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Cytogenetic and molecular characterization of marker chromosomes in patients with mosaic 45,X karyotypes

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Summary. Cytogenetic and molecular techniques were employed to determine the origin of marker chromosomes in five patients with mosaic 45,X karyotypes. The markers were shown to be derived from the X chromosome in three female patients and from the Y chromosome in one female and one male. One of the female patients, with a very small, X-derived ring chromosome, had additional phenotypic abnormalities not typically associated with Turner syndrome. In this patient, both the ring and the normal X chromosomes replicated early; perhaps the unusual phenotype is the result of both chromosomes remaining transcriptionally active. These studies illustrate the power of resolution and utility of combined cytogenetic and molecular approaches to some clinical cases.

Introduction

Only slightly more than half of the patients with Turner syndrome are monosomic for the X chromosome (Fryns et al. 1983). Most of the remaining patients have a structurally abnormal X chromosome or a mosaic karyotype where the second lineage of cells may contain a structurally normal or abnormal sex chromosome. It is important to search for a second cell population and determine its composition because female individuals with a Y chromosome and gonadal dysgenesis have about a 20% risk of developing gonadoblastoma (Verp and Simpson 1987; Page 1987). Page has postulated that this predisposition depends on the presence of sequences that map to the centromeric region or long arm of the Y chromosome (Page 1987). Individuals without a Y chromosome are not at increased risk.

If the second cell population contains a small, structurally abnormal chromosome (a marker chromosome), its identity often cannot be determined without ambiguity by classical cytogenetic methods. In these cases current medical practice would dictate removal of the individual's gonads (Verp and Simpson 1987). However, using a combination of cytogenetic and molecular techniques, it should be possible to characterize any marker and avoid this surgical procedure when only X chromosomal material is present.

We have taken such a combined approach to determine the origin of the marker chromosome of five patients, four females and one male, who had mosaic 45,X karyotypes. Three of the four female patients had physical characteristics usually associated with Turner syndrome. However, one of the female patients, in addition to some of the typical Turner stigmata, had developmental delay and dysmorphic features. Her phenotype may be the result of two active copies of sequences around the X centromere that are usually inactive on the late replicating X chromosome.

Materials and methods

Patients studied

Patient 1 was a 32-year-old participant in a donor egg program designed to help women with Turner syndrome have children. She had primary amenorrhea and was 4 feet 6 inches tall with full breast development, normal female external genitalia and Tanner IV pubic hair and no other Turner stigmata were noted. She never received hormone replacement but was treated for hyperthyroidism. Reportedly, a previous cytogenetic study done elsewhere had found only a 45,X cell population.

Patient 2 was born at 38 weeks gestation by Cesarean section performed for fetal distress. She did not respire spontaneously and required resuscitation for meconium aspiration. Her weight, length,

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and head circumference were all at the tenth percentile. Her external genitalia were those of a female. She exhibited several characteristics of Turner syndrome, including a narrow high arched palate, micrognathia, excessive nuchal skin, edematous hand and feet, hyperconvex nails, an atrophic right kidney, and an enlarged left kidney with a double collecting system. She also possessed several facial features atypical of Turner syndrome, including marked hypertelorism, frontal bossing, a large crimson glabellar hemangioma, a broad nasal bridge, a small nose, and long philtrum. Her heart defects, namely a small ventricular septal defect, patent foramen ovale, and patent ductus arteriosus, are also not typical of Turner syndrome. She had bilateral simian creases. Her growth and development have been delayed. By 9 months her weight and length had fallen significantly below the fifth percentile. At 14 months, she was unable to sit without support and had little language development.

Patient 3 was examined at 14 months when her height and weight were below the fifth percentile. She had puffy hands and feet, a low posterior hairline, and prominent auricles. No other abnormalities were noted, and signs of cardiac or renal abnormalities were absent. A structure that was thought to be a uterus was seen on ultrasound examination, and her genitalia were normal. She had met all developmental milestones at the appropriate times.

Patient 4 was an 18 year old with normal female external genitalia, but primary amenorrhea. Her physical findings included short stature, excessive nuchal skin, widely spaced nipples, and mild obesity. A pelvic sonogram failed to detect a uterus or ovaries. Her intellectual development was not assessed, but she attended normal schools.

Patient 5 was first evaluated 2 years of age for short stature. He was found to have a short neck, hypogonadism, and a systolic heart murmur. At 13 years his height, weight, and head circumference were all well below the fifth percentile. He had no dysmorphic features other than mild webbing of the neck. His external genitalia were normal for a prepubertal male. His early development was described as normal by his parents, but he now attends special education classes.

Cytogenetic and molecular studies

Peripheral blood samples were obtained from each patient and used to prepared chromosomes and DNA. Lymphocytes from patients 2, 3 and 4 were transformed by Epstein-Barr virus, and these lymphoblastoid cell lines were used when indicated. Chromosome preparation, Giemsa-banding, quinacrine staining, and C-banding were performed using standard techniques. Replication studies were performed on lymphoblastoid cell lines using continuous 5-bromodeoxyuridine (BrdU) labeling for 5.5 h and differential staining by Giemsa (Verma and Babu 1989). DNA extraction and Southern hybridization were carried out as previously described (Yang-Feng et al. 1985). The methods for in situ hybridization using tritiated (Yang-Feng et al. 1985) and biotinylated (Cremer et al. 1988; Lichter et al. 1988) probes have also been described.

One probe for the X chromosome, XC, was employed in these studies. It is a 2-kb *Bam*HI fragment composed of alphoid sequences unique to the X chromosome centromere (Yang et al. 1982; Jabs and Persico 1987). The remaining probes detect sequences on the X and the Y or just the Y chromosome. YC is a 1.2-kb *Hin*dIII fragment of alphoid sequences from the Y chromosome centromere (Jabs et al. 1989). The probe hYfin is a 1.3-kb cDNA for the zinc finger Y chromosome gene (ZFY) (Lau and Chan 1989), which hybridizes with 3.5-kb *Eco*RI fragment from the short arm of the Y chromosome and a 1.8-kb *Eco*RI band from the short arm of the X chromosome (Page et al. 1987a). This sequence maps to within 250 kb of SRY, the putative sex determining gene on the Y chromosome (Sinclair et al. 1990; Page et al. 1990). The probe pDP230 (DXYS20) is a 2.2-kb *Hin*dIII fragment and detects highly repetitive pseudoautosomal sequences (Page et al. 1987b). Many of the other Y probes used to characterize the idic(Y) of patient 4 are described in Table 3.

Results

In each of these five patients, cytogenetic analysis of 20 to 35 G-banded cells revealed a line with cells that contained one normal X chromosome and a marker or ring chromosome (Fig. 1). Cells with a 45,X karyotype were present at frequencies from 0% to 90% (Table 1). In patients 1, 2, and 3 the abnormal chromosome appeared to be a ring. The ring in patient 2 was quite small (smaller than a G group chromosome), while the ring chromosomes in patients 1 and 3 were larger (larger than or equal in size to a G group chromosome). The marker chromosome in patient 5 was very small but was probably a ring in light of the presence of larger rings in some cells. The markers of patients 1 and 3 were dully fluorescent after quinacrine staining, and all four of these markers (patients 1, 2, 3, and 5) had a single site at the centromere that stained positively after C-banding. Although routine cytogenetic studies excluded the presence of the brilliantly fluorescent end of the Y chromosome long arm (Yq12), they failed to identify positively the origin of any of these four ring chromosomes.

The marker chromosome of patient 4 was approximately the size and shape of a G-group chromosome, but it did not have the characteristic G-bands of the Y chromosome (Fig. 1). The banding pattern of the marker suggested that it might be an isodicentric Y chromosome with two copies of Yp and proximal Yq but no copy of distal Yq [idic(Y)(q11.2)]. Q- and C-banding results

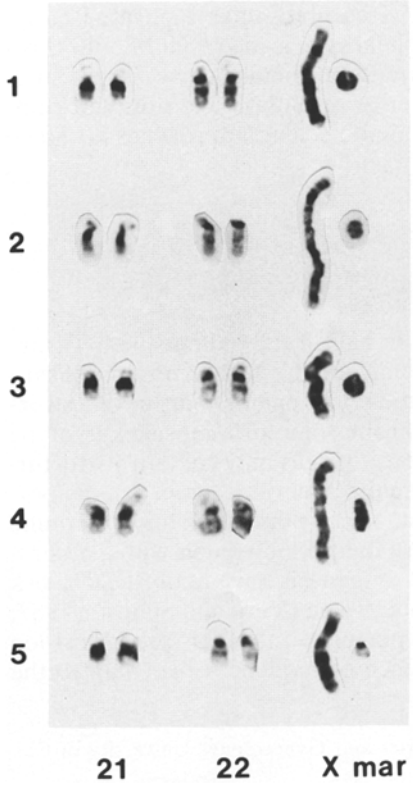

Fig. 1. Partial karyotypes from each of the five patients showing chromosomes 21 and 22 for size reference and the X and the marker *(mar)* chromosomes. The numbers to the left of each row refer to the patient number

Table 1. Patient data

Patient	Age	External genitalia	Clinical features	Karyotype
1	32 years	Normal adult female	Some Turner stigmata	45,X/46,X,r(?) 10%
2	4 months	Normal prepubertal female	Turner stigmata	45,X/46,X,r(?) 85%
	14 months		Developmental delay, growth delay	
3	14 months	Normal prepubertal female	Some Turner stigmata	45,X/46,X,r(?) 35%
4	18 years	Normal adult female	Turner stigmata	45,X/46,X,?idic(Y)(q11.2) 60%
5	2 years	Male, small testicles	Short, microcephaly	46,X,mar or r(?)
	13 years	Normal prepubertal male	Short, small, webbed neck	45,X/46,X,mar or r(?) 70%

Table 2. Analysis of markers. ND, Not done

Patient	Cytogenetic		Molecular			
	Q-banding	C-banding	Southern hybridization			In situ hybridization
			XC	YC	hyfin	
1	Yq12 absent	+ at centromere	+	−	−	ND
2	ND	+ at centromere	+	−	−	+ with biotinylated and tritiated XC
3	Yq12 absent	+ at centromere	+	−	−	+ with biotinylated and tritiated XC
4[a]	Yq12 absent	Two sites with centromeric pattern	+	+	+	Two sites with tritiated hyfin and pDP230
5	ND	+ at centromere	ND	+	+	+ with tritiated YC

[a] Other Southern hybridization results are given in Table 3

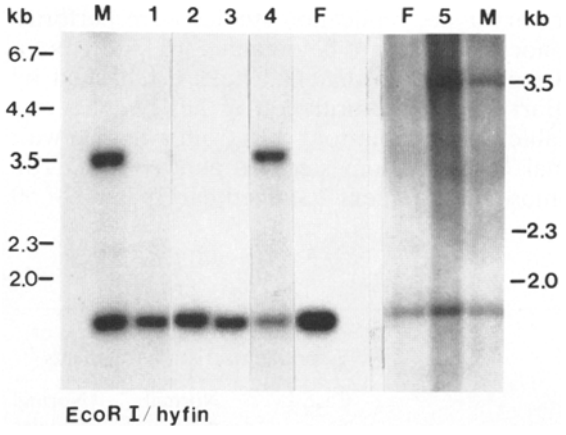

Fig. 2. Southern blot analysis of patient DNA *(1–5)* digested with *Eco*RI and hybridized to hYfin. Control DNA from a female *(F)* has a single 1.8-kb band representing the ZFX locus on the X chromosome. Control DNA from a male *(M)* has the 1.8-kb band in addition to the 3.5-kb band representing the ZFY locus on the Y chromosome. Only patients 4 and 5 have the Y-specific band

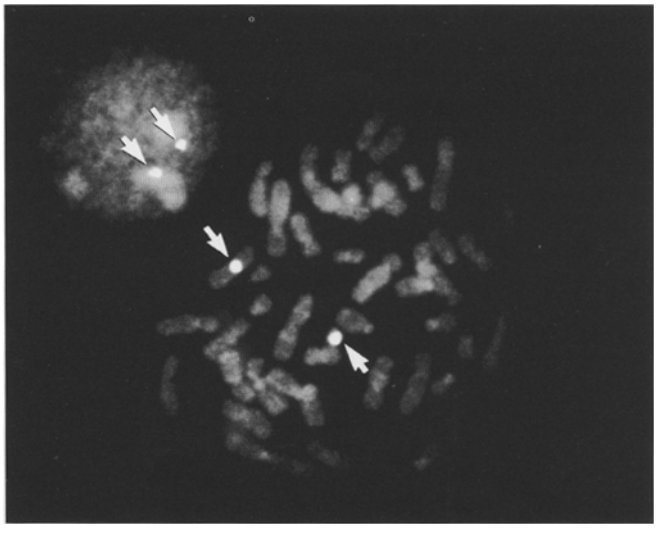

Fig. 3. Metaphase spread from lymphocytes of patient 2 after in situ hybridization with biotinylated XC. Hybridization signals *(arrows)* are present over both the X chromosome and the ring

were consistent with this interpretation. The marker did not fluoresce brilliantly as would be expected of band Yq12. Two sites stained positively after C-banding indicating the presence of two centromeres, one of which, without the usual centromeric constriction, is presumably inactive.

Molecular studies were undertaken to establish the identity of the marker chromosomes in the cases where classical cytogenetic methods failed to do so and to confirm and define the nature of the chromosome thought to be isodicentric. The DNA of patients 1, 2, and 3 displayed identical patterns of Southern blots hybridized to probes for the X and Y chromosomes. Each hybridized to XC, a probe for the centromeric region of the X chromosome, as expected since each contained a normal X chromosome (data not shown, Table 2). However, none of the three hybridized to YC, a probe for the Y-chro-

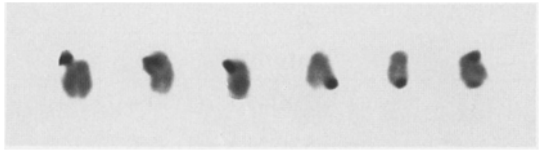

Fig. 4. Row of marker chromosomes from lymphoblastoid cells derived from patient 4, after in situ hybridization with tritiated hYfin. Either the short arm or the distal end of the long arm of the marker is labeled; the last marker chromosome *(right)* is labeled at both sites

mosome centromere (data not shown, Table 2), and each had patterns characteristic of females in that the Y-specific band was absent when hybridized to hYfin, a probe with homologies to X and Y chromosome sequences (Fig. 2). These results strongly suggest that each of these markers is derived from an X chromosome.

The X-chromosome origin was verified in the case of patients 2 and 3 by in situ hybridization of biotinylated XC to lymphocytes (Fig. 3). For patient 2, of a total 99 interphase cells that were scored, 42 (42%) had a single hybridization signal, while the remaining 57 cells (58%) each had two sites. The percentage of cells (58%) with a marker (two hybridization sites) differed from the figure (85%) obtained in the study of Giemsa-banded cells (Table 1). This is very unlikely due to the hybridization procedure as 35 of 35 metaphase cells and 99 out of 100 interphase cells from a normal control female scored revealed two hybridization sites. Since cells with the ring may have been selected in the chromosomal analysis, the percentage from the hybridization analysis may be more accurate. For patient 3, of 108 interphase cells scored, 69 (64%) had one hybridization signal and 39 (36%) had two. Although metaphase cells were not scored, the probe clearly hybridizes with the rings in both patients. When tritiated XC was hybridized to lymphoblasts established from patients 2 and 3, nearly every ring was covered with grains (data not shown).

The Southern hybridization patterns of DNA from patients 4 and 5 identified their markers as abnormal Y chromosomes. Both hybridized to YC (data not shown, Table 2), and each had the 3.5-kb *Eco*RI fragment that hybridizes to hYfin and is specific for the Y chromosome (Fig. 2). In situ hybridization studies confirmed these findings. Lymphocytes from patient 5 were hybridized with tritiated YC. Nearly every marker was heavily labeled with grains (data not shown), proving that Y sequences are present in the marker chromosome. Lymphoblasts established from cells of patient 4 were hybridized with tritiated hYfin and pDP230. For the probe hYfin, analysis of 47 cells that contained the marker chromosome revealed that 8 of 78 (10%) grains were over the marker chromosome and 7 grains (9%) were at band p21 of the X chromosome. These grains labeled either the short arm or the end of the long arm; one marker had grains at both ends (Fig. 4). After in situ hybridization with pDP230, both ends of every marker chromosome scored, as well as the distal region of Xp, exhibited clusters of grains (data not shown). Finally, DNA from patient 4 was hybridized with a battery of probes for the Y chromosome that recognize loci spanning its entire length. Every sequence except one that maps to the most distal band of the long arm (Yq12) was present (Table 3). Thus, the marker is an isodicentric chromosome containing Yp through Yq11.2, as its banding pattern suggested.

Because the phenotype of patient 2 seemed unusual given her karyotype, replication studies were performed. Lymphocytes could not be obtained for study, but a lymphoblastoid cell line that had been established by Epstein Barr virus transformation of her lymphocytes was available. Lymphoblastoid cells from a female with two normal X chromosomes served as a control. The ring chromosome of patient 2 stained darkly in 50 of 50

Table 3. Y-DNA analysis of case 4 [idic(Y)] by Southern blot hybridization[a]

Interval[b]	DNA hybridization probes		Reference	Presence (+) or absences (−) of Y-specific restriction fragments		
	Probe/locus	Stringency[c]		Case 4	Normal male	Normal females
1A1A	pDP1225 (SRY)	H	Page et al. (1990)	+	+	−
1A1B	pDP1056 (RPS4Y)	H	Fisher et al. (1990)	+	+	−
1A2	pDP1007 (ZFY)	H	Page et al. (1987a)	+	+	−
3	50f2/A, B	M	Guellaen et al. (1984)	+	+	−
3	pDP105/A	H	D.C. Page, unpublished	+	+	−
4B	50f2/D	M	Guellaen et al. (1984)	+	+	−
4B	pDP97 (DYZ3)	H	D.C. Page, unpublished[d]	+	+	−
5	pDP527	H	D.C. Page, unpublished	+	+	−
6	50f2/E, C	M	Guellaen et al. (1984)	+	+	−
7	pY431-*Hin*fA (DYZ2)	M	K. Smith, unpublished	−	+	−

[a] All probes were hybridized to *Eco*RI-digested human genomic DNAs
[b] Vergnaud et al. (1986); Page (1986); Page et al. (1990): intervals 1 and 3 correspond to Yp11.3 and Yp11.2, respectively; 4B represents pericentromeric region; 5, 6 correspond to Yq11.2; 7 is the heterochromatic region of Yq (Yq12)
[c] H, High stringency (hybridization at 47°C, wash at 65°C); M, medium stringency (hybridization at 42°C, wash at 55°C)
[d] Probe derived from cosmid Y97 (Wolfe et al. 1985)

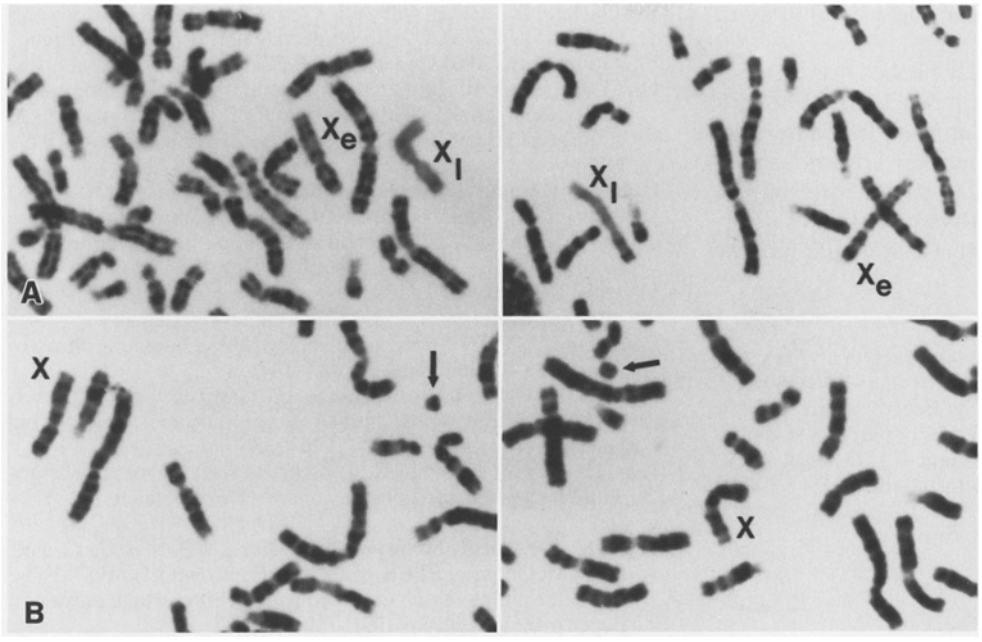

Fig. 5A, B. Replication patterns of the X chromosomes from lymphoblastoid cells of a female control (**A**) and patient 2 (**B**). Early replicating X chromosomes *(X_e)* stain darkly after the protocol while late replicating X chromosomes *(X_l)* stain very lightly. The control has one late and one early replicating X chromosome. Both the normal X and the ring chromosome *(arrow)* of patient 2 are early replicating

cells with a ring after BrdU treatment, which resulted in light staining of the late replicating X chromosome of the control in 48 or 50 cells (Fig. 5). Therefore, the ring chromosome is not late replicating.

Discussion

Identification of marker sex chromosomes is important for the clinical management of phenotypically female patients with a mosaic karyotype. Some studies have used G-11, C-banding, and distamycin A/DAPI methods to distinguish the X from the Y chromosomes (Wisniewski and Hirschhorn 1982; Magenis and Donlon 1982). These techniques rely on differential staining of the centromeric regions and do not always provide clearcut results, especially in the case of very small marker chromosomes (Gemmill et al. 1987) or small ring chromosomes where the centromere cannot be seen for topological reasons. In contrast, molecular probes for the centromeres and other portions of the sex chromosomes offer more definitive characterization (Crolla and Llerena 1988).

We have studied the marker chromosomess of one male and four female individuals using both cytogenetic and molecular methods. One of the female patients and the male patient had abnormal Y chromosomes, an isodicentric and a ring, respectively. The female phenotype associated with the isodicentric is presumably a consequence of mosaicism for the marker (Daniel 1985); a critical proportion of cells in critical tissues lost the isodicentric. The origin of this type of abnormal Y chromosome, called a Y^{nf} (nonfluorescent Y), has been the subject of some discussion in the literature (Daniel 1985). Our studies establish its isodicentric composition in this patient, as was found to be the case in a previous study of the three patients with Y^{nf} chromosomes (Gänshirt-Ahlert et al. 1987).

The remaining three female patients each had ring chromosomes derived from the X chromosome. Two of these individuals had classic features of Turner syndrome (Rosenfeld 1989). They had ring chromosomes of intermediate size, not large enough to contain the entire X chromosome but large enough to contain a substantial portion of it. In contrast, patient 2 had a very small ring chromosome and atypical facial features and developmental delay, in addition to typical features of Turner syndrome. This unusual phenotype might be explained if the ring chromosome were transcriptionally active because it lacked the inactivation center or centers on the X chromosome (Therman et al. 1979; Nakagome 1982; Brown et al. 1991). Replication studies of lymphoblasts indicated that the ring was active and supported this interpretation of the phenotype.

This explanation has previously been invoked to account for syndactyly, severe mental retardation, and coarse facial features in two individuals who were mosaic for ring X chromosomes (Kushnick et al. 1987). Approximately 30% of the rings in these unrelated individuals were early replicating. While these two patients share some features with our patient such as significant mental retardation and some facial characteristics, other findings like syndactyly were not present in our patient. The overlapping but different phenotypes might be reconciled if the assumption is made that rings, by necessity, have the same sequences near the centromeres but the breaks occurred in different places on the short and long arms. Thus, different parts of the X chromosomes are expressed at elevated levels. In addition, six other patients with mosaic 45,X karyotypes and small ring X chromosomes reported in the literature have demonstrated mental retardation and unusually severe growth retardation as well as some other clinical features (Van Dyke et al. 1991). Although replication studies were not performed, lack of an inactivation center and early replica-

tion were proposed to account for the phenotypes in these cases as well.

Although the choice of molecular probes was obvious in these cases, the same general approach could be employed in cases where cytogenetic analysis failed to identify the origin of supernumerary marker chromosomes. The initial cytogenetic studies might provide information about the marker (for example, C-band positive or negative, satellited or non-satellited, etc.) that would narrow the possibilities to be tested.

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References

Brown CJ, LaFrenier RG, Powers VE, Sebastio G, Ballabio A, Pettigrew AL, Ledbetter DH, Levy E, Craig IW, Willard HF (1991) Localization of the X inactivation centre on the human X chromosome in Xq13. Nature 349:82–84

Cremer T, Tesin D, Hopman AHN, Manuelidis L (1988) Rapid interphase and metaphase assessment of specific chromosomal changes in neuroectodermal tumor cells by in situ hybridization with chemically modified DNA probes. Exp Cell Res 176:199–220

Crolla JA, Llerena JC (1988) A mosaic 45,X/46,X,r(?) karyotype investigated with X and Y centromere-specific probes using a non-autoradiographic in situ hybridization technique. Hum Genet 81:81–84

Daniel A (1985) Y isochromosomes and rings. In: Sandberg AA (ed) The Y chromosome, part B: Clinical aspects of Y chromosome abnormalities. Liss, New York, pp 105–135

Fisher EMC, Beer-Romero P, Brown LG, Ridley A, McNeil JA, Lawrence JB, Willard HF, Bieger FR, Page DC (1990) Homologous ribosomal protein genes for the human X and Y chromosomes: escape from X inactivation and possible implications for Turner syndrome. Cell 63:1205–1218

Fryns JP, Kleczkowsk A, Vanden Bergh H (1983) The X chromosome and sexual development: clinical aspects. In: Sandberg AA (ed) Cytogenetics of the mammalian X chromosome, part B: X chromosome anomalies and their clinical manifestations. Liss, New York, pp 115–126

Gänshirt-Ahlert D, Pawlowitzki IH, Gal A (1987) Three cases of 45,X/46,XYnf mosaicism: molecular analysis revealed heterogeneity of the nonfluorescent Y chromosome. Hum Genet 76: 153–156

Gemmill RM, Pearce-Birge L, Bixenman H, Hecht BK, Allanson JE (1987) Y chromosome-specific DNA sequences in Turner-syndrome mosaicism. Am J Hum Genet 41:157–167

Guellaen G, Casanova M, Bishop C, Geldwerth D, Andre G, Fellous M, Weissenbach J (1984) Human XX males with Y single-copy DNA fragments. Nature 307:127–173

Jabs EW, Persico MG (1987) Characterization of human centromeric regions of specific chromosomes by means of alphoid DNA sequences. Am J Hum Genet 41:374–390

Jabs EW, Gable CA, Cutting GR (1989) Macromolecular organization of human centromeric regions reveals high-frequency, polymorphic macro DNA repeats. Proc Natl Acad Sci USA 86:202–206

Kushnick T, Irons TG, Wiley JE, Gettig EA, Rao KW, Bowyer S (1987) 45X/46X,r(X) with syndactyly and severe mental retardation. Am J Med Genet 28:567–574

Lau Y-FC, Chan K (1989) The putative testis-determining factor and related genes are expressed as discrete-sized transcripts in adult gonadal and somatic tissues. Am J Hum Genet 45:942–952

Lichter P, Cremer T, Bordern J, Manuelidis L, Ward DC (1988) Delineation of individual human chromosomes in metaphase and interphase cells by in situ suppression hybridization using chromosome specific library probes. Hum Genet 80:224–234

Magenis E, Donlon T (1982) Nonfluorescent Y chromosomes: cytologic evidence of origin. Hum Genet 60:133–138

Nakagome Y (1982) Inactivation centers in the human X chromosome. Am J Hum Genet 34:182–194

Page DC (1986) Sex reversal: deletion mapping the male-determining function of the human Y chromosome. Cold Spring Harbor Symp Quant Biol 51:229–235

Page DC (1987) Hypothesis: a Y-chromosomal gene causes gonadoblastoma in dysgenetic gonads. Development 101:151–155

Page DC, Mosher R, Simpson EM, Fisher EMC, Mardon G, Pollak J, McGillivray B, Chapelle A de la, Brown LG (1987a) The sex-determining region of the human Y chromosome encodes a finger protein. Cell 51:1091–1104

Page DC, Bieker K, Brown LG, Hinton S, Leppert M, Lalouel JM, Lathrop M, Nystrom-Lahti M, Chapelle A de la, White R (1987b) Linkage, physical mapping, and DNA sequence analysis of pseudoautosomal loci on human X and Y chromosomes. Genomics 1:243:256

Page DC, Fisher EMC, McGillivray B, Brown L (1990) Additional deletion in sex-determining region of human Y chromosome resolves paradox of X,t(Y;22) female. Nature 346:279–281

Rosenfeld RG (1989) Turner syndrome: a guide for physicians. The Turner's Syndrome Society, Stanford, California

Sinclair AH, Berta P, Palmer MS, Hawkins JR, Griffiths BL, Smith MJ, Foster JW, Frischauf A-M, Lovell-Badge R, Goodfellow PN (1990) A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. Nature 346:240–244

Therman E, Sarto GE, Palmer CG, Kallio H, Denniston C (1979) Position of the human X inactivation center on Xq. Hum Genet 50:59–64

Van Dyke DL, Walker A, Roberson JR, Weiss L (1991) Mental retardation in Turner syndrome. J Pediatr 118:415–417

Vergnaud G, Page DC, Simmler M-C, Brown L, Rouyer F, Noel B, Botstein D, Chapelle A de la, Weissenbach J (1986) A deletion map of the human Y chromosome based on DNA hybridization. Am J Hum Genet 38:109–124

Verma RS, Babu A (1989) Human chromosomes: manual of basic techniques. Pergamon Press, New York

Verp MS, Simpson JL (1987) Abnormal sexual differentiation and neoplasia. Cancer Genet Cytogenet 25:191–218

Wisniewski LP, Hirschhorn K (1982) Distamycin A-DAPI banding of nonfluorescent Y (Y^{nf}) chromosomes in 45,X/46,XY^{nf} mosaicism. Hum Genet 60:130–132

Wolfe J, Darling S, Erickson R, Craig I, Buckle V, Rigby P, Willard H, Goodfellow P (1985) Isolation and characterization of an alphoid centromeric repeat family from the human Y chromosome. J Mol Biol 182:477–485

Yang TP, Hansen SK, Oishi KK, Ryder OA, Hamkalo BA (1982) Characterization of a cloned repetitive DNA sequence concentrated on the human X chromosome. Proc Natl Acad Sci USA 79:6593–6597

Yang-Feng TL, Floyd-Smith G, Nemer M, Drouin J, Francke U (1985) The pronatriodilatin gene is located on the distal short arm of the human chromosome 1 and on mouse chromosome 4. Am J Hum Genet 37:1117–1128