CYTOGENETIC STUDIES OF SMALL APE (*HYLOBATIDAE*) CHROMOSOMES

© *R. Stanyon*

Department of Evolutionary Biology, University of Florence, Italy;
e-mail: roscoe.stanyon@unifi.it

Each genus of small apes has a highly distinctive karyotype (karyomorph) at every level of cytogenetic analysis. Early workers using classical staining and banding had problems integrating the karyolocial data with that of other primates. Chromosome painting allowed syntenic homology maps to be constructed for each of the four karyomorphs (2n = 38, 44, 50 and 52). They revealed that the great apes and Old World monkeys had strongly conserved karyotypes while those of small apes were highly rearranged. However, they provided contradictory phylogenetic results to other bio-molecular tree of small ape evolution. More recently BAC-FISH investigations using a panel of about 900 BACs defined each breakpoint by spanning or flanking BAC clones The syntenic map was refined and now includes small segments of homology which had previously gone undected, marker order (synteny block orientation) and the location of ancestral and Evolutionarily New Centromeres. However, the BAC-FISH data similar to other biomolecular methods used up to now could not resolve the phylogenetic tree of hylobatids. These difficulties may be explained by the rapid divergence of crown hylobatids, reticulate evolution and incomplete lineage sorting. The lack of significant cytogenetic landmarks at the nodes of the gibbon tree could indicate that chromosomal rearrangements did not play a primary role in hylobatid speciation.

Key words: small apes, chromosomes, karyotype.

This paper is a summary of a talk made at Chromosome 2012 in Novosibirsk. Small apes (gibbons and siamang) also known as «lesser apes» to distinguish them the «greater apes» (orangutan, gorilla, chimpanzee, bonobo) are classified within the Hominoidea are among the closest relatives of humans. These primates diverged from the other hominoids around 18 million years ago. Small apes (Hylobatidae) are composed of about 16 species divided into 4 genera distributed in Southeast Asia from India to Indonesia. Each genus has a distinctive karyotype at every level of analysis, which are often referred to as karyomorphs. The chromosomes of gibbons have been the subject of much interest over the last 50 years.

Early chromosome staining and banding

Chiarelli (1972) summarized the classically staining data and found that each genus had a different diploid number, *Hylobates* 2n = 44, *Symphalangus* 2n = 50, *Nomascus* 2n = 52. He found an individual for which he had only a few metaphases with 2n = 38. Later Prouty (Prouty et al., 1983) showed that this was the characteristic diploid number of the genus *Hooloch,* which was originally called initially call *Brunopithecus.*

Chiarelli (1972) erroneously took the similar chromosome morphology he found between the genus *Hylobates* and Colobine monkeys to indicate that the small apes should be classified with the Catarrhine monkeys and not with the Hominoidea. Chiarelli was the not the only cytogeneticist that had problems with the small apes. With the advent of banding it became clear that the gibbon chromosome were extremely difficult to match with those of other primates. It was even hard to find chromosomes with similar banding patterns between small ape genera with different diploid numbers. Dutrilluax (1979) probably the foremost worker of the time just left them out of his grand scheme of primate chromosome phylogeny. Bernstein et al. (1980) made an error greater than that of Chiarelli when they concluded that gibbons were phylogenetically more distant from humans than Old World monkeys for which banding homologies were readily found.

Mapping syntenic homology by chromosome painting

The first chromosome painting papers soon showed why there was so much confusion about the small apes. These first papers established complete between species chromosome homology on Hominoids **(**chimpanzee, gorilla, orangutan and *Hylobates lar* (Jauch et al., 1992) and macaques (Wienberg et al., 1992**)**. They revealed that the great apes and Old World monkeys had strongly conserved karyotypes while the genomes of small apes were highly rearranged. Chiarelli's mistake was confusing convergence with homology; a problem that was resolved with chromosome painting which establishes homology on the basis of DNA content not morphological similarity. Bernstein et al. error was basing their assessment on phenetic similarity, which results from confusing conserved, ancestral similarity with close, phyletic relationship. A cladistic analysis of derived chromosome characters shows that small apes are indeed hominoids as thought all along by morphologists.

Over about a ten-year period, 1992 to 2003, painting maps of all 4 small ape karyomorphs were established (Jauch et al., 1992; Koehler et al., 1995a, 1995b; Nie et al., 2001). These studies included reciprocal painting (Muller et al., 1998, 2003), which also in this case was a technique applied for the first time in gibbons (Arnold et al., 1996). Other molecular cytogenetic techniques were also used to study small apes including Spectral Karyotyping (Schrock et al., 1996) and Multicolor FISH from microdissected chromosome segments (Mrasek et al., 2003). R_X FISH and color bar coding were also dependent on pools of sorted gibbon chromosomes.

Although these papers it showed that gibbons belonged in hominoids it left considerable doubt about the phylogenetic relationships and divergence sequence between the four genera. For example Müller's phylogenetic scheme (2003) (Müller et al., 2003) *Hoolock-Hylobates-Symphalangus*/*Nomascus*, with an unusual linking of *Symphalangus* and *Nomasus,* contradicted almost all other bio-molecular trees of small ape evolution.

BAC-FISH investigation of Hylabid Karyotypes

It is well appreciated that Chromosome painting is a particularly good methods for tracing translocations, but that it is very poor at documenting inversions. Further, breakpoint location with chromosome painting even reciprocal painting is only approximate. Thankfully, FISH with cloned DNA such as BACs can provide marker order along chromosomes, document inversions, locate Evolutionarily New Centromeres (ENC) and provide a high-resolution definition of breakpoints. Recently BAC FISH provided the basis for hypotheses of primate ancestral karyotypes which also included marker order and centromere position including an ancestral karyotype for a catarrhine primates and for hominoids (Stanyon et al., 2008).

The experimental procedure was straightforward. A panel of human BACs about equally spaced along the human genome was hybridized to each small ape karyomorph. Breakpoints were ideally determined when a human BAC spanned a breakpoint providing 4 signals in the ape metaphases. In other cases, the breakpoint was flanked by a BAC on each side. On average about 900 BACs were hybridized to each karyomorph. BACs can also be reciprocally FISHed if a BAC library is available from non-human primate. The following publications detail the information of BAC-FISH experiments in small apes genera: 1) *Hylobates* (Misceo et al., 2008), 2) *Nomascus* (Carbone et al., 2006; Roberto et al., 2007), 3) *Symphalangus* and *Hoolock* (Capozzi et al., 2012). The higher level of resolution of BACs (about 200 Kb) compared to chromosome points also allowed the identification of a good number of syntenic blocks that had previously gone unrecognized. They synteny block orientation was also established.

A comparison of breakpoints and synteny blocks then allowed a reconstruction of the Hylobatidae ancestral karyotype. The hypothesized Hominoidea ancestor was used as the starting point (Stanyon et al., 2008). When the four gibbon karyomorphs shared a specific breakpoint, we assumed that this break occurred in the last common ancestor of all Hylobatidae. The definition of the ancestral synteny organization facilitated an understanding of the cascade of chromosomal changes from the Hominoidea ancestor to the Hylobatid ancestral karyotype to the present day karyomorphs. The majority of the breakpoints found in small apes occurred in the Hylobatidae ancestor. The analysis showed that 33 rearrangements probably occurred in gibbon ancestor after its divergence from Hominidae and before gibbon radiation. The last common ancestor probably had a diploid number of 2n = 58 (Capozzi et al., 2012).

Rearrangements that occurred in the common ancestor of all lesser apes were essentially translocations and inversions. Rates and types of chromosome evolution differ in the diverse lineages. For instance, the most notable difference between the *Hooloch* karyomorph and the Hylobatidae ancestor is the dramatic evolutionary reduction in chromosomal number from 58 to 38. The reduction was due to 10 chromosomal fusions.

Hylobatid Phylogeny

Gibbon taxonomy is still highly disputed. Various approaches from morphology to biomolecular investigations have provided different phylogenetic trees and different taxonomies. It was proposed that detailed BAC-FISH analysis of small apes karyotypes would provide detail information to reconstruct their phylogeny and evolutionary relationships. It was reasoned that rapidly evolving systems provide high resolution to clarify the evolutionary tree of closely related species. Chromosomal rearrangements often produce changes that serve as unique landmarks at divergence nodes because they are rare changes subject to minimal homoplasy.

Finally, chromosome rearrangements are thought to generate reproductive isolation due to reduced fitness in hybrids and recombination suppression and were hypothesized to have had a role in small ape speciation (Jauch et al., 1992; Koehler et al., 1995a, 1995b; Nie et al., 2001; Hirai et al., 2007; Carbone et al., 2009; Girirajan et al., 2009; Capozzi et al., 2012). Further, since chromosome rearrangements were so frequent in small apes it seemed like an ideal situation to determine how chromosome mutations were related to large-scale phenomena such as speciation.

We compared the four gibbon genera in search of a coherent temporal order of genus divergence. In this context and according to cladistics procedures we considered only shared derived rearrangements (Table). Surprisingly, chromosome rearrangements did not provide a consistent, simple dichotomic phylogeny. Other types of biomolecular data have also provided contrasting, inconsistent results. In spite of the fact that the genetic distances between the four small ape genera probably equal or exceed the one between *Homo* and *Pan* biomolecular studies have failed to conclusively resolve the Hylobatidae phylogenetic relationships. These studies either place *Hoolock* or *Nomascus* as basal and *Hylobates* as the last genus to emerge (Roos, Geissmann, 2001; Takacs et al., 2005; Baena et al., 2007; Matsudaira, Ishida, 2010; Thinh et al., 2010; Perelman et al., 2011). One recent study present two different phylogenies for small apes (Perelman et al., 2011).

Why is it so hard to draw a phylogenetic tree for Hylobatids. There may be a number of factors involved. They could be rapidly diverging. There may be hybridization between diverging lineages (reticulate evolution). Demographic factors could randomly fix ancestral polymorphisms and incomplete lineage sorting could be an important factor.

The chromosome finding, along with phylogenetic inconsistencies in other data sets, suggests that gibbon divergence occurred in a relatively short period of time. This important conclusion is supported by recent molecular works (Matsudaira, Ishida, 2010; Thinh et al., 2010). Matsudaira and Ishida

The chromosome associations

Genus	Chromosome Association																		
	1/2	1/12	2/7	2/17	3/8	3/11	3/12	4/5	4/10	5/8	5/16	5/22	6/10	7/11	9/17	11/18	12/19	15/21	Other
Hoolock	X	X	X	X	X	X	X		X	X	X			X	X	X	X		16
Hylobates		X	X	X	X	X	X		X		X	X			X	X	X	X	7
Symphalangus	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	6
Nomascus			X	X	X	X	X	X	X		X	X	X			X	X		12

N o t e. This table shows the chromosome associations common to 2 or more small ape genera (listed on the left): 9 associations are common to all small ape genera. However, the other common linking associations provide no convincing pattern for building an evolution tree.

inferred that the genera *Nomascus, Symphalangus* and *Hylobates* diverged from each other in less than 1 million years. They also concluded that lineage sorting would account for the apparent discrepancies between various data sets. In line with this finding, Thinh et al. (2010) calculated that the four Hylobatidae lineages diverged in less than 1.5 million years, between 6.7 and 8.3 mya.

In agreement with the lineage sorting scenario Capozzi et al. (2012) hypothesized that the last common ancestor of the Hylobatidae was heterozygous for variant forms of at least 4 chromosomes (6, 8, 9, and 18). Importantly, chromosome data may have the possibility to reveal underlying features of the speciation process in small apes just because it does not provide an easy phylogenetic tree.

Role of Chromosome in Hylobatid Speciation

Unexpectedly, the lack of significant cytogenetic landmarks at the nodes of the gibbon tree could indicate that chromosomal rearrangements did not play a primary role in genera differentiation. Additionally, in contrast to the great differences among genera, species within-genera are characterized by karyological uniformity, further supporting the view that multiple speciation events within each genus have occurred without any concomitant chromosome rearrangements whatsoever.

It is also dubious if the very few difference found between nodes could have had any significant effects on fertility and consequent reproduction isolation. It is noteworthy that captive hybrids between gibbon genera have been reported: between *Symphalangus* and *Hylobates* (Myers, Shafer, 1979) and between *Hylobates* and *Nomascus* (Hirai et al., 2007). Although considered unlikely, it is unknown if these intergeneric hybrids are fertile, and the fact that such hybrids exists even if in captivity lessens the arguments that chromosomes were involved as isolating mechanisms in initial small ape speciation or lead to increased rates of protein divergence.

Therefore, it seems a reasonable hypothesis, therefore, that karyological changes seen at the cytogenetic (large scale) level were not the primary, necessary, or sufficient causes of small ape speciation. This hypothesis does not exclude the possibility that fine-scale rearrangements, insertion and deletions as well as the proliferation of repetitive sequencing, and conversion may have had a significant role in speciation. However, data available up to now show that there is no increase in fine-scale rearrangements in small apes (Roberto et al., 2007) compared to great apes and humans.

The proposed lack of a primary role of (Dobigny et al., 2005) large-scale rearrangements in gibbon speciation does not mean that apomorphic rearrangements did not have biological significance after the initial divergence including an accumulation of changes after speciation to insure reproductive isolation or adaptation. Intensive research at the sequence level will be needed to examine this possible role**.**

Mechanism explaining the High rate of chromosome rearrangements in Hylobatid

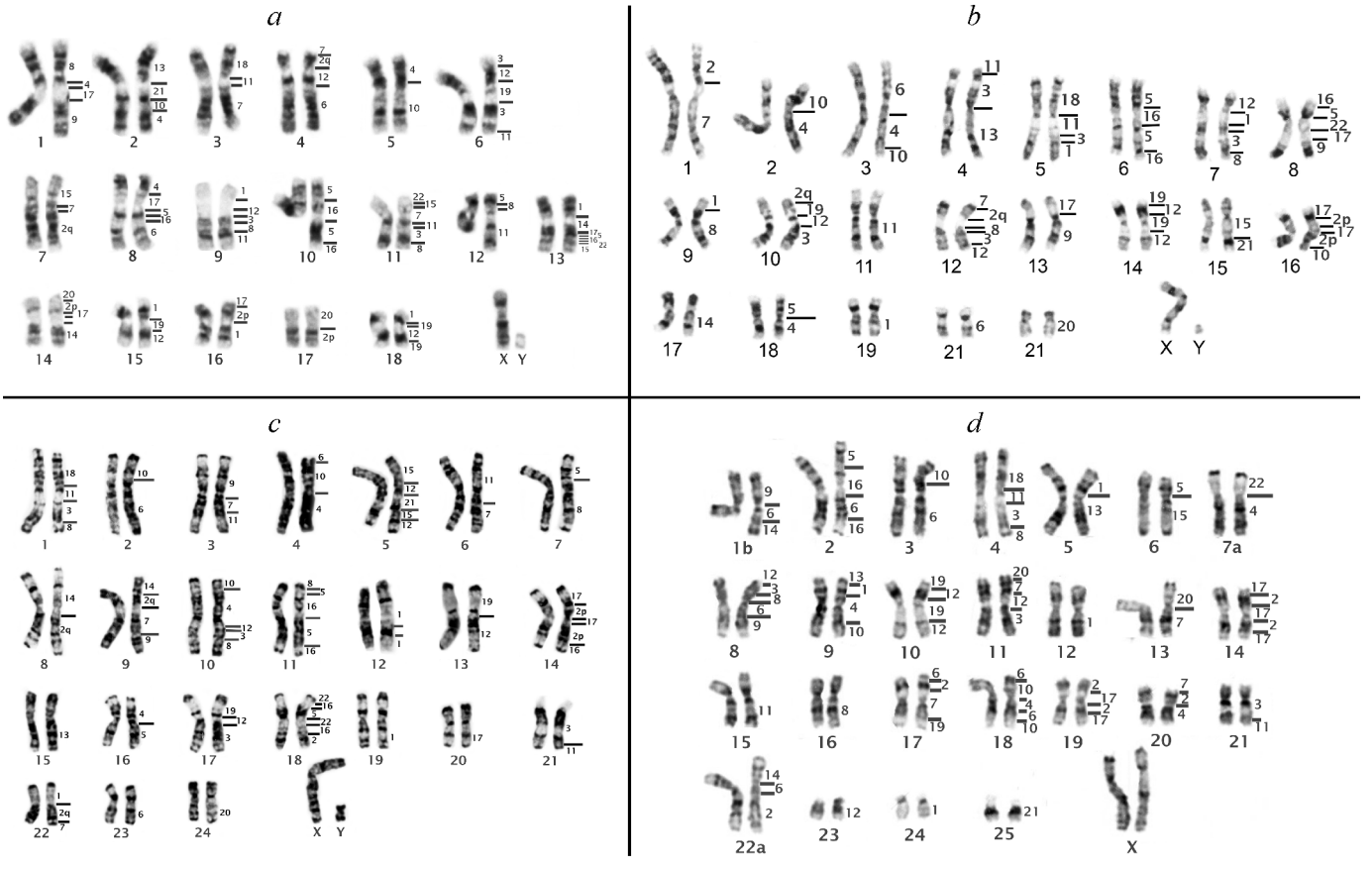
The small apes (gibbons) are one of the most dramatic examples of extremely rapid karyotype evolution. Chromosomal changes in gibbons are up to 20 times that of the average mammalian rate. Higher rates of evolution are only found in some gerbils (Dobigny et al., 2005) and in the karyotypic evolution of onager, donkey, and zebras (Trifonov et al., 2008).

However, the mechanisms, processes and reasons behind this high rate of chromosomal rearrangements remain unclear. The importance of understanding their rapid genome evolution is also provided by their phylogenetic affinity to humans.

Recently Capozzi et al. (2012) searched for genomic features that could be associated with small ape chromosome breakpoints by permutation test based on the human genome sequence. There was a significant overlap of breakpoint regions with genes, segmental duplications, Alu and SVA, but not for LINE or ERV repeats. SVA elements are infrequent in gibbons so this relationship would have to indirect. Segmental duplication may be a driving force in gibbon chromosome evolution because a consistent number of rearrangements involving. It is intriguing to note that hybridization-induced perturbation of mobile element methylation and stability has been proposed as a mechanism for promoting genome-shuffling in small apes (Carbone et al., 2009).

Future Research

It seems likely that the high rate of chromosome evolution is probably paralleled by sequence variability in and between small apes species. However, as yet we have no way to know if this is true. A more conclusive test of this and the molecular mechanism behind their extraordinary chromosome evolution will have to await the sequencing of the complete genome of at least one species from each of the four karyomorph. Detailed information at the sequencing level will allow a deeper understanding of hylobatid relationships and phylogeny. Perhaps such an effort is not beyond the scope of the new Theodosius Dobzhansky Genome Center for Genome Bioinformatics in St. Petersburg that was highlighted during the conference.



Trypsin G-banded karyotypes from the four genera of small apes.

a — Hoolock, 2n = 38, *b — Hylobates*, 2n = 44, *c — Symphalangus*, 2n = 50 and *d — Nomascus*. The small ape chromosomes are numbered below and to the right the syntenic homology with human chromosomes, based on all current data with special reference to BAC-FISH analysis.

Further figures related to this brief summary can be found at the following web site of the University of Bari (Mariano Rocchi) : http://www.biologia.uniba.it/evo-amb/PhD_programs/genetics/primate.html; http://www.biologia.uniba.it/hoolock/; http://www.biologia.uniba.it/gibbon/; http://www.biologia.uniba.it/lar/.

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ЦИТОГЕНЕТИЧЕСКИЕ ИССЛЕДОВАНИЯ ХРОМОСОМ МАЛЫХ ЧЕЛОВЕКООБРАЗНЫХ ОБЕЗЬЯН (*HYLOBATIDAE*)

Р. Станион

Отдел эволюционной биологии, Флорентийский университет, Италия;
e-mail: roscoe.stanyon@unifi.it

Каждый род гиббонов имеет характерный кариотип (кариоморф) на каждом уровне цитогенетического анализа. У прежних исследователей, использовавших классическое окрашивание и бандирование, были проблемы соединения этих кариологических данных с данными на других приматах. FISH-метод позволил построить карты синтенной гомологии для каждого из четырех кариоморфов (2n = 38, 44, 50 и 52). Они показали, что у человекообразных обезьян и обезьян Старого Света кариотипы строго консервативны, в то время как у малых обезьян они подверглись значительным перестройкам. Однако они представили филогенетические результаты, противоречащие другому биомолекулярному древу эволюции гиббонов. Совсем недавно методом BAC-FISH с использованием панели около 900 BAC были определены все точки разлома по охватывающим или фланкирующим BAC клонам. Синтенная карта была доработана и теперь включает в себя небольшие участки гомологии, которые ранее оставались невыявленными, маркер порядка (блок ориентации синтении) и положение древних и эволюционно новых центромер. Тем не менее данные BAC-FISH-метода, подобно другим биомолекулярным методам, использовавшимся до сих пор, не смогли установить филогенетическое древо гиббонов. Эти трудности могут быть объяснены очень быстрой дивергенцией в кроне древа *Hylobatidae*, сетчатой эволюцией и несовершенной классификацией. Отсутствие значительных цитогенетических ориентиров в узлах древа гиббонов может означать, что хромосомные перестройки не играют ведущей роли в видообразовании *Hylobatidae*.

Ключевые слова: гиббоны, хромосомы, кариотип.