Evolution of man in the light of molecular genetics: a review. Part I. Our evolutionary history and genomics

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The discovery in the mid 1970s of efficient methods of DNA sequencing and their subsequent development into more and more rapid procedures followed by sequencing the genomes of many species, including man in 2001, revolutionised the whole of biology. Remarkably, new light could be cast on the evolutionary relations of different species, and the tempo and mode of evolution within a given species, notably man, could quantitatively be illuminated including ongoing evolution possibly involving also the size of the brains. This review is a short summary of the results of the molecular genetic investigations of human evolution including the time and place of the formation of our species, our evolutionary relation to the closest living species relatives as well as extinct forms of the genus Homo. The nature and amount of genetic polymorphism in man is also considered with special emphasis on the causes of this variation, and the role of natural selection in human evolution. A consensus about the mosaic nature of our genome and the rather dynamic structure of our ancestral population is gradually emerging. The modern gene pool has most likely been contributed to several different ancestral demes either before or after the emergence of the anatomically modern human phenotype in the extent that even the nature of the evolutionary lineage leading to the anatomically modern man as a distinct biological species is disputable. Regulation of the function of genes, as well as the evolution of brains will be dealt with in the second part of this review.

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The discovery of the basis of genetic variation has opened inroads to understanding our history as a species. It has revealed the remarkable genetic similarity we share with other individuals as well as with our closest primate relatives. To understand what makes us unique, both as individuals and as a species, we need to consider the genome as a mosaic of discrete segments, each with its own unique history and relatedness to different contemporary and ancestral individuals.

Svante Pääbo (Păabo 2003)

Invention of efficient methods for sequencing DNA in the mid 1970s by Maxam and Gilbert (1977) and Sanger et al. (1977) followed by automation and subsequent development of more and more rapid applications of these methods soon led to the sequencing of complete genomes of a variety of species, and – regarding man – culminated in the publication of the draft of the complete nucleotide sequence of the human genome by two teams in 2001 (International Human Genome Sequencing Consortium 2001; Venter et al. 2001). The final version of the nucleotide sequence of the euchromatic part of the human genome was published three years later in 2004 (International Human Genome Sequencing Consortium 2004). Results of the studies like these have meant a real revolution in the whole of biology, and consequently the present time in biology is commonly called the postgenomic era. Biology and its applied sciences, including medicine, have experienced a radical shift in the methods used, and most of the central problems of biology, like evolution, and speciation in particular, can now be approached from a completely new perspective which, regarding evolution in particular, is a quantitative one (reviewed by Garrigan and Hammer 2006).

After the publication of the nucleotide sequence of the human genome comparative genomics of our species soon started to evolve. Extensive reviews (Crawford et al. 2005) and exhaustive original publications (The International HapMap Consortium 2003, 2005; Goldstein et al. 2005; Hinds et al. 2005; Cheung et al. 2006; Conrad et al. 2006; Redon et al. 2006) on the nature and amount of genetic polymorphism of man has already been published. These and other similar studies has led to deep understanding of the origins and evolution of man based on quantitative data instead of earlier more or less qualitative analyses.

The publication of the initial nucleotide sequence of the chimpanzee (Pan troglodytes) and its comparison with the human genome (The Chimpanzee Sequencing and Analysis Consortium 2005) has given special light on the formation of our species indicating a complex speciation of humans and chimpanzees (Patterson et al. 2006). Likewise, sequencing of the mitochondrial genome from a total of twelve specimens (Krings et al. 1997, 1999, 2000; Ovchinnikov et al. 2000; Schmitz et al. 2002;
Serre et al. 2004; Lalueza-Fox et al. 2005; Caramelli et al. 2006; Orlando et al. 2006) as well as partial sequencing of the chromosomal genome (Green et al. 2006; Noonan et al. 2006) of the Neanderthal man, dealt with later, substantially elucidates the taxonomic and evolutionary relationship of the modern man to the Neanderthal man.

The very recent sequencing of the genome of the rhesus macaque (Macaca mulatta) by the Rhesus Macaque Genome Sequencing and Analysis Consortium (2007) makes it now possible, by comparing the genomes of the three sequenced primate species, to reconstruct a draft of the ancestral primate genome. By performing comparisons between the three species, we are now able in the near future, for example, to home the regions of the genome that contributed to the evolution of humans. Also, for instance, when a difference between chimpanzee and man in the DNA is observed, we can now, by checking this difference against the macaque sequence, figure out whether the chimpanzee or the human carries the more ancient version of the DNA. These possibilities of research will become even better over the next few years as other non-human primate sequences will be added to our methodological resources.

Comparative genomics within the human species as well as between us and our closest living relatives has also shed light on the roles of positive and negative natural selection during the evolution of man (reviewed by Sabeti et al. 2006). Typically, human characteristics of evolution, such as fast evolving genes, has been observed, and these genes seem in several instances to be different regulatory genes or cis-acting regulatory elements, which are notably expressed during the development of the brains, and mainly located in the non-coding DNA (Berezikov et al. 2006; Chen and Rajewsky 2006; Pennacchio et al. 2006; Pollard et al. 2006). These and other studies (Evans et al. 2005; Mekel-Bobrov et al. 2005) suggest ongoing adaptive evolution of the human brain.

These recent studies have led to a reconstruction of our evolutionary history and phylogeny providing a direct genetic witness of the origin of our species (Garrigan and Hammer 2006; Stanyon et al. 2006). However, the field evolves very rapidly, and our comprehension of the evolution of the human genome, which seems to be actually a mosaic of discrete segments, each with its own unique history and relatedness to different contemporary and ancestral individuals (Paabo 2003), is gradually emerging. Furthermore, our genome is also a mosaic of surprisingly many structural variations, such as deletions, insertions, inversions, copy-number variants and segmental duplications (Check 2005a, 2005b). Actually, our genome seems to be a dynamic cybernetic system consisting of a multitude of regulation circuit networks of complex protein coding and complex regulatory elements (Check 2005b; Pearson 2006). Understanding the genetic basis of the physical and behavioural traits that distinguish human beings from each other, and the human species from other primates, i.e. understanding humanity, presents one of the great future challenges of science.

Chimpanzees and us: the basis of the genetic difference

The publication of the initial sequence of the genome of chimpanzee in 2005 (The Chimpanzee Sequencing and Analysis Consortium 2005) was a remarkable turning point regarding our understanding of the biology and evolution of man. We now have a rather clear picture about the genetic differences that make us, on the one hand, so different from our closest living relatives in the animal kingdom, and on the other hand, at the same time so similar.

The comparison of the genome sequence of the chimpanzee with the complete nucleotide sequence of the human genome (International Human Genome Sequencing Consortium 2001, 2004; Venter et al. 2001) makes it possible to see what the basic genetic differences are between these two species. At the level of the nucleotide sequence, the difference is surprisingly small. Approximately 98% of our DNA is common with that of chimpanzees, and we share nearly all of our genes with our cousin species.

The chromosomal complement of our species, however, differs substantially from that of the chimpanzee. On the other hand, these two karyotypes, like those of all living hominids, can be derived from each other. The main difference between the haploid chromosomal complements of man and other living hominids is that, instead of the big metacentric human chromosome number 2, the other hominids have two acrocentric chromosomes which correspond to the arms of our chromosome number 2. Furthermore, there are several smaller differences like duplications, deletions, insertions and small inversions (Strachan and Read 1996). These differences can, of course, also been observed in the nucleotide sequences of man and chimpanzee.

The mean rate of the single nucleotide substitutions between the genomes of man and chimpanzee is 1.23 percent, with 1.06 percent or less corresponding to fixed divergence between the species (The Chimpanzee Sequencing and Analysis Consortium 2005). As
an absolute amount of nucleotide pairs this means, however, as much as 33.6 million nucleotide pairs. In addition to this, regarding duplications, our genome differs from that of chimpanzees with 3%, and regarding insertions and deletions together (indels), with 2.7%. Approximately five million indels and other chromosome mutations, like duplications, makes in addition to the single nucleotide substitutions, the difference between the genomes of man and chimpanzee (THE CHIMPANZEE SEQUENCING AND ANALYSIS CONSORTIUM 2005).

By comparing the ratio between the amounts of non-synonymous and synonymous nucleotide substitutions, an estimate can be given regarding the importance of negative and positive natural selection in the evolutionary changes, which have led to the emergence of man. Let us designate with $K_A$ the amount of non-synonymous and with $K_S$ the amount of synonymous nucleotide substitutions. If, in protein encoding genes in man, the ratio $K_A/K_S$ is significantly smaller than one, there has been strong negative selection against the alleles in question in the human lineage. If, however, there has been only weak negative selection against the alleles or continuous positive selection in favour of them, the ratio is approximately one or higher than one.

13 454 orthologous pairs of genes in man and chimpanzee were compared, which constitutes approximately half of all genes in these species. The mean of $K_A/K_S$ was observed to be 0.23. This indicates a rather strong negative selection in the common lineage of man and chimpanzee. Assuming that synonymous mutations are neutral regarding natural selection, the result shows that 77% of amino acid substitutions in the hominid polypeptides have been sufficiently harmful to be targets of negative natural selection in the hominid lineage (THE CHIMPANZEE SEQUENCING AND ANALYSIS CONSORTIUM 2005).

Concerning human genes only, the $K_A/K_S$ ratio was observed to be 0.208, and concerning chimpanzee genes only, it was observed to be 0.194. These numbers do not differ significantly from each other, but are clearly higher than those for mouse (0.142) or rat (0.137). Consequently, in the lineages of the latter species, there has been a stronger negative selection than in the hominid lineage in general (THE CHIMPANZEE SEQUENCING AND ANALYSIS CONSORTIUM 2005).

Comparing the $K_A$ values of the coding regions and relating them to the respective values of non-coding regions ($K_I$) of different genes, an understanding of which genes have evolved most rapidly can be derived. In other words, it can be measured which genes that are in favour of strong positive selection, and consequently adaptively significant for the species. If the ratio is higher than one, there is strong positive selection in favour of the gene. Only 585 such genes out of 13 454, or 4.4%, in the common lineage of man and chimpanzee, were found (THE CHIMPANZEE SEQUENCING AND ANALYSIS CONSORTIUM 2005).

This result indicates that in the lineage common to man and chimpanzee, the amount of favourable mutations has not necessarily been very high. The highest values of $K_A/K_I$ were observed for some genes involved in immunological resistance and reproduction.

Of considerable importance is the role of the regulation of gene function in the evolution of man. The study of this is presently, however, rather difficult since we are not yet able to identify sequences in DNA which are linked to gene regulation. Very interesting is, however, the observation that a group of genes encoding for transcription factors is the most rapidly evolving one of the human genes when they are compared to the respective genes of chimpanzees. Considering all genes, this difference is, however, an exception. In general, no systematic difference in the rates of evolution between the lineages of man and chimpanzee at the level of genes was observed (THE CHIMPANZEE SEQUENCING AND ANALYSIS CONSORTIUM 2005).

One of the biggest challenges of the present day evolutionary biology is to find a satisfactory explanation for what evolutionary changes and forces in fact have led to the emergence of man. Regarding the time of the separation of human and chimpanzee lineages, the analysis of genetic differences between man and chimpanzee by Patterson et al. (2006) shows that human–chimpanzee speciation occurred less than 6.3 million years ago and probably more recently. Certain unexpected features of molecular genetic analyses, like the fact that the X chromosome shows a very young divergence time, would be explained if the human and chimpanzee lineages after having initially diverged, later exchanged genes before separating permanently.

The sequencing of the chimpanzee Y chromosome, and its comparison with that of man (Kuroki et al. 2006), firstly indicated a greater sequence divergence between the human and chimpanzee Y chromosome than between the whole genomes, indicating an accelerated evolutionary rate of the Y chromosome. Secondly, the reconstruction of the common ancestral Y chromosome, based on comparison of the DNA sequences in man and chimpanzee, unveiled a complex evolutionary pathway during the separation of these species.

Genome-wide surveys of structural variation between human and chimpanzee genomes have indicated a significant impact of variation on lineage-specific
evolution of both species. Notably, the changes leading to structural variation have at the same time resulted in gene expression differences between the species suggesting that this type of variation may be a more common and more important feature of the evolution of our genome than previously realized (Fortna et al. 2004; Cheng et al. 2005; Feuk et al. 2005; Newman et al. 2005).

In conclusion, the separation of the human and chimpanzee lineages has most likely been a complex process, and will be discussed more closely in the following chapter.

THE AFRICAN ORIGIN OF MANKIND: MOLECULAR GENETIC EVIDENCE

Although fossils provide unique and invaluable information regarding the origin of man, they are very limited in quantity and quality. Huge gaps remain in the human fossil record, and it is difficult to assess, for example, whether there was continuity between the archaic and the modern human. Genetic data, on the contrary, are easy to collect and they are accumulating rapidly. Ancient demographic and evolutionary events has left imprints that can be observed in present-day gene differences. Therefore, genetic investigations of present-day human populations can illuminate the evolutionary history of our species.

Genetic methods and data are providing fresh perspectives on, for example, a long-standing debate about the origin of our species, which in its simple form, can be summarized as two competing hypotheses. The Multiregional hypothesis suggests that modern humans evolved directly from archaic forms in several different locations in the Old World. Gene flow among these populations, combined with natural selection for advantageous genes, maintained genetic homogeneity of the species. Under this hypothesis, our species had hundreds of thousands, perhaps millions, of ancestor individuals for most of the last million years. Without a large population gene flow among populations distributed widely over the temperate and tropical Old World, this would have been impossible.

The other hypothesis is called the Single origin model or the Recent African origin model. According to this hypothesis, a specific population, ancestral to modern humans, underwent demographic expansion and populated those parts of the world occupied by archaic forms, and then beyond into northern parts of Eurasia and eventually into the New World. The contribution of archaic populations to the modern gene pool was believed to be negligible. Further, according to this hypothesis, the number of ancestor individuals just before the expansion of modern humans was small, only several thousand breeding adults.

A clear difference between these two hypotheses is the implied size of the past human population. If the size of the human population had been large throughout most time of its history, extant genetic variation should be substantial. Conversely, a small human population would result in relatively little genetic variation (Harpending et al. 1998). In addition to the number of generations past, estimates of the effective population sizes are based on the amount of genetic variation found in present populations and on mutation rate. The former can be observed by means of comparative genomics, and the latter, for man, has been estimated to be in the order of $10^{-5}$ per locus (Vogel and Motulsky 1997 p. 396 and p. 417) and of $2 \times 10^{-8}$ per nucleotide per generation (Kondrashov 2002).

At the end of the 1980s, the first studies of human molecular diversity suggested that our species evolved from a small African population that had subsequently colonized the whole world, supplanting former hominids, approximately 120 000–200 000 years ago (Wainscoat et al. 1986; Cann et al. 1987; Vigilant et al. 1991). This timing and placing coincides quite well with the oldest fossil records of the anatomically modern humans in the Omo Valley in southwestern Ethiopia dating 195 000 years ago (Day 1969; McDougall et al. 2005).

A majority of studies have shown that African populations of man harbour more genetic diversity than non-African populations for mitochondrial DNA (mtDNA) sequences, Y chromosome microsatellites, Y chromosome sequences, Y chromosomal single-nucleotide polymorphisms (SNPs), X chromosome sequences, autosomal microsatellites, autosomal sequences as well as autosomal SNPs (Excoffier 2002). This basic result is generally interpreted as evidence for an African origin of our species. The African origin could, however, be either a recent one or an older one. The former alternative assumes a single African origin model, but the latter alternative assumes the African origin as part of the multiregional model. According to this explanation the species of man emerged in several regions, and only those originating from Africa survived.

If the multiregional evolution model or a non-African origin model cannot be ruled out, and were favoured for explaining past human demography, the larger genetic diversity found in Africa would nevertheless imply that the effective population size of sub-Saharan Africa has been much larger than that of the sum of all other continents for much of the recent
human history (Eller 2001; Takahata et al. 2001). In that case, most of the genetic diversity of modern humans would still have originated in Africa, resulting in patterns extremely similar to that expected under the recent African origin model (Takahata et al. 2001). However, the observation that a majority of nuclear loci shows signs of past expansion (Stephens et al. 2001; Excoffier 2002) is difficult to explain under the multiregional evolution model, but would be compatible with a speciation event geographically restricted to a small area, and a subsequent range expansion(s) apparently from somewhere in sub-Saharan Africa (Excoffier 2002).

In the light of evidence from the analyses of human mitochondrial DNA, it is clear that the dispersal of modern humans from Africa occurred via the Horn of Africa to the Persian Gulf, and further along the tropical coast of the Indian Ocean to Southeast Asia and Australasia approximately 60,000–75,000 years ago (Forster and Matsumara 2005; Macaulay et al. 2005; Mellaars 2006; Torroni et al. 2006). The colonization of West Eurasia and North Africa, however, occurred later (40,000–45,000 years ago) after a lengthy pause in migration, and is thought to have a common source in the Levant (regions around the eastern coast of the Mediterranean) (Macaulay et al. 2005; Mellaars 2006; Olivieri et al. 2006).

In their review of the signatures of past expansions on human molecular diversity, Harpending et al. (1998) compared different models of the demographic history of our species. They concluded that genetic evidence denies any version of the multiregional model of modern human origins, and implies instead that our ancestors were effectively a separate species for most of the Pleistocene. According to the hypothesis of Harpending et al. (1998) “We are descended from a population that was effectively a separate species for at least the last 1 or 2 million years. Although the size of this population must have fluctuated over time, it was often reduced to the level of several thousands of adults.” (p. 1967).

More recent studies, however, strongly suggest a more complicated nature of human speciation. Even the human–chimpanzee speciation has most likely been a complex event, as shown by Patterson et al. (2006). They were able to show, by comparing about 20 million base pairs of aligned sequences from humans and chimpanzees, that the human–chimpanzee speciation occurred less than 6.3 million years ago and probably even more recently, conflicting with some interpretations of ancient fossils. More strikingly, the X chromosome shows an extremely young divergence time, the age difference between chromosome X and the autosomes being about 1.2 million years. These unexpected features would be explained if the human and chimpanzee lineages have exchanged genes after their initial divergence but before permanent separation of the species.

Even more exciting are the results of Garrigan and Hammar (2006). They compared genetic polymorphism in mitochondrial DNA, the X chromosome, the Y chromosome and autosomes, and concluded that it is time to consider new working models for the human origin. After presenting putative evidence for admixture between the anatomically modern man and previously isolated archaic demes, and referring to the similar observation of Plagnol and Wall (2006) of at least five percent admixture, they even disputed the nature of the lineage leading to the anatomically modern man as a distinct biological species. They wrote (p. 677): “Although most of the AMH [anatomically modern human] genome might descend from a single African population, if further studies confirms a non-negligible contribution of archaic genetic material to the AMH genome, it would imply that the evolutionary lineage leading to AMH did not evolve reproductive isolation from other archaic hominid subpopulations and, therefore, cannot be considered a distinct biological species.” Garrigan and Hammar (2006) discussed four possible models of recent human evolution, which will be presented and discussed in the next chapter.

MODES AND MODELS OF HUMAN EVOLUTION

The evolution of Homo sapiens can be conceptually divided into two distinct epochs, which can be reconstructed not only through palaeontological and archaeological records, but also from patterns of neutral DNA polymorphism in the human genome. The first epoch includes the evolutionary processes that took place in the lineage that culminated in the emergence of the anatomically modern man. The second epoch focuses on the demographic processes that accompanied the global diaspora of anatomically modern humans after their origin in Africa. Was there a bottleneck or bottlenecks associated with migrations of anatomically modern humans out of Africa? What were the sizes of ancestral populations in the Pleistocene, and were did they first begin to grow dramatically? When did ancestral populations diverge from one another and how much gene flow occurred among their descendant populations? Did anatomically modern humans completely replace archaic forms without interbreeding? Some of these questions have already been answered at least partly in the foregoing chapter, and the rest will be discussed here mainly following the
Many of the studies consider potential changes in effective population size during both epochs of the human evolutionary history. Surrounding the earlier epoch the first question is whether the origin of the anatomically modern human phenotype, approximately 200,000 years ago, was accompanied by a radical change in the effective population size in the form of speciation bottleneck, i.e., a reduction in the population size, which caused the birth of the human species. For a more recent epoch of human history, a second question focuses on whether a bottleneck or bottlenecks occurred as the anatomically modern humans emigrated from Africa. A third question asks when the local populations began to grow.

Some authors who have investigated genomic polymorphism in man suspect the existence of a speciation bottleneck. On the other hand, a consensus has been reached about a rather strong reduction in the effective population size at the time of migration out of Africa (GARRIGAN and HAMMER 2006). The discrepancy between the conclusions of different authors concerning the existence of a specific speciation bottleneck may be solved by assuming that the ancient population was more or less structured, i.e., divided into smaller subpopulations (GARRIGAN and HAMMER 2006). According to GARRIGAN and HAMMER (2006) such a population structure could have mitigated the effects of the speciation bottleneck.

Currently, most but not all of the fossil evidence seems to support the recent African origin model of human evolution (FOLEY and LAHR 1997; DUARTE et al. 1999). From a genetic perspective, we can rephrase the question on the origin of human species in terms of what contribution archaic human populations have made on contemporary human gene pool. The multiregional model predicts that this contribution is negligible. Other models predict intermediate contributions of archaic populations to the modern gene pool (BRAUER 1984).

PLAGNOL and WALL (2006) approached the question whether there has been admixture between the gene pool of the modern man and that of the Neanderthal man by analysing the pattern of linkage disequilibrium in contemporary human populations. In theory, admixture would lead to extensive linkage disequilibrium in a population with otherwise long lasting random mating and hence with no linkage disequilibrium. The more extensive the linkage disequilibrium found, the more recent the admixture occurred. For example, at the very moment of the admixture linkage disequilibrium would extend across the whole chromosome. Their method, which is a generalization of that of WALL (2000), relied on the hypothesis that the genetic signature of ancient admixture is so strong that even tens or thousands of years of random mating is not enough to obscure it (WALL 2000). The method of WALL (2000) on its part is an extension of the method presented by NORDBORG (1998, 2000).

The above authors found strong evidence for ancient admixture in both the European and one West African (Yoruba) population. They observed that there was a contribution of at least five percent from some archaic deme to the modern gene pool. While Neanderthals form an obvious archaic source population candidate in Europe, there is not yet a clear source population candidate in West Africa. The observation of non-negligible contributions of the archaic populations to the modern gene pool are inconsistent with strict forms of the recent African origin model, which posits that the modern humans evolved in a single location in Africa and from there spread and replaced all other existing hominids. Instead, a more complex speciation process must be assumed.

Consequently the authors suggested that the lineage of the modern man and that of the Neanderthal man diverged from each other approximately 400,000 years ago. The African and the European populations of the modern man diverged approximately 130,000 years ago and most likely there was no migration between them thereafter. Subsequently, in the African population extensive growth began approximately 80,000 years ago, and in the European population approximately 100,000 years ago. However, in the beginning of the growing period, there was a very strong bottleneck in the European population approximately 60,000 years ago followed by admixture with the Neanderthals approximately 50,000 years ago.

GARRIGAN and HAMMER (2006) collected evidence from polymorphism in the mitochondrial, non-recombinant Y chromosomal, X chromosomal and autosomal DNAs. They concentrated on the question of the changes in the effective population size, and then reviewed the studies that suggested that the ancestral population might have been geographically structured. Finally they discussed the implications of these inferences for the recent African origin model of human evolution. Specifically they investigated the divergence of haplotypes and the range of linkage disequilibrium in order to draw conclusions about the population structure of the human lineage during its recent evolution.
The authors quoted above observed contrasting patterns of evolution at different loci throughout the genome, and concluded that an increasing amount of evidence is incompatible with a simple single origin hypothesis. Thereafter they presented and discussed three other different models, which are variations of the recent African origin model of the human evolution.

These models are: 1. High-migration model, which assumes frequent movement between different demes in Africa before the apparent speciation bottleneck in Africa. Thus, multiple demes contribute equally to the modern human gene pool. 2. Low-migration model, which is otherwise similar to the high migration model but assumes only a little migration between demes in Africa. Thus, only one of the archaic demes living in Africa was the major contributor to the gene pool of the modern man. 3. Isolation and admixture model, which assumes that there was no migration between different demes in Africa before the speciation bottleneck, only one of the archaic demes exclusively contributed to the modern gene pool, but that there was admixture after the speciation bottleneck between the non-African human populations and some other taxonomic group, presumably Neanderthals, also originating from Africa. This third model is similar to a range of other models that allow for the hybridization between the anatomically modern man and archaic populations in Eurasia (Garrigan and Hammer 2006). All three models are identical in assuming a strong bottleneck in the non-African population before the growing period and no migration between the African and non-African population after the speciation bottleneck.

According to Garrigan and Hammer (2006) the model of the ancestral population structure with low migration (model number 2 here) seems to be more strongly supported by the current data than either the single origin or high-migration model (model number 1 here). The discovery of a subset of loci with highly divergent haplotypes and long-range linkage disequilibrium, suggest a rather recent admixture between the anatomically modern man and some previously isolated archaic demes (model number 3 here).

Taken together, a rather dynamic picture of ancestral population structure is emerging. The observed mosaic nature of our genome might be most easily explained by models, which incorporate gene flow among a group of ancestral demes. Further analyses of sequence data are needed, specifically of many independent regions of the genome that are from functional regions, to avoid the possible confounding effects of natural selection. Analyses of such data could help to resolve whether admixture, if it occurred, was before (low-migration model) or after (isolation-admixture model) the emergence of the anatomically modern human phenotype.

It should be noted, however, that alternative models of sustained population subdivision, such as metapopulation models, also remain feasible (Harding and McVean 2004). Although the conclusions reached by different recent authors are remarkably similar, further studies are needed. Further theoretical predictions, that are based on different models, must also be obtained before the specific nature of the putative historical subdivision of the ancestral population of man, and its dynamics can be fully addressed.

A CLOSER LOOK AT THE RELATIONSHIP BETWEEN THE NEANDERTHAL MAN AND THE MODERN MAN

The mitochondrial genome for a total of twelve specimens of the Neanderthal man has been completely sequenced (Introduction). All published Neanderthal mitochondrial DNA (mtDNA) sequences are quite different from all known modern human mtDNA sequences, and it is extremely unlikely that Neanderthals have made any contribution to the present modern human mtDNA gene pool. According to GARRIGAN and Hammer (2006) firstly concluded that modern human and Neanderthals are not necessarily mean that during ancient times anatomically modern humans and Neanderthals would not have interbred et al. It should, namely, be noted that in the population genetic models and analyses mtDNA, which does not undergo any recombination, behaves as a single locus. Consequently, it is impossible to make any strong inferences from these single locus data because of the randomness inherent in the underlying evolutionary process. To have any statistical power in the analyses, we must have data from multiple unlinked loci.

Recently GReen et al. (2006) and Noonan et al. (2006) performed this type of analyses. The former group was able to sequence over one million base pairs of Neanderthal nuclear DNA from one bone of a 38 000-year-old male fossil from Croatia. The latter group on its part sequenced 65 250 base pairs of nuclear DNA from the same specimen.

Both groups compared orthologous sequences from different chromosomes, including sex chromosomes, from modern humans, Neanderthals and chimpanzees, and calculated the similarities and differences between these sequences. Doing so, GReen et al. (2006) firstly concluded that modern human and Neanderthal DNA sequences diverged about 500 000 years ago. Secondly, and more importantly, by investigating single nucleotide polymorphisms, they
asked how many genes of the Neanderthals have the ancestral allele (that is, the same allele seen in chimpanzee) versus the derived (or novel) allele at sites where humans carry a single nucleotide polymorphism. In fact, they found that the Neanderthal sample had the derived allele in approximately 30% of all single nucleotide polymorphisms. This high level of derived alleles in the Neanderthals is incompatible with a single split speciation model, and may suggest gene flow between modern humans and Neanderthals. Green et al. (2006) observed that the Neanderthal X chromosome shows a higher degree of divergence than the autosomes, suggesting that gene flow may have occurred predominantly from modern human males into Neanderthals. This hypothesis would explain the fact that, despite plausible interbreeding, mitochondrial DNA from the Netherlands differs that much from that of the modern man.

Noonan et al. (2006), on their part, observed no signs of the Neanderthal-genome in the present day human gene pool. This observation is compatible with the hypothesis of a unidirectional gene flow from modern human males into Neanderthals only. Thus, Noonan et al. (2006) suggested that the speciation event, in which the lineages of Neanderthals and modern humans diverged from each other, was gradual. They concluded that the lineages started to diverge approximately 706,000 years ago, but the actual split between ancestral humans and Neanderthals occurred only ca 370,000 years ago. According to McDougall et al. (2005), the earliest known anatomically modern humans came into existence ca 195,000 years ago.

HOW VARIABLE IS OUR GENOME?

Single nucleotide polymorphism

The amount of single nucleotide polymorphism (SNP) is the most precise and best, though not the sole, measure of the general amount of genetic polymorphism in a given species. In recent years several extensive investigations on single nucleotide polymorphism in man has been carried out. In a study comprising 269 individuals from four populations living on different parts of the globe, the total amount of SNPs was observed to be over 10 million (The International Hapmap Consortium 2005). It was possible to observe the existence of at least one SNP per every 5000 nucleotide pairs of DNA. Moreover, ten stretches consisting 500,000 nucleotide pairs of DNA from every individual were sequenced completely for the detection of SNPs. The same amount of SNPs was observed in another study comprising 137 individuals from USA representing different ethnic groups (Crawford et al. 2005).

On the basis of these results, The International Hapmap Consortium (2005) estimated that every 279th nucleotide pair is polymorphic in the human population, while Crawford et al. (2005) reached an even higher estimate of polymorphism. They namely estimated that every 180th nucleotide pair would be polymorphic. Thus, regarding SNP, we differ from each other only with 3.6–5.6%. The respective figure for big mammals in general is usually approximately 10%.

It was also observed that the amount of human SNP in USA was higher among people of African origin than in people of European origin reflecting the common African past of these ethnic groups (Crawford et al. 2005). When comparing any two individuals, every 1110th nucleotide pair in the mean was different in people of African origin, while the respective figure in the people of European origin was every 1435th. Taking into account that the haploid human genome consists of 3200 million nucleotide pairs of DNA, one can calculate that any two individual genomes differ by 2.89 million nucleotide pairs in the former group, and by 2.23 million nucleotide pairs in the latter group.

Hinds et al. (2005) studied the distribution of over 1.5 million single nucleotide polymorphisms (SNPs) in 71 Americans of European, African, and Asian ancestry. They found that 93.5% of these SNPs could be observed in the people of African ancestry, 81.1% in people of European, and 73.6% in people of Asian ancestry. African-Americans also had overwhelmingly more (218,500) so called private SNPs, which are segregating in only one population, than European-American (44,500) or Asian-American individuals (25,957). Thus, the studies of Crawford et al. (2005) and Hinds et al. (2005) both complement and confirm each other in showing that the populations of African origin are the most variable, while populations of European or Asian origin are less variable, suggesting an African origin of mankind.

Haplotype variation

The amount and nature of haplotype variation also suggest an African origin. The International HapMap Consortium (2005) observed in an analysis of three group of people, one consisting of one African, the second of one European-American, and the third of two Asian populations, that although the groups are characterized both by different haplotype frequencies and, to some extent, different combinations of SNPs inside the haplotypes, both common and rare haplotypes are often shared across the populations.
Likewise, in a survey of haplotype structure across 12 Mb of DNA sequence in 927 individuals representing 52 populations from different parts of the world, it was found firstly that the diversity of haplotypes decreases as distance from Africa increases. Second, although the extent of linkage disequilibrium varied markedly across the populations, considerable sharing of haplotype structure exists, and inferred recombination hot-spot locations, demarcating the haplotypes, generally match across the groups (Conrad et al. 2006).

**Structural variation**

The first data concerning molecular polymorphism in the human genome, presented above, revealed that SNPs would be the main source of genetic and phenotypic human variation. Accordingly, a striking observation was the extent of DNA-sequence similarity among individuals from around the world: any two human individuals are thought to be about 99.9% identical in their DNA sequence (Przeworski et al. 2000; Reich et al. 2002).

However, the advent of genome scanning technologies (Lucito et al. 2003; Fiegler et al. 2006; Komura et al. 2006) has now uncovered an unexpectedly large extent of what is termed structural variation in the human genome. This comprises microscopic and, more commonly, submicroscopic variants, which include deletions, duplications and large-scale copy-number variants—collectively termed copy-number polymorphisms—as well as insertions, inversions and translocations. Rapidly accumulating evidence indicates that structural variants can comprise millions of nucleotides of heterogeneity within every individual genome, and are thus likely to make an important contribution to human diversity (reviewed by Feuk et al. 2006).

A surprisingly large amount of both fine-scale and large-scale structural variations, like copy number polymorphism, insertions, deletions and inversions, has recently been found in the human genome (Iafrate et al. 2004; Sebat et al. 2004; Dhami et al. 2005; Sharp et al. 2005; Stefansson et al. 2005; Visser et al. 2005; Tuzun et al. 2005; Khaja et al. 2006). It has been estimated that there are for example some 100 copy-number variants per individual, each over 50 kb in size. In addition to these large copy-number variants, a significant number of intermediate-sized copy-number variants and inversions (8 to 40 kb) are being identified in the human genome, as are numerous smaller structural variants (1 to 8 kb) (Feuk et al. 2006).

By comparing structural variation in the genomes of man, chimpanzee and rhesus macaque Harris et al. (2007) found 130 human specific breakpoints. Of these 64 are insertions, 7 deletions, 16 inversions and 43 breakpoints, that could not be unambiguously assigned to a specific type of rearrangement. These authors identified 58 genes affected by insertions including 36 gene copies fully contained within insertions. An additional 22 genes were either partially duplicated or contained an insertion. Of the 36 fully duplicated genes, 7 were previously identified as human-specific (Cheng et al. 2005). The average size of detected rearrangements on the human genome was 110,063 base pairs (bp), ranging from 20 to 1,365,171 bp.

Compared with other mammals, the genomes of human and other primates show an enrichment of large interspersed segmental duplications with high level of sequence identity. There is also evidence for a strong association between chromosomal locations of duplications, genomic instability and large-scale chromosomal rearrangements (Sharp et al. 2006). These exciting new findings, reviewed by Bailey and Eichler (2006), suggest that segmental duplications have not only created novel primate gene families, but might have also influenced current human genotypic and phenotypic variation on a previously unappreciated scale. As indicated already in the chapter dealing with the relation of our species to chimpanzees, structural variation has in fact had an important role in the separation of the lineages leading to man on the one hand and to chimpanzees on the other.

Overall, different international research groups, quoted above, have found 1,447 discrete, heterogeneously distributed, copy number variable regions (CNVRs), which cover twelve percent of the human genome. CNVRs contain different classes of functional elements. Although many copy-number variants (CNVs) preferably lie outside genes, by using gene ontology categories the authors were able to show that genes that are involved in cell-adhesion functions, sensory perception of smell and response to chemical stimuli are enriched in CNVs. Conversely, cell signaling and proliferation, as well as kinase- and phosphorylation-related categories were underrepresented among CNVs. Interestingly, ultraconserved elements are strongly excluded from these regions (Skipper 2007). Feuk et al. (2005) on their part found 1,576 probable inversions, and confirmed 23 of which three differed among human individuals.

Taking the relatively small amount of overlap between different studies into account, it seems that the calculations of the total amount of structural variation made hitherto are underestimates (Sharp et al. 2006). Probably the best estimate to date is that of Tuzun et al. (2005). They suggested that approximately 250 copy number variation with a mean size of 15 kb, or a total of $3.75 \times 10^6$ base pairs of structural
polymorphism, exist between any two diploid human genomes.

In conclusion

The earlier estimate, based on the amount of SNPs, showing 99.9% genome-sequence identity between humans, might thus be considered an underestimate. Moreover, recent analyses, quoted above, of the human and chimpanzee genomes indicate that different structural variations, notably segmental duplication events, have had a greater effect on altering the genome than single nucleotide pair changes. This observation calls for further studies on structural variation of the genome from the evolutionary perspective. In fact, it has been calculated that SNPs constitute a 1.2% genetic difference between man and chimpanzee, whereas large segmental duplications constitute a 2.7% difference (Cheng et al. 2005; Sharp et al. 2006). This observation immediately suggests that large-scale variations play a significant and stronger role than hitherto believed in both micro- and macroevolution of man.

The great DNA sequence identity between human beings has been viewed as biological support for the human equality (Check 2005a). In fact, all biological reasons for human inequality can be discarded on the basis of our extreme DNA sequence identity. Do the new findings of a more extensive genetic variation between us mean anything in this respect? No, we are still one human family, of course, but our DNA landscapes are more varied than we have thought. Human equality needs no biological grounds. In actual fact judgements of human equality should not include biological reasoning. Rather such judgements must involve ethical argumentation.

CHARACTERISTICS OF EVOLUTION SPECIFIC FOR THE HUMAN LINEAGE

The central question concerning the structural variation of our genome is: does it matter? There is already lot of evidence that it does. Many of the large structural changes of the genome have been associated with devastating diseases (reviewed by Buckland 2003). It has also been shown that many of the genes found in structural variants influence our interaction with the environment (Tuzun et al. 2005). Some make proteins that break down drugs, or help our immune system respond to diseases. Gonzales et al. (2005) analysed the average number of copies of an immune system gene in African, European, Asian and American populations, and found that extra copies of the gene which codes for an immune-system protein called CCL3L1, helped protect people against HIV. These individuals progressed more slowly towards full-blown AIDS than those with fewer copies. There is also good reason to hope that structural variation will shed new light on different complex disorders.

Studies comparing us with our chimpanzee cousins and other living hominids have already linked structural variation to our divergence from the apes. Fortna et al. (2004) found 1005 genes that differed in copy number among humans and the great apes. Newman et al. (2005) on their part reported 651 likely structural rearrangements between chimpanzee and man. They identified 245 separate genes overlapped by these variants. These genes, including some genes involved in reproduction, receptors and drug metabolism, may be affected by the chromosomal breakpoints associated with the rearrangements.

The same research group also found that segmental duplications have created much more of our genomic differences from chimps than single base-pair differences (Cheng et al. 2005). There are 177 complete or partial genes (88 and 89 respectively) showing evidence of the human-specific duplication. In contrast, only 94 genes were duplicated in chimpanzees but not in humans. As segmental duplications are known to be hotspots of evolution, those 177 genes could be partly responsible for creating the traits that make us human. According to Cheng et al. (2005), the changes, i.e. break points, that have created duplications which differ between chimpanzee and man, have also resulted in gene expression differences between the species. Of specific interest are human lineage-specific amplifications of certain duplications of genes that are involved in the development of the brain. These genomic changes will be dealt with more closely in the second part of this review.

The comparison of the complete sequences of genomes of man and chimpanzee (The Chimpanzee Sequencing and Analysis Consortium 2005), connected with an analysis of rates of evolution of different genes in these species, revealed that the fastest rates were observed for genes involved in immunological resistance or reproduction. These changes, however, are not human- or even hominid-specific because similar features of evolution can also be observed in murids.

On the contrary, mutations which lead to the silencing of certain genes, like indels residing in the middle of coding regions, are partly human-specific. Compared to chimpanzees, 53 such silent genes were found in the human genome (Li and Saunders 2005). Such genes probably control the development of specific human characters like lack of body hair and preservation of some juvenile traits into adulthood and expansion of cranium. These so called
neotenic traits, which typically represent a certain kind of lack of adult development, may well be attributed to loss-of-function mutations like for example disruptive indels.

Likewise, one human specific phenomenon seems to be the accelerated rate of evolution of genes coding for transcription factor activity. A group of 348 human genes, coding for transcription factors, have accumulated 47% more amino acid changes than their chimpanzee orthologues (The Chimpanzee Sequencing and Analysis Consortium 2005). These genes, with accelerated divergence in humans, include genes for homeotic, forkhead and other transcription factors, that play a key role in development. However, given the small number of changes involved, additional data were required by the authors to confirm the observed trend. Changes in transcription factors and other elements of gene regulation are in general important in human evolution, and will be more closely discussed in the second part of this review.

A mutation, which possibly is strongly favoured in evolution, may be the mutation in the FOXP2 (forkhead box P2) gene, which controls the human ability of speech. Consequently this gene is most likely one of several genes which contributed to the emergence of language as a unique human trait. This mutation is a point mutation, and FOXP2 protein in man differs with two amino acid residues from those of chimpanzee and gorilla (Enard et al. 2002). FOXP2 has had an accelerated rate of evolution and has been the target of selection during recent human evolution (Enard et al. 2002; Zhang et al. 2002). Needless to say, FOXP2 is a transcription factor.

NATURAL SELECTION IN THE HUMAN LINEAGE

Comparison of DNA polymorphism within species and divergence between species enables the discovery of molecular adaptation in evolutionary constrained genes as well as the differentiation of weak negative selection from strong purifying selection (Kimura 1968a, 1968b; Hudson et al. 1987; Mcdonald and Kreitman 1991; Sawyer and Hartl 1992).

By contrasting patterns of coding sequence polymorphism, identified by direct sequencing of 39 human individuals for 11624 protein-coding genes to divergence between humans and chimpanzees, Bustamante et al. (2005) found strong evidence that natural selection has shaped the recent molecular evolution of our species. The analysis discovered 304 (9.0%) out of 3377 potentially informative loci showing evidence of rapid amino acid evolution. Furthermore, 813 (13.5%) out of 6033 potentially informative loci showed a paucity of amino acid differences between humans and chimpanzees, indicating weak negative selection and/or balancing selection operating on mutations at these loci.

Bustamante et al. (2005) also found that the distribution of negatively and positively selected genes varies greatly among biological processes and molecular functions. Some classes, such as transcription factors, show an excess of rapidly evolving genes, whereas others, such as cytoskeletal proteins, show an excess of genes with extensive polymorphism within humans and yet little amino acid divergence between humans and chimpanzees.

Of rather considerable importance in this connection are the very recent findings of Bakewell et al. (2007) indicating that the amount of positively selected genes in chimpanzee is higher than in man. They compared approximately 14000 matching genes of chimpanzee and man, and found 233 of them have been under positive selection in the lineage of chimpanzees but only 154 in the human lineage. This seemingly surprising observation might be due to the fact that, for much of our histories, chimpanzees had the larger effective population size. Humans, with a smaller and more fragmented population, may have been shaped by random, erratic changes.

Bustamante et al. (2005) also observed that 10767 (92.6%) out of 11624 genes investigated showed some form of coding nucleotide variability either within human subjects or between humans and chimpanzees. Furthermore, the ratio of non-synonymous to synonymous differences (23.76%) is smaller than the ratio of non-synonymous to synonymous polymorphisms (38.42%), indicating a highly significant excess of amino acid variation relative to divergence. This is consistent with the previous studies of human polymorphism, suggesting that a large proportion of amino acid variation in the human genome is slightly to moderately deleterious (Cargill et al. 1999; Halushka et al. 1999; Stephens et al. 2001; Sunyaev et al. 2001; Livingston et al. 2004; Williamson et al. 2005).

Of importance is the result of the extensive analysis of Bustamante et al. (2005), which confirmed the earlier result of The Chimpanzee Sequencing and Analysis Consortium (2005) that transcription factors as a group seem to be rapidly evolving. Similarly, they found evidence that the categories of nuclear hormone receptors, which, like transcription factors, are also involved in the regulation of the transcription of genes, and genes involved in nucleoside, nucleotide and nucleic acid metabolism have an excess of rapidly evolving genes.
Considering structural variation of the human genome and natural selection, the finding of Stefansson et al. (2005), for example, is significant. They found that haplotype structure of a 900-kb inversion on chromosome 17 of man is indicative of positive selection. Furthermore, they were able to show that the lineage of that inversion is still undergoing positive selection in the Icelandic population, such that carrier females have more children than non-carriers.

Of structural variations, segmental duplications seem to be the most important in the evolution of primates. Compared with other mammals, the genomes of man and other primates show an enrichment of large, interspersed segmental duplications with high levels of sequence identity (Bailey and Eichler 2006). Analysis of the chimpanzee genome suggests a slightly higher level of recent duplication compared with the human genome. Furthermore, the analysis also indicates that as many as one third of all duplications, with >94% identity, differ in copy number or content between the two species (Cheng et al. 2005).

A striking feature of human and chimpanzee segmental duplications is their non-random distribution at the chromosomal level (Courseaux and Nahon 2001; Johnson et al. 2001; Courseaux et al. 2003; Stankiewicz et al. 2004; Ciccarelli et al. 2005; Horvath et al. 2005). Other species also show clustering of duplications, but what truly distinguishes human and chimpanzee genomes from other sequenced species is the abundance of interchromosomal and interspersed intrachromosomal duplications (Bailey et al. 2004; Tuzun et al. 2004; Bailey and Eichler 2006; She et al. 2006).

Duplication of genomic sequences is the primary mechanisms for the creation of new genes (Müller 1936; Ohno et al. 1968; Zhang 2003; Taylor and Raes 2004). Of special interest in this connection are the many observations that strong signatures of positive selection of segmentally duplicated genes are common in the human lineage and in hominids in general (Johnson et al. 2001; Semple et al. 2003; Birtle et al. 2005; Linardopoulou et al. 2005; The Chimpanzee Sequencing and Analysis Consortium 2005).

King and Wilson (1975) were the first to suggest, over 30 years ago, that evolutionary changes in gene expression account for most phenotypic differences between species, in particular between man and apes. According to the recent review by Khaitovich et al. (2006), on the other hand, the differences found between the genomes of human, other primates and other mammals are exactly of the magnitude that could be expected in the light of the neutral gene theory of evolution. This theory, created by Motoo Kimura in the late 1960s (Kimura 1968a, 1968b), postulates that the vast majority of DNA sequence substitutions observed both within and between species have no effect on the phenotype of an organism and are evolutionary neutral. The initial assumption of the theory is that the majority of nucleotides can be divided into two types: those that are under strong negative selection, and almost never change, and those that are neutral and change through random evolutionary drift.

Tomoko Ohta (Ohta 1973, 2002) expanded the neutral gene theory of evolution to include not only a large number of neutral and of deleterious mutations, but also a large number of nearly neutral mutations that are slightly deleterious; that is that they have a very small selective effect, and therefore evolve neutrally in small populations, but are negatively selected in large populations.

Today the neutral and nearly neutral theory of molecular evolution is a widely accepted null hypothesis for nucleotide sequence evolution. Importantly, the neutral gene theory provides a theoretical background to test whether positive selection or influences other than negative selection have been in action during the recent evolutionary history of a given species.

Following these theoretical guidelines, it has been observed that negative selection seems to be the dominant factor in the evolution of primates also in the case of gene expression differences (Khaitovich et al. 2005; Lemos et al. 2005; Gilad et al. 2006). Very recently the Rhesus Macaque Genome Sequencing and Analysis Consortium (2007) estimated the ratio of rates of non-synonymous and synonymous nucleotide substitutions in 10,376 orthologous genes of man, chimpanzee and rhesus macaque, and observed that most likely only 178 or 1.7 percent of them are under positive natural selection. Consequently, it seems that human evolution did not require any genetic changes that are qualitatively different from the general principles and laws of molecular evolution.

Considering natural selection in man, there is, however, one notable exception, namely the evolution of brain. Positive natural selection as such has been observed in the human lineage in various functional classes of genes. More importantly, the most recent studies suggest that this selection is still going on. In addition to brains, positive selection has been found for genes regulating the development of immune response, reproduction, and sensory perception, but the overall picture is consistent with studies in other mammals, and as said, the results seem plausible in
terms of evolutionary predictions (Sabeti et al. 2006). Also the genes found to be under positive selection by the Rhesus Macaque Genome Sequencing and Analysis Consortium (2007) are for the most part genes regulating defence response, immune response, T-cell mediated immunity, signal-transduction and cell adhesion.

Positive selection acting on immune system, reproduction, and sensory perception is not, however, unique for man, but brain positive selection seems to be human-specific among primates. The only genome-wide feature specific to humans detected so far is the acceleration of evolution of genes expressed in the brain (Khahtovich et al. 2006). This feature of our evolution will be more closely dealt with in the second part of this review.

THE MOSAIC NATURE OF OUR GENOME

As appears from the previous chapters, our genome is a mosaic not only of many structural rearrangements, but also of remnants from interbreeding in the dawn of the origin of our species with other demes, as well as presumably with our closest extinct cousin species. Taking this into account, we perhaps have to reconsider the taxonomic status of the human lineage leading to the anatomically modern man as a distinct biological species.

Further, analysing 76% of the human genome, Li et al. (2001) estimated that around 43% of the human genome is occupied by different classes of interspersed repetitive elements. The authors also concluded that many repetitive elements would have degenerated to the extent that could not be detected by the computer program used. Thus, more than 50% of the human genome would have come from insertions of repetitive elements.

It is true that: “Rather than thinking about ‘populations’, ‘ethnicities’ or ‘races’, a more constructive way to think about human genetic variation is to consider the genome of any particular individual as a mosaic of haplotype blocks. A rough calculation reveals that each individual carries in the order of 30% of the entire haplotype variation of the human gene pool.” And further: “...each of us contain a vast proportion of the genetic variation found in our species.” (Pääbo 2003).

Our evolutionary history is illustrated in our genome as a colourful mosaic of multitude of pieces having different age and telling different stories, but all witnessing of our relatedness with virtually all other species, some close, some more distant.

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