, Pääbo studied mitochondrial DNA isolated from the brain of a 7,000-year-old human sample, using the PCR technique for the first time [8].

The analysis of the results of this work showed that the contamination of samples with genetic material of contemporary humans presents a challenge for studying the ancient human DNA, as even a small dust particle from the human skin (for example, a long-dead museum director) may distort the research results. This prompted S. Pääbo to focus on improving the technique for isolation and sequencing of ancient DNA. To do this, he switched to studying the DNA of ancient animals, such as giant sloths, mammoths and marsupial wolves, thus making a number of interesting discoveries. For example, he proved that giant flightless moa birds, which were exterminated in New Zealand well 500 years ago, were genetically closer to the Australian emu ostrich than to the flightless kiwi bird currently living in New Zealand. S. Pääbo also proposed a method of conservative primers for studying mitochondrial DNA isolated from dried or alcohol-treated tissue samples of mammals, birds and fish. This method opened new perspectives for research in the field of evolutionary genetics; it could also be applied to systematize knowledge about the genetic diversity of natural populations. The publication describing this method in the PNAS journal [9] has about 6,000 citations and is currently the second most popular work by Svante Pääbo.

Over next several decades, S. Pääbo studied the changes that occur in DNA over time (fragmentation, contamination with the genetic material of microorganisms, chemical modification of nucleotides, for example deamination of cytosine to uracil)

and prevent obtaining correct results. Eventually, he and the laboratory staff developed more advanced techniques for isolation and analysis of ancient DNA. S. Pääbo used special clean rooms for DNA isolation, developed silica-based DNA purification techniques, discovered the connection between the presence of endogenous DNA and a degree of amino acid racemization [10], determined the rate of DNA decay under different conditions and established optimal conditions for its safe storage (for example, permafrost), suggested using a system of mandatory reproduction of research results obtained by other laboratories.

These researches continued even after S. Pääbo moved to Europe in 1990 to work on a professor position at the University of Munich (Germany), which he got by a random coincidence of circumstances. A year before, Pääbo came to his girlfriend in Munich and held a seminar at the university, after which he was offered to submit an application for a professorship. After a year of considering the application, he already broke off the relationship with the girlfriend, yet agreed to the university's offer. This is how fate brought Svante Pääbo to the University of Munich, where he was destined to launch one of his most ambitious projects – the study of Neanderthal genome – the closest human relatives that extinct 30-40 thousand years ago.

The remains of a Neanderthal were first found in 1856 in the *Kleine Feldhofer Grotte* near the Neandertal Valley in North Westphalia (Germany), which gave the name to this hominid. The valley itself was named after Joachim Neander, a Calvinist theologian of the 17-th century, who often traveled through it near Dusseldorf, composing praise hymns in honor of the divine beauty of nature, and died at the age of 30 from tuberculosis. At the time of the strange bones discovery, people were convinced that our ancestors had always been like us, all the way back to Adam. Charles Darwin's outstanding on the Origin of Species, in which the theory of human evolution from apes was first presented, was published only 3 years later. Therefore, scientists decided that the discovered anomalous skeleton belonged to a lost crook-legged Cossack suffering from rickets, and the enlarged brow arches suggested that the poor Cossack was constantly frowning in pain caused by rickets. Only in 1864, the British geologist William King admitted that the skeleton found belonged to an extinct human species, and gave it the name Neanderthal – *Homo neanderthalensis*. However, King described this person as a "morally dark" and unintelligent beast, similar to representatives of the "savage races" of Africa or Oceania. Later, the image of Neanderthals was often refracted through the prism of other ideologies, sometimes racist [11]. Svante Pääbo did a lot to change these perceptions, but more on that later.

Having received a Neanderthal humerus bone sample from the Rhine Museum of Bonn, S. Pääbo isolated and successfully sequenced mitochondrial DNA. The publication of the results of this undertaking in the Cell journal in 1997 [12] is considered a turning point in the development of evolutionary genetics. Comparison of the mitochondrial DNA sequences of Neanderthals, humans from different geographical regions, and chimpanzees showed that modern humans originated from Africa (as Wilson claimed), where a common ancestor of all humans lived 120,000 to 150,000 years ago. Moreover, this work showed not only that DNA can be successfully isolated and sequenced from Neanderthal remains, but also that Neanderthals and modern humans were completely different groups that had nothing in common with each other in terms of mitochondrial genes and diverged approximately 550-690 thousand years ago.

After this success, in 1997, Svante Pääbo was offered a position of director of the Genetics Department at the new Max Planck Institute for Evolutionary Anthropology in Leipzig. The design of the ultra-modern glass-and-concrete building of the Institute in the shape of a crescent and equipped with hall plasma screens demonstrating primates was performed to meet the personal preferences and the Swedish mentality of S. Pääbo: inside the building, from the first to the last floor, a rock-climbing wall was constructed with a roof sauna on top. Pääbo was offered this fantastic proposition not only for his scientific achievements. After reunification of Germany, the central authorities allocated huge funds for foundation of scientific institutions in East Germany, which had far fewer institutions of the kind than in West Germany. Special attention was paid to the sciences that were poorly developed in this part of Germany, especially anthropology, the decline of which was associated with the ill-favored legacy of the Nazi era. For example, a notorious doctor, Josef Mengele known by a nickname Angel of Death, who carried out terrible medical experiments on prisoners of Auschwitz concentration camp and killed tens of thousands of people, worked as an

assistant and defended his thesis at the Kaiser Wilhelm Institute of Anthropology, Human Genetics and Eugenics (Berlin) founded in 1927 with the aim of finding scientific justifications for the concept of "racial hygiene" for the German people. That is why German scientists were reluctant to have any relation to anthropology for many years.

The impressive research potential of the new Institute made it possible to implement the even more ambitious Pääbo project – the sequencing of the complete nuclear genome of Neanderthals, which was inherited along both parental lines and had a size of about 3 billion nucleotide pairs, which meant it exceeded the mitochondrial genome by almost 200,000 times.

It should be noted that not even a modern human nuclear genome had yet been sequenced by that time. In 1990, the largest ($3 billion) international biological research project The Human Genome was launched, which was headed by James Watson, the scientist who received Nobel Prize for the discovery of the DNA molecule structure in 1962 in cooperation with Francis Crick and Maurice Wilkins. The first working version of the genome was published in 2001 [13]. By 2003, 85% of the human genome was sequenced, and only in April 2022 the project was completed (99.99% of the genome sequenced) [14]. It should be noted that in 1998, a similar commercial project worth only $300 million was started by a private company Celera Corporation (USA), headed by the famous geneticist and biotechnologist Craig Venter, who intended to patent part of the DNA sequences (especially since Venter himself became one of the donors, whose genome was published in 2001 [15]). After all, under the pressure of US President Bill Clinton, the results of Celera's work were transferred to the national Human Genome Project. Huge financial infusions, new electronic equipment and computerization of research, as well as competitive environment stimulated the development of new generation sequencing methods that became increasingly productive and cost-effective.

The complexity of Neanderthal genome sequencing was preconditioned not only by its large size, but also by the fact that over thousands of years the Neanderthal bones were so immensely colonized by bacteria and fungi that almost all the DNA contained in them was exogenous. Moreover, the remains of Neanderthal DNA were all about short fragments that needed to be assembled like a giant puzzle. Many scientists believed the mission was impossible.

However, hard work, extensive experience and novel methods of ancient DNA sequencing used by S. Pääbo's team made it possible to overcome all the obstacles. The advanced computer programs used to reconstruct the Neanderthal genome compared DNA fragments from ancient bones with the already known chimpanzee`s and human genomes. A new highly productive genome sequencing technique able of processing 25 million nucleotides with an accuracy of 99% or higher in one four-hour cycle, developed by 454 Life Sciences Corp. (Branford, Connecticut, USA), also contributed to the project [16]. In the end, all above efforts were crowned with a publication in 2010 of the draft genome of a Neanderthal who lived tens of thousands of years ago, and five comparative genomes of modern people from different regions of the planet, as well as the stunning conclusion of the study: Neanderthals and modern people, despite significant differences, had 1-4% of common genetic material due to interbreeding of a small number of Neanderthals and early humans, which probably occurred approximately 60-70 thousand years ago, when the ancestors of modern humans had left Africa and settled in Eurasia [17].

This same year, S. Pääbo and his colleagues reported another fundamental discovery made through the analysis of mitochondrial DNA isolated from a finger bone found in 2008 in the Denisova Cave in the Altai Mountains in southern Siberia. The bone belonged to a girl from an unknown group of hominids named Denisovans by the researchers after the place of discovery [18]. For the first time in the history of science, a new hominid was identified only with the help of genetic analysis. In 2012, the Denisovan nuclear genome was sequenced [19]. It turned out that they were very different from both Neanderthals and modern people, while Denisovans transferred up to 4-6% of their genome to people who live today in certain parts of Southeast Asia and in Melanesia, on some island groups in the Pacific Ocean northeast of Australia.

So, the discoveries of Svante Pääbo significantly influenced the understanding of our evolutionary path. It turned out that the ancestors of modern humans (Homo sapiens), who originated in Africa 150-200 thousand years ago and migrated to Eurasia 60-70 thousand years ago, coexisted and interbred for 20-30 thousand years with others, now extinct species of human ancestors, such as Neanderthals – mainly in Europe and Denisovans – in Asia, who genetically significantly differed from each other and

transferred a small portion of their genes to modern people. After sequencing the genomes of ancestors of the modern people from Romania [20] and Western Siberia [21], which lived about 40,000 years ago, S. Pääbo discovered signs of interbreeding with Neanderthals and borrowing part of their genes. Interbreeding could have given modern humans genes useful for adapting to a climate colder than Africa's. Perhaps, scientists concluded that the ancestors of modern humans and other hominid species were on the brink of biological compatibility, and their hybrid male offspring probably suffered from high infertility [22]. The Neanderthal genome was found to contain mutations in three genes, which caused immune rejection of male fetus in pregnant female *Homo sapiens* that inherited these mutations from a Neanderthal father [23].

It is interesting that the Neanderthal remains were also found in Ukraine, for example in Lviv, Chernivtsi regions and Crimea. According to the assessment by famous archaeologist Thorsten Uthmeier from the Institute of Early History of the University of Erlangen-Nuremberg (Germany), the remains of Neanderthals found in the Crimea were at least 10 thousand years younger than any other known similar finds. Moreover, archaeological excavations at this Neanderthal site revealed evidence of their coexistence with modern humans [24].

Another find by Svante Pääbo at Denisova Cave in Altai is the proximal phalanx of a toe, which turned out to belong to a Neanderthal. The study of the find in 2014 made it possible to almost completely decode the Neanderthal genome and compare it with the genomes of other people [25]. The research results greatly contributed to clarification of timeframe for branching different types of hominids in the process of evolution, to learn about the small population and strangeness of Neanderthals (by signs of closely related crosses, inbreeding, and poor genetic diversity), as well as about their interbreeding with Denisovans.

Subsequently, Svante Pääbo examined many samples of Neanderthal and Denisovan remains from around the world, and obtained even more complete data on their genomes and population genomic variation. Significant success was obtaining the second (2017) and third (2020) complete Neanderthal genomes, characterized by a high degree of DNA sequence coverage, which was isolated from the remains found in Vindija Cave in Croatia and Chagyrskaya Cave in Altai, respectively.

Numerous finds of Neanderthal remains from Spain to Siberia have contributed to archaeological and genetic research, the results of which have changed the perception of Neanderthals as hefty, fearsome, and stupid "ape-men", who had no moral and could not smile. It turned out that the abilities and behavior of Neanderthals were in many respects similar to those of humans. They made specialized tools, ornaments from shells, dark feathers and bird claws, cared for wounded, buried dead tribesmen, made ocher and other pigments to paint their faces and bodies, prepared glue from birch bark by heating it to high temperatures, used toothpicks and left us abstract cave drawings of lines and dots [11]. In 2007, Svante Pääbo showed that Neanderthals shared two evolutionary changes in FOXP2 gene, responsible for the development of speech and the ability to speak, with modern humans, which suggested the existence of language in Neanderthals [26].

Moreover, it became possible to recognize the physiological features of modern people who inherited certain gene alleles or haplotypes (groups of genes inherited from one parent) from extinct hominids. For example, it turned out that the Denisovan gene version that encode the subunit of EPAS1 transcription factor (the protein also known as HIF-2α — hypoxia-inducible factor 2α) was widespread among Tibetans. HIF-2α is induced when the oxygen concentration decreases while ascending to a high altitude and allows adaptation to a hypoxic high-altitude environment, in particular to the air of the Himalayas at an altitude of 4000 m, which contains only 40% of the normal oxygen content [27]. By the way, this archaic allele of the HIF-2α gene is also known as the "super-athlete gene" reflecting its responsibility for achieving higher sports results.

Neanderthals also made a genetic contribution to the phenotypes of modern Europeans. This applies, for example, to some physical and behavioral characteristics such as skin and hair color, height, sleep patterns, mood and smoking predisposition. Interestingly, Neanderthal haplotypes contribute to both lighter and darker skin and hair color. This indicates that the Neanderthals themselves probably differed from each other in these features [28]. By the way, the archaic haplotype encoding HYAL proteins involved in the metabolism of hyaluronic acid and responsible for the response of cells to ultraviolet light, is widespread in modern people (mainly in East Asia). Interestingly, *Homo sapiens* lost this haplotype while migrating from Africa to Eurasia, and then received it again from Neanderthals [29].

Other examples are the genes of extinct hominids that have an influence on our immune response to various types of infections. As a result of migration, the ancestors of modern people got to Europe and Western Asia, where they mixed with archaic people who had lived there for more than 200 thousand years and were well adapted to local pathogens, thus eliciting a significant immune advantage provided by the archaic alleles.

For example, ancient haplotypes encoding the three Toll-like receptors TLR6, TLR1, and TLR10 are common in modern humans, two of which originate from Neanderthals and the third one from Denisovans. These receptors are key components of the innate immune system, which constitute an important first line of immune defense against bacteria, fungi, and parasites. Archaic alleles of TLR genes induce increased resistance to pathogens of infectious diseases, yet contribute to onset of allergic diseases [30].

Humans that inherited ancient variants of certain genes from extinct hominids may differ from the rest of people in the body's response to viruses due to the archaic allele of Stat2 gene, which encodes a transcription factor important for signal transmission from interferon, the main antiviral cell protection cytokine [31], as well as due to archaic haplotypes encoding 2'-5'-oligoadenylate synthases (OAS) – enzymes that synthesize 2'-5'-oligoadenylates, which, responding to the interferon signal, activate latent ribonuclease, which destroys RNA (including a viral one) in a cell, thereby preventing the virus from multiplying [32].

Archaic haplotypes can exert both positive and negative effects on COVID-19 course. For example, the Neanderthal haplotype, located on chromosome 12, which encodes proteins– enzyme activators important for the process of infection with RNA viruses, protects against the severe course of the disease at the same time [33]. Today, approximately 50% of people in South Asia and 16% of people in Europe are carriers of a genomic segment of about 50 thousand nucleotide pairs in chromosome 3, inherited from Neanderthals. This segment is responsible for a severe course of COVID-19, when patients more often need artificial ventilation of lungs and more often die from the infection [34].

In addition to Neanderthals and Denisovans, Svante Pääbo studied the genetic material of other hominids. In 2012, he studied a femoral bone found in 2008 on the Irtysh River near the village of Ust-Ishim in Siberia by fossil hunter Nikolai Peristov, who was searching for mammoth tusks in the muddy banks. The DNA analysis showed that the bone belonged to a male human (called Ust'-Ishim man), who lived 45 thousand years ago and belonged to a group that gave rise to all non-African people, but had not yet divided into Neanderthals and Denisovans [35].

Svante Pääbo admits that the most technically challenging task for his group was to disclose the nuclear DNA sequence of an unknown human species, which remains of 28 approximately 430-thousand-year-old individuals were found in the Sima de los Huesos cave complex (Pit of Bones) in the Sierra de Atapuerca mountains in northern Spain. It emerged that these ancient people, named Heidelberg people (*Homo heidelbergensis*), were more closely related to Neanderthals than to Denisovans [36].

The creation of highly effective platforms for DNA sequencing made it possible to study the diversity of human genomes. In 2010, the results of the pilot phase of the International Research Consortium 1000 Genomes project were published, the purpose of which was to study the variability of the human genome among the largest populations, as well as the relationship between genotype and phenotype [37]. By the way, this publication in the Nature journal became the most popular scientific work of Svante Pääbo as one of the authors (about 11,400 citations). In addition, in 2016, the Genome Diversity Project was completed under the auspices of the James Simons Foundation, a well-known American mathematician and philanthropist. As part of this project, the genomes of 300 people from 142 different populations were studied, reflecting the widest possible anthropological, linguistic and cultural human diversity [38]. An ENCODE (Encyclopedia of DNA Elements) project for mapping genome regulatory elements and other sequences, including epigenomic ones, launched in 2003 by the American National Institute for Human Genome Research, was also implemented, which findings showed that the human genome was comprehensively transcribed, which meant that the significant part of the non-protein coding regions remained functional. The discovery expanded the perception of chromatin structure [39]. The results of the projects on the study of human genomic variations have become important sources of knowledge for understanding the genetics of human population and researching our evolutionary past, in particular, the origin and migration paths of the ancestors of various peoples all over the world.

For example, it became known that the ancestors of the native inhabitants of America came from northeastern Siberia to the now flooded area called Beringia, which then was a land bridge between Eurasia and America. They lived there for 6,000 to 8,000 years, and with the beginning of melting American glaciers, they set upon moving along the coast of the Pacific Ocean (about 13,000 to 15,000 years ago) and gradually populated North and South America. Unfortunately, the great diversity of populations that arose under the favorable conditions on new lands was largely destroyed after the discovery of America by Europeans. The genomic research made it possible to find out why the modern inhabitants of Siberia and America are not genetically related. It turned out that the ancestors of Americans came from a group related to the ancient North Siberians, genetically different from Europeans and Asians, which mixed with the natives of East Asia moving north about 20 thousand years ago. Instead, the ancestors of the inhabitants of Siberia emerged as a result of two later waves of interbreeding with East Asians and the displacement of earlier populations [40, 41]. It is interesting that according to the results of DNA sequencing, the oldest known close relative of Native Americans outside America is a 14,000-year-old male whose tooth fragment has been lying in a drawer left by Soviet archaeologists for several decades after it was found in 1976 near the village Ust-Kyakhta, located between the southern shore of Lake Baikal and the Mongolian border, some 4.5 thousand km from Beringia [42].

The majority of Europeans appeared to descend from steppe tribes of pit herders who lived 6,000 years ago north of the Black Sea, in particular on the territory of modern Ukraine, and about 4,500 years ago migrated to Central Europe, spreading the early form of the Indo-European language and giving rise to the Corded Ware Culture [43]. These tribes were different for their practice of burying dead members of a same family in the embryo position in burial mounds, having them sprinkled with red ocher, which symbolized life, light and purification. Dishes with food, stone (rarely copper) tools and weapons were usually scattered around those buried. The ancestors of Ukrainians are also known for the fact that they were the tallest inhabitants of Europe and invented one of the first wheeled vehicles – a cart pulled by oxen [44].

The study of British genomes revealed that over the past 2,000 years, alleles of genes that account for: 1) blond hair and blue eyes, which are often inherited along with fair skin; 2) the ability of adults to absorb lactose and digest milk; 3) functional features of some receptors of the immune system, have spread in the population. In addition, tiny changes in hundreds of genes relate to such traits as height, head circumference of babies, and hip size of women, which are crucial for childbirth [45]. Light skin and the ability to digest milk probably allow for more vitamin D in the sunlight-deficient conditions of British islands. Similar trends are characteristic of the whole Europe: genes for light skin and the gene for lactose tolerance began to spread among dark-skinned Europeans whose ancestors migrated from Africa 5.8 thousand and 4.3 thousand years ago, respectively. Beyond that, the pit culture tribes brought genes of tall stature to Europe [46].

From time to time people have discovered unique finds of hominid remains that differ from known species of ancient humans. Thus, in 2003, a skeleton of just about a meter tall 66-87-thousand-year-old adult woman was found in a remote cave on the Indonesian island of Flores, who was named a "hobbit" or *Homo floresiensis* [47]. In 2013, the remains of more than 15 ancient representatives of a new species of hominid named *Homo naledi* ("naledi" means "star" in the local Sotho language), were found in the Rising Star Cave in South Africa. They were tall, slender hominids with long legs, which combined features of modern humans (rounded skull; foot adapted for upright walking) and monkey features (small brain; shoulders and fingers adapted for climbing trees) [48].

Svante Pääbo does not rule out that other, yet unknown species of extinct hominids could have existed. He is enthusiastic about the research of the ancient people of China and their evolutionary connections with Neanderthals and Denisovans. The migration routes of ancient people, which were obviously quite intricate, also require further research. There is evidence that migration probably took place not only from Africa to Eurasia, but also in the opposite direction. The study of the first isolated DNA of an ancient African human, whose 4.5-thousand-year-old remains were found in a high-altitude Mota Cave in southwestern Ethiopia, suggest a migration of farmers from the Middle East to Africa and their interbreeding with Africans [49]. The return migration of Eurasians to Africa resulted in the presence of 0.3% Neanderthal DNA in the genome of North Africans [50].

The research in the genomes of ancient Africans is quite challenging issue due to accelerated degradation of DNA in a tropical climate. An exception is mummified human remains, some of which may contain preserved DNA samples. Researchers of the Egyptian mummy genomes managed to isolate DNA of the causative agents of malaria and toxoplasmosis, as well as the DNA of a number of plants, such as fir and pine (considered components of embalming resins), castor, linseed, olive, almond and lotus [51].

Now, Svante Pääbo and his team are working on new methods that would enable reconstructing DNA from even more damaged fragments contained in smaller samples. Perhaps, these methods will make it possible to study more ancient DNA, as well as genomes of ancient people who lived in a hot and humid climate. Meanwhile, other researchers propose to isolate DNA from different layers of cave soil, which might contain blood and epithelium of archaic people who lived in one place for thousands of years [52], or to extract from the remains not DNA, but proteins, which are more stable and usually better preserved (for example, collagen) [53].

More cost-effective sequencing methods opened the door to determining the genome sequence of each human and thereby heralded a new era of personalized medicine, which is based on a choice of diagnostic, therapeutic and preventive means that are optimal for each individual, taking into account his/her genetic, physiological, biochemical and other individual characteristics. The progress in the field of genomics is really impressive, as in the 1980s, sequencing the human genome was considered an almost unattainable task of biology for the next 100 years with billions of dollars invested, while today $100 genome sequencing tests are popular among Americans, with the help of which one can find out the own racial origin just for fun [54]. By the way, forensic criminology currently benefits from a small and affordable device for DNA sequencing – MinION™, developed by Oxford Nanopore Technologies (Great Britain), which allows all interested to quickly identify a biological species by its genome [55].

Despite the rapid progress of paleogenetics, the question of extinction of all other archaic human species, which over hundreds of thousands of years had adapted well to living conditions in Eurasia, remains unsolved. Did modern humans, having superior intelligence, overtake other ancient human species in the struggle for resources, or did they perhaps exterminate them all? The likely reason is that archaic humans lived in small, isolated populations with a high level of inbreeding and could not compete with the ancestors of modern humans, who multiplied and spread rapidly. So, most likely, the real competition between ancient hominids and early modern humans did not manifest itself in local fights for food or territory, but took the form of a silent demographic marathon that lasted for millennia, when each species tried to reproduce at highest possible rate, until some disappeared falling so far behind. Whatever the mechanism of this displacement may be, it seems suggesting that our breed appeared to be more successful than those extinct. After all, we are still alive, while the ancient hominids ceased to exist as soon as our paths crossed [11].

What features of modern humans made them a special species that dominated other biological species on Earth?

The brain of modern humans differs from the one of apes in size, shape, and cerebral cortex organization, especially in the frontal lobe, which is responsible for complex cognitive tasks, such as social cognition, using tools, and language (these structural differences appeared 1.7-1.5 million years ago) [56]. Even the brilliant Charles Darwin emphasized that special, prominently developed features of modern human were an aptitude for cooperation, social learning and cumulative culture. The emergence of such a unique feature of our species as using language was probably predispositioned by a need to facilitate the process of cooperation. The aptitude for social learning and conformity has led to the emergence of new factors that constrain and motivate human behavior, such as morality, social norms, and social institutions. Constant cooperation has led to evolution of a strong coalitional psychology, which unites us whenever we feel that our group is facing external threats (this trait may appear to be prominently developed in Ukrainians) [57].

However, it is not entirely clear how to explain the significant difference between apes and humans, as the difference between the genomes of these two species makes only 1-2%. The family of human genes, which expanded very quickly during evolution, became a group of brain genes, the size of which has increased more than twice. Beyond that, it turned out that humans differ from other animal species in the rate of acquiring new genes and disposing of unnecessary ones. This turnover of genes in hu-

mans appeared to be 1.6 times faster than the one in apes, and 2.8 times faster than in dogs or rodents [58]. Supposedly, genes able to regulate the speed of evolution exist, providing the process with a variety of genetic material.

And it turned out that APOBEC cytidine deaminases, which recognize certain sequences of DNA and RNA (common to viruses) and cause point mutations (changing cytosine to uracil), are in fact capable not only of fighting viruses but also possibly speed up the evolution of species, if these mutations occur in the DNA of germline cells. An increase in the number of mutations contributes to higher risk of malignant tumors, but at the same time it may influence the genome of future generations and, ultimately, change the course of evolution. For example, the analysis of genomes of modern humans, Denisovans, Neanderthals, and chimpanzees revealed about 37,000 mutations in key genome segments that might be caused by APOBEC3G protein, while the genomes of mice, rhesus macaques, and orangutans remained unchanged [59]. Interestingly, that instruments for artificial RNA editing for treatment of cancer, muscular dystrophy and other diseases are currently being developed on the basis of APOBEC (and proteins capable of other nucleotide substitutions) and CRISPR/Cas technology, [60].

These incredible discoveries and the rapid development of paleogenetics over the past 20 years have become possible through the genius and hard work of one person, yet we remember that these achievements have been accomplished by virtue of the latest advances in modern biology and informatics, bioinformatics, mathematics, and, in particular, the cumulative scientific progress reached by many thousands of scientists. At the same time, we clearly know that this is only the beginning – brilliant and successful – of a fantastic and wonderful history of comprehending the HUMAN origin and that soon we will become witnesses and/or participants of new discoveries about the history of our origin and genesis.

The exciting impressions from the discovery of human evolution secrets afford us an opportunity to once again ask the sacred question: "Who are we, people, and what is our place, our role and our future on planet Earth and beyond?" And, in the end, they remind about the main thing – the responsibility of people for the future of our planet. Wars, the threat of using weapons of mass destruction and dangerous "dual-use" materials, the destruction of the natural environment, the extinction of living species, forests, climate change, and so on – this is an incomplete list of threats created by human activity on the planet that pose a real threat to our life on Earth.

Since childhood, Svante Pääbo have dreamed of being like Indiana Jones, an archaeologist, a seeker of historical treasures, and persistently pursued his dream. However, in fact he exceeded his wildest expectations having invented a new way of comprehending history, while absolutely no one believed in the feasibility of the method.

At a press conference at the Max Planck Institute for Evolutionary Anthropology on the occasion of awarding the Nobel Prize, Svante Pääbo admitted: "The thing that's amazing to me is that you now have some ability to go back in time and actually follow genetic history and genetic changes over time. It's a possibility to begin to actually look on evolution in real time, if you like" [61]. Saying other words, Svante Pääbo discovered an evolutionary time machine for mankind, made another step on the path of progress towards the science of the future. And here the lines from the famous novel The Time Machine (1895) by the British writer Herbert Wells come to mind: "We all have our time machines, don't we? Those that take us back are memories. And those that carry us forward, are dreams…"

ТАЄМНИЦІ ГЕНОМІВ ВИМЕРЛИХ ГОМІНІДІВ АБО ЧИ МОЖЕ ПАЛЕОГЕНОМІКА ДАТИ ВІДПОВІДЬ НА ПИТАННЯ: ХТО МИ, ЛЮДИ, Є ТАКІ? НОБЕЛІВСЬКА ПРЕМІЯ З ФІЗІОЛОГІЇ ТА МЕДИЦИНИ 2022 РОКУ

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Нобелівську премію з фізіології та медицини у 2022 р. присуджено шведському дослідникупалеогенетику, фахівцю в галузі еволюційної генетики, директору відділу генетики Інституту еволюційної антропології імені Макса Планка в Лейпцигу (Німеччина) професору Сванте Пеебо (Svante Pääbo) за «відкриття, що стосуються геномів вимерлих гомінідів і еволюції людини». Пояснюючи значення робіт С. Пеебо,

Нобелівський комітет зазначив, що «він розробив методи аналізу та відновлення прадавньої ДНК. У давніх кістках ДНК розкладається, зазнає хімічного пошкодження, а також сильно забруднюється від контакту з бактеріями та людьми, які працюють зі зразками. Використовуючи наявні технології в міру їх розвитку, С. Пеебо створив власні методи для уточнення аналізу прадавньої ДНК».

Ключові слова: Нобелівська премія з фізіології та медицини 2022 року, Сванте Пеебо, еволюція людини, геном, гомініди.

References

1. Physiology or Medicine. 2022 Citation Laureates. Regime of access : https://clarivate.com/citation-laureates/physiology-or-medicine-2022/
2. Press release: The Nobel Prize in Physiology or Medicine 2022. Regime of access : https://www.nobelprize.org/prizes/medicine/2022/press-release/
3. Svante Pääbo. Wikipedia. Regime of access : https://en.wikipedia.org/wiki/Svante_Pääbo
4. Hedestam GK. Discoveries concerning the genomes of extinct hominins and human evolution. Regime of access : https://www.nobelprize.org/prizes/medicine/2022/advanced-information/
5. Zuckerkandl E, Pauling L. Molecules as documents of evolutionary history. *J Theor Biol*. 1965; 8(2): 357-366.
6. Pääbo S. Molecular cloning of Ancient Egyptian mummy DNA. *Nature*. 1985; 314(6012): 644-645.
7. Cann RL, Stoneking M, Wilson AC. Mitochondrial DNA and human evolution. *Nature*. 1987; 325(6099): 31-36.
8. Pääbo S, Wilson AC. Polymerase chain reaction reveals cloning artefacts. *Nature*. 1988; 334(6181): 387-388.
9. Kocher TD, Thomas WK, Meyer A, Edwards SV, Pääbo S, Villablanca FX, Wilson AC. Dynamics of mitochondrial DNA evolution in animals: amplification and sequencing with conserved primers. *Proc Natl Acad Sci USA*. 1989; 86(16): 6196-6200.
10. Poinar HN, Höss M, Bada JL, Pääbo S. Amino acid racemization and the preservation of ancient DNA. *Science*. 1996; 272(5263): 864-866.
11. Mooallemjan J. Neanderthals were people, too. Regime of access : https://www.nytimes.com/2017/01/11/magazine/neanderthals-were-people-too.html
12. Krings M, Stone A, Schmitz RW, Krainitzki H, Stoneking M, Pääbo S. Neandertal DNA sequences and the origin of modern humans. *Cell*. 1997; 90(1): 19-30.
13. Lander ES, Linton LM, Birren B, 253 co-authors; International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature*. 2001. 409(6822): 860-921.
14. Nurk S, Koren S, Rhie A, 96 co-authors, Phillippy AM. The complete sequence of a human genome. *Science*. 2022; 376(6588): 44-53.
15. Venter JC, Adams MD, Myers EW, 270 co-authors, Zhu X. The sequence of the human genome. *Science*. 2001; 291(5507): 1304-1351.
16. Margulies M, Egholm M, Altman WE, 52 co-authors, Rothberg JM. Genome sequencing in microfabricated high-density picolitre reactors. *Nature*. 2005; 437(7057): 376-380.
17. Green RE, Krause J, Briggs AW, 52 co-authors, Pääbo S. A draft sequence of the Neandertal genome. *Science*. 2010; 328(5979): 710-722.
18. Krause J, Fu Q, Good JM, Viola B, Shunkov MV, Derevianko AP, Pääbo S. The complete mitochondrial DNA genome of an unknown hominin from southern Siberia. *Nature*. 2010; 464(7290): 894-897.
19. Meyer M, Kircher M, Gansauge MT, 30 co-authors, Pääbo S. A high-coverage genome sequence from an archaic Denisovan individual. *Science*. 2012; 338(6104): 222-226.
20. Fu Q, Hajdinjak M, Moldovan OT, 12 coauthors, Pääbo S. An early modern human from Romania with a recent Neanderthal ancestor. *Nature*. 2015; 524(7564): 216-219.
21. Fu Q, Li H, Moorjani P, 24 coauthors, Pääbo S. Genome sequence of a 45,000-year-old modern human from western Siberia. *Nature*. 2014; 514(7523): 445-449.
22. Callaway E. Modern human genomes reveal our inner Neanderthal. Regime of access : https://www.nature.com/articles/nature.2014.14615
23. Gibbons A. Modern human females and male Neandertals had trouble making babies. Here's why. Regime of access : https://www.science.org/content/article/modern-human-females-and-male-neandertals-had-trouble-making-babies-here-s-why

24. Uthmeier T. On the trail of the last Neanderthals. Regime of access : https://www.fau.eu/2013/06/05/news/research/on-the-trail-of-the-last-neanderthals/
25. Prüfer K, Racimo F, Patterson N, 41 co-authors, Pääbo S. The complete genome sequence of a Neanderthal from the Altai Mountains. *Nature*. 2014; 505(7481): 43-49.
26. Krause J, Lalueza-Fox C, Orlando L, Enard W, Green RE, Burbano HA, Hublin JJ, Hänni C, Fortea J, de la Rasilla M, Bertranpetit J, Rosas A, Pääbo S. The derived FOXP2 variant of modern humans was shared with Neandertals. *Curr Biol*. 2007; 17(21): 1908-1912.
27. Huerta-Sánchez E, Jin X, Asan, 23 coauthors, Nielsen R. Altitude adaptation in Tibetans caused by introgression of Denisovan-like DNA. *Nature*. 2014; 512(7513): 194-197.
28. Dannemann M, Kelso J. The Contribution of Neanderthals to Phenotypic Variation in Modern Humans. *Am J Hum Genet.* 2017; 101(4): 578-589.
29. Ding Q, Hu Y, Xu S, Wang J, Jin L. Neanderthal introgression at chromosome 3p21.31 was under positive natural selection in East Asians. *Mol Biol Evol*. 2014; 31(3): 683-695.
30. Dannemann M, Andrés AM, Kelso J. Introgression of Neandertal- and Denisovan-like Haplotypes Contributes to Adaptive Variation in Human Toll-like Receptors. *Am J Hum Genet.* 2016; 98(1): 22-33.
31. Mendez FL, Watkins JC, Hammer MF. A haplotype at STAT2 Introgressed from neanderthals and serves as a candidate of positive selection in Papua New Guinea. *Am J Hum Genet.* 2012; 91(2): 265-274.
32. Mendez FL, Watkins JC, Hammer MF. Neandertal origin of genetic variation at the cluster of OAS immunity genes. *Mol Biol Evol*. 2013; 30(4): 798-801.
33. Zeberg H, Pääbo S. A genomic region associated with protection against severe COVID-19 is inherited from Neandertals. *Proc Natl Acad Sci USA*. 2021; 118(9): e2026309118.
34. Zeberg H, Pääbo S. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. *Nature*. 2020; 587(7835): 610-612.
35. Zimmer C. Man's genome from 45,000 years ago is reconstructed. Regime of access : https://www.nytimes.com/2014/10/23/science/research-humans-interbred-with-neanderthals.html
36. Meyer M, Arsuaga JL, de Filippo C, Nagel S, Aximu-Petri A, Nickel B, Martínez I, Gracia A, Bermúdez de Castro JM, Carbonell E, Viola B, Kelso J, Prüfer K, Pääbo S. Nuclear DNA sequences from the Middle Pleistocene Sima de los Huesos hominins. *Nature*. 2016; 531(7595): 504-507.
37. 1000 Genomes Project Consortium, Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA. A map of human genome variation from population-scale sequencing. *Nature*. 2010; 467(7319): 1061-1073.
38. Mallick S, Li H, Lipson M, 75 co-authors, Reich D. The Simons Genome Diversity Project: 300 genomes from 142 diverse populations. *Nature*. 2016; 538(7624): 201-206.
39. Moraes F, Góes A. A decade of human genome project conclusion: Scientific diffusion about our genome knowledge. *Biochem Mol Biol Educ*. 2016; 44(3): 215-223.
40. Davis N. Ancient Siberia was home to previously unknown humans, say scientists. Regime of access : https://www.theguardian.com/science/2019/jun/05/ancient-siberia-was-home-to-previously-unknown-humans-say-scientists
41. Wade L. Mummy genomes reveal just how catastrophic European contact was for New World. Regime of access : https://www.science.org/content/article/mummy-genomes-reveal-just-how-catastrophic-european-contact-was-new-world
42. Price M. Oldest cousin of Native Americans found in Russia. Regime of access : https://www.science.org/content/article/oldest-cousin-native-americans-found-russia
43. Balter M. Mysterious Indo-European homeland may have been in the steppes of Ukraine and Russia. Regime of access : https://www.science.org/content/article/mysterious-indo-european-homeland-may-have-been-steppes-ukraine-and-russia
44. Yamnaya culture. Wikipedia. Regime of access : https://en.wikipedia.org/wiki/Yamnaya_culture
45. Pennisi E. Humans are still evolving – and we can watch it happen. Regime of access : https://www.science.org/content/article/humans-are-still-evolving-and-we-can-watch-it-happen
46. Gibbons A. How Europeans evolved white skin. Regime of access : https://www.science.org/content/article/how-europeans-evolved-white-skin

47. Gramling C. The 'hobbit' was a separate species of human, new dating reveals. Regime of access: https://www.science.org/content/article/hobbit-was-separate-species-human-new-dating-reveals
48. Gibbons A. New human species discovered. Regime of access : https://www.science.org/doi/10.1126/science.349.6253.1149
49. Gibbons A. First DNA extracted from an ancient African skeleton shows widespread mixing with Eurasians. Regime of access : https://www.science.org/content/article/first-dna-extracted-ancient-african-skeleton-shows-widespread-mixing-eurasians
50. Price M. Africans, too, carry Neanderthal genetic legacy. *Science*. 2020; 367(6477): 497.
51. Marchant J. Egyptian mummies yield genetic secrets. Regime of access : https://www.nature.com/news/egyptian-mummies-yield-genetic-secrets-1.12793
52. Gibbons A. DNA from cave dirt tells tale of how some Neanderthals disappeared. Regime of access : https://www.science.org/content/article/dna-cave-dirt-tells-tale-how-some-neanderthals-disappeared
53. Warren M. Biggest Denisovan fossil yet spills ancient human's secrets. *Nature*. 2019; 569(7754): 16-17.
54. Bahrampour T. They considered themselves white, but DNA tests told a more complex story. Regime of access : https://www.washingtonpost.com/local/social-issues/they-considered-themselves-white-but-dna-tests-told-a-more-complex-story/2018/02/06/16215d1a-e181-11e7-8679-a9728984779c_story.html
55. Vasiljevic N, Lim M, Humble E, Seah A, Kratzer A, Morf NV, Prost S, Ogden R. Developmental validation of Oxford Nanopore Technology MinION sequence data and the NGSpeciesID bioinformatic pipeline for forensic genetic species identification. *Forensic Sci Int Genet*. 2021; 53: 102493.
56. Ponce de León MS, Bienvenu T, Marom A, Engel S, Tafforeau P, Alatorre Warren JL, Lordkipanidze D, Kurniawan I, Murti DB, Suriyanto RA, Koesbardiati T, Zollikofer CPE. The primitive brain of early Homo. *Science*. 2021; 372(6538): 165-171.
57. Richerson PJ, Gavrilets S, de Waal FBM. Modern theories of human evolution foreshadowed by Darwin's Descent of Man. *Science*. 2021; 372(6544): eaba3776.
58. Dolgin E. Evolutionary sprint made us human. Regime of access : https://www.science.org/content/article/evolutionary-sprint-made-us-human
59. Pennisi E. Virus fighter may have played a key role in human evolution. Regime of access : https://www.science.org/content/article/virus-fighter-may-have-played-key-role-human-evolution
60. Reardon S. Step aside CRISPR, RNA editing is taking off. *Nature*. 2020; 578(7793): 24-27.
61. Grover N. Swedish geneticist wins Nobel medicine prize for decoding ancient DNA. Regime of access : https://www.reuters.com/world/svante-paabo-wins-2022-nobel-prize-medicine-2022-10-03/

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