What has made us human?

A timeline of human evolution

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What makes us human? That we walk upright, on two legs? That we have complex language? That we use tools? Or is it our ability to ask this question? For centuries, philosophers and scientists have all grappled with this fundamental question.

The evolutionary history of humans, beginning at the origin of single-celled organisms, has traditionally been pieced together with the aid of the fossil record. This invaluable source of information about creatures that lived millions of years ago enabled the generation of evolutionary trees based on comparing anatomies of extinct and extant species. Unfortunately, some of the crucial traits that differentiate modern humans from their ancestors cannot be preserved in fossils.

We now understand that every trait seen in the fossil record and in existing species is determined by the genome. Therefore each change that occurred in evolutionary history must be underpinned by one or, more likely, multiple changes to the genome.

In this era of biochemistry and genetics, we can take advantage of this knowledge to increase our understanding of *how* these traits came about. This includes insights into the evolution of life in general, answering questions such as 'how did nervous systems arise?' These studies can also shed light on the evolution of genes, and other functional genomic elements, with human-specific functions by comparing our genome with closely (and distantly) related species.

So, when trying to understand how humans are unique, perhaps it is more interesting to ask 'what *has made* us human?'

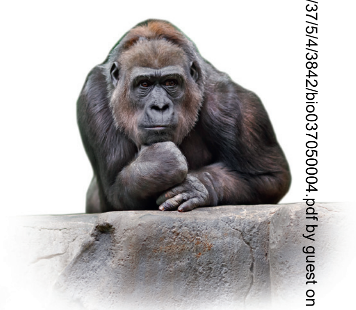
To answer this question, the articles in this issue of *The Biochemist* discuss some of the key changes that occurred between the first single-cell lifeforms which appeared 3.8 billion years ago (BYA) and the complex species seen today, including *Homo sapiens*.

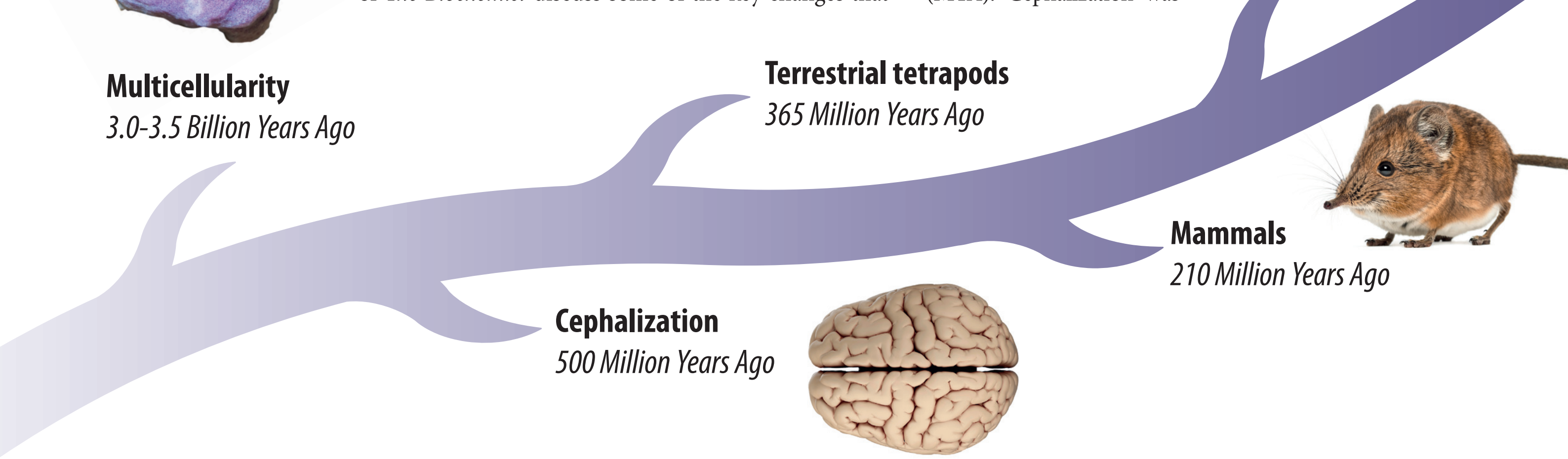
It is impossible to cover more than a fraction of the extraordinary evolution of life in one issue. However, the timeline shown across these pages not only provides the context for the events discussed in this issue, but also includes other key events without which humans, as we know them, wouldn't exist today.

A (brief) history of life

A big challenge for our single-celled ancestors was how to acquire sufficient energy, as it is difficult to accomplish lots of tasks simultaneously and efficiently if they all have to be performed by the same cell. This is probably why multicellular organisms, and examples of endosymbiosis (see page 6), began to arise between 3.0 and 3.5 billion years ago.

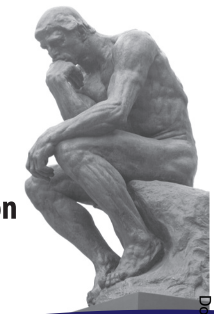
In these pioneering lifeforms, the genes necessary for rudimental 'neuronal' function arose (see page 12). Although specialized neurons did not appear until much later, the presence of these genes laid the way for the formation of nerves and a brain-like structure, a process known as cephalization, which can be seen in fossils from 500 million years ago (MYA). Cephalization was





a key adaptation, as it placed the sensory organs close to the information-processing nerve cells allowing for quick responses to the environment.

Up until 400 MYA, animal life was restricted to the oceans, after which creatures started evolving mechanisms of moving and breathing in shallow swamps and then on land. After these pioneers had conquered land, the diversification of insects and land animals began. The first mammal is thought to have appeared around 210 MYA and is likely to have been a small shrew-like creature. At this time, the presence of carnivorous dinosaurs probably kept these early mammals small, but all that changed after the fateful meteorite strike of 65 MYA. The loss of these major predators allowed the expansion of mammalian species, allowing them to grow in size and increase in variety. The mammalian lineage shows significant signs of brain enlargement and the formation of the neocortex, traits that are considered especially important in primates, hominids and humans (see page 16). In this grand timescale, primates and their evolutionary descendants are latecomers; the earliest primate in the fossil record is from a trifling 55 MYA and the first '*Homo*' fossil is only 2.8 million years young[1]!



Molecular view of evolution

A large number of evolutionary events had been observed or discerned from fossils long before the fields of modern genetics and biochemistry developed. In several of these cases, however, additional comparative genetic analysis can provide a more detailed understanding of *how* these traits came about.

The size and shape of mammalian skull bones told the story of cortical expansion long before we began to understand how differential expression patterns in progenitors could result in the evolutionary expansion of the cerebral cortex. The remodelling of the human forelimb and digits to form an opposable thumb was obvious from fossils. Now it has been attributed in part to the accumulation of only 16 human-specific nucleotide changes[2] in an enhancer region over the 6 million years since the last common ancestor of humans and chimpanzees.

The origin of agriculture drastically altered the path of human evolution by generating the first 'manmade' selection pressures. Archaeological and fossil records have generated a rich description of this social development: the ability to produce a year-round food supply enabled previously nomadic tribes to form more stable developed societies. Our genomes tell a different slant on this story. Variations in the copy number of the amylase gene[3] allowed early hominids to rely more on cultivated cereals as a food source and led to developments in agriculture and animal domestication. These changes in turn lead to lactase persistence (see page 20).

There are some traits that can only be explained by examining genetics, as it is impossible for them to be captured in the fossil record. A very notable example of this is language; the ability to speak cannot be discerned from a fossil. However, a human-specific mutation in the *FOXP2* gene that occurred before the Neanderthal–hominid split around 400,000 years ago, is thought to be important for the evolution of language[4]. A perhaps less obvious example is the duplication of the gene *SRGAP2* 2.4 MYA that has been shown to have boosted synaptic connectivity in the cortex[5].

This special issue ends with a look towards how future discoveries may be made. The Encyclopaedia of DNA Elements (ENCODE) project (see page 24) has and will continue to revolutionize our view of the gene regulatory mechanisms and the biochemical controls of 'human characteristics'. This will open new avenues to not only understand our past, but also discover ways to change our own future.

Now, more than ever, biochemists are set to contribute much in the quest to answer what has made us human. ■

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