Foreword

There is at present a consensus that the 21st century will be the century of biology, just as the 20th century was the century of physics. Biology now has larger budgets and a larger workforce than physics, and it faces problems of great significance and relevance to the understanding of human nature and the conduct of human life. The core of all biological research and understanding is the theory of evolution; evolution by natural selection is the central unifying concept of biology. As the great 20th century evolutionist Theodosius Dobzhansky asserted in 1973, "Nothing in biology makes sense except in the light of evolution."

The theory of evolution has transformed our understanding of life on planet Earth. Evolution provides a scientific explanation for why there are so many different kinds of organisms and why they all share the same chemical components in similar proportions, and why all organisms share DNA as their hereditary material, and why enzymes and other proteins, which are the fundamental constituents and engines of cell processes, are all made up of the same 20 amino acids, despite hundreds of amino acids existing in organisms. Evolution demonstrates why some organisms that look quite different are in fact related, while other organisms that may look similar are only distantly related. It accounts for the origins of humans on Earth and reveals our species' biological connections with other living things in varying degrees. Evolution explains the similarities and differences among modern human groups and modern human individuals. It enables the development of effective new ways to protect ourselves against constantly evolving bacteria and viruses, and to improve the quality of our agricultural products and domestic animals.

We owe the concept of evolution by natural selection to Charles Darwin. Natural selection was proposed by Darwin primarily to account for the adaptive organization, or design, of living beings; it is a process that preserves and promotes adaptation. Evolutionary change through time and evolutionary diversification (multiplication of species) often ensue as byproducts of natural selection fostering the adaptation of organisms to their milieu. Evolutionary change is not directly promoted by natural selection and, therefore, it is not its necessary consequence. Indeed, some species remain unchanged for long periods of time, as Darwin noted. Nautilus, *Lingula*, and other so-called living fossils were used by Darwin as examples of organisms that have remained unchanged in their appearance for millions of years.

Evolution affects all aspects of an organism's life: morphology (form and structure), physiology (function), behavior, and ecology (interaction with the environment). Underlying these changes are changes in the hereditary materials. Hence, in genetic terms, evolution consists of changes in an organism's hereditary makeup and can be seen as a two-step process. First, hereditary variation arises by mutation; second, selection occurs by which useful variations increase in frequency and those that are less useful or injurious are eliminated over the generations. As Darwin (*The Origin of Species*, 1859) saw it, individuals having useful variations "would have the best chance of surviving and procreating their kind" (p. 81). As a consequence, useful variations increase in frequency over the generations, at the expense of those that are less useful or are injurious.

Natural selection is much more than a "purifying" process, for it is able to generate novelty by increasing the probability of otherwise extremely improbable genetic combinations. Natural selection in combination with mutation becomes, in this respect, a creative process. Moreover, it is a process that has been occurring for many millions of years, in many different evolutionary lineages, and in a multitude of species, each consisting of a large number of individuals. Evolution by mutation and natural selection has produced the enormous diversity of the living world with its wondrous adaptations and it accounts for our presence, *Homo sapiens*, on planet Earth.

There is a version of the history of ideas that sees a parallel between two scientific revolutions, the Copernican and the Darwinian. In this view, the Copernican Revolution consisted of displacing the Earth from its previously accepted locus as the center of the universe, moving it to a subordinate place as just one more planet revolving around the sun. Similarly, in a congruous manner, the Darwinian Revolution is viewed as consisting of the displacement of modern humans from their exalted position as the center of life on Earth, with all other species created for the service of humankind. According to this version of intellectual history, Copernicus had accomplished his revolution with the heliocentric theory of the solar system. Darwin's achievement emerged from his theory of organic evolution. (Sigmund Freud refers to these two revolutions as "outrages" inflicted upon humankind's self-image and adds a third one, his own. He sees psychoanalysis as the "third and most bitter blow upon man's craving for grandiosity," revealing that man's *ego* "is not even master in his own house.")

What the standard versions of the Copernican and Darwinian revolutions say is correct but inadequate. It misses what is most important about these two intellectual revolutions, namely that they ushered in the beginning of science in the modern sense. These two revolutions may jointly be seen as the one Scientific Revolution, with two stages, the Copernican and the Darwinian.

The Copernican Revolution was launched with the publication in 1543, the year of Nicolaus Copernicus' death, of his *De revolutionibus orbium celestium* (*On the Revolutions of the Celestial Spheres*), and it bloomed in 1687 with the publication of Isaac Newton's *Philosophiae naturalis principia mathematica* (*The Mathematical Principles of Natural Philosophy*). The discoveries by Copernicus, Kepler, Galileo, Newton, and others, in the 16th and 17th centuries, had shown that Earth is not the center of the universe, but is a small planet rotating around an average star; that the universe is immense in space and in time; and that the motions of the planets around the sun can be explained by the same simple laws that account for the motion of physical objects on our planet. These include laws such as $f = m \times a$ (force = mass × acceleration) or the inverse-square law of attraction, $f = g(m_1 m_2)/r^2$ (the force of attraction between two bodies is directly proportional to their masses, but inversely related to the square of the distance between them).

These and other discoveries greatly expanded modern human knowledge. The conceptual revolution they brought about was more fundamental yet: a commitment to the postulate that the universe obeys immanent laws that account for natural phenomena. The workings of the universe were brought into the realm of science: explanation through natural laws. Potentially, all physical phenomena could be accounted for, as long as the causes were adequately known.

The advances of physical science brought about by the Copernican Revolution had driven humankind's conception of the universe to a split-personality state of affairs, a condition that persisted well into the mid-19th century. Scientific explanations, derived from natural laws, dominated the world of nonliving matter, on the Earth as well as in the heavens. Supernatural explanations, which depended on the unfathomable deeds of the creator, were accepted as explanations of the origin and configuration of living creatures. Authors, such as William Paley in his *Natural Theology* (1802), had developed the "argument from design," the notion that the complex design of organisms could not have come about by chance, or by the mechanical laws of physics, chemistry, and astronomy, but was rather accomplished by an omnipotent deity, just as the complexity of a watch, designed to tell time, was accomplished by an intelligent watchmaker.

Darwin completed the Copernican Revolution by drawing out for biology the notion of nature as a lawful system of matter in motion that modern human reason can explain without recourse to supernatural agencies. Darwin's greatest accomplishment was to show that the complex organization and functionality of living beings can be explained as the result of a natural process: natural selection. The origin and adaptations of organisms in their profusion and wondrous variations were thus brought into the realm of science.

Darwin's theory of evolution by natural selection disposed of Paley's arguments: the adaptations of organisms are not outcomes of chance, but of a process that, over time, causes the gradual accumulation of features beneficial to organisms. There is "design" in the living world: eyes are designed for seeing, wings for flying, and kidneys for regulating the composition of the blood. But the design of organisms is not intelligent, as would be expected from an engineer, but imperfect and worse: defects, dysfunctions, oddities, waste, and cruelty pervade the living world. Darwin's focus in *The Origin of Species* (1859) was the explanation of design, with evolution playing the subsidiary role of supporting evidence.

It follows from Darwin's explanation of adaptation that evolution must necessarily occur as a consequence of organisms becoming adapted to different environments in different localities, and to the ever-changing conditions of the environment over time, and as hereditary variations become available at a particular time that improve, in that place and at that time, the organisms' chances of survival and reproduction.

Origin's evidence for biological evolution is central to Darwin's explanation of design, because this explanation implies that biological evolution occurs, which Darwin therefore seeks to demonstrate in the second half of the book.

Darwin and other 19th century biologists found compelling evidence for biological evolution in the comparative study of living organisms, in their geographic distribution, and in the fossil remains of extinct organisms. Since Darwin's time, the evidence from these sources has become stronger and more comprehensive, while biological disciplines that have emerged recently – genetics, biochemistry, ecology, animal behavior (ethology), neurobiology, and especially molecular biology – have supplied powerful additional evidence and detailed confirmation. Accordingly, evolutionists are no longer concerned with obtaining evidence to support the fact of evolution, but rather are concerned with finding out additional information of the historical process in cases of particular interest. Moreover and most importantly, evolutionists nowadays are interested in understanding further and further how the process of evolution occurs.

Nevertheless, important discoveries continue, even in traditional disciplines, such as paleontology. Skeptical contemporaries of Darwin asked about the "missing links," particularly between the extant apes and modern humans, but also between major groups of organisms, such as between fish and terrestrial tetrapods or between reptiles and birds. Evolutionists can now affirm that these missing links are no longer missing. The known fossil record has made great strides over the last century and a half. Many fossils intermediate between diverse organisms have been discovered over the years. Two examples are *Archaeopteryx*, an animal intermediate between reptiles and birds, and *Tiktaalik*, intermediate between fishes and tetrapods.

The missing link between apes and humans is not, either, missing any longer. Not one, but hundreds of fossil remains from hundreds of individual hominins have been discovered since Darwin's time and continue to be discovered at an accelerated rate. The history of hominin discoveries is narrated in this encyclopedia, as well as the anatomical and other changes that occur through time.

Darwin wrote two books dedicated to human evolution: *The Descent of Man, and Selection in Relation to Sex* (2 vols, 1871) and *The Expression of the Emotions in Man and Animals* (1872). What we now know about human evolution is immensely more than what Darwin knew. But, even concerning hominin fossil history, much remains to be discovered. Indeed, the sequence that goes from the most primitive hominins to *Homo sapiens*, our species, is not resolved. That is, in many cases we do not know whether a particular hominin fossil belongs to the line of descent that goes to our species, or whether it belongs to a lateral branch.

There are many other important issues concerning the evolutionary origin of modern human traits – anatomical, physiological, behavioral, and cultural – that remain largely unknown. I will briefly point out three great research frontiers that seem to me particularly significant: ontogenic decoding, the brain/mind puzzle, and the ape-to-human transformation. By ontogenetic decoding I refer to the problem of how the unidimensional genetic information encoded in the DNA of a single cell becomes transformed into a four-dimensional being, the individual that develops, grows, matures, and dies. Cancer, disease, and aging are epiphenomena of ontogenetic decoding. By the brain/mind puzzle I refer to the interdependent questions of (a) how the physicochemical signals that reach our sense organs become transformed into perceptions, feelings, ideas, critical arguments, aesthetic emotions, and ethical values; and (b) how, out of this diversity of experiences, there emerges a unitary reality, the mind or self. Free will and language, social and political institutions, technology, and art are all epiphenomena of the modern human mind. By the ape-to-human transformation I refer to the mystery of how a particular ape lineage became a hominin lineage, from which emerged, after only a few million years, modern humans able to think and love, who have developed complex societies and uphold ethical, aesthetic, and religious values. But the modern human genome differs little from the chimp genome.

I will refer to these three issues as the egg-to-adult transformation, the brain-to-mind transformation, and the ape-to-human transformation. The egg-to-adult transformation is essentially similar, and similarly mysterious, in modern humans and other mammals, but it has distinctive human features. The brain-to-mind transformation and the ape-to-human transformation are distinctively human. These three transformations define the *humanum*, that which makes us specifically modern human. Few other issues in human evolution are of greater consequence for understanding ourselves and our place in nature.

The instructions that guide the ontogenetic process, or the egg-to-adult transformation, are carried in the hereditary material. The theory of biological heredity was formulated by the Augustinian monk Gregor Mendel in 1866, but it became generally known by biologists only in 1900: genetic information is contained in discrete factors, or genes, which exist in pairs, one received from each parent. The next step toward understanding the nature of genes was completed during the first quarter of the twentieth century. It was established that genes are parts of the chromosomes, filamentous bodies present in the nucleus of the cell, and that they are linearly arranged along the chromosomes. It took another quarter century to determine the chemical composition of genes: deoxyribonucleic acid (DNA). DNA consists of four kinds of nucleotides organized in long, double-helical structures. The genetic information is contained in the linear sequence of the nucleotides, very much in the same way as the semantic information of an English sentence is conveyed by the particular sequence of the 26 letters of the alphabet.

The first important step toward understanding how the genetic information is decoded came in 1941 when George W. Beadle and Edward L. Tatum demonstrated that genes determine the synthesis of enzymes; enzymes are the catalysts that control all chemical reactions in living beings. Later it became known that amino acids (the components that make up enzymes and other proteins) are encoded, each by a set of three consecutive nucleotides. This relationship accounts for the linear correspondence between a particular sequence of coding nucleotides and the sequence of the amino acids that make up the encoded enzyme.

Chemical reactions in organisms must occur in an orderly manner; organisms must have ways of switching genes on and off since different sets of genes are active in different cells. The first control system was discovered in 1961 by François Jacob and Jacques Monod for a gene that encodes an enzyme that digests sugar in the bacterium *Escherichia coli*. The gene is turned on and off by a system of several switches consisting of short DNA sequences adjacent to the coding part of the gene. (The coding sequence of a gene is the part that determines the sequence of amino acids in the encoded enzyme or protein.) The switches acting on a given gene are activated or deactivated by feedback loops that involve molecules synthesized by other genes. A variety of gene control mechanisms were soon discovered, in bacteria and other micro-organisms. Two elements are typically present: feedback loops and short DNA sequences acting as switches. The feedback loops ensure that the presence of a substance in the cell induces the synthesis of the enzyme required to digest it, and that an excess of the enzyme in the cell represses its own synthesis. (For example, the gene encoding a sugar-digesting enzyme in *E. coli* is turned on or off by the presence or absence of the sugar to be digested.)

The investigation of gene-control mechanisms in mammals (and other complex organisms) became possible in the mid-1970s with the development of recombinant DNA techniques. This technology made it feasible to isolate single genes (and other DNA sequences) and to multiply them, or "clone" them, to obtain the quantities necessary for ascertaining their nucleotide sequence. One unanticipated discovery was that most genes come in pieces: the coding sequence of a gene is divided into several fragments separated one from the next by noncoding DNA segments. In addition to the alternating succession of coding and noncoding segments, mammalian genes contain short control sequences, like those in bacteria but typically more numerous and complex, that act as control switches and signal where the coding sequence begins.

Much remains to be discovered about the control mechanisms of mammalian genes. The daunting speed at which molecular biology is advancing has led to the discovery of some prototypes of mammalian gene control systems, but much remains to be unraveled. Moreover, understanding the control mechanisms of individual genes is but the first major step toward solving the mystery of ontogenetic decoding. The second major step will is the puzzle of differentiation.

A modern human being consists of one trillion cells of some 300 different kinds, all derived by sequential division from the fertilized egg, a single cell 0.1 mm in diameter. The first few cell divisions yield a spherical mass of amorphous cells. Successive divisions are accompanied by the appearance of folds and ridges in the mass of cells and, later on, of the variety of tissues, organs, and limbs characteristic of a human individual. The full complement of genes duplicates with each cell division, so that two complete genomes are present in every cell. Yet different sets of genes are active in different cells. This must be so for cells to differentiate: a nerve cell, a muscle cell, and a skin cell are vastly different in size, configuration, and function. The differential activity of genes must continue after differentiation, because different cells fulfill different functions, which are controlled by different genes. Nevertheless, experiments with other animals (and some with humans) indicate that all the genes in any cell have the potential of becoming activated. (The sheep Dolly was conceived using the genes extracted from a cell in an adult sheep.)

The information that controls cell and organ differentiation is ultimately contained in the DNA sequence, but mostly in very short segments of it. In mammals, insects, and other complex organisms there are control circuits that operate at higher levels than the control mechanisms that activate and deactivate individual genes. These higher-level circuits (such as the so-called homeobox genes) act on sets of genes rather than individual genes. The details of how these sets are controlled, how many control systems there are, and how they interact, as well as many other related questions, are what needs to be resolved to elucidate the egg-to-adult transformation. The DNA sequence of some controlling elements has been ascertained, but this is a minor effort that is only helped a little by plowing the way through the entire 3000 million nucleotide pairs that constitute the modern human genome. Experiments with stem cells are likely to provide important knowledge as scientists ascertain how stem cells become brain cells in one case, muscle cells in another, and so on.

The benefits that the elucidation of the egg-to-adult transformation will bring to humankind are enormous. This knowledge will make possible understanding the modes of action of complex genetic diseases, including cancer, and therefore their cure. It will also bring an understanding of the process of aging, which kills all those who have won the battle against other infirmities.

Cancer is an anomaly of ontogenetic decoding: cells proliferate despite the welfare of the organism demanding otherwise. Individual genes (oncogenes) have been identified that are involved in the causation of particular forms of cancer. But whether or not a cell will turn out cancerous depends on the interaction of the oncogenes with other genes and with the internal and external environment of the cell. Aging is also a failure of the process of ontogenetic decoding: cells fail to carry out the functions imprinted in their genetic code script or are no longer able to proliferate and replace dead cells.

The brain is the most complex and most distinctive modern human organ. It consists of 30 billion nerve cells, or neurons, each connected to many others through two kinds of cell extension, known as the axon and the dendrites. From the evolutionary point of view, the animal brain is a powerful biological adaptation; it allows the organism to obtain and process information about environmental conditions and then to adapt to them. This ability has been carried to the limit in modern humans, in which the extravagant hypertrophy of the brain makes possible abstract thinking, language, and technology. By these means, humankind has ushered in a new mode of adaptation far more powerful than the biological mode: adaptation by culture.

The most rudimentary ability to gather and process information about the environment is found in certain single-celled micro-organisms. The protozoan *Paramecium* swims apparently at random, ingesting the bacteria it encounters, but when it meets unsuitable acidity or salinity its advance is checked and it starts off in a new direction. The single-celled alga *Euglena* not only avoids unsuitable environments but seeks suitable ones by orienting itself according to the direction of light, which it perceives through a light-sensitive spot in the cell. Plants have not progressed much further. Except for those with tendrils that twist around any solid object and the few carnivorous plants that react to touch, they mostly react only to gradients of light, gravity, and moisture.

In animals the ability to secure and process environmental information is mediated by the nervous system. The simplest nervous systems are found in corals and jellyfishes; they lack coordination between different parts of their bodies, so any one part is able to react only when it is directly stimulated. Sea urchins and starfish possess a nerve ring and radial nerve cords that coordinate stimuli coming from different parts; hence, they respond with direct and unified actions of the whole body. They have no brain, however, and seem unable to learn from experience. Planarian flatworms have the most rudimentary brain known; their central nervous system and brain process and coordinate information gathered by sensory cells. These animals are capable of simple learning and hence of variable responses to repeatedly encountered stimuli. Insects and their relatives have much more advanced brains; they obtain precise chemical, acoustic, visual, and tactile signals from the environment and process them, making possible complex behaviors, particularly in search for food, selection of mates, and social organization.

Vertebrates are able to obtain and process much more complicated signals and to respond to the environment more variably than do insects or any other type of invertebrate. The vertebrate brain contains an enormous number of associative neurons arranged in complex patterns. In vertebrates the ability to react to environmental information is correlated with an increase in the relative size of the cerebral hemispheres and of the neopallium, an organ involved in associating and coordinating signals from all receptors and brain centers. In mammals, the neopallium has expanded and become the cerebral cortex. Modern humans have a very large brain relative to their body size, and a cerebral cortex that is disproportionately large and complex even for their brain size. Abstract thinking, symbolic language, complex social organization, values, and ethics are manifestations of the wondrous capacity of the modern human brain to gather information about the external world and to integrate that information and react flexibly to what is perceived.

With the advanced development of the modern human brain, biological evolution has transcended itself, opening up a new mode of evolution: adaptation by technological manipulation of the environment. Organisms adapt to the environment by means of natural selection, by changing their genetic constitution over the generations to suit the demands of the environment. Modern humans, and modern humans alone to any substantial degree, have developed the capacity to adapt to hostile environments by modifying the environments according to the needs of their genes. The discovery of fire and the fabrication of clothing and shelter have allowed the ancestors of modern humans to spread from the warm tropical and subtropical regions of the Old World, to which we are biologically adapted, to almost the whole Earth; it was not necessary for wandering hominins that they wait until genes would evolve providing anatomical protection against cold temperatures by changing their physiology or by means of fur or hair. Nor are modern humans biding their time in expectation of wings or gills; we have conquered the air and seas with artfully designed contrivances: airplanes and ships. It is the modern human brain (the human mind) that has made humankind the most successful, by most meaningful standards, living species.

There are not enough bits of information in the complete DNA sequence of a modern human genome to specify the trillions of connections among the 30 billion neurons of the modern human brain. Accordingly, the genetic instructions must be organized in control circuits operating at different hierarchical levels so that an instruction at one level is carried through many channels at a lower level in the hierarchy of control circuits. The development of the modern human brain is indeed one particularly intriguing component of the egg-to-adult transformation.

Within the last two decades, neurobiology has developed into one of the most exciting biological disciplines. An increased commitment of financial and human resources has brought an unprecedented rate of discovery. Much has been learned about how light, sound, temperature, resistance, and chemical impressions received in our sense organs trigger the release of chemical transmitters and electric potential differences that carry the signals through the nerves to the brain and elsewhere in the body. Much has also been learned about how neural channels for information transmission become reinforced by use or may be replaced after damage; about which neurons or groups of neurons are committed to processing information derived from a particular organ or environmental location; and about many other matters. But, for all this progress, neurobiology remains an infant discipline, at a stage of theoretical development comparable perhaps to that of genetics at the beginning of the 20th century. Those things that count most remain shrouded in mystery: how physical phenomena become mental experiences (the feelings and sensations, called "qualia" by philosophers, that contribute the elements of consciousness), and how out of the diversity of these experiences emerges the mind, a reality with unitary properties, such as free will and the awareness of self, that persist through an individual's life.

I do not believe that the mysteries of the mind are unfathomable; rather, they are puzzles that modern humans can solve with the methods of science and illuminate with philosophical analysis and reflection. And I will place my bets that, over the next half century or so, many of these puzzles will be solved. We shall then be well on our way toward answering the biblical injunction: "Know thyself."

A contemporary development that would have greatly delighted Darwin is the determination of the DNA sequence of the modern human genome, an investigation that was started under the label, the Human Genome Project, which opens up the possibility of comparing the modern human DNA sequence with that of other organisms, observing their similarities and differences, seeking to ascertain the changes in the DNA that account for distinctively modern human features. The Human Genome Project was initiated in 1989, funded through two US agencies, the National Institutes of Health (NIH) and the Department of Energy (DOE), with eventual participation of scientists outside the USA. The goal set was to obtain the complete sequence of one human genome in 15 years at an approximate cost of $3000 million, coincidentally about $1 per DNA letter. A private enterprise, Celera Genomics, started in the USA somewhat later, but joined the government-sponsored project in achieving, largely independently, similar results at about the same time. A draft of the genome sequence was completed ahead of schedule in 2001. In 2003 the Human Genome Project was finished, but the analysis of the DNA sequences chromosome by chromosome continued over the following years. Results of these detailed analyses were published on June 1, 2006. The draft DNA sequence of the chimpanzee genome was published on September 1, 2005 (an entry in the encyclopedia presents the first fossil evidence of panins ever to be discovered). In the regions of the genome that are shared by modern humans and chimpanzees the two species are about 99% identical. These differences may seem very small or quite large, depending on how one chooses to look at them: 1% is only a small fraction of the total, but it still amounts to a difference of 30 million DNA nucleotides out of the 3 billion in each genome.

Twenty-nine percent of the enzymes and other proteins encoded by the genes are identical in both species. Out of the one hundred to several hundred amino acids that make up each protein, the 71% of nonidentical proteins that differ between modern humans and chimps do so by only two amino acids, on average. If one takes into account DNA stretches found in one species but not the other, the two genomes are about 96% identical, rather than nearly 99% identical as in the case of DNA sequences shared by both species. That is, a large amount of genetic material, about 3% or some 90 million DNA nucleotides, have been inserted or deleted since ancestors went their separate evolutionary ways, about 8–6 million years ago. Most of this DNA does not contain genes coding for proteins, although it may include toolkit genes and switch genes that impact developmental processes, as the rest of the noncoding DNA surely does.

Comparison of the modern human and chimpanzee genomes provides insights into the rate of evolution of particular genes in the two species. One significant finding is that genes active in the brain have changed more in the human lineage than in the chimp lineage (Khaitovich et al. 2005). Also significant is that the fastest-evolving modern human genes are those coding for transcription factors. These are switch proteins which control the expression of other genes; that is, they determine when other genes are turned on and off. On the whole, 585 genes have been identified as evolving faster in humans than in chimps, including genes involved in resistance to malaria and tuberculosis. (It might be mentioned that malaria is a severe disease for humans but much less so for chimps.)

Genes located on the Y chromosome, found only in the male, have been much better protected by natural selection in the human than in the chimpanzee lineage, in which several genes have incorporated disabling mutations that make the genes nonfunctional. Also, there are several regions of the human genome that contain beneficial genes that have rapidly evolved within the past 250,000 years. One region contains the *FOXP2* gene, involved in the evolution of speech.

Other regions that show higher rates of evolution in humans than in chimpanzees and other animals include 49 segments, dubbed human accelerated regions or HARs. The greatest observed difference occurs in *HAR1F*, an RNA gene that is expressed specifically in Cajal-Retzius neurons in the developing human neocortex from 7 to 19 gestational weeks, a crucial period for cortical neuron specification and migration.

Extended comparisons of the human and chimpanzee genomes and experimental exploration of the functions associated with significant genes will surely advance further our understanding, over the next decade or two, of what it is that makes us distinctively human, what is it that differentiates *H. sapiens* from our closest living species, chimpanzees and bonobos, and will surely shine some light on how and when these differences may have come about during hominin evolution of the human species. Surely also, full biological understanding of the ape-to-human transformation will only come if we solve the other two conundrums: the egg-to-adult transformation and the brain-to-mind transformation. The distinctive features that make us modern human appear early in development, well before birth, as the linear information encoded in the genome gradually becomes expressed into a four-dimensional individual, an individual who changes in configuration as time goes by. In an important sense the most distinctive human features are those expressed in the brain, those that account for the human mind or for human identity.

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