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Satellite DNA relationships in man and the primates

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ABSTRACT

We have investigated the genomes of a series of primates to identify the presence of sequences related to human satellite DNAs I, II and III by restriction enzyme digestion and hybridisation with probes of these satellite DNAs. Where we have found such related sequences we have examined the extent to which they have diverged by measuring the stability of the hybrids. DNA satellite III is the oldest sequence being common to species which have diverged some 24 million years ago. In contrast DNA satellites I and II are of much more recent origin.

Our results permit us to draw conclusions about the way these sequences have evolved, and how the evolution of repeated DNA sequences may be related to the evolution of the primate lineage.

INTRODUCTION

Using the technique of in situ hybridisation, Jones et al. (1) first showed that DNA sequences with some homology to human DNA satellite III were present in the genomes of the chimpanzee and orangutan. In later studies they isolated a satellite DNA from chimpanzee (Pan troglodytes) (chimp A) and homologous sequences were shown to be present within the human genome. Although the evidence was indirect, it was assumed that chimpanzee A satellite and human satellite III were related sequences. A more detailed analysis of the chromosome distribution in the higher primates of DNA sequences homologous to human DNA satellite III (2), and to human DNA satellites I, II and IV (3) confirmed the earlier findings that the higher primates shared common repeated DNA sequences.

Hydroxylapatite chromatography was used to isolate repetitive DNA sequences from the orangutan, gibbon, rhesus monkey, slow loris and man and the densities of the isolated fractions were compared in neutral caesium chloride (4). These species were selected to span the Order Primates and it was concluded from the analysis of the DNA sequences of these diverse Primates that the organisation of the repetitive DNA families was similar

within the Order although within each species a particular DNA family (as defined by its buoyant density) might be more or less frequent than in other species. A new class of DNA with sequences with a low frequency of repetition in man, bonnet monkey and galago have been examined and appear to have mutation rates similar to those of single-copy DNA sequences (5). However, considerable divergence had occurred between these sequences in man and galago as shown by the thermal stabilities of the heteroduplexes.

More recently restriction endonucleases have been used to analyse the complexity of the repeated sequences in certain primate DNAs. When total human DNA is restricted with either EndoR HaeIII or EndoR EcoRI and analysed by agarose gel electrophoresis, a ladder consisting of DNA fragments with sizes based upon a monomer of 170 b.p. is observed (6). The relationship between the restriction profile of total human DNA and those of the isolated human satellite DNAs has now been established (7,22) and the evolutionary relationships between the individual satellites characterised (22). Studies on other primate DNAs, however, have been limited to only a few species of Old World monkeys of the family Cercopithecidae. Singer and Donehower examined the degree of homology between the 170 b.p. fragment isolated from an EndoR Hind III digest of African green monkey DNA and equivalent sized fragments obtained from baboon DNA when restricted with EndoR Hind III or EndoR Bam HI (8). Although the African green monkey (Hind III) fragment is homologous to repeated DNA sequences within the baboon genome the DNA sequences are organised differently in their respective genomes. The Bam HI fragment has recently been sequenced and compared with equivalent sequences in the African green monkey and man demonstrating that some areas of sequence homology have been conserved during a relatively lengthy evolutionary time scale (9).

It is now becoming clear that the organisation of repeated DNA sequences within the genomes of the primates share many common features. A major drawback in the studies to date, however, is the limited number of primate species which have been examined. In this report we present data from individuals belonging to four separate super families: the hominoidea, as represented by man, chimpanzee (Pan troglodytes), pygmy chimpanzee (Pan paniscus), lowland gorilla (Gorilla gorilla gorilla), orangutan (Pongo pygmaeus) and siamang (Hylobates syndactylus): the Cercopithecoidea (Old World monkeys) represented by Macaca silenus, Presbytis johni and Pygathrix nemeaus: the Ceboidea (New World monkeys) represented by Ateles paniscus, Callicebus torquatus and Pithecia pithecia; and the Lemuroidea represented

by Lemur macaco. Our primary concern has been to examine the evolution of human DNA satellite I, II and III and show that DNA satellite II appears to be the most recently evolved human satellite, whereas sequences homologous to DNA satellite III can be detected in New World monkeys.

MATERIALS AND METHODS

DNA Preparation

DNA was prepared from spleen of male animals (10) and stored in 0.01 M Tris pH 7.50 at -10°C. Spleen tissue from the orangutan was a gift from the Yerkes Primate Centre. The other primate species were provided by San Diego Zoological Park. Human satellite DNAs were prepared as previously described (22) with the exception that the vertical rotors of the Sorvall OTD-65 centrifuge were employed (11).

Restriction Endonucleases

The enzymes were purchased from New England Biolabs and digestion conditions of DNA samples followed the recommended procedure of the manufacturer.

Gel Electrophoresis

DNA samples were separated on 1.5% agarose gels and the fragments located by staining with ethidium bromide (12).

Hybridisation conditions

Transfer of DNA fragments onto nitrocellulose paper followed the procedure of Southern (13). Nick-translation of DNA probes, hybridisation to filters, and subsequent washings at increasing temperatures were carried out as previously described using 0.12 M phosphate buffer pH 6.80 as the solvent (12,22). Filters challenged with more than one probe were heated in two changes of dist. H_2O at 85°C for 1 hr., dried and checked for retention of radioactivity before hybridisation with the second probe.

DNA reassociation and HAP chromatography

Unlabelled DNA at a concentration of 100 µg/ml was reassociated in the presence of tracer amounts of labelled satellite DNA and fractionated on hydroxylapatite (2).

RESULTS

Buoyant Density Characteristics

Of the primate species studied only the DNA from Callicebus torquatus exhibits a satellite DNA component in neutral caesium chloride. The DNAs from the other primates exhibit a unimodal profile in caesium chloride with

buoyant densities typical of mammalian DNAs. As in man (14) satellite DNAs can be isolated from the DNAs of the Hominoidea using silver/caesium sulphate gradients (Mitchell and Ryder, manuscript in preparation).

Satellite III Hybridisation to the family Hominidae

Fig. 1a shows an ethidium bromide-stained 1.5% agarose gel in which DNA from man, chimpanzee, pygmy chimpanzee, gorilla, orangutan, macaque and siamang have been separated by electrophoresis after digestion with EndoR Hae III. The digestion products of this enzyme in human DNA have been well characterized (6,12), the Hae III ladder series being based on a monomer repeat length of 170 b.p. Similar sized digestion products are obtained when DNAs from the other Hominoidea are digested with EndoR Hae III. The restriction profile from Macaca silenus (an Old World Monkey) shows the presence of Hae III digestion products of identical size to those of the Hae III ladder in man. Although the products in Fig. 1a are from a limit digest, the proportion of DNA within each particular size fragment varies according to the individual species being examined. In man, for example, the dimer is the most pronounced band and this is true for the gorilla and Macaca silenus whilst the siamang has a higher proportion of restricted DNA in the tetramer band. The human "male band" 3.4 kb fragment (25), is only detectable in man; no similar sized Hae III product can be seen in the DNA from any of the other species (Fig. 1a).

When nick-translated human satellite III DNA isolated from a male placenta is used as a probe and hybridised to a nitrocellulose filter containing DNA treated as in Fig. 1a and transferred from the agarose gel by the procedure of Southern, the result shown in Fig. 1b is obtained. It is clear from Fig. 1b that sequences homologous to human DNA satellite III are present in all members of the superfamily Hominoidea. Little if any hybridisation is detected with Macaca silenus under the rather stringent conditions of reassociation employed. The hybridisation of human DNA satellite III corresponds to the Hae III ladder. To examine the stability of the homo- and heteroduplexes illustrated in Fig. 1b, the filter was washed under progressively more stringent conditions (see Materials and Methods) and the results are shown in Fig. 1c. This result suggests that both the homo- and heteroduplexes are well matched. The stabilities of the homo- and heteroduplexes were further characterised by hydroxylapatite chromatography. The heteroduplexes formed between human DNA satellite III and gorilla, chimpanzee (Pan troglodytes) and orangutan show biphasic melting profiles similar to the homologous reaction (22). In contrast, the

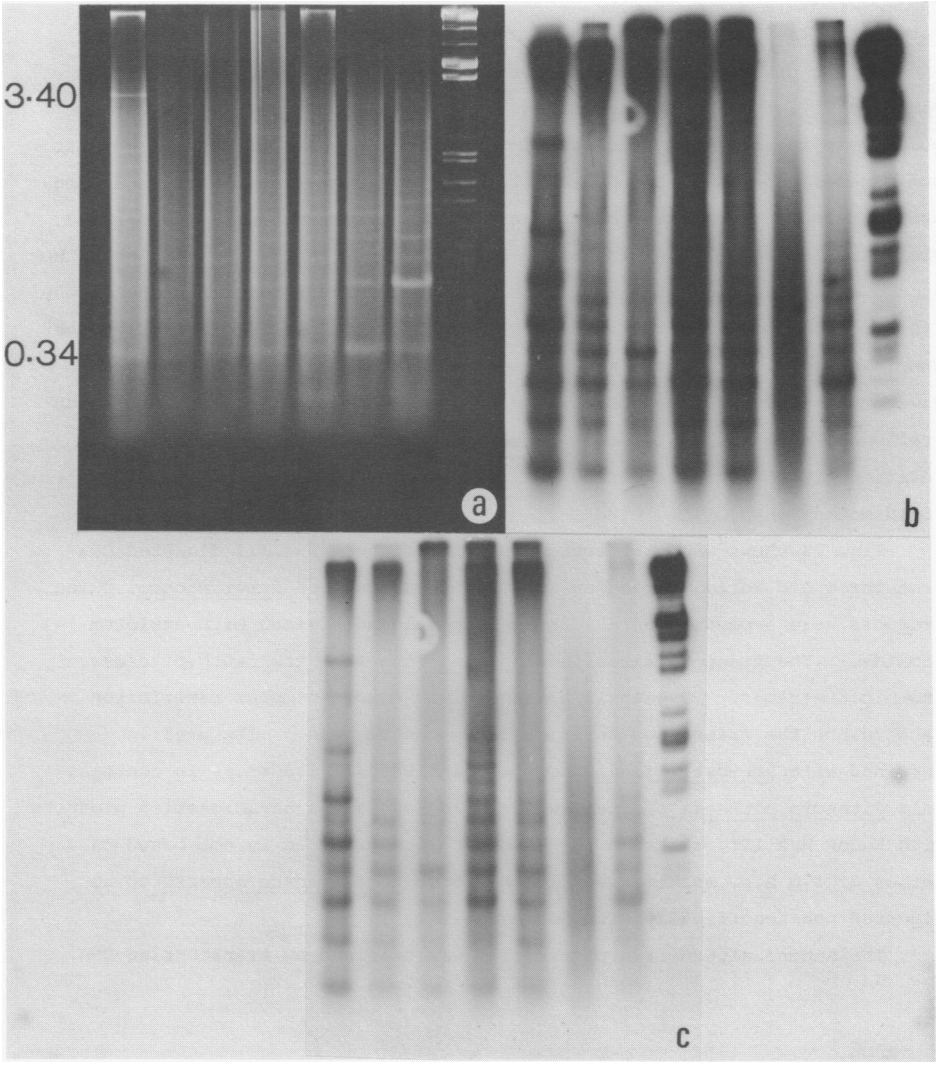

Fig. 1. a) Hae III restricted DNAs separated on a 1.5% agarose gel: tracks from left to right contain DNA from man, chimpanzee, pygmy chimpanzee, gorilla, orangutan, macaque and siamang. Lambda DNA digested with EcoRI/ Hind III is the marker DNA in track 8. b) and c) are autoradiographs obtained when human male satellite III is hybridised to a nitrocellulose filter containing a Southern transfer of the DNA shown in Fig. 1a and washed under increasingly stringent conditions: 1b 65°C/2xSSC and 1c 76°C/0.12 M PB. Each wash was for 2 hrs with 4 solvent changes.

heteroduplex with the siamang shows a unimodal melting profile (see Table 1).

Satellite III Hybridisation to Old and New World monkeys

In the previous section, hybridisation of human satellite to an Old World monkey, the lion-tailed macaque (Macaca silenus) (Fig. 1b), did not positively identify DNA sequences in this species which were homologous to human satellite III. EndoR Hae III, however, demonstrated that digestion products indicative of the human Hae III ladder were present (Fig. 1a). There are two possible explanations for this discrepancy. First, that the products of digestion with Hae III fortuitously gave a pattern based on the 170 b.p. monomer, particularly since a 170 b.p. monomer is present in other species when digested with a series of restriction endonucleases (15). However, the alternative possibility, that the conditions of reassociation precluded detection of heteroduplexes, prompted us to re-examine the relationship of human satellite III to sequences present in Old and New World monkey DNAs.

Fig. 2a shows the restriction profile of EndoR Hae III digested DNA from three Old World, three New World monkeys and from Lemur macaco. The products were separated on a 1.5% agarose gel and stained with ethidium bromide. The fragment sizes in Macaca silenus show the 340 b.p. dimer, 680 b.p. tetramer. Pygathrix nemeaus gives a more complex restriction pattern but the trimer and tetramer sizes can be seen. The profile obtained with Presbytis johni shows a faint Hae III ladder. In contrast, only Pithecia pithecia of the New World monkeys gives any digestion products with EndoR Hae III, although the fragment size produced is not based on a series of 170 b.p. multimers. The DNA from Lemur macaco appears to be digested non-specifically with EndoR Hae III.

The second alternative possibility was examined by transferring DNA

TABLE 1

SPECIES	Percentage of high thermal stability duplexes	Tm	Percentage of low thermal stability duplexes	Tm
Man	56	84.0	44	70.0
Chimpanzee	24	83.5	76	69.0
Gorilla	25	87.0	75	70.5
Orangutan	16	87.0	84	68.5
Siamang	-	-	100	70.0

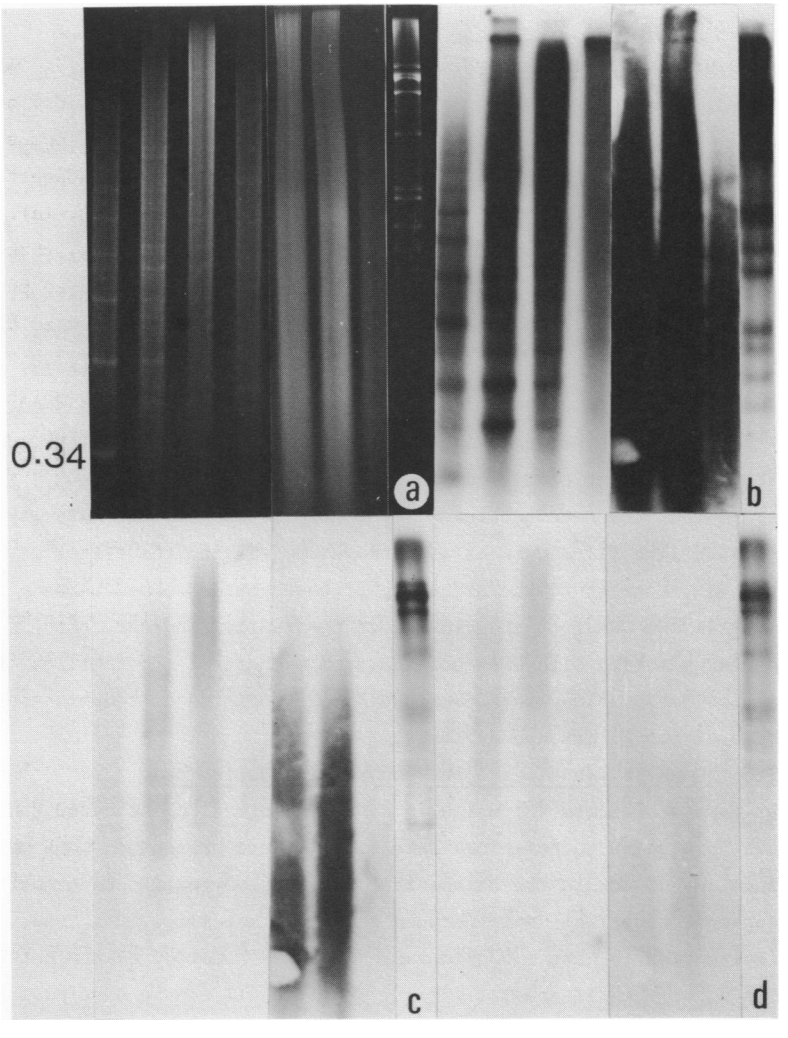

Fig. 2. Hae III restricted DNAs separated on a 1.5% agarose gel. From left to right the tracks contain DNA from Macaca silenus, Pygathrix nemeaus, Presbytis johnii (Old World monkeys), Pithecia pithecia, Callicebus torquatus, Ateles paniscus (New World monkeys) and Lemur macaco (lemur). b), c) and d) are autoradiographs of Southern transfers of the DNA in Fig.2a hybridised with male satellite III at 50°C/3xSSC/0.1% S.L.S. and subsequently washed at b) 50°C/2xSSC, c) 60°C/1xSSC, d) 65°C/1xSSC. Lambda DNA is the marker in track 8.

fragments from a gel similar to that of Fig. 2a onto a nitrocellulose filter, and hybridised with human satellite III under more relaxed hybridisation conditions (50°C in 3 x SSC). The result is shown in Fig. 2b and clearly shows that sequences homologous to human DNA satellite III can be detected in all the Old World monkey species used in the experiment. The relative degree of hybridisation as judged by the density of the autoradiograph appears similar in the three Old World monkey DNAs, suggesting that the copy numbers of DNA sequences homologous to human satellite III are similar in these animals. Of the family Ceboidae (New World monkeys) only the DNA from Pithecia pithecia produces identifiable digestion products with Hae III. There is, however, some hybridisation of DNA satellite III to the DNA from these animals although no specific size products can be seen. The stabilities of the heteroduplexes were tested by washing the filter under increasingly stringent conditions as described above. Figs. 2b-d. demonstrate that the heteroduplexes are poorly matched. The majority of the labelled satellite III sequences are removed by washing the filter at 65°C in 1 x SSC. In contrast to the stability of the hybrids formed between human satellite III and DNA from individuals of the family Pongidae, the heteroduplexes formed with DNA isolated from members of the families Cercopithecoidae, Cebidae and Lemuridae are dissociated at temperatures indicative of poorly matched duplexes.

Satellite II - Hybridisation to the superfamily Hominoidea

Our earlier results (3) using in situ hybridisation indicated that sequences homologous to human DNA satellite II were present in both gorilla and orangutan but not in the chimpanzee (Pan troglodytes). Later work on the sequence interrelationship between the human satellite DNAs, however, showed quite clearly that a considerable sequence homology exists between human DNA satellites II and III (22). Satellite II can be distinguished from satellite III using the restriction endonuclease EcoRI (22) so we have used this property to re-examine the distribution of satellite II within the Hominoidea. Human DNA digested with this enzyme gives primarily a ladder based upon a 340 b.p. dimer (6). A fragment of this size can be seen in the channels containing human and chimpanzee (Pan troglodytes) DNA (Fig. 3a). Hybridisation of nick-translated human DNA satellite II to a nitrocellulose filter containing EcoRI restricted DNA is shown in Fig. 3b. The channel containing human DNA is rather overexposed in an attempt to increase the density of grains over the remainder of the samples. Hybridisation of DNA satellite II to human DNA is predominantly to the fragments of 1.35, 1.77

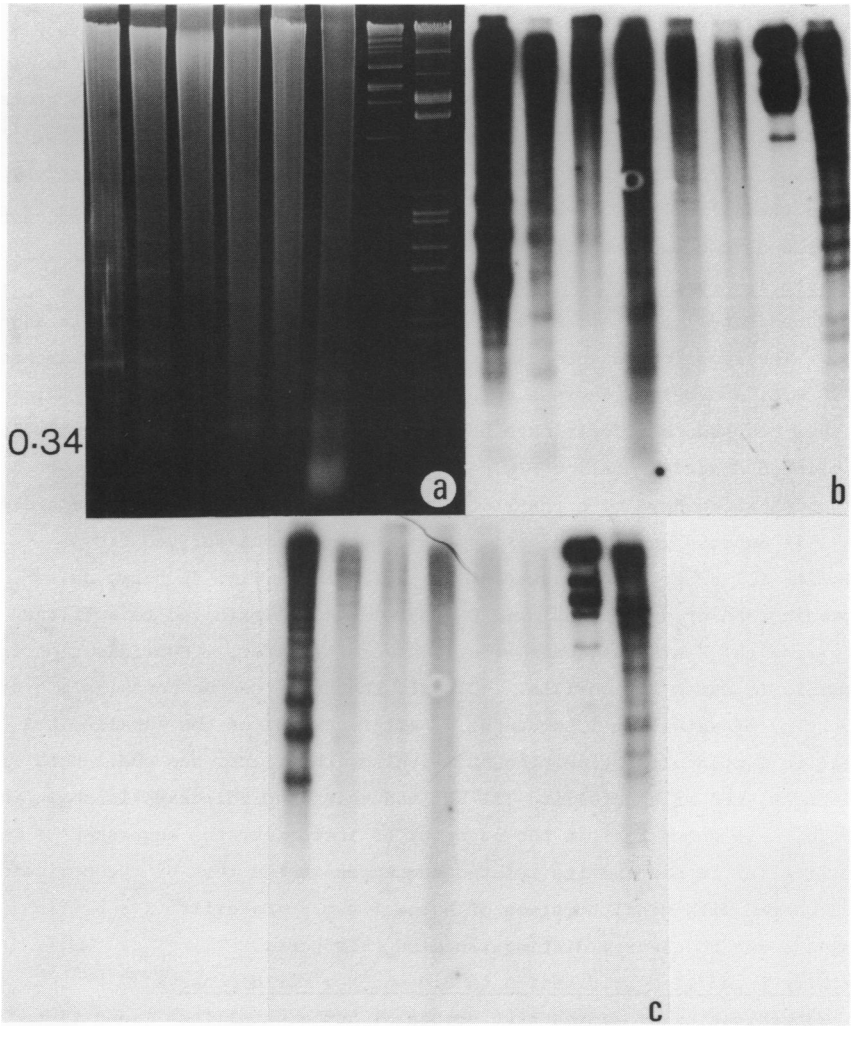

Fig. 3. a) EcoRI digested DNAs separated on a 1.5% agarose gel. The tracks from left to right contain human male DNA, chimpanzee DNA, pygmy chimpanzee DNA, gorilla DNA, orangutan DNA and siamang DNA. Lambda DNA digested with EcoRI and EcoRI/Hind III was run in tracks 7 and 8 respectively. Fig. 3b and c illustrate autoradiographs when human DNA s atellite II is hybridised to a nitrocellulose filter containing a Southern transfer of the DNA in Fig. 3a and subsequently washed at b) 65°C/2xSSC and c) 76°C.0.12 M PO_4.

and 2.20 k.b. The other members of the Hominoidea contain DNA sequences that hybridise with human satellite II to a much lesser degree and only in the gorilla and the two chimpanzee species can it be clearly detected. An assessment of the autoradiograph intensity suggests that the gorilla contains more satellite II equivalent sequence than either of the two chimpanzee species. The stability of the duplexes shown in Fig. 3b was measured by washing the filter in 0.12 M PB. The heterologous duplexes are clearly not as stable as the homologous reaction. (Fig. 3c).

Satellite I - Hybridisation to the Hominoidea

Huamn satellite I and satellite III cross-hybridise to a certain degree (22). The restriction endonuclease Hinfl cuts satellite III to fragments of 1.0 k.b. and below, whereas satellite I is uncut by this enzyme, which can thus be used to discriminate between the two satellite DNAs (Mitchell, unpublished observations). Fig. 4a shows DNA from the members of the Hominoidea which have been restricted with Hinfl and the products separated on a 1.5% agarose gel. The maximum size of fragments derived from satellite III after Hinfl digestion is indicated. Fig. 4b shows an autoradiograph of nick-translated DNA satellite I hybridised to a filter containing the Hinfl fragments after Southern transfer. Hybridisation is primarily to human and gorilla. Clearly the human genome contains a greater proportion of satellite I sequences. After removal of the labelled DNA satellite I molecules by melting and washing, the filter was challenged with nick-translated male satellite III DNA and this autoradiograph is shown in Fig. 4c. It shows that in the majority of instances, the sequences of DNA satellite III in man and its related sequences in the rest of the Hominoidea are digested with Hinfl to sizes of below 1 k.b. Satellite I specific sequences can be clearly distinguished on this basis.

Satellite I and II Hybridisation to Old and New World monkeys

Hybridisation of radioactive probes of human satellites I and II to filters containing DNA from Old and New World monkey species failed to demonstrate any homology.

DISCUSSION

Restriction endonucleases have recently been used to examine repeated DNA sequences in various Primates. Donehower and Gillespie (16) compared eighteen examples from the sub-family Cercopithecinae and one example from the sub-family Colobinae using a variety of restriction endonucleases (see Table 1 from Donehower and Gillespie). The prominent basic repeat sizes

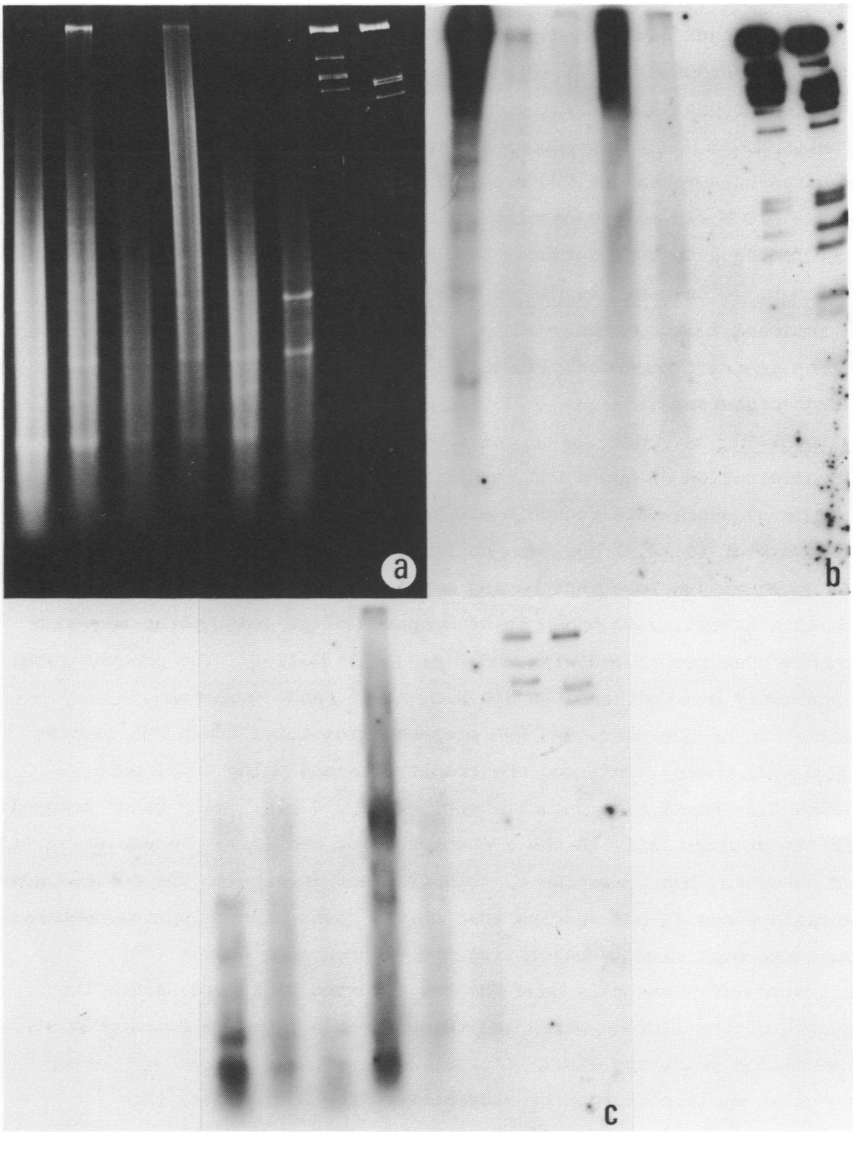

Fig. 4. Hinfl digested DNAs separated on a 1.5% agarose gel. From left to right the tracks contain human male DNA, chimpanzee DNA, pygmy chimpanzee DNA, gorilla DNA, orangutan DNA and siamang DNA. Tracks 7 and 8 contain lambda DNA digested with EcoRI and EcoRI/Hind III. Fig. 4b is an autoradiograph of human male satellite I hybridised to a Southern transfer of the DNA shown in Fig. 4a to a nitrocellulose filter. Fig. 4c is the result obtained when human male satellite III is hybridised to the same filter depicted in 4b after removal of the labelled DNA satellite I molecules.

were either 240 b.p. or 170 b.p. fragments. Similar repeat sizes were detected by Singer and Donehower when DNA from the African Green monkey was digested with EndoR Hind III (8). In the present paper it can be seen that restriction of DNAs from all the members of the Hominoidea examined in this study with EndoR Hae III produces a complex array of restriction fragment sizes based on a repeat of 170 b.p. This pattern of organisation extends to the three Old World monkey species used in these experiments; however, the Hae III ladder cannot be detected in any of the New World monkeys nor in the black lemur. The basic repeat of 170 b.p. now appears to be an organisational feature widely distributed in eukaryotic DNA although different restriction endonucleases are required to produce this pattern in different organisms (15).

Satellite III

Hybridisation of human DNA satellite III has shown clearly that homologous sequences are found in all species of the hominoidea. Thus earlier work of (1,17,2) has been confirmed and extended to include members of the sub-family Hylobatinae having sequences homologous to human satellite III. This satellite is known to be composed of at least three sequence components when restricted with EndoR Hae III (22,12). The present results show that only man contains the 3.4 k.b. 'male band' component. Hybridisation of the male band DNA prepared from total human DNA (a gift from Dr. H.J. Cooke) confirmed the result obtained using total male satellite III DNA (A.R.M. unpublished). The 3.4 k.b. 'male band' fragment hybridises predominantly to the Y chromosome of man (12). Szabo *et al.* (18) failed to detect hybridisation of this fragment *in situ* to the chromosomes of the gorilla which is the species that on the basis of cytological data has a Y chromosome most closely resembling the Y chromosome of man (19). Amplification of human male band DNA has occurred therefore, since the divergence of the lineage which led to modern man from the Hominoidea stock some 4 million years ago (20).

A clear distinction can be made between the Hominoidea, the Cercopithecoidea and the Ceboidea on the basis of the satellite III results. The fossil record and molecular evidence indicate that the Hominoidea as a group diverged some 24 million years ago from the Old World monkeys (Cercopithecoidea) whereas the New World monkeys separated some 5-10 million years before that (20,21). Therefore, the amplification event leading to the establishment of DNA satellite III in man and its homologous sequences in the other hominoids (as defined by the hybridisation criteria of 3 x SSC

at 65°C) occurred since divergence. Lowering of the stringency of hybridisation has shown that one can detect sequences homologous to human satellite III in the Cercopithecidae and that the hybridisation pattern obtained corresponds to the Hae III type pattern observed in the Hominoidea. Thus the ancestral sequence of human satellite III is at least 24 million years old.

Donehower et al. (9) have, by direct sequencing, compared the basic monomer repeat fragments from man, African green monkey and baboon. Although they can detect an overall pattern of similarity, the mismatch between the sequence present in man and the two Old World monkeys averages 33.19%. It is likely that the sequences examined by Donehower and those from the present series of experiments are the same, since human satellite III produces at 340 b.p. fragment when digested with EcoRI (22). Donehower and Gillespie (16) have suggested an evolutionary role for the repeating 170 base-pair periodicity in the primates and the present finding that the basic 170 b.p. repeat unit is conserved within the Hominoidea and Old World monkey groups, while the sequence within this repeat undergoes considerable change, is consistent with their proposal.

Little work has been carried out on the DNA of New World monkeys and our present results suggest to us that although ancestral sequences to human DNA satellite III can be detected in the three species of Ceboidae examined, the organisation of the sequences into the present-day structure took place after the lineages of the Old and New World monkeys diverged.

Satellite II

Earlier in situ data (1,3) indicated that human satellite II was absent from the chimpanzee, although it was detected in the chromosomes of the gorilla and orangutan (3). More recently it has been shown that DNA satellites II and III cross-react to some extent, although they can be distinguished on the basis of their restriction profiles (22). Our present results show that with the exception of man, DNA satellite II hybridises poorly to primate DNAs. The difference between these results, and those obtained by hybridisation in situ (3) is not immediately explicable, although several possibilities exist: in the previous studies, human satellite DNAs were prepared in conventional angle rotors, and the vertical rotor system gives preparations of a greater degree of purity (and rather different distribution in the gradient). The possibly greater contamination of satellite II with satellite III in the early preparations, however, does not explain the apparent absence of satellite II from

chimpanzee and its clear hybridisation to orangutan and gorilla chromosomes. Hybridisation in situ in some cases has clear differences in sensitivity from filter hybridisation (Mitchell, in preparation) in that a somatic cell hybrid with little satellite DNA detectable by filter hybridisation may have a clear site of hybridisation in situ, while a second hybrid containing different human chromosomes may show the presence of satellite DNA not detected by hybridisation in situ (23).

Since the parameters of hybridisation in situ are still, after 11 years, not entirely resolved, in any conflict the data from filter hybridisation are to be preferred. The fact that the hybridisation patterns produced show restriction profiles associated with the satellite III type sequence leads us to interpret them as duplexes formed with the satellite III equivalent sequences in these species. On this evidence we suggest that true DNA satellite II sequences are present only in man.

Satellite I

Satellites I and II are restricted to the superfamily Hominoidea and have evolved more recently than human DNA satellite III. The findings that these satellite DNAs are inter-related to each other to varying degrees (22) suggest the presence of 'core' satellite sequences within the primates as a whole. Hatch et al. (24) have suggested that satellite DNAs may have played an important role in the speciation of kangaroo rats (Dipodomys). Many primates contain homologous chromosomes although they do not contain the large blocks of repetitive DNA present in the chromosome arms of some kangaroo rat species. The presence of these heterochromatic regions was the basis of the model proposed by Hatch. It does appear, however, that the evolution of the major primate lineages seem to be associated with the amplification of certain satellite DNA sequences. Although these sequences may not themselves be playing an active role in the evolutionary mechanism, our results indicate that evolution of the primates is accompanied by divergence of their satellite DNA sequence.

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