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.

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 Drosoptila 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 (Zenni 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