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X-Autosome Translocations: Cytogenetic Characteristics and Their Consequences

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Summary. To define the principal characteristics of X-autosome translocations, the authors present a study of 105 cases, five of which are personal observations. The autosomal pairs 15, 21, and 22 are affected by t(X-Aut) more often than would be expected. The distribution of breakpoints on the X chromosome does not differ significantly from the expected distribution. The analysis of different patterns of inactivation seems to confirm that the inactivation could occur at random, but would be followed by a cellular selection favoring the better genetic balance. An estimate of the incidence of t(X-Aut) is proposed, based upon the conclusions that only one chromosome is susceptible to translocation in meiosis in both males and females and that all affected men will be sterile, as will be 50% of women.

Introduction

X-Autosome translocations [t(X-Aut)] have always held a particular attraction for geneticists, not only for their rarity, but also for the variety of associated phenotypes depending on the nature of the inactivated X chromosome. In fact, in cases of structural abnormality of the X chromosome, random inactivation is usually not found, as proposed by Mary Lyon (1961) for the normal female. Thus, to establish a phenotype-karyotype correlation in t(X-Aut), a dynamic study is required.

About 100 cases of t(X-Aut) have been reported in the literature since the techniques of chromosome banding were first used to study this chromosomal rearrangement (Allderdice et al. 1971; Buckton et al. 1971; Cohen et al. 1972; Dutrillaux et al. 1972). The present study is an attempt to define the principal characteristics of t(X-Aut), based on cases diagnosed at the Center for Medical Genetics, Marseille (CGM), and those in the literature. These characteristics include the involved autosomes, the breakpoints on the X chromosome, the X-inactivation patterns, and the incidence of this chromosomal rearrangement.

Patients and Methods

We analyzed 105 cases of t(X-Aut), all confirmed by chromosome banding techniques, except for two that showed no ambiguity concerning the affected autosome (Engel et al. 1971; Thelen et al. 1971). Five cases were diagnosed at CGM, two of which have been published previously (Mattei et al. 1978). Two cases are personal communications (Colombies and Bourrouillou; Geneix et al.). Ninety-eight cases were found in the literature. These 105 cases, including some family studies, include 90 different balanced t(X-Aut) (Appendix 1) and 41 unbalanced t(X-Aut) (Appendix 2). In both appendices the translocations have been classified according to the number of the affected autosome and, for each autosome, in alphabetical order of author. In addition, we have shown the X-inactivation patterns and the phenotype for each translocation when these have been recorded.

Involvement of the Various Autosomes in t(X-Aut). To determine the expected number of X chromosome translocations for each autosome we analyzed the 105 collected cases of t(X-Aut) using the model described by Valenzuela (1979), modified to take account of the lack of gonosomes in the total number of involved chromosomes. This model allows not only for the length of the chromosomes [given in series D of the Paris Conference (1971)], but also the type of rearrangement. Translocations which result from two breakpoints on two separate chromosomes will have a different incidence compared to inversions, which require two breakpoints on only one chromosome. The incidence of each autosome in t(X-Aut) was compared to the incidence of each autosome in balanced, non-Robertsonian, autosome-autosome translocations, i.e., t(Aut-Aut). We used the following 356 cases of balanced t(Aut-Aut): Aurias et al. (1978), 97 cases; Evans et al. (1978), 11 cases; Jacobs et al. (1974), 43 cases; Jalbert et al. (1980), 123 cases; Nakagome and Chiyo (1976), 9 cases; Turleau et al. (1975), 19 cases; CGM (unpublished data), 54 cases. Using the model of Valenzuela (1979), we calculated the expected incidence of each autosome in t(Aut-Aut) from these 356 translocations (712 breakpoints).

Distribution of Breakpoints on the X Chromosome. The X chromosome was divided into seven approximately equal regions; [p11], [p21], and [p22] on the short arm and [q11 → q13], [q21], [q22 → q25], and [q26 → q28] on the long arm. A total of 102 breakpoints were identified with sufficient accuracy to be localized to one of these seven regions.

The X-Inactivation Patterns. These were determined from those cases studied by dynamic chromosome analysis, i.e., in 74 balanced t(X-Aut) and 33 unbalanced t(X-Aut). Two techniques of dynamic study have been used by various authors. The earlier technique, autoradiography after incorporation of tritiated thymidine is time consuming and inaccurate, and enables only a small number of mitoses to be studied. More recently, the use of 5-bromodeoxyuridine incorporation (BrdU) followed by staining with acridine orange or Giemsa has enabled both the recognition of the late-replicating X chromosome and the identification of all the autosomes. In addition, a large number of mitoses can be studied. To simplify the different X-inactivation patterns, we shall call X-translocated (Xt) that chromosome which is derived from the t(X-Aut) and which is

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Appendix 1. References of 90 balanced X-autosome translocations (L = lymphocytes, F = fibroblasts, GM = human genetic mutant cell repository)

Reference	Karyotype	Late replication	Phenotype
Dutrillaux et al. (1972)	46,X,t(X;1)(q28;q31)	Xn	adult: normal
Kahan and Demars (1975)	46,X,t(X;1)(q27;q2)	Xn	—
Laurent et al. (1975)	46,X,t(X;1)(p21;p34)	Xn 87% der(X) 13%	child: mental retardation, congenital anomalies
Leichtman et al. (1978)	46,X,t(X;1)(p11;q44)	Xn	adult: normal
Lindenbaum et al. (1979)	46,X,t(X;1)(p21;p34)	Xn	child: Duchenne muscular dystrophy
Noel (cited by Forabosco et al. 1979)	46,X,t(X;1)(q13;p13)	Xn	adult: amenorrhea II
Pearson et al. (1978)	46,X,t(X;1)(q13;q32)	—	—
Punnett et al. (1974) Marshall et al. (1978)	46,X,t(X;1)(q26;q12)	Xn	child: Wiedemann-Beckwith syndrome
Van der Hagen and Molne (1978)	46,X,t(X;1)(q24;p36)	Xn	adult: amenorrhea I, streak gonads
Frantz and Noel (1975)	46,X,t(X;2)(p111;q372)	Xn	adult: normal
Gilgenkrantz et al. (1975)	46,X,t(X;2)(q21;p25)	Xn	adult: amenorrhea I, streak gonads
Jacobs et al. (1974)	46,X,t(X;2)(q2;q2)?	—	adult: infertility
Mashkova and Verlinskaya (1976)	46,X,t(X;2)(p11;q36)	Xn	adult: normal
Turleau et al. (1977)	46,X,t(X;2)(p223;q323)	Xn	adult: normal
Canki et al. (1979)	46,X,t(X;3)(p21;q13)	Xn 93% der(X) 7%	child: mental retardation, dysmorphy, Duchenne muscular dystrophy
Carpenter et al. (1980)	46,X,t(X;3)(q22;p11)	Xn	adult: amenorrhea I, streak gonads
de la Chapelle et al. (1975) Hellkuhl et al. (1982)	46,X,t(X;3)(q28;q21)	— L: Xn 100% — F: Xn 65% der(X) 35%	adult: normal
Mariani et al. (1980)	46,X,t(X;3)(q21;q12)	Xn	adult: impuberism ovarian dysgenesis
Pearson et al. (1978)	46,X,t(X;3)(q26;q12)	Xn	adult: normal
Biemont et al. (1978)	46,X,t(X;4)(q21;p13)	Xn	adult: secondary sterility
Cervenka et al. (1976)	46,X,t(X;4)(q27;q25)	Xn	adult: normal
Hagemeijer et al. (1977)	46,X,t(X;4)(q21;q13)	Xn	adult: amenorrhea
Phelan et al. (1977)	46,X,t(X;4)(q26;q21)	Xn	adult: amenorrhea II, gonadal dysgenesis
Garcia et al. (1977)	46,X,t(X;5)(q28;p13)	Xn	adult: normal
Mann and Higgins (1974)	46,X,t(X;5)(q13;qter)	Xn	adult: amenorrhea I, streak gonads
Shows et al. (1978)	46,X,t(X;5)(q22;q35)	—	—
Stengel-Rutkowski et al. (1976)	46,Y,t(X;5)(q28;q11)	—	adult: azoospermia, some features of Klinefelter syndrome
Forabosco et al. (1979) Giorgi et al. (1979)	46,X,t(X;6)(q21;q27)	Xn	adult: amenorrhea I
Gaal and Laszlo (1977)	46,X,t(X;6)(p21;p24)?	?	adult: normal
Hagemeijer et al. (1977)	46,X,t(X;6)(p21;q26)	Xn 85% der(X) 15%	adult: normal
Lejeune et al. (1973)	46,X,t(X;6)(q21;q27)	—	adult: amenorrhea I, hypoplastic uterus
Vianna-Morgante et al. (1981)	46,X,t(X;6)(p21;q21)	Xn	child: Duchenne muscular dystrophy
Colombies and Bourrouillou (personal communication)	46,X,t(X;7)(p22;p13)	—	child: mental retardation, dysmorphy
Sauer et al. (1977)	46,X,t(X;7)(q21;p22)	—	adult: amenorrhea II, streak gonads
Dutrillaux et al. (1974)	46,X,t(X;8)(q21;p23)	Xn	adult: amenorrhea II, ovarian hypoplasia
Tipton (1974)	46,X,t(X;8)(q26 or 28;q12)	Xn	adult: normal
Cohen et al. (1972)	46,X,t(X;9)(q12;p24)	Xn 68% Xn+der(9) 32%	child: mental retardation, congenital anomalies
Leddet-Chevallier et al. (1981)	46,X,t(X;9)(q22;q12)	Xn	adult: amenorrhea
Leisti et al. (1975)	46,X,t(X;9)(q11;q32)	Xn 84% Xn+der(9) 16%	adult: normal
Mattei et al. (1978)	46,X,t(X;9)(p22;q12)	der(X)	child: mental retardation, dysmorphy
Mijin et al. (1981)	46,X,t(X;9)(q24;q34)	Xn	adult: oligomenorrhea

Appendix 1 (continued)

Reference	Karyotype	Late replication	Phenotype
Sands (1980)	46,X,t(X;10)(qter;q11)	Xn 55% der(X) 45%	adult: severe mental retardation, minor congenital abnormalities
Barnabei et al. (1979)	46,X,t(X;11)(q22;q11 or 12)	—	adult: normal
Dorus et al. (1979)	46,X,t(X;11)(q22;q13)	—	adult: amenorrhea I, streak gonads
Greenstein et al. (1980)	46,X,t(X;11)(p2105;q13)	Xn	adult: Duchenne muscular dystrophy
Rudak et al. (1979)	46,X,t(X;11)(q25 or 26;q23)	Xn	adult: oligomenorrhea, gonadal dysgenesis
Forabosco et al. (1979)	46,X,t(X;12)(q21;q24)	Xn	adult: amenorrhea I
Madan et al. (1981)	46,X,t(X;12)(q22;p12)	Xn	adult: normal
Sarto et al. (1973)	46,X,t(X;12)(q23;q2)	Xn	adult: amenorrhea I, hypogonadism
Van Dyke et al. (1977)	46,X,t(X;12)(q22;q24)	Xn	adult: gonadal dysgenesis
Cross et al. (1977) Nichols et al. (1980)	46,X,t(X;13)(pter;q12 or 13)	— L: Xn — F: der(X)	child: retinoblastoma
Hida et al. (1980)	46,X,t(X;13)(p22;q13)	Xn	child: bilateral retinoblastoma
Latt et al. (1976)	46,X,t(X;13)(q21 to 23;q21 to 31)	Xn 78% der(X) 22%	child: short stature, muscular pseudo-hypertrophy
Allderdice et al. (1971) Allderdice et al. (1978)	46,X,t(X;14)(q13;q32)	Xn	adult: normal
Buckton et al. (1971)	46,X,t(X;14)(p11;qter)	Xn	adult: normal
Franke et al. (1976)	46,X,t(X;14)(p22;q21)	Xn	adult: normal
Bartsch-Sandhoff et al. (1976)	46,X,t(X;15)(p22;p1)	Xn	adult: short stature
Dutrillaux et al. (1974)	46,X,t(X;15)(p11;q11) or (q11;p11)	Xn	adult: mental retardation, congenital anomalies
Fraccaro et al. (1977) Cuoco et al. (1980)	46,X,t(X;15)(p113;p1)	Xn 67% der(X) 33%	adult: normal
Lucas and Smithies (1973)	46,X,t(X;15)(q13;p13)	Xn	adult: amenorrhea I, sexual infantilism
Shimizu et al. (1977)	46,X,t(X;15)(p11;q11)	—	—
Solomon et al. (1976)	46,X,t(X;15)(p11;q11)	Xn	—
Sujansky et al. (1973)	46,X,t(X;15)(q13;p12)	Xn	adult: amenorrhea I
Zabel et al. (1978)	46,X,t(X;15)(p22;q15)	Xn	adult: normal
Geneix et al. (personal communication)	46,X,t(X;15)(q21;q25)	—	adult: amenorrhea I, ovarian hypoplasia
Davis et al. (1976)	46,X,t(X;16)(p11;q24)	Xn	adult: normal
GM 3884	46,X,t(X;16)(q26;q24)	Xn	— Klippel-Feil syndrome
Hagemeijer et al. (1977)	46,X,t(X;17)(p11;q24)	Xn	adult: normal
Palmer et al. (1980)	46,X,t(X;17)(p22;p13)	Xn 86% der(X) 14%	adult: normal
Yamamoto et al. (1979)	46,X,t(X;17)(q13;q21)	Xn	adult: normal
Centre de Génétique Médicale, Marseille (no. 7282)	46,X,t(X;17)(q25;p12)	Xn	adult: amenorrhea I
Thelen et al. (1971)	46,X,t(X;18)(pter;q11)	der(X) 79% Xn 21%	child: mental retardation, some features of 18q− syndrome
Gerald et al. (1973) Latt et al. (1976)	46,X,t(X;19)(q23 or 25;q13)	Xn	adult: mental retardation, amenorrhea I
Hellkuhl and Grzeschik (1978)	46,X,t(X;19)(q22;q133)	Xn	—
Opitz et al. (1978)	46,X,t(X;19)(q13;q13)	Xn	adult: amenorrhea II, streak gonads
Mohandas et al. (1980)	46,X,t(X;20)(Xp20q;Xq20p) i.e. 46,X,t(X;20)(cen;cen)	Xn	child: mental retardation, multiple malformations
Cann et al. (1975)	46,X,t(X;21)(q22;q22)	—	adult: normal
Couturier et al. (1979)	46,X,t(X;21)(q2700;q11)	Xn	adult: normal

Appendix 1 (continued)

Reference	Karyotype	Late replication	Phenotype
Faed et al. (1979)	46,Y,t(X;21)(q23;q11)	—	adult: azoospermia
Kallio (1973)	46,X,t(X;21)(q23;q2)	Xn	adult: amenorrhea I, streak gonads
Summitt et al. (1974)	46,X,t(X;21)(q11;p11)?	Xn	adult: normal
Verellen et al. (1978)	46,X,t(X;21)(p21;p12)	Xn	child: Duchenne muscular dystrophy
Zabel et al. (1978)	46,X,t(X;21)(p11;p11)?	Xn 70% der(X) 30%	child: mental retardation, dysmorphy
Buhler et al. (1977)	46,X,t(X;22)(q12;p11)	Xn	adult: normal
Cuoco et al. (1980)	46,Y,t(X;22)(q26;q11)	—	adult: azoospermia
Lejeune (cited by Forabosco et al. 1979)	46,X,t(X;22)(q27;q11)	Xn	adult: normal
Marmor et al. (1980)	46,Y,t(X;22)(q25;qter)	—	adult: azoospermia
Mattei et al. (1978)	46,X,t(X;22)(q11–12;q112)	Xn	adult: normal
Palmer et al. (1973)	46,X,t(X;22)(q22;q13)	Xn	adult: amenorrhea I
Pearson et al. (1974)	46,X,t(X;22)(q23;q13)	Xn	adult: amenorrhea I

Appendix 2. References of 41 unbalanced X-autosome translocations

Reference	Karyotype	Late replication	Phenotype
Leichtman et al. (1978)	46,X,der(X),t(X;1)(p11;q44)	der(X)	short stature, amenorrhea I
Zuffardi et al. (1977)	46,X,der(X),t(X;1)(p11;q24)	der(X)	mental retardation, minor congenital abnormalities
Frantz and Noel (1975)	46,X,der(X),t(X;2)(p111;q372)	der(X)	growth retardation, streak gonads
Mashkova and Verlinskaya (1976)	46,X,der(X),t(X;2)(p11;q36)	der(X)	—
Turleau et al. (1977)	46,X,der(X),t(X;2)(p223;q323)	der(X)	severe mental retardation, hypotrophia
Oorthuys et al. (1981)	46,X,der(X),t(X;3)(p21;q12)	—	polymalformations
Pearson et al. (1978)	46,X,der(X),t(X;3)(q26;q12)	der(X)	mental retardation, congenital anomalies
Centre de Génétique Médicale, Marseille (no. 6135)	46,X,der(X),t(X;3)(p21;p12)	Xn 48% der(X) 52%	mental retardation, dysmorphy
Cervenka et al. (1976)	46,X,der(X),t(X;4)(q27;q25)	—	mental retardation, multiple anomalies
Garcia et al. (1977)	46,X,der(X),t(X;5)(q28;p13)	der(X)	amenorrhea II
Gaal and Laszlo (1977)	46,X,+der(6),t(X;6)(p21;p24)	—	amenorrhea I, Turner phenotype
Hagemeijer et al. (1977)	46,XX,−6,+der(6),t(X;6)(p21;q26)	Xn	mental retardation, short stature, minor abnormalities
Cohen et al. (1972)	46,X,der(X),t(X;8)(q28;q11)	der(X)	mental retardation, congenital anomalies
Mikkelsen and Dahl (1973)	46,X,der(X),t(X;8)(p22;q21)	Xn	severe mental retardation, congenital anomalies
Tipton (1974)	46,X,der(X),t(X;8)(q26 or 28;q12)	der(X)	mental retardation, some features of trisomy 8 syndrome
Dumars et al. (1975)	47,XXYqs,−9,+t(X;9)(q+;p−)	—	mental retardation, multiple anomalies
Leisti et al. (1975)	46,X,+der(9),t(X;9)(q11;q32)	der(9) 95% Xn+der(9) 5%	mental retardation
Pescia et al. (1979)	47,XY,+der(X),t(X;9)(q24;q31)	der(X)	mental retardation, congenital malformations
Barnabei et al. (1979)	46,X,der(X),t(X;11)(q22;q11 or 12)	—	multiple congenital anomalies
Turleau et al. (1975)	46,Y,der(X),t(X;12)(q25;q11)	—	—
Crandall et al. (1974) Mohandas et al. (1981)	46,X,der(X),t(X;13)(q27;q12)	der(X)	some features of trisomy 13 syndrome

Appendix 2 (continued)

Reference	Karyotype	Late replication	Phenotype
Allderdice et al. (1978)	47,Y,t(X;14)(q13;q32),+der(14)	1 der(14)	mental retardation, Klinefelter syndrome
Buckton et al. (1971)	45,X/46,X,der(X),t(X;14)(p11;qter)	der(X)	short stature
Bartsch-Sandhoff et al. (1976)	46,X,der(X),t(X;15)(p22;p1)	der(X)	short stature
Bernstein et al. (1979)	45,X/45,X,−X,−15,+t(X;15)(p11;q11) or (q11;p11)	der(X)	mental retardation
Engel et al. (1971)	45,X,−X,−15,+tan(Xqter;15q11)	der(X) 75% Xn 11% der(X)+Xn 10%	severe congenital anomalies
Fraccaro et al. (1977)	46,X,der(X),t(X;15)(p113;p1)	der(X)	normal
Zabel et al. (1978)	46,X,der(X),t(X;15)(p22;q15)	der(X) 75% Xn 25%	mental retardation dysmorphy
Davis et al. (1976)	46,X,der(X),t(X;16)(p11;q24)	der(X)	gonadal dysgenesis
Centre de Génétique Médicale, Marseille (no. 8000)	46,X,der(X),t(X;16)(p113;q13)	der(X) 93% Xn 7%	mental retardation, dysmorphy
Hagemeijer et al. (1977)	46,X,der(X),t(X;17)(p11;q24)	der(X)	congenital anomalies
Palmer et al. (1980)	46,X,der(X),t(X;17)(p22;p13)	der(X)	congenital anomalies
Yamamoto et al. (1979)	46,X,+der(17),t(X;17)(q13;q21)	—	mental retardation, facial dysmorphy
Cann et al. (1975)	46,XY,+der(X),t(X;21)(q22;q22),−21	—	congenital anomalies, some features of monosomy 21 syndrome
Couturier et al. (1979)	46,X,der(X),t(X;21)(q27;q11)	der(X)	dull, some features of trisomy 21 syndrome
	45,X,+der(X),−21	der(X)	mental retardation, dysmorphy
Summitt et al. (1974)	46,XX,−21,+der(21),t(X;21)(q11;p11)	Xn+der(21) 94% Xn 6%	mental retardation, congenital anomalies
Taysi et al. (1981)	46,X,der(X),t(X;21)(q28;q11)	der(X)	some features of trisomy 21 syndrome
Buhler et al. (1977)	46,XX,−22,+der(22),t(X;22)(q12;p11)	Xn+der(22)	congenital anomalies
Jenkins et al. (1974)	45,X/45,X,−22,+der(X),t(X;22)(q28;q11)	—	normal
	45,X,−22,+der(X),t(X;22)(q28;q11)	—	mental retardation
	46,XY,−22,+der(X),t(X;22)(q28;q11)	der(X)	mental retardation, hypogonadism
Mattei et al. (1978)	46,X,der(22),t(X;22)(q11-12;q112)	der(22)	mental retardation, hypotrophia
GM 4514	45,X/45,X,−22,+dic(X;22)(q22;p12)	der(X)	facial dysmorphy

capable of inactivation, i.e., the one which carries the inactivation center (IC). We think, with Therman et al. (1974), that there is only one IC, which is situated in the proximal region of the long arm of the X chromosome (Mattei et al. 1981). So, according to the position of the breakpoint on the X chromosome, the IC will be carried on one of the resulting chromosomes (Fig. 1). For a breakpoint situated between the distal extremity of the short arm (p ter) and the centromere (cen) the IC will be situated on the derived chromosome containing the centromere of the X chromosome, i.e., der(X). The same will be true for a breakpoint between the IC and the distal extremity of the long arm (q ter). In contrast, when the breakpoint is between the centromere and the IC of the X chromosome, the IC will be transferred to the autosomal derivative, der(Aut). We shall call the normal X chromosome Xn.

The Incidence of t(X-Aut). The incidence of a translocation in the general population depends both on the probability of its occurrence and on its transmission from one generation to the next, which depends directly on the reproductive functions of affected individuals. We have, therefore, studied the fertility of both males and females with balanced t(X-Aut). There were 20 males (Appendix 3) among both familial and isolated cases, but only nine had reached the age of puberty with known gonadal function. The 64 postpubertal females of known phenotype were identified in the 90 cases of balanced t(X-Aut) (Appendix 1).

Results

Distribution of Autosomes in t(X-Aut). Table 1 compares the observed and expected incidence of translocation for each autosome in the 356 cases of balanced t(Aut-Aut) and in the 105 cases of t(X-Aut). The autosomal pairs 15, 21, and 22 are affected by t(X-Aut) more often than would be expected. This difference is highly significant (Fig. 2). On the other hand, the pairs 7 and 10 are slightly less common than expected in these translocations. The involvement of the chromosomal pairs 9, 18, 21, and 22 in balanced t(Aut-Aut) is much higher than expected. Pairs 4, 10, and 13 are affected slightly more often than expected, whereas pairs 1, 2, 3, 6, 17, and 19 are affected less often than

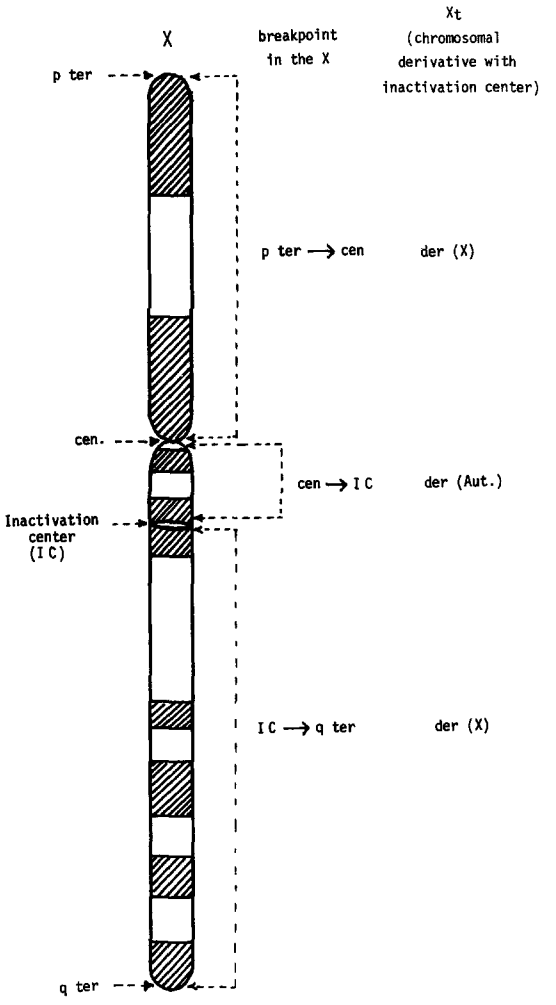


Fig. 1. Identification of the chromosome derivative containing the inactivation center (IC), related to the site of the breakpoint of the X chromosome: derX = derivative containing the centromere of the X chromosome; derAut = derivative containing the centromere of the autosome; cen = centromere of the X chromosome; pter, qter = telomeric extremities of the X chromosome

expected. Thus, there is a much greater incidence of both types of translocation involving chromosomes 21 and 22. The excess of (X;21) and (X;22) translocations seems to be related more to the nature of the autosomal pairs 21 and 22 than to that of the X chromosome. Moreover, further analysis of the (X;21) translocations (Table 2) shows that in six of the eight cases the breakpoints were localized in the pericentric region of the chromosome 21,[21p13→21q11], whereas they were spread evenly along the whole length of the X chromosome. It seems, therefore, that there is a fragile zone on chromosome 21. Similarily for chromosome 22, in six of the nine (X;22) translocations the breakpoints are in the region [22p13→22q11], whereas they are spread along the whole length of the single long arm of the X chromosome (Table 2). It seems then that the centromeric region of the chromosome 22 is also particularly fragile. As for chromosome 15 the incrased incidence of translocations is only seen with t(X-Aut), indicating a special relationship between chromosome 15 and the X chromosome. The pericentric region of chromosome 15, [15p13→15q11], clearly seems to be a fragile zone as it is involved in nine of 11 cases (Table 2). However, the X chromosome seems to play some part in these (X;15) translocations, since the breakpoints are in

Appendix 3. References of 20 males with balanced X-autosome translocation

Reference	Karyotype	Gonadal function
Dutrillaux et al. (1972)	46,Y,t(X;1)(q28;q31)	Azoospermia
Leichtman et al. (1978)	46,Y,t(X;1)(p11;q44)	Prepubertal
	46,Y,t(X;1)(p11;q44)	One child: 46,XY
Turleau et al. (1977)	46,Y,t(X;2)(p223;q323)	Prepubertal
Pearson et al. (1978)	46,Y,t(X;3)(q26;q12)	Prepubertal
Cervenka et al. (1976)	46,Y,t(X;4)(q27;q25)	Prepubertal
Garcia et al. (1977)	46,Y,t(X;5)(q28;p13)	Prepubertal
Stengel-Rutkowski et al. (1976)	46,Y,t(X;5)(q28;q11)	Prepubertal
	46,Y,t(X;5)(q28;q11)	Azoospermia
Madan et al. (1981)	46,Y,t(X;12)(q22;p12)	Prepubertal
Buckton et al. (1971)	46,Y,t(X;14)(p11;qter)	Azoospermia
	46,Y,t(X;14)(p11;qter)	One child: 46,XY
Franke et al. (1976)	46,Y,t(X;14)(p22;q21)	Prepubertal
Fraccaro et al. (1977)	46,Y,t(X;15)(p113;p1)	Severe oligospermia
Hagemeijer et al. (1977)	46,Y,t(X;17)(p11;q24)	Prepubertal
Yamamoto et al. (1979)	46,Y,t(X;17)(q13;q21)	Prepubertal
Couturier et al. (1979)	46,Y,t(X;21)(q2700;q11)	Prepubertal
Faed et al. (1979)	46,Y,t(X;21)(q23;q11)	Azoospermia
Cuoco et al. (1980)	46,Y,t(X;22)(q26;q11)	Azoospermia
Marmor et al. (1980)	46,Y,t(X;22)(q25;qter)	Azoospermia

Table 1. Comparison of observed breakpoints in balanced t(Aut-Aut) and in t(X-Aut) with the expected distribution of breakpoints using the model of Valenzuela et al. (1979)

Chromosome	Series D Paris (%)	Balanced autosome-autosome translocations			X-Autosome translocations		
		Expected		Observed	Expected		Observed
1	8.44	60.09	***	32	8.86		10
2	8.02	57.10	*	38	8.42		5
3	6.83	48.63	**	29	7.17		7
4	6.30	44.86	*	60	6.61		4
5	6.08	43.29		41	6.38		4
6	5.90	42.01	**	24	6.19		5
7	5.36	38.16		34	5.63	*	2
8	4.93	35.10		26	5.18		4
9	4.79	34.10	***	57	5.03		7
10	4.59	32.68	*	47	4.82	*	1
11	4.61	32.82		33	4.84		4
12	4.65	33.11		31	4.88		5
13	3.74	26.63	*	39	3.93		4
14	3.56	25.35		31	3.74		3
15	3.46	24.64		32	3.63	***	11
16	3.36	23.92		15	3.53		3
17	3.25	23.14	*	13	3.41		4
18	2.93	20.86	***	36	3.07		1
19	2.67	19.01	*	8	2.80		3
20	2.56	18.23		18	2.69		1
21	1.90	13.53	***	32	1.99	***	8
22	2.07	14.74	***	36	2.17	***	9
Total	100	712		712	105		105

* $P<0.05$; ** $P<0.01$; *** $P<0.001$

Appendix 4. Statistical estimation of the incidence of X-autosome translocations

Given that T is the incidence of reciprocal translocation in live births,
N is the number of translocations arising de novo,
H is the number of inherited translocations,
P is the probability of a breakpoint occurring on the X chromosome (taking account of its length),

we can calculate F, the incidence of t(X-Aut) from the following formula:

$$F = PTN + PT\ (H \times 0.5 \times 0.5).$$

This formula includes a correction for those women who have a translocation but who are infertile, and cannot, therefore, transmit the defect.

$$F = (0.0371)(0.001)(0.20) + (0.0371)(0.001)(0.8 \times 0.5 \times 0.5)$$

$$F = 0.000018.$$

occur at random, but the normal X chromosome underwent late replication in every cell (pattern a, Fig. 4). Different inactivation patterns were seen in 14 cases (Table 3). Of these, ten cases (13.5%) had a heterogeneous pattern (pattern b, Fig. 4), although the proportion of cells with the inactivated Xn was still very much greater than those with the inactivated Xt. This pattern resembles the 60 cases with inactivation of the Xn in every cell. In one case (Sands 1980) the number of cells with the inactivated Xn or Xt was equal (pattern c, Fig. 4). In the last three cases (Thelen et al. 1971; Mattei et al. 1978; Nichols et al. 1980), cells with the inactivated Xn were in the minority, or absent (Fig. 4, patterns d and e). Table 3 also shows that the last four cases, which are exceptions to the usual inactivation pattern in balanced t(X-Aut), have breakpoints very distal on either the long or the short arm of the X chromosome. Two other cases are

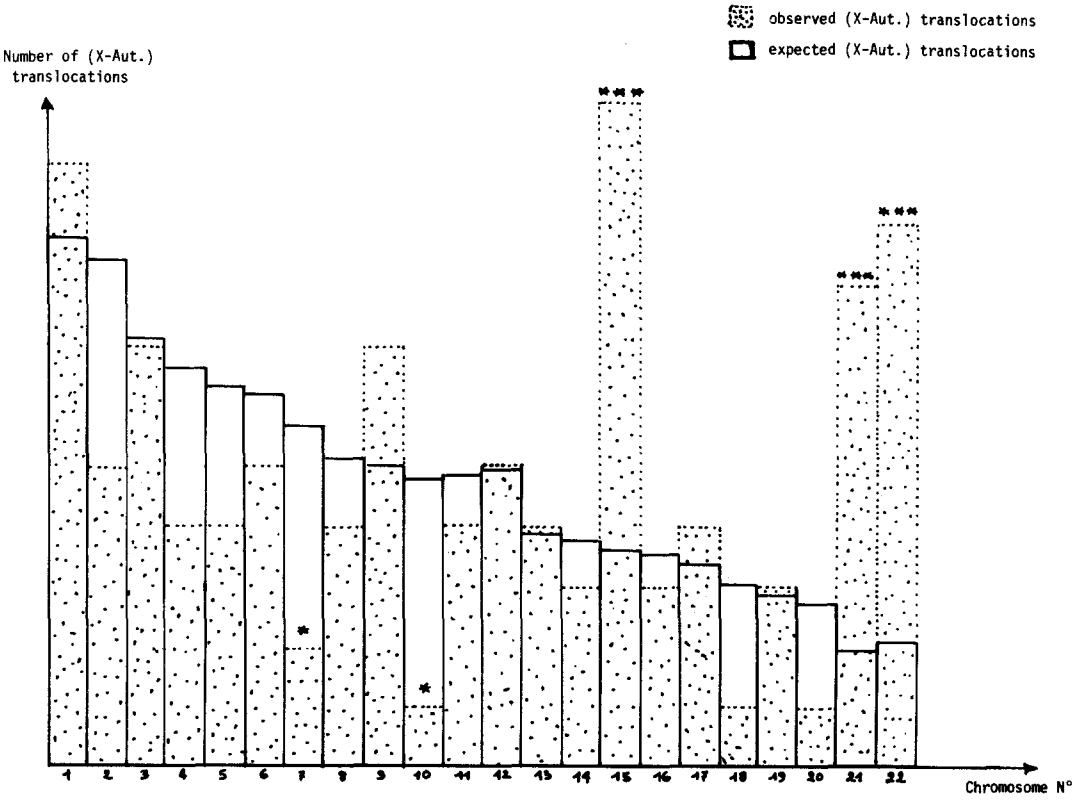


Fig. 2. Comparison of observed and expected numbers of translocations of the X chromosome with each autosome in 105 t(X-Aut). * $P < 0.05$, *** $P < 0.001$

its centromeric region, i.e., [Xp11→Xq11], in five of the 11 cases.

Distribution of Breakpoints on the X Chromosome. Figure 3 shows the distribution of the 102 breakpoints on the X chromosome in t(X-Aut). If the seven regions of the chromosome are taken to be equal, the expected average number of breakpoints in each region would be 14.57. The observed numbers do not differ significantly from this number.

Different Inactivation Patterns. Cytogenetic studies of X chromosome inactivation are limited to the cases with two X chromosomes, that is, almost exclusively to females.

Seventy-four females with balanced t(X-Aut) were examined by dynamic studies enabling the X chromosome inactivation pattern to be determined. In 60 (81.1%), this inactivation did not surprising in that a portion of cells are "nullisomic" for virtually all of Xq, as a result of the inactivation of both the Xn and the Xt. These findings could be due to the lack of resolution of autoradiography, particularly when the metaphases are very rich in autoradiographic grains, as shown by Gilgenkrantz et al. (1975).

Of the 41 cases of unbalanced t(X-Aut) shown in Appendix 2, 33 have undergone dynamic study (two of these were males with at least two X chromosomes). In 24 of the 33 cases, the Xt was inactivated in all the cells (pattern e, Fig. 4). The nine cases with different inactivation patterns are shown in Table 4.

Four cases had a heterogeneous X-inactivation pattern, but with a pattern very close to that of the majority of unbalanced translocations, i.e., with a very high proportion of cells with an inactivated Xt (pattern d, Fig. 4).

Table 2. Details of breakpoints in t(X;21), t(X;22) and t(X;15)

t(X-Aut)	Reference	Breakpoint on the X	Breakpoint on the autosome
t(X-21)	Cann et al. (1975)	Xq22-23	21q22
	Couturier et al. (1979)	Xq2700	21q11
	Faed et al. (1979)	Xq23	21q11
	Kallio et al. (1973)	Xq24-25	≅21q2
	Summitt et al. (1974)	Xq11	21p11
	Taysi et al. (1981)	Xq28	21q11
	Verellen et al. (1978)	Xp21	21p12
	Zabel et al. (1978)	Xp11	21p11
t(X-22)	Buhler et al. (1977)	Xq12	22p11
	Cuoco et al. (1980)	Xq26	22q11
	GM 4515 (1981)	Xq22	22p12
	Jenkins et al. (1974)	Xq28	22q11
	Lejeune (cited by Forabosco et al. 1979)	Xq27	22q11
	Marmor et al. (1980)	Xq25	22qter
	Mattei et al. (1978)	Xq11-2	22q112
	Palmer et al. (1973)	Xq22	22q13
	Pearson et al. (1974)	Xq23	22q13
t(X-15)	Bartsch-Sandhoff et al. (1976)	Xp22	15p1
	Bernstein et al. (1979)	Xp11 (ou q11)	15q11 (ou p11)
	Dutrillaux et al. (1974)	Xp11 (ou q11)	15q11 (ou p11)
	Engel et al. (1971)	Xqter	15p11
	Fraccaro et al. (1977)	Xp113	15p1
	Geneix et al. (pers. communic.)	Xq21	15q25
	Lucas and Smithies (1973)	Xq13	15p13
	Shimizu et al. (1977)	Xp11	15q11
	Solomon et al. (1976)	Xp11	15q11
	Sujansky et al. (1973)	Xq13	15p12
	Zabel et al. (1978)	Xp22	15q15

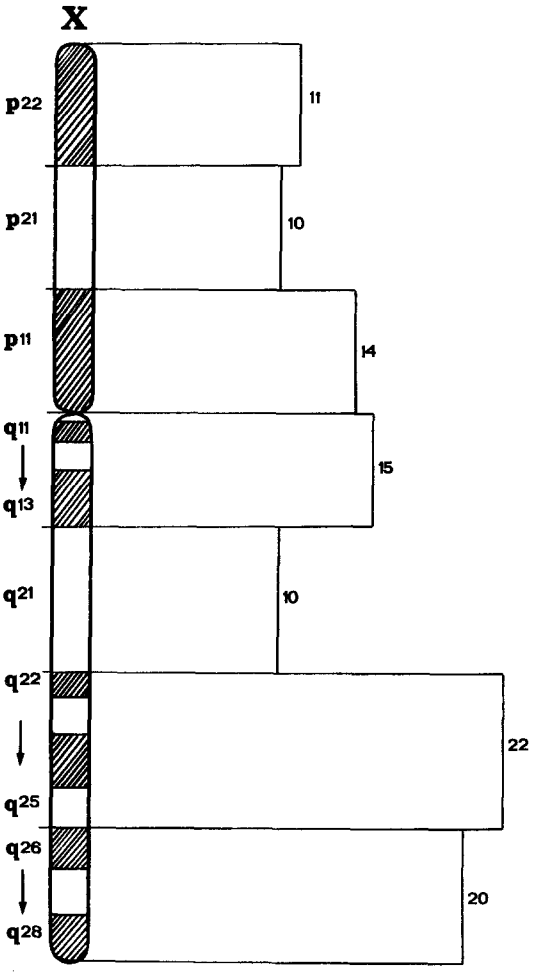
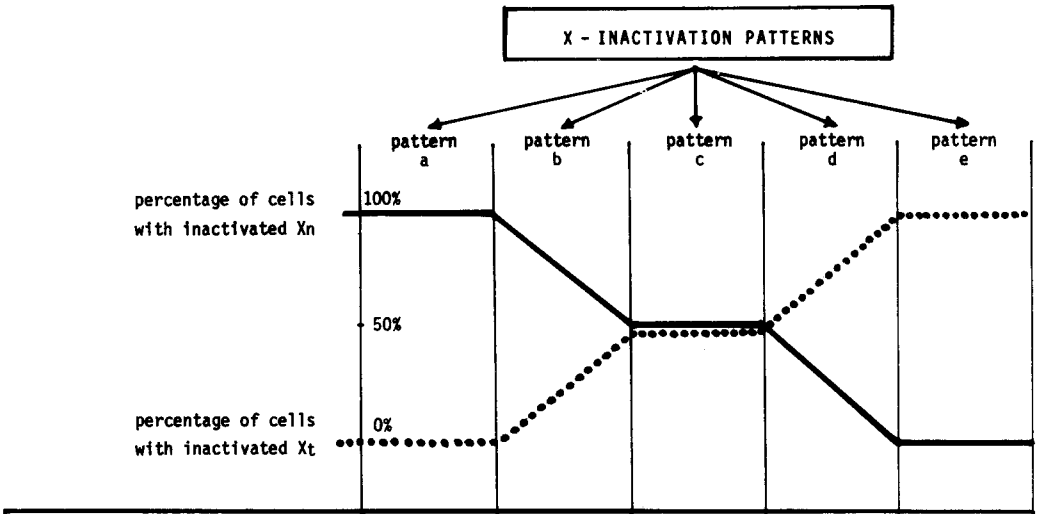


Fig. 3. Distribution of breakpoints in the seven regions of the X chromosome in 102 cases of t(X-Aut)

Three other cases (Summitt et al. 1974; Buhler et al. 1977; Hagemeijer et al. 1977) are unique in that their karyotype contains two normal X chromosomes in addition to the autosomal derivative of the t(X-Aut) (Table 4). Compensation for the "gene dose effect" would require that all but one of the X chromosomes be inactivated in each cell. The expected pattern would be inactivation of the Xt, which is the usual pattern in unbalanced t(X-Aut) with, in addition, inactivation of one of the normal X chromosomes. One case (Buhler et al. 1977) follows this model exactly, corresponding to pattern e in Fig. 4, and another case (Summitt et al. 1974) corresponds to pattern d in Fig. 4. However, this model depends on the presence of the IC in the autosomal derivative, which was not the situation in the case reported by Hagemeijer et al. (1977). In this case only a short fragment of the short arm of the X chromosome was translocated to the autosomal derivative der(6), resulting in a return to the normal inactivation pattern of one of the two Xn. Only two cases are not in line with the expected pattern of inactivation in unbalanced t(X-Aut). The more surprising of these is the case reported by Mikkelsen and Dahl (1973), with pattern a inactivation, in which all the cells have the inactivated Xn. However, in this case the breakpoint is again very distal on the short arm of the X chromosome. The other is case 6135 of the CGM, with equal numbers of cells with inactivated Xt and Xn.

Incidence of t(X-Aut). The incidence of t(X-Aut) in the general population is related, on the one hand, to the occurrence of the abnormality during meiosis, which depends both on the length of the X chromosome and on the number of X chromosomes susceptible to translocation and, on the other hand, to the possibility of transmitting such an abnormality, which depends on the viability and fertility of affected individuals. These last two factors may be sex-dependent. The ideal way to estimate this incidence would be to consider only those cases of t(X-Aut) discovered by systematic chromosomal analysis of whole populations of neonates. Three such studies with karyotype analysis have been published (Hamerton et al. 1975; Nielsen and Sillesen 1975; Nielsen and Krag-Olsen 1981; Buckton et al. 1980). Their results are summarized in Table 5. From a total of about 30,000 live births, no case of t(X-Aut) was detected, underlining the rarity of this kind of rearrangement. We, therefore, tried to estimate the incidence of t(X-Aut) from a study of the fertility of affected individuals, which indicates the likelihood of transmission of the chromosomal rearrangement.

In nine male postpubertal subjects with a balanced t(X-Aut) (Appendix 3), seven showed azoospermia, but two had one normal son with a 46,XY karyotype (Buckton et al. 1971; Leichtman et al. 1978) (Table 6).



	pattern a	pattern b	pattern c	pattern d	pattern e
Percentage of balanced (X-Aut.) translocations in the different patterns	81,1% (n= 60)	13,5% (n= 10)	1,3% (n= 1)	1,3% (n= 1)	2,7% (n= 2)
Percentage of unbalanced (X-Aut.) translocations in the different patterns	3% (n= 1)	0% (n= 0)	3% (n= 1)	15,1% (n= 4 + 1)	75,8% (n= 24 + 1)

Fig. 4. Percentage of balanced and unbalanced t(X-Aut) showing different patterns of inactivation: Xn inactivated in all cells (pattern **a**); more cells with Xn inactivated than with Xt inactivated (pattern **b**); equal numbers of cells with Xn and Xt inactivated (pattern **c**); more cells with Xt inactivated than with Xn inactivated (pattern **d**); Xt inactivated in all cells (pattern e)

Of the 90 cases of balanced t(X-Aut), the phenotype of 80 females was known of which 64 had reached the age of puberty. In these, fertility was assessed in relation to the localiztation of the breakpoint on the X chromosome (Fig. 5). Of the 64 patients, 30 showed ovarian dysfunction, either primary or secondary amenorrhea, ovarian dysgenesis, or sterility. In 30 others the phenotype was normal and, of the remaining four cases, two were mentally retarded, one had Duchenne myopathy, and the other was of very small stature.

Discussion

Incidence of Different Autosomes in t(X-Aut). Chromosomes 21 and 22 show a significantly raised incidence of t(X-Aut) and of balanced t(Aut-Aut). Their increased involvement in t(X-Aut) could be explained by the proximity at meiosis on the sex vesicle and the acrocentric nucleolar organizers observed by some authors (Knibiehler et al. 1981). However, analysis of the breakpoints suggests that the pericentromeric region of pairs 21 and 22 is involved in this increased incidence of translocations. It is possible that the centromeric heterochromatin and, in particular, the nucleolar organizers are involved in this increase, which is even larger in view of the small size of the chromosomes. This would explain why the other acrocentric chromosomes 13, 14, and 15 do not show a significant increase in balanced t(Aut-Aut). However, chromosome 15 is often involved in translocations with the X chromosome and its centromeric region appears to be important in this respect. It is, of course, very different biochemically from the centromeric region of the other acrocentric chromosomes because it contains DNA rich in both 5-methylcytosine and pairs of Adenine-Thymine bases (Okamoto et al. 1981), and is specifically stained by the Distamycin A/DAPI technique (Schweizer et al. 1978). Several different factors could theorectically influence, separately or in conjunction, the production of (X;15) translocations, including the biochemical properties of the centromeric region of chromosome 15, a possible structural analogy between the DNA of the centromeric regions of chromosomes X and 15, or the spatial organization of the nucleus in interphase in which the site of fixation of the chromosomes to the nuclear membrane could be nearer or further apart.

Distribution of Breakpoints on the X Chromosome. In view of the size of the sample studied we can draw only tentative conclusions, but analysis of a greater number of (X-Aut) translocations suggests that there are two regions, [Xq21] and [Xp21], of the X chromosome less often affected. It is of interest that a study of the time course of DNA replication on the X chromosome (Willard and Latt 1976) showed that the [Xq21] band was the last to replicate, preceded shortly by the [Xp21] band. Similarly, sister chromatid exchanges, although the result of a different mechanism, can give an indication of the likelihood of rearrangements in the different regions of the X chromosome. Haglund and Zech (1979) and Hoo and Parslow (1979) showed that sister chromatid exchanges were more common in the regions of early DNA replication. It is possible that the regions of late DNA replication could be less susceptible to rearrangements in general, whether translocations or sister chromatid exchanges.

Table 3. Different inactivation patterns in those cases of balanced t(X-Aut) which do not follow the usual inactivation pattern (inactivation of Xn in all cells)

Reference and karyotype	Late replication			Method	Informative metaphases
	Xn	Xt	Xn+Xt		
Canki et al. (1979) 46,X,t(X;3)(p21;q13)	93%	7%	—	BrdU	58
Laurent et al. (1975) 46,X,t(X;1)(p21;p34)	87%	13%	—	BrdU	15
Palmer et al. (1980) 46,X,t(X;17)(p22;p13)	86%	14%	—	BrdU	124
Hagemeijer et al. (1977) 46,X,t(X;6)(p21;q26)	85%	15%	—	BrdU	70
Leisti et al. (1975) 46,X,t(X;9)(q11;q32)	84%	—	16%	^{3}H-Thymidine	28
Latt et al. (1976) 46,X,t(X;13)(q21 to 23; q21 to 31)	78%	22%	—	BrdU	260
Zabel et al.(1978) 46,X,t(X;21)(p11;p11)	70%	30%	—	BrdU	—
Cohen et al. (1972) 46,X,t(X;9)(q12;p24)	68%	—	32%	^{3}H-Thymidine	50
Fraccaro et al. (1977) 46,X,t(X;15)(p113;p1)	67%	33%	—	BrdU	30
Hellkuhl et al. (1982)	Fibroblasts				
46,X,t(X;3)(q28;q21)	65%	35%	—	BrdU	70
Sands (1980) 46,X,t(X;10)(qter;q11)	55%	45%	—	^{3}H-Thymidine	22
Thelen et al. (1971) 46,X,t(X;18)(qter;q11)	21%	79%	—	^{3}H-Thymidine	65
Mattei et al. (1978) 46,X,t(X;9)(p22;q12)	—	100%	—	BrdU	100
Nichols et al. (1980)	Fibroblasts				
46,X,t(X;13)(pter;q13)	—	100%	—	BrdU	—

Table 4. Different inactivation patterns in those cases of unbalanced t(X-Aut) which do not follow the usual inactivation pattern (inactivation of Xt in all cells)

Reference and karyotype	Late replication			Method	Informative metaphases
	Xn	Xt	Xn+Xt		
Leisti et al. (1975) 46,X,+der(9)t(X;9) (q11;q32)	—	95%	5%	^{3}H-Thymidine	20
Centre de Génétique Médicale, Marseille (no. 8000) 46,X,der(X)t(X;16) (p113;q13)	7%	93%	—	BrdU	50
Engel et al. (1971) 45,X,−15,+tan(X;15) (qter;q11)	11%	75%	10%	^{3}H-Thymidine	—
Zabel et al. (1978) 46,X,der(X)t(X;15) (p22;q15)	25%	75%	—	BrdU	—
Centre de Génétique Médicale, Marseille (no. 6135) 46,X,der(X)t(X;3) (p21;p12)	48%	52%	—	BrdU	100
Mikkelsen and Dahl (1973) 46,X,der(X)t(X;8) (p22;q21)	100%	—	—	^{3}H-Thymidine	23
Hagemeijer et al. (1977) 46,XX,−6,+der(6) t(X;6)(p21;q26)	100%	—	—	BrdU	40
Summitt et al. (1974) 46,XX,−21,+der(21) t(X;21)(q11;p11)	6%	—	94%	^{3}H-Thymidine	31
Buhler et al. (1977) 46,XX,−22,+der(22) t(X;22)(q12;p11)	—	—	100%	BrdU + ^{3}H-Thymidine	—

Different Inactivation Patterns. In individuals affected by a t(X-Aut) the inactivation of one of the X chromosomes is not found at random (Lyon 1961), but usually follows the pattern most favorable to the individual. Thus, in the case of balanced t(X-Aut), the Xn is usually inactivated (pattern a, Fig. 4). In fact, when the Xt chromosome is inactivated, the adjacent autosomal segment may also be inactivated by a "spreading effect" creating a partial autosomal monosomy. In contrast, in unbalanced t(X-Aut), the Xt is usually inactivated (pattern e, Fig. 4). it is possible, in this case, that the extension of the inactivation from the Xt by a spreading effect, would reduce or even suppress the chromosomal disequilibrium. A number of balanced t(X-Aut) had a different inactivation pattern, which was, however, similar to the most favorable pattern for the individual since a large majority of cells had an inactivation Xn (pattern b, Fig. 4). The existence of this pattern gives support to the hypothesis of Gartler and Sparkes (1963) who suggested that, in the presence of a structural abnormality of the X chromosome, inactivation could occur at random, but would be followed by a cellular selection favoring the better genetic balance. Similarly for unbalanced t(X-Aut), the pattern d in Fig. 4 seems to be a step towards pattern e, which is the most favorable to the individual. Nearly 95% of balanced t(X-Aut) and 91% of unbalanced t(X-Aut) follow the most favorable model of inactivation. In those cases with a different pattern of inactivation, there does not seem to be a link with the nature of the translocated autosome, although the breakpoint on both the long and short arms of the X chromosome is very telomeric. A case reported by Yamada et al. (1982) follows the same argument: a woman with an unbalanced (X-Y) translocation, that is, 46,X,der(X)t(X;Y)

Table 5. Translocations found in studies of neonates, karyotyped with a chromosome banding technique

Reference	Newborn infants: (total no.)	Robertsonian translocations	Reciprocal translocations	X-Autosome translocations
Hamerton et al. (1975)	13,939	13	11	0
Nielsen et al. (1975, 1981)	11,148	17	15	0
Buckton et al. (1980)	3,993	3	4	0
Total	29,080	33	30	0

Table 6. Reproductive function of 20 males with balanced t(X-Aut), related to the site of the breakpoint of the X chromosome

20 Males with balanced (X-autosome) translocations			
Breakpoint in X	Prepubertal patients	Azoospermic patients	Patients with one child (46,XY)
Xp	5	2	2
Xq	6	5	0
Total	11	7	2

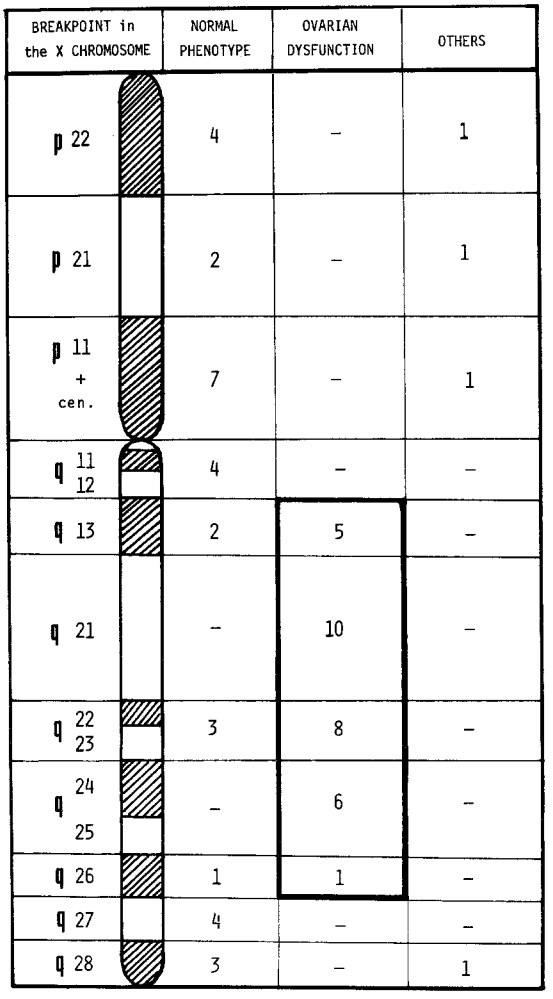


Fig. 5. Phenotype of 64 postpubertal females with a balanced t(X-Aut) related to the site of the breakpoint on the X chromosome, and localization of the "critical region" from the middle of [Xq13] to the middle of [Xq26]

(p22:q11), had an unusual pattern of inactivation, with 73 of 82 cells having an inactivated normal X chromosome. This telomeric localization of the breakpoints in Xp22 or Xq28 could, in some cases, prevent the propagation of the inactivation to the translocated autosome. In these circumstances neither cell line would be selected by virtue of its inactivation pattern, and the proportion of cells with inactivated Xn or Xt would be about 50%, as in the case reported by Sands (1980). However, this hypothesis does not explain the cases reported by Thelen et al. (1971), Mikkelsen and Dahl (1973), Mattei et al. (1978), or Nichols et al. (1980) which do not follow the most favorable pattern of inactivation, and for which there could be inverse cellular selection. It could be that, in these unusual cases, a particular genetic context favors the multiplication of cells, the inactivation pattern of which could be less favorable for the phenotype of the individual. This could explain the discordance of inactivation patterns found in different tissues of the same subject (Nichols et al. 1980; Hellkuhl et al. 1982). Since genetic activity is not the same in different cell types, it is possible that the selective forces also differ. In future, it must be remembered that the inactivation pattern observed in one tissue is not necessarily characteristic of the whole individual.

Incidence of X-Autosomal Translocations. The incidence of t(X-Aut) in the general population depends firstly on the probability of the rearrangement occurring, which is related to the number of X chromosomes available to undergo translocation. Since there is only one X chromosome in the male, this will, in theory, reduce by half the incidence of X chromosome translocations. In the female, there are two X chromosomes, but although one is inactivated in the somatic cells at a very early stage of embryogenesis, the position in the germinal cells is unknown. These cells in which the translocations occur differentiate at about 21 days, but it is not clear whether there are one or two active X chromosomes at this stage. If the germinal cells undergo X inactivation, they must undergo a reactivation before starting meiosis as it is known that both X chromosomes are active during meiosis. The evidence on this point is conflicting, both cytologically and from studies of enzymatic variants of glucose-6-phosphate-dehydrogenase. Gartler et al. (1975) and Semenova-Tien-Shanskaja and Patking (1978) believe that only one X chromosome is active in the human oogonia, the other being inactivated. Ohno et al. (1962) and Migeon and Jelalian (1977), on the other hand, are in favor of two active X chromosomes in human oogonia. This question is still unresolved in humans, but it has been shown in the mouse that an inactivated X chromosome is present in a late stage of oogenesis (Gartler et al. 1980) and during the decondensation phase of the preleptotene, just before meiosis (Hartung and Stahl 1977). Similarly, in sheep, Luciani et al. (1979) have shown the same picture of an inactivated X during the preleptotene stage. It is tempting to assume that a similar ontogenesis of the X inactivation occurs in humans. If this were true, t(X-Aut) would affect almost exclusively the non-inactivated X chromosome undergoing early replication. It is thought that translocation usually occurs during DNA synthesis in the oogonia, or even during the last premeiotic synthesis in the preleptotene stage, that is, at a time when only one X chromosome would be active. The inactivated X chromosome, undergoing DNA replication later than the other chromosomes, would be unlikely to be affected by translocations. Therefore, if it is accepted that the germ cells in the female are subject to the phenomenon of inactivation, there would be only one X chromosome available for translocations in the female as well as in the male.

The incidence of t(X-Aut) also depends on its transmission, that is, on the fertility of affected individuals with balanced t(X-Aut). Of the nine male postpubertal subjects with a balanced t(X-Aut), two have had one normal son with karyotype 46,XY. In these two cases (Buckton et al. 1971; Leichtman et al. 1978) it is surprising that the autosomal translocation took place on the short arm of the X chromosome (Table 6), which is usually essential for a normal meiotic pairing (short arm of X with the

short arm of Y). In neither case could paternity be confirmed or disproved by blood grouping. When the breakpoint is in the short arm of the X chromosome, the resulting inability to undergo meiotic pairing is a likely explanation for the sterility which is usually found in men with a balanced t(X-Aut). There is no obvious reason for this sterility when the breakpoint is on the long arm of the X chromosome. Lifschytz and Lindsley (1972) proposed a reversible inactivation of the X chromosome in primary spermatocytes I in those species with heterogametic males. This inactivation, which could be essential for normal spermatogenesis, could be inhibited by the presence of autosomal material on the X chromosome in t(X-Aut). However that may be, the majority of authors agree that affected males with balanced t(X-Aut) are usually sterile and cannot transmit the translocation.

Fertility was studied in 64 women with balanced t(X-Aut). As some authors (Sarto et al. 1973; Hagemeijer et al. 1977; Forabosco et al. 1979) have demonstrated a "critical region" in the X chromosome that is necessary for normal ovarian function, it is interesting to correlate the phenotypes of the 64 women in our sample with the site of the breakpoint on the X chromosome (Fig. 5). The 30 subjects with ovarian dysfunction all have a breakpoint between the [Xq13] and [Xq26] bands of the X chromosome. In the case of a break in the [Xq13] band, two of the seven affected individuals had a normal phenotype (Allderdice et al. 1978; Yamamoto et al. 1979). It could be that the breakpoint in these two translocations is at the proximal limit of the [Xq13] band. On the other hand, the observation by Pearson et al. (1978) of a case with a breakpoint in [Xq26] and a normal phenotype suggests that this could be the distal limit for the "critical region". It could be, in analogy with the translocations in [Xq13], that in this case the breakpoint is at the distal edge of the [Xq26] band. Thus, it seems likely that the "critical region" of the X chromosome, which must be intact for normal fertility and for transmission of the translocation, extends from the middle of the [Xq13] band to the middle of the [Xq26] band. The hypothesis usually invoked to explain the abnormal phenotype in women with a balanced t(X-Aut) in the "critical region" is the effect of gene position (Sarto et al. 1973; Forabosco et al. 1979). According to this hypothesis, the displacement of one or more genes involved in ovarian development, and normally present in the "critical region", would affect their activity and consequently ovarian function. However, there are three exceptions to this rule. The cases reported by Cann et al. (1975), Barnabei et al. (1979), and Madan et al. (1981) all have a normal phenotype and a balanced t(X-Aut) with the breakpoint in the [Xq22] band within the "critical region". Madan et al. (1981) suggest a mechanism of variable penetrance similar to that which enables some 45,X women to conceive. This would depend on the retention of a small number of oocytes into adult life. Overall, 47% of women with a balanced t(X-Aut) have a level of ovarian function incompatible with the transmission of their chromosomal rearrangement, and they all had a breakpoint in the "critical region" of the X chromosome. In contrast, those women in whom the breakpoint is outside the "critical region" seem to be normally fertile.

However, that may be, it is evident why t(X-Aut) is a rare event in the general population. An estimate of the incidence of this rearrangement can be made using the conclusions we have reached: only one X chromosome is susceptible to translocation in meiosis in both males and females and that all men affected by a balanced t(X-Aut) will be sterile, as will be 50% of the women. This leads to an estimated incidence of one in three per 10,000 live births. It is, therefore, not surprising that systematic studies of 30,000 live births detected no case of t(X-Aut). There is a further indication of the rarity of these translocations in that the known cases have been detected because of investigation for some pathological condition, such as sterility or developmental disorders. It is possible that these cases are not a representative sample of all t(X-Aut), in that those cases with the least phenotypic effect would be systematically missed. As any resulting sample bias can be neither estimated or corrected on present evidence, we put this forward only as a theoretical possibility.

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