CARYOLOGIA Vol. 57, no. 3: 312-325, 2004

The Evolution of Human Chromosome 7 Syntenies in Eutheria, with Special Attention to Primates

Daniela Romagno[1] and Luca Sineo[2*]

[1] Laboratori di Antropologia – Dipartimento di Biologia Animale e Genetica – Università degli Studi di Firenze, via del Proconsolo 12, 50122 Firenze, Italy
[2*] Dipartimento di Biologia Animale – Università degli Studi di Palermo – via Archirafi 18, 90123 Palermo, Italy

Abstract — 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. Recently, the "Chromosome painting" approach indicated a strong conservation of syntenies in Eutheria. At present, a more precise identification of breakpoints and evolutionary related rearrangements can be obtained by BAC and locus specific *in situ* hybridisation. In spite to this situation the evolutionary history of different human autosomes remains a dilemma; at the same time, high resolution banded chromosome analysis confirms to be a valuable tool for the preliminary detection of fine rearrangements. This review critically describes current information concerning the evolution of human chromosome 7 orthologous in several Eutherian groups. Included in this analysis are data on species belonging to 11 orders. Nevertheless, this study has been mainly focused on Primates were we considered data from 9 species of Prosimians, 25 species of Platirrhinae, and 51 species of Catarrhinae. Chromosome 7 synteny appeared in a mammalian ancestor in a dual form, generally described as 7a and 7b forms. These chromosomes underwent to several line-specific rearrangements in the different orders. A particular complexity in chromosome rearrangements has been highlighted in Primates. A chronologically fossil-tuned dynamic of the synteny is proposed, starting from classical and molecular cytogenetics specific landmarks which appeared throughout evolution.

Key words: Evolution, Human chromosome 7, Mammals, Primates, Syntenies.

THE DEVELOPMENT OF HUMAN CHROMOSOME 7 COMPLEX SYNTENY

Human evolution is still a central theme in contemporary biology. Palaeontological, achaeological and genetical testimonies are debated with increasing frequency and well based hypotheses to many questions have been provided. From a zoological point of view humans are encephalised primates with a complex behaviour called "culture". Many biological characteristics of modern humans evolved in a common ancestor to humans and other primate species. Comparative ethology of primates and of the entire class of Mammalia provides clues to our behavioural phylogeny.

Living primates include 200 species, with a growing complexity in phenotypical and functional characters, from prosimians to our species.

As a group, primates are surprisingly ancient; even if certain primate fossils date from Eocene period (previous *Plesiadapiformes* (†) are now included in a sister order of ancestral specialised Cretaceous mammals) a late Cretaceous appearance must be considered (Martin 1993). As fossil records are generally rare, and in some case almost absent (as in South American tertiary harbours), comparative evolutionary biology utilises different multidisciplinary approaches, and chromosomal reconstruction of primate phylogeny is considered a valuable tool (Novaceck 1992). The increased quality of chromosome banding and FISH technology, together with the Human genome project results provide a deep insight into human chromosomes.

FISH technology and comparative gene mapping has been widely applied for the comparative analysis of humans and different mammals species. Much effort has gone into charting genome homology between the primates from Prosimians to humans and extensive work has also been done in Ungulata, Carnivora, Edentata, Artiodactila, Lagomorpha, Cetacea and Proboscidata. This studies suggest that wide stretches of syntenic homology persist across mammalian orders (Wienberg and Stanyon 1998; O'Brien *et al.* 1999; Murphy *et al.* 2001).

In spite to this, only a very small proportion of mammalian species have been studied at any level, and large tracts of the genomes remains uncharted.

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* Corresponding author: fax +39-91-6230144; e-mail: llsineo@unipa.it.

From a chromosomal point of view, human syntenic association are clearly conservative but, on the same time, the fine genesis of many chromosomes remains to be defined as the comparative analysis of high resolution GTG banding demonstrates (ROMAGNO *et al.* 2004).

This review gathers all available cytogenetic information concerning the evolution of the syntenic homologous of Human chromosome 7 in Eutherians, with special attention to Primates. We then propose a chronology for the cytogenetic landmarks that characterise the phylogeny of these homologs throughout mammalian evolution.

Included in this analysis are data on eleven eutherian orders: Chiroptera (VOLLETH *et al.* 1999; VOLLETH *et al.* 2002), Cetacea (BIELEC *et al.* 1998), Artiodactyla (O'BRIEN *et al.* 1999; ANTONIOU *et al.* 2002; CAETANO *et al.*1999; FRONICKE *et al.*, 1997a; FRONICKE and WIENBERG 2001; SCHIBLER *et al.* 1998; GOUREAU *et al.* 1996; BRUCH *et al.* 1996), Tubulidentata, Perissodactyla (RICHARD *et al.* 2001; RAUDSEPP *et al.* 1996; CAETANO *et al.* 1999), Insectivora (O'BRIEN *et al.* 1999; SVARTMAN *et al.* 2004), Rodhentia (RICHARD *et al.* 2000; WATANABE *et al.* 1999; CARVER and STUBBS 1997; STANYON *et al.* 2003), Lagomorpha (KORSTANJE *et al.* 1999), Edentata (RICHARD *et al.* 2000), Carnivora (NASH *et al.* 1998; FRONICKE *et al.* 1997b; WIENBERG *et al.* 1997; CAETANO *et al.* 1999; YANG *et al.* 2000; MURPHY *et al.* 2000; RICHARD *et al.* 2000; GRAPHODATSKY *et al.* 2001; GRAPHODATSKY *et al.* 2002; CAVAGNA *et al.* 2000), Proboscidea (YANG *et al.* 2000; YANG *et al.* 2003; FRONICKE *et al.* 2003), and Scandentia (RICHARD *et a*l. 2000; MULLER *et al.* 1999 (Tab. 1).

Among Primates, in addition to Great apes, we considered 9 species of Prosimians (CARDONE *et al.* 2002; RICHARD *et al.* 2000; MULLER *et al.* 1997; MULLER *et al.* 1999; STANYON *et al.* 2002; MASTERS *et al.* 1987; STANYON *et al.* 1987), 25 species of Platirrhinae (NEUSSER *et al.* 2001; MULLER *et al.* 2001; STANYON *et al.* 2000; GARCIA *et al.* 2002; RICHARD *et al.* 1996; CARLÀ CAMPA *et al.* 1992; RICHARD *et al.* 2000; CONSIGLIERE *et al.*1996; CONSIGLIERE *et al.* 1998; STANYON *et al.* 2001; SEUANEZ *et al.* 2001; MORESCALCHI *et al.* 1997; STANYON *et al.* 2003), in Catarrhinae we considered 20 species of Papionini (STANYON *et al.* 1988; WIENBERG *et al.* 1992; RUIZ-HERRERA *et al.* 2002a; RUIZ-HERRERA *et al.* 2002b; MULLER and WIENBERG 2001) 8 species of Colobinae (NIE *et al.* 1998; STANYON *et al.* 1992; PONSÀ *et al.* 1983; KINGSLEY *et al.* 1997), 13 species of Cercopithecini (FINELLI *et al.* 1999; SINEO *et al.* 1986; RICHARD *et al.* 2000; SINEO 1986; CLEMENTE *et al.* 1990; PONSÀ *et al.* 1981; O'BRIEN 1993; O'BRIEN *et al.*1993; STANYON and SINEO 1983; ROMAGNO *et al.* 2004),.10 species in Hylobatidae (NIE *et al.* 2001; JAUCH *et al.* 1992; STANYON *et al.* 1987; DESILVA *et al.* 1999; KOEHLER *et al.* 1995a; KOEHLER *et al.* 1995b; MULLER and WIENBERG 2001) (Tab.2).

Eutherian mammals - In most of the species outside of primates, with the exception of rat and mouse (WATANABE *et al.* 1999; CARVER and STUBB 1997), the synteny of human chromosome 7 and the homologous sequences are distributed on two chromosomes.

There is usually a large segment homologous to most of HSA7 and additionally a small segment associated with HSA 16 sequences, in most or in at least one of the species of every mammalian order. The small segment of chromosome 7 has proved difficult to detect and sometimes goes unnoticed by chromosome painting. This segment was overlooked in the initial painting studies in cat (WIENBERG *et al.* 1997), pig (GOUREAU *et al.* 1996) and horse (RAUDSEPP *et al.* 1996). It is likely that in many of the reports on various species the chromosome painting signal for this small segment probably escaped detection: *Rhinolopus mehely* (Chiroptera), *Sores araneus* (Insectivora), *Ailuropoda melanoleuca*, *Tremarctos ornatus*, *Phoca vitulina*, *Mustelia putorius furo* (Carnivora), and *Tupaia belangieri* (Scandentia).

The analysis of reciprocal painting as well as gene and genomic maps demonstrates that, usually, this small fragment contains sequences found in chromosome bands HSA7p22, 7q11.2, 7q21.11 and 7q22. The sequences of HSA16 with which this segment is frequently associated derive from 16p.

By definition, in humans, sequences belonging to bands 7q11.2, 7q21 and 7q22 are present together with the sequences of the larger segment of HSA7 to form a single syntenic chromosome, but this consideration have to be reconsidered on the light of new data on the BAC hybridisation and in silicio study conducted on HSA7 and othrologous in primates (MULLER *et al.* 2004). However, in some species this synteny is secondarily fragmented and is often associated with different human chromosomal syntenies. For example a number of intra-chromosomal rearrangements was demonstrated in cattle (ANTONIOU *et al.* 2002) and in the cat (MURPHY *et al.* 2000).

Primates: Prosimians - Prosimians painting data are available for two species of Galagonidae and three species of Lemuridae. In *Otolemur crassicaudatus* there is a possible evidence of the ancestral eutherian association HSA7/HSA16. In this species, in fact, most of the part homologous to HSA7 forms an acrocentric chromosome (OCR 6), similar in banding to PPY10q, whereas a small segment of HSA7 and part of HSA 16 are found together on another chromosome (OCR7) where they are separated by a seg-

Table 1 — Human chromosome 7 orthologous syntenies in Mammalia with the exclusion of Order Primates.

ORDER	SPECIES	CODE	2n	Sources for comparative analysis	METHODS
Chiroptera					
	Glossophaga soricina	GSO	2n=32	Volleth et al., 1999	ZOO-FISH
				Richard et al, 2000	Chromosome painting
	Myotis myotis	MMY	2n=44	Volleth et al., 2002	ZOO-FISH
	Mormopterus planiceps	MPL	2n=48	Volleth et al., 2002	ZOO-FISH
	Hipposideros larvatus	HLA	2n=32	Volleth et al., 2002	ZOO-FISH
	Rhinolopus mehely	RME	2n=58	Volleth et al., 2002	ZOO-FISH
	Eonycteris spelaea	ESP	2n=36	Volleth et al., 2002	ZOO-FISH
	Tarsiops truncatus	TTR	2n=44	Bielec et al., 1998	Chromosome painting
Artiodactyla					
	Bos taurus	BTA	2n=60	O'Brien et al., 1999	Comparative genomics
				O'Brien et al., 1999	Gene mapping
				Antoniou et al., 2002	Gene mapping
	Ovis aries	OAR	2n=54	O'Brien et al., 1999	Comparative genomics
				Fronicke and Wienberg 2001	Chromosome painting
				Schibler et al., 1998	Gene mapping
	Capra hircus	CHI	2n=60	Schibler et al., 1998	Gene mapping
	Muntiacus muntjak vag.	MMV	2n=6/7	O'Brien et al., 1999	Comparative genomics
	Sus scrofa	SSC	2n=38	Fronicke et al., 1997a	Chromosome painting
				Goureau et al., 1996	Comparative genomics
				Bruch et al., 1996	Gene mapping
				Goureau et al., 2001	Chromosome painting
				Fronicke and Wienberg 2001	Chromosome painting
Perissodactyla					
	Equus zebra	EZE	2n=32	Richard et al., 2001	Chromosome painting
	Equus caballus	ECA	2n=64	Raudsepp et al., 1996	ZOO-FISH
Insectivora					
	Sores araneus	SAR	2n=20	O'Brien et al., 1999	Comparative genomics
	Macroscelidae proboscidens	MPR	2n=26	Svartman et al., 2004	Chromosome painting
Rodhentia					
	Menetes berdmorei	MBE	2n=40	Richard et al., 2000	Chromosome painting
	Sciurus carolinensis	SCA	2n=40	Stanyon et al., 2003	Chromosome painting
	Rattus norvegicus	RNO	2n=42	Watanabe et al., 1999	Comparative genomics
	Mus musculus	MMU	2n=40	Carver and Stubb, 1997	Comparative genomics
				Stanyon et al., 1999	Chromosome painting
Lagomorpha					
	Orictolagus cuniculus	OCU	2n=44	Korstanie et al., 1999	Chromosome painting
				Robinson et al., 2002	Chromosome painting
Edentata					
	Dasypus novemcinctus	DNO	2n=64	Richard et al., 2000	Chromosome painting
Carnivora					
	Ailuropoda melanoleuca	AME	2n=42	Nash et al., 1998	Chromosome painting
	Tremarctos ornatus	TOR	2n=52	Nash et al., 1998	Chromosome painting
	Phoca vitulina	PVI	2n=32	Fronicke et al., 1997b	ZOO-FISH
	Felix cattus	FCA	2n=38	Wienberg et al, 1997	Comparative genomics
				Wienberg and Stanyon, 1995	Chromosome painting
				Wienberg and Stanyon, 1997	Chromosome painting
				Yang et al., 2000	Chromosome painting
				Murphy et al., 2000	Chromosome painting
	Panthera leo	PLE	2n=38	Richard et al., 2000	Chromosome painting
	Canis familiaris	CFA	2n=78	Yang et al., 2000	Chromosome painting
	Mustela vision	MVI	2n=30	Graphodatzky et al., 2001	Chromosome painting
				Graphodatzky et al., 2002	Chromosome painting
	M.putorius furo	MPF	2n=40	Cavagna et al., 2000	Chromosome painting
Tubulidentata					
	Orycteropus afer	OAF	2n=20	Yang et al., 2000	Chromosome painting
Proboscidea					
	Loxodonta africana	LAF	2n=56	Yang et al., 2000	Chromosome painting
				Fronicke et al., 2003	Chromosome painting
	Elephas maximus	EMA	2n=56	Yang et al., 2000	Chromosome painting
Scandentia					
	Tupaia chinensis	TCH	2n=62	Richard et al., 2000	Chromosome painting
	T. belangieri	TBE	2n=62	Muller et al., 1999	Chromosome painting
	T. glis	TGL	2n=60	Toder et al., 1992	Comparative cytogenetics

Table 2 — Human chromosome 7 orthologous syntenies in Primates.

ORDER	SPECIES	CODE	2n	Sources of comparative analysis	METHODS
Primates					
Strepsirrhinae					
FAMILY					
Loridae					
	Nycticebus coucang	NCO	2n=50	Stanyon et al., 1987	Comparative cytogenetics
	Otolemur crassicaudatus	OCR	2n=62	Stanyon et al., 2002	Chromosome painting
	O. garnettii	OGA	2n=62	Masters et al., 1987	Comparative cytogenetics
	Galago moholi	GMO	2n=38	Stanyon et al., 2002	Chromosome painting
Lemuridae					
	Eulemur macaco	EMA	2n=44	Muller et al., 1997	Chromosome painting
				Cardone et al., 2001	BAC and PAC mapping
	E. fulvus mayottensis	EFU	2n=60	Richard et al., 2000	Chromosome painting
				Muller et al., 1999	Chromosome painting
	Lemur catta	EFU	2N=56	Cardone et al., 2002	BAC and PAC mapping
Haplorrhinae					
Platirrhinae					
FAMILY					
Cebidae					
Atelinae					
	Ateles geoffroy	AGE	2n=34	Morescalchi et al., 1997	Chromosome painting
	Ateles paniscus	APE	2n=34	Seuanez et al., 2001	Comparative Genomics
	Ateles belzebuth	ABE	2n=34	Garcia et al., 2002	ZOO-FISH
	Lagothrix lagothrica	LLA	2n=62	Stanyon et al., 2001	Chromosome painting
				Neusser et al., 2001	Chromosome painting
Alouattinae					
	Alouatta belzebul	ABL	2n=49/50	Consigliere et al., 1998	Chromosome painting
	A. caraya	ACA	2n=52	de Oliveira et al., 2002	Chromosome painting
	A. fusca clamitans	AFU	2n=45	de Oliveira et al., 2002	Chromosome painting
	A. f. fusca fusca	AFF	2n=49/50	de Oliveira et al., 2002	Chromosome painting
	A. seniculus macconelli	ASM	2n=46	de Oliveira et al., 2002	Chromosome painting
	A. s. arctoidea	ASA	2n=40	Consigliere et al., 1998	Chromosome painting
	A. s. sara	ASS	2n=46	Consigliere et al., 1998	Chromosome painting
	A. seniculus	ASE	2n=46	Stanyon et al., 1995	Chromosome painting
Pithecinae					
	Pithecia pithecia	PPI	2n=48	Richard et al., 2000	Chromosome painting
Callicebinae					
	Callicebus moloch	CMO	2n=46	Stanyon et al., 2000	Chromosome painting
	C. lugens	CLU	2n=16	Stanyon et al., 2003	Chromosome painting
Cebinae					
	Cebus nigrivitatus	CNI	2n=52	Garcia et al., 2002	ZOO-FISH
	C. capucinus	CCA	2n=54	Richard et al., 1996	ZOO-FISH
				Carlà Campa 1992	Chromosome banding
				O'Brien et al., 1993	Comparative genomics
	C. albifrons	CAL	2n=54	Garcia et al., 2002	ZOO-FISH and G-banding
	C. apella	CAP	2n=54	Garcia et al., 2002	ZOO-FISH and G-banding
				Murray, 1990	Chromosome banding
	Saimiri sciureus	SSC	2n=44	Stanyon et al., 2000	ZOO-FISH and G-banding
Aotinae					
	Aotus azarae	AAZ	2n=49/50	Mudry et al., 1990	Chromosome banding
Callithricidae					
Callithricinae					
	Cebuella pygmaea	CPY	2n=44	Neusser et al., 2001	Chromosome painting
	Callithrix argentata	CAR	2n=44	Neusser et al., 2001	Chromosome painting
	C. jacchus	CJA	2n=46	Neusser et al., 2001	Chromosome painting
				Shaerlok et al., 1996	Chromosome painting
	Saguinus oedipus	SOE	2n=46	Neusser et al., 2001	Chromosome painting
				Muller et al., 2001	Chromosome painting
	Callimico goeldi	CGO	47/48	Neusser et al., 2001	Chromosome painting
Catarrhinae					
FAMILY					
Cercopithecidae					
Cercopithecinae				Dutrillaux et al., 1975	Chromosome banding
Tribe Papionini			2n=42		
	20 different species		”	Stanyon et al., 1988	Chromosome banding
	Macaca mulatta	MMU	”	Small et al., 1985	Chromosome banding
	Macaca fuscata	MFU		Wienberg et al., 1992	Chromosome painting
	M. sylvana	MSY	”	Wienberg et al., 1992	Chromosome painting
	M. fascicularis	MFA	”	Ruiz-Herrera et al., 2002 a,b	ZOO-FISH
	M. nemestrina	MNE	”	Muller and Wienberg, 2001	Chromosome painting

ORDER	SPECIES	CODE	2n	Sources of comparative analysis	METHODS
Colobinae			”		
	Colobus guereza	CGU	2n=44	Bigoni et al., 1997a	Chromosome painting
	Trachipithecus cristatus	TCR	”	Bigoni et al., 1997b	Chromosome painting
				Kingsley et al., 1997	Chromosome painting
			”	Romagno et al., 2004	Chromosome mapping
	Trachipithecus obscurus	TOB	”	Ponsà et al., 1983	Chromosome banding
	Presbytis rubicunda	PRU	”	Sineo, 1986	Chromosome banding
	Nasalys larvatus	NLA	”	Bigoni et al., 2003	Chromosome painting
	Semnopithecus francoisi	SFR	”	Nie et al., 1998	Chromosome painting
	S.phayrei	SPH	”	Nie et al., 1998	Chromosome painting
Cercopithecinae Tribe Cercopithecini					
	Allenopithecus nigroviridis	ANI	2n/2=23	Clemente et al., 1990	Chromosome banding
				Sineo, 1986	Chromosome banding
	Erythrocebus patas	EPA	2n=54	Clemente et al., 1990	Chromosome banding
				Ponsà et al., 1981	Chromosome banding
	Miopithecus talapoin	MTA	2n=54	Clemente et al., 1990	Chromosome banding
				Sineo, 1986	Chromosome banding
	Chlorocebus aethiops	CAE	2n=60	Finelli et al., 1999	Chromosome painting
				Sineo et al., 1986	Chromosome banding
				Romagno et al., 2000	Single locus probe
	Cercopithecus diana	CDI	2n=58	Richard et al., 2000	Chromosome painting
	C. l’hoesti	CHO	2n=60	Stanyon and Sineo, 1983	Chromosome banding
				Sineo, 1986	Chromosome banding
	C.neglectus	CNE	2n=62	Stanyon and Sineo, 1983	Chromosome banding
	C. hamlymi	CHA	2n=64	Stanyon and Sineo, 1983	Chromosome banding
	C. ascanius	CAS	2n=66	Stanyon and Sineo, 1983	Chromosome banding
	C. cephus	CCE	2n=66	Clemente et al., 1990	Chromosome banding
	C. petaurista	CPE	2n=66	Clemente et al., 1990	Chromosome banding
	C. mona	CMO	2n=66	Clemente et al., 1990	Chromosome banding
	C. nictitans	CNI	2n=70	Sineo 1990	Chromosome banding
	C. mitis	CMI	2n=70	Sineo, 1990	Chromosome banding
	C. albougularis	CAL	2n=72	Sineo, 1990	Chromosome banding
FAMILY Hylobatidae					
	Bunopithecus hoolock	BHO	2n=38	Nie et al., 2001	Chromosome painting
	Hylobates lar	HLA	2n=44	Jauch et al., 1992	Chromosome painting
				Stanyon et al., 1987	Chromosome banding
				DeSilva et al., 1999	Comparative genomics
	Hylobates klossy	HKL	2n=44	Stanyon et al., 1987	Chromosome banding
	H. muelleri	HMU	”	Stanyon et al., 1987	Chromosome banding
	H. pileatus	HPI	”	Stanyon et al., 1987	Chromosome banding
	H. moloch	HMO	”	Stanyon et al., 1987	Chromosome banding
	H. agilis	HAG	”	Stanyon et al., 1987	Chromosome banding
	Symphalangus syndactylus	SSY	2n=50	Koheler et al., 1995b	Chromosome painting
				Muller and Wienberg, 2001	Chromosome painting
	Nomascus concolor	NCO	2n=52	Koheler et al., 1995a	Chromosome painting
				Muller and Wienberg, 2001	Chromosome painting
	N. leucogenys	NLE	2n=52	Nie et al., 2001	Chromosome painting
FAMILY Hominidae					
				Dutrillaux et al., 1975	Chromosome banding
				Dutrillaux et al., 1980	Chromosome banding
				Ledbetter et al., 1992	Chromosome painting
				Matera and Marks, 1993	Chromosome painting
				Luke and Verma, 1995	Single locus probe
				Muller et al., 2000	Chromosome painting
				Romagno 1989	Chromosome banding
				Romagno et al., 2000	Single locus probe
				Sineo et al., 2002	Single locus probe
	Pongo pygmaeus	PPY	2n=48	Jauch et al., 1992	Chromosome painting
				DeSilva et al., 1999	Comparative genomics
				Kingsley et al., 1997	Chromosome painting
				Muller et al., 2004	BAC hybridisation
	Gorilla gorilla	GGO	2n=48	Jauch et al., 1992	Chromosome painting
				DeSilva et al., 1999	Comparative genomics
				Kingsley et al., 1997	Chromosome painting
				Muller et al., 2004	BAC hybridisation
	Pan troglodytes	PTR	2n=48	Jauch et al., 1992	Chromosome painting
				DeSilva et al., 1999	Comparative genomics
				Muller et al., 2004	BAC hybridisation

ment homologous to HSA 12 (STANYON *et al.* 2002). The associations along OCR7 (HSA16/HSA12/HSA7/HSA12) make it a plausible hypothesis that an inversion disrupted the ancestral HSA7/HSA16 association, after a translocation with a segment of chromosome HSA12. Apparently, the HSA16 sequences on OCR7 derive from the 16p. The same situation may be present in *Galago moholi* even if HSA7 sequences have been detected only in a single chromosome. In fact, STANYON *et al.* (2002) suggests that the signal of the small segment of HSA7 associated with HSA16 may have escaped the detection. A very similar banding pattern in *Galago garnetti* (MASTERS *et al.* 1987) and in *Nycticebus coucang* (STANYON *et al.* 1987) makes it reasonable to hypothesise that the 7/16 association will eventually be found in these species.

In Lemuridae, homologs to HSA7 are constituted by an acrocentric chromosome (*Eulemur fulvus mayottensis*, *Lemur catta*), or an arm of a metacentric chromosome (*Eulemur macaco*). These chromosomes all have a banding pattern similar to PPY10 (MULLER *et al.* 1997, 1999; CARDONE *et al.* 2002). The remaining HSA7 sequences constitute a microchromosome in *Eulemur fulvus mayottensis* and *Eulemur macaco* (MULLER *et al.* 1997, 1999). Possibly on the same chromosome of *E. macaco*, RICHARD *et al.* (2000) detected also the presence of another not specified human synteny. The small signal relative to HSA7 found in EFM and EMA may have gone undetected by CARDONE *et al.* (2002) in *Lemur catta,* since they did not obtain signals for HSA2 and HSA4 paints and had no signals for some chromosomal region and some micro-chromosomes. A small acrocentric in this species could be homologous to the small fragment of HSA7 synteny, which is found associated to HSA16 sequences in Eutherian mammals.

Primates: Platyrrhinae - In almost all New World primates analysed with chromosome painting most of HSA7 is constituted by a single acrocentric chromosome with a PPY10q like banding features or, in Callithrichinae and *Saimiri*, a submetacentric chromosome. Further, in some species it constitutes a large chromosomal segment or whole arm, associated with different syntenies (CONSIGLIERE *et al.* 1996; STANYON *et al.* 2000). The remaining small part of HSA7 is associated with HSA 5 sequences (RICHARD *et al.* 2000). A single hybridisation signal has been detected only in three of over twenty analysed species (two in Alouattinae, CONSIGLIERE *et al* 1996; one in Callicebinae, STANYON *et al.* 2000); however, it can not be excluded that the signal of the small part of HSA7 associated with HSA 5 sequences escaped detection.

Saguinus oedipus WCP probes tested on Alouattinae genomes (DEOLIVEIRA, 2002) and *Lagothrix lagothricha* whole chromosome probes tested on *Callimico goeldii* genomes (NEUSSER *et al.* 2001, STANYON *et al.* 2001) demonstrated the presence of segments homologous to HSA7p22/7q11.2-7q21. The mapping of GUSB gene on *Cebus capucinus* chromosomes (O'BRIEN *et al.* 1993) demonstrated the presence of HSA7p22, 7q11.2 and 7q21 bands in the association with HSA5 sequences. The mapping of the PGP gene (HSA 16p) on chromosome 16 in *Cebus capucinus* (O'BRIEN *et al.* 1993) could be a symptom of an ancestral mammalian 7-16 syntenic retention not detected with the chromosome painting. Another sign of this ancestral association could be present in *Callicebus lugens,* where chromosome painting revealed the alignment on the same chromosome of HSA5, HSA7 and HSA16 sequences (STANYON *et al.* 2003). However, the association HSA7/HSA16 is more probably a derived trait because this chromosome has several human syntenies and HSA16 synteny is highly disrupted,

Primates: Catarrhinae - In all Papionini, a karyologically conservative group, the syntenic association HSA7/HSA21 forms chromosome number 2 (STANYON *et al.* 1988; WIENBERG *et al.* 1992; MORESCALCHI *et al.,* 1997; RUIZ-HERRERA *et al.* 2002 a,b; MULLER and WIENBERG 2001). In the HSA7 homologous segment the banding pattern is very similar to PPY10.

In Cercopithecini, marked by high karyotypic variability, painting data are limited, and many species have been studied only with banding techniques. In *Chlorocebus aethiops* HSA7 sequences constitute the large acrocentric chromosome 21, with banding similar to PPY 10q, and the small acrocentric chromosome 28 with banding similar to PPY10p. Reciprocal painting on HSA chromosomes demonstrate the presence of HSA7p21-cen, 7q21, 7q31-qter sequences on CAE 21, and 7p22, 7q11.2, 7q22 on CAE 28 (FINELLI *et al.* 1999). Williams-Beuren locus mapping confirmed the presence of 7q11.23 sequences on chromosome CAE 28 (ROMAGNO *et al.* 2004). Other gene mapping data, however, reveal that sequences of HSA7q21.11 and of HSA7q22 are also present, respectively, on CAE 28 and CAE 21 (O'BRIEN 1993). Reciprocal painting data demonstrated almost the same situation for chromosome 21 and 25 in *Erytrocebus patas* (STANYON, *personal communication*). In this case, however, it is evident the presence of HSA7q22 sequences on both chromosomes EPA25 and EPA21. In *Cercopithecus l'hoesti* the banding analysis shows two chromosomes, similar to CAE 21 (or EPA21) and CAE 28 or (EPA 25). This data confirm a period of common evolution to these three species like previously hypothesised on the basis of R-banding (DUTRILLAUX *et al.* 1982) and molecular data (TOSI *et al.* 2003).

Chromosome painting in *Cercopithecus diana* shows a single signal on a submetacentric chromosome (RICHARD *et al.* 2000) with banding identical to PPY10; the same situation, even if without a molecular validation, can be hypothesised for *Allenopithecus nigroviridis*, a species thought to be the closest guenon to the ancestral stock of Cercopithecinae on the basis of karyological evidences (DUTRILLAUX *et al.* 1980), morphological and molecular data (STRASSER and DELSON 1987; TOSI *et al.* 2003).

In *Cercopithecus neglectus* HSA 7 synteny is conserved in a single submetacentric chromosome (STANYON *personal communication*) with a banding pattern surprisingly similar to the homologous in Gorilla. A chromosome with very similar banding is also present in *Cercopithecus mona*, *Cercopithecus cephus, Cercopithecus ascanius*, *Cercopithecus petaurista,* *Cercopithecus nictitans and Cercopithecus mitis* (SINEO 1986). As these species on the basis of R-banding (DUTRILLAUX *et al.* 1982; CLEMENTE *et al.* 1990) and molecular data (TOSI *et al.* 2003) are grouped together in the reconstruction of the phylogenetic tree of Cercopithecini; it is possible that they share a common pericentric inversion in an ancestral homologous to HSA7 similar to that of *Allenopithecus nigroviridis* (ANI) and *Cercopithecus diana* (CDI). The same inversion probably occurred in the lineage leading to African great apes and man, and it would represent an example of convergent evolution at least at the light microscope level of resolution.

In the other species considered it was not possible identify a clear banding homology.

Colobinae monkeys analysed with the painting approach, belonging to genera Trachypithecus, Colobus, Nasalis and Semnopithecus, present HSA 7 synteny in a single chromosome, similar in banding pattern in the different species (NIE *et al.* 1998) but different from any HSA7 homologous of the other species of Cercopithecidae. William-Beuren locus and subtelomeric HSA7p probe mapping in *Trachypithecus cristatus* and other primates (ROMAGNO *et al.* 2004; KINGSLEY *et al.* 1997) reveal the occurrence of complex intrachromosomal rearrangements (ROMAGNO *et al.* 2004); in Trachypithecus, Colobus and Semnopithecus a p-terminal area without any hybridisation signal was reported (NIE *et al.* 1998).

Among the lesser apes, only *Hylobates lar* presents a single signal for HSA 7 synteny on the q-arm and on the proximal part of the p-arm of a large metacentric chromosome (JAUCH *et al.* 1992). The banding pattern of this region is identical to PPY10. The WS probe maps in the pericentromeric region of the p-arm indicating that in this area there are sequences of HSA7q11.23 (DE SILVA *et al.* 1999). The other gibbon species with 2n=44 show identical banding patterns and likely the same hybridisation pattern. In *H. hoolock* most of HSA 7 synteny is associated with other human syntenies in a submetacentric chromosome (NIE *et al.* 2001) and the banding pattern is similar to PPY 10q. The small remaining part is translocated to another chromosome. In *H. concolor* and *H. syndactylus* HSA7 synteny was variously fragmented into three segments.

After the synteny of human chromosome 7 (HSA7) was established, as a chromosome similar to *Pongo pygmaeus* chromosome 10, it was then subject to a pericentric and then a paracentric inversion in the phylogenetic line leading to *H. sapiens*. Specifically, high resolution chromosome analysis demonstrated that chromosome 7 in homo and chimpanzee differ from the orthologous in Gorilla by a paracentric inversion which differ from the ancestral like by a pericentric inversion. It derives that the gorilla chromosome represent the intermediate form that characterise the hominoid lineage (YUNISH and PRAKASH 1982).

Muller and colleagues (MULLER *et al.* 2004) recently demonstrated that pericentric and paracentric inversions that characterise hominoid lineage occurred in 7p22.1 and 7q22.1 breakpoints (respectively at 6.8 Mb and at 97.1 Mb on the reference sequence map) and 7q11.23 and 7q22.1 (respectively at 76.1-76.3 Mb and 101.9 Mb on the reference sequence map). The analysis pointed the attention to the importance of a fine BAC mapping and, more importantly, revealed the presence of "large segmetal duplications" of low copy repeats (LCRs) flanking these hot spots. Segmental duplications have been already described in association with several important rearrangements in primates (SARMONTE *et al.* 2002) and their presence, prior to the rearrangement (their spread in occurrence of the rearrangements seems a less probable event) and their causative role in chromosomal rearrangements has been proposed (MULLER *et al.* 2004).

Even if chromosome painting shows that chromosome 7 synteny is highly conserved in higher Primates, banding comparison BAC mapping and single locus mapping (as the Williams-Beuren syndrome *locus; WS* - HSA7q11.23*),* among the Hominoidea and Cercopithecoidea, suggest the occurrence of phylogenetically significant rearrangements (i.e. pericentric and paracentric inversions), undetected with whole chromosome paints (ROMAGNO *et al.* 2004).

DISCUSSION

An analysis of the data presented above allows us to hypothesise the presence in the ancestral eutherian karyotype, of an acrocentric chromosome containing most of HSA7 (RICHARD *et al.* 2000; MURPHY *et al.* 2001). A small, probably submetacentric, chromosome would contain the rest of HSA7 associated with HSA16p sequences. This last chromosome presumably contains sequences related to chromosome bands HSA7p22, 7q11.2, 7q21.11 and 7q22 bands.

The presence, in Prosimians, of a large (7a) and a small (7b) acrocentric chromosome containing only HSA7 sequences (MULLER *et al.* 1997, 1999) could indicate that the ancestral HSA7/HSA16 association was disrupted very early, during primate evolution. MULLER *et al.* (1999) proposed, on painting data in *Tupaia belangieri,* the presence of a single submetacentric, ancestral chromosome. On the contrary, RICHARD *et al.* (2000) proposed two chromosomes in the ancestral primate homologous to segments of HSA7: a large acrocentric chromosome and a small acrocentric chromosome. The small acrocentric chromosomes probably contains the same sequences associated with HSA16p in the ancestral eutherian karyotype. This last hypothesis is based, first**,** on the presence of a large and a small acrocentric chromosomes entirely composed of HSA7 sequences in Strepsyrrhini, and, second, on the detection of two signals produced by HSA7 probes in *Tupaia chinensis*, with the smaller acrocentric associated with HSA16 sequences. As TODER *et al.* (1992) affirm that banding of *Tupaia belangieri* and *Tupaia chinensis* chromosomes is identical, it is likely that the small signal concerning HSA7 sequences in *Tupaia belangieri* escaped detection in MULLER *et al.* (2001).

The situation becomes even more complex if we consider the more recent data on Galagonidae (STANYON *et al.* 2002). These data open the possibility that the small chromosome with HSA7/HSA16 association was also present in the primate ancestral karyotype. This hypothesis implies the occurrence of two independent fission events, which disrupted the HSA7/HSA16 association in lemurs and in the lineage leading to simians, as it has not been found in any analysed primate species. Reciprocal painting, subchromosomal probe and mapping data on Otolemur and Galago, together with painting analysis on a larger number of prosimians species, will be necessary to definitively elucidate the situation.

In the ancestral karyotype of New World Monkeys we can hypothesise the presence of an acrocentric chromosome, with most part of HSA7 synteny similar to that of prosimians ancestral karyotype, and of a submetacentric chromosome with the remaining part of HSA7 associated with HSA5 synteny, generated by a translocation (RICHARD *et al.* 2000; NEUSSER *et al.* 2001; and STANYON *et al.* 2003). This new syntenic association, which in some species comprises only a part of HSA5, secondarily underwent different translocations in various species. An inversion involving the HSA5/HSA7 association in a common lineage leading to Atelinae and Alouattinae, or independently in the two subfamilies, could have led to the alignment HSA7-HSA5-HSA7 observed in most of the Alouattine species and all Atelinae species. Reciprocal painting (NEUSSER *et al.* 2001; MULLER *et al.* 2001) and gene map data (O'BRIEN *et al.* 1993) demonstrated the involvement of HSA7p22, 7q11.2 and 7q21 bands in the association with HSA 5 sequences; this could confirm the homology with the HSA7 segment associated with HSA16 sequences in the ancestral eutherian karyotype.

In the ancestral karyotype of Old World Monkeys, HSA7 sequences constitute a single chromosome, which was probably similar to PPY10. This chromosome could be derived from the fusion of two primates ancestral chromosomes similar to those proposed by RICHARD *et al.* (2000).

During the evolution of Cercopithecini after the divergence of *A. nigroviridis* and *C. diana*, the ancestral chromosome underwent a pericentric inversion in the lineage leading to the other arboreal species with the formation of a chromosome similar to HSA7 homologs in Gorilla, and a fission in the linage leading to the terrestrial species. Further, even in consideration of the very low probability of back mutations with recurrent breakpoints, we have to consider that this last rearrangement could have restored in these species the ancestral primate.

A very similar submetacentric chromosome, containing the whole HSA7 synteny, is present in all Colobinae studied. This indicate this synteniy as the ancestral form for this group. This chromosome indeed has a peculiar banding pattern, possibly derived from the ancestral Catarrhinae form by a pericentric inversion, and other complex intrachromosomal rearrangements. In Papionini the ancestral HSA7 chromosome underwent a translocation with to form and an association with the homolog to HSA21.

In Hylobatidae the ancestral HSA7 chromosome was probably unchanged in respect to that of the ancestral Old World Monkey karytoype. It underwent a translocation with a chromosomal segment containing HSA2 sequences in *Hylobates lar* "group species" and a fragmentation in two (*H. hoolock*) or three segments (*H. syndactylus* and *H. concolor*) which are found associated with different human syntenies in various species.

A chromosome similar to PPY10 and therefore similar to Catarrhinae ancestral HSA7 chromosome was probably present in the ancestral karyotype of Hominoidea. This chromosome was involved in a pericentric inversion in the common lineage leading to *Gorilla*, *Pan* and *Homo* and a paracentric inversion in the lineage leading to *Pan* and *Homo*.

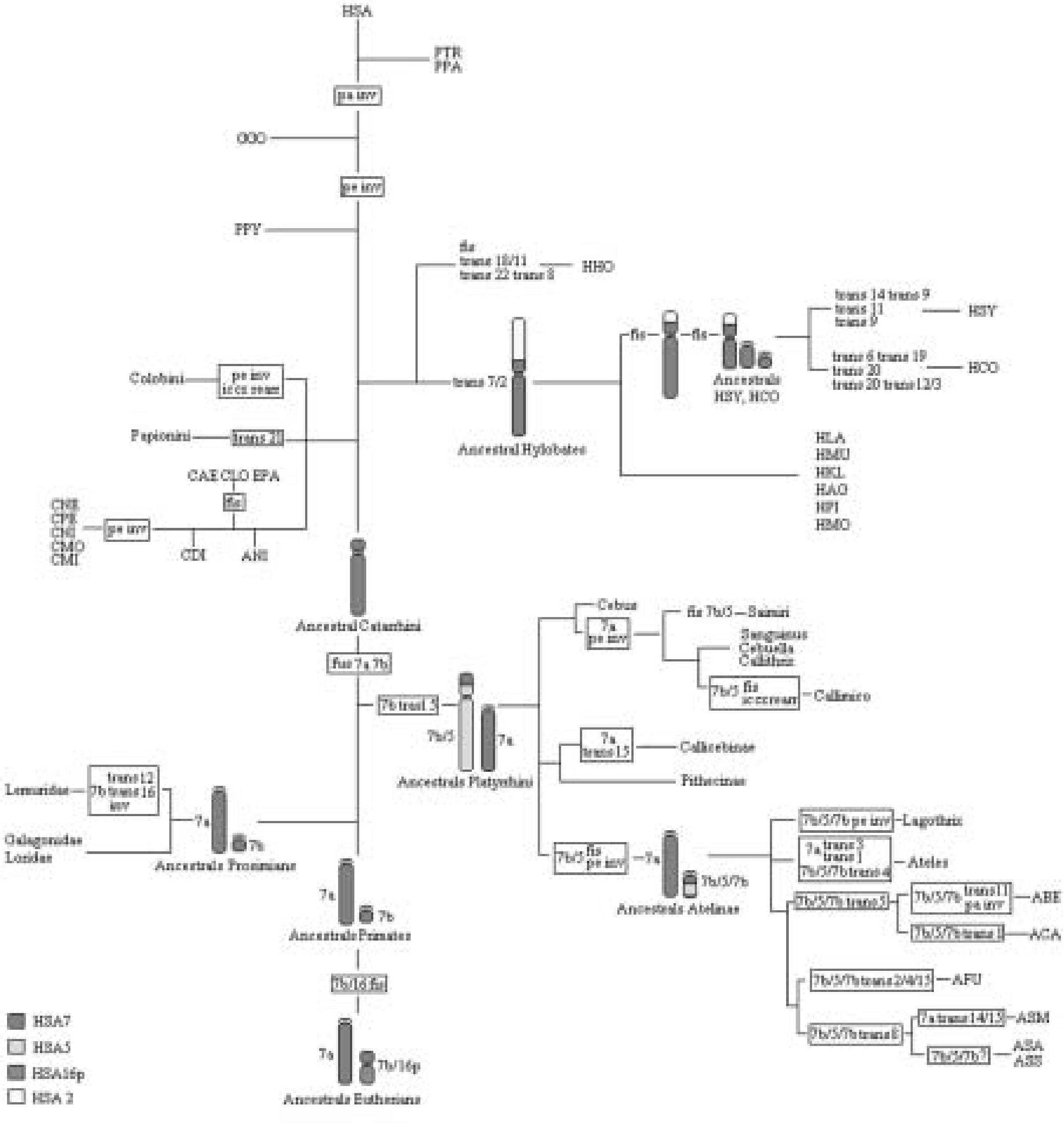

Fig. 1 — The proposed sequence of the rearrangements occurred during Primate evolution. The tree starts from the presumed ancestral Eutherian chromosomes.
Legend: fis=fission, trans=translocation, pe inv=pericentric inversion, pa inv=paracentric inversion, ic cx rear=complex intra-chromosomal rearrangement.
ASS=*Alouatta seniculus sara*, ASA=*Alouatta seniculus arctoidea*, ASM=*Alouatta seniculus macconelli*, ABE=*Alouatta belzebul*, CNE=*Cercopithecus neglectus*, CMO=*Cercopithecus mona*, CPE=*Cercopithecus petaurista*, CNI= *Cercopithecus nictitans*, CMI=*Cercopithecus mitis*, CAE=*Chlorocebus aethiops*, CLO= *Cercopithecus lhoesti*, EPA=*Erythrocebus patas*, HSY=*Hylobates symphalangus*, HCO=*Hylobates concolor*, HHO=*Hylobates hoolock*, HAG=*Hylobates agilis*, HKL=*Hylobates klossi*, HLA=*Hylobates lar*, HMO *Hylobates molock*, HMU *Hylobates muelleri*, HPI *Hylobates pileatus*, HCO=*Hylobates concolor*, PPY=*Pongo pygmaeus*, GGO=*Gorilla gorilla*, PTR=*Pan troglodytes*, PPA=*Pan paniscus*, HAS= *Homo sapiens*

Chromosome 7 evolution and synteny dynamics - Even if reports of reciprocal painting and gene mapping in Primates are few, all the data lead us to hypothesize that the p arm of the ancestral chromosome in Catarrhinae, the associated HSA7/HSA5 sequences in Platyrrhinae, and the small chromosome constituted by HSA7 sequences, present in the common ancestor of the prosimians, are homologous regions.

Further, this segment, associated with HSA16p homologous segments, characterises the common eutherian ancestral genome. The most consistent weakness of this hypothesis is the lack of data for HSA7q22 sequences in the small segment homologous to HSA7 associated with HSA5 in Platyrrhini. Because there are frequent rearrangements in New World monkeys which involve this region, the limitations and incongruities of available data must be considered.

In chromosomal evolution the occurrence of rearrangements from breakpoints that appear to be localised in the same regions are not rare, and chromosome 7 is not an exception. In primates, repeated breaks at the same sight could be explained by the presence of fragile sites in specific areas. For example HSA7p22 band and the homologous one in PTR, GGO and MFA, or HSA7q11.2 and the homologous band in GGO and PPY (Smeets *et al.* 1990), contain a fragile site. Duplicated segments are also hypothesised to promote chromosome rearrangements and in humans and great apes there is a duplicated region in HSA7q22 (DeSilva *et al.* 1999; Muller *et al.* 2004)). Improvements in analytical technology will put light on these issues. As Muller *et al.* (2004) demonstrated by fine BAC mapping, "homologous" breakpoints have, in reality, a different localisation at a molecular level of resolution.

In general the data on the evolution of chromosome 7 indicate that the conservation of syntenies in mammals is important from a functional point of view (Murphy *et al.* 2001; Novelli *et al.* 1999). It could be hypothesised that gene clusters (or group of genes) share regulatory elements acting at the local level. As gene order inside conservative syntenies is often not the same it is possible that the same regulatory elements determine a different pattern of gene expression and consistent phenotypical diversity in various species in front of the syntenic conservation.

A chronology of the events in the evolution of the HSA7 synteny can be hypothesised on the base of fossil evidences and chromosome constitution of extant species (Fig. 1).

Human chromosome 7 evolved recently via a pericentric, after the divergence of African apes, and paracentric inversion before the Homo/Pan divergence. These rearrangements probably happened (Sineo *et al.* 2000) in the last 10 -7 million of years before present.

A 7 (a) and a 7(b)+16p association characterised the ancestral mammalian chromosome in Cretaceous. The 7-16 fission originated in the ancestral primate situation in Eocene, even if a 7-16 association was sometime maintained or re-proposed in Prosimians.

The 7a-7b fusion that characterise the ancestral base for further evolution, presumably resulted from the rise of anthropoids simians, the first evolutionary trend in Oligocene. We can put the early divergence between Platyrrhini and Catarrhyni, near 40 mya (Ciochon and Chiarelli 1980). This divergence is chromosomally marked by a 7b-5 translocation in New World Primates and by the 7a-7b fusion in african monkeys. This fusion signs the origin of the human chromosome 7 synteny that remained unchanged since the Dryopithecinae radiation (Pilbeam and Young 2001) and is present in Pongo, that share an ancestral chromosome 10 homologous of Human 7.

Acknowledgements - The authors thank Roscoe Stanyon for precious comments in the preparation of this review. LS greatly appreciated the suggestions of Roberto Vitturi and the help of Francesca Dumas and Daniela Carrillo.

The study was financially supported by MIUR funds to Luca Sineo (ex 60% - 2002 - University of Palermo-Italy).

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Received July 30, 2004; Accepted October 24, 2004