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On the Mode of Evolution of Alpha Satellite DNA in Human Populations

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Summary. The hypothesis that highly reiterated satellite DNAs in present-day populations evolve by molecular mechanisms that create, by saltatory amplification steps, new long arrays of satellite DNA, and that such long arrays are used for homogenization purposes, has been tested both in mouse and in humans. In mouse, the data obtained are consistent with this hypothesis. This was tested in more detail on chromosomes 13 and 21 of the human genome. A Centre d'Etudes du Polymorphisme Humain family, which in some individuals exhibits strong supplementary DNA bands following TaqI restriction endonuclease digestion and conventional gel electrophoresis, was analyzed by pulse field gel electrophoresis following restriction by BamHI. The supplementary bands on chromosome 13 (18 times the basic alpha satellite DNA repeat) and on chromosome 21 (a 9.5-mer) segregated with centromeric alpha satellite DNA blocks of 5 and 5.3 megabases, respectively. These are by far the largest alpha satellite block lengths seen in all chromosome 13 and chromosome 21 centromeric sequences so far analyzed in this manner. The possibility that these supplementary alpha satellite sequences were created in single individuals by saltatory amplification steps is discussed in light of our own data and that published by others. It is proposed that deletion events and unequal cross-overs, which both occur in large satellite DNA arrays, contribute to the homogenization of size and sequence of the alpha satellite DNA on most chromosomes of humans.

Key words: Satellite DNA — Mouse — Human chromosomes 13 and 21 — Evolution — Saltatory amplification — Homogenization

Introduction

Most higher eukaryotes contain tandemly repeated sequences in their centromeric regions. These have been called satellite DNAs because they generally band at discrete densities in cesium gradients. In the mouse, the major light satellite DNA (Kit 1961) consists of a repeat unit of 234 bp (Southern 1975; Hörz and Altenburger 1981). This is present on every mouse chromosome, and no marked divergence in DNA sequence occurs between the satellite DNAs present on different chromosomes (Dod et al. 1989). In the human, five satellite DNAs, called I to IV and alpha, were originally isolated by gradient centrifugation (Singer 1982). As sequence data became available, it appeared that two broad classes of human satellite DNAs exist. The first consists of relatively short oligonucleotide tandem repeat units organized in long chromosome-specific arrays (Cooke 1976). The second, known as the alpha satellite, consists of 171-bp tandem repeats localized to the centromeric region of each human chromosome (Manuelidis 1978). Almost all chromosomes have, however, developed specific subset(s) of the basic repeats. These share only 70–80% homology with one another (Willard and Waye 1987), so that sufficiently stringent conditions will discriminate, via Southern blotting, the centromeric alpha satellite DNA sequences of each chromosome. Chro-

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mosomes 13 and 21, however, share an alpha satellite DNA subset with almost 100% homology and cannot therefore be discriminated from each other with the corresponding probe (Jorgensen et al. 1987). More recent studies have revealed a third human satellite family, the beta satellite, which is unrelated in structure and sequence to the former two (Waye and Willard 1989).

The role of these sequences, if any, is still obscure. In spite of this, many studies have been conducted to determine their genomic organization and to attempt to elucidate the molecular mechanisms involved in their amplification and concerted evolution (Dover 1982). Data we have published on mouse satellite DNA (Dod et al. 1989) led us to propose that when satellite DNA is amplified or homogenized, large blocks of satellite DNA, comprising hundreds or thousands of tandem repeats, could be involved.

In this paper, we show that as a necessary consequence of the above theory, a high variation in the size of the satellite DNA blocks among populations is found both in mouse and humans. In humans, saltatory amplification steps of alpha satellite DNA arrays, which were presumed to occur in single individuals, have been detected on both chromosomes 13 and 21. It is shown that the supplementary alpha satellite arrays cover large domains of several megabases (Mb). A model is proposed to explain the evolution of satellite DNA in present-day populations of mouse and humans.

Material and Methods

DNA Samples. Mouse livers from *Mus musculus domesticus* and *Mus spretus* individuals caught in the wild (F. Bonhomme's gift) were cut into small pieces with scissors and suspended in 10 ml PBS buffer (0.145 M NaCl, 0.76 mM $NaH_2PO_4 \cdot H_2O$, 2.24 mM $Na_2HPO_4 \cdot 7H_2O$, pH 7.2). These were sheared five times in a Potter-Elvehjem tissue grinder. The suspension obtained was centrifuged and washed with PBS two times at 8500 rpm, and the final pellet was resuspended in 1 ml PBS. The OD_{258} was measured by adding 10 µl of the vortexed suspension to 1 ml of 1% SDS. One OD_{258} unit was considered to correspond to a DNA concentration of 50 µg/ml. The concentration of cells was adjusted with PBS to give a final DNA concentration of 200 µg/ml in the agarose inserts. These were made by adding an equal volume of 1% Gel Pulse Agarose (Appligène, Illkirch, France) to the cell suspension with both the agarose and the cell suspension preheated at 50°C prior to mixing. The DNA inserts (10 µg DNA each) were treated in 0.5 M EDTA-Na_2, 1% lauryl sarcosyl with 0.5 mg/ml of proteinase K (Appligène) for 48 h at 50°C. The human DNA samples were prepared similarly after the tissue cultures obtained from CEPH (Centre d'Etude du Polymorphisme Humain) had been suspended in the same PBS buffer.

Pulse Field Gel Electrophoresis (PFGE). Prior to digestion with restriction enzymes, the DNA samples were thoroughly washed with TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0) followed by restriction buffer. Each agarose block was finally suspended in 150 µl of restriction buffer and 50–100 units of enzyme was added for every 10 µg of DNA. Digestion was performed overnight at the appropriate temperature.

The apparatus and pulsing device used for PFGE were the same as those already described in Marçais et al. (1990a). The particular conditions for each gel are indicated in the figure legends.

DNA Hybridizations. After electrophoresis, DNA samples were transferred to Hybond-N^+ membranes (Amersham), which were hybridized using the conditions given in Dod et al. (1989) for the mouse samples and in Marçais et al. (1990a) for human samples.

Results

Polymorphism of Satellite DNA Block Size in Mouse Populations

If the evolutionary scheme based on the amplification and differential homogenization of large blocks of satellite sequence we proposed (Dod et al. 1989) is valid, one should be able to detect a polymorphism related to these large satellite segments in mouse populations. We therefore collected mouse individuals in the wild from two species, *M. m. domesticus* and *M. spretus*. In these two species the satellite DNA is present at high reiteration levels, these being one million and fifty thousand times, respectively (Brown and Dover 1980). Using satellite DNA rare cutting enzymes (Marçais et al. 1990a), it is possible to release the satellite DNA blocks with few or no breaks. The resulting DNA fragments can then be resolved by PFGE (Schwartz and Cantor 1984) as shown in Fig. 1. The three individual DNAs presented here are representative of others not shown; they are all quite different from each other, with most of the bands unique to each individual. This polymorphism, which presumably reflects satellite DNA block size variations, is found in both species. It could be the consequence of the mechanisms of amplification and homogenization that are postulated to involve large blocks of satellite DNA, here represented by differences in length of several hundred kilobases (kb).

Polymorphism of Alpha Satellite DNA Block Size in Human Populations

For human genetic purposes (Marçais et al. 1990a,b) and also because it is difficult to study this phenomenon further in a species where it is not possible to distinguish individual chromosomes, we have analyzed in detail the same type of polymorphism in human populations on chromosomes 13 and 21.

Analysis of the DNA in a CEPH family by PFGE following restriction using the alpha satellite DNA rare cutting enzyme BamHI is shown in Fig. 2. This confirms our finding that the alpha satellite DNA

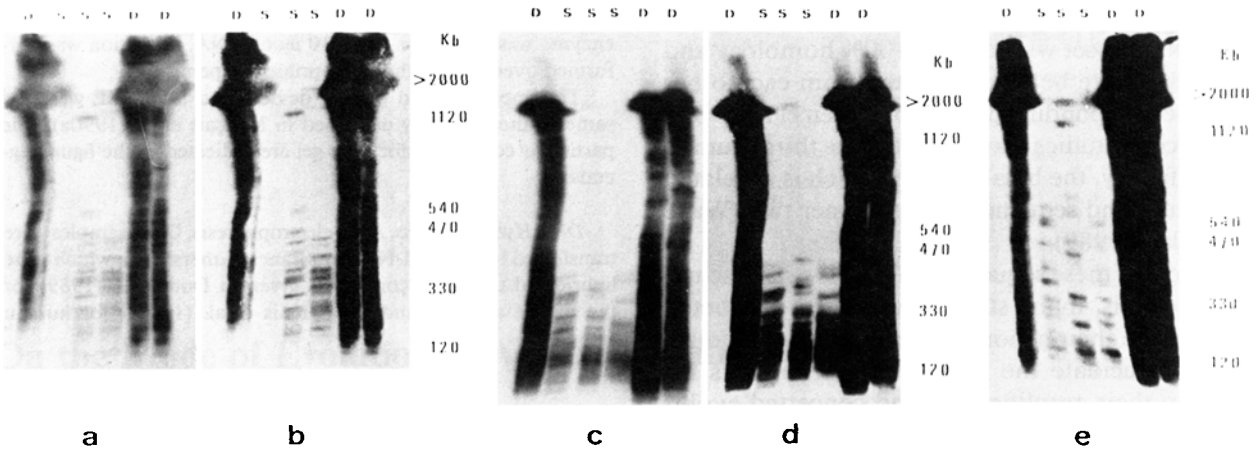

Fig. 1. Analysis by PFGE of the light satellite DNA in unrelated individuals of *M. m. domesticus* and *M. spretus*. The DNAs of three *M. m. domesticus* (D) and *M. spretus* (S) unrelated individuals were treated by EcoRI (a, b), HindIII (c, d), and BamHI (e). Completion of the reaction was checked in normal gel electrophoresis (not shown). As *M. m. domesticus* contains almost 20 times more satellite DNA repeats than *M. spretus* (Dod et al. 1989) it was difficult to simultaneously obtain clear patterns with both species. In less exposed autoradiographs however (a, c), it is possible to distinguish some bands that are different from one individual to the other, as is obvious in the *M. spretus* samples. Gel was 1% in agarose; pulse times were 110 s, 80 s, and 60 s for 18 h each.

block sizes are highly variable, with most individuals, if not all, being heterozygous at both centromeric loci (Marçais et al. 1990a). The Mendelian mode of inheritance is also confirmed in this family. This family was also analyzed with an alpha satellite DNA frequent cutting enzyme (TaqI) with which it also exhibited polymorphisms, one present on chromosome 13 and the other on chromosome 21 (Marçais et al. 1990b). This result, and linkage analysis with other markers from the CEPH data base, allowed us to assign the different DNA bands unambiguously to chromosomes 13 and 21 that were of paternal origins (Fig. 3). No marker was informative to assign similarly the DNA bands of maternal origin.

We do not yet have sufficient individual precise estimates of the alpha satellite DNA block sizes on both chromosomes 13 and 21 to draw a histogram representative of human caucasian populations. The data shown in Fig. 3 are, however, representative of others determined in the CEPH family analyzed in Marçais et al. (1990a) and others not yet published. Therefore, a number of observations can be made. First, the chromosome 21 centromeric sequence on which the 9.5-mer TaqI variant is found also contains by far the largest block of alpha satellite DNA yet seen. This appears to be greater than 5 Mb, 13 times the size of the smallest alpha satellite block (Marçais et al. 1990a). Secondly, the 9.5-mer supplementary band generated by TaqI is extremely intense compared to the normal 11-mer band, especially considering that it is generated from only one chromosome, whereas the 11-mer is from four. If their respective intensities in a single chromosome are compared, one can conclude that the supplementary domain contained in this chromosome is large, probably on the order of several Mb. The above also holds with the supplementary domain in chromosome 13, which is likewise not interspersed with the normal 11-mer domain, and which is tentatively represented by the bands shown in Fig. 2. This also segregates with a large alpha satellite DNA block of presumably about 5 Mb.

Discussion

The hypothesis we made (Dod et al. 1989) concerning the molecular mechanisms at the basis of the amplification and homogenization of satellite DNAs in the present-day mouse and human populations has been tested against experimental data.

We first verified that in mouse populations the DNA fragments generated from the centromeric DNA blocks by satellite rare cutting enzymes were, indeed, highly variable in size between nonrelated individuals. This was as expected from the above hypothesis. It does not establish validity of the hypothesis, but it is prerequisite to any further investigation. If only small length variations were found it would have been necessary to conclude that unequal crossing-over by one or a few monomers of the basic repeat is the main basis of the present-day evolution of these tandemly repeated sequences, as is often postulated.

After treatment with alpha satellite rare cutting enzymes, the DNA from individuals belonging to a CEPH family, in which TaqI variants on chromosomes 13 and 21 had been previously shown to occur, was analyzed by PFGE. The supplementary

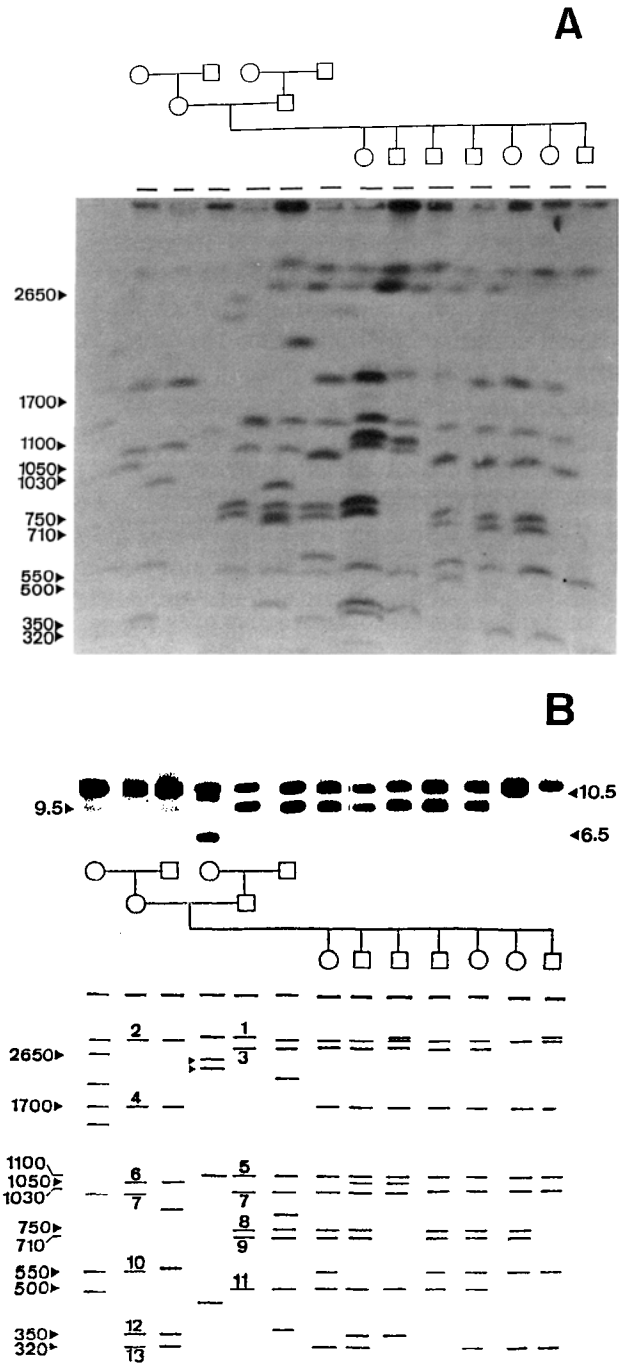

Fig. 2. A Analysis by PFGE of DNA from the CEPH family cut by BamHI for chromosome 13 and 21 centromeric alpha satellite DNA sequences. Gel was 1% in agarose; pulse times were 150 s, 120 s, and 90 s for 18 h each. The PFGE DNA bands obtained in A are schematically represented in **B**. The polymorphisms exhibited by the same samples when digested with TaqI, as described in Marçais et al. (1990b), are shown in the upper part of this diagram. The DNA bands (1–13) of paternal and maternal origins are only indicated in B. The two bands that are tentatively considered to contain the supplementary domain of chromosome 13 are indicated by arrows.

bands, which are 18 times (18-mer) and 9.5 times (9.5-mer) the 171-bp alpha satellite basic repeat unit, respectively, have been shown by Marçais et al. (1990b) to represent supplementary domains. These

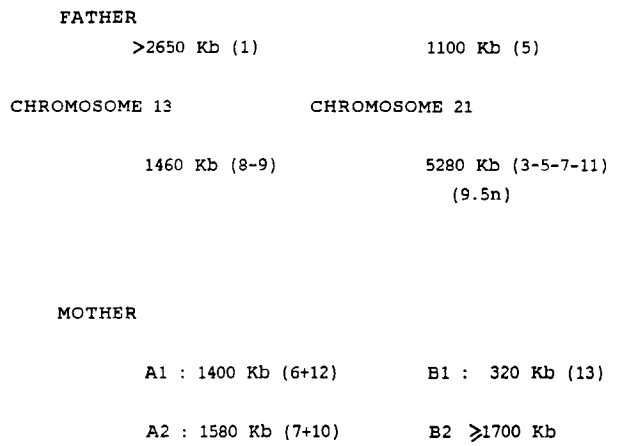

Fig. 3. Lengths of the different alpha satellite blocks of the father and mother of this CEPH family. The segregation of chromosomes 13 and 21 were determined by linkage analysis using the CEPH data base. The B2 maternal allele is at least 1700 kb long, bands 2 and 4 being not attributable precisely.

are separate from the normal 11-mer domain, which is common to all other chromosome 13 and 21 centromeric sequences. In this CEPH family, the 18-mer and 9.5-mer domains segregate together with the largest centromeric alpha satellite alleles of chromosomes 13 and 21 we have found so far, these being 5 and 5.3 Mb, respectively.

This allows us to conclude that these supplementary alpha satellite domains represent very long arrays of units of a higher order (18-mer and 9.5-mer), similar to the normal 11-mer higher order unit.

If one follows the general belief that unequal crossing-over is the basic mechanism for the increase in copy number of satellite DNAs, one expects that these 18-mer and 9.5-mer variants will be shared by a large proportion of the population in which they are detected, and that intermediate levels of amplification will also be found. This is not the case, as the 9.5-mer variant has been detected only twice in the CEPH panel representing 320 independant chromosome 21 centromere sequences (Warren et al. 1990). It has never been found in about 50 other nonrelated individuals examined (Marçais et al. 1990b).

We can, therefore, conclude that the supplementary 9.5-mer variant domain on chromosome 21 has been generated in a single individual ancestral to the grandfather of this CEPH family. A second saltatory event of the same type might have occurred in another individual ancestral to the second family of the CEPH panel which exhibits it, unless the two families, which have been recruited in the Paris area, are actually related to each other.

The same probably holds for the supplementary 18-mer variant domain on chromosome 13. Although it was detected in a fairly high proportion of the caucasian population studied (around 10%),

no intermediate levels of amplification were detected (Marçais et al. 1990b).

We must add, moreover, that the 18-mer and 9.5-mer domains are not interspersed with the normal 11-mer domains found on chromosomes 13 and 21, a situation not expected if unequal crossing-overs were acting frequently to generate new copies of alpha satellite DNA. This is again consistent with the saltatory amplification steps we postulate to occur in single individuals.

The saltatory generation of supplementary satellite arrays we have found is supported also by cytogenetic evidence from the literature, which also suggests that it is still acting in present-day human populations. In several reports, it has been shown that the amount of heterochromatin can greatly increase or decrease in children derived from parents with normal-sized heterochromatin blocks (Craig-Holmes et al. 1975; Seabright et al. 1976). Recently, molecular cytogenetic evidence of alpha satellite sequences specific to chromosome 6 has been reported in two individuals with 2- and 2.5-fold increases in their alpha satellite DNA content (Jabs and Carpenter 1988). Similarly, an exceptionally large short arm on chromosome 14 was shown to contain 4–5 times more alpha satellite DNA sequences than normal, indicating a saltatory step of amplification in this individual (Dale et al. 1989). Separate supplementary alpha satellite domains have also been detected in other chromosomes. This is true for chromosome 1 (Waye et al. 1987a), chromosome Y (Tyler-Smith and Brown 1987), chromosome 7 (Waye et al. 1987b), and also for all acrocentric chromosomes (Choo et al. 1989, 1990) in which variants of higher order units or of the basic DNA sequence are tandemly repeated in single separate arrays several hundred kilobases long.

We propose, therefore, that this saltatory amplification step is not restricted to the examples we have shown here, but that it is general to all centromeric sequences of the human genome, and presumably also to all centromeric sequences of the mouse genome.

Regarding the molecular mechanisms that would lead to the homogenization of satellite DNAs within populations, and therefore to their concerted evolution, one has to take into account two major facts. First, the differences in size found between the alpha satellite DNA blocks on chromosomes 13 and 21 are large, being several hundred kilobases in length, and sometimes more. Also, it is obvious from the analysis of this family and others (Marçais et al. 1990a) that generally the homologous sequences on chromosomes 13 and 21 that pair with each other are extremely different in size with respect to their centromeric alpha satellite sequences. The consequence of this in potential unequal cross-overs at

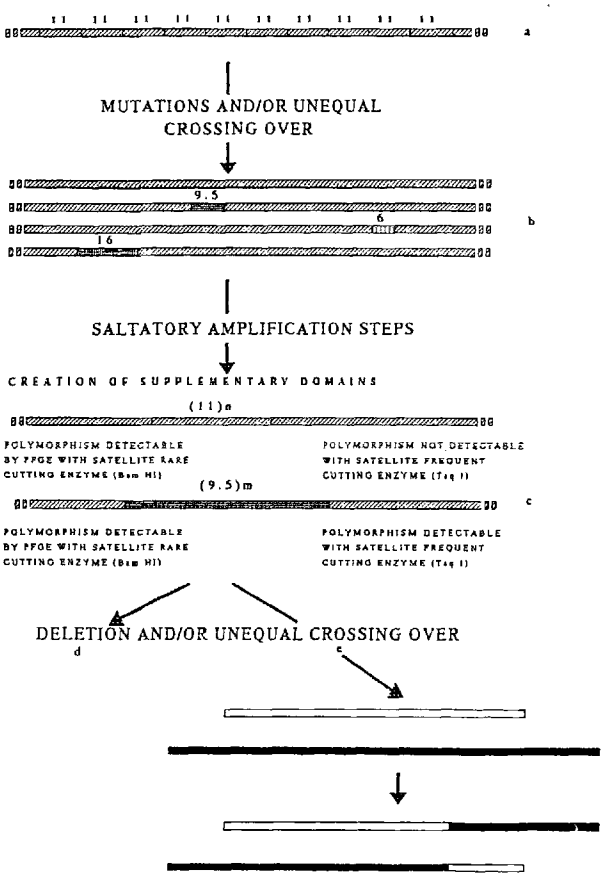

Fig. 4. Evolution of alpha satellite DNA centromeric sequences on chromosome 21 in present-day human populations. The model is presented with the example of chromosome 21, but holds, in its principles, for chromosomes 13 and probably for all other human chromosomes, with peculiarities discussed in the text for the Y chromosome. **a** All human alpha satellite DNA blocks of chromosome 21 consist of hundreds to thousands of a higher order unit that is 11 times the 171-bp basic repeat. These blocks are variable in lengths by several hundred kilobases. **b** Occasionally either a mutation or unequal crossing-over will create a higher order unit different from the normal 11-mer one. The population of chromosomes 21 alpha satellite DNA is therefore composed of long arrays of tandemly repeated 11-mers of variable lengths, with occasional and randomly spread repeat length(s) deviating from the norm (here 9.5, 6, and 16 as examples). **c** Saltatory amplification steps occur in single individuals with a frequency that is impossible presently to estimate. A supplementary alpha satellite DNA domain will be created that will contribute to the polymorphism of block sizes detectable by PFGE. Rarely, however, the amplification step may involve one of the variants that has been generated as described in b. When such a variant becomes amplified (here the 9.5-mer) a polymorphism will be detected by alpha satellite frequent cutting enzymes (here TaqI). The exact molecular mechanism responsible for these saltatory amplification steps is not known, but it could be, for example, comparable to the rolling circle amplification process (Hourcade et al. 1973) known to occur in ribosomal genes. **d** Deletion events will counterbalance the otherwise indefinite expansion of alpha satellite DNA and/or **e** unequal cross-overs will allow the homogenization of alpha satellite in both block sizes and sequence.

meiosis I is that several hundred kilobases of alpha satellite DNA could pass from one homologous chromosome to the other. This could cause homogenization of block size, and eventually of sequence, if conversion events were associated. It is, however, not possible to estimate the rate of such events in centromeric regions of chromosomes as there is only the general belief that they are suppressed (Charlesworth et al. 1986). Second, as indicated above, a deletion mechanism is also acting. This may prevent centromeric constitutive heterochromatin from becoming so large that it perturbs the sequence of centromere separation, as has been postulated by Vig (1983). The consequences of this would be to contribute, again, to the homogenization of the satellite block sizes. This could also allow homogenization of the sequence itself, if one postulates, and this is pure speculation, that the more divergent alpha satellite arrays will be preferentially eliminated by this process.

It should be interesting, too, to discuss the role of genetic drift in finite populations (Ohta 1983) but in the absence of real data, it is impossible to compare the contribution of this process to that of meiotic crossing-over. We present a model in Fig. 4, which accounts for the facts and hypotheses that have been shown and discussed in this paper.

The size distribution of alpha satellite DNA on the Y chromosome, shown by Oackey and Tyler-Smith (1990) is extremely interesting when compared to that found on chromosomes 13 and 21. In the Y chromosome, the sizes cluster in two separate peaks with mean lengths of 300 and 900 kb, which are quite small compared to what we have found. This confirms the finding that Y chromosomes have no detectable centromeric constitutive heterochromatin (CCH) (Vig 1983) and have small kinetochores (Peretti et al. 1986; Cherry and Johnston 1987). There may be cytogenetic reasons preventing the saltatory amplification steps from occurring too frequently on Y chromosomes and likewise preventing them from involving very large new arrays of alpha satellite DNA. It is striking to note, moreover, that the 42 different Y chromosomes analyzed in the study of Oackey and Tyler-Smith (1990) have a distribution of size increments of about 50 kb. This could be easily explained by the fact that a Y chromosome will never meet another Y except in sister chromatid exchanges in which two identical chromosomes pair. This could also explain the differences in size variation between the Y chromosome and chromosomes 13 and 21.

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