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Origin and Development of Primates Comparative Cytogenetics

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Genetic and cytogenetic comparison in between man and non-human primates has largely contributed to the knowledge of the evolution of the Order Primates and in particular of man.
Since Darwin's first intuition about the close relationship of man and apes a growing number of evidences confirmed this hypothesis. More recently in 1956 and later in the 1960s pioneering chromosomal studies defined the correct chromosome number of man and apes. Early immunogenetics analysis placed human/apes divergence at about five millions years, and recently on the base of all biological evidences surprisingly revision of the Hominoidea group have been proposed.
Further, the "biological evidences" have been progressively confirmed even in the paleontological field. Our strong relationship with Pan and Gorilla is out of discussion as described by the molecular analysis of common chromosomal syntenies obtained by *in situ* FISH analysis. A new strong tool for the *study* of our genome organisation is the comparative chromosome mapping of single locus or single gene probes. The detection of several human single locus probes in non-human primates, with special regards to apes, permits a better definition of the evolutionary steps in our genome.
The molecular biology techniques has had a fast and extraordinary impact on the studies on the evolution of man. Researchers today have in front of them an outstanding landscape of possibilities: the unfolding study of the human genome, advances in computer technology coupled with sophisticated interpretative mathematical models and many other advances in technology and physical sciences too numerous to list here. It some times appears that modern biology will soon be able to respond to the question: What made us human? However we should not fall in molecular reductionism. At present there are clear limits of what biology can say about evolution (or disease for a matter): genetic simplicity has a very complicate epigenetic counterpart.
There is not doubt that great apes and man are closely related. One of the achievements of early molecular and karyological studies was that they left little doubt that the African apes were much closer to human than the Asiatic orang-utan (1, 2). Several evidences, first of all the DNA sequences analysis, and the hybridisation data now suggest that our closest relative is Pan.
Darwin firstly hypothesised this relationship on the base of anatomical evidences. Several paleontological data in the XIX century suggested a, for that times, astonishing truth man originated by evolution from primates - man is not a direct divine product. We must wait the XX century and the rise of biology to better understand our position. The first biological evidence of this deriving was the description of the chromosomal morphology of man and apes[1] and the analysis of immunological diffusion patterns, protein polymorphisms, or micro-complement fixation[3-4]. These data and several others, coupled and analysed in a "Molecular clock" allowed the location of a man/apes time divergence at 4.5 million years, a very short period of time in a geological scale; man and gorilla should have been diverged7 millions years ago[5].
These hypothesis only apparently do not fit well with paleontological data that recently pre-dated the man/apes divergence at 8-10 millions years[6]. But it is a question of bone and molecules time calibration: in any case man and apes are phylogenetically related and the root of the human family is deeply anchored in the Miocene. The separation in the two lineages may initially have been driven by chromosomal differences and /or mutations that elevated the reproductive barrier between groups[7]; in any case, when speciation occurred the effective reproductive isolation meant that specific patterns of intragenomic sequences exchange could result in increasing differences between species.
A common "andante" says that man and Pan are genomically identical for almost the 98.76%[8] but epigenetic differences are absolutely manifest even to the strongest reductionist. Human alleles are often related to orthologous genes in Pan than to other human alleles, a clear evidence that some allele predate the divergence *(il* HLA-DR), while other alleles are newly arisen by duplication (Human IgK genes are duplicated in human 2p but are not in the gorilla or chimpanzee).
Non-coding sequences of the Beta-globin gene diverge in the comparison between humans and pongo. Higly repetitive DNA has a very high rate of divergence[9]. Similar divergence can be found even in telomeric sequences meanwhile hypervariable satellites highly polymorphic in humans are monomorphic in apes[10]. Alu families sequences are common to man and apes and could be found even in lower primates but in man there
exists subset such Alu Sb1 and Sb2 that are human specific. Generally speaking man

lineages has undergone a series of bottle neck but non-coding DNA sequences from human and apes have high-levels of homology. This is a very important datum in terms of evolution. we can note that in respect to apes, man has a very high level of nucleotide
Conservation and low level of genetic variability in intronic sequences (for example in ZFY
gene)[11].
Primate cytogenetics had a significant improvement with the correct definition of humanchromosome by Tijo and Levan[12]. The following ten years were prolific in this sense and a first karyotype was performed for the most part of the genera of the order,
expecially by Chiarelli (for a comprehensive discussion see 13).
The great importance of cytogenetics stimulated the need for a standardisation in nomenclature in man[14].
A significant improvement in the analysis came with the description of differential chromosome banding techniques at the end of sixties. The first banding was by quinacrine mustard, a fluorescent microscopy technique that allows the definition of a constant banding pattern in the chromosome arms[15]. The same banding pattern can be achieved by trypsin treatment of the chromosome preparation[16-17]; a "reverse" pattern can be obtained using BrdU[18]. These technical improvements were discussed in the Paris conference Standardisation, the first concrete point of reference for human cytogenetists using banding. In this occasion a nomenclature for non-human primates was proposed but without great success. The problem of presumptive homologies in between human and non-human chromosome patterns was considered and led to the conclusion that chromosome morphology did not conveniently express the phylogenetic relationship.
A precise high resolution banding pattern comparison of human, Pan, Gorilla and Pongo was performed by Yunish and Prakash[19]: the more convincing prove of the strong conservation of banding pattern between these species. Major structural rearrangements, apart from the well known recent fusion of two chromosomes to form the human number 2 or the reciprocal traslocation in Gorilla involving chromosomes homologous to human 5 and human 17, are inversions (paracentric and pericentric). In the eighties a great number of publications dealt with primates banding comparison; a great effort in this sense was performed by the laboratory of cytogenetics directed in Florence, Italy, by
Roscoe Stanyon (see 20 *for* an updated review of non-human primates chromosome studies).
In the meantime a consensus gradually arose that hypotheses of chromosomal homologies should be supported by gene mapping studies[21]. Although gene localisation was grooving in human, only few genes were mapped in non human primates, and only in species of bio-medical interest[22].
The end of eighties were characterised by the use of new fluorochromes for the characterisation of chromatine, mostly proposed by Johannes Wienberg, the same researcher that, together with colleagues, ushered the modern molecular comparative cytogenetics[23].
Wienberg introduced comparative fluorescent in situ hybridisation (FISH), chromosome painting using chromosomal or large subchromosomal probes, for establishing chromosomal homology between species. Chromosome painting appeared immediately superior to the traditional banding comparison or to the traditional gene mapping as there is not guarantee that chromosomal regions between markers are actually homologous[23]. Chromosome painting provided a rapid and fruitful tool for establishing chromosomal homologies not only in Primates but in the whole class of mammalians[25-26-27-28].
With this tool researchers demonstrated the almost complete conservation of chromosomal syntenies between humans and great apes. Chromosome painting technique demonstrated the almost complete conservation of the genetic synthenies in mammals[29] and the genomic organisation is very strong in primates with very few exceptions represented by the representatives of the Hylobatidae family[30-31] where syntenies are highly fragmented and, in a minor extent, in Cercopithecinae. The symplesiomorphic status of our genome organisation was demonstrated by the proposal of an ancestral karyotype (2n=50); at this purpose comparative gene-mapping data obtained to date indicate that genomes are highly conserved and the default pattern of genome rearrangement is slow, the fixation of a new rearrangement is supposed to occur every 10 millions years[32]. On the contrary rodens genomes show very high rates of rearrangement with 1 rearrangement per million year[33]. Very small and complex rearrangements are almost invisible to the painting approach as like the gene order in the conserved segments. At this purpose a single gene mapping approach gives the opportunity to define fine rearrangements and to assign to primate chromosomes human genes. This is not only a catalogue producing effort but, will have interesting rebounds on the studies on gene evolution, function and regulation.
Detailed information on intra-chromosomal rearrangements which have occurred in evolution are still extremely limited. Investigations regarding single locus or regional mapping are generally limited to great apes and are mainly conclusions based on banding pattern comparisons[34-35-36-37-38]. Data on a greater range of species are limited.
The most significant results are the mapping of several loci in Owl monkey[39-40]; the mapping of RB1 (Retinoblastoma gene)[42]; and a complex chromosomal rearrangement in Macaca detected by a human 3 subchromosomal probe. Recently the chromosome organisation of the 14,15 and 17 human homologous in Apes and Cercopithecoidea have been investigated[43-44]. This approach resulted in the comparative mapping of several genes of biomedical interest and defined the mechanisms of fine evolution of these Chromosomes.
In any case molecular cytogenetics demonstrated that most of chromosomal homologies proposed on the base of high resolution banding were true and confirmed by the in situ hybridisation.

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