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# Human Satellite III DNA: Genomic location and sequence homogeneity of the TaqI-deficient polymorphic sequences

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**Abstract.** Human Satellite III DNA is a major tandem repeat in the human genome and presents a TaqI-specific hypervariable restriction fragment length polymorphism when a Satellite III related sequence (228S) is used as a probe. In situ examination shows this sequence to be near specific for the region 9qh on chromosome 9 when it is used at low probe concentrations. However the region 9qh does not appear to be the only or even the primary source of the TaqI-deficient polymorphic sequences (TDPS). Rather, such sequences appear to be mostly present in chromosomes 20, 21, and 22, and these represent the largest regions of homogeneous Satellite III in the genome; they are also resistant to digestion with a range of other restriction endonucleases. The TDPS do not arise from either of the two currently recognized Satellite III-enriched genomic regions, namely autosomal 'K-domains', which form part of 15p in chromosome 15 or the heterochromatin of chromosome Y.

## Introduction

The human Satellite III like family of sequences comprises major tandem repeats located typically in the pericentric and centric heterochromatin of about one-third of the chromosome complement (Burk et al. 1985). They are diverged in sequence, the major recognised division being between Satellite III and Satellite II (Prosser et al. 1986). The former has a high proportion of the 'core' pentameric tandem repeat sequence 5′TTCCA 3′, whilst the latter is believed to be a degenerate and more recently diverged form of this (Hollis and Hindley 1988). The proportion of these two related sequences within individual chromosomes differs, and thus chromosome-specific 'domains' enriched in one or the other sequence type exist (Burk et al. 1985; Cooke and Hindley 1979; Higgins et al. 1985; Jeanpierre et al. 1985; Moyzis et al. 1987).

Satellite III enriched domains are a source of extreme interindividual variation (Fowler et al. 1987, 1988a). The principal cause of this appears to be a C-G point mutation in the pentameric repeat 5′TTCCA 3′, thereby creating a TaqI site (TCGA). These TaqI restriction sites are randomly located in the tandemly repeating blocks of Satellite III and thus provide the observed polymorphism (Fowler et al. 1988a).

This TaqI-specific Satellite III polymorphism is best observed in fragments of size range about 4 to 25 kb. About 10 to 20 such fragments exist in any one individual and these show Mendelian inheritance (Fowler et al. 1988a). There are in addition abundant numbers of Satellite III related fragments smaller than this in size, but these become increasingly difficult to resolve electrophoretically. Therefore the fragments greater than about 4 kb in size are the most informative. These sequences are only a minor portion of total Satellite III DNA and are here called the TaqI-deficient polymorphic sequences (TDPS).

It has been suggested (Fowler et al. 1988a) that the TDPS arose from autosomes, and probably those containing so-called 'K-domain' (Burk et al. 1985) Satellite III regions. These are typified by 3.6 and 1.8 kb KpnI tandem repeat fragments which have been mapped to chromosome 15 (Burk et al. 1985; Higgins et al. 1985) and chromosome 9 (Jeanpierre et al. 1985). This study further resolves the genomic location and properties of the TDPS.

## Materials and methods

*Tritium-labelled probes.* A probe was prepared from the Satellite III related sequence 228S (Fowler et al. 1987) by primed synthesis of the complementary strand of the M13 template as previously described (Fowler et al. 1988a), but for in situ techniques [$^3$H]dATP (65 Ci/mmol) and [$^3$H]dCTP (50 Ci/mmol) were incorporated rather than [$^{35}$S]dATP.

*Biotin-labelled probe.* The single-stranded M13 vector containing the sequence 228S (Fowler et al. 1987) was biotinylated by the photobiotin method (McInnes et al. 1987) following the Bresatec protocol (Bresatec, South Australia).

*Preparation of metaphase chromosomes.* Phytohaemagglutinin-stimulated lymphocyte cultures were prepared from individuals of normal karyotype. The lymphocyte cultures were treated with 200 μg/ml bromodeoxyuridine for 16 h, then the cells were washed and incubated in fresh medium containing 2.4 μg/ml thymidine for 6 h. Colchicine (5 ng/ml) was added 20 min before harvest. Cells to be probed with the biotin-labelled probe were not pre-treated with

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**Table 1.** Human/rodent hybrid cell panel[a]

| Cell line | Human chromosomes present |
|---|---|
| 64063[b] | 9q |
| HORL I[b] | 15 |
| CY14[c] | 16(p13.3→qter), 4(q31→4qter), 1, 4, 12, 14, 20, 21 |
| PK14[c] | 46, XY.-16, +der(16)t(4,16)(q31;p13.3) |
| CY9[d] | del(16q), 4, 13, 21 |
| CY13[d] | 16(p13.11→qter), 1(q44→1qter), 3, 11, 14, 17, 20, 21, 22 |
| CY15[d] | 16(p12 or p13→qter), 11, 14, 17, 21 |
| T85-43[c] | 46,XX,del(16)(p12 or p13) |
| CY4[c] | der(13)t(13;16)(q34,q22.1) |

[a] All hybrids are mouse/human except 64063 which is a hamster/human hybrid
[b] Obtained from Dr. P. Goodfellow, Imperial Cancer Research Fund, London, UK
[c] D.F. Callen (unpublished)
[d] Callen (1986)

bromodeoxyuridine and thymidine, but rather incubated with colchicine only, added 60 min prior to harvest. The cells were fixed and spread on slides, treated with RNAse and the chromosomes denatured and dehydrated (Simmers et al. 1986).

*In situ hybridization using tritium-labelled probes.* The probe (0.01 ng/μl) was hybridized to metaphase spreads, the slides then being dipped in Kodak NTB-2 emulsion and developed after 1 to 4 days (Simmers et al. 1986). Chromosomes were then banded as previously described (Callen et al. 1987).

*In situ hybridization using biotinylated probe.* Hybridization was for 17 h at 37° C in a humid chamber. Probe concentration was between 0.01 and 0.02 ng/μl dissolved in 25 μl hybridization buffer, pH 7.0 [2 × SSC (300 mM NaCl, 30 mM sodium citrate), 50% deionized formamide, 5% dextran sulphate, 0.1 mM disodium EDTA, 0.05 mM Tris-HCl, pH 7.3, 50 μg/ml sheared salmon sperm DNA]. Washing of the slides, and detection and amplification of the biotin were done essentially by the method of Burns et al. (1985).

*Source and isolation of genomic DNA.* DNA was isolated from nucleated cells in human blood and human sperm cells by standard methods described previously (Fowler et al. 1988a, b) as was the DNA from rodent/human hybrids. DNA from two rodent/human hybrids (64063 and HORL I) was a gift from Dr. P. Goodfellow, The Imperial Cancer Research Fund, Lincoln's Inn Fields, London, UK. Hybrids examined are detailed in Table 1.

*Digestion of DNA.* The DNA was digested with restriction enzymes TaqI, HaeIII, KpnI, MspI, HpaII, AvaI, PstI, MboI, AluI, RsaI, or EcoRI (Boehringer Mannheim), precipitated and prepared for electrophoresis as described previously (Fowler et al. 1988a). DNA was recovered from preparative agarose gels using Gene-Clean (Bio-101).

*Electrophoresis and Southern blotting.* The DNA was separated by either conventional electrophoresis (Fowler et al. 1988a), or by field inversion gel electrophoresis (FIGE). Polarity switching, at constant voltage, was ramped in time intervals from 0.3 s forwards, 0.15 s reverse at the start, to 0.7 s forwards, 0.35 s in reverse at the finish, in continuous 15 min cycles so as to reach a defined number of 'minirамps' as described in detail elsewhere (Fowler et al. 1988b). Gels were blotted to nylon membranes as described previously (Fowler et al. 1988a). DNA molecular size standards were labelled with [$^{35}$S]-dATP and included in each gel or measured after staining the gel with ethidium bromide.

*Probe preparation, hybridization, washing and exposure.* The Satellite III sequence related probe 228S and the satellite

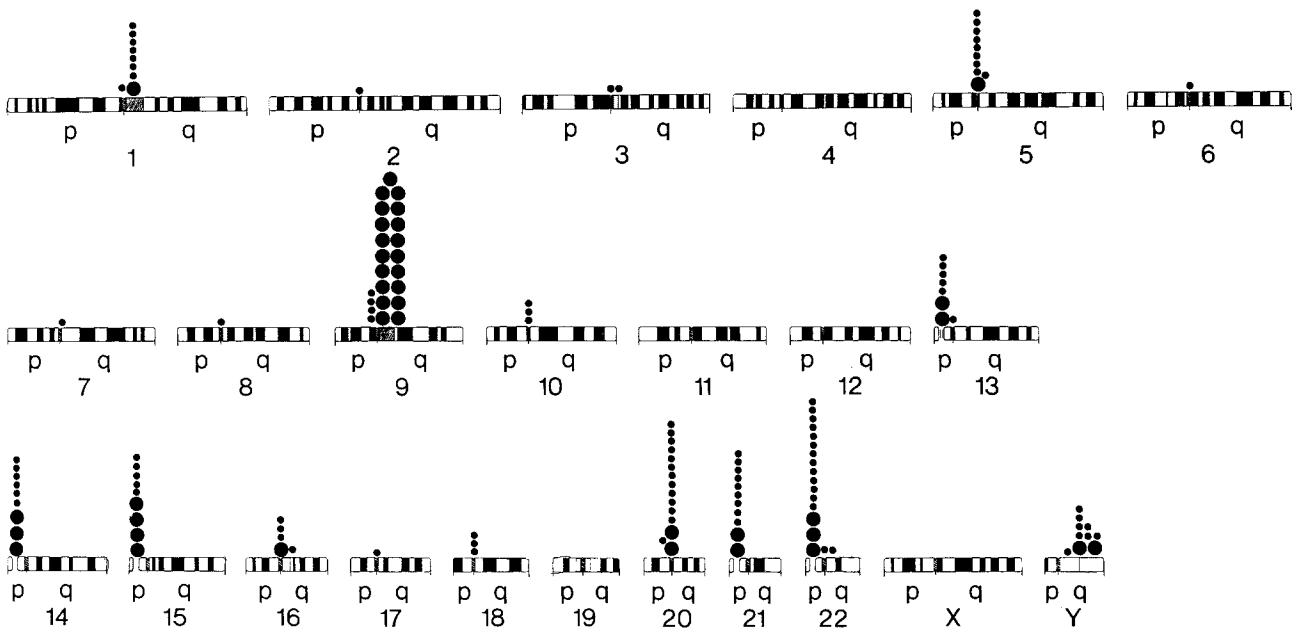



**Fig. 1.** Chromosomal location and distribution of sequences homologous to ($^3$H-labelled) clone 228S by in situ hybridization. Final wash stringency 2 × SSC, 50% formamide, 39° C. • single grain; ● multiple grain clusters

alphoid sequence related probe 216S were labelled with [$^{35}$S]dATP and used as previously described (Fowler et al. 1988a).

## Results

*In situ hybridization using probe 228S*

The distribution of grain counts on 15 metaphases is shown for probe 228S (final wash stringency 2 × SSC, 50% formamide at 39° C; Fig. 1). The major region of in situ hybridization is region 9qh. Other genomic regions also contribute. These are: the short arms of chromosomes 13, 14, 15, 21 and 22; the centromeric heterochromatin of chromosomes 1 and 20; and region Yq (Fig. 1). The biotinylated probe 228S is near specific for region 9qh (Fig. 2) when used at probe concentrations less than about 0.01 ng/μl and high stringency (0.1 × SSC at 65° C). This suggests that the TaqI/Satellite III polymorphism revealed by probe 228S in Southern analyses (final wash stringency 0.1 × SSC at 55° C) may predominantly arise from region 9qh. Alternatively, this 9qh-specific result may be due to the reduced sensitivity of the biotin 228S probe compared with the same sequence labelled with tritium and the relatively large quantity of Satellite III in region 9qh.

The in situ hybridization results indicate only the genomic distribution of 228S homologous sequences. They do not necessarily correlate with the genomic location of the TDPS. Previous evidence has indicated that the Satellite III polymorphism is of autosomal origin, excluding Yq, and also excluding chromosome 16 and probably chromosome 1 (Fowler et al. 1988a). Therefore attempts were made better to define the location of the TDPS.

*Genomic location of the Satellite III polymorphism*

*Examination of K-domains.* Human DNA was digested with KpnI. The DNA from the 3.6 and 1.8 kb regions was recovered from a preparative agarose gel. Part of the recovered DNA was digested further with TaqI. The resultant fragments were examined by Southern analysis using 228S as a probe (Fig. 3). The initial KpnI digest showed 3.6 and 1.8 kb K-domain Satellite III fragments. The same fragments were however extensively digested with TaqI, and therefore neither can be included in the TDPS, since these are represented by sequences whose TaqI spacing is greater than about 4 kb. Furthermore, if such KpnI tandem repeats were to represent all the Satellite III component of chromosome 15 (Burk et al. 1985) and chromosome 9 (Jeanpierre et al. 1985), this would tend to exclude these chromosomes from contributing to the Satellite III polymorphism.

*Examination of rodent/human somatic cell hybrids.* The DNAs from seven different somatic cell hybrids (Table 1) were digested with TaqI and the fragments separated by FIGE and then blotted and probed with 228S. Background mouse and hamster genomic DNA do not hybridize with the satellite III related probe 228S (Fowler et al. 1988a; see also Discussion).

Hybrid 64063 (Fig. 4, lane 8) showed about six distinct TaqI fragments greater than about 4 kb (within a moderately intense background smear) but by comparison an increasing number of fragments smaller than this size, particularly below about 2 kb. Hybrid 64063 contains 9q as the

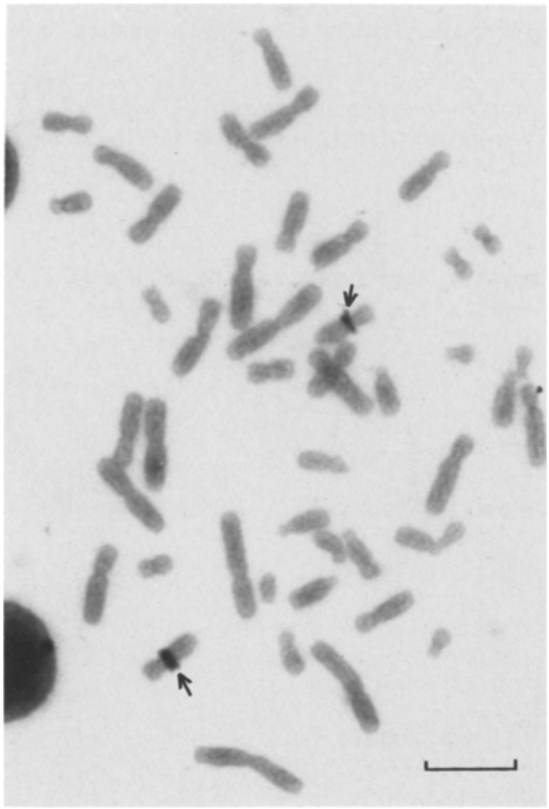


**Fig. 2.** In situ hybridization of biotinylated probe 228S to unbanded metaphase chromosomes. Hybridization (*arrowed*) is near specific for region 9qh (established in Fig. 1). Final wash stringency 0.1 × SSC, 65°. Bar represents 10 μm

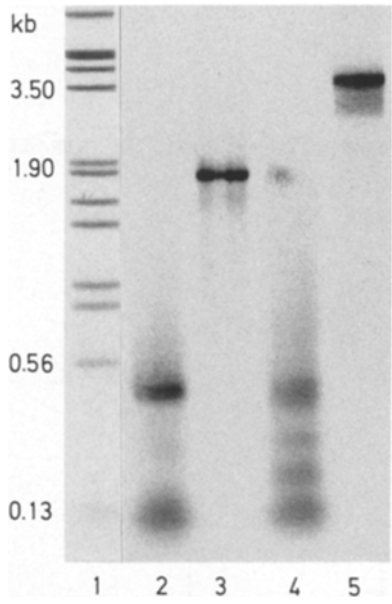



**Fig. 3.** TaqI digestion of isolated 1.8 and 3.6 kb KpnI 'K-domain' Satellite III fragments. Electrophoresis (1.8% agarose) and Southern analysis using $^{35}$S-labelled 228S. *Lane 1* lambda molecular size standard; *lane 2* KpnI + TaqI double digestion of KpnI 1.8 kb isolate; *lane 3* original KpnI 1.8 kb isolate; *lane 4* KpnI + TaqI double digestion of KpnI 3.6 kb isolate; *lane 5* original KpnI 3.6 kb isolate. Film exposure 48 h

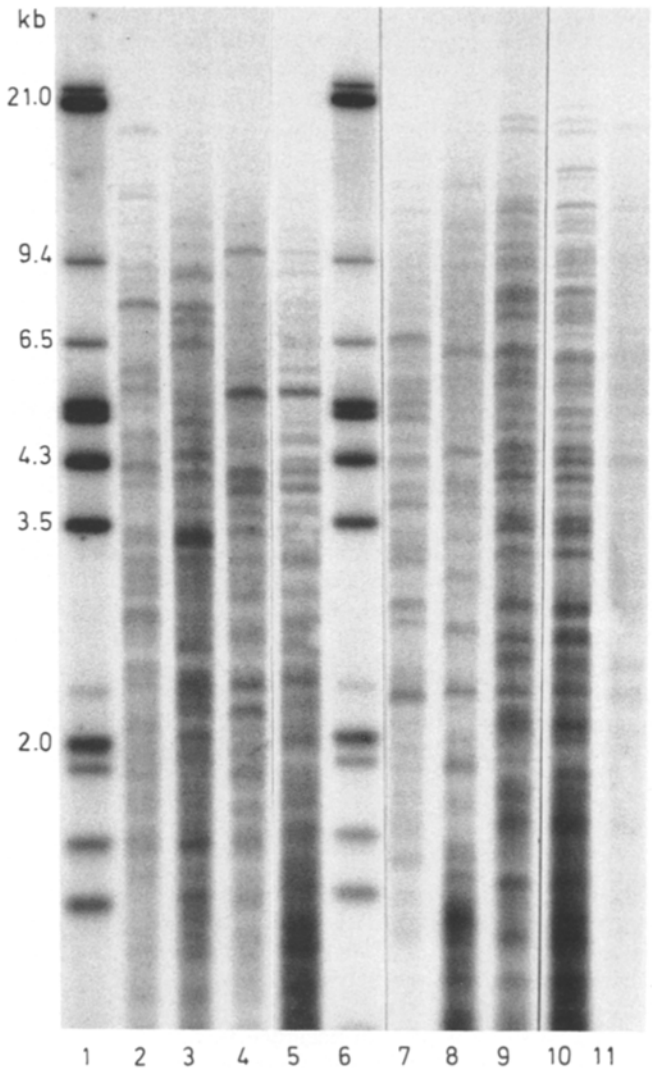



**Fig. 4.** TaqI digestion, field inversion gel electrophoresis (FIGE, 54 miniramps), and Southern analysis of somatic cell hybrids (Table 1) using $^{35}$S-labelled 228S. *Lane 1* lambda molecular size standard; *lane 2* CY9; *lane 3* CY13; *lane 4* CY15; *lane 5* T85-43; *lane 6* as 1; *lane 7* HORL I; *lane 8* 64063; *lane 9* CY14; *lane 10* PK14; *lane 11* CY4. Each lane, 5 μg except T85-43 and PK14, 2 μg each. Film exposure 60 h

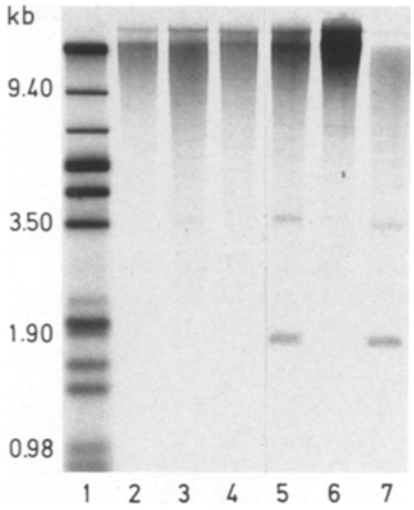



**Fig. 5.** KpnI digestion and Southern analysis of selected somatic cell hybrids using $^{35}$S-labelled 228S. *Lane 1* lambda molecular size standard; *lane 2* CY9; *lane 3* CY13; *lane 4* CY15; *lane 5* CY14; *lane 6* 64063; *lane 7* HORL I. Each lane, 4 μg; film exposure 20 h

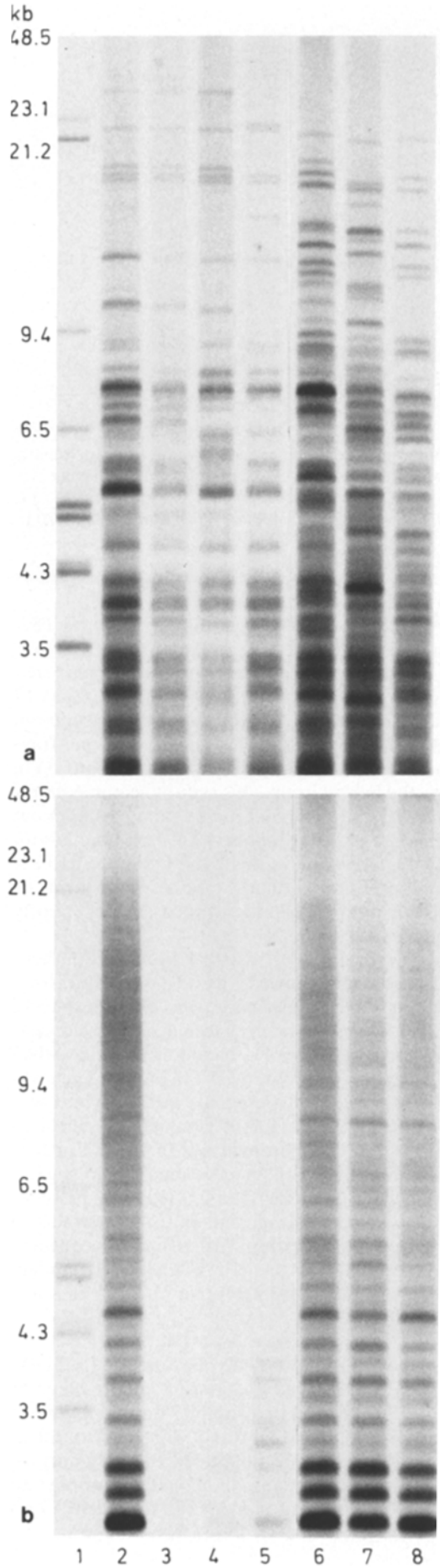
only human chromosome. About ten fragments greater than about 4 kb (with seven being smaller than 6 kb) were present in hybrid HORL I (lane 7). This hybrid contains chromosome 15 as its only human chromosome. There were also far fewer fragments smaller than 4 kb in hybrid HORL I than were seen in hybrid 64063, particularly below 2 kb (Fig. 4).

Hybrids CY9, CY13, CY14 and CY15 (Table 1) showed a larger proportion of their TaqI fragments to be greater than 4 kb in size compared with either hybrid 64063 or hybrid HORL I (Fig. 4). For example, 17 fragments were seen in hybrid CY14, 14 in hybrid CY9, 10 in hybrid CY13 and 2 intense bands in CY15. These hybrids contained various combinations of chromosomes 20, 21, and 22 (Table 1) as their predominant Satellite III DNA containing chromosomes. The band intensity of their TaqI fragment patterns was very varied. Hybrid CY4, which contains only chromosome 13 as its Satellite III source showed limited hybridization to the probe 228S with only a few fragments greater than about 4 kb (Fig. 4).

The DNAs from two human cell lines, PK14 and T85-43, which were used to generate CY14 and CY15 respectively were also digested with TaqI and the results compared with their respective hybrids (Fig. 4). Hybrid CY14 has 17 out of 23 fragments greater than about 4 kb in common with its parent PK 14. However it appears that one fragment, at about 13 kb, and possibly another at about 6 kb, were unique to the hybrid itself. This cannot be immediately explained. Hybrid CY15 has 6 (2 intense and 4 minor) out of 17 fragments greater than about 4 kb in common with its parent T85-43. One band in this hybrid, at about 10 kb, was markedly more intense than the same fragment in its parent, as were a number of other, much smaller, poorly resolved fragments.

Digestion of hybrid HORL I with KpnI and Southern analysis using probe 228S showed 1.8 and 3.6 kb KpnI fragments, confirming them to originate from chromosome 15 (Fig. 5). No like fragments were detected in KpnI digests of the other hybrids (Table 1), including hybrid 64063 (Fig. 5). The exception was hybrid CY14 (Fig. 5). The presence of 1.8 and 3.6 kb KpnI fragments in this hybrid was surprising in that distamycin/DAPI staining had failed to identify whole or part of chromosome 15 in it. Furthermore, the band intensity of these fragments would suggest that this should have been easily identified. The presence of two TaqI hybrid-specific fragments in CY14 (see above) suggests some de novo alteration of Satellite III sequences in this hybrid. Alternatively this KpnI/Satellite III tandem repeat may exist in chromosomes other than 15 in some individuals (see Discussion).

*Sequence homogeneity of the TDPS.* The Satellite III TDPS are generally resistant to double digestion with a range of other restriction enzymes. For example, double digestion of the DNA from one individual firstly with TaqI and then either HaeIII, AluI or RsaI little altered the polymorphic pattern of this person (Fig. 6a), though it did appear to alter the relative intensity of some TaqI fragments. This may in part have been due to losses resulting from the




more extensive manipulations required in preparing double digests. Double digestion with RsaI showed the greatest effect with, for example, the disappearance of a band at about 27 kb and the appearance of a band at about 13 kb. Stripping the membrane of probe 228S and reprobing with 216S clearly confirmed that the additional digestions had actually taken place (Fig. 6b).

Similar double digest experiments were made using TaqI with either PstI, KpnI, EcoRI or MboI (results not shown). The TDPS were similarly resistant to digestion with these enzymes. The greatest alterations in TaqI patterns were seen when either EcoRI or MboI were used, the results being similar to those seen with TaqI + RsaI (Fig. 6a). Double digestion with TaqI + KpnI little altered the polymorphic patterns, confirming that the K-domain Kpn 3.6 and 1.8 kb fragments are not themselves part of the TDPS.

## Discussion

Satellite III like sequences represent the dramatic expansion of the pentameric repeat TTCCA (Frommer et al. 1982; Prosser et al. 1986), mostly in the centric and pericentric regions of some autosomes and the long arm of the Y chromosome (Fig. 1). The amplification of this sequence is recent in evolutionary time. Satellite III sequences are common to humans and higher primates only, while the related Satellite II repeat is apparently unique to humans (Mitchell et al. 1981).

### *Genomic location of the TDPS in human Satellite III DNA*

The in situ distribution of genomic sequences homologous to the 228S probe (Fig. 1) is similar to that of a cloned Satellite III sequence specific to a chromosome 22 library (Jeanpierre et al. 1985). There is less similarity with a cloned Satellite III sequence near specific for 15p (Higgins et al. 1985), and still less with an uncloned satellite III sub-fraction (Yq 3.4) isolated by gel electrophoresis (Burk et al. 1985).

The results show that the TDPS detected by the probe 228S do not arise from either of the two currently recognised Satellite III domains, namely autosomal K-domains (Burk et al. 1985) or Yq (Nakahori et al. 1986). Both these regions, though relatively pure in TTCCA repeats, have many TaqI sites in their repeat units and thus would not contribute to the polymorphism. Rather, the TDPS arise from other Satellite III regions characterised not only by their few TaqI sites per unit length, but also by a more general lack of restriction endonuclease sites, other than HinfI (Prosser et al. 1986).

The primary locations of these TaqI-deficient domains and hence the TDPS are probably the heterochromatin of

**Fig. 6. a** TaqI and TaqI + other double digestion of DNA from one individual (no. 1) compared with TaqI digestion of three other unrelated individuals (nos. 2, 3, 4). FIGE (88 miniramps), and Southern analysis using ($^{35}$S)-labelled 228S. *Lane 1* lambda molecular size standard; *lane 2* TaqI control no. 1; *lane 3* TaqI + HaeIII no. 1; *lane 4* TaqI + AluI no. 1; *lane 5* TaqI + RsaI no. 1. Compare with single TaqI digests in lane 6, no. 2; lane 7, no. 3, lane 8, no. 4. About 2.5 µg each lane; film exposure 60 h. **b** Membrane in **a** stripped and reprobed with $^{35}$S-labelled 216S to confirm equivalence of all TaqI digestions and to confirm TaqI + other double digestions. Film exposure 24 h

chromosome 20, and the short arms of chromosomes 21 and 22. Limited support for this is the similarity of the situ distribution using 228S and that from the Satellite III sequence specific for the chromosome 22 library (Jeanpierre et al. 1985). Other minor contributory regions are the pericentric heterochromatin of chromosome 9 and the short arms of chromosomes 15 and perhaps 13 and 14. There may well be marked inter-individual variation in the proportion of the contribution from each of these.

Given the near specificity of the biotinylated probe 228S for region 9qh at high stringency and low probe concentration (Fig. 2) it was expected this region would be the predominant source of the TDPS. This appears not to be so, since this region contributed relatively few bands to the TDPS. The 9qh-specific in situ hybridization result may thus be explained by either the biotinylated 228S probe preferentially locating this major block of Satellite III sequence at limiting probe concentration, or else the sequence 228S is most complementary to a region of Satellite III of relatively high TaqI frequency.

The TDPS represent only a minor proportion of total genomic Satellite III and it is not known if they are contiguous or are in any way separate from the bulk of Satellite III sequences which have a far greater TaqI frequency per unit length. Cytogenetic evidence using high resolution in situ techniques indicates that there are separate regions of Satellite III within individual chromosomes, e.g. within region 9qh and separate regions localized to the centromere and terminal knobs of all Satellite III-containing acrocentric chromosomes (Frommer et al. 1988). It is confirmed that K-domain fragments segregate from chromosome 15. However, not all the Satellite III DNA in this chromosome is K-domain (normally well digested with TaqI – Fig. 3) because hybrid HORL I also contained some moderately large TaqI-deficient fragments (lane 7, Fig. 4). This distinction in Satellite III/TaqI fragment size may eventually be found to correlate with their separate locations on chromosome 15 (Frommer et al. 1988).

These results also show that some 1.8/3.6 kb KpnI Satellite III fragments could arise from chromosomes other than 15 (Fig. 5). It is possible that such regions of localized amplification are individual specific. Alternatively, the results may be evidence for the instability of such sequences, particularly in hybrids. Reported examples of the instability of 15 p is its translocation to chromosome 22 (Buhler and Malik 1988) and to chromosomes X, 3 and 9 followed by expansion of the 1.8 kb KpnI Satellite III unit by unequal sister chromatid exchange (Holden et al. 1987).

### *Homogeneity of the TDPS*

The general inertness of TDPS to restriction enzymes such as HaeIII, AluI, PstI, KpnI, and to a lesser degree EcoRI, MboI and RsaI is unusual compared with the frequency of restriction by these enzymes in other genomic sequences. This inertness appears to be greater the fewer the number of TaqI sites per unit length of Satellite III. The restriction map of Yq, for example, includes 64 TaqI sites and 5 RsaI sites within 3.5 kb (Nakahori et al. 1986) but one TDPS fragment apparently contained only a single RsaI site in 27 kb (Fig. 6a). The TDPS therefore appear featureless and difficult to map by conventional methods.

Two conclusions can be made. First, the TDPS are only rarely and intermittently interrupted by either non-satellite III sequences or regions of Satellite III which have a low frequency of 'rare' restriction sites. The extensive regions of apparently homogeneous Satellite III sequences which comprise the TDPS have not themselves accumulated by random drift any marked degeneracy in sequence and therefore probably represent examples of very recent TTCCA amplification events in the genome. Previous evidence has shown the Satellite III polymorphism to be TaqI specific and unlikely to have arisen from non-reciprocal recombination events (Fowler et al. 1988a). It is therefore more likely caused by DNA amplification, with post amplification TaqI point mutation or perhaps pre-existing TaqI sites being caught up in an amplification event(s).

Second, this restriction enzyme immunity suggests a very low level of transposon invasion, e.g. by Alu or LI, into such regions, either because of environmental unsuitablity or because of their very recent amplification. These observations are broadly consistent with the reported minimal hybridization of Alu and LI sequences to heterochromatin (Korenberg and Rykowski 1988) and consistent with induction of C-banding in human chromosomes by restriction enzymes (Babu et al. 1988).

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