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Human origins from a genomic perspective

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Humans with skeletons indistinguishable or almost indistinguishable from those of present-day humans appear for the first time in the fossil record of Africa between 100,000 and 200,000 years ago. These "anatomically modern humans" then appear outside Africa shortly before 100,000 years ago, and shortly before 50,000 years ago start to spread across Eurasia and the rest of the world. By that point, their behavior is in several respects radically different from that of earlier forms of humans that had existed in Africa for several million years and in Eurasia for about two million years. For example, while earlier forms of humans had made much the same sorts of stone tools for hundred of thousands of years, modern human technology changed rapidly, such that stone tools become different in different geographical regions. Art in a form that present-day humans intuitively recognize as art appears only after modern humans had appeared. And modern humans start spreading across the entire world by crossing even bodies of water where land is not visible on the other side. With one possible exception, this had never been done before.

These new human behaviors that appear with modern humans reflect cultural developments that set present-day humans apart from all other primates and has allowed them to become extremely numerous, to populate areas of the world where they could not survive without technology, and eventually to dominate parts of the biosphere. A fundamental question in modern biology is to understand the genetic underpinnings of these changes.

In order to begin to do this it is necessary to compare the genomes of present-day humans to those of our closest relatives, so-called "archaic humans", who are not "modern humans" in the sense that they did not share these behaviors. The closest and best-known relatives of modern humans are the Neandertals, who appear in the fossil record of Europe about 300,000 or 400,000 years ago and live in western Eurasia until they become extinct about 30,000 years ago. Over the past thirty years my laboratory

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has developed techniques that have led to the recent determination of DNA sequences from the entire genome of Neandertals (Green *et al.*, 2012) as well as from another closely related group of extinct humans, the Denisovans, in southern Siberia (Reich *et al.*, 2010; Meyer *et al.*, 2012). This allows us to begin to address two fundamental questions with regard to the origins of modern humans, which I briefly outline below.

Genetic traces of archaic humans in people today

A question debated among paleontologists for decades is whether modern humans mixed genetically with archaic humans when they spread across Africa and Eurasia or whether modern humans replaced archaic humans without any mixture.

Since genetic variation in Africa is greater than in the entire rest of the world and most genetic variants that exist outside Africa are very similar to variants found inside Africa, genetic anthropologists had generally inferred that a total replacement of all archaic humans by modern humans had occurred, even if some were of a different opinion (e.g. Wall *et al.*, 2009). However, when the Neandertal genome was sequenced (Green *et al.*, 2012), it was found that Neandertals shared slightly more genetic variants with present-day people outside Africa than with people inside Africa. This is best explained by a scenario in which modern humans, when they emerged out of Africa, mixed with Neandertals, perhaps in the Middle East, and then carried a genetic contribution from Neandertals along with them when they spread across the world. They then passed this contribution on to their children such that on the order of 1-4 percent of the genomes of people outside Africa today stem from Neandertals. Recently, the size distribution of the segments of Neandertal DNA in present-day people has been used to date the mixing of modern humans and Neandertals to sometime between 40,000 and 90,000 years ago (Sankararaman *et al.*, 2012).

Using similar techniques of DNA retrieval from ancient bones, the genome of a Denisovan, a relative of Neandertals, was determined from the Altai Mountains in southern Siberia (Reich *et al.*, 2010; Meyer *et al.*, 2012). When this genome was compared to those of present-day humans it was found that they have contributed on the order of 5 percent of the genomes of people that now live in Papua New Guinea and other parts of Melanesia. In addition, it has been shown that people in eastern Asia carry slightly more Neandertal DNA sequences than people in Europe (Meyer *et al.*, 2012). It is therefore possible that mixing of modern humans and Neandertals occurred not only in the Middle East but also later as modern humans spread across Eurasia. In addition, patterns of variation in Africa have

been interpreted to mean that also in Africa, other groups of archaic humans mixed genetically with modern humans (Hammer *et al.*, 2011).

It is therefore clear that present-day humans carry a direct genetic contribution from earlier extinct forms of humans. This contribution is found scattered in pieces across the genome of any one individual. Each such piece exists in a few percent of people today, and in a single individual they add up to a few percent of the genome. The rest of the genome of any single non-African individuals, well over 90 percent, originates within the past 200,000 years in Africa where the transformation to modern human behavior and anatomy occurred. Some of the pieces of the genome that come from Neandertals and other archaic humans may contribute to physiological differences among people today, for example in how the immune system functions (Abi-Rached *et al.*, 2011), but most of these variants are likely to have no functional consequences whatsoever. Nevertheless, it is of interest that present-day humans carry genetic contributions from earlier forms of humans whom they encountered as they spread across the globe. When we study the genetic origins of modern humans it is therefore appropriate to use the plural form, *origins*, as different parts of our genome have different origins.

The genetic basis of the modern human condition

Of fundamental importance for understanding, from a biological perspective, what sets modern humans apart from earlier forms of humans is to identify all genetic changes that are shared in identical form among all or almost all humans today but where our closest evolutionary relatives, such as the Neandertals and the Denisovans, shared other variants with the apes and other primates. These are genetic changes which together define modern humans as a group as distinct from our closest extinct relatives as well as all other primates. They are, in a sense, a "genetic recipe" for being a modern human.

The recent determination of a complete Denisovan genome (Meyer *et al.*, 2012) has allowed the compilation of a list of almost all such changes. It contains all positions in the genome where all or almost all humans today, no matter where on the planet we live, are identical but where the Denisovan is identical to the apes. Interestingly, this list is not extremely long. It contains 111,812 single nucleotide changes among the approximately 3 billion nucleotides that make up the entire human genome. It also contains 9,499 insertions and deletions of a number of adjacent nucleotides. These changes go back to mutations that occurred in modern human ancestors after their separation from the ancestors of Neandertals and Denisovans some 400,000 to 600,000 years ago and before perhaps 50,000 years ago,

after which the dispersal of humans across the planet made it impossible for any genetic change to spread to all humans.

A major challenge for human biology in the next decade is to investigate which of these changes have functional consequences and to understand how they have contributed to the unique cultural developments that have characterized the last 50,000 years of human history. How could this be achieved?

Investigations of genetic features unique to modern humans

The investigation of biological features unique to humans is not a trivial task since the very fact that these changes are unique to humans means that no obvious animal models are available. In spite of this, I believe that three approaches are possible.

First, the human genome is small enough and the number of new mutations that occur in each newborn baby large enough (~50-100) that all mutations compatible with human life exist in the current world population. However, most of them are very rare. In the future, when new technologies will make it possible to sequence the genomes of millions of people it will become possible to identify even rare variants that represent mutations back to an earlier, ancestral state. The physiological consequences of these mutations can then be studied.

Second, induced pluripotent stem cells are cells derived from adult tissues that can be induced to become, for example, nerve cells or liver cells in the laboratory. In such cells, DNA sequences can be "back-mutated" to the ancestral state and their effects on cellular functions can be studied in different cell types under different conditions. This will also make it possible to combine several, and eventually many, such changes affecting a certain organ system or biochemical pathway.

Third, to study the effects of mutations in a living organism, human mutations can be introduced into a model organism such as the mouse and aspects of human-specific traits studied.

Each of these approaches has obvious limitations. For example, they are limited to the identification or introduction of one or a few mutations whereas many mutations may exhibit effects only in concert with other mutations. Similarly, many mutations may not function in the same way in the laboratory mouse as in human beings due to differences in the genetic make-up between mice and humans. Nevertheless, the study of this list of human-specific genetic changes is an undertaking worth pursuing because an understanding of what constitutes the biological basis for modern humans, especially in the realm of cognition, is of fundamental importance

for understanding how modern humans came to explode in population size and dominate the biosphere. It may also provide an additional inroad into an understanding of diseases that affect cognitive traits that are unique to modern humans, such as language delay, speech disorders, or autism.

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