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Human evolution

Svante Pääbo

The origin, history, and singularity of our species has fascinated storytellers, philosophers and scientists throughout, and doubtless before, recorded history. Anthropology, the modern-era discipline that deals with these issues, is a notoriously contentious field, perhaps because the topic at hand – the nature of our own species – is one that is difficult or impossible to approach in an unbiased way. Recently, molecular genetics has increasingly contributed to this field. Here, I briefly discuss three areas where I believe molecular studies are likely to be of decisive importance in the future. These concern the questions of where and when our species originated, what the genetic background for characters that differ between us and apes is, and how the phenotypic traits that vary among human groups have evolved.

Studies of the genetic variation of humans, the concern of the field of molecular anthropology, attempt to produce objective data with which to arrive at new insights about human history. These insights can be of great practical importance, as in the quest for genetic variation associated with disease susceptibility. They can also bear on questions about human history within the past few thousand years, such as the colonization of previously uninhabited areas and subsequent migrations. However, for many of these issues, other sources of knowledge, such as archaeological or historical records, can often be of equal or greater importance. Here, rather, I would like to discuss briefly three questions for which molecular studies are likely to be of decisive importance. Where do we come from? Why do we look different from one another? Why are we so different from other species? First, I will outline how we have begun recently to understand when and where the earliest genetic differences that occur in our gene pool emerged. Then, I describe the early beginnings of insights into the genetic background of one of the most obvious differences among humans – that of pigmentation – and, finally, I discuss how we might hope to approach the as-yet-unknown genetic foundations of the differences between our own species and our closest evolutionary relatives, the African apes.

Origins of human genetic variation

The questions of when and where our species originated might seem quite straightforward, but, in fact, the definition of the origin of a species is not trivial. However, from a molecular-genetic perspective, it is clear that the DNA sequences found in contemporary individuals have been passed down to them from previous generations. It is also clear that, in every generation, some DNA sequences are not passed on because some individuals have no children or the sequence fails to be transmitted during meiosis. Therefore, the genealogy of a DNA sequence will trace back to fewer and fewer ancestors until it comes together in one common ancestor. To reconstruct this genealogy, the most straightforward approach is to determine DNA sequences from individuals that are distributed such that they represent the entire species. We can then use mathematical techniques to estimate the age of the most recent common ancestor of this collection of contemporary DNA sequences. However, because the genealogy of sequences at different locations in the genome differs owing to recombination and segregation, the age and place of the origin will be different for each genetic locus. Thus, from a genetic perspective, there will not be a single answer to the question of when and where our species emerged. Only if many loci show the same or a similar pattern can one infer that some kind of a population phenomenon occurred, as such an event would affect several parts of the genome.

The mitochondrial genome is the locus for which the most information on DNA sequence diversity in humans is currently available. The great majority of estimates of the age of the deepest divergence among human mitochondrial genomes fall between 100 000 and 200 000 years ago (for a review, see Ref. 1). When a

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TABLE 1. Some loci for which DNA sequence variation in humans has been studied

Locus	No. of sequences	Approx. age depth	Refs
mtDNA	$>10^3$	200 000	1[a]
Y chromosome	$>10^2$	200 000	2[a]
Xq13.3	70	500 000	8
β-globin	349	800 000	3
PDHA1	35	1 900 000	6
ACE	11	1 000 000	7
LPL	142	N/A	4,5

[a]Reference is given for example only. Abbreviations: ACE, angiotensin converting enzyme; LPL, lipoprotein lipase; N/A, not available; PDHA1, pyruvate dehydrogenase E1 α subunit.

root is sought for the variation, Africans tend to be distributed in the entire tree and thus on both sides of the root, while non-Africans are present in only some of the main branches that have diverged later. The simplest explanation for this is that the earliest divergences in the current mitochondrial gene pool occurred in Africa and that subsequently some, but not all, mitochondrial lineages took part in the colonization of the rest of the world.

The mitochondrial genome is transmitted solely through the mother to the offspring. Its natural counterpart is the Y chromosome, which is transmitted from father to son. Generally, there is comparatively little DNA sequence variation on the human Y chromosome. However, the studies that have been performed tend to arrive at dates for the earliest variation of less than 200 000 years, similar to that of the mitochondrial DNA[2]. Recently, Underhill *et al.* have produced a tree that reflects variation at 167 single-nucleotide polymorphisms on the Y chromosome (P. Underhill, pers. commun.). In this tree, Africans are found on all the major branches close to the root of the tree, whereas non-Africans are restricted to fewer branches. Thus, the two genetic systems that reflect the female and male history tend to agree both on a date and on a place for the origin of the variation.

Less is known about DNA sequence variation at nuclear loci outside the Y chromosome. This is because it is necessary to sequence several thousand base pairs from many individuals to observe enough variable positions to gauge the variation adequately. This has been done for very few genes (encoding β-globin[3], lipoprotein lipase[4,5], a pyruvate dehydrogenase subunit[6] and the angiotensin converting enzyme[7]) and one non-coding region on the X chromosome[8]. The time depths of the variation in these DNA sequences falls between 500 000 and 1.9 million years (Table 1). However, to my mind, these dates do not represent any real disagreement with the mitochondrial and Y chromosome data. First of all, the times back to a common ancestor of X-chromosomal and autosomal loci are expected to be threefold and fourfold longer. This is because the larger number of chromosomes transmitted in the population pushes the time of the common ancestor back proportionally to the number of chromosomes. In addition, these estimates include large standard errors, and, even leaving estimation errors aside, large stochastic variation in times back to the common ancestor is expected because the loss of lineages in a population is a stochastic process. Finally, it is useful to keep in mind that the ancestry of some genes, for which selective forces have held many variants in the population, could go back very far[9].

On balance, the general pattern in these studies, as well as studies of other loci such as microsatellites[10], is that the extent of variation in humans is limited – but that the greatest variation is found in Africa. Furthermore, studies of minisatellites[11] and microsatellites associated with unique events, such as deletions[12], have found that the variation seen in the entire world outside Africa is a subset of the variation seen in Africa. Thus, in terms of the variation at most loci, we all seem to be Africans, either living on that continent or in recent exile.

Ancient DNA

How does the picture of our ancestry described above fit with the picture of human origins provided by paleontology? Here, we run into the problem that, while geneticists specialize in studying the genes in people that exist today, which thus are bound to have had ancestors in the past, paleontologists study fossils that might not have descendants. A potentially valuable approach to resolve this problem would be to study DNA sequences from fossils, as this would allow direct inference of the genetic relationship of extinct hominids and contemporary humans. Since the invention of the polymerase chain reaction, there has been slow but steady progress in the techniques for the retrieval of ancient DNA sequences[13]. However, much difficulty remains, particularly for the study of archaeological remains of humans, because human DNA is, not surprisingly, the most common source of contamination of specimens as well as laboratory reagents[14]. As a consequence, much confusion has been and continues to be caused by the publication of findings that are probably the result of contamination with modern DNA.

By applying all criteria of authenticity that we find practical, we recently deduced the sequence of two hypervariable parts of the mitochondrial genome[15,16] from the Neanderthal-type specimen, representing the archaic human form that inhabited Europe and western Asia until about 30 000 years ago. These sequences fall outside the variation found within human populations throughout the world and point to a common ancestry of the mitochondrial genomes of modern humans and Neanderthals about 500 000 years ago. From these results, it is clear that Neanderthals have not contributed any mitochondrial DNA to the current human gene pool. This could either be because no interbreeding between Neanderthals and modern humans occurred or because the Neanderthal mitochondrial contribution has become lost by random genetic drift[17]. The results do not mean that Neanderthal genes outside the mitochondrial genome were all very different from the current human gene pool. Indeed, as the common ancestries of many human nuclear genes are older than the putative separation of Neanderthal and modern humans (Table 1), it is likely that some contemporary human nuclear DNA sequences are more closely related to Neanderthal DNA sequences than to other human sequences (Fig. 1). Two consequences arise from this. First, Neanderthals are not likely to have been as different from modern humans as the mitochondrial picture superficially might suggest. Second, it is clear that, if we are interested in the possibility of interbreeding of Neanderthals or other archaic human forms with modern humans, only genetic systems such as the mitochondrial genome or the Y chromosome, where all current DNA sequences share a common ancestor well after the separation of archaic and modern human populations, are suitable for detecting such interbreeding. With further technical advances, it might become possible to study the genetics of fossil hominids from the past few hundred thousand years more generally.

Human traits

The human gene pool is, in general, very mixed, whereas some phenotypic traits show a distribution that seems to vary with geography in a systematic way, such as skin colour, facial features, hair texture and aspects of the digestion of foods. One striking observation is that such traits are located at places where our bodies interact directly with the environment. Therefore, it is easy to imagine that selection could have shaped these differences in a relatively short time, particularly if much of our history has taken place in rather small groups of individuals.

To date, very little is known about the genetic background of these traits, but progress is beginning. For example, although pigmentation is clearly a multifactorial trait, a screen of variation in the gene encoding the melanocyte-stimulating hormone receptor (MSHR) among English and Irish individuals revealed amino acid substitutions that show some correlation with red hair and fair skin[18]. Recently, a study of MSHR in several populations around the world[19] showed that the variation in the MSHR gene is unusually high among human genes. Furthermore, Africans carry one ancestral variant, whereas non-Africans carry this variant as well as several others. A plausible explanation is that a variant that allows dark pigmentation has been maintained by selection in Africa, for example to protect the body from the effects of ultraviolet irradiation. Outside Africa, this selection could have been released, or there could have been selection for loss of pigmentation. However, even individuals with the ancestral MSHR variant can be pale, so additional loci must be involved in determining human pigmentation. So far, no systematic worldwide study of variation at such loci exists. Eventually, it will be interesting to know how many genetic changes underlie the continuum of hues seen in humans.

The genetics of several phenotypic traits that show geographic differences are likely to become clarified in the future. They are of substantial interest, not only from a genetic perspective, but also because some of them could have had cultural consequences. For example, the retention of the juvenile expression of lactase in the intestine allows a high proportion of adult members of certain groups to ingest unfermented milk products. This trait shows a correlation with dairy farming, and the possibility that this genetic variant has not only promoted certain cultural practices, but has also been selected by such practices, is an intriguing one[20].

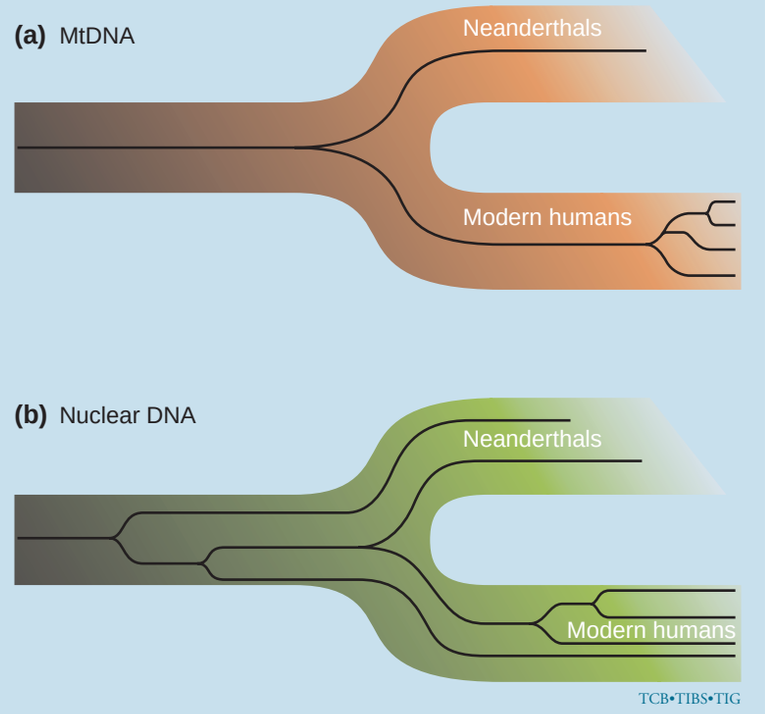

FIGURE 1. (a) Diagram showing how the mitochondrial DNA (mtDNA) sequences detected in Neanderthals and humans are related. The possibility of gene flow between Neanderthals and humans is not illustrated because it has not affected the current human mitochondrial gene pool. (b) The putative relationship of a nuclear DNA sequence where the variation is older than the putative population split between Neanderthals and humans (about 500 000 years ago). Note that, even in the absence of gene flow, some contemporary human sequences are more closely related to some Neanderthal sequences than they are to other human sequences.

What makes us human?

A number of abilities set us apart from other species on this planet. Perhaps the most notable among these are cognitive skills, such as the use of a complex language, long-term planning and an advanced ability to give and receive instructions. These features, which together are generally used to define us as human, emerged in an ancestral species after our lineages diverged from its closest living relatives – the African apes. It would seem that the identification of the genetic differences between humans and the apes should shed light on the genetic basis of these skills.

The first question that arises is which species is our closest relative? In a close contest, the accumulated weight of genetic evidence has awarded the chimpanzee, and not the gorilla, the dubious honour of being most closely related to humans[21]. So, we can now ask in what genetic respects do we differ from chimpanzees? The first, albeit crude, answer came in 1975 when DNA–DNA hybridization experiments showed that the non-repetitive parts of the chimpanzee genome are 98–99% identical to those of the human genome[22]. This result has held up remarkably well in the face of primary sequence data. For example, in a region of 10 kb of noncoding DNA on the X chromosome, chimpanzees differ by 0.94% from humans[8]. The mere accumulation of point mutations is just one aspect of how we differ genetically from apes; another is large chromosomal rearrangements[23]. However, the overwhelming majority of both of these types of changes are unlikely to cause the species-defining phenotypic differences. Rather, it is possible, or even likely, that what matters are changes in the structure or expression of a few genes that exert their effects either during development or in adulthood. Even though this possibility was pointed out over 20 years ago[22], virtually nothing is known about it to date. In fact, only one biochemical difference between humans and other mammals is well characterized. This is the failure of humans to express a hydroxylated form of a sialic acid (*N*-glycolyl-neuraminic acid) on the surface of cells and secreted proteins[24]. This difference, which affects most cells, is caused by a 92-bp deletion in the gene encoding the relevant hydroxylase[25] and could have consequences for interactions with pathogens that use sialic acids as receptors, and for cell–cell interactions. A whole-scale comparison of the genomes and transcriptomes of chimpanzees and humans is likely to provide the inroad to more such differences.

Concluding remarks

For the first of the three areas discussed here, the origins of genetic variation in humans, it is clear that many more worldwide studies of genetic variation at different loci are needed. This work is likely to be performed in the near future, not least because it will be of great importance for finding genes that are involved in complex traits. Hopefully, it will be performed in a coordinated way, such that the data will be compiled and compared rationally. However, an all-out sequencing approach will not determine the genetic legacy, or lack of one, of fossil human forms to our current gene pool. Unfortunately, there are enormous technical difficulties associated with working on ancient human DNA, and the contribution of ancient DNA sequences to the understanding of human evolution is likely to remain limited until further technical advances have been achieved.

For most of the phenotypic traits that vary between human groups, it is likely that several different mutations that result in the same phenotype coexist in a population, as in the case of the red-hair variants. Thus, even the few traits that do differ between different regions of the world probably result from several independent mutations. In other words, fixed genetic differences

between regions are probably extremely rare or even non-existent. In fact, the claims of fixed differences between continental groups made to date (e.g. Ref. 6) are premature because they are based on such small sample sizes that they are likely to disappear upon further study.

The situation is probably different for traits that differ between humans and chimpanzees. In this case, all humans are likely to share the same genetic changes. However, the nature of these differences might only become visible after the accumulation of a great deal of primary DNA sequence and gene expression data. In fact, the interpretation of the human genome sequence would be enhanced greatly by comparable data from the chimpanzee. The generation of such data must be one of the major priorities in the field of molecular anthropology for the next decade.

In conclusion, in the future, the genetic investigation of our species is likely to extend beyond the current focus on ourselves and our recent past to our deepest roots and our closest relatives. This parallels the recent trend in cultural anthropology that redefines cultural traits to permit their identification in chimpanzees[26]. At the same time, comparative cognitive studies are producing complementary information on the similarities and differences between humans and apes[27]. Thus, at the dawn of the new millennium, anthropology is likely to see the human species increasingly within its context of our evolutionary relatives.

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Were they right?

In 1993, *Trends in Genetics* invited five eminent geneticists to speculate on what genetics in the year 2000 would hold. Here are some selected quotes.

The availability of complete genomic sequences will change, dramatically and permanently, the work in which we geneticists think and work. … By the year 2000 geneticists working with bacteria and yeast will no longer have to suffer the manual, *de novo* sequencing of one or more genes for each and every project. This rite of passage will join other bygone rites (like purifying one's own *Bam*HI or blowing one's own glassware) in the dustbin of technological history. Progress in understanding biological functions will accelerate as biologists in the post-sequence era study and manipulate more than just one or two genes at a time.

David Botstein

Also appearing on our computer screens will be 4D models of gene expression during mouse, and probably *Drosophila*, development. Serial sections of successive embryonic stages will be translated into a computerized mouse embryo that we can rotate, fast-forward and zoom into. Onto this moving image will be painted the expression pattern of each gene.

Ann McLaren

We will be seeing a major change of emphasis in clinical genetics, away from monogenic disease and towards identifying and characterizing the genes involved in common polygenic disorders. … We will have a much greater understanding of the molecular and cellular basis of cancer. … Some of this knowledge will have spilled over into the clinic, for identifying individuals susceptible to particular cancers and for other diagnostic purposes.

David J. Weatherall