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Extensive DNA sequence homologies between the human Y and the long arm of the X chromosome

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It has been proposed that sequence homology should exist between the short arms of the human sex chromosomes, in the regions pairing at meiosis. Out of 40 clones picked at random from a collection of non-repetitive DNA sequences derived from the human Y chromosome, we have found nine sequences which show very high homology with sequences located on the X chromosome. All nine probes originate from the euchromatic part of the Y chromosome. All the homologous sequences are located within the Xq12-Xq22-24 region. None of them map to the short arm of the X chromosome. We conclude that an important part of the euchromatic region of the Y chromosome is homologous to the middle of the X chromosome long arm, possibly as a result of recent translation event(s).

Key words: chromosomal mapping/Y DNA sequences/X-Y homology/sex chromosome evolution

Introduction

It is generally accepted that the vertebrate sex chromosomes evolved from a common ancestor (Ohno, 1967) and have retained a high degree of homology among the lower vertebrates. The dimorphism of vertebrate sex chromosomes first appears in several orders of reptiles and culminates in the more evolved classes, birds and mammals (Austin and Edwards, 1981). In contrast to this dimorphism, pairing between the X and Y chromosomes during meiosis has been observed (Solari, 1970, 1980; Chandley, 1984) and is usually attributed to the existence of DNA sequence homologies between the sex chromosomes (Polani, 1982; Burgoyne, 1982).

In man, homology between the sex chromosomes is assumed to involve mainly the distal parts of the short arms for the following reasons: (i) X-Y pairing at meiosis first involves the short arm of the Y chromosome and one of the tips of the X chromosome – probably the Xp tip (Pearson and Bobrow, 1970; Moses *et al.*, 1975). (ii) Genes from the distal part of the short arm of the X chromosome escape inactivation in females. Equal dosage between males and females could be possible if such genes were also present in human males on Y-located homologous loci. Furthermore, some of these genes could be exchanged between the tips of X and Y through cross-over in the pairing regions (Burgoyne, 1982).

Such homologies have been strongly suggested by the existence of a locus which maps to both the X and Y chromosomes and controls the expression of the cell-surface antigenic determinant 12E7 (Goodfellow *et al.*, 1983). On the other hand numerous reports on the presence of X-Y homologous sequences have accumulated recently (Daiger *et al.*, 1982; Page *et al.*, 1982; Bishop *et al.*, 1983 and 1984; Kunkel *et al.*, 1983; Müller *et al.*, 1983; Cooke *et al.*, 1984; Heilig *et al.*, 1984; Koenig *et al.*, 1984; Rappold *et al.*, 1984; Wolfe *et al.*, 1984a and b). Some sequences exhibit a certain degree of divergence between both chromosomes, whereas others appear as highly conserved.

However, mapping studies have always failed to reveal sequence homologies between both short arms. In a new attempt to detect sequence homologies between Xp and Yp we have characterized those probes from our Y-derived sequence collection that show a very high homology to X-located fragments. We undertook a regional mapping of these fragments on the X using interspecies somatic cell hybrids carrying well characterized human X chromosomal deletions. A mapping of the probes on the Y chromosome, using a Yq^- deletion and a Yq11-qter translocation is also reported.

Results

Heterogeneity among X-Y homologies

The sequences from the human Y chromosome have been isolated and characterized as described previously (Bishop *et al.*, 1983 and 1984). Y location of these probes has been confirmed by hybridization dosage with DNA from human cell line carrying 4 Y chromosomes (49,X4Y). Out of 26 Y-derived probes 13 detect fragments on the X chromosome as confirmed by detection of identical bands in DNA digests from human females and either of two independent human-rodent cell hybrids Horl9X and Mog13.9 in which the X chromosome is the sole detectable human genetic material (Bishop *et al.*, 1984).

For one of the 13 probes, homology to the X chromosome could only be detected after non-stringent washings of the hybridized probe (Figure 1a and 1b). In the other instances (12 out of 13), homology to the X chromosome could be detected after stringent washings. One of these probes, p12f, detects numerous homologous sequences on the X chromosome as well as on autosomes (Bishop *et al.*, 1984). The 11 remaining probes detect no autosomal sequences. A strong conservation of the X and Y sequences detected by these 11 probes is further suggested because of the size identity of the hybridizing fragments, and a comparable intensity of the hybridization signal on male and female DNA digests (Figure 1c).

Among the different degrees of X-Y homology detected by the Y-derived probes, these 11 latter probes may define a rather homogeneous category characterized by an apparently high degree of sequence conservation. Nine of these 11 independently derived probes were used for a more accurate estimation of the degree of homology between the X and Y related sequences.

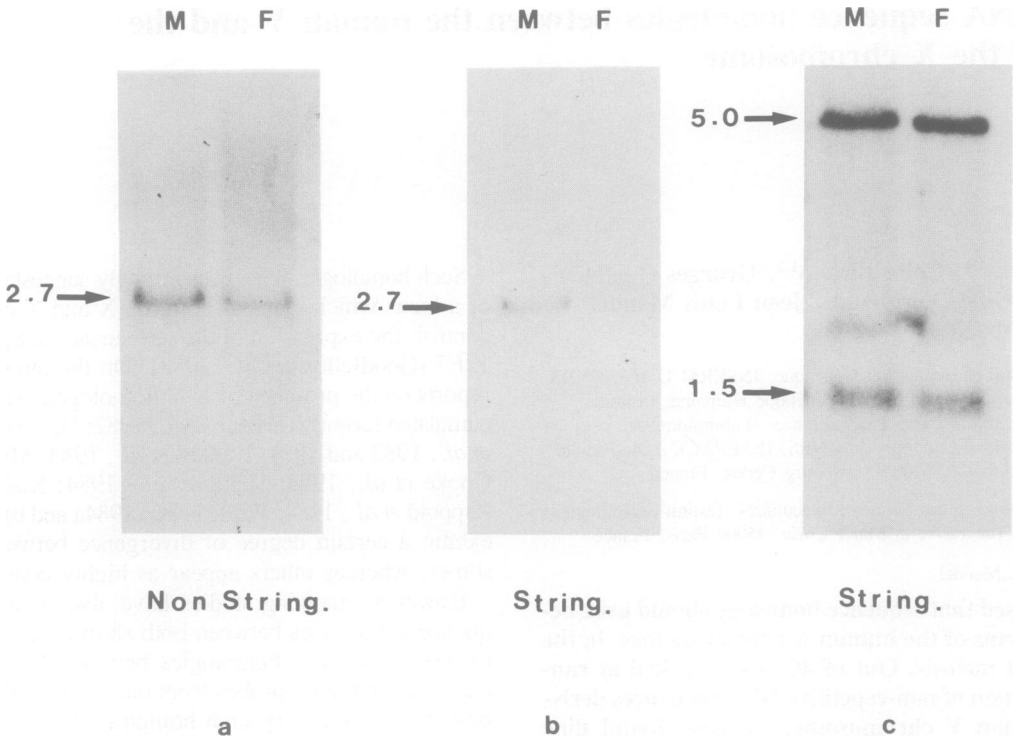

Fig. 1. Autoradiograms of Southern blots of human male (M) and female (F) genomic DNA restricted with *Pst*I (**a** and **b**) and *Bgl*II (**c**). Filters were hybridized with ^{32}P-labeled probes 52d (a and b) and 7b (c) derived from the human Y chromosome. Hybridization was carried out overnight at 42°C in the presence of 50% formamide. Filters were washed twice for 30 min in 2x standard saline citrate (SSC) at 68°C (non-stringent conditions) and additionally twice for 30 min in 0.1 x SSC at 68°C (stringent conditions). Positions of marker fragments are marked with sizes in kb.

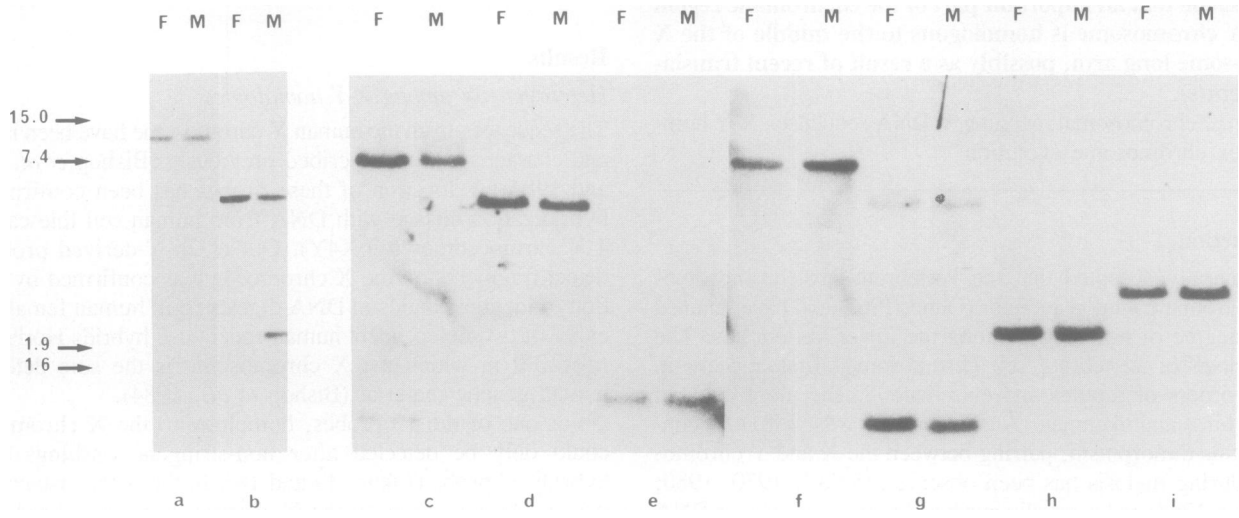

Fig. 2. Autoradiograms of Southern blot of human male (M) and female (F) genomic DNA cleaved with *Pvu*II (**a**), *Taq*I (**b**), *Xba*I (**c**), *Bgl*II (**d**), *Eco*RI (**e**), *Sac*I (**f**), *Pst*I (**g**), *Bam*HI (**h**), *Hind*III (**i**). DBM blots were hybridized with ^{32}P-labeled probe 1 derived from the human Y chromosome. Hybridization and stringent washings were as in Figure 1. Positions of marker fragments are marked with sizes in kb.

Numerous Y-derived sequences are highly homologous to X DNA fragments

The nine probes were hybridized to digests of male and female DNA restricted by nine different enzymes: *Bam*HI, *Bgl*II, *Eco*RI, *Hind*III, *Pst*I, *Pvu*II, *Sac*I, *Taq*I and *Xba*I. Differences between male and female hybridization patterns were noticed for one to three digests at most (Figure 2). In a few instances, the supplementary band of the differential patterns was observed in female DNA, suggesting the occurrence of an X-linked polymorphism. This was tested and confirmed for one of the corresponding probes by segregation studies (data not shown). Male supplementary bands have been observed more frequently, especially in *Taq*I digests (Figure 2). These bands have always proved to be male-specific by hybridization to the appropriate digests of 10 male and female DNAs (data not shown). Moreover, in these digests, parallel to the presence of male-specific bands, at least one of the male-female-common bands always proved to be X-specific (see dosage effect on *Taq*I common band in Figure 2). The male-specific bands also showed dosage effect in DNA digests of the 49,X4Y cell line. Conversely this dosage

Table I. Hybridization of Y-derived probes to *Eco*RI digests of DNA extracted from human-rodent hybrid cell lines with different X translocations (for characterization of translocations see Materials and methods)

Hybrid clone	Part of the human X chromosome present in the hybrid clone	Probe hybridized								
		p7b	p1	p47z	p16	p13d	p115	p8j	p22b	p17
Rag 194	Xpter-Xq28	+	+	+	+	+	+	+	+	+
A9 HRBC2	Xqter-Xp22	+	+	+	+	+	+	+	+	+
Rag PI	Xqter-Xp22	+	+	+	+	+	+	+	+	+
Rag GO	Xqter-Xp11	+	+	+	+	+	+	+	+	+
Rag Anly	Xqter-Xq12	+	+	+	+	+	+	+	+	+
58 A9	Xqter-Xq13	+	ND	+	ND	+	+	+	+	+
A9 89	Xqter-Xq22-24	−	−	−	−	−	−	−	−	−
Cerc H	Xqter-Xq11	+	ND	ND	ND	+	+	ND	ND	ND
Cerc S	Xpter-Xq11	−	ND	ND	ND	−	−	ND	ND	ND
C34X	Xqter-Xp22	+	+	+	+	+	+	+	ND	ND
C35A	Xqter-Xq23	ND	ND	ND	ND	−	−	−	ND	ND
X regional mapping of the detected fragment		q13 to q22−24	q12 to q22−24	q13 to q22−24	q12 to q22−24	q13 to q23	q13 to q23	q13 to q23	q13 to q22−24	q13 to q22−24

+, presence of a hybridizing *Eco*RI fragment of the same size as the probe tested.
−, absence of any hybridizing *Eco*RI fragment of the same size as the probe tested.
ND: Not determined. (The Y-derived probes are all *Eco*RI restriction fragments.)

was not observed with the X-specific bands. The above data demonstrate the location on the Y chromosome of the male-specific supplementary bands. Assuming that the appearance of such bands is due to a single base pair change, the homology between the X and Y sequences tested has been estimated (Nei and Tajima, 1983) to be between 97 and 99%.

Regional mapping of the homologous sequences on the X chromosome

Regional mapping of the X-located fragments was carried out by hybridization of the probes to DNA extracted from human-rodent hybrid cell lines with different X translocations, digested by *Eco*RI and transferred onto *DBM* blots. The X translocations have been characterized as mentioned in Materials and methods. All the lines contain a single portion of a human X chromosome (Table I). Cytological studies of the different hybrids have not shown the presence of the human Y chromosome, even for the hybrids A9 HRBC2, Rag G0 and C35A, the human parents of which are males. Moreover, well characterized Y-specific probes from our collection always failed to detect Y material in these hybrids (data not shown). The presence of the human Y chromosome can therefore be ruled out in the hybrid lines used in this mapping.

A typical hybridization profile obtained with this translocation panel is represented in Figure 3, along with human, mouse and Chinese hamster DNA. The results obtained with the nine probes are summarized in Table I. The occasional occurrence of rodent cross-hybridizing bands could always be discriminated on the basis of fragment size differences. The sizes of the human *Eco*RI fragments from the hybrid lines are identical to the sizes observed on *Eco*RI DNA digests from human females. Since the presence of the human Y chromosome can be ruled out in the hybrids, we conclude that the non-rodent fragments detected correspond to the human X-located sequences. According to the characterizations of the X translocations used in this study the fragments homologous to the probes map in the region between Xq12 and Xq22-24. For seven of them the region can be further restricted to Xq13 to q22-24.

These conclusions are strengthened by the following considerations: (i) The hybrid cell panel used in this study has also been used in regional mapping of X-derived probes, and has always given consistent results, even for probes from the short arm (Camerino *et al.*, 1984; Heilig *et al.*, 1984; Koenig *et al.*, 1984; Hanauer and Mandel, 1984; Oberlé *et al.*, in preparation). (ii) Using this translocation panel, locus DXYS1 (Page *et al.*, 1982) has also been mapped in the Xq12-Xq22-24 region. This result is in agreement with the regional assignment independently obtained for this locus by both chromosomal *in situ* hybridization and deletion mapping experiments (Page *et al.*, 1984). (iii) Results obtained from a different translocation panel with other X-Y homologous probes have been confirmed with the panel used in this study (Cooke, personal communication).

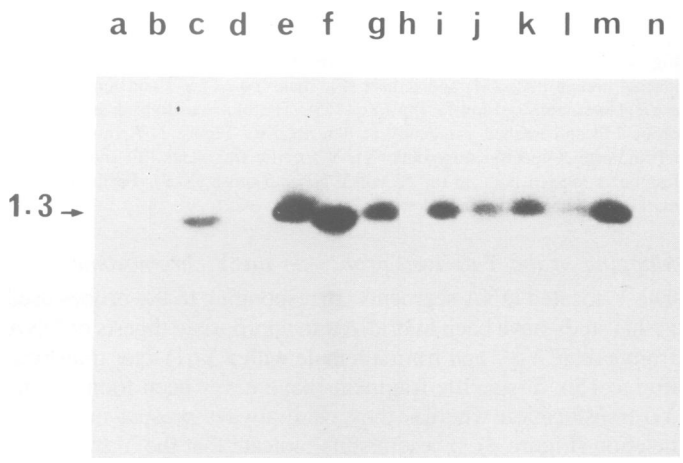

Fig. 3. Autoradiogram of a Southern DBM blot of *Eco*RI cleaved DNA from Chinese hamster (**a**), mouse (**n**), female human lymphocytes (**f**), hybrid cell lines C35A (**b**), C34X (**c**), Cerc S (**d**), Cerc H (**e**), Rag 194 (**g**), A9 89 (**h**), 58 A9 (**i**), Rag Anly (**j**), Rag GO (**k**), Rag PI (**l**), A9 HRBC2 (**m**) (for characterization of translocations see Materials and methods). The blot was hybridized with probe 115 and washed stringently as described for Figure 1. Differences in intensity of signal are due to differences in the percentage of cells containing human chromosomes. Position of the marker fragment is marked with size in kb.

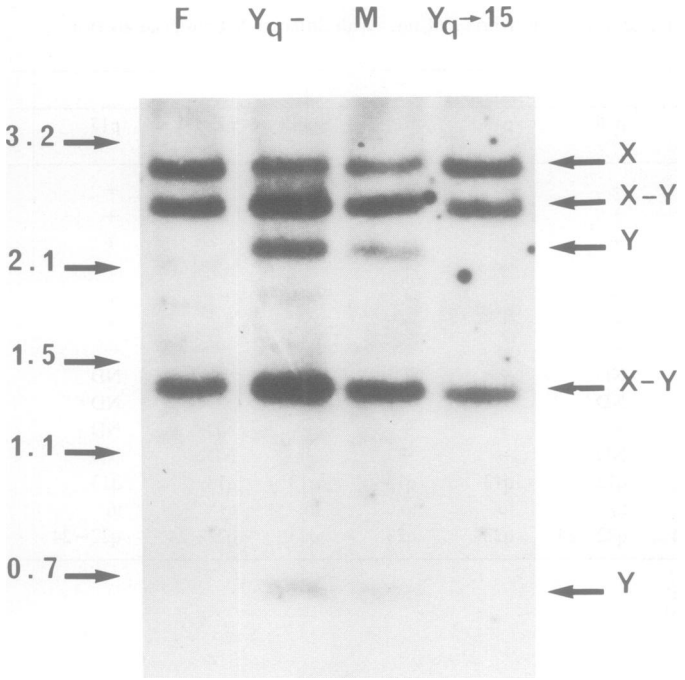

Fig. 4. Autoradiogram of a Southern blot of *TaqI* DNA digests from normal human male (M) and female (F), male Yq^- (Yq^-) and female with a Yq11-qter translocation to 15p (Yq→15). The blot was hybridized with probe 115 and washed stringently as described for Figure 1. Arrows on the left indicate X-specific fragments (X), Y-specific fragments (Y) and fragments located both on the X and Y chromosomes (X-Y). Positions of marker fragments are marked with sizes in kb.

Mapping of the Y-derived probes on the Y chromosome

The Y-located DNA segments corresponding to the probes used in this study have been hybridized to appropriate digests of DNA from a male Yq^- and from a female with a Yq11-qter translocation to 15p. Y-specific fragments have never been found in the Yq translocation whereas they were always present in the Yq deletion (Figure 4). These results indicate that the Y fragments corresponding to these X-Y common sequences are located between Ypter and Yq11.

Discussion

Unexpectedly no homology has been found between Xp and the nine Y-derived unique sequences, randomly selected and highly homologous to X sequences. This result can be explained in two different ways. (i) There could be a bias in the construction of our Y clone collection leading to an underrepresentation of regions from the Y short arm pairing segment. Deletion mapping of our probes on the Y chromosome first confirms their location between Ypter and Yq11. Moreover, the Y short arm pairing segment is the most likely candidate for bearing the male sex-determining factor (Bühler, 1980; Polani, 1982). The Y-specific fragments of locus DXYS5 have already been found in several cases of XX maleness (Guellaën *et al.*, 1984); several other probes used in this study also detect Y-specific material in XX males (Vergnaud *et al.*, in preparation) and may therefore map close to sex-determining factor. This strongly suggests the presence of Yp DNA sequences among the probes studied. (ii) Alternatively, as proposed by Ashley (1984), synapsis between the X and Y short arms may not necessitate sequence homology. Although homology between Xp and Yp cannot be excluded from our study, it must be restricted to smaller subregions possibly interspersed by sequences specific to each chromosome, as suggested by Polani (1982).

Sequence homologies between the human X and Y chromosomes have been reported recently. They are in one of the two categories outlined above. On the one hand, those detected by cDNA probes of the arginosuccinate synthetase (Beaudet *et al.*, 1982; Daiger *et al.*, 1982), or human skeletal actin (Heilig *et al.*, 1984) or of a HeLa mRNA (Kunkel *et al.*, 1983) display a notable divergence, since restriction sites are apparently not conserved. Furthermore these sequences are also located on autosomes. The Y DNA sequence homologous to locus DXS31 shares a sequence homology estimated to be 80% (Koenig *et al.*, 1984), and also belongs to the category of the less conserved X-Y homologous sequences. On the other hand, the sequences reported by Page *et al.* (1984) and Cooke *et al.* (1984) display a very high sequence conservation and are very similar in that respect to the sequences described in this study. However, probe pUC9H1 (Cooke *et al.*, 1984) detects sequences which appear to be strictly homologous on each chromosome whereas the locus identified by Page *et al.* (1984) as well as those reported here exhibit some differences. Furthermore, the fragments detected by probe pUC9H1 are located on the distal long arm of both sex chromosomes, in contrast to the locations reported here and for locus DXYS1 (Page *et al.*, 1984), which involve the middle of Xq and the euchromatic part of Y.

It should be emphasized that the present study concerns ~25% of our probe collection; this suggests that an important part of the human Y chromosome shares strong homologies with the middle of Xq. According to cytogenetic observations the Xq12-Xq24 region is not involved in X-Y pairing; the very high sequence conservation reported can thus hardly be explained by regular exchange events between the two chromosomes. Most of the probes used in this study only hybridized to the X chromosome in chimpanzee, like probe pDP34 for locus DXYS1 (Page *et al.*, 1984; Page, personal communication). Thus, the strong sequence homologies observed here between the X and Y chromosomes are probably the result of one or more recent translocation events.

Our observations raise the question of the organisation on both X and Y chromosomes of the homologous loci presented in this study. Do they appear as a single cluster on each chromosome or are they interspersed? A more accurate mapping of our probes on the Y chromosome is in progress. Some of the probes detect X-linked polymorphisms which may allow the estimation of chromosomal distances respectively to each other and to other X-linked markers.

Since the DXYS loci reported here represent an important amount of DNA sequences, the presence of active genes within these loci should be tested. Could such genes be active on the Y chromosome? In this case, would the X counterpart escape chromosomal inactivation in females?

Materials and methods

Cell lines

Mouse-human hybrids Rag 194, Rag GO, Rag Anly, Rag PI and 58 A9 (Grzeschik, 1976; Hellkuhl *et al.*, 1978) were obtained from Dr. K.H.Grzeschik (Universität Munster, FRG). Note that the characterization of the human parent 58 is actually (X, 14) (q13,q32), the original paper given in reference containing a typographical error. The hybrid cell lines were cultivated in HAT medium, and the karyotype and presence of X-linked enzymatic markers (G6PD, HPRT and PGK) were checked before preparing DNA. The hybrid lines A9 HRBC2 and A9 89 (DiCioccio *et al.*, 1975; Mohandas *et al.*, 1980) were provided by Dr. M.Siniscalco (Sloan Kettering Institute, New York). A recent finding (Koenig *et al.*, 1984) suggests that a terminal deletion of the short arm of the X chromosome

has occurred in the A9 HRBC2 line. Results to be published (Oberlé *et al.*, in preparation) suggest an ambiguity exists concerning the characterization of the A9 89 line, which is therefore presented as Xqter-Xq22-24 (initially reported as Xqter-Xq22, it was recently given as Xqter-Xq24 in Balazs *et al.*, 1984). The two hybrid lines were cultivated in HAT medium but they were not further karyotyped. Chinese hamster-human hybrid lines C35A, and derived from human parents 34 and Cer (Weil *et al.*, 1978; Turleau *et al.*, 1977; Hors-Cayla *et al.*, 1981) were obtained from Drs D.Weil and M.C.Hors-Cayla (INSERM U 12, Paris). The translocation breakpoint originally reported as Xq13 in the Cer line has been shown recently to be in q11 using high resolution banding analysis (M.G.Mattei and J.F.Mattei, personal communication). All the DNAs have been tested for the presence of twenty X chromosome specific sequences distributed along the whole length of the chromosome.

Y chromosome anomalies

Cells harboring Y chromosome anomalies were obtained from blood samples provided by Dr. B.Noel (Centre de Transfusion Sanguine, Chambéry, France). Cells from the first patient (CHMO18), a 46,XY male with azoospermia, carried a Yq^- chromosome with a characterized centromere. The second sample (CHMOO8) was from an apparently normal female with a 46,XX,der(15), t(Y;15)(q12;p11) karyotype.

Preparation of DNAs and blot hybridization

DNA was prepared as previously described from cell lines and lymphocytes (Bishop *et al.*, 1984). Digestion of DNAs with restriction enzymes, blotting onto DBM paper and hybridization were as described (Wahl *et al.*, 1979; Bishop *et al.*, 1984).

Use of hybridization probes

Most of the probes listed hereafter detect DNA loci which have been named with their symbol as attributed at the Human Gene Mapping Conference VII (Skolnick *et al.*, 1984). X and Y restriction fragments have always been characterized under stringent washing conditions. The DNA hybridization probes used are as follows: (i) p7b: this probe defines locus DXYS2; it detects an *Eco*RI fragment of 3 kb common to the X and Y chromosomes, and an *Msp*I Y-specific fragment of 6 kb. (ii) p8j: this probe defines locus DXYS9; it detects an *Eco*RI fragment of 5 kb common to the X and Y chromosomes, and an *Msp*I Y-specific fragment of 3.2 kb. (iii) p13d: this probe defines locus DXYS7; it detects an *Eco*RI fragment of 1.8 kb common to the X and Y chromosomes, and a *Taq*I Y-specific fragment of 6 kb. (iv) p22b: this probe detects an *Eco*RI fragment of 0.8 kb common to the X and Y chromosomes. (v) p47z: this probe defines locus DXYS5 as probe 47c; it detects an *Eco*RI fragment of 2.6 kb common to the X and Y chromosomes, and a *Taq*I Y-specific fragment of 4.3 kb. (iv) p115: this probe defines locus DXYS8; it detects an *Eco*RI fragment of 5 kb common to the X and Y chromosomes, and a *Taq*I Y-specific fragment of 2.2 kb. (vii) p1: this probe defines locus DXYS4; it detects an *Eco*RI fragment of 1.3 kb common to the X and Y chromosome, and a *Taq*I Y-specific fragment of 2 kb. (viii) p16: this probe defines locus DXYS6; it detects an *Eco*RI fragment of 1.5 kb common to the X and Y chromosome, and a *Taq*I Y-specific fragment of 2.1 kb. (ix) p17: this probe detects an *Eco*RI fragment of 0.6 kb common to the X and Y chromosome.

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