

ZOO-FISH Suggests a Complete Homology between Human and Capuchin Monkey (*Platyrrhini*) Euchromatin

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Chromosome comparisons using *in situ* hybridization of all human chromosome-specific libraries on Capuchin monkey (*Cebus capucinus*, Cebidae, Platyrrhini) metaphases were performed with a new technique simultaneously revealing a G-banding and chromosome "painting." A complete homology between human (HSA) and *C. capucinus* (CCA) chromosomes was demonstrated, except for constitutive heterochromatin. Eleven *C. capucinus* chromosomes are homologous to 11 human chromosomes: CCA 2 = HSA 4; CCA 3 = HSA 6; CCA 12 = HSA 9; CCA 16 = HSA 11; CCA 10 = HSA 12; CCA 11 = HSA 13; CCA 20 = HSA 17; CCA 8 = HSA 19; CCA 23 = HSA 20; CCA 24 = HSA 22; and CCA X = HSA X. Ten *C. capucinus* chromosomes are homologous to parts of human chromosomes: CCA 13 = HSA 8q; CCA 14 = HSA 2q; CCA 15 = HSA 1p + 1q proximal; CCA 17 = HSA 7 part; CCA 18 and 19 = HSA 3 part; CCA 21 and 22 = HSA 1q distal; CCA 25 = HSA 10p; and CCA 26 = HSA 15q part. Six *C. capucinus* chromosomes are homologous to parts of two human chromosomes: CCA 1 = HSA 5 + 7 part; CCA 4 = HSA 2p + q proximal + 16q; CCA 5 = HSA 10q + 16p; CCA 6 = HSA 14 + 15 part; CCA 7 = HSA 8p + 18; and CCA 9 = HSA 3 part + 21. Many previous banding comparisons were confirmed but several cryptic or complex rearrangements could be identified. With the *C. capucinus* karyotype having been shown to be fairly ancestral, this comparison opens the possibility to compare human chromosomes to most Cebidae species. © 1996 Academic Press, Inc.

INTRODUCTION

After chromosome banding comparisons, it was proposed that multiple, and possibly complete, homologies existed between the chromosomes of man and those of great apes (Turleau *et al.*, 1972; Lejeune *et al.*, 1973; Pearson, 1973). This was further extended to comparisons with more distantly related primates (Dutrillaux, 1979a; Dutrillaux *et al.*, 1981). A number of these pro-

posed homologies were confirmed by comparative gene mapping (O'Brien and Marshall Graves, 1990) and more recently by *in situ* hybridization of whole chromosome libraries (Wienberg *et al.*, 1990, 1992; Jauch *et al.*, 1992; Blakey *et al.*, 1993; Ried *et al.*, 1993; Sherlock *et al.*, 1996). Even for the comparison between human and nonprimate chromosomes such as those of rabbit (Dutrillaux *et al.*, 1980) and cat (Dutrillaux and Couturier, 1983), homologies were confirmed by comparative gene mapping and single-gene *in situ* hybridization (O'Brien and Nash, 1982; Lemieux and Dutrillaux, 1992). Human chromosome painting can demonstrate homologies between human and nonprimate chromosomes, even in the absence of banding similarities (Scherthan *et al.*, 1994; Hayes, 1995).

Among the karyotypes of many species, that of the Capuchin monkey (*Cebus capucinus*) was particularly interesting. It can be compared to that of many platyrrhine (Dutrillaux *et al.*, 1986), lemur (Dutrillaux and Rumpler, 1980), Carnivora (Dutrillaux and Couturier, 1983), and catharrhine species, including man (Dutrillaux, 1979b). For this reason, it was assumed to have conserved quite ancestral chromosomes (Dutrillaux and Couturier, 1981; Dutrillaux, 1988). It also possesses unusually large amounts of constitutive heterochromatin (Dutrillaux *et al.*, 1978; Garcia *et al.*, 1983). Some of these interpretations were confirmed by comparative gene mapping (Créau-Goldberg *et al.*, 1987), but to our knowledge, no study was performed enabling a complete comparison of human and *C. capucinus* karyotypes by heterologous chromosome "painting" techniques. In this study, specific libraries for each human chromosome were hybridized on *C. capucinus* metaphases, demonstrating a complete homology between human and *C. capucinus* chromosomes, except for constitutive heterochromatin. A similar conclusion was recently reported about the comparison between marmoset and human chromosomes (Sherlock *et al.*, 1996).

MATERIALS AND METHODS

Fibroblast cultures of a male *C. capucinus*, obtained from the ménagerie du Muséum National d'Histoire Naturelle of Paris, were de-

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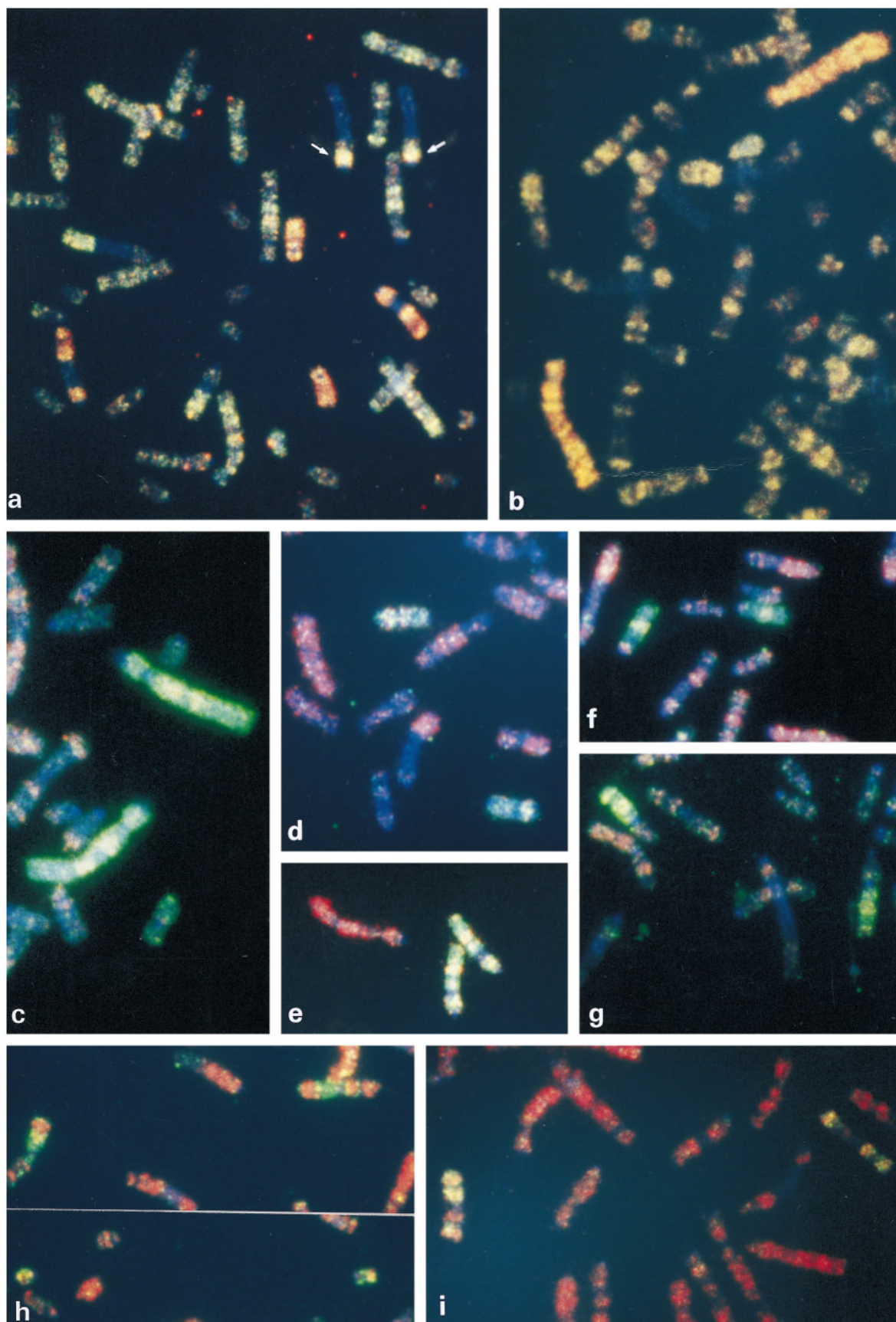


FIG. 1. Examples of chromosome painting using human (HSA) whole chromosome-specific libraries on *Cebus capucinus* (CCA) metaphases. (a) HSA 3 library painting CCA 18 and 19; in addition a recurrent pale signal exists on chromosome 9 but is barely visible in this photograph (arrow). (b) HSA 4 library painting CCA 2. For these two metaphases, the painting is revealed in red and G-bands are stained in yellow-green. (c) HSA 6 library painting CCA 3. (d) HSA 11 library painting CCA 16. (e) HSA 12 library painting CCA 10. (f) HSA 17

veloped from our own collection preserved in liquid nitrogen. Cultures were synchronized by adding 5-fluoro-2-deoxyuridine (FdU, 40 ng/ml) and the block was released by adding bromodeoxyuridine (BrdU, 6.25 μ g/ml) during the last 10 h of culture (Webber and Garson, 1983). Chromosome banding and chromosome-specific libraries were simultaneously detected according to the method described by Richard and Dutrillaux (in press). Briefly, a G-banding was revealed by an incubation with an anti-BrdU antibody (Boehringer, Mannheim, Germany) (6.7 μ g/ml), followed by an incubation with an anti-mouse antibody conjugated with a fluorochrome (Boehringer) (8 μ g/ml). Whole chromosome-specific libraries (Biosys S.A., Compiègne, France) were detected by an incubation with a goat anti-biotin antibody (Vector Laboratories, Burlingame) (10 μ g/ml) followed by an anti-goat FITC-conjugated antibody (Cambio-Biosys S.A.) (5 μ g/ml). In addition, a counterstaining by DAPI (1 μ g/ml, 5 mn) was performed. Observations were performed using a Nikon Microphot-FXA microscope with a triple bandpass filter.

RESULTS

The cell synchronization using FdU induced an accumulation of cells blocked at mid-S-phase. After releasing the block, an incorporation of BrdU during the second half of the S-phase was obtained. BrdU was detected by specific antibodies, revealed by a second antibody conjugated to a fluorochrome. This induced a brilliant G-banding pattern, with a pale blue staining of R-bands due to DAPI staining. Chromosome-specific libraries could be revealed by either rhodamine (red) or FITC (green), but better results were obtained when the chromosome-specific library was detected with FITC, and thus BrdU incorporation with rhodamine (Fig. 1). Under these conditions, the painted chromosomes had a green R-banding and an orange G-banding, without blue staining by DAPI, with the other chromosomes having a red G-banding and a dark blue R-banding (Figs. 1c to 1i). Constitutive heterochromatin was blue, although it is late replicating in *C. capucinus* and had incorporated BrdU (Couturier and Dutrillaux, 1981). This particularity of heterochromatin is not limited to *C. capucinus* and may be explained by a lack of accessibility of anti-BrdU antibodies (Vogel *et al.*, 1986; Latos-Bielenska *et al.*, 1987). For almost all human chromosome-specific libraries hybridized on *C. capucinus* chromosomes, a background, due to nonspecific hybridization, was observed and could not be suppressed. This, however, did not constitute a real limitation; the intensity of fluorescent signals on the painted chromosomes or chromosome segments was always much greater than the background. The human Y chromosome-specific library did not cross-hybridize with any *C. capucinus* chromosome; no signal was observed. A similar observation was reported on bovine chromosomes (Hayes, 1995). This may be due to the very large amount of repeated DNA sequences not detected by the chromosome-specific library.

TABLE 1

Chromosome Homologies between Human (HSA) and *Cebus capucinus* (CCA)

HSA chromosome	Homoeologous CCA chromosome, ^a proposed after R-banding	Homologous CCA chromosome, corrected after ZOO-FISH
1p + 1q	15 + 19	15 + 21 + 22
2p + 2q	4q + 14	4q + 14
3	18 + 6p	18 + 19 + 9 proximal
4	2	2
5	1q + 1p proximal	1q + 1p proximal
6	3	3
7	26 + 17	1p proximal + 17
8p + 8q	7p + 13	7p + 13
9	12	12
10p + 10q	5	25 + 5q
11	16	16
12	10	10
13	11	11
14	6q + 6p proximal	6q + 6p distal
15	23 + ?	6p proximal + 26
16p + 16q	21 + 4p	5p + 4p
17	20	20
18	7q	7q
19	8	8
20	22	23
21	9q proximal	9q intercalary
22	24	24
X	X	X
Y	Y	No hybridization signal

^a Homoeologies between CCA and human chromosomes were proposed in Dutrillaux (1979b) and Couturier and Dutrillaux (1981).

The observed homologies between human and *C. capucinus* chromosomes (constitutive heterochromatin excluded) are summarized in Table 1 and Fig. 2, which show the following:

— 11 chromosomes of *C. capucinus* (CCA) are homologous to 11 human (HSA) chromosomes: CCA 2, 3, 12, 16, 10, 11, 20, 8, 23, 24, and X versus HSA 4, 6, 9, 11, 12, 13, 17, 19, 20, 22, and X, respectively;

— 10 complete chromosomes of *C. capucinus* are homologous to a part of a human chromosome: CCA 13, 14, 15, 17, 18, 19, 21, 22, 25, and 26 versus HSA 8q, 2q, 1p + 1q proximal, 7 part, 3 part, 3 part, 1q part, 1q part, 10p, and 15q part, respectively;

— 6 chromosomes of *C. capucinus* are homologous to two different human chromosomes: CCA 1, 4, 5, 6, 7, and 9 versus HSA 5 + 7, 2 + 16, 10 + 16, 14 + 15, 8 + 18, and 3 + 21, respectively.

DISCUSSION

The technique used for this comparative cytogenetic work enables a simultaneous identification of all chro-

library painting CCA 20. (g) HSA 18 library painting CCA 7q. (h) HSA 15 library painting CCA 26 and part of CCA 6 (the metaphase was cut to exhibit the four painted chromosomes). (i) HSA 14 library painting the rest of CCA 6. In panels c to i, the painted chromosome segments are revealed in green and G-bands are stained in red. In all figures, the large segments of constitutive heterochromatin are stained dark blue.

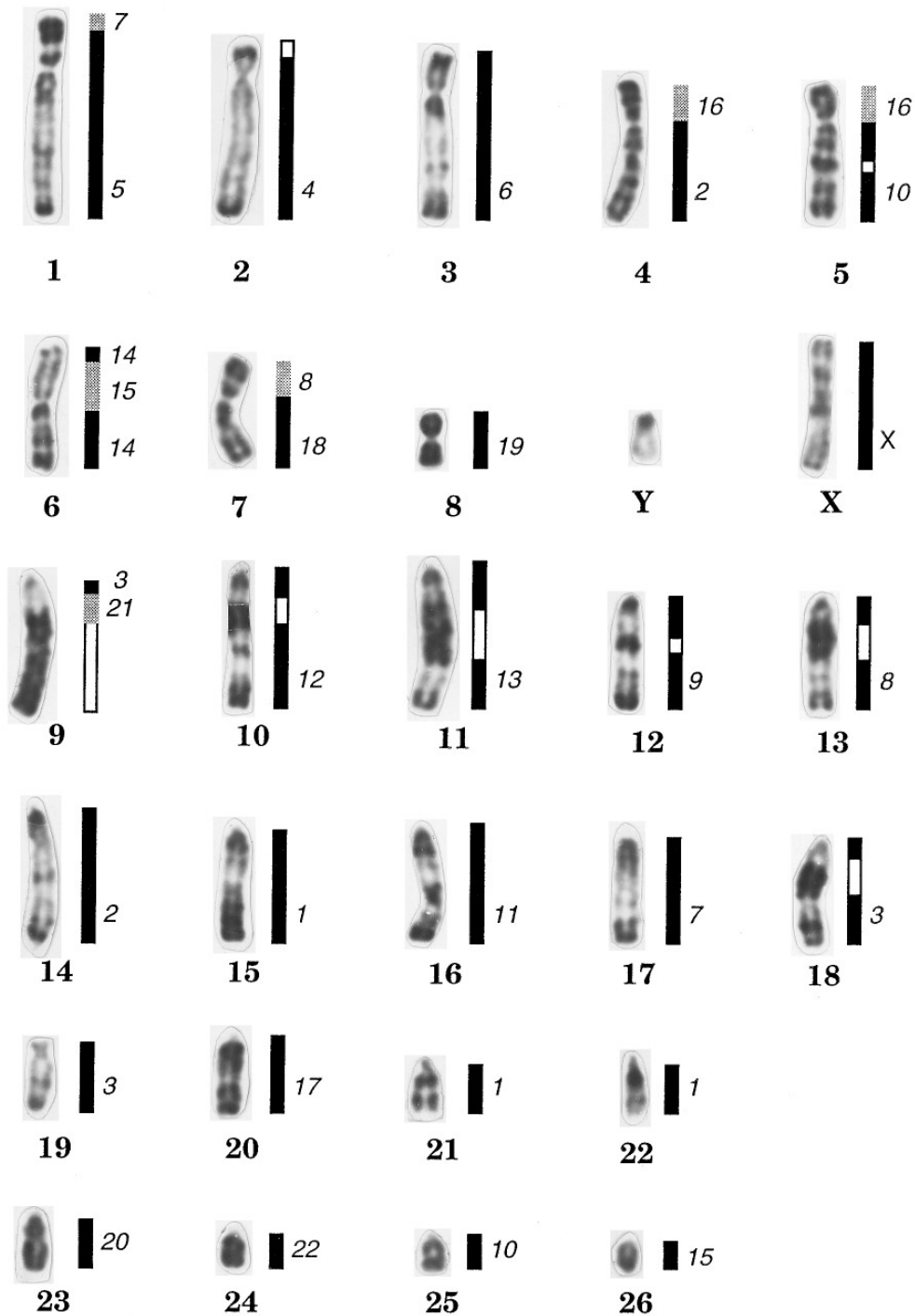


FIG. 2. Demonstrated homologies between *C. capucinus* and human chromosomes. Left: *C. capucinus* R-banded chromosomes; right: black and gray bars, corresponding human chromosomes; white bars, additional constitutive heterochromatin in *C. capucinus*. No analogy was detected by human Y chromosome library.

mosomes in addition to a specific painting. By comparison to other methods, it appears to be quite efficient. As proposed after chromosome banding studies, the karyotype of *C. capucinus* can be fairly well compared to that of human. No change could be detected between HSA X and CCA X, HSA 13 and CCA 11 (heterochromatin excepted), HSA 19 and CCA 8, and HSA 22 and CCA 24. Only intrachromosomal rearrangements oc-

curred for seven chromosomes, equivalent to HSA 4, 6, 9, 11, 12, 17, and 20. No simple Robertsonian translocations differentiate the two karyotypes.

Six human chromosomes each correspond to two *C. capucinus* chromosomes, and two human chromosomes each correspond to three *C. capucinus* chromosomes. Conversely, six *C. capucinus* chromosomes each correspond to two human chromosomes.

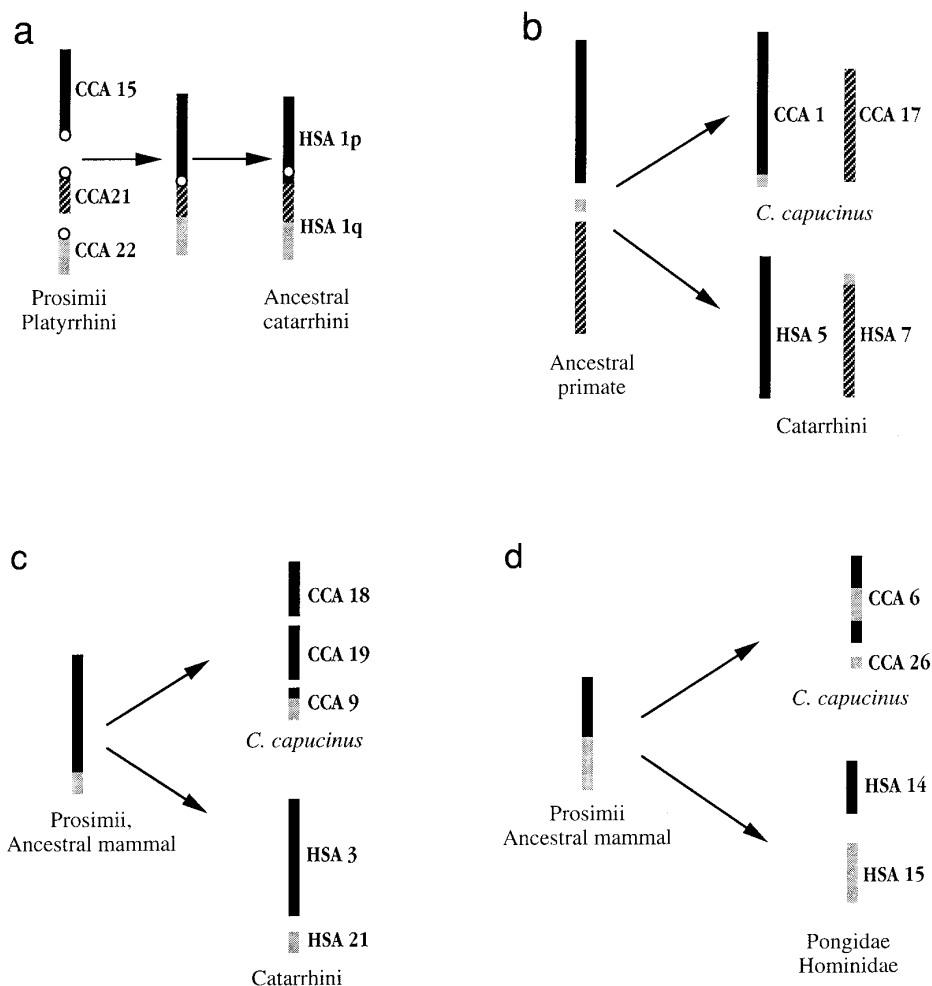


FIG. 3. Summary of reconstructed evolution of chromosomes equivalent to: (a) HSA 1; (b) HSA 3 and 21; (c) HSA 5 and 7; (d) HSA 14 and 15. Centromeres and constitutive heterochromatin were omitted except in a where centromeres are indicated by open circles. The ancestral chromosomes were proposed after chromosome banding studies.

To our knowledge, the comparison of *C. capucinus* chromosomes to those of human was reported by our group only, using R-, Q-, T-, and C-bandings and BrdU incorporation studies (Dutrillaux, 1979b; Couturier and Dutrillaux, 1981). Some of these interpretations were confirmed by Créau-Goldberg *et al.* (1987) using somatic hybrids. Table 1 shows that heterologous chromosome-specific hybridizations confirm most of the proposed homologies: about 85% of the length of the karyotype was correctly compared after chromosome banding. Thus, about 15% of the length of the karyotype either was erroneously compared or could not be compared, principally because the karyotype of *C. capucinus* comprises a number of small acrocentrics, hardly identifiable by chromosome banding techniques.

Indeed, the interest of ZOO-FISH is not limited to the confirmation or invalidation of results obtained by chromosome banding: it enables the detection of complex rearrangements involving short chromosome segments, which remained cryptic by chromosome band-

ing only. Such rearrangements involve two human and two *C. capucinus* chromosomes.

HSA 1 corresponds to CCA 15, 21, and 22 (Fig. 3a). Banding analyses suggested that all of the HSA 1p arm and the proximal q arm corresponded to CCA 15. This last chromosome is ancestral and is observed in other primate and nonprimate species (Dutrillaux *et al.*, 1981). The equivalent of the rest of the HSA 1q arm was not identified by banding, but CCA 21 was identified as a part of it by comparative gene mapping (Créau-Goldberg *et al.*, 1987). Altogether, these data indicate that HSA 1q (intercalary) corresponds to CCA 22 and HSA 1q distal to CCA 21. The translocations leading to the formation of the equivalent of the whole HSA 1 occurred in the trunk common to all Cercopithecidae, Pongidae, Hylobatidae, and Hominidae, as proposed (Dutrillaux, 1979a).

HSA 3 is homologous to a very short proximal segment of CCA 9, and whole CCA 18 and 19. In various primate and nonprimate species, it was proposed and confirmed by ZOO-FISH that the equivalent of HSA 3

and 21 were associated (Hayes, 1995; Rettenberger *et al.*, 1995) to form a large acrocentric chromosome, which was thus assumed to correspond to an ancestral chromosome (Apiou *et al.*, 1996). In Platyrrhini, the equivalents of HSA 3 and HSA 21 were assumed to be separated. It was expected that a fission occurred in a trunk common to all Simii, after separation with that of Prosimii, which still possess the large acrocentric composed of HSA 3 + 21. However, in various Platyrrhini species, the presumed equivalent to HSA 21 was found to be slightly larger than HSA 21 (Dutrillaux and Couturier, 1981). In addition, a large segment of constitutive heterochromatin forms the distal segment of this chromosome, in *Cebus* species. The present result (Fig. 3b) confirms that the equivalents of HSA 3 and HSA 21 together formed an ancestral chromosome, and demonstrates that the fission that occurred involved different breakpoints for Platyrrhini and Catarrhini. Thus, fissions independently occurred in the branches leading to Catarrhini and Platyrrhini.

CCA 1 is formed by the equivalent of the whole HSA 5 plus a small segment of HSA 7. It was proposed that the ancestral chromosomes were formed by three acrocentrics, one large acrocentric corresponding to HSA 5, one medium-sized acrocentric corresponding to the largest part of HSA 7, and one small acrocentric corresponding to the rest of HSA 7 (Dutrillaux, 1979a). The small and the medium-sized acrocentrics underwent a translocation and are fused in Catarrhini. The small acrocentric underwent another translocation with the equivalent of HSA 5 in *C. capucinus* (Fig. 3c). It remains to be determined, by ZOO-FISH, whether this translocation is shared by other Platyrrhini, which would indicate its ancestral origin for all Platyrrhini or for the genus *Cebus* only.

CCA 6 is formed by the equivalents of the whole HSA 14 and a part of HSA 15. The rest of HSA 15 forms a small acrocentric: CCA 26. Equivalents of HSA 14 and HSA 15 were found to be associated in a large number of primate (Garver *et al.*, 1977; Créau-Goldberg *et al.*, 1987) and nonprimate species (O'Brien and Nash, 1982; Hayes, 1995; Rettenberger *et al.*, 1995). Thus, they formed a unique ancestral chromosome. The fission leading to HSA 14 and HSA 15, shared with Pongidae but not with Cercopithecidae, is of recent origin. Indeed, the rearrangement leading to CCA 6 and CCA 26 is completely independent (Fig. 3d). As proposed, other rearrangements involving the equivalent of HSA 14 and HSA 15 occurred in other Platyrrhini species (Dutrillaux *et al.*, 1986).

In conclusion, the use of chromosome painting techniques demonstrates that all human chromosomes except chromosome Y have their counterpart in the *C. capucinus* karyotype, which possesses large additional segments of constitutive heterochromatin shared by other *Cebus* species only. This method allowed us to reconstruct a number of rearrangements that were missed by chromosome banding studies, and most ho-

mologies proposed after chromosome banding comparisons (Dutrillaux, 1979a,b) are now confirmed.

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