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Gonadal dysgenesis in a patient with an X;3 translocation: case report and review

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SUMMARY A patient with primary amenorrhoea and absence of secondary sex characteristics was found to have a balanced X;3 translocation. This phenotype is reported in approximately one-third of the balanced X;autosome translocation cases. The normal X chromosome is inactive in the present case which is in agreement with most of the similar cases. A review of the 66 balanced X;autosome translocations reported to date is presented.

Up to mid 1979, 102 cases of balanced and unbalanced X;autosome translocations have been the subjects of 53 reports. These cases have provided information on the patterns of inactivation of the X chromosome and on the relative position of various loci on this chromosome. Associated with these chromosomal rearrangements are a variety of clinical findings including amenorrhoea, hypogonadism, and multiple congenital anomalies and mental retardation (MCA–MR) in the majority of the balanced carriers and MCA–MR syndromes in the unbalanced carriers.

We present a patient with a balanced de novo X;3 translocation. A review of the phenotypes and patterns of X inactivation in patients with balanced X;autosome translocations reveals the complexities of X chromosome inactivation.

Case report

A 17-year-old girl was referred for primary amenorrhoea and lack of secondary sex characteristics. During a laparoscopy, bilateral streak gonads and a markedly hypoplastic uterus were noted. A normal vagina and cervix were present and no abnormalities of the external genitalia were observed. The serum follicle stimulating hormone (FSH) level was greater than 100 mouse uterine units/24 h and the luteinising hormone (LH) level was 36 mIU/ml at the age of 14. Repeat gonadotrophin levels at the age of 15 gave values of greater than 100 mouse uterine units/24 h for FSH and 59 mIU/ml for LH. Her weight and height were 37 kg and 156 cm, respectively.

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The patient has three sisters, all of whom have had normal sexual development. There is no family history of similar developmental disorders. There was no consanguinity between the parents. The ages of the mother and father at the time of the patient's birth were 33 and 35 years, respectively.

A buccal smear was 24% positive for sex chromatin. The Barr bodies appeared normal in size. Karyotype analysis from peripheral blood revealed a balanced X;3 translocation (fig 1). The G banded karyotype was 46,X,t(X;3)(Xpter→Xq22::3p11→3pter;3qter→3p11::Xq22→Xqter). Fig 2 illustrates the breakpoints in the long arm of the X chromosome and the short arm of chromosome 3. Using the BUdR terminal pulse technique followed by staining with acridine orange,[1] the normal X chromosome was identified as late replicating in all of the 49

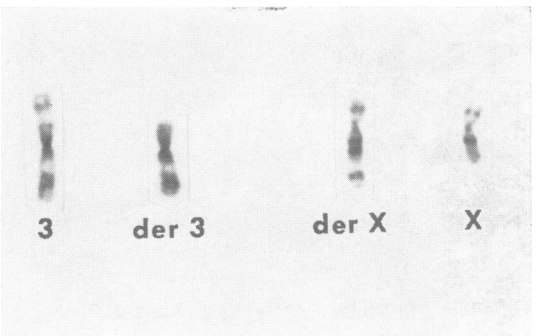

FIG 1 *G banding of the normal and derivative 3 and X chromosomes of the patient.*

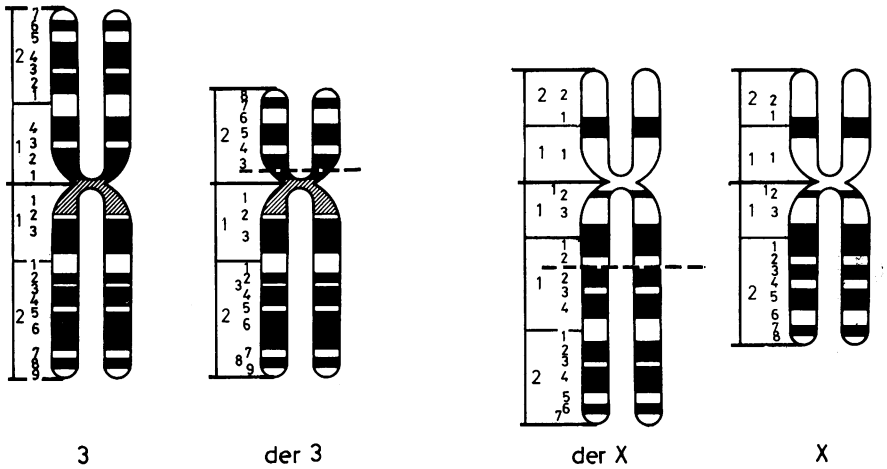

FIG 2 *Diagram of the translocation breakpoints.*

metaphases analysed. The karyotypes of the parents were normal.

Dermatoglyphic analysis of the proband showed an essentially normal pattern with a total finger ridge count of 138. Gene marker studies including red cell antigens, Xg^a, and 20 selected enzymes on the proband and her parents were not informative.

Discussion

X;autosome translocations have been reported involving each of the autosomes except for chromosomes 10 and 11, and a large number of breakpoints on the X chromosome and the autosomes have been identified. Carriers of unbalanced translocations present with MCA–MR syndromes reflecting the partial aneuploidy of the autosomal segments involved and the X inactivation pattern. The balanced translocation carriers express different phenotypes ranging from clinically normal females to those with MCA–MR syndromes. In the patients with MCA–MR syndromes, a position effect or spreading of inactivation over the autosomal loci involved may be the underlying cause. A review of the 66 balanced translocation cases included in the 45 reports to date is given in the table. Seventeen of these patients, including the case reported here, had primary amenorrhoea. In two separate studies, a total of 150 women with primary amenorrhoea were identified and two were found to have X;autosome translocations (1·3%).[22 36] However, a report of 429 women with primary amenorrhoea including these two cases gave an incidence of 0·5%.[47] Two hypotheses have been proposed to explain the gonadal dysfunction observed in such patients: (1) the effective hemizygosity of a recessive gene inhibiting gonadal development as a result of inactivation of one X chromosome, and (2) the breakage or deletion of a gene for gonadal development as a result of translocation. Sarto *et al*[36] identified a 'critical region' for such loci from approximately Xq21 to Xq25. Summitt and associates[48] propose extending the boundaries of this region to Xq13 and Xq27.

Patterns of X inactivation in these cases have been shown by terminal pulsing of chromosome cultures with ^3H thymidine or bromodeoxyuridine (BUdR) before autoradiography or differential staining with acridine orange. Therman *et al*[49] proposed that an X inactivation centre on the proximal part of Xq is essential for inactivation of any X chromosome. In cases of balanced X;autosome translocations, the normal X is usually found to be late replicating (inactive) as in the present case.[47] A few exceptions have been reported in which the X portion of the translocated chromosome,[7 13 18 19 23 26 31 32] or the entire translocated X,[6 40 46] is late replicating. It is not known whether there is preferential inactivation of the normal X chromosome or random inactivation followed by selective survival of cells in which the translocated X remains active. Inactivation usually results in the least genetic imbalance and thus the expression of the mildest phenotypic effects. However, the exceptional case reported by Thelen *et al*[40] in which the patient expressed the characteristics of the 18q− syndrome through inactivation of the translocated autosomal as well as the X chromosomal segment points out the unpredictability of this phenomenon.

During genetic counselling of fertile balanced

TABLE *Summary of replication patterns and phenotypes in balanced X;autosome translocations*

Authors	*Karyotype as defined by authors*	*Late replicating chromosome*		*Phenotype*
		Autoradiography	*BUdR*	
Allderdice *et al*[2]	46,X,t(Xq−;14q+)	Xn	—	Normal
Bartsch-Sandhoff *et al*[3]	46,X,t(X;15)(p22;pl)	—	—	Short stature, short neck, cubitus valgus
Buckton *et al*[4]	46,X,t(Xp−;14q+)	Xn	—	Normal
Buhler *et al*[5]	46,X,t(X;22)(q21;p11)	—	Xn	Normal
Canki *et al*[6]	46,X,t(X;3)(p21;q13)	—	Xn 93% entire Xt 7%	Dysmorphic syndrome, mental retardation, Duchenne muscular dystrophy
Cohen *et al*[7]	46,X,t(Xq−;9p+)	Xn 68% Xn+X portion of Xt 32%	—	Multiple congenital abnormalities
Davis *et al*[8]	46,X,t(X;16)(p11;q24)	—	—	Normal
de la Chapelle and Schroeder[9]	46,X,rcp(X;3)(q28;q13)	Xn	—	Normal
Dutrillaux *et al*[10]	46,X,t(X;1)(q31;q28)	—	—	Normal
Dutrillaux *et al*[11]	46,X,t(X;8)(q21;p23)	—	Xn	Oligomenorrhoea, ovarian hypoplasia
Dutrillaux *et al*[11]	46,X,t(X;15)(p11;q11) or (q11;p11)	—	Xn	Multiple congenital abnormalities, mental retardation
Forabosco *et al*[12]	46,X,rcp(X;6)(q21;q27)	—	Xn	Primary amenorrhoea, absence of secondary sexual development
Forabosco *et al*[12]	46,X,rcp(X;12)(q21;q24)	—	Xn	Primary amenorrhoea, hypoplastic genitalia, hypoplastic uterus
Fraccaro *et al*[13]	46,X,t(X;15)(p11.3;pl)	Xn 67% X portion of Xt 33%	Xn 62% X portion of Xt 38%	Normal
Francke *et al*[14]	46,X,t(X;14)(p22;q21)	—	Xn	Normal
Frantz and Noel[15]	46,X,t(X;2)(p11;q37)	—	Xn	Normal
Gaal and Laszlo[16]	46,X,t(X;6)(p21;p24)	—	—	Normal
Gerald *et al*[17]	46,X,t(Xq−;19q+)	Xn	—	Primary amenorrhoea, mental retardation
Gilgenkrantz *et al*[18]	46,X,t(X;2)(q21;p25)	Xn 95% Xn + X portion of Xt 5%	Xn	Primary amenorrhoea, hypoplastic uterus, facial dysmorphology
Hagemeijer *et al*[19]	46,X,t(X;4)(q21;q13)	—	Xn	Primary amenorrhoea
Hagemeijer *et al*[19]	46,X,t(X;6)(p21;q26)	—	Xn 85% X portion of Xt 15%	Normal
Hagemeijer *et al*[19]	46,X,t(X;17)(p11;q24)	—	Xn	Normal
Jacobs *et al*[20]	46,X,t(X;2)(q2;q2)	—	—	Primary amenorrhoea
Jenkins *et al*[21]	45,X/45,X,−22,t (Xq;22q)	—	—	Normal
Kallio[22]	46,X,t(Xq−;21q+)	Xn	—	Primary amenorrhoea, hypoplastic genitalia, hypogonadism, 'eunuchoid habitus'
Laurent *et al*[1]	46,X,t(X;1)(p21;p34)	—	Xn	Facial dysmorphology, poor psychomotor development
Leisti *et al*[23]	46,X,rcp(X;9)(q11;q32)	Xn 84% Xn + X portion of Xt 16%	—	Normal
Lejeune cited in Forabosco *et al*[12]	46,X,t(X;22)(q27;q11)	—	Xn	Normal
Lejeune cited in Forabosco *et al*[12]	46,X,t(X;21)(q27;q11)	—	Xn	Normal
Lucas and Smithies[25]	46,X,t(Xq−;15p+)	Xn	—	Primary amenorrhoea, hypogonadism
Mann and Higgins[26]	46,X,t(Xq−;5q+)	Xn + portion of Xt	—	Primary amenorrhoea, hypoplastic genitalia, hypogonadism
Marshall *et al*[27]	46,X,t(X;1)(q26;q12)	—	Xn 66% neither X 34%	Beckwith-Wiedemann syndrome
Mattei *et al*[28]	46,X,t(X;22)(q112;q13)	—	Xn	Normal
Mattei *et al*[28]	46,X,t(X;9)(p22;q12)	—	X portion of Xt	Multiple congenital abnormalities
Mohandas *et al*[29]	46,X,t(X;20)(p11?;p11?)	—	Xn	Dysmorphic syndrome, mental retardation
Noel cited in Forabosco *et al*[12]	46,X,t(X;1)(q13;p13)	—	Xn	Secondary amenorrhoea
Opitz *et al*[30]	46,X,t(X;19)(q13;q13)	Xn	—	Secondary amenorrhoea, streak gonads
Palmer *et al*[31]	46,X,t(X;22)(q22;q13)	Xn	—	Primary amenorrhoea
Palmer *et al*[32]	46,X,t(X;17)(p22;p13)	—	Xn X portion of Xt (few)	Normal
Pearson *et al*[33]	46,X,t(X;22)(q23;q23)	Xn	—	Primary amenorrhoea

TABLE—*continued*

Authors	*Karyotype as defined by authors*	*Late replicating chromosome*		*Phenotype*
		Autoradiography	*BUdR*	
Pearson *et al*[34]	46,X,t(X;3)(q26;?)	—	—	Normal
Phelan *et al*[35]	46,X,rcp(X;4)(q26;q21)	Xn	—	Secondary amenorrhoea, streak gonads, hypogonadism
Sarto *et al*[36]	46,X,t(Xq−;12q+)	Xn	—	Primary amenorrhoea, underdeveloped ovaries
Sauer *et al*[37]	46,X,t(X;7)(q21;p22)	—	—	Secondary amenorrhoea, streak gonads, hypogonadism
Sujansky *et al*[38]	46,X,t(X;15)(q13;p12)	Xn	—	Primary amenorrhoea
Summitt *et al*[39]	46,X,rcp(X;21)(q11;p11)	Xn	—	Normal
Thelen *et al*[40]	46,X,t(Xp+;18q−)	Xn 21·5% entire Xt 78·5%	—	Mental retardation, multiple congenital abnormalities
Thorburn *et al*[41]	46,X,t(Xq;Cq−?)	Xn	—	Primary amenorrhoea, streak gonads, hypoplastic genitalia, 'eunuchoid habitus'
Tipton cited in Leisti *et al*[23]	46,X,rcp(X;8)(q26;q12)	Xn	—	Normal
Turleau *et al*[42]	46,X,t(X;2)(p223;q323)	—	Xn	Normal
Van Der Hagen and Molne[43]	46,X,t(X;1)(q24;p36)	—	—	Primary amenorrhoea, streak gonads, delayed secondary development
Van Dyke *et al*[44]	46,X,t(X;12)(q22;q24)	—	Xn	Gonadal dysgenesis
Verellen *et al*[45]	46,X,t(X;21)(p21;p12)	Xn	Xn	Duchenne muscular dystrophy
Zabel *et al*[46]	46,X,t(X;15)(p22;q15)	—	Xn	Normal
Zabel *et al*[46]	46,X,t(X;21)(p11;p11)	—	Xn 70% Xt 30%	Multiple congenital abnormalities, mental retardation
This report	46,X,t(X;3)(q22;p11)	—	Xn	Primary amenorrhoea, streak gonads, absence of secondary sexual development

X;autosome translocation carriers, the risk of having unbalanced offspring with multiple congenital anomalies should be emphasised. The parents of patients with reproductive failure and de novo translocations, however, can be counselled with confidence that the risk of recurrence of the same abnormality in other female family members is remote.

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