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What history tells us XXIII. The genetic distance between humans and chimpanzees: What did Mary-Claire King and Allan Wilson really say in 1975?

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1. Introduction

Some scientific articles have been so often quoted and commented upon that scientists who feel they are fully conversant with their contents may actually be wrong. In 1975, King and Wilson proposed that the genetic distance between human beings and chimpanzees was less than 1% (King and Wilson 1975). Twenty-six years later, the well-known paleoanthropologist Svante Pääbo (2001) emphasized the impact that this article had, and the blow it was to our feeling of uniqueness and supremacy: chimpanzees and humans had been shown to be very close by the measure of the genetic distance between them. However, when the first draft of the chimpanzee genome was published in 2005, the facts turned out to be less simple (The Chimpanzee Sequencing and Analysis Consortium 2005). The famous 1% had become a myth (Cohen 2007) that had prevented a clear perception of the true differences. In fact, 1% represents the frequency of point mutations that occurred after the divergence of the human and chimpanzee lineages, but other genetic events, such as insertions and deletions of small DNA fragments and gene duplication, have to be taken into account to faithfully describe the genetic difference between humans and chimpanzees.

What did King and Wilson really say? Reading their article is a shock: the interpretation that they gave for the 1% value differs greatly from that with which many, especially in the media, have become familiar. They considered, in fact, that the low genetic distance contrasts sharply with the huge morphological and behavioural transformations that occurred after the separation of the human and chimpanzee lineages. This means that measurement of the genetic distance is important when dating evolutionary events (*see* later), but not in explaining the major features in evolution. Evolution is the consequence of rare regulatory changes in a limited set of genes by chromosomal rearrangements. The article by Mary-Claire King and Allan Wilson is a mixture of what retrospectively appears as true and wrong statements and cannot be understood outside its scientific context.

2. The 1975 article

The value of 1% did not result from a direct comparison of the genomes: In 1975, genetic engineering was still in its infancy. It originated from four parallel studies: the direct comparison of protein sequences (an approach initiated 10 years earlier by Linus Pauling and Emile Zuckerkandl), an immunological comparison of proteins [using the microcomplement assay developed by Vincent Sarich and Allan Wilson previously (Sarich and Wilson 1966)], the comparison of the electrophoretic migration of proteins, and the DNA-DNA hybridization technique used to estimate the genetic distance between different species – when DNAs from different organisms are re-annealed, the imperfect pairing between the bases leads to a decrease in the melting temperature, which can be easily measured, and automatically converted into a measure of the genetic distance. Two-thirds of the paper was devoted to the description of these methods, and the caveats with which their results have to be considered. In this case, however, the four methods gave the same value of 1%, a small value for the huge morphological differences between humans and chimpanzees. The last third of the paper dealt with the

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interpretation of the results. Previous results obtained on birds and frogs gave completely different results: similar species, indistinguishable to the observer, corresponded to genetic distances far greater than that measured between humans and chimpanzees. The conclusion was obvious to King and Wilson: organismal evolution is the result of mutations occurring in a small group of regulatory genes. The title and subtitle of the article emphasize these conclusions: 'Evolution at two levels in humans and chimpanzees' and 'their macromolecules are so alike that regulatory mutations may account for their biological differences'.

King and Wilson were more explicit on the nature of the regulatory mutations. They hypothesized that the mutations probably affected the level of gene expression, by modifying the proteins encoded by the regulatory genes or by altering the nucleotide sequence of the promoters. They favoured the latter hypothesis, but immediately emphasized the crucial role of gene rearrangements in these variations of expression. It is difficult to understand from the reading of this article why they favoured gene and genome rearrangements. The answer should probably be sought in Wilson's previous publications, and the coherent picture that emerged from this early work. Wilson discovered in highly different organisms – birds, frogs, plants (Levin and Wilson 1976) – that there was an excellent parallel between the amplitude of morphological evolution and the number of chromosomal rearrangements, whereas there was a full discrepancy between the genetic distance and the amplitude of organismal transformation. In addition, evolutionary loss of the potential for inter-specific hybridization was correlated with the amplitude of chromosomal rearrangements, and not with the genetic distance (Wallace *et al.* 1971; Wilson *et al.* 1974a; Prager and Wilson 1975). There was also an inverse relation between the amplitude of chromosomal changes and the size of the populations: the smaller the population, the greater the amplitude (Wilson *et al.* 1975). The explanation was simple: the accommodation of big changes as chromosome rearrangements may more readily occur in small populations with a higher degree of inbreeding. So, formation of new species, morphological transformations and chromosomal rearrangements occur in parallel in small populations (Wilson *et al.* 1974b)

From the estimated value of the genetic distance between humans and chimpanzees, and using the molecular clock, it was possible to estimate the time of divergence between humans and chimpanzees: 5 million years, a value at odds with the value of about 30 million years proposed by paleoanthropologists from the study of prehuman fossils such as *Ramapithecus* (Sarich and Wilson 1967; Wilson 1967; Wilson and Sarich 1969). Such a result was revolutionary, and later confirmed: the dating of prehuman fossils had to be dramatically reconsidered. But despite his numerous studies on the evolution of primates, Wilson never questioned the traditional order of relation between humans, chimpanzees and gorillas, in which it was considered that the last two had diverged at the same time as humans, or after the separation of the human lineage. Ten years later, using a technique previously used by Wilson – DNA hybridization – Charles Sibley and Jon Ahlquist argued that chimpanzees and humans were close cousins, whereas the gorilla lineage had diverged earlier (Sibley and Ahlquist 1984). This result was heavily discussed and was not immediately accepted.

3. A critical analysis of the article

This article was highly heterodox in many of its conclusions. By looking at the personal and scientific context, it is possible to cast some light on the origin of these heterodox opinions.

The attention paid by Wilson to regulatory mutations was not new. He immediately grasped the evolutionary consequences of the distinction introduced by François Jacob and Jacques Monod between structural and regulatory genes: mutations in the latter were likely to have more dramatic consequences than mutations in the former. At the end of the 1960s, he initiated a series of experiments using '*in vitro* evolution' of bacteria to confirm this hypothesis (Wilson *et al.* 1977). The strategy was somewhat similar to that developed later by Richard Lenski, but the results were different. The majority of adaptive mutations were shown by Wilson to be mutations affecting the level of expression. Quantitative evolution was more important than qualitative evolution.

Wilson did not limit his conclusion to the statement that evolution was due to regulatory mutations, and felt compelled to associate these regulatory changes with chromosomal rearrangements, explicitly referring to the macromutations advocated by Richard Goldschmidt. Wilson was apparently open to original and unorthodox hypotheses. In 1985, in an article published in *Scientific American* (Wilson 1985), he ascribed to changes in human behaviour to be the driving force in human evolution, reiterating without quoting the model of James Baldwin (Baldwin 1896).

King and Wilson's article might also be considered to anticipate the present day views of most specialists of evo-devo: morphological evolution is the result of mutations in the *cis*-regulatory sequences controlling gene expression. And the experiments of Svante Pääbo's group in 2002 showing a difference in gene expression patterns in the brain between humans and chimpanzees (Enard *et al.* 2002), a result which was not confirmed later, might have been done by Wilson had the technology been available at the time.

However, for Wilson, it was a general principle of evolution affecting bacteria as well as multicellular organisms (Wilson *et al.* 1977). Adaptive evolution in bacteria was also the result of regulatory mutations. For Wilson, there was no place for a distinction between morphological evolution and other forms

of evolution as in evo-devo. And regulatory mutations did correspond to chromosomal rearrangements.

4. The article in its scientific context

King and Wilson's publication was one of many in the 1960s and 1970s to provide molecular data on evolution and to challenge traditional evolutionary models. The problem emerged when, at the beginning of the 1960s, Linus Pauling and Emile Zuckerkandl suggested that the main source of information on evolution would soon be the comparison of protein sequences, and when the early results of this comparison revealed a regular rate of variation, the so-called molecular clock. Historians have shown how these new molecular data supported the development of the neutralist model of evolution by Motoo Kimura (Kimura 1968; Suarez and Barahona 1996; Morgan 1998; Dietrich 1998), Jack King and Thomas Jukes (King and Jukes 1969). To explain the discrepancies between observations made at the molecular and organismal levels, King and Wilson offered another explanation: morphological evolution is the result of mutations in a limited set of regulatory genes. As we have seen earlier, they also favoured a specific form of genetic variation – chromosomal rearrangements. Both statements were at odds with Modern Synthesis.

The 1970s and early 1980s were a difficult time for Modern Synthesis. The dominant role of natural selection was questioned by the neutralist theory, and also by an emphasis on the existence of constraints in evolution, as affirmed by Stephen Jay Gould and Richard Lewontin (Gould and Lewontin 1979). The model of punctuated equilibria – the alternation of stasis and rapid change – proposed by Niles Eldredge and Stephen Jay Gould (Gould and Eldredge 1977) was confirmed by the careful studies of Williamson (Williamson 1981). There was a huge debate to appreciate the significance of these observations, whether they demonstrated that the action of natural selection was limited by constraints in the construction of organisms. The notion of 'tinkering' – 'bricolage' in French – introduced by François Jacob (Jacob 1977) was not anti-Darwinian; in fact, it was used for the first time by Darwin himself. Nonetheless, the expression 'tinkering' suggested that the same pieces were used during evolution, but were expressed and associated in a new way: regulatory mutations were more congruent with tinkering than mutations affecting the structure and function of proteins.

The debate on Modern Synthesis culminated in 1981–1982 at different meetings, some of them organized to mark the 100th anniversary of Darwin's death (Lewin 1982a, b). In the background of the debates were already the efforts made by creationists to deny any value to the theory of evolution.

It would be wrong to say that there was a clear conclusion to these debates. Nevertheless, a general feeling was that the accumulation of molecular data would lead to an evolution of Modern Synthesis more than to a revolution (Fitch 1982; Stebbins and Ayala 1981). It was also admitted that molecular observations made so far were peripheral to the mechanisms of evolution: only a precise description of the mechanisms of development could open the door to a description of the mechanisms of evolution.

It is remarkable that Allan Wilson followed these conclusions and, at the end of the 1980s, used molecular data simply as a reporter of recent evolutionary events. By comparing the restriction maps of the mitochondrial DNA in different human populations, he confirmed the African origin of modern humans, a result popularized under the image of an 'African Eve' (Cann *et al.* 1987). He also became one of the founders of molecular archaeology: the new possibility of extracting and characterizing DNA from fossils. It was not until the beginning of the 2000s, and the achievement of the human genome sequencing programme, that there were renewed attempts to explain human evolution in molecular terms.

5. Conclusions

The fact that King and Wilson's article became an icon is also the result of a shared fascination for numbers. A quantitative estimate of the genetic distance between humans and chimpanzees seemed to have a value by itself, whereas only the comparison of this value with other values may have a meaning (Marks 1999). One percent can be considered huge if it is converted into an absolute number of mutations between humans and chimpanzees.

Another example of a fascination for numbers was already discussed by Harold Wyatt in the case of the Hershey–Chase experiment, which demonstrated the role of DNA in the reproduction of the bacteriophage (Hershey and Chase 1952; Wyatt 1974). Nevertheless, and in contrast with the King and Wilson's article, the conclusions of the commentators, often based on a modification of the values provided by Alfred Hershey and Martha Chase, were similar to those of these two authors.

Great is the 'distance' between what is ascribed to King and Wilson's article in the scientific literature and its conclusion! The idea that humans and chimpanzees are close was not the opinion of Mary-Claire King and Allan Wilson. The heterodox face of the article has remained invisible: no reference is made to the role of chromosomal rearrangements. Such a discrepancy between the conclusions of a scientific article and the role this article plays later in the scientific literature is not uncommon. Who noticed that base-pairing was incorrect in Watson and Crick's 1953 article (two hydrogen bonds between G and C instead of three) (Watson and Crick 1953), that in Jacob and Monod's famous 1961 *Journal of Molecular Biology* article the repressor was an RNA (Jacob and Monod 1961), and that the results of Alfred Hershey and Martha Chase were not 100% in favour of DNA as a genetic

material? But the historical deformation has been much more significant in the case of King and Wilson's publication: the result was kept, but the interpretation thereof made was totally different.

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