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The Origin of Telocentric Chromosomes in Man: A Girl with tel(Xq)

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Summary. A mentally retarded girl with several Turner symptoms had the chromosome constitution 46,X,tel(Xq). The abnormal X chromosome appeared to be completely telocentric and stable. It was late-replicating and formed a smaller than normal Barr body. The origin of telocentric chromosomes is discussed.

Introduction

The existence of truly telocentric chromosomes in natural populations has been under considerable dispute (White 1973). However, observations on fission of two-armed chromosomes into two telocentrics has provided the best evidence that telocentric chromosomes are formed and that they are functional. Fission may also have played a role in the creation of new chromosome numbers during evolution (Southern 1969).

The present study deals with a stable telocentric Xq chromosome in a mentally retarded girl with some Turner symptoms. Her clinical picture will be compared with that of other women with a tel(Xq) chromosome (unpublished work).

Case History

The patient (KP 10 04 69) was ascertained at the age of $3^{7}/_{12}$ years in the Madison Blind Study (Trunca unpublished work). The patients were chosen for study if they had idiopathic mental retardation (IQ $\leq$ 70) and at least three other, presumably unrelated, anomalies. In this patient the anomalies consisted of a poorly differentiated right ear lobe, a highly arched palate, slightly increased hirsutism, and a small, cavernous hemangioma.

When the patient was born her mother was 34 and her father 39 years old. She was the youngest of four children. There were no recorded abortions or stillbirths. At birth she weighed 2752 g and was 49.5 cm long.

She was followed on a regular basis since her ascertainment, and in general, her health was good. She was always short compared with her peers. Breast development and pubic hair appeared at the age of 15 years; menarche occurred at 16. At the age of 17 years her height was 140 cm and she weighed 29.6 kg (Fig. 1). She has the following anomalies: short stature, low posterior hairline, cubitus valgus, short IV metacarpal, highly arched palate, auricle anomaly mentioned above, micrognathia, and retarded bone age. She did not display shield chest, increased number of pigmented nevi, nail anomaly, hearing defect, cardiovascular anomalies, webbed neck, epicanthic folds, short neck, ptosis, or other eye anomalies. She has well developed breasts, and moderate amount of pubic and axillary hair. She menstruates every 3–4 weeks and suffers from dysmenorrhea. She is severely mentally retarded (IQ ~ 30).

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Her three sibs are healthy. The two brothers are 183 cm tall; the older sister who is 165 cm tall shows normal sexual development.

Materials and Methods

The patient's chromosomes were studied in several lymphocyte cultures between 1963 and 1975. Chromosomes and Barr bodies were analyzed in cultured fibroblasts. The X-chromatin was also studied in buccal smears. Q-banding and C-banding were used in the chromosome analysis. Autoradiography was performed in cultured lymphocytes.

Results

The patient had one normal X chromosome, one tel(Xq), and a normal autosome complement. Of 99 analyzed cells only three

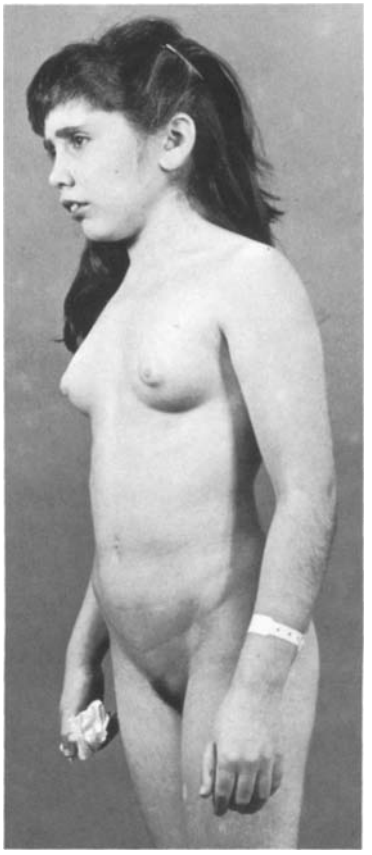

Fig. 1. Patient at the age of 15 years showing normal sexual development, micrognathia, malocclusion, and a large ear lobe

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Table 1. Chromosome analysis

Tissue	Stain	No. of chromosomes			
		45	46	47	Total
Skin	Orcein	—	5	—	5
Lymphocytes	Orcein	2	42	1	45
	Q-banding	3[a]	46	—	49
	Total	5	93	1	99

[a] Missing chromosome tel(Xq); all other cells had seven D-like chromosomes

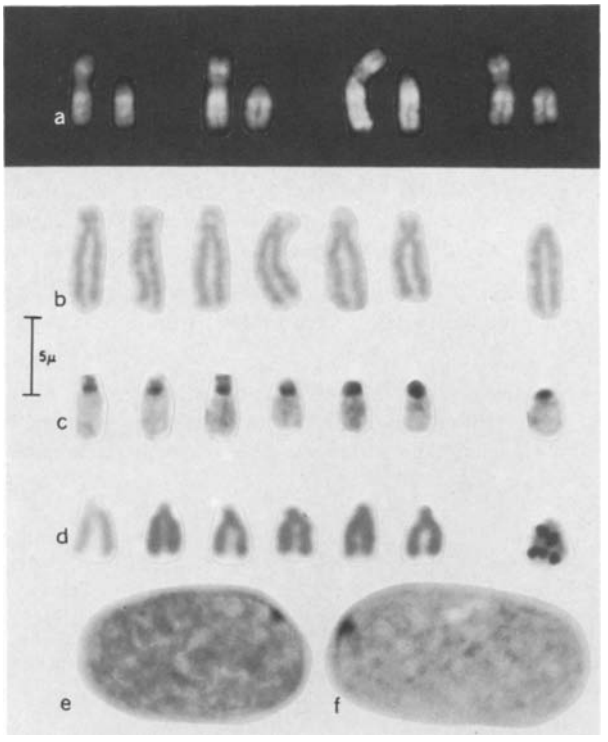

Fig. 2. a Normal X and tel(Xq) from four lymphocytes (Q-banding). **b** D group and tel(Xq) from a fibroblast (orcein). **c** C-banded D-group and tel(Xq). **d** Unlabeled D-group and labeled tel(Xq). **e** Normal Barr body (**f**) compared with sex chromatin formed by tel(Xq) in fibroblast nuclei (Feulgen) (**e**)

lacked the abnormal X chromosome (Table 1). The frequency of 45,X cells is not greater than that found in many normal women.

The abnormal X chromosome (Fig. 2a–d) is similar to the D chromosomes; however, it can be distinguished from them, even without banding, by the total lack of the short arm (Fig. 2a–c). The C-band appears to be at the very end of the chromosome (Fig. 2c). Autoradiography revealed that in 15 informative cells the telocentric was the heaviest labeled chromosome (Fig. 2d). In one additional cell one D chromosome was equally heavily labeled.

The frequency of Barr bodies in a buccal smear was 25% which is in the range found in normal females in our laboratory. The X-chromatin masses appeared somewhat smaller than those formed by a normal X chromosome (Fig. 2e and f). To test whether this difference was real, the following experiment was performed on fibroblast nuclei of the patient and a normal control. Feulgen-stained interphase nuclei from the patient and the control were selected for technical suitability by a technician, photographed, and given random code numbers from 1 through 63. The Barr bodies were then given one of the ranks: 0 for small, 1 for uncertain, or 2 for large. This scoring was done independently by Gloria Sarto on the one hand and by Eeva Therman and Evelyn Kuhn on the other. For each Barr body, the two ranks were added and classified into small (total rank 0), large (total rank 4), and ambiguous (total rank 1, 2, or 3). The results are shown below.

Size classes	Patient	Control	Total	
Small (total rank 0)	24	6	30	Fisher's test: $P = 0.00014$*
Large (total rank 4)	7	18	25	
Subtotals	31	24	55	
Ambiguous (total rank 1, 2, or 3)	1	7	8	
Totals	32	31	63	

* Two-tailed

When compared to a normal X chromosome, the tel(Xq) forms a significantly smaller Barr body ($P = 0.00014$).

The parents of the patient had normal chromosomes.

Discussion

Telocentric chromosomes fall into three categories. Fully stable telocentrics divide normally and are not lost. A second group consists of telocentrics which are fairly stable, but are sometimes lost or converted into isochromosomes (metacentrics whose two arms are genetically identical). The third type is unstable and survives at most a few divisions before they are lost or undergo misdivision. Steinitz-Sears (1966) has explained the variable behavior of telocentrics on the basis of the size of the centromere. The smaller the portion of the original centromere the telocentric contains, the less stable it is. Whether this hypothesis is correct may become known when the fine structure of the mammalian centromere is clarified (Ris and Witt 1979).

Centromeric fission, a misdivision that takes place during G_2-prophase-metaphase, has been observed in several different organisms. It has been described in a grasshopper (Southern 1969), a primate (Egozcue 1971), and three times in man. Fission of chromosome 7 was found in a healthy male (Hansen 1975); the resulting two telocentrics were present in all the cells studied. Dallapiccola et al. (1976) found the arms of chromosome 4 as two separate telocentrics in a woman with two trisomy 4p children. A centromeric fission of chromosome 10 was reported in a psychiatric patient and his 5½-year-old normal daughter (Fryns et al. 1980). In a pseudodiploid Chinese hamster cell line, 2.9% of all the chromosomes underwent fission (Kato et al. 1973). In two sibs with Bloom's syndrome, the lymphocyte chromosomes showed a tendency to break through the centromere, the centromeres of chromosomes 1 and 2 being special hot spots (Kuhn and Therman 1979). Whether the resulting telocentrics in this instance are stable, is not known.

A more common origin of telocentrics is misdivision of univalents in meiosis. In *Fritillaria,* 98% of the univalents undergo

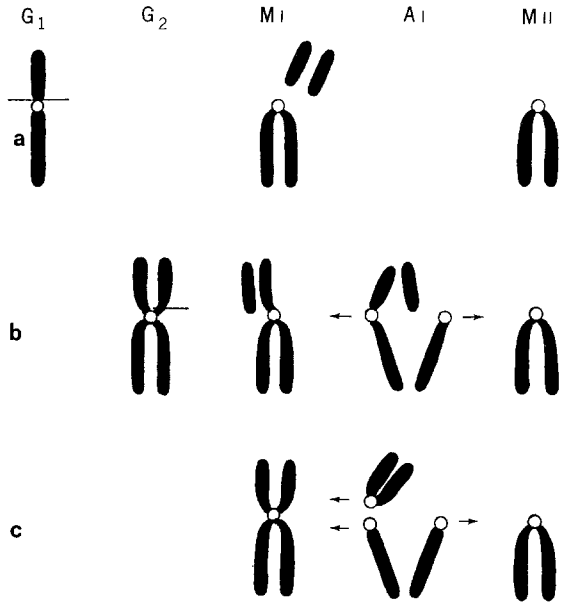

Fig. 3. The most probable modes of origin of a telocentric chromosome in man. a Break in G_1. b Chromatid break in G_2-metaphase. c Misdivision of the centromere into three parts

misdivision (Darlington 1939) and in wheat some 40% (Sears 1952). Misdivision of the centromere into two parts gives rise to an isochromosome for each arm while a misdivision of a centromere into three (Fig. 3c) or four parts results in the formation of two or four telocentrics, respectively. If, however, a univalent divides normally in the first meiotic division, the resulting chromatids usually undergo misdivision into two telocentrics in the second (Darlington 1939; Sears 1952). Once a centromere has misdivided it often remains unstable, the isochromosome giving rise to telocentrics and vice versa.

Several human mosaics in which one cell line contains an isochromosome and the other the corresponding telocentric have been found. Either chromosome type may have originated from the other through misdivision. The first such mosaic in which a chromosome 13 (determined using autoradiography) was involved was described by Therman et al. (1963), and two further cases by Sinha et al. (1972) and Fryns et al. (1979). Corresponding mosaicism for chromosome 21 also exists (Atkins and Feingold 1969; Guanti and Maritato 1978). An X chromosome mosaic showed the cell lines 46,X,i(Xq) and 47,X,i(Xq), tel(Xq) (Halbrecht et al. 1977). The most probable origin for the tel(Xq) chromosome in this case is a misdivision of the isochromosome into three parts with the isochromosome and one telocentric going to the same pole.

In humans, only long arm isochromosomes and telocentrics involving the X chromosome have been observed. Although i(Xp) and tel(Xp) should arise with a comparable frequency, no confirmed case of either has been described. This has been explained by assuming that the proximal part of the Xq contains the X inactivation center, chromosomes lacking this region, are not inactivated and do not form Barr bodies. Consequently a cell with tel(Xp) or i(Xp) would have two or three active X short arms, respectively, and presumably would be inviable (Therman et al. 1974).

The abnormal X chromosome in the present patient appears to be completely devoid of the short arm. Only three of 99 cells lacked the telocentric X chromosome; this is not significantly higher than the loss of the inactive X chromosome in many normal women. The tel(Xq) in this case can thus be regarded as stable. A high proportion, possibly the majority, of i(Xq) chromosomes have two C-bands (Niebuhr and Skovby 1977). Such chromosomes obviously came about through a chromosome break and a joining of the sister chromatids. The presence of a 45,X cell line in practically all cases with a dicentric i(Xq) (Niebuhr and Skovby 1977) also supports this interpretation. It is possible that many telocentrics have a similar origin (Fig. 3a, b). However, in this instance the sister chromatids have not rejoined.

The possible modes of origin of telocentrics and isochromosomes are listed below.

(1) Fission (misdivision in G_2-prophase-metaphase) which would lead to the formation of two telocentric chromosomes.

(2) Misdivision of the centromere into two parts in anaphase gives rise to two isochromosomes, while misdivision of a normal or an isochromosome into three or four parts results also in the formation of telocentrics.

(3) If a univalent divides normally in the first meiotic division, misdivision of the resulting single chromatids usually results in two telocentrics in the second division.

(4) Misdivision of a telocentric leads to the formation of an isochromosome, while a "nude" centromere is assumed to go to the other pole.

(5) Chromosome or chromatid breaks next to the centromere at a suitable stage without rejoining of the sister chromatids may result in the formation of telocentrics while rejoining gives rise to isochromosomes.

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