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Analysis of Distribution in the Human, Pig, and Rat Genomes Points toward a General Subtelomeric Origin of Minisatellite Structures

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We have developed approaches for the cloning of minisatellites from total genomic libraries and applied these approaches to the human, rat, and pig genomes. The chromosomal distribution of minisatellites in the three genomes is strikingly different, with clustering at chromosome ends in human, a seemingly almost even distribution in rat, and an intermediate situation in pig. A closer analysis, however, reveals that interstitial sites in pig and rat often correspond to terminal cytogenetic bands in human. This observation suggests that minisatellites are created toward chromosome ends and their internalization represents secondary events resulting from rearrangements involving chromosome ends.

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INTRODUCTION

Tandem repeats are classified, according to the overall size of the repeat sequence, among satellites (largest, megabases long), minisatellites (in the kilobase size range), and microsatellites (10 to 40 nucleotides long). Satellite DNA is preferentially associated with centromeric heterochromatin, and microsatellites are distributed throughout the genome. Similarly, in the mouse (Jeffreys et al., 1987; J ulier et al., 1990; Mariat et al., 1993), bovine (Georges et al., 1991), and rat genomes (Pravenec et al., 1996) at least, minisatellites are spread over the genome. In contrast, the minisatellites characterized so far in human show a marked clustering in the terminal cytogenetic bands of each chromosome (Royle et al., 1988; Wells et al., 1989; Vergnaud et al., 1991).

This apparent discrepancy may be an artifact due to the cloning procedures that have been used: clustering in human is suggested by a variety of independent approaches performed in different laboratories, whereas the work in the mouse, rat, and bovine relies in each case essentially on a single approach. Furthermore, a very limited number of the supposed minisatellites detected (Jeffreys et al., 1987; J ulier et al., 1990; Mariat et al., 1993) or cloned (Georges et al., 1991) from animal genomes have been characterized at the sequence level to confirm their minisatellite nature. Alternatively, this discrepancy could reflect differences in the evolutionary forces that shape mammalian genomes.

To investigate this issue, we cloned minisatellites in human, pig, and rat using identical techniques and compared their chromosomal localization in the three genomes. Clones containing minisatellites were identified in genomic libraries using both synthetic tandem repeats as screening probes (Vergnaud et al., 1991) and a new procedure that is based only on the structural characteristics of the minisatellites and does not require a hybridization step. The cosmids were assigned to a cytogenetic band by in situ hybridization assisted when appropriate by linkage analyses. Striking differences were observed in the distribution patterns of these sequences, with subtelomeric clustering confirmed in human, a majority of internal loci in the rat,
and an intermediate situation in pig. The comparative mapping of the minisatellite-containing regions in the three genomes is consistent with the hypothesis that minisatelites have a subtelomeric origin. These results underline the interest of minisatellites for comparative genome analysis.

**MATERIALS AND METHODS**

**Minisatellite Cloning**

Cosmid clones from commercially available libraries (Clontech Refs. HL 1145y, RL1032m, and PL1008m for human, rat, and pig, respectively, on pWE15 vector) were plated at a low density and picked in 96- or 384-well microtiter plates. Replicas were made on nylon filters with a comb.

Procedure without hybridization screening. The clones were grown individually in 2-ml LB medium cultures with shaking at 37°C. After 20 h growth, 24 cultures were pooled, and the cosmid DNA was extracted by the alkaline SDS lysis method as described in Sambrook et al. (1989). The cosmid DNA pools were suspended in 300 µl of 10 mM Tris, pH 8, 1 mM EDTA (TE).

Procedure with hybridization screening using synthetic tandem repeat probes. This procedure was described in detail in Vergnaud et al. (1983). The synthetic probes used were 13C1, 14C3, 14C5, 14C21, 14C24, 14C31, 15C3, 16C4, 16C7, 16C17, 16C20, 16C22, 16C23, 16C24, 16C26, and 16C27. DNA from positive clones was extracted by the alkaline SDS lysis method from 50 ml MLS (Sambrook et al., 1989) medium culture and suspended in 300 µl of TE. In both procedures, three aliquots of 20 (for pools of clones) or 1 µg (for individual clones) of cosmid DNA were digested respectively with the restriction endonucleases AluI and HaeIII, AluI and Hinfl, and Hinfl and HaeIII in a total volume of 100 µl following the supplier's instructions (New England Biolabs or Appligene). After an overnight digestion, the samples were ethanold precipitated, suspended in 5 µl of TE, and loaded for electrophoresis on a 1% horizontal agarose gel. The gel was then stained with ethidium bromide. Fragments above 1.5 kb (from pools) or above 1 kb (from individual clones) were sliced out of the gel and recovered by centrifugation as described by Heery et al. (1990). One to five nanograms of insert DNA was then directly [32P] labeled by random priming (Feinberg and Vogelstein, 1983) ([32P]dCTP from New England Nuclear). One to five nanograms was hybridized in presence of an excess of sonicated rat genomic competitor DNA (200 µg/ml) and salmon sperm DNA (100 µg/ml) and prehybridized for 3 h at 37°C. In situ hybridization, detection of the signals, and interpretation of the results were performed as described previously (Yerle et al., 1992).

**Minisatellite Subcloning and Sequencing**

Minisatellite inserts were subcloned into PUC 18 or 19 and partially sequenced from both ends using [32P]-labeled universal and reverse M13 primers and the cycle sequencing kit deltaTaq from USB/Amersham.

**Identification of Conserved Regions**

Restriction fragments from pig cosmids were purified from agarose gel as described before and used as probes to screen a human chromosome 1 library obtained from the Max-Planck Institute for Molecular Genetics: c112 Reference Library, ICRF (Lehrach, 1990). This library consists of two high-density gridded filters of 20,000 clones on each membrane. Each clone is named by the number of the library, c112, and a specific number (for example, c112 F0525). Hybridization on the library filters was at 60°C as described by Vergnaud (1989). Cross-hybridizing fragments from the human cosmids were identified by hybridization with the pig fragments on restriction digests of human cosmids.

Conserved fragments from both species were subcloned in PUC 18 or 19 and sequenced as described before. Direct (universal) and reverse M13 primers were used for sequencing of both ends, and specific primers were ordered to continue the sequence reaction. The accession numbers of the sequences generated in the course of this project are AJ001115 to AJ001156.

**RESULTS**

**Cloning of Minisatellites**

Minisatellites were isolated from human, pig, and rat cosmid libraries by two procedures. The first procedure screens cosmid libraries with synthetic tandem repeat probes (Vergnaud, 1989) and the second ("large fragment procedure") does not need a hybridization step (see Materials and Methods). Briefly, hybridization-selected individual cosmids or pools of random cosmids are digested with two frequently cutting restriction enzymes, and fragments above 1 kb (from hybridization-selected cosmids) or 1.5 kb (from pools of random cosmids) are tested by Southern blot hybridization for the presence of a minisatellite.

The number of minisatellites isolated with each method is given in Table 1. Sixty-six, 34, and 43 minisatellites were isolated from human, pig, and rat, respectively, using this procedure.
satellites were isolated from human, pig, and rat libraries, respectively. The efficiency of the large fragment procedure varies from one species to another, with yields of 0.72% in human, 0.41% in rat, and only 0.2% in pig.

The efficiency of synthetic probes is different in the three species. Probes allowing the detection of minisatellites were $13C_1$, $14C_{21}$, $16C_2$, $16C_4$, $16C_{17}$, and $16C_{27}$ in human; $14C_{24}$, $15C_3$, $16C_2$, $16C_7$, $16C_{22}$, $16C_{23}$, $16C_{24}$, and $16C_{26}$ in pig; and $13C_1$, $14C_3$, $14C_5$, $14C_{31}$, $16C_2$, $16C_4$, $16C_{17}$, $16C_{20}$, $16C_{24}$, and $16C_{27}$ in rat. The most successful STR probes in the detection of minisatellites were $16C_{27}$ in human and $16C_{23}$ and $16C_{26}$ in pig, allowing the detection of 14, 6, and 6 minisatellites, respectively.

**Identification of Minisatellite Structures and Sequences**

The fragments detected were identified as minisatellites according to their hybridization pattern on Southern blots, i.e., a strong hybridization as expected for a tandem repeat probe. To confirm minisatellite structure, we subcloned and sequenced 20, 15, and 15 fragments from human, rat, and pig, respectively. A tandem repeat structure is observed in the three species for each fragment sequenced. In all but four cases, a repeat unit, with length ranging from 9 to 128 nucleotides, can be defined. Four fragments detecting multilocus hybridization patterns on Southern blots even under high stringency conditions are composed of successive di-, tri-, or tetranucleotide repeats interspersed with a large number of variant repeats. Consensus sequences of four minisatellites from each of the three species are presented in Table 2, together with the length of the repeat unit and internal variations among units. The majority of variants is due to transition events (represented by letters Y and R). Transversions (S, K, or W) and sometimes three possible variants at the same position (represented by letters D, H, V, and B) are also observed. The number of variant sites in repeat units differs between the minisatellites from 2 variants/51 nucleotides in human minisatellite CEB84 and 30 variants/50 nucleotides in pig minisatellite ADGE S1. A length heterogeneity of the units resulting from insertion/deletion is sometimes observed [repeat (AGGG), in CEB1].

**Chromosomal Assignment of the Minisatellite Loci**

The cosmids were assigned to a cytogenetic band by a combination of fluorescence in situ hybridization (FISH) and segregation analyses. This second approach was most appropriate for human loci because a physical assignment of highly polymorphic loci can usually be deduced from segregation data of CEPH families (Spurr et al., 1994) and the knowledge of the physical assignment of close-by markers (Bray-Ward et al., 1996) from the CEPH database. Thirty-nine, 33, and 34 cosmids were mapped by FISH in human, pig, and rat, respectively.

**TABLE 1**

<table>
<thead>
<tr>
<th>Species</th>
<th>Number of minisatellite-containing cosmids isolated</th>
<th>Number of cosmids localized by FISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>Pig</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>Rat</td>
<td>15</td>
<td>34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>Number of minisatellite-containing cosmids isolated</th>
<th>Number of cosmids localized by FISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>36 (5000)</td>
<td>39</td>
</tr>
<tr>
<td>Pig</td>
<td>7 (3500)</td>
<td>33</td>
</tr>
<tr>
<td>Rat</td>
<td>28 (7400)</td>
<td>34</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Name$^a$</th>
<th>Unit sequence$^b$</th>
<th>Unit length$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEB 1</td>
<td>GRGGGAGGAGGAGGGG</td>
<td>37–43 bp</td>
</tr>
<tr>
<td>CEB 8</td>
<td>GGGGRAGBDT</td>
<td>10 bp</td>
</tr>
<tr>
<td>CEB 62</td>
<td>AYCTRCCCRGGS</td>
<td>30–31 bp</td>
</tr>
<tr>
<td>CEB 84</td>
<td>GTCTACACGTGGGGG</td>
<td>51 bp</td>
</tr>
<tr>
<td>ADGE S1</td>
<td>AYWGWGKTYTBBYYC</td>
<td>49–50 bp</td>
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<tr>
<td>ADGE S2</td>
<td>GGACTGGRGGCRGGAC</td>
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</tr>
<tr>
<td>ADGE S12</td>
<td>HAGITTCAGGCTAGT</td>
<td>19–20 bp</td>
</tr>
<tr>
<td>ADGE S40</td>
<td>T(Y)AGARRR(J)GCGGWGTGTCTCYCTTCAGCCYGGGG(G)TYC(Y)</td>
<td>35–40 bp</td>
</tr>
<tr>
<td>CEB R10</td>
<td>CCC(AAT)AT</td>
<td>5–8 bp</td>
</tr>
<tr>
<td>CEB R15</td>
<td>AYBGKGBH(CJ)TICC</td>
<td>11–13 bp</td>
</tr>
<tr>
<td>CEB R21</td>
<td>AGYRCCASRGYRYRR</td>
<td>16 bp</td>
</tr>
<tr>
<td>CEB R31</td>
<td>DTYCTGCAAGGGAGGYGTCC(G)AKTGAGA</td>
<td>28–29 bp</td>
</tr>
</tbody>
</table>

$^a$ Minisatellite name (CEB, human minisatellites; CEB R, rat minisatellites; ADGE S, pig minisatellites).
$^b$ Sequence of the elementary unit of the minisatellite loci. Variant positions are underlined. (R = A or G; Y = C or T; M = A or C; K = G or T; S = G or C; W = A or T; H = A, T, or C; B = G, T, or C; D = G, A, or T; N = A, G, C, or T; V = G, A, or C; IUB coding rules). The sequence presented is a consensus sequence deduced from the sequence of different motifs.
$^c$ Observed length of the different units.
Chromosomal localization of minisatellites loci on human (A), pig (B), and rat (C) chromosomes (Giemsa banding). Minisatellites localized by both FISH and linkage analyses are represented by black circles. Minisatellites localized only by linkage analysis to physically assigned polymorphic markers are represented by open circles. The two loci represented at the tip of the short arm of the X chromosome are within the X–Y pseudoautosomal region and are also represented at the tip of Yp.

**FIG. 1.** Chromosomal localization of minisatellites loci on human (A), pig (B), and rat (C) chromosomes (Giemsa banding). Minisatellites localized by both FISH and linkage analyses are represented by black circles. Minisatellites localized only by linkage analysis to physically assigned polymorphic markers are represented by open circles. The two loci represented at the tip of the short arm of the X chromosome are within the X–Y pseudoautosomal region and are also represented at the tip of Yp.
human loci), 1B (pig loci), and 1C (rat loci). A prominent subtelomeric clustering of the minisatellites is a common feature of a chromatid pair of human and pig genomes. In human, 59 among 66 loci isolated (90%) are in the terminal cytogenetic band of a chromosome. Of 23 terminal human bands with minisatellites, 10 are “major clusters,” which we define as the presence of three or more minisatellites. These 10 terminal bands alone contain 60% of minisatellites reported here. The most striking cluster is found on chromosome 1p36.3. The lower proportion of subtelomeric minisatellites in pig (23 of 34; 66%) results from a few interstitial clustered or isolated loci (on chromosomes 5, 6, 7, 8, 10, 12, 13, and 17). In the rat genome, the situation is different, with a much lower rate of terminal band clustering (30%).

**Comparative Localization of the Minisatellites in the Three Genomes**

**Human–Pig Comparison**

Chromosome 6 alone accounts for 3 of the 11 interstitial sites detected in pig. Interestingly, the physical assignment of the minisatellite cluster at 6q21–q22 corresponds to the position of an ancestral chromosome fusion event with remnants of telomere arrays (Gu et al., 1996). The proximal side of the fusion event is homologous to part of human chromosome 1p36, and the distal side is homologous to human chromosome 1p36–p33 as deduced from heterologous chromosome painting experiments (Goureau et al., 1996) and a number of gene assignments (Yerle et al., 1997). We have identified conserved regions within cosmids containing the pig chr 6q minisatellites to characterize more precisely the homology between pig chr 6q minisatellite loci and human (Fig. 2).

The different fragments obtained after an EcoRI digestion of the four pig cosmids containing minisatellites ADGE S26, S37, S16, and S3 were used to screen a human chromosome 1 cosmid library at moderate stringency. Clones giving a hybridization signal with at least two fragments from the same pig cosmid and no signal with fragments from another cosmid were selected. No clone satisfying this criterion was obtained when fragments from the ADGE S26 cosmid were used. In the three other cases, cross-hybridizing fragments were identified and sequenced, and the human homologous cosmids were assigned to a chromosome 1 cytogenetic band by FISH.

Following is a characterization of the conserved sequences.

**Minisatellite Cloning**

Minisatellite cloning in the human, pig, and rat genomes. The combination of two independent procedures was highly efficient for the cloning of these loci from genomic cosmid libraries. The method involving synthetic tandem-repeat hybridization probes has already proved its efficiency in detecting polymorphic loci in complex genomes (Mariat and Vergnaud, 1992) and was initially tested on a smaller scale for the cloning of such loci in human (Vergnaud et al., 1991). The species-specific efficiency of a given synthetic probe in minisatellite cloning in the human, rat, and pig genomes parallels our earlier observations on Southern
blots of genomic DNA in a larger range of species (Mariat et al., 1992) and might indicate the existence of species-specific minisatellite families. The second method uses a repeat structure criterion and avoids the selection bias introduced by cross-hybridization. This method showed different isolation efficiencies for human, rat, and pig (0.7, 0.4, and 0.2%, respectively, of the cosmid clones analyzed; Table 1), suggesting that the frequency of minisatellites is highest in human or, alternatively, that on average human minisatellite alleles are longer.

Results reported here are in agreement with earlier ones conducted in human and suggesting minisatellite clustering in subtelomeric regions of human chromosomes (Royle et al., 1988; Vergnaud et al., 1991, 1993). Because the same methodology was here applied in a single laboratory to the three genomes, it is clear that the distribution of minisatellite localizations reported now is not an artifact introduced by cloning bias. Three different situations are observed, with 90% of subtelo-
meric clustering for human minisatellite loci, 66% for pig loci, and only 30% for rat loci. In addition, we demonstrate that minisatellites are not found equally at all chromosome ends. In this respect, human 1pter is most remarkable compared to 1qter. It may be relevant to note that 1p36 is a very strong T band (Dutrillaux, 1973) characterized by a high concentration of H3 isochores, CpG islands, and genes (Saccone et al., 1996; Zoubak et al., 1996). The much more homogeneous distribution of minisatellites observed in rat would then also be correlated with GC level, which is distributed more homogeneously in rodent chromosomes (Sadou et al., 1993). However, a number of discrepancies exist between the location of minisatellite clusters (for instance human 6qter is a minisatellite cluster; Fig. 1) and the location of T bands (6qter is not a T band; Dutrillaux, 1973). More generally, what is the reason for the relative paucity of minisatellites at some chromosome ends: does it reflect a more recent telomeric location or rather a specific behavior of some subtelomeric domains promoting the creation of minisatellites (either at a higher density or at a comparable density in a larger domain). Further studies and especially sequencing of a number of subtelomeric regions may help address these issues.

Comparative Analysis of Minisatellite-Containing Regions

Comparative gene mapping data available show a correspondence between pig interstitial minisatellite-containing regions and human chromosome extremi-

**FIG. 3.** Comparative mapping between rat chromosome 1 and human and mouse chromosomes. (a) Localization of rat minisatellites (represented by black circles) by FISH. (b) Localization of rat minisatellites (small black circle and name R-) among genes as determined by linkage analysis. Genetic distances in cM between minisatellites and closest genes are indicated. (c) Localization of the homologous genes in human (physical localization). (d) Localization of the homologous genes in mouse (genetic localization: on the right of the black line are gene names and chromosome numbers and on the left the position of the gene in centimorgans on the genetic map). The relative positions of genes in human and mouse were obtained from NCBI (http://www.ncbi.nlm.nih.gov/SCIENCE 96/) for human and from The Jackson Laboratory (http://www.jax.org/) for mouse.
ties. The genes RNR2 and VWF (Von Willebrand Factor) localized respectively on pig chr 10p12–p13 and chr 5q21 (Miyake et al., 1988; Sjoberg et al., 1996) in the vicinity of interstitial pig minisatellites (Fig. 1) map on human terminal bands on chromosome 14p12 and chromosome 12p13.3, respectively (the VWF gene is also subtelomeric in cattle (chr 5q35), sheep (chr 3q35), and goat (chr 5q35); Janel et al., 1996).

Pig chromosome 6 results from a telomeric fusion between two chromosomes (Gu et al., 1996). Heterologous painting experiments (Rettenberger et al., 1995; Goureau et al., 1996) and comparative gene mapping reveal that the two extremities involved are homologous with human chromosome 1p and chromosome 19q (Fig. 2). Pig minisatellites ADGE S26 and ADGE S37 are localized in the band containing the telomere fusion between the two synteny groups, and the human homologue of the ADGE S37 locus is indeed located in 1p36, showing that the pig interstitial chromosome 6 minisatellite cluster is conserved syntenically with the human chromosome 1pter minisatellite cluster. Strikingly, the human homologue of the 6pter pig cosmid containing minisatellite ADGE S3 is located at 1p31–p32, from which we independently characterized a minisatellite locus (Fig. 1).

Although the situation in rat is expectedly much more complex, results from the localization of rat minisatellites provide further support for the hypothesis of a subtelomeric origin of minisatellite loci. As a general rule, comparative analysis between human and rat genomes is hampered by the paucity of mapped genes in rat (Bihoreau et al., 1997) and by the large number of chromosomal rearrangements between rodent and human genomes. The number of conserved segments between human and mouse is estimated to be at least 180 (DeBry and Seldin, 1996), whereas it is estimated at less than 50 between human and pig (Rettenberger et al., 1995; Goureau et al., 1996). Comparative mapping of genes in human, mouse, and rat chromosomes X showed the extent of complex rearrangements within a single chromosome (Millwood et al., 1997). The rat chromosome 1 provides a good model for comparative mapping and chromosomal evolution because it is the longest rat chromosome (about 10% of the genome), and the presence of susceptibility loci for multifactorial diseases (Gauguier et al., 1996) has led to a dramatic improvement in the density of the linkage map (Bihoreau et al., 1997).

There is evidence of conservation between rat chromosome 1 and mouse chromosome 7 with an inversion of a segment at the extremity of mouse chromosome 7 (genes Drd4 and Igf2). Starting from the extremity of the long arm, rat chr 1 is homologous to segments from human chromosomes 10q24–q25, 11q12–q13, 11p15.5, 10q25q26, 16p13.1–p11, 11p15, and 19q13. R30 is located between PygM and Cyp2c12, which are on two different chromosomes in human. Moreover, minisatellite loci R10 and R15 are located immediately proximal and immediately distal to the two genes Drd4 and Igf2, which are in the terminal 11p15.5 human band.

This collection of observations, together with the striking distribution of minisatellites in human, supports the hypothesis of a subtelomeric formation of minisatellites followed by internalization through chromosomal rearrangements. This hypothesis predicts that interstitial minisatellites are markers of ancestrally telomeric regions of the genome. Not exclusively, one could postulate movements of minisatellites within the genome by a number of mechanisms, as reported, for instance, in Wong et al. (1990), Eichler et al. (1996), and Monfouilloux et al. (1998). However, the events described in these reports produce duplications, triplications, etc., of relatively small domains (less than a few hundred kilobases in Monfouilloux et al. (1998) and 26 kb in Eichler et al. (1996)), whereas the interstitial pig minisatellite cluster on chromosome 6 described here is part of a very large conserved segment between human and pig and has not been duplicated. Interestingly, in the two independent examples reported in Wong et al. (1990) and Eichler et al. (1996), one of which contains a minisatellite, the ancestral site of the transposition event is telomeric (at respectively 6pter and Xq28) and both target sites are within band 16p11.

No general function has been attributed to minisatellites, but some of them do have a biological role. They can be coding sequences (Boguski et al., 1986; Paulsson et al., 1992) or regulatory elements (Krontiris et al., 1993; Bennett et al., 1995). The abnormal expansion of a minisatellite can create a fragile site (Virtanen et al., 1997; Yu et al., 1997). The analysis of neomutated alleles at other, nonpathological hypermutable minisatellites has shown that they evolve predominantly by gene-conversion-like mechanisms, presumably initiated by double-strand breaks (Buard and Vergruen, 1994; Jeffreys et al., 1994), whereas microsatellites most likely mutate by replication slippage mechanisms (Heale and Petes, 1995). Therefore, a good knowledge of domains in which minisatellites are likely to be found within the human genome may accelerate the identification of genetic disorders associated with this type of tandem repeat element.

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