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Opposite deletions/duplications of the X chromosome: two novel reciprocal rearrangements

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Paralogous sequences on the same chromosome allow refolding of the chromosome into itself and homologous recombination. Recombinant chromosomes have microscopic or submicroscopic rearrangements according to the distance between repeats. Examples are the submicroscopic inversions of factor VIII, of the *IDS* gene and of the FLN1/emerin region, all resulting from misalignment of inverted repeats, and double recombination. Most of these inversions are of paternal origin possibly because the X chromosome at male meiosis is free to refold into itself for most of its length. We report on two *de novo* rearrangements of the X chromosome found in four hypogonadic females. Two of them had an X chromosome deleted for most of Xp and duplicated for a portion of Xq and two had the opposite rearrangement (class I and class II rearrangements, respectively). The breakpoints were defined at the level of contiguous YACs. The same Xp11.23 breakpoint was found in the four cases. That of the long arm coincided in three cases (Xq21.3) and was more proximal in case 4 (Xq21.1). Thus class I rearrangements (cases 1 and 2) are reciprocal to that of case 3, whilst that of case 4 shares only the Xp breakpoint. The abnormal X was paternal in the three cases investigated. Repeated inverted sequences located at the breakpoints of rearrangements are likely to favour the refolding of the paternal X chromosome and the recombination of the repeats. The repeat at the Xp11 may synapse with either that at Xq21.3 or that at Xq21.1. These rearrangements seem to originate as the Xq28 submicroscopic inversions but they are identifiable at the microscopic level and result from a single recombination event. *European Journal of Human Genetics* (2000) **8**, 63–70.

Introduction

Unequal crossing-over between similar or identical sequences located either in introns belonging to the same gene or being part of tandemly arrayed homologous genes has long been known to be responsible for both intragenic deletions and duplications. Examples are defective LDL receptor genes,[1] lepore and antilepore haemoglobins,[2] and colour-vision abnormalities involving red–green pigment genes.[3] The progress of long-range sequencing analysis has shown a variety of other genomic disorders associated with chromosomal misalignment of repeated sequences located outside the gene itself. Intrachromatid recombination at male meiosis, via the parallel alignment of two inverted repeats, one inside a factor VIII intron and one 500 kb upstream, is known to disrupt the gene, giving rise to haemophilia A.[4,5] The same mechanism has been indicated as a cause of Hunter syndrome. In 13% of these patients, the *IDS* gene is disrupted by an homologous recombination event between the gene and the 90 kb telomeric IDS pseudogene.[6,7] Mispairing and recombination of the inverted repeats flanking the filamin

and the emerin gene in Xq28 are responsible for the benign inversion of the 48 kb region found in nearly 20% of the X chromosomes.[8] As the distance between repeats increases, the rearrangement becomes visible at the chromosomal or at least at interphasic level. The latter is the case of the reciprocal 1.5 Mb duplication or deletion of the CMT1A-REP in 17p12, associated respectively, with peripheral neuropathy Charcot-Marie-Tooth disease type 1A (CMT1A) and the hereditary neuropathy with liability to pressure palsies (HNPP).[9,10]

Several examples are known of rearrangements detectable at the level of metaphasic chromosomes whose origin is assumed to be due to abnormal crossovers between repeated sequences (for a review see Lupski[11]). The 5 Mb deleted region in 17p11.2, associated with Smith-Magenis syndrome (SMS), is flanked by a repeat gene cluster that is likely to mediate the reciprocal duplication.[12] The deletions at 15q11–q13, 7q11.23 and 22q11.2, associated with Prader-Willi, Williams and diGeorge syndrome, respectively, are likely to be mediated by repeated sequences flanking each deletion region and the same holds true for the common 8p deletion duplication.[13]

Here we describe two types of rearrangement involving the X chromosome at male meiosis and leading to deletion/duplication for opposite regions, which appear to be the reciprocal products of abnormal misalignment between repeated and inverted sequences located in Xp and Xq.

Subjects and methods
Patients
Case 1, EM She was born after normal pregnancy and delivery. At the age of 6 months she underwent surgery for an interventricular defect. At the age of 15 years she started growth hormone therapy because of short stature. Dysmenorrhea was reported. Her serum gonadotropin levels were increased (LH:30 U/L; FSH: 85 U/L). At the age of 18 her height was 150 cm and her weight 51 kg. Her psychomotor development was normal.

Case 2, NO She underwent clinical examination at the age of 73 years. At the time her height was 142 cm and her weight was 30 kg. Cubitus valgus was present. Primary amenorrhea was reported. Her intelligence was average.

Case 3, DS She was born after a normal pregnancy with a birth weight of 2800 kg. Psychomotor development was normal. At 16 years and 6 months investigations were carried out for primary amenorrhea. Increased levels of LH and FSH were found (LH 64 U/L; FSH 125 U/L) with hypoplastic uterus and ovaries. She was 170.5 cm tall, with a mid-parental height of 151.5 cm. Her weight was 75 kg. Clinical examination showed low posterior hairline, micrognathia, genus valgus and flat feet.

Case 4, ML She was born following normal delivery with a birth weight of 3150 g. Her growth and psychomotor development was normal. Serum LH and FSH, determined because of primary amenorrhea were increased (LH:60 U/L; FSH:120U/L). Clinical examination at 25 years of age showed a normal facies, rather short neck, dorso-lombar scoliosis, hyperconvex nails, brachymetacarpia. Her height was 171 cm (mid-parental height 169.5) and weight 63 kg.

Methods
Cytogenetic studies were performed on whole blood cultures, lymphoblastoid cell lines and, in case 1, also on skin fibroblasts, after GTG, QFQ and high resolution banding.[14] Fluorescent *in situ* hybridisation (FISH) was carried out on patients' metaphases with CEPH and ICRF YACs spread along chromosome X according to Carrozzo *et al*.[15] Genotyping of microsatellites (DNA VNTRs) was performed on the patients and their parents or their relatives by standard procedures.[13] The primers for DMD-STR49 were those given by Clemens *et al*[16] The primers for DXS8054 were CACACCACACCATC-CAG on the left and GAGCTATTTGACCCAAGCC on the right; the primers for DXS1223 were TGCCAATTTTTGCTTTTGTTATG on the left and AGGATTTTGCCACTCACTTCA on the right; the primers for DXS6804 were CCCAGATATTTTGACCACCA on the left and GGCATGTGGTTGCTATAACC on the right.

For each pair of primers 35 cycles of denaturation (94°C for 45 s), 45 s of annealing at the appropriate temperature, and 1 min of elongation at 72°C in a PTC-100TM (MJ Research Inc, Watertown, MA, USA) were performed. For the quantitative PCR (case 3, primers DMD-STR49), the number of cycles was reduced to 20. The PCR was performed in a total volume of 12.5 ml, containing 20 ng of genomic DNA, 1.25 mM of each nucleotide primer, 1.25 ml dNTPs (2 mM), 0.25 ml dATP35S, 0.75 ml MgCl2 (25 mM), 0.6 U Taq polymerase (Promega, Madison, WI, USA), 1.25 ml 10 × PCR buffer (Promega). The samples were preheated for 5 min at 94°C. PCR products were electrophoresed on a 7% polyacrylamide gel. Probe CRI-S232 (DXS278; Xp22.3, Yq11) was used in case 1 in Southern blot experiments according to Bardoni *et al*.[17] This probe recognises a set of polymorphic X-specific bands (four per chromosome in TaqI blots) and a set of constant Y-specific bands.

Results
In each of the four cases cytogenetic analysis revealed an abnormal X chromosome. We found no 45,X cells despite counting more than 100 metaphases in all tissues examined. In cases 1 and 2 the abnormal X chromosome was at first interpreted as an isochromosome for the long arms, but in cases 3 and 4 as an X chromosome with a deletion of the Xq26–qter portion. In lymphocytes from all cases and in skin biospy fibroblasts from case 1, the abnormal X chromosome was consistently late replicating, as revealed by the analysis of metaphases obtained after culturing in a medium containing 0.2 mg/ml BrdU for the last 6 hours.

Table 1   Results of STRP, Southern blot and FISH analyses

LOCUS	PROBE	POSITION	cM	1 E.M.	2 N.O.	3 D.S.	4 A.F.
DXYS60	yOX88	Xp22.3	0.38	−	−	++	++
DXS278	CRI-S232	Xp22.1	11	del(p)		nd	nd
DXS1223		Xp22.31	15	nd	del(p)*		
DSS	332F10	Xp21	42	del(p)	del(p)	nd	nd
STR49	DMD	Xp21.3	44	del(p)	ni	dup(p)	
DXS1058	957F5	Xp11.4	56	−	−	++	++
DXS8054		Xp11.3	73		del(p)*		
DXS1003	964C7	Xp11.23	77	−	−	++	++
DXS426	ICRFy900C1228	Xp11.23	79	−	−	++	++
DXS426 DXS1367	ICRFy900C1022	Xp11.23	79	+	+	+	+
DXS6849	ICRFy900C0874	Xp11.22	81	+	+	+	+
DXS8023	787F5	Xp11.22	85	+	+	+	
DXS8092	767C9	Xq21.2	96				+
DXS441	959H11	Xq21.2	96				+
WI-7287	955A12	Xq21.2	96				−
DXS1167	922B5	Xq21.3	100				−
DXS472	10GH4	Xq21.3	103				−
DXS1217	30HF9	Xq21.3	105	+	+	+	−
DXYS34	31HF3**	Xq21.3	105	+	+	+	−
DXY107	208A4	Xq21.3	105	++	++	−	−
DXYS10	33DC10	Xq21.3	105	++	++	−	
PLP	122G11	Xq22.2	117	++	++	−	
DXS1191	780H1	Xq22.3	117	++	++	nd	
COL4A5	4AC12	Xq22.3	119	++	nd	−	
DXS6804		Xq24	130	nd	nd	del(p)	
DXS7144	737D6	Xq25	143	++	nd	nd	
DXS1206	727D3	Xq26	147	nd	nd	del(p)	
DXS1047		Xq26	150	++	++	−	
DXS52	St14	Xq27	189	++,ni	nd	nd	

The green indicates the Xp region that is deleted in class I rearrangements and duplicated in those of class II. The red indicates the Xq region that is duplicated in class I rearrangements and deleted in those of class II.

+,-   indicates repectively presence and absence of hybridization signals on the abnormal X chromosome.
++   indicates the presence of a double set of hybridization signals on the abnormal X chromosome.
**del(p):** absence of paternal allele.
ni e nd: not informative and not done respectively.
*   the origin of the abnormal X has been deduced indirectly (see results).
**   this YAC maps also in Xp11.2.

Since the cytogenetic interpretations were unconvincing we decided to investigate all cases by FISH and DNA microsatellites. The results are summarised in Table 1.

According to the whole of the data the final cytogenetic interpretation was 46,X, deldup(X)(Xqter->q21.3–p11.23->qter) for cases 1 and 2 (Figure 1 a,c),
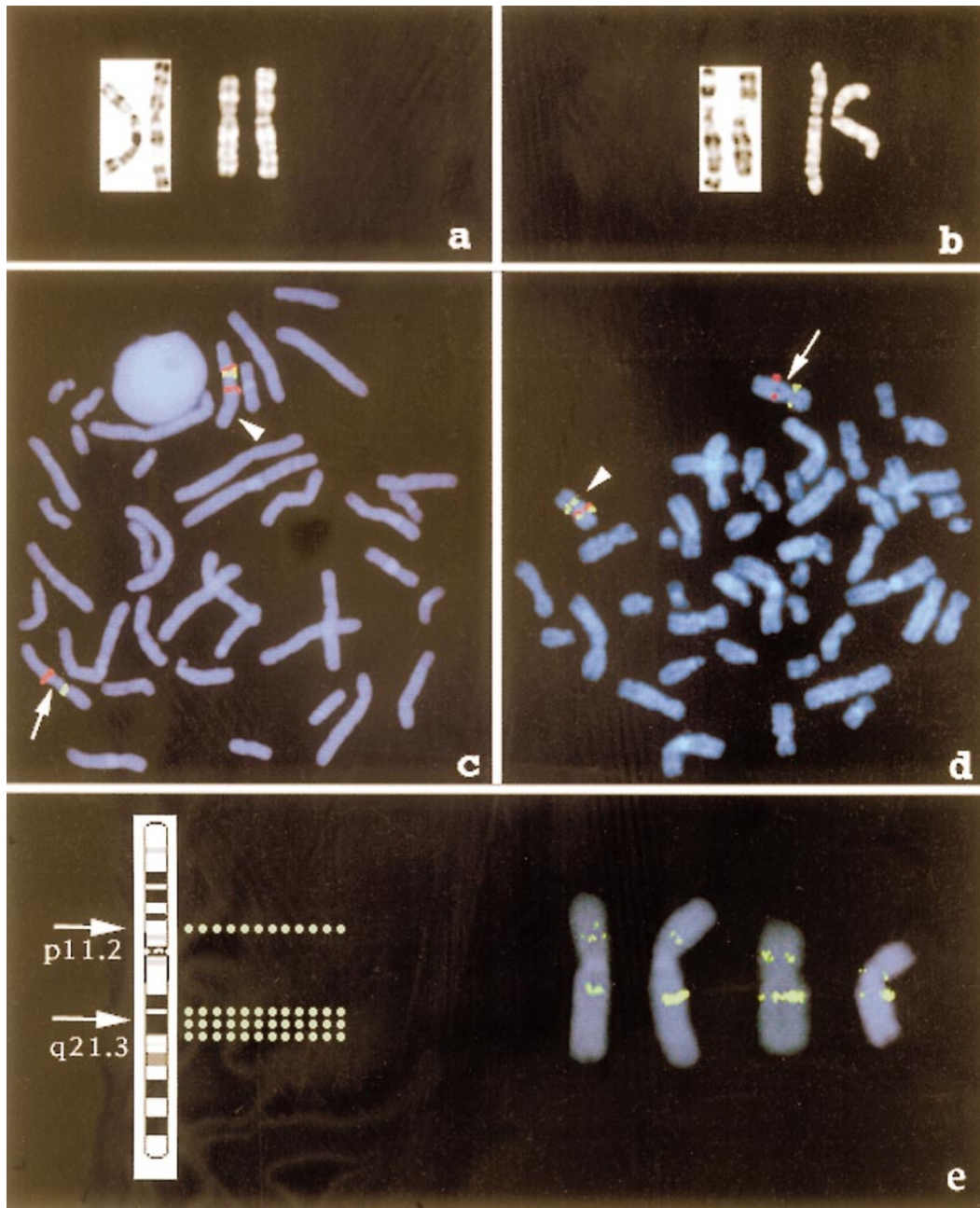
Figure 1a, b Cut-out from a G- (left) and a Q-banded (right) metaphase from case 2 **a** and case 3, **b** showing the normal (left) and the abnormal (right) chromosome X. The abnormal X has been interpreted as Xqter->Xq21.3–Xp11.23->Xqter in **a**, and as Xpter->Xq21.3–Xp11.23->Xpter in **b**. **c, d** FISH on metaphase chromosomes from cases 2 and 3. **c** FISH with YACs 33DC10 (red) (Xq21.3) and 787F5 (green) (Xp11.22). **d** FISH with YACs 905A8 (Xq21.3) and 964C7 (Xp11.23). Arrows indicate the normal X, arrowheads the abnormal ones. In **c** the abnormal X shows a red signal on the normal Xq. In the other arm, the green signal of the short arm is adjacent to the red one indicating the duplicated region. In **d** the abnormal X shows a green signal on the normal Xp. In the other arm the red signal of the Xq is adjacent to the green one indicating the duplicated region. **e** ideogram of the X chromosome (left) and four normal X (right) with hybridisation signals after FISH with YAC 31HF3 mapping to Xq21.3 and with less efficiency to Xp11.2.

46,X,deldup(X)(Xpter->Xq21.3–Xp11.23->qter) for case 3 (Figure 1 b,d) and 46,X,deldup(X)(Xpter->Xq21.1–Xp11.23->qter) for case 4. First type rearrangements, with Xq duplication and Xp deletion, are herein referred to as class I and those of cases 3 and 4 as class II. Both class I and class II rearrangements share the same breakpoint at Xp (Table 1) between YACs ICRFy900C1022 (DXS426 and DXS1367) and ICRFy900C1228 (DXS426) inside contig MPIMG-X1-ctg7 of the ICRF YACs library (The Genome Database: gdb.tigem.it). At Xq (Table 1), cases 1–3 have the same breakpoint between the two YACs 31HF3 (DXS1217, DXYS34, DXYS1, DXYS42) and 208A4 (DXYS107 and DXYS5).[18] The two YACs are separated by DXYS49. YAC 905A8, which covers DXYS49 and partially overlaps 31HF3 and 208A4, did not give clear hybridisation signals at Xq. It must be noted that YAC 31HF3 gave a double set of hybridisation signals along the X. We analysed 36 normal X chromosomes after FISH with 31HF3; all had the signal at Xq21.3 and only 12 at Xp11.2 (Figure 1e). Case 4 has an almost 10 cM more proximal breakpoint between YACs 959H11 (CHLC.GATA69D06, DXS441) and 955A12 (WI-7287, CHLC.GATA6G11) both at the 96 cM.

Microsatellite analyses of cases 1 and 3 and of their parents revealed the paternal origin of the abnormal X. In case 1, Southern blot experiments with CRI-S232 at Xp22.1, in the deletion region, showed only maternal alleles (Figure 2a). The same holds true for PCR analysis of CA repeats at STR49-DMD (Xp21), also in the deletion region (Figure 2b). In case 3,

quantitative PCR analysis at this locus, which in this case is duplicated, showed the paternal allele with double intensity of the maternal one (Figure 2e), whilst PCR analysis at DXS6804, at Xq24 which is deleted, demonstrated the absence of the paternal allele (Figure 2f). In case 2, only the blood of the sister was available. At loci DXS1223 (Xp22.3) and DXS8054 (Xp11.3), both in the deleted region of the abnormal X, the single allele present in the proposita's lane is not shared by her sister (Figure 2c,d) and thus it must be of maternal origin. The paternal allele, by definition from a single X chromosome, should have been present in both sisters. The sisters had the same father, as demonstrated by the finding that they share the same two alleles in six out of ten autosomal polymorphic loci (data not shown). These data consistently suggest that also in case 2 the abnormal X was of paternal origin. Parents of case 4 were not available.

Discussion

This report describes four rearrangements of the X chromosome, cases 1 and 2 resulting in Xq duplication and Xp deletion (Xqter->q21.3::p11.23->qter) (class I rearrangements) and cases 3 and 4 in Xp duplication and Xq deletion (respectively Xpter->Xq21.3–Xp11.23->qter and Xpter->Xq21.1–Xp11.23->qter) (class II rearrangements) which are mutually reciprocal (Figure 3a and b). All cases share the same breakpoint at Xp between YACs ICRFy900C1022
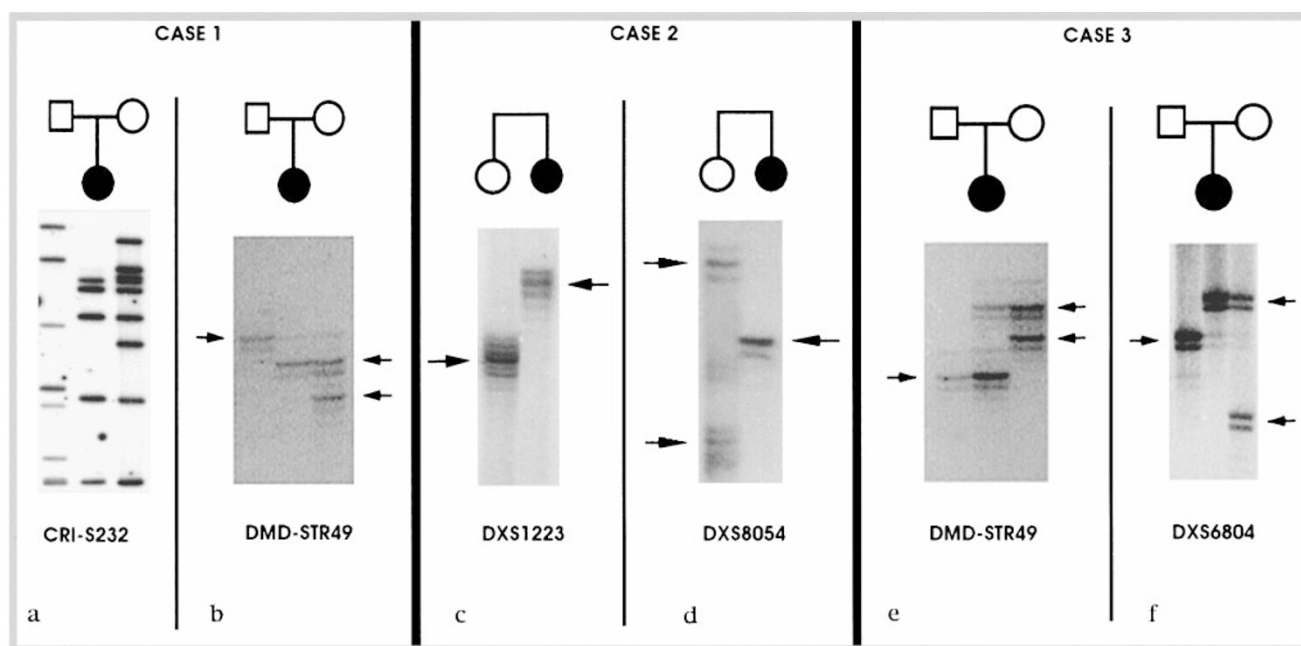
Figure 2 DNA analysis of cases 1, 2 and 3 and their relatives by Southern blot **a** and PCR **b, c, d, e, f**. **a, b** the proposita shows only the maternal alleles at loci CRI-S232 (Xp22.1) and DMD-STR49 (Xp21), both in the deleted region of the abnormal X. **c, d** proposita's alleles at loci DXS1223 (Xp22.31) and DXS8054 (Xp11.22), both in the deleted region of the abnormal X, are not shared by her sister and thus are of maternal origin (see text). **e** quantitative PCR at DMD-STR49 (Xp21), in the duplicated region of the abnormal X, shows that in the proposita the paternal allele has double intensity in respect to the maternal one. **f** the proposita shows only the maternal alleles at locus DXS6804 (Xq24), in the deleted region of the abnormal X.

(DXS426 and DXS1367) and ICRFy900C1228 (DXS426) (Table 1). At Xq, cases 1–3 have the same breakpoint between YACs 31HF3 (DXYS1217, DXYS34, DXYS1, DXYS42) and 208A4 (DXY107, DXYS5), whilst case 4 has an almost 10 cM more proximal breakpoint between 959H11 (CHLC.GA-TA69D06, DXS441) and 955A12 (WI-7287, CHLC.GA-TA6G11). Parental origin of the abnormal X was assessed in cases 1–3 and resulted in paternal (Figure 2).

The consistent localisation of the breakpoints and the identical parental origin of the abnormal chromosomes led us to suspect that a common mechanism was responsible for the two reciprocal rearrangements. We postulate that inverted repeated sequences are located at the breakpoints allowing, at paternal meiosis, synapses and recombination between the short and the long arms of the X chromosome refolded into itself (Figure 3a' and b'). The double set of signals at Xp11.2 and Xq21.3 displayed by normal X chromosomes hybridised with YAC31HF3 (Figure 1e) indeed suggests that these two bands contain the same DNA sequence.

This observation would indicate that also the X chromosome, as other chromosomes,[19] contains paralogous sequences spread along its length. The finding of two different breakpoints in Xq, one at DXYS5 (cases 1–3) and the other between DXS441 and WI-7287 (case 4), suggests that at

least two repeats with the same orientation are spread along Xq so that misalignment with that at Xp11.2 can occur either with one or the other. At paternal meiosis the X and the Y chromosomes pair at the Xp-Yp pseudoautosomal region but are free for the rest of their length. It has been demonstrated that this configuration favours refolding of the chromosomes into themselves, leading in turn to intrachromosome synapses and recombination between repeated sequences. Examples are the inversions disrupting the factor VIII gene that causes severe haemophilia A[4] and the inversion disrupting the IDS gene causing Hunter's disease.[6,7] It has been estimated that such exchanges are about 300-fold more frequent during male gametogenesis[5] probably because at female meiosis refolding is prevented by the synapsis along the two X chromosomes. Intrachromosome recombination of the paternal X seems also to be the most likely explanation for the filamin/emerin inversion.[8]

In these cases, the rearrangement is balanced, although it may or may not have pathological effects. To explain its dynamics, one has to assume the occurrence of two exchanges within the misaligned region, since a single exchange would produce an acentric or a dicentric product.[8] In our deleted duplicated X chromosomes a single exchange along the mispaired region would produce both class I and class II rearrangements, whilst two exchanges would lead to
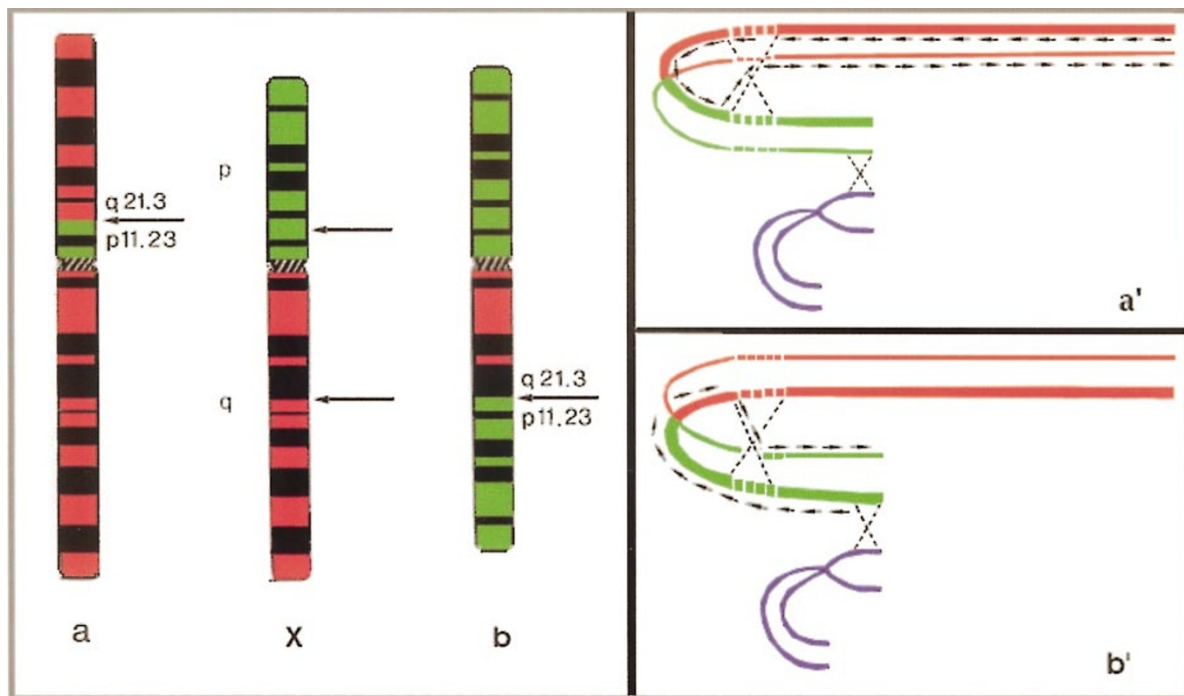
Figure 3 **left** Normal X chromosome between the abnormal ones found in cases 1 and 2 **a** and in case 3 **b**. In case 4 the Xp breakpoint is the same, whilst that in Xq is more proximal. **right** Proposed mechanism of the origin of cases 1 and 2 **a'** and 3 **b'** during male meiosis. The X (red and green), joint to the Y (violet) at PAR1 (crossing between the X and the Y), refolds into itself allowing the repeated sequences (dotted lines) at Xp11.23 and Xq21.3 to synapse and recombine. According to the Xq breakpoint of case 4, the repeat at Xp11.23 can also recombine with a repeat at Xq21.1. A single crossover between the chromatids leads to the two reciprocal products (arrows), Xqter- > Xq21.3–Xp11.23- > Xqter **a'** and Xpter- > Xq21.3–Xp11.23- > Xpter **b'**.

an inverted X chromosome similar to that reported by Keitges et al[20] and Pfeiffer et al.[21]

Females with structural abnormalities of the X chromosome frequently have the Turner phenotype or present with primary or secondary amenorrhea. An i(Xq), dicentric in the great majority of cases, is by far the most frequent structural anomaly associated with Turner syndrome, followed by X chromosome rings, Xp deletions and pseudodicentric chromosomes with breakpoints along Xp or Xq.[22] In the latter, as in the r(X), mosaicism for a 45,X cell line significantly contributes to Turner phenotypes. In the other rearrangements, Turner stigmata derive by monosomy for the X short arm[23] as in the case of our patients 1 and 2. We were able to find in the literature two cases similar to our class I rearrangements (Callen et al[24] case WD; Jacobs et al,[22] case 95/2770). In both, the rearrangement had a paternal origin. It is possible that such class I rearrangements are underestimated and interpreted as Xq isochromosomes. The case reported by Callen et al[24] was in fact found while studying the parental origin of X isochromosomes.

Primary or secondary amenorrhea without major Turner signs is associated both with Xq deletions and reciprocal X/autosome translocations.[18,25] Thus in our cases 3 and 4 primary amenorrhea is due to the Xq21-qter deletion rather than to Xp duplication. In fact large Xp duplications do not have any influence on female fertility, as demonstrated by the mothers of XY patients with sex reversal due to Xp21 duplication.[26–30] Another patient with amenorrhea and a rearrangement similar to those of class II has been reported.[31] It is of interest to note that this patient, as cases 3–4, is taller than average, or at least than expected from her mid-parental height. This seems to be related to the additional copy of the SHOX gene, located in the Xp/Yp pseudoautosomal region, which has been suggested to be a major locus involved in linear growth.[32] Thus class II rearrangement is related to a syndrome characterised by primary/secondary amenorrhea with hypergonadotropic hypogonadism and increased height. It is interesting to note that our first classification of the rearrangement in cases 3 and 4 was del(X)(q26). The fact that in a review of the Xq deletions,[33] high stature was present among cases with del(X)(q25–26), who also have primary/secondary amenorrhea, suggests that such deleted chromosomes might be class II rearrangements.

Acknowledgements

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