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ORIGINAL INVESTIGATION

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# Phenotypic effects of balanced X-autosome translocations in females: a retrospective survey of 104 cases reported from UK laboratories

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**Abstract** Females with balanced X-autosome translocations are a clinically heterogeneous group of patients in which X breakpoint position and replication behaviour may influence phenotypic outcome. This study reviewed all cases reported by UK cytogenetics laboratories over a 15-year period (1983–1997). Publication bias was avoided by reviewing all reported cases. One hundred and four female carriers were identified, 62 of who were probands. By reason for referral, these were: multiple congenital abnormalities and/or developmental delay (MCA/DD): 26 (42%); gonadal dysfunction: 22 (35%); phenotypically normal with or without recurrent miscarriage (NRM): 9 (15%); recognized X-linked syndrome: 5 (8%). The information obtained was compared with published data and with data from the authors' own laboratories of female patients with balanced autosome-autosome translocations ($n$=115). We concluded that: (1) MCA/DD cases were significantly over-represented compared to previous published data ($P$<0.005) and were more common than in female probands with balanced autosome-autosome translocations ($P$<0.05). (2) MCA/DD cases showed random breakpoint distribution along the X chromosome ($P$>0.05). MCA/DD cases with subtelomeric breakpoints at Xp22 or Xq28 were not always associated with deviation from the expected pattern of X-inactivation where this was known. De novo cases were significantly more likely to be assigned as MCA/DD than any other category ($P$<0.005). (3) Gonadal dysfunction (GD) was invariably associated with a 'critical region' breakpoint, Xq13– q26, (20/22 probands). However, 7/44 (16%) of patients surveyed had breakpoints within Xq13-Xq26 and proven fertility. (4) Recognized 'X-linked syndrome' cases were significantly under-represented ($P$<0.001) compared to previous published data.

A collaborative study on behalf of the UK Association of Clinical Cytogeneticists (ACC)

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## Introduction

Female balanced X-autosome translocation carriers are a clinically heterogeneous group of patients (Mattei et al. 1982; Schmidt and Du Sart 1992; Katz-Fuller et al. 1999). They fall into four broad phenotypic categories. They may be: phenotypically normal, but have a history of recurrent miscarriage (NRM); have some form of gonadal dysfunction (GD); have a well-defined X-linked recessive or dominant disorders (XLD), or have congenital abnormalities and/or developmental delay (including learning difficulties) (MCA/DD).

The importance of X-breakpoint position was demonstrated in cytogenetic studies of females with gonadal dysfunction in the form of premature ovarian failure (POF). Sarto et al. (1973), Madan (1983) and Therman et al. (1990) noted that POF was usually confined to patients with breaks within a 'critical region' between Xq13 and Xq26, although Madan (1983) noted that patients with a breakpoint at Xq22 escaped POF. Gonadal dysfunction may arise, either from temporally inappropriate gene expression following incomplete pairing of X chromosomes at pachytene (Therman et al. 1990) or as a result of haploinsufficiency within the critical region. Disruption of critical gene expression may result from a 'position effect' (local alteration of chromatin conformation), or as a result of deletion of one or more POF-related genes (Sala et al. 1997). Two groups of candidate POF-related genes have

been identified: *POF1* within Xq26-q27 (Tharapel et al. 1993) and *POF2* within Xq13-q21 (Powell et al. 1994). Sala et al. (1997) reported that at least eight different genes within a 15-Mb region at Xq21 might be involved in ovary development. Candidate POF genes have been identified, e.g. *DIA* (a human homologue of the *Drosophila* diaphanous gene) (Bione et al. 1998). Fine mapping studies of *POF1* (Davison et al. 2000) and *POF2* (Prueitt et al. 2000) are in progress.

Cytogenetic investigation of females with well-defined X-linked disorders who were 'manifesting heterozygotes', showed that a proportion of these patients were carriers of X-autosome translocations. Translocations were first described in patients with Duchenne muscular dystrophy (Lindenbaum et al. 1979, Jacobs et al. 1981). These cytogenetic observations were exploited to map and define the dystrophin gene at Xp21 (Ray et al. 1985, Boyd et al. 1987, Cockburn et al. 1992). Subsequently, this approach has been applied to other X-linked disease genes, e.g. X-linked lissencephaly (Matsumoto et al. 1998), and at least one form of X-linked mental retardation (Zemni et al. 2000).

Mattei et al. (1982) systematically reviewed X inactivation in X-autosome (X-aut) balanced carriers. They noted that in these patients the normal X chromosome is invariably inactive, and suggested that this non-random pattern of inactivation was selected for in order to achieve functional monosomy for X chromosome gene expression. Departure from the expected pattern of X inactivation would result in late replication and inactivation of the derived (X) t(X-aut) chromosome that contained the X inactivation centre (XIC) at Xq13. This pattern would give rise to functional autosomal monosomy (assuming the portion of autosomal material on the derived X is inactivated) and equally importantly, functional X chromosome disomy for the portion of the X chromosome translocated onto the active reciprocal translocation product (Schmidt and Du Sart 1992). Departure from the expected pattern of inactivation has been associated with an abnormal phenotype (Hagemeijer et al. 1977, Mattei et al. 1978, Sands 1980, Wolff et al. 1998). This might result from functional autosomal monosomy and/or functional X chromosome disomy. Where the derived X chromosome was late replicating, the 'spreading effect' of inactivation from X-chromatin to contiguous autosomal chromatin was incomplete or non-contiguous, as judged by cytogenetic techniques (Mattei et al. 1982, Keitges and Palmer 1986). This had implications for predicting phenotypic outcome in cases where late replication status had been established. Spreading effects, as judged by phenotypic observation, also escaped detection by molecular cytogenetic markers of X inactivation such as H4-acetylation studies and XIST mRNA hybridization studies (Keohane et al. 1999). The molecular basis for 'spreading effects', and their apparent variability, is not yet understood. Gene expression studies in somatic cell hybrids have confirmed earlier cytogenetic observations that the process may be discontinuous (White et al. 1998).

Schmidt and Du Sart (1992), in a large survey ($n$=122), observed that for balanced carriers there was an association between an abnormal MCA/DD phenotype and breakpoints clustered at the ends of the X chromosome, in bands Xp22 and Xq28. They proposed that relaxed selection pressure in these patients gave rise to functional partial X disomy for the small portion of X chromosome translocated onto the autosomal derivative product. They argued that this functional X disomy was the critical factor in determining an abnormal phenotypic outcome, rather than the reciprocal functional partial autosomal monosomy. Functional Xp disomy, rather than gene disruption, has also been proposed as the major causative factor in patients with hypomelanosis of Ito (Hatchwell 1996). This disorder does not fit either an X-linked dominant or recessive pattern of inheritance. It is characterized by streaks or whorls of hypopigmented skin, underlying CNS abnormalities and chromosomal mosaicism associated with patches of hypopigmented skin (Donnai et al. 1986). Patients with this disease have been described with X-autosomal translocations (Hatchwell et al. 1996, Rivera et al. 2000). In contrast to the Schmidt and Du Sart patient group, these patients have X chromosome breakpoints at or near the centromere, which may indicate that a different underlying mechanism gives rise to the functional Xp disomy seen in a proportion of these patients' cells (Rivera et al. 2000).

We attempted to determine whether cases with an abnormal phenotype, including patients with multiple congenital abnormality or developmental delay (MCA/DD), were under- or over-represented in the literature by reason for referral. UK laboratories were retrospectively surveyed for all available reported cases irrespective of their publication status.

## Patients and methods

All laboratories ($n$=33) offering an appropriate cytogenetic service in the United Kingdom were surveyed for cases where an apparently balanced t(X-aut) female chromosome complement had been ascertained and reported. The circulated questionnaire asked for laboratory identification, sample identification, referral reason, karyotype, results of X-replication studies, and the availability of a permanent cell-line. No patient samples were requested or received. No limit was placed on laboratories as to the time that had elapsed since the cases had been originally reported. G-banded analysis had been performed on all cases. Data were compared where possible with patient data entered into the UK Oxford Chromosome Abnormality Database.

## Results

Returns were received from 18 laboratories, one of which reported there were no cases to submit. A total of 104 two-break rearrangements (Table 1) and 3 three-break rearrangements (data not shown) were reported. The latter were excluded from subsequent analysis. Sixty-two probands (new referrals/index patients) were identified from the 104 returns. A further 42 patients were identified as a result of family follow-up of index patients who either had a balanced t(X-aut) karyotype (probands in this study) or had an unbalanced t(X-aut) karyotype. Data

**Table 1** Female balanced X-autosome carriers (*Abscan* abnormal findings on scan, *amen* amenorrhoea, *Chr abn* chromosomal abnormality, *DD* developmental delay, *Dys* dysmorphic, *F/H* family history of, *Hypo* hypomelanosis, *LD* learning difficulties, *POF* premature ovarian failure, *Rec misc* recurrent miscarriage, *DoB* date of birth, *DoR* date of receipt of sample, *N/A* not known or not available)

| Case[a] | Lab. | Lab. ref. | Proband group | Referral reason | X band | Karyotype | DoB | DoR | $X^R$ status[d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | SA | B3876/89[b] | | Normal; F/H trans | p22 | 46,X,t(X;5)(p22.33;p15.1) | 15/10/38 | 13/10/89 | 126/150 |
| 2 | SA | B91/698[b] | | Child: der(X)t(X;5) | | 46,X,t(X;5)(p22.33;p15.1)mat | 5/5/68 | 13/2/91 | 2/3 |
| 3 | GU | 87/00341[b] | | Child: der(20)t(X;20) | | 46,X,t(X;20)(p22.31;q13.3) | 10/27/57 | 1/23/87 | |
| 4 | BR | 88/3244 | | Child: der(X)t(X;5) | | 46,X,t(X;5)(p22.3;p15.1) | 5/5/68 | 30/9/88 | |
| 5 | BR | 93/2531 | | Children: der(9)t(X;9) | | 46,Xt(X;9)(p22.3;q12) de novo | 26/8/40 | 20/5/93 | |
| P6 | GA | S37 | NRM | Rec misc | | 46,X,t(X;1)(p22.1;p31) | 12/9/56 | 10/3/97 | |
| P7 | BM | B95/0503 | MCA/DD | MCA | | 46,X,t(X;1)(p22.1:p32) de novo | 6/10/94 | 24/1/95 | |
| 8 | OX | 93B/0174[b] | | Relative: t(X;9) | | 46,X,t(X;9)(p22.1;q12)mat | N/A | 5/2/93 | |
| 9 | OX | 93B/1611 | | Short | | 46,X,t(X;9)(p22.1;q12) | 10/7/32 | 3/2/93 | |
| P10 | SH | S527/97 | MCA/DD | Abscan TOP (20 weeks) | | 46,X,t(X;4)(p22.1;p15.2) de novo | 22/9/69 | 14/4/97 | |
| P11 | BM | B93/5795 | | Child: der(4)t(X;4) | | 46,X,t(X;4)(p22.1;q35) | 16/6/63 | 25/10/93 | |
| 12 | BM | B94/1811 | | F/H Chr abn | | 46,X,t(X;4)(p22.1:q35) | 11/8/88 | 23/3/94 | 100% |
| P13 | GU | 95/3726 | NRM | Rec misc | | 46,X,t(X;6)(p22.13;q11.2)mat, t(2;6)(q14;q21)pat | 10/16/69 | 6/5/95 | |
| 14 | GU | 95/4871 | | Rec misc, child: t(X;6) | | 46,X,t(X;6)(p22.13;q11.2) | 2/5/45 | 7/18/95 | |
| P15 | SH | B907/96 | MCA/DD | DD, Dys | | 46,X,t(X;19)(p22.1;p13.1) de novo | 6/6/92 | 3/7/96 | |
| 16 | SH | B467/92 | | Child: der(X)t(X;22) | | 46,X,t(X;22)(p22.1;q11.1) | 27/5/64 | 6/4/92 | |
| 17 | SH | B4842 | | Daughter + grandson: der(X)t(X;4) | | 46,X,t(X;4)(p22;p16) | 19/8/86 | 17/9/86 | |
| P18 | SA | B4108/90[b] | MCA/DD | ASD, LD, ?fragile X | | 46,X,t(X;4)(p22;q27) de novo | 11/3/79 | 23/11/90 | 100% |
| 19 | SA | B171/73 | | Children: der(X)t(X;9) | | 46,X,t(X;9)(p22;q12) | N/A | N/A | |
| P20 | DU | 99/0118 | MCA/DD | PND; abscan; fetus: t(X;12) | | 46,X,t(X;12)(p22;q24) de novo | TOP | 17/2/99 | |
| P21 | SA | B1286/89[b] | XLD | DMD, short stature | p21 | 46,X,t(X;9)(p21.2;q21.3) de novo | 6/7/86 | 5/6/89 | 100/100 |
| P22 | CR | 2365/86 | NRM | Child: der(X)t(X;4) | | 46,X,t(X;4)(p21.1;q33) | N/A | N/A | 100% |
| P23 | NO | B99/1158 | XLD | Muscular dystrophy | | 46,X,t(X;9)(p21;q22) | 15/10/92 | 29/4/99 | |
| 24 | BR | 93/5454 | | Fetus: der(X)t(X;11) | | 46,X,t(X;11)(p21;q14)mat | 5/10/72 | 19/10/93 | |
| 25 | BR | 94/5096 | | Mother of no. 24 | | 46,X,t(X;11)(p21;q14) de novo | 3/7/48 | 16/9/64 | |
| P26 | CM | KB496 | MCA/DD | MCA, DD, ?Bloom's | | 46,X,t(X;22)(p21;q13) de novo | 7/6/72 | 10/7/77 | |
| P27 | GU | 93/2128[b] | XLD | Fetus: ?Norries | p11.4 | 46,X,t(X;1)(p11.4;p36.3) de novo | 10/5/55 | 3/26/93 | |
| P28 | SM | B341/96 | NRM | Rec misc | | 46,X,t(X;7)(p11.4;q36.2)mat | 16/5/65 | 23/2/96 | |
| P29 | NE | B98/2239 | MCA/DD | LD, neck webbing | | 46,X,t(X;8)(p11.4;p21.3) de novo | 27/12/94 | 11/1/99 | 48/50 |
| 30 | SM | B654/96 | | Child: t(X:7) | | 46,XX,t(X;7)(p11.4;q36.2) | 16/12/34 | 16/7/96 | |
| P31 | LI | B95/3265 | GD | ?Turners, POF | p11.3 | 46,X,t(X;4)(p11.3;q21.2) | 15/12/56 | 25/11/95 | |
| P32 | ED | 83–963 | MCA/DD | MCA | | 46,X,t(X;7)(p11.3;q36) | N/A | N/A | 23/23 |
| P33 | ED | 88–2140 | MCA/DD | Dys/IUGR | | 46,X,t(X;18)(p11.23;p11.21) | 28/10/88 | 5/11/88 | |
| 34 | BM | B95/1181 | | Child: t(X;19) | p11.2 | 46,X,t(X;19)(p11.23;p13) | 14/7/76 | 22/3/95 | |
| 35 | SA | B1644/87 | | PND; fetus: t(X;22) | | 46,X,t(X;22)(p11.23;q13.1) de novo | 6/11/58 | 1/6/87 | |
| 36 | GU | 94/5486[b] | | F/H translocation | | 46,X,t(X;2)(p11.2;q31)mat | 7/30/94 | 8/8/94 | 30/30 |
| 37 | GU | 94/5990[b] | | F/H translocation | | 46,X,t(X;2)(p11.2;q31)mat | 2/9/93 | 9/1/94 | 30/30 |
| 38 | GU | 94/2727[b] | | F/H translocation | | 46,X,t(X;2)(p11.2;q31)mat | 12/18/74 | 4/25/94 | |

**Table 1** (continued)

| Case[a] | Lab. | Lab. ref. | Proband group | Referral reason | X band | Karyotype | DoB | DoR | $X^R$ status[d] |
|---|---|---|---|---|---|---|---|---|---|
| P39 | SA | B488/83 | MCA/DD | DD, ?fragile X | | 46,X,t(X;19)(p11.2;q13.3) de novo | 25/5/73 | 28/2/83 | |
| 40 | BM | B96/2246[b] | | child: der(X)t(X;6) | | 46,X,t(X;6)(p11.2;p21.1) | | | 26/26 |
| P41 | OX | 92B/0712 | MCA/DD | PND | | 46,X,t(X;8)(p11.2;q24.1) | 18/3/92 | 20/3/92 | 100% |
| P42 | CR | 92/3474 | MCA/DD | DD | | 46,X,t(X;16)(p11.2;q13) | 8/2/91 | 8/3/93 | 100% |
| P43 | CM | GB97/1165 | MCA/DD | DD, Schwannoma | | 46,X,t(X;22)(p11.2;q11.2) de novo | 9/2/71 | 14/11/97 | |
| P44 | OX | 96B/2333 | MCA/DD | DD | | 46,X,t(X;22)(p11.2;q11.2) de novo | 1/3/93 | 4/11/96 | 60/60 |
| 45 | NO | B81/2786 | | Child: der(X)t(X;9) | p11.1-q11 | 46,X,t(X;9)(?p10;?q10) | 3/4/54 | 6/4/82 | 5/ 5 |
| P46 | SA | B2065/94[b] | XLD | Hypo of Ito | | 46,X,t(X;17)(p10;q10) de novo | 17/4/69 | 24/6/94 | 100/100 |
| 47 | CR | 3531–91 | | PND: fetus with ASD | | 46,X,t(X;19)(p10;q10) | 10/11/56 | 19/11/91 | |
| P48 | SA | B2206/96[b] | XLD | Hypo of Ito; known t(X;13) | | 46,X,t(X;13)(q11;q10) de novo | N/A | 14/6/96 | 38/50 (skin-normal) |
| P49 | SA | B506/83[b] | NRM | Rec misc | q13 | 46,X,t(X;8)(q13.1;p11) | 16/3/54 | 11/2/83 | 105/105 |
| P50 | SA | B2212/80[b] | MCA/DD | DD | | 46,X,t(X;14)(q13.1;q11.2) de novo | 24/11/79 | 3/8/80 | 100/100 |
| P51 | NE | B92/0983 | MCA/DD | MCA | | 46,X,t(X;22)(q13.1;q11.21) | 3/3/92 | 28/7/92 | 50/50 |
| P52 | BM | B97/3513 | MCA/DD | ?Fragile X, DD | | 46,X,t(X;12)(q13;q15) de novo | | | 100% |
| P53 | GU | 92/0595[b] | NRM | Sibling: DD | | 46,X,t(X;15)(q13;q21)mat | 10/23/82 | 1/20/92 | |
| 54 | GU | 92/9050[b] | | Sibling: DD | | 46,X,t(X;15)(q13;q21)mat | 4/29/84 | 12/21/92 | 23/25 |
| 55 | GU | 92/4249[b] | | Child: t(X;15) | | 46,X,t(X;15)(q13;q21) | 9/27/58 | 6/1/92 | |
| P56 | CM | B94/2816 | GD | Primary amen (18 years) | | 46,X,t(X;22)(q13;q11.1) | 5/7/76 | 22/12/94 | |
| P57 | NE | B95/1242 | GD | Oligomenorrhoea, ?POF | | 46,X,t(X;6)(q13;q14.2) de novo | 22/2/77 | 31/10/95 | 25/25 |
| P58 | SA | B 3022/78 | GD | POF | q21 | 46,X,t(X;2)(q21.1;q37) | 13/7/44 | 22/11/78 | |
| P59 | SH | B41/95 | GD | Secondary amen | | 46,X,t(X;7)(q21.32;q11.23) | 4/3/77 | 25/1/95 | |
| P60 | SA | B2897/81[b] | GD | Primary amen | | 46,X,t(X;9)(q21.1;q34.3) de novo | 7/8/64 | 15/10/81 | 100/100 |
| P61 | OX | 91B/1169[b] | GD | Infertility, oligomenorrhoea | | 46,X,t(X;9)(q21.2;p22.3) | 31/1/61 | 25/02/91 | 25/25 |
| P62 | SA | 98/5022 | NRM[c] | PND; 1:47 Downs risk | | 46,X,t(X;11)(q21.1;q21) de novo | 6/2/98 | 8/7/98 | 62/62 |
| P63 | BR | 83/0257 | GD | Primary amen | q22 | 46,X,t(X;2)(q22;p23) de novo | 8/12/64 | 27/1/83 | |
| P64 | CM | KB6677[b] | GD | Ovarian dysfunction | | 46,X,t(X;10)(q22.1;p11.2) | 11/10/63 | 19/8/98 | 100% |
| 65 | BM | B91/5260 | | Child: der(X)t(X;15) | | 46,X,t(X;15)(q22:p11) | 6/7/54 | 21/11/91 | 100% |
| 66 | CR | 772/88 | | Child: der(X)t(X;17) | | 46,X,t(X;17)(q22.1;q23.3) | N/A | N/A | 100% |
| 67 | ED | 86–2635 | | Child: del(X)(q22) | | 46,X,t(X;17)(q22.1;q24.2) | 2/3/57 | 11/12/86 | |
| P68 | NO | B90/2452 | GD | Secondary amen | | 46,X,t(X;21)(q22.1;p13) | 3/1/53 | 21/1/91 | |
| P69 | NE | B90/0183 | GD | POF | | 46,X,t(X;22)(q22.1;p12) | 29/8/65 | 6/4/90 | 34/34 |
| P70 | LI | 87149B | GD | ?Turners, POF | | 46,X,t(X;2)(q22;p13) | N/A | N/A | |
| P71 | OX | 90B/0110 | GD | Primary amen | | 46,X,t(X;2)(q22;q24.2) | 9/3/65 | 5/3/90 | |
| P72 | GA | 1831/97[b] | GD | POF | | 46,X,t(X;3)(q22;q12) | 19/10/64 | 22/8/97 | |
| P73 | SH | S1569/93 | MCA/DD | Abscan, TOP (19 weeks) | | 46,X,t(X;7)(q22;q32) de novo | 22/12/66 | 26/11/93 | |
| P74 | SH | B7585 | GD | Resistant ovarian syndrome | | 46,X,t(X;9)(q22;q21) de novo | 16/9/88 | 6/10/88 | |
| P75 | KG | 96l/1298 | MCA/DD | MCA | | 46,X,t(X;10)(q22;q23.2) | 18/7/96 | 29/7/96 | |
| P76 | AB | B93/1065 | GD | Amen | | 46,X,t(X;15)(q22;p11) | | | |
| P77 | NE | B89/0658 | GD | Short stature, oligomenorrhoea | q23 | 46,X,t(X;3)(q23;p13) | 3/1/73 | 18/8/89 | 30/30 |
| P78 | BM | B98/12127 | GD | POF | q24 | 46,X,t(X;5)(q24;p15.1) | | | |

**Table 1** (continued)

| Case[a] | Lab. | Lab. ref. | Proband group | Referral reason | X band | Karyotype | DoB | DoR | $X^R$ status[d] |
|---|---|---|---|---|---|---|---|---|---|
| 79 | LI | B93/3196 | | F/H of DMD | | 46,X,t(X;14)(q24;p13) de novo | 27/6/69 | 28/10/93 | 70/70 |
| P80 | SM | B1459/96 | GD | POF | | 46,X,t(X;15)(q24;p13) | 15/11/78 | 17/7/96 | |
| P81 | ED | 90–1166 | GD | Primary amen | q25 | 46,X,t(X;11)(q25;p11.2) | 19/10/72 | 26/6/90 | |
| 82 | SA | B3421/94[b] | | Daughter: t(X;10) | q26 | 46,X,t(X;10)(q26.3;q23.3) | 14/11/14 | 13/10/94 | |
| 83 | SA | B326/94[b] | | Child: der(X)t(X;10) | | 46,X,t(X;10)(q26.3;q23.3)mat | 29/3/42 | 27/9/94 | 31/38 |
| P84 | BR | 95/4756 | MCA/DD | Fetus: abscan | | 46,X,t(X;1)(q26;p22)mat | 6/12/60 | 20/7/95 | |
| 85 | BR | N/A | | Mother: abscan fetus | | 46,X,t(X;1)(q26;p22) de novo | N/A | N/A | |
| 86 | NO | B81/2562 | | PND; same in fetus | | 46,X,t(X;3)(q26;p21) | 22/1/49 | 10/5/82 | |
| P87 | NE | B91/0373[c] | MCA/DD | LD, Dys | | 46,X,t(X;3)(q26;q21) | 7/4/49 | 7/6/91 | 30/30 |
| P88 | SH | 8906/93 | GD | Primary amen | | 46,X,t(X;3)(q26;q23) | 12/2/76 | 6/7/93 | |
| P89 | NO | B86/1001 | MCA/DD | DD | | 46,X,t(X;7)(q26;q22) de novo | 21/5/84 | 2/10/86 | |
| P90 | NO | B89/0163 | NRM | Rec misc | | 46,X,t(X;13)(q26;q12) | 13/1/63 | 12/5/87 | |
| P91 | NE | B97/1451 | MCA/DD | mLD, Dys | | 46,X,t(X;9)(q26;p21) | 26/4/51 | 17/9/97 | |
| 92 | NO | B85/1358 | | Child: der(X)t(X;13) | | 46,X,t(X;13)(q26;q12) | N/A | 23/9/85 | |
| P93 | CM | B92/2166 | NRM | Rec misc | q27 | 46,X,t(X;3)(q27;p13) | 7/6/63 | 27/8/92 | |
| 94 | SA | B3661/86 | | Child: der(X)(tX;7) | | 46,X,t(X;7)(q27;q22) | 6/1/44 | 26/9/86 | 39/50; 50/50 (skin) |
| 95 | SA | B5188/86 | | Mother: t(X;7) | | 46,X,t(X;7)(q27;q22)mat | 28/4/68 | 8/12/86 | 50/50 |
| 96 | CM | 94/2081 | | Child: der(X)t(X;18) | | 46,X,t(X;18)(q27;p11.2) | 25/10/68 | 5/9/94 | |
| P97 | NE | B90/0642 | MCA/DD | mLD, Dys | q28 | 46,X,t(X;3)(q28;q12) | 31/12/59 | 20/8/90 | 37/44 |
| P98 | CM | B95/0681 | MCA/DD | LD | | 46,X,t(X;8)(q28;q11.23)mat | 24/8/93 | 14/3/95 | 100% |
| 99 | CM | B95/1295 | | LD + child: t(X:8) | | 46,X,t(X;8)(q28;q11.23) | 5/5/54 | 26/5/95 | 100% |
| P100 | GU | 94/1010 | MCA/DD | Abscan: cleft lip/palate | | 46,X,t(X;11)(q28;p14) de novo | 12/26/69 | 2/11/94 | |
| P101 | GU | 96/1843[b] | GD | Short, primary amen | | 46,X,t(X;19)(q28;p13.3) de novo | 10/15/82 | 3/1/96 | |
| 102 | CM | KB4762 | | Child: der(X) t(X:20) | | 46,X,t(X;20)(q28;q11.2) | 17/9/50 | 4/3/86 | 21/21 |
| 103 | KG | 96L/1215 | | Child: der(X)t(X;20) | | 46,X,t(X;20)(q28;q11.2) | 16/9/61 | 6/8/96 | |
| 104 | ED | 88–2010 | | Child: der(X)t(X;21) | | 46,X,t(X;21)(q28;q11) de novo | ?/61 | 18/10/88 | 100% |

[a]'P' prefix denotes proband
[b]Denotes cell-line availability
[c]Proband P62 NRM: normal development at 18 months (see text for proband group details)
[d]Late replication status of normal X homologue (the number of metaphases observed was given where available)

were returned for a 15-year period, 1983–1997. The number of cases submitted was compared with returns to the UK Oxford Chromosome Abnormality Database, which continuously compiles cytogenetic data from all UK laboratories, providing a diagnostic service. One hundred and ten two-break t(X-aut) balanced translocations were reported to this database over the survey period. We concluded that the data submitted were representative for the collection period.

Probands ($n$=62) were grouped by reason for referral as: multiple congenital abnormalities and/or developmental delay (MCA/DD): 26 (42%); gonadal dysfunction (GD): 22 (35%); phenotypically normal with or without recurrent miscarriage (NRM): 9 (15%); recognized X-linked syndrome (XLD): 5 (8%). Prenatal cases were included in the proband categories where outcome was known. The data presented in this paper were compared to data compiled by Schmidt and Du Sart (1992) from a survey of cases ($n$=122) from the published literature where X chromosome replication studies had been performed (see Table 2). No other comparable published or unpublished data were available. Comparison revealed that there was significant over-representation of the MCA/DD group ($P$<0.01) and under-representation of the recognized X-linked syndrome group ($P$<0.001) in our data set.

### Comparison with unpublished data for female autosomal-autosomal translocation carriers by reason for referral

Data from two of the authors' laboratories (Birmingham and Oxford) were obtained for all reported cases of female probands with balanced autosome-autosome translocations, t(aut-aut), by reason for referral ($n$=115). Data were compared with t(X-aut) data (Table 2). For MCA/DD cases there was a significant difference between the aut-aut and the X-aut group: MCA/DD cases were over-represented ($P$<0.05). The two groups of patients were considered to be subject to the same ascertainment bias.

### X chromosome breakpoint distribution

All X chromosome breakpoints are tabulated in Table 1. For all probands ($n$=62), chromosome breakpoint distribution and clinical category assignment were tabulated (Table 3). Breakpoints were divided into the following G-band groups: Xp22, Xp21, Xp11.4, Xp11.3, Xp11.2, Xp11.1-Xq11, Xq12, Xq13, Xq21, Xq22, Xq23, Xq24, Xq25, Xq26, Xq27 and Xq28. Proband data from Table 3 were compared with the expectation that breakpoints were randomly distributed according to band length/total X chromosome length. Band lengths as a percentage of total X chromosome length (%XL) were calculated from an X chromosome idiogram (ISCN 1995). A significant over-representation of probands was observed for band Xq22 ($P$<0.005). No other significant differences were observed.

### X chromosome late replication studies

Late replication studies were performed in 40 out of 104 patients in total and in 24 out of 62 probands. The results are shown in Table 1. Eight patients showed a deviation from the expected pattern of consistent early replication of the derived X chromosome and late replication of the normal X chromosome. One patient, P48, had a breakpoint at Xq10 and hypomelanosis of Ito (Hatchwell et al. 1996). A second patient, P29, with a breakpoint at Xp11.4, had learning difficulties, slight neck-webbing and normal stature. The other six patients had breakpoints at Xp22.3 or Xq26.3-Xq28. Five of these patients were not probands and were phenotypically normal (cases 1, 2, 54, 83 and 94). For case 2, only three metaphases were scored. Case 94 showed 39/50 cells in blood and 50/50 cells in skin with the normal X late replicating. The sixth patient, P97, had a karyotype of 46,X,t(X;3)(q28;q12) and showed 37/44 cells with the normal X late replicating in a blood sample. This patient was categorized phenotypically as 'MCA/DD' and is described in more detail below.

**Table 2** X-autosomal translocations in females by reason for referral [probabilities ($P$) are shown where there was a significant difference between this study's X-aut data set and other data]

| | Females carriers with t(X-aut) (probands) | Females carriers with t(aut-aut) | Data from Schmidt and Du Sart (1992) |
|---|---|---|---|
| Total cases | 62 | 115 | 119[a] |
| MCA/DD | 26 (42%) | 29 (23%) $P$<0.05 | 25 (21%)[b] $P$<0.01 |
| Gonadal Dysfunction (GD) | 22 (35%) | 3 (2%) n.d. | 30 (25%)[c] $P$>0.05 |
| Recognized X-linked disorder (XLD) | 5 (8%) | 0 (0%) n.d. | 28 (24%)[d] $P$<0.001 |
| Normal, recurrent miscarriage (NRM) | 9 (15%) | 29 (23%) | 36 (30%) |

[a]The Schmidt and Du Sart data were re-examined with respect to reason for referral and 119 out of 122 cases identified which could be categorized

[b]Cases were classed as MCA/DD irrespective of whether gonadal dysfunction was also present

[c]Cases were classed as GD (gonadal dysfunction) where this was an isolated finding, ranging from primary amenorrhoea to premature ovarian failure, and no other significant clinical problems were described

[d]Cases were classed as XLD (recognized X-linked disorder) where the disorder was well defined and where no additional non-syndromic MCA/DD was present

**Table 3** X chromosome breakpoint by band for each referral category [*NRM* normal phenotype (with or without recurrent miscarriage), *GD* gonadal dysfunction, *MCA/DD* multiple congenital abnormality or developmental delay, *XLD* defined X-linked disorder *%XL* band length as percentage of total chromosome length (from ISCN 1995)]

| | NRM | GD | MCA/DD | XLD | %XL |
|---|---|---|---|---|---|
| p22 | 2 | – | 5 | – | 13.6 |
| p21 | 1 | – | 1 | 2 | 9.7 |
| p11.4 | 1 | – | 1 | 1 | 3.8 |
| p11.3 | – | 1 | 2 | – | 1.9 |
| p11.2 | – | – | 5 | – | 8.7 |
| p11.1–q11 | – | – | – | 2 | 2.6 |
| q12 | – | – | – | – | 3.8 |
| q13 | 2 | 2 | 3 | – | 8.7 |
| q21 | 1 | 4 | – | – | 13.6 |
| q22 | – | 9 | 2 | – | 4.8 |
| q23 | – | 1 | – | – | 4.8 |
| q24 | – | 2 | – | – | 2.8 |
| q25 | – | 1 | – | – | 5.8 |
| q26 | 1 | 1 | 4 | – | 4.8 |
| q27 | 1 | – | – | – | 5.8 |
| q28 | – | 1 | 3 | – | 4.8 |
| Total cases | 9 | 22 | 26 | 5 | – |

### Patients with gonadal dysfunction and the 'critical region'

Twenty out of 22 (91%) probands with gonadal dysfunction ranging from primary amenorrhoea to premature ovarian failure, as the sole reason for referral, had breakpoints within the 'critical region' at Xq13-Xq26 (Tables 3 and 1). In addition, nine patients (55, 65, 66, 67, 82, 83, 85, 86,92) with breakpoints at the boundaries of this region Xq13 or Xq26 or within Xq22 had achieved a clinically recognizable pregnancy (Table 4). Seven of these patients had produced live-born offspring. Two probands, P31 and P101, had gonadal dysfunction with an X breakpoint outside the region at Xp11.3 and Xq28 respectively.

### Patients with MCA/DD

Nineteen out of 22 informative probands had a de novo chromosome rearrangement. Eighteen (95%) of these were associated with an abnormal phenotypic outcome ($P< 0.001$). Fourteen were MCA/DD referrals and four were XLD referrals (P21, P27, P46, P48). Eight out of 26 probands with MCA/DD had breakpoints within the subtelomeric bands Xp22 or Xq28. In total, 11 probands had breakpoints within Xp22 or Xq28. MCA/DD referrals showed random distribution on a length-for-length basis ($P>0.05$) and were not over-represented at Xp22 or Xq28 ($P>0.05$). Late replication studies were performed on a total of 12 out of 26 probands with MCA/DD. All but two of these, probands P29 and P97 showed the expected pattern of X chromosome replication. Patient P97, was described as dysmorphic (epicanthic folds, hirsutism) and obese. She had mild mental handicap and suffered from schizophrenia. She had a karyotype of 46,X,t(X;3)(q28;q12) and demonstrated an aberrant replication pattern, with seven out of 44 cells showing late replication of the der(X)t(X;3) chromosome. Her mother was deceased so it was not possible to establish whether the translocation had arisen de novo in this case. Apart from case P97, replication data were only available on one other MCA/DD proband with a breakpoint within Xp22 and Xq28. This patient, P98, showed a normal pattern of replication.

## Discussion

This survey of largely unpublished cases reported from UK laboratories clearly demonstrated that published data were unrepresentative with respect to the reasons for clinical referral of female carriers of balanced X-autosome translocations. Insufficient prenatal cases ($n=7$) were submitted to allow any conclusions concerning ascertainment bias, which may be reflected in published reports as well as in the case data collected in this survey.

Cases with well-defined X-linked syndromes were over-reported in the literature. This was to be expected be-

**Table 4** Classification of t(X-aut) proband females by referral category with breakpoints within the 'critical region', (Xq13-q26). Probands were tabulated in two groups: probands GD and other probands (NRM, MCA/DD and XLD). t(X-aut) females (non-probands) with breakpoints within the 'critical region' and proven fertility are also shown. [*NRM* normal phenotype (with or without recurrent miscarriage), *GD* gonadal dysfunction, *MCA/DD* multiple congenital abnormality or developmental delay, *XLD* defined X-linked disorder]

| X band | Probands GD | Other probands | Non-proband (proven fertility) |
|---|---|---|---|
| q13 | P56, P57 | MCA/DD: P50, P51, P52, NRM: P49, P53 | 55 |
| q21 | P58, P59, P60, P61 | | |
| q22 | P63, P64, P68, P69, P70, P71, P72, P74, P76 | MCA/DD: P73, P75 | 65, 66, 67 |
| q23 | P77 | | |
| q24 | P78, P80 | | |
| q25 | P81 | | |
| q26 | P88 | MCA/DD: P84, P87, P89, P91; NRM: P90 | 82, 83, 92 |

cause of their considerable value in mapping X-linked disease genes. In addition, 22 probands were referred because of gonadal dysfunction, ranging from primary amenorrhoea to early menopause (premature ovarian failure). As was to be expected, they invariably had breakpoints within the 'critical-region', Xq13-Xq26 (Mattei et al. 1982, Madan 1983). Seven patients with breakpoints within this region had proven fertility. Four of these had breakpoints within Xq13 or Xq26, at the boundaries of this region. It is possible that these breakpoints lie outside the 'critical region' within these bands. A further three patients with proven fertility had breakpoints clustered within Xq22. The observation of patients with proven fertility with breaks within Xq22 was consistent with earlier cytogenetic findings (Sarto et al. 1973, Madan et al. 1983). However, a further nine patients with gonadal dysfunction also had Xq22 breakpoints. It is conceivable that a number of the females with Xq22 breakpoints and proven fertility may still experience premature gonadal failure at a later stage. Fine mapping studies may eventually allow critical and non-critical breakpoints to be distinguished within Xq22 with respect to gonadal function (Prueitt et al. 2000).

The high proportion of patients with multiple congenital abnormalities and/or developmental delay (including learning difficulties) in our survey demonstrated that this group of patients (MCA/DD), with poorly defined phenotypic outcomes, was significantly under-reported in the literature. Mental retardation with or without metabolic, mitochondrial or biochemical disorder is a very common phenotype (Lubs et al. 1999). Such disorders, which may be divided into syndromic and non-syndromic forms, are over-represented on the X chromosome (Chelly 1999, Neri et al. 1999, Toniolo et al. 2000). New X-linked syndromes involving mental retardation continue to be defined and mapped (Reyniers et al. 1999). Chelly (1999) has convincingly argued that this over-representation is more apparent than real because of the haplo-functional status of most X-linked genes and the relative ease in mapping X-linked forms of mental retardation (XLMR). The presence of genes involved in cognitive development along the entire length of the X chromosome is clearly important when considering the mechanisms involved in phenotypic outcome.

Overall, X chromosome breakpoint distribution in probands ($n$=62) was apparently random, except for over-representation at Xq22. Mattei et al. (1982), in a large survey of published cases, found no significant deviation from random breakpoint distribution. Schmidt and Du Sart (1992) noted that MCA/DD patients had X chromosome breakpoints clustered in the subtelomeric bands (Xp22 and Xq28) and that such cases departed from the expected pattern of X-inactivation. Other workers have used these findings as the basis for their cytogenetic work-up of prenatal cases (Feldman et al. 1999). In our survey, MCA/DD cases showed random X chromosome breakpoint distribution with no significant over-representation at Xp22 (the sub-terminal region of the short arm) or at Xq28 (the sub-terminal region of the long arm). In general, sub-telomeric breakpoint position was not a reliable indicator for aberrant X chromosome late replication pattern, although the number of cases was small ($n$=8). Where aberrant late replication was seen, as reported to this survey, patients did not necessarily show an abnormal phenotype. Patient, P97, with a breakpoint at Xq28, showed an aberrant replication and therefore appeared to fit the Schmidt and Du Sart criteria. In seven out of 44 cells examined she was functionally disomic for Xq28-Xqter. In addition, an X-autosome 'spreading effect' into 3q12 –3qter on the derived X chromosome may have contributed to the aberrant phenotype by causing partial or complete monosomy for 3q12–3qter. The data from this patient supported the Schmidt and Du Sart hypothesis that persistence of cells that are functionally disomic for part of the X chromosome may give rise to an abnormal phenotype. However, in general, these data did not show the markedly skewed X breakpoint distribution, and accompanying deviation from the expected pattern of X-inactivation, seen in the comparable group of MCA/DD patients recorded by Schmidt and Du Sart. It seems likely, therefore, that gene disruption, rather than functional X disomy, was the causative factor in many MCA/DD cases in our survey. We considered that the basis for selection by Schmidt and Du Sart of published cases with known X inactivation status may well have resulted in over-representation of cases with unusual, aberrant patterns of X-inactivation behaviour, which were intrinsically more likely to be submitted for publication.

De novo rearrangements were associated with an abnormal phenotypic outcome (MCA/DD or XLD referral categories) in 18 out of 19 cases. This suggested that de novo status assignment for an X-autosomal translocation appeared to be the most important risk factor in predicting phenotypic outcome. In those cases with an abnormal phenotypic outcome this was particularly likely to be within the MCA/DD referral category. The overall risk figure for de novo simple reciprocal translocations was quoted as 3% above a background risk by Warburton (1991). The additional unpredictable complications of 'critical region' breakpoints, aberrant X-chromosome replication behaviour and disruption of X-linked Mendelian disease genes, add to this risk but were not in themselves reliable indicators of phenotypic outcome.

This type of survey has some limitations. The data requested and made available by individual laboratories were limited and chromosome breakpoint data were not independently examined. However, the clerical accuracy of data submission was independently confirmed against the UK Oxford Chromosome Abnormality Database. The phenotypic (referral) categories used in this report were broad and not necessarily mutually exclusive. For instance young patients with MCA/DD as the mode of ascertainment may also have developed gonadal dysfunction. Likewise, patients with a normal phenotype with or without recurrent miscarriage (NRM) may have later developed premature ovarian failure.

In summary, female X-autosome translocation carriers had a significantly higher burden of clinical problems in-

cluding developmental delay and learning difficulties (the MCA/DD referral category), than would be expected from a review of the literature. De novo breakpoints were significantly more likely to be associated with an abnormal outcome and, in particular, with the MCA/DD referral category. Breakpoints within the critical region were highly likely to be associated with gonadal dysfunction. In general, however, X chromosome breakpoint position and X-inactivation behaviour were not always reliable indicators of the likely phenotypic outcome in this group of patients.

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