

Evolution from first hominids to modern humans: philosophy, bioarchaeology and biology - Review

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Abstract

What made us human? Evolution from first hominins (*Homo habilis*) to modern humans (*Homo sapiens sapiens*) is a fascinating subject, for obvious reasons. That is related not only to the use of tools (which other animals may also handle), but –most importantly– to self-consciousness and, consequently, wondering about the three big philosophical questions of life. Thus, at a point in human evolution, we started to ask ourselves about where do we come from, what is our purpose in life and what comes after death. Different approaches have been taken to try to address such questions, including religion (beliefs), philosophy (thoughts) and science (experiments). Fortunately, recent breakthroughs in technology allow to apply science, in general, and molecular biology like sequencing of ancient DNA (aDNA) genomes, in particular, to decipher the most fundamental basis of human evolution. The conclusion is exciting, since it seems that such biological changes were due to duplication, repair and conversion of Notch Homolog 2 (*NOTCH2*) genes into Notch Homolog 2 N-terminal-Like (*NOTCH2NL*) ones. That caused the expansion of brain cortex and made us human. But, unfortunately, that is also related to recurrent neurodevelopmental diseases, to which humans are specially prone, in relation to other animals.

Key words: metaphysics, Darwin, Australopithecus, Hominoidea, lesser apes, great apes.

Resumen

¿Qué nos hizo humanos? La evolución desde los primeros homínidos (*Homo habilis*) a los humanos modernos (*Homo sapiens sapiens*) es un tema fascinante, por razones obvias. Ello está relacionado no solo con el uso de herramientas (que otros animales también pueden usar), sino –y más

importante— con la consciencia (conciencia de sí mismo), para preguntarse las tres grandes cuestiones filosóficas de la vida. Así, en un momento de la evolución humana, comenzamos a preguntarnos sobre de dónde venimos, el sentido de la vida y qué hay tras la muerte. Se han usado diferentes aproximaciones para tratar de dar respuesta a dichas cuestiones, incluyendo religión (creencias), filosofía (ideas) y ciencia (experimentos). Afortunadamente, los recientes avances en tecnología permiten aplicar la ciencia, en general, y la biología molecular como la secuenciación de genomas de ADN antiguo (ADNa), en particular, para descifrar la base más fundamental de la evolución humana. La conclusión es apasionante, ya que parece que dichos cambios biológicos fueron debidos a la duplicación, reparación y conversión de genes homólogos de muesca 2 (NOTCH2; del inglés, “Notch Homolog 2”) en genes similares a N terminal de homólogos de muesca 2 (NOTCH2NL; del inglés, “Notch Homolog 2 N-terminal-Like”). Ello causó la expansión del córtex cerebral y nos hizo humanos. Pero, lamentablemente, ello está también relacionado con enfermedades recurrentes del desarrollo neurológico, a las que los humanos son especialmente propensos, en relación con otros animales.

Palabras clave: metafísica, Australopithecus, Hominoidea, monos, gibones, grandes simios.

Introduction

Current monkeys include Old World monkeys (catarrhines) and New World monkeys (platyrrhines). The former also include apes (Hominoidea superfamily), with two extant (living) branches: lesser apes (gibbons) and great apes or hominids. The latter belong to the Hominidae family of primates, including four genera and eight extant species: i) Bornean, Sumatran and Tapanuli orangutans (*Pongo* spp.); ii) eastern and western gorillas (*Gorilla* spp.); iii) common chimpanzee and bonobo (*Pan* spp.); and iv) *Homo* spp., including modern humans (*Homo sapiens sapiens*). Apes appeared 10 million years ago (Mya) in Africa, being represented by *Nakalipithecus nakayamai*, which evolved into *Ouranopithecus* spp. (nine Mya), being Gorilla-Human Last Common-Ancestor (GHLCA) or Gorilla-Human Most Recent Common-Ancestor (GHMRCA), with subsequent separation and evolution into Gorillini and Hominini. The latter evolved into *Sahelanthropus tchadensis*, probably being bipedal (seven Mya). That evolved into *Orrorin tugenensis* (six Mya), being Chimpanzee-Human Last Common-Ancestor (CHLCA) or Chimpanzee-Human Most Recent Common-Ancestor (CHMRCA). The latter evolved into Hominini (hominins) 5.5 Mya, which includes *Homo* spp. (but not *Gorilla* spp.). It is not clear if *Pan* spp. should be included in the former. That is due to complex speciation processes and bipedalism development in proto-humans. On the other hand, it has been recently proposed that our species did not evolve from a single population/region of Africa, but instead from several related ones, across such continent (Scerri et al, 2018).

Then arose *Ardipithecus* spp. (4.5 Mya), with features reflecting adaptation to bipedalism. That evolved into *Australopithecus* spp (3.5 Mya), which –interestingly– used stone tools to ate meat, by carving animal carcasses (McPherron et al, 2010). Nevertheless, such tool usage was quite simple, similar to the one observed on current African apes, like chimpanzees and

gorillas. This way, they handled simple tools like stones to crack nuts, sticks to capture termites from mounds and spears for hunting, albeit without throwing them.

The evolution from hominins (*Australopithecus* spp) to first hominids (*Homo habilis*) started three Mya. It continued with *Homo ergaster* (three Mya). Interestingly, it has been recently discovered that they emigrated into Asia (*Homo erectus*) 2.1 Mya instead of 1.85 Mya, as previously thought (Zhu et al, 2018). It has been proposed that early African *Homo* known as *H. habilis*, *H. rudolfensis* and *H. erectus* were indeed the same; variations among them would simply reflect diversity (Lordkipanidze et al, 2013). Later on, they controlled fire (1.5 Mya). They are considered the beginning of early human evolution, with technological innovations, including tools like stone hand-axes and cooking with fire, creating specific cultural manifestations. That led to animals that thought and solved problems in an unprecedented way. They also wondered about big questions related to the meaning of life, including where do we come from, what is our purpose in life and what comes after death.

This way, *Homo heidelbergensis*, also known as *Homo rhodesiensis*, lived 700,000 years ago (ya). Represents the first *Homo* species who buried their dead, as found inside a pit called “Sima de los Huesos” located in “Sierra de Atapuerca”, at Atapuerca village (Spain), containing 28 hominin skeletons (Meyer et al, 2014, 2016). Interestingly, these humans were indeed early Neanderthals (*Homo sapiens neanderthalensis*) of western Eurasia, that separated from Denisovans subspecies of southern Siberia (*Homo sapiens denisova*) 430,000 ya (Meyer et al, 2016). They were met by modern humans when they emigrated out of Africa and the Near East 75,000 ya. Modern humans separated from their Neanderthals subspecies 370,000 ya, sharing a common ancestor that lived 706,000 ya (Noonan et al, 2006). Humans inbred with Denisovans and Neanderthals (Dorado et al, 2010, 2013, 2015; Prufer et al, 2014; DerSarkissian et al, 2015; Ermini et al, 2015; Hofreiter et al, 2015; Knapp et al, 2015; Pääbo, 2015; Perry and Orlando, 2015; Vernot and Akey, 2015). Additionally, it has been recently discovered that there were ancient genetic admixtures between Denisovans and Neanderthals subspecies. Such ancient genetic-admixtures are not surprising, since they were not different species, but subspecies. But Denisovans and Neanderthals were less diverse than modern humans, and possibly this would be one of the causes of their extinction (Warren, 2018).

Curiously, *H. heidelbergensis* had a similar morphology of skeletal structures and, thus, auditory capacities of outer and middle ear than modern humans. They allow high sensitivity in the range of 2 to 4 kHz, which is relevant for spoken language. Yet, most other anthropoids do not have such anatomy and capability. Therefore, *H. heidelbergensis* and descendants (Neanderthals and Denisovans) probably communicated by some kind of primitive language (Martínez et al, 2004; Mithen, 2007).

Additionally, *H. heidelbergensis* used pigments like red iron oxides (hematite). Later on, Neanderthals also used them, at least since 250 kya, together with red manganese oxides, as also found for African humans. Yet,

their purposes are not clear, and in any case, no works of art have been found so far (Roebroeks et al, 2012). Curiously, *H heidelbergensis* was right-handed, like modern humans, as found by dental wear analyses of 28 hominids from Atapuerca dated 500,000 ya. That is not a trivial topic, since handedness is a result of brain specialization. Besides, the latter allows development of higher cognitive capabilities, as found in humans, including language and technology (Lozano et al, 2009). In relation to that, spears and hafted stone points have been found in Africa (500,000 ya) and Germany (400,000 ya). It should be highlighted that hafting stone points to spears represents an important weaponry technological accomplishment. That may be relevant for general survival, and for hunting in particular. So, it seems that Denisovans, Neanderthals and modern humans did not invent, but rather inherited such technology from *H. heidelbergensis*, being their last common ancestor (Wilkins et al, 2012). On the other hand, Denisovans and Neanderthals probably wore simple (cape-like) non-tailored clothing, whereas modern humans made more sophisticated and specialized clothing, to better protect themselves from cold weather (Wales, 2012; Collard et al, 2016). Arrival of modern humans brought impressive cultural and technological developments to the present day.

But, how to answer the three big questions related to the meaning of life previously described (origin, life and death)? There are many possible approaches and thus answers to such questions, including religion (beliefs), philosophy (thoughts) and science (experiments). Religion is based on dogmas, and therefore, cannot be challenged, by definition. On the other hand, philosophy can be debated, discussed and argued, but ultimately may not be demonstrated. Fortunately, science uses the scientific method, which is based on establishment of hypothesis, which are experimentally challenged, to become refuted or accepted to build theories. That gives science a tremendous potential for discovering and technological development. Indeed, such growth has been exponential since the scientific method was implemented.

The time at which hominids became also humans is represented by archaeological remains including ceremonial burials. They usually contain archaeological artifacts. Sometimes, nucleic acids from biological remains of such beings can be analyzed. For many years, those remains were the subject of social sciences (including arts and humanities). Modern molecular biology methodologies have allowed to amplify and sequence DNA from such remains, being therefore also the subject of experimental sciences. That was first possible applying techniques like Polymerase Chain-Reaction (PCR), as well as nucleic-acid and peptide sequencing. Now, it is even possible to sequence DNA from such remains without previous amplification, using Third-Generation Sequencing (TGS). That, coupled with new developments in hardware (semiconductor lithographic-process technology for smaller nodes and many-core microprocessors) and software (bioinformatics) parallelization, has allowed the development of a brand new and revolutionary bioarchaeology, including sequencing of ancient DNA (aDNA) genomes and proteomes (Dorado et al, 2007-2017).

Evolution of species through struggle for limited resources and reproductive selection

Charles Darwin discontinued his medical education –much to the discomfort of his father– for his real passion: natural sciences. He embarked His Majesty's Ship (HMS) *Beagle* on 27th December 1831, as a young graduate, being 22 years old. On 30th December of 1831, he was aboard in the Bay of Biscay (Spain) “wretchedly out of spirits & very sick”. Indeed, he was tempted to return home, due to such severe seasickness. Fortunately, he continued, albeit spent as much time as possible on land instead of the ship –due to such “fortunate” sickness–, while traveling around the world for almost five years (until 2nd October of 1836). Thus, such problem helped him to, methodically and industriously, collect more data and samples of fossils, plants and animals during such long voyage than if he had stayed aboard.

Most interestingly, Darwin was surprised to find that some species like mockingbirds and finches at Galápagos islands resembled the ones living in continental land, being also different from island to island. Additionally, he was inspired in 1838 by reading the sixth edition of “An Essay on the Principle of Population” (short title) or “An Essay on the Principle of Population, as it Affects the Future Improvement of Society. With Remarks on the Speculations of Mr. Godwin, M. Condorcet and Other Writers” (long title), by Thomas Robert Malthus, who was first anonymously published 40 years before (Malthus, 1798). On 28th September of 1838, Darwin noted the shocking fact that natural resources grow arithmetically or linearly (eg., $2n$, being n the number of generations, assuming a simplified scenario of two descendants per genitor, for the sake of the argument), yet biological populations grow exponentially or logarithmically (eg., 2^n , in the simplified example above). Thus, human populations double every 25 years when resources are available and no reproductive control is exerted. The consequence is overpopulation, famine, starvation and deaths (Malthusian's catastrophe), unless birth control is implemented.

Darwin was also aware of the interesting idea of “warring of the species” or “nature's war”, by Swiss botanist Augustin Pyramus (or Pyrame) de Candolle, that described plants as being “at war one with another”, for space and resources. Likewise, such researcher acknowledged that new and similar features (later on named as analogy) may arise in different species, yet not showing in a common evolutionary ancestor. Indeed, Darwin invited him to dinner when he visited Great Britain in 1839.

The study of all these evidences made Darwin conceive his theory of natural selection in the struggle for life in 1838. After 12 years writing the book manuscript about such scientific ideas, he was shocked to receive a 20-page essay describing similar ones for publication from Alfred Russel Wallace, if considered worthwhile, on 18th June of 1858. Such researcher was at Maluku Islands (Moluccas archipelago within Banda Sea, Indonesia). As they say, “great minds think alike” or “clever minds think alike”. New ideas usually arise due to the influence of other surrounding ones. Indeed, our brain usually works

by ideas' association, jumping from one to another, starting from known ones and sometimes reaching surprising scenarios.

Darwin sent Wallace's manuscript to two friend scientists (Joseph Dalton Hooker and Charles Lyell). They arranged the joint presentation of two scientific papers, entitled "On the Tendency of Species to Form Varieties; and on the Perpetuation of Varieties and Species by Natural Means of Selection", at the Linnean Society of London, on 1st July of 1858. This way, Wallace's work ("On The Tendency of Varieties to Depart Indefinitely from the Original Type"), with extracts from a Darwin's unpublished essay (1844) and abstract of letter to the scientist Asa Grayn (1857), were presented at such scientific meeting. The articles "On the Tendency of Species to form Varieties" (Wallace) and "On the Perpetuation of Varieties and Species by Natural Means of Selection" (Darwin) were read out and printed on 20th August of 1858, yet passed mostly unnoticed in the scientific community.

Wallace's manuscript encouraged Darwin to finish his book, albeit as a reduced version of his former intention. Such revolutionary theory was entitled "On the Origin of Species" (short title) or "On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life" (long title), being published on 24th November of 1859. Later on, he published more scientific articles and books, including "The Descent of Man, and Selection in Relation to Sex" (1871), "The Expression of the Emotions in Man and Animals" (1872) and "The Formation of Vegetable Mould, Through the Actions of Worms" (1881).

It should be pointed out that Darwin considered both Wallace's and his ideas alike, in relation to natural selection. Yet, some scholars have highlighted that the former viewed natural selection as having similar effects than artificial selection (carried out by humans using selective breeding), emphasizing natural selection via competition. On the other hand, Wallace did not mention artificial breeding of varieties or species. Rather, he focused on group selection through ecological pressures, to adapt to specific environments, instead of selection on individual variation. Additionally, Darwin's work was much more comprehensive, being indeed a book, besides other scientific publications, as previously described.

Such discoveries changed our knowledge about the origin of species in general, and humans in particular. They established the concept of natural selection and evolution. This way, they opened the door to further research about evolution from first hominids to modern humans, related to brain development, culture and technology of our species.

From first hominids to modern humans

Archaeological studies can be fascinating. That coupled with molecular biology has allowed bioarchaeology to produce unprecedented scientific results (Dorado et al, 2007-2017; Reich, 2018). Thus, archaeological studies have found that, at a point in the biological evolution from first hominids into modern humans, ceremonial burials were constructed, including artifacts that point to

religious beliefs of life beyond death. Additionally, language was developed and all that generated an exponential growth of cultural and technological accomplishments. Not surprisingly, that is related to some changes suddenly generated in human nature (human genome and brain), allowing such achievements. They were further fueled by the development of agriculture in a broad sense, by microorganism, plant and animal breeding. This way, humans could settle, instead of being nomads in search for food. In turn, that brought a new wave of cultural and technological developments.

Interestingly, it was initially thought that humans gathered in communities first, supported by agriculture, then developing religious beliefs, represented by temple constructions. Yet, the surprising discoveries in the oldest religious temple known to date at Gobekli Tepe (Turkey) proved the contrary. As its main archaeologist (Klaus Schmidt) said: “first came the temple, then the city” (Dietrich et al, 2012). In other words –and quite surprisingly–, religion and temple construction existed before agriculture, at the time when humans were still nomads (gatherers and hunters). All that also demonstrates the deep basis of religion within human nature (Dorado et al, 2014).

Brain development and ancient genome sequencing

Currently, there is arguably no more complex and interesting scientific task than brain research. The molecular basis of biological changes –first in genome, and then in brain, as a consequence of the former–, from first hominids to modern humans have remained elusive for many years. Fortunately, two new and amazing papers, from two independent research teams have shed light on brain development-related genes in genome, in relation to such evolutionary changes. Such findings have been recently published in *Cell*, which is one of the most prestigious scientific journals (Fiddes et al, 2018; Suzuki et al, 2018).

They describe that Notch Homolog 2 (*NOTCH2*)-derived gene family, named Notch Homolog 2 N-terminal-Like (*NOTCH2NL*), were generated from partial duplication, repair and conversion of *NOTCH2*. Such paralogs include *NOTCH2NLA*, *NOTCH2NLB* and *NOTCH2NLC* genes, which are involved in cortical development of human brain, being a driving force of its evolution from first hominids to modern humans.

Recent developments in molecular biology have allowed to sequence, align and compare genomes of Denisovans (Meyer et al, 2012) and Neanderthals (Prüfer et al, 2014, 2017), as well as archaic and modern humans (Lazaridis et al, 2014). This way, a dendrogram or phylogenetic tree from *NOTCH2* to *NOTCH2NL* gene-family has been generated (Fig. 1).

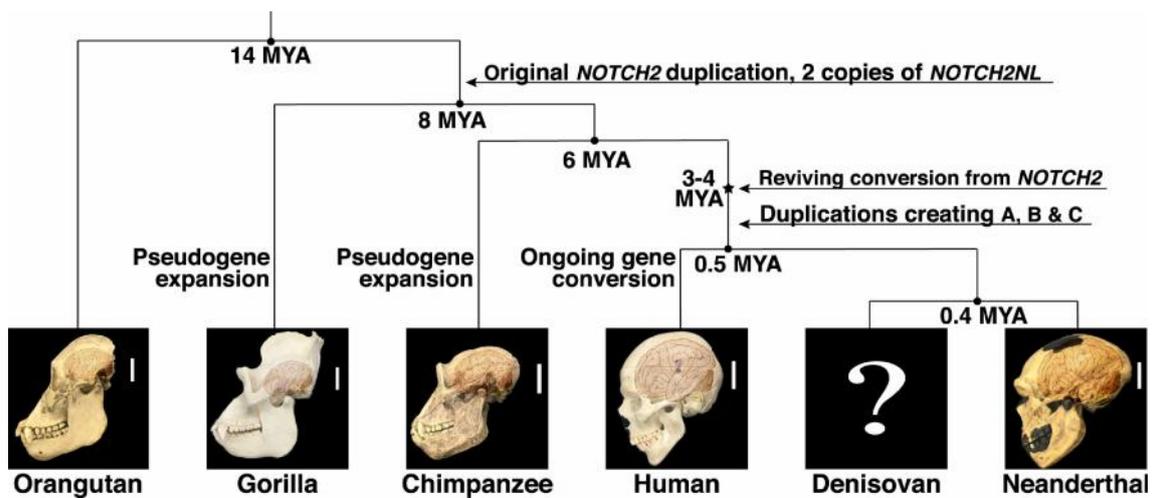


Figure 1. Great-apes dendrogram in relation to *NOTCH2NL*. Phylogenetic tree includes orangutan, gorilla, chimpanzee, human, Denisovan and Neanderthal. © 2018 Elsevier (Fiddes et al, 2018).

Some people (86%) have also *NOTCH2NL*-related gene (*NOTCH2NLR*), which is therefore absent in 14% of healthy population, suggesting that it is a non-functional pseudogene (Mallick et al, 2016). *NOTCH2NLA*, *NOTCH2NLB*, and *NOTCH2NLC* are located in 1q21.1 locus, whereas *NOTCH2NLR* is in p-arm of chromosome 1, near *NOTCH2*. *NOTCH2NL* genes encode *NOTCH2NL* proteins, which are related to several biological functions. They include calcium-ion and protein binding.

Curiously, they contain Epidermal Growth-Factor (EGF)-like domains. Their involvement in brain development stems from the fact that they enhance differentiation of cortical stem cells into neurons. That increases the number of neurons generated during brain development, further expanding certain functional areas in cerebral cortex. In turn, that increases cortex size, and therefore overall brain size.

Actually, human brains are threefold larger than the ones of other hominids, due to larger cerebral cortex. Interestingly, such functional genes are exclusive of humans. Indeed, they are not present in other primates (like macaques) or even great apes, like orangutans, being truncated and inactive in our closest relatives (gorillas and chimpanzees). So, amazingly, it seems that gene duplication, repair, conversion and activation of Notch signaling, via overexpression of these genes, allowed expansion of human cerebral cortex and thus the evolution from first hominids to modern humans. In particular, *NOTCH2NLB* activates Notch signaling and its overexpression produces clonal expansion of cortical progenitors and neurons (Fig. 2).

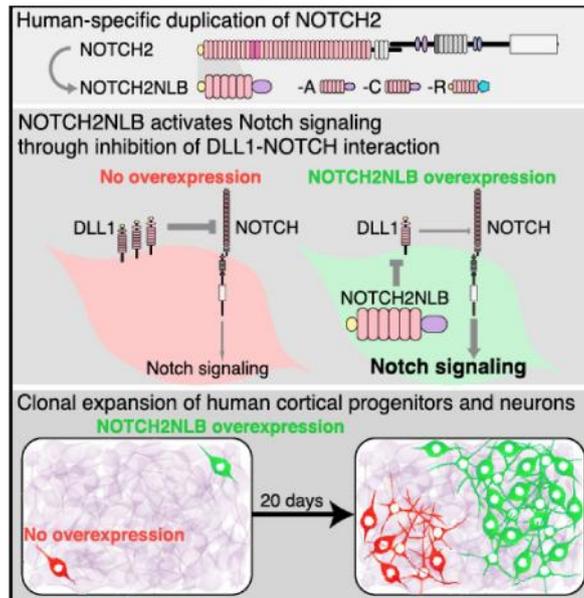


Figure 2. *NOTCH2NL* contribution to expansion of human cerebral cortex. Top) *NOTCH2* duplication; **Middle)** Notch signaling activation by *NOTCH2NLB*; and **Bottom)** Clonal expansion of cortical progenitors and neurons by *NOTCH2NLB* overexpression. © 2018 Elsevier (Suzuki et al, 2018).

On the other hand, *NOTCH2NL* overexpression delays neuronal differentiation, whereas its deletion accelerates it. And, unfortunately, there is a drawback: curiously, *NOTCH2NLA* and *NOTCH2NLB* genes are located in chromosomal regions associated to neurodevelopmental disorders. Thus, duplication, repair and conversion of one or both *NOTCH2NLA* and *NOTCH2NLB* genes may be related to macrocephaly, whereas deletions of one or both of them have been associated to microcephaly (Fig. 3).

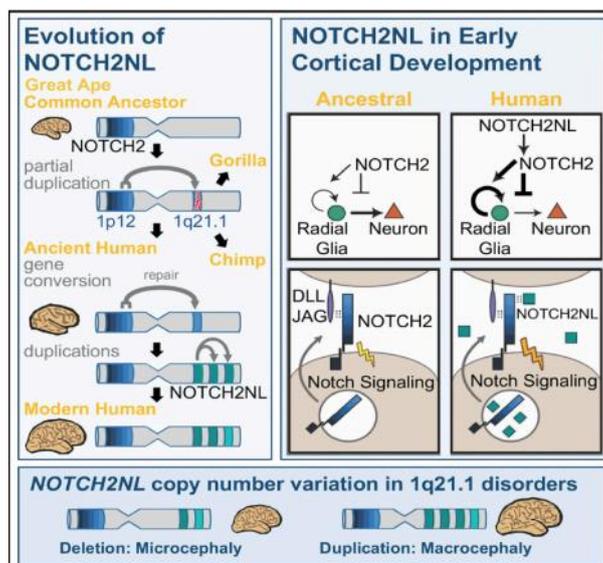


Figure 3. *NOTCH2NL* evolution. Left) From great ape common ancestor to ancient and modern human; **Right)** *NOTCH2NL* in early cortical development, comparing ancestral to human; and **Bottom)** *NOTCH2NL* duplication, repair and conversion may be associated to macrocephaly and autism, whereas deletions may be related to microcephaly and schizophrenia. © 2018 Elsevier (Fiddes et al, 2018).

Concluding remarks and future prospects

The potential of the discovery of *NOTCH2NL* gene-family involvement in brain development and recurrent neurodevelopmental diseases is breathtaking. For the first time, evolution from first hominids to modern humans has been explained with sound scientific basis. That involves genes triggering cerebral cortex development and growth. Besides, a comparison for such gene family has been carried out between extinct and modern humans at the genomic level. That highlights the relevance and potential of modern bioarchaeology to explain biological evolution, in general, and human evolution, in particular. But future prospects are even more astonishing. Not only to cure neurological disorders via techniques like Clustered Regularly-Interspaced Short-Palindromic Repeats (CRISPR), but even to generate superhumans and other intelligent animals. Obviously, this has critically important ethical implications, that should be properly addressed (Dorado et al, 2017). Biology, in general, and bioarchaeology, in particular, have never been so interesting, thanks to molecular biology.

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Bibliographic references

- Collard M, Tarle L, Sandgathe D, Allan A (2016): Faunal evidence for a difference in clothing use between Neanderthals and early modern humans in Europe. *Journal of Anthropological Archaeology* 44: 235-246.
- Darwin C (1859): “*On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*”. John Murray (London).
- DerSarkissian C, Allentoft ME, Ávila-Arcos MC, Barnett R, Campos PF, Cappellini E, Ermini L, Fernández R, da Fonseca R, Ginolhac A, Hansen AJ, Jónsson H, Korneliussen T, Margaryan A, Martin MD, Moreno-Mayar JV, Raghavan M, Rasmussen M, Velasco MS, Schroeder H, Schubert M, Seguin-Orlando A, Wales N, Gilbert MT, Willerslev E, Orlando L (2015): Ancient genomics. *Philos Trans R Soc Lond B Biol Sci* 370: 20130387 (12 pp).
- Dietrich O, Heun M, Notroff J, Schmidt K, Zarnkow M (2012): The role of cult and feasting in the emergence of Neolithic communities. New evidence from Gobekli Tepe, south-eastern Turkey. *Antiquity* 86: 674-695.
- Dorado G, Jiménez I, Rey I, Sánchez-Cañete FJS, Luque F, Morales A, Gálvez M, Sáiz J, Sánchez A, Rosales TE, Vásquez VF, Hernández P (2013): Genomics and proteomics in bioarchaeology - Review. *Archaeobios* 7: 47-63.
- Dorado G, Luque F, Pascual P, Jiménez I, Sánchez-Cañete FJS, Pérez-Jiménez M, Raya P, Gálvez M, Sáiz J, Sánchez A, Rosales TE, Vásquez VF, Hernández P (2015): Second-generation nucleic-acid sequencing and bioarchaeology - Review. *Archaeobios* 9: 216-230.
- Dorado G, Luque F, Pascual P, Jiménez I, Sánchez-Cañete FJS, Pérez-Jiménez M, Raya P, Sáiz J, Sánchez A, Martín J, Rosales TE, Vásquez VF,

- Hernández P (2016): Sequencing ancient RNA in bioarchaeology - Review. *Archaeobios* 10: 103-111.
- Dorado G, Luque F, Pascual P, Jiménez I, Sánchez-Cañete FJS, Raya P, Sáiz J, Sánchez A, Rosales TE, Vásquez VF (2017): Clustered Regularly-Interspaced Short-Palindromic Repeats (CRISPR) in bioarchaeology - Review. *Archaeobios* 11: 179-188.
- Dorado G, Rey I, Rosales TE, Sánchez-Cañete FJS, Luque F, Jiménez I, Gálvez M, Sáiz J, Sánchez A, Vásquez VF (2009): Ancient DNA to decipher the domestication of dog - Review. *Archaeobios* 3: 127-132.
- Dorado G, Rey I, Rosales TE, Sánchez-Cañete FJS, Luque F, Jiménez I, Morales A, Gálvez M, Sáiz J, Sánchez A, Hernández P, Vásquez VF (2010): Biological mass extinctions on planet Earth – Review. *Archaeobios* 4: 53-64.
- Dorado G, Rosales TE, Luque F, Sánchez-Cañete FJS, Rey I, Jiménez I, Morales A, Gálvez M, Sáiz J, Sánchez A, Vásquez VF, Hernández P (2011): Ancient nucleic acids from maize - Review. *Archaeobios* 5: 21-28.
- Dorado G, Rosales TE, Luque F, Sánchez-Cañete FJS, Rey I, Jiménez I, Morales A, Gálvez M, Sáiz J, Sánchez A, Vásquez VF, Hernández P (2012): Isotopes in bioarchaeology - Review. *Archaeobios* 6: 79-91.
- Dorado G, Sánchez-Cañete FJS, Pascual P, Jiménez I, Luque F, Pérez-Jiménez M, Raya P, Gálvez M, Sáiz J, Sánchez A, Rosales TE, Vásquez VF, Hernández P (2014): Starch genomics and bioarchaeology - Review. *Archaeobios* 8: 41-50.
- Dorado G, Vásquez V, Rey I, Luque F, Jiménez I, Morales A, Gálvez M, Sáiz J, Sánchez A, Hernández P (2008): Sequencing ancient and modern genomes - Review. *Archaeobios* 2: 75-80.
- Dorado G, Vásquez V, Rey I, Vega JL (2007): Archaeology meets Molecular Biology - Review. *Archaeobios* 1: 1-2.
- Ermini L, DerSarkissian C, Willerslev E, Orlando L (2015): Major transitions in human evolution revisited: a tribute to ancient DNA. *J Hum Evol* 79: 4-20.
- Fiddes IT, Lodewijk GA, Mooring M, Bosworth CM, Ewing AD, Mantalas GL, Novak AM, VanDenBout A, Bishara A, Rosenkrantz JL, Lorig-Roach R, Field AR, Haeussler M, Russo L, Bhaduri A, Nowakowski TJ, Pollen AA, Dougherty ML, Nuttle X, Addor MC, Zwolinski S, Katzman S, Kriegstein A, Eichler EE, Salama SR, Jacobs FMJ, Haussler D (2018): Human-specific *NOTCH2NL* genes affect Notch signaling and cortical neurogenesis. *Cell* 173: 1356-1369.
- Hofreiter M, Paijmans JL, Goodchild H, Speller CF, Barlow A, Fortes GG, Thomas JA, Ludwig A, Collins MJ (2015): The future of ancient DNA: Technical advances and conceptual shifts. *Bioessays* 37: 284-293.
- Knapp M, Lalueza-Fox C, Hofreiter M (2015): Re-inventing ancient human DNA. *Investig Genet* 6: 4 (11 pp)
- Lazaridis I, Patterson N, Mittnik A, Renaud G, Mallick S, Kirsanow K, Sudmant PH, Schraiber JG, Castellano S, Lipson M, Berger B, Economou C, Bollongino R, Fu Q, Bos KI, Nordenfelt S, Li H, de Filippo C, Prifer K, Sawyer S, Posth C, Haak W, Hallgren F, Fornander E, Rohland N, Delsate D, Francken M, Guinet JM, Wahl J, Ayodo G, Babiker HA, Bailliet G, Balanovska E, Balanovsky O, Barrantes R, Bedoya G, Ben-Ami H, Bene J, Berrada F, Bravi CM, Brisighelli F, Busby GB, Cali F, Churnosov M, Cole DE, Corach D, Damba L, VanDriem G, Dryomov S, Dugoujon JM, Fedorova SA, Gallego Romero I, Gubina M, Hammer M, Henn BM, Hervig T, Hodoglugil U, Jha AR, Karachanak-Yankova S, Khusainova R, Khusnutdinova E, Kittles R, Kivisild T, Klitz W, Kucinskas V,

- Kushniarevich A, Laredj L, Litvinov S, Loukidis T, Mahley RW, Melegh B, Metspalu E, Molina J, Mountain J, Nakkalajarvi K, Nesheva D, Nyambo T, Osipova L, Parik J, Platonov F, Posukh O, Romano V, Rothhammer F, Rudan I, Ruizbakiev R, Sahakyan H, Sajantila A, Salas A, Starikovskaya EB, Tarekegn A, Toncheva D, Turdikulova S, Uktveryte I, Utevska O, Vasquez R, Villena M, Voevoda M, Winkler CA, Yepiskoposyan L, Zalloua P, Zemunik T, Cooper A, Capelli C, Thomas MG, Ruiz-Linares A, Tishkoff SA, Singh L, Thangaraj K, Vilems R, Comas D, Sukernik R, Metspalu M, Meyer M, Eichler EE, Burger J, Slatkin M, Pääbo S, Kelso J, Reich D, Krause J (2014): Ancient human genomes suggest three ancestral populations for present-day Europeans. *Nature* 513: 409-413.
- Lordkipanidze D, Ponce de León MS, Margvelashvili A, Rak Y, Rightmire GP, Vekua A, Zollikofer CP (2013): A complete skull from Dmanisi, Georgia, and the evolutionary biology of early Homo. *Science* 342: 326-331.
- Lozano M, Mosquera M, Bermúdez de Castro JM, Arsuaga JL, Carbonell E (2009): Right handedness of *Homo heidelbergensis* from Sima de los Huesos (Atapuerca, Spain) 500,000 years ago. *Evolution and Human Behavior* 30: 369-376.
- Mallick S, Li H, Lipson M, Mathieson I, Gymrek M, Racimo F, Zhao M, Chennagiri N, Nordenfelt S, Tandon A, Skoglund P, Lazaridis I, Sankararaman S, Fu Q, Rohland N, Renaud G, Erlich Y, Willems T, Gallo C, Spence JP, Song YS, Poletti G, Balloux F, VanDriem G, de Knijff P, Romero IG, Jha AR, Behar DM, Bravi CM, Capelli C, Hervig T, Moreno-Estrada A, Posukh OL, Balanovska E, Balanovsky O, Karachanak-Yankova S, Sahakyan H, Toncheva D, Yepiskoposyan L, Tyler-Smith C, Xue Y, Abdullah MS, Ruiz-Linares A, Beall CM, Di Rienzo A, Jeong C, Starikovskaya EB, Metspalu E, Parik J, Vilems R, Henn BM, Hodoglugil U, Mahley R, Sajantila A, Stamatoyannopoulos G, Wee JT, Khusainova R, Khusnutdinova E, Litvinov S, Ayodo G, Comas D, Hammer MF, Kivisild T, Klitz W, Winkler CA, Labuda D, Bamshad M, Jorde LB, Tishkoff SA, Watkins WS, Metspalu M, Dryomov S, Sukernik R, Singh L, Thangaraj K, Pääbo S, Kelso J, Patterson N, Reich D (2016): The Simons Genome Diversity Project: 300 genomes from 142 diverse populations. *Nature* 538: 201-206.
- Malthus TR (1798): "An Essay on the Principle of Population, as it Affects the Future Improvement of Society. With Remarks on the Speculations of Mr. Godwin, M. Condorcet and Other Writers" (Johnson, London).
- Martínez I, Rosa M, Arsuaga JL, Jarabo P, Quam R, Lorenzo C, Gracia A, Carretero JM, Bermúdez de Castro JM, Carbonell E (2004): Auditory capacities in Middle Pleistocene humans from the Sierra de Atapuerca in Spain. *Proc Natl Acad Sci USA* 101: 9976-9981.
- McPherron SP, Alemseged Z, Marean CW, Wynn JG, Reed D, Geraads D, Bobe R, Bearat HA (2010): Evidence for stone-tool-assisted consumption of animal tissues before 3.39 million years ago at Dikika, Ethiopia. *Nature* 466: 857-860.
- 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, Prufer K, Pääbo S (2016): Nuclear DNA sequences from the Middle Pleistocene Sima de los Huesos hominins. *Nature* 531: 504-507.
- Meyer M, Fu Q, Aximu-Petri A, Glocke I, Nickel B, Arsuaga JL, Martínez I, Gracia A, De Castro JM, Carbonell E, Pääbo S (2014): A mitochondrial

- genome sequence of a hominin from Sima de los Huesos. *Nature* 505: 403-406.
- Meyer M, Kircher M, Gansauge MT, Li H, Racimo F, Mallick S, Schraiber JG, Jay F, Prufer K, de Filippo C, Sudmant PH, Alkan C, Fu Q, Do R, Rohland N, Tandon A, Siebauer M, Green RE, Bryc K, Briggs AW, Stenzel U, Dabney J, Shendure J, Kitzman J, Hammer MF, Shunkov MV, Derevianko AP, Patterson N, Andrés AM, Eichler EE, Slatkin M, Reich D, Kelso J, Pääbo S (2012): A high-coverage genome sequence from an archaic Denisovan individual. *Science* 338: 222-226.
- Mithen M (2007): *"The Singing Neanderthals - The Origins of Music, Language, Mind, and Body"*. Harvard University Press (Cambridge, Massachusetts, USA).
- Noonan JP, Coop G, Kudaravalli S, Smith D, Krause J, Alessi J, Chen F, Platt D, Pääbo S, Pritchard JK, Rubin EM (2006): Sequencing and analysis of Neanderthal genomic DNA. *Science* 314: 1113-1118.
- Pääbo S (2015): The diverse origins of the human gene pool. *Nat Rev Genet* 16: 313-314.
- Perry GH, Orlando L (2015): Ancient DNA and human evolution. *J Hum Evol* 79: 1-3.
- Prufer K, de Filippo C, Grote S, Mafessoni F, Korlevic P, Hajdinjak M, Vernot B, Skov L, Hsieh P, Peyregne S, Reher D, Hopfe C, Nagel S, Maricic T, Fu Q, Theunert C, Rogers R, Skoglund P, Chintalapati M, Dannemann M, Nelson BJ, Key FM, Rudan P, Kucan Ž, Gusic I, Golovanova LV, Doronichev VB, Patterson N, Reich D, Eichler EE, Slatkin M, Schierup MH, Andrés AM, Kelso J, Meyer M, Pääbo S (2017): A high-coverage Neandertal genome from Vindija Cave in Croatia. *Science* 358: 655-658.
- Prufer K, Racimo F, Patterson N, Jay F, Sankararaman S, Sawyer S, Heinze A, Renaud G, Sudmant PH, de Filippo C, Li H, Mallick S, Dannemann M, Fu Q, Kircher M, Kuhlwilm M, Lachmann M, Meyer M, Ongyerth M, Siebauer M, Theunert C, Tandon A, Moorjani P, Pickrell J, Mullikin JC, Vohr SH, Green RE, Hellmann I, Johnson PL, Blanche H, Cann H, Kitzman JO, Shendure J, Eichler EE, Lein ES, Bakken TE, Golovanova LV, Doronichev VB, Shunkov MV, Derevianko AP, Viola B, Slatkin M, Reich D, Kelso J, Pääbo S (2014): The complete genome sequence of a Neanderthal from the Altai Mountains. *Nature* 505:43-49.
- Reich D (2018): *"Who We Are and How We Got Here - Ancient DNA and the New Science of the Human Past"*. Pantheon Books (New York, NY, USA).
- Roebroeks W, Sier MJ, Nielsen TK, De Loecker D, Parés JM, Arps CE, Mocher HJ (2012): Use of red ochre by early Neandertals. *Proc Natl Acad Sci USA* 109: 1889-1894.
- Scerri EML, Thomas MG, Manica A, Gunz P, Stock JT, Stringer C, Grove M, Groucutt HS, Timmermann A, Rightmire GP, D'Errico F, Tryon CA, Drake NA, Brooks AS, Dennell RW, Durbin R, Henn BM, Lee-Thorp J, DeMenocal P, Petraglia MD, Thompson JC, Scally A, Chikhi L (2018): Did our species evolve in subdivided populations across Africa, and why does it matter? *Trends in Ecology & Evolution* 33: 582-594.
- Suzuki IK, Gacquer D, VanHeurck R, Kumar D, Wojno M, Bilheu A, Herpoel A, Lambert N, Cheron J, Polleux F, Detours V, Vanderhaeghen P (2018): Human-specific *NOTCH2NL* genes expand cortical neurogenesis through Delta/Notch Regulation. *Cell* 173: 1370-1384.

- Vernot B, Akey JM (2015): Complex history of admixture between modern humans and Neandertals. *Am J Hum Genet* 96: 448-453.
- Wales N (2012): Modeling Neanderthal clothing using ethnographic analogues. *J Hum Evol* 63: 781-795.
- Warren M (2018): Mum's a Neanderthal, dad's a Denisovan: First discovery of an ancient-human hybrid. *Nature* 560: 417-418.
- Wilkins J, Schoville BJ, Brown KS, Chazan M (2012): Evidence for early hafted hunting technology. *Science* 338: 942-946.
- Zhu Z, Dennell R, Huang W, Wu Y, Qiu S, Yang S, Rao Z, Hou Y, Xie J, Han J, Ouyang T (2018): Hominin occupation of the Chinese Loess Plateau since about 2.1 million years ago. *Nature* 559: 608-612.

