Further dicentric X isochromosomes and deletions, and a new structure i(X)(pter→q2102→pter)

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SUMMARY A new dicentric X isochromosome i(X)(pter→q2102→pter) of similar size to a normal X is described in a girl with gonadal dysgenesis. In this non-mosaic case with an X short arm duplication, most of the stigmata associated with Turner's syndrome were absent. This structure was compared with that of six i(Xq) and three del(X). The del(Xq) structures all possessed a regular sized C band, but in the i(Xq) this was double sized in each case. Phenotypic comparisons are made in the Xq deletions, and some presumptive short arm isochromosomes are reinterpreted as Xq deletions. Incomplete centromeric suppression is suggested as the causal mechanism of mosaicism of sex isochromosomes with 45,X cells, and it is argued that an exchange event between homologues is an unlikely mechanism to explain sex isochromosome origin.

X isochromosomes in man have been reviewed by de la Chapelle and Stenstrand (1974), Therman *et al.* (1974), Priest *et al.* (1975), Howell *et al.* (1976), Fujita *et al.* (1977), Niebuhr and Skovby (1977), and Verlinskaya and Mashkova (1977). Of considerable interest and significance as to their genesis is the proportion of isochromosomes that prove to be dicentric. Centromeric misdivision was proposed as the mechanism of origin of isochromosomes by Darlington (1939), who also predicted the existence of dicentric isochromosomes which he termed iso-dicentrics (Darlington and Wylie, 1953). This concept was developed in human material (de la Chapelle *et al.*, 1966) and possible infracentromeric breakpoints and dicentric-producing long or short arm breaks were described. Therman *et al.* (1974) showed that dicentric X structures such as end-to-end X fusions fitted the model of G1 chromatid break with G2 sister chromatid reunion, producing a dicentric chromatid at the following anaphase. A second alternative proposed by Therman *et al.* was a G2 chromatid exchange after homologous pairing of the adjacent type, analogous to the U type exchanges within a bivalent observed in plants (Jones, 1969). Though the existence of Xp isochromosomes has been doubted after the reinterpretation of one as an Xq deletion (de la Chapelle and Schröder, 1975), it has been suggested (Howell

et al., 1976) that a G1 break followed by G2 sister reunion in the proximal third of the X long arm would produce an i(X) similar in size and shape to the normal X. It is such an i(X) that is reported here and compared with some i(Xq) and Xq deletions.

Case report

The clinical histories of cases 1 to 10 are summarised in Table 1. The following is the clinical history of case 1.

The proband was referred at 17½ years of age for investigation of primary amenorrhoea. She was of average intelligence and the elder of two daughters with three older brothers. The younger sister of the proband was of normal development and stature, menstruating at 14 years of age. Her father was aged 44 years and her mother 34 years at the time of conception. On physical examination (Fig. 1), she was a girl of low normal stature (157 cm), slightly obese, with infantile genitalia, and a complete absence of pubic and axillary hair. There were no other systemic defects. Of other features of Turner's syndrome present, there was a lack of breast development with widely spaced and hypoplastic nipples, a high narrow palate, and cubitus valgus. Certain features of Turner's syndrome that were specifically examined for and found not to be present were: short and/or webbed neck, low posterior hairline, strabismus, 5th finger clinodactyly

Table 1   *Abnormal X and phenotype of cases 1 to 10 at diagnosis*

Case	Abnormal X	Age (y)	% 45,X cells (blood)	Height (cm)	Primary amenorrhoea	Other features before treatment
1 2347–77*	i(X)(pter →q2102→pter)	17½	0%	157	+	No pubic or axillary hair, average intelligence, obese, infantile genitalia, widely spaced, hypo- plastic nipples, high narrow palate, cubitus valgus
2 1204–76	del(X) ?(q21→q28)	18	0%	157	Secondary, in mid-20s	Minimal breast and pubic hair development, obese, 26% (small) X chromatin masses in buccal mucosa
3 1353–76	del(X) ?(q24→q28)	8	43%	<3rd centile	Infant	Widely spaced nipples, cubitus valgus, bone age of 4–5 years
4 966–76	del(X) ?(q21→q28)	19	50%	137	+	Normal breast and pubic hair development, obese, no webbed neck, cubitus valgus, or low hairline. Laparoscopy showed small ovaries, normal uterus, and tubes
5 624–76	i(X)(qter→p11→qter)	20	66%	Short	+	Cubitus valgus, slightly webbed neck, mentally slow, streak gonads, low hairline, infantile 2° sex characteristics
6 1513–76	i(X)(qter→p11→qter)	19	30%	140	+	Low hairline
7 1390–76	i(X)(qter→p11→qter)	60	80%	145	+	Mixed aortic valve lesion, pigmented naevi, shield chest, low hairline, parents early 20s at conception, poor 2° sex characteristics, short and webbed neck, wide spaced nipples, short 4–5 metacarpal
8 1270–77	i(X)(qter→p11→qter)	18	21%	150	+	Cubitus valgus, shield chest, multiple pigmented naevi, hypoplastic nipples, infantile 2° sex characteristics
9 169–77	i(X)(qter→p11→qter)	15	78%	134	+	Aortic stenosis, mentally slow, cubitus valgus, infantile 2° sex characteristics
10 529–76	i(X)(qter→p11→qter)	20	0%	134	+	Streak gonads, low hairline, cubitus valgus, many bony abnormalities: short metacarpal 4–5, bony spurs on femoral condyles. Short neck, obese, no neck webbing or pigmented naevi

*Lab. No

and short 4th metacarpal, multiple pigmented naevi, and congenital heart disease. Laboratory investiga- tions included FSH (100 IU/l), which was at postmenopausal level, and vaginal cytology, which was consistent with low oestrogen effect. A CAT scan of the pelvic region showed a uterus and

Fig. 1   *Proband at 17½ years of age.*

fallopian tubes of normal size, but the ovaries were not defined as separate structures indicating gross hypoplasia.

Cytogenetic studies

G and C bands and photography were performed as described previously (Daniel and Lam-Po-Tang, 1976), and air dried preparations were used exclu- sively. The G and C bands on case 1 are shown in Fig. 2, on the del(Xq) cases 2 to 4 in Fig. 3, and on the i(Xq) cases 5 to 10 in Fig. 4. The G-banding pattern of the abnormal X in case 1 (Fig. 2) was seen to be a mirror image duplication of the X short arm and upper long arm with a breakpoint in proximal q21. This structure was interpreted as an isochromosome. The G positive band in the centre was slightly less than half the size of the regular Xq21 band and, therefore, a breakpoint excising all but the proximal 2/10 of q21 (that is, a breakpoint in q2102) could explain the G-banding pattern. There were two C banded regions in the isochromosomes of case 1 and in cases 5 to 8, while in cases 9 and 10 the C band block was twice the regular size. In cases 5 to 8, but most clearly in case 1 (Fig. 2, lower row), chromatid separation occurred frequently at one of the C band regions. In the Xq deletions of cases 2 to 4, there was a single regular X sized C band block. In case 3, which of the X deletions most resembled an isochromosome, the G positive band
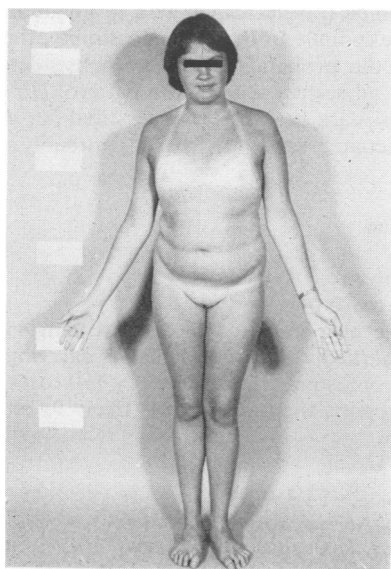
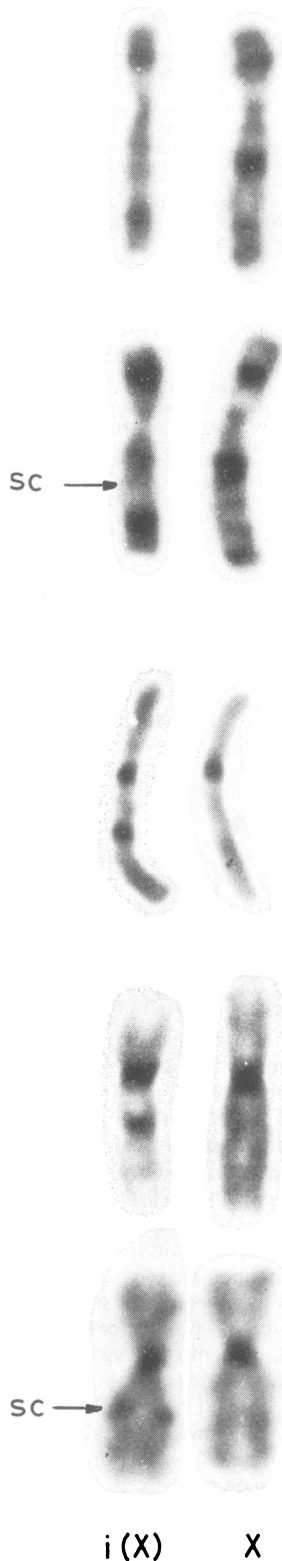Fig. 3   *Deleted (X) chromosomes from cases 2, 3, and 4. In each case, G bands: normal X, left; del(X), middle; and C bands del(X), right. Note in case 3, which most resembles an isochromosome, that the G positive terminal Xp band is only present in one arm of the del(X).*

on the terminal region of the X short arm was present on one arm only. In cases 2 and 4, the abnormal Xq seems to terminate within band Xq21. It is not clear from the preparations whether these deletions (cases 2 to 4) are interstitial or terminal, or whether the abnormal Xs are one product of *de novo* X/autosome translocations with terminal autosome arm breakpoints. In the latter possibility, the karyotype of the probands would be consistent with a der X— adjacent I segregation pattern. However, if these cases are examples of interstitial Xq deletions then a second breakpoint (in q28 ?) probably occurred in each.

Discussion

PHENOTYPE AND STRUCTURE OF SEX ISOCHROMOSOMES

Since the proportion of mosaicism with 45,X cells varies markedly between probands carrying similar X isochromosomes, for example, i(Xq) cases 6 and 7 in this report, the phenotype is likely to reflect this

Fig. 2   *Isochromosome in case 1; i(X) (pter→q2102→pter). Normal X, right; i(X), left. Top two rows G bands; lower three rows C bands. Note chromatid separation at one centromere of the dicentric i(X) in rows 1, 2, and 5.*

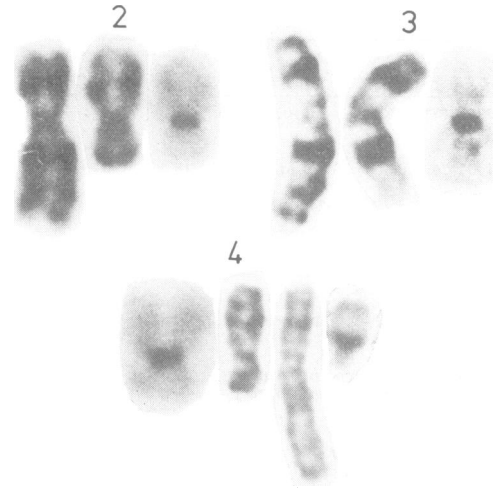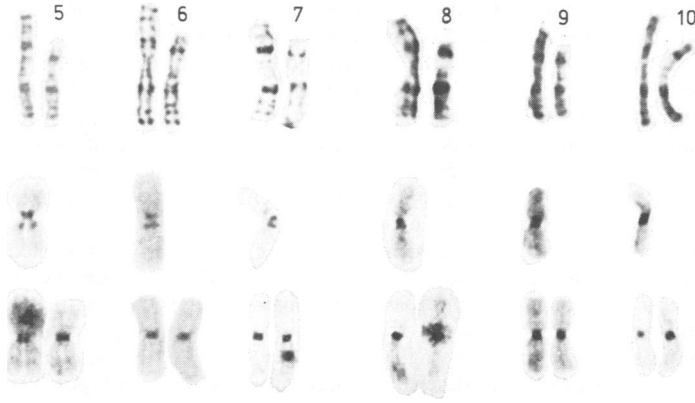Fig. 4   *Dicentric isochromosomes i(Xq) of cases 5–10 arranged with the longest i(Xq) intercentric gaps on the left. Top row: G bands of i(X), left and normal X, right. Middle row: C banded i(X) from each case. Lower row: C banded chromosome pair 3 from each case. Note in cases 9 and 10 that there is a single C band block but that this is double sized (in the isochromosomes).*

Table 2   *Phenotype in non-mosaic deletion X cases studied with G-banding*

Case	Davis et al. (1976) 1	de la Chapelle et al. (1975) 1	2	3	Van den Berghe et al. (1973)	Present study 2
Deletion	Xp t(X;16)	Xp	Xq proximal 2/3	Xq distal ½	Xq distal 2/3	Xq distal 2/3
Height (cm)	132	149	146	159	160	157
2° sex characteristics	Infantile	Minimally developed (normal)	Normal	Infantile	Normal	Minimally developed (normal)
Age	16	18	46	17	18	17½
Primary amenorrhoea	+	No	No	+	+	+ (Secondary)
Obesity	+	+	?	+	No	+
Renal abnormalities	−	−	−	+	−	−
Hypoplastic nails	−	+	−	−	−	−
Pigmented naevi	−	+	−	−	−	−
Genu valgum	−	+	−	−	−	−
Low hairline	−	+	+	−	−	−
Short neck	−	+	+	+	−	−
Shield chest	+	+	−	−	−	−

After de la Chapelle *et al.* (1975).

predominantly rather than the influence of isochromosome structure. In fact, there are few differences between 45,X and 45,X/46,X,i(Xq) syndromes (Table 2 in Santana *et al.*, 1977).

X isochromosomes, like those derived from the Y chromosome (Giraud *et al.*, 1977), have been reported with a wide variety of breakpoints. They have been described with breakpoints in the terminal long arm (Therman *et al.*, 1974; Sinha *et al.*, 1976; Maraschio *et al.*, 1977) and terminal short arm (Distèche *et al.*, 1972; de la Chapelle and Stenstrand, 1974; Ruthner and Golob, 1974; Fraisse *et al.*, 1975; Sillesen *et al.*, 1976). Some of the X/X translocations tabulated by Kim *et al.* (1974) are probably prebanding interpretations of these large X isochromosomes. As data accumulates, it is to be expected that non-mosaic cases of these i(X) types should have some features in common with XXX females. Those i(X) with infracentromeric or proximal short arm breakpoints [i(Xq)] are more frequently clinically ascertained and have been recognised since the early years of human cytogenetics (see the review of 35 cases by Ferguson-

Smith, 1965, and the recent reviews in the introduction to the present report). Unconfirmed reports of i(X) with proximal long arm breakpoints [i(Xp)] have been made by Fraccaro and Lindsten (1964), de la Chapelle *et al.* (1972) (now withdrawn as an Xq−), Keogh *et al.* (1973), Van den Berghe *et al.* (1973), and Fitzgerald and Donald (1975). From their Figs., the 'i(X)' in the latter two reports are likely also to be Xq deletions. Though in both cases the abnormal X is metacentric, the G-banding pattern is asymmetrical and there is a single regular-sized C band block in each case. The (X/X) translocation reported by Kim *et al.* (1974) could also be an i(X) with the breakpoint of formation in the mid short arm band p21, though in this case the carrier mother was fertile and with the above interpretation monosomic for part of p21→pter. The fertility of probands with X deletions of this region has recently been shown by Fraccaro *et al.* (1977). With this hypothetical perspective, it can be understood why i(Xq) of the regular type are most commonly clinically ascertained, presumably because of the

more frequent Turner's stigmata and primary amenorrhoea. Completing this spectrum of breakpoints is the i(X) of case 1 of the present series with a breakpoint $\frac{1}{3}$ from the centromere in the long arm. In this particular non-mosaic case, there is a duplication of the X short arm and proximal long arm. In the absence of mosaicism with 45,X cells, the phenotype of i(X) cases should reflect the i(X) structure. In this connection it is of considerable interest that the i(X) in case 1 should phenotypically resemble some Xq deletion cases (for example, case 2, Table 1) in that there are few Turner's syndrome stigmata present. This correlates with the principle that Xp monosomy rather than Xq monosomy most resembles the 45,X clinical presentation. This point becomes clearer if del(X) cases are briefly considered.

PHENOTYPE IN G BANDED DEL(X)
Much of the previous correlation in X deletion phenotypes is uninformative, and similarly shaped deleted Xs may exclude quite different interstitial regions (de la Chapelle et al., 1975). These authors have shown that the interpretation of interstitial deletions presents considerable difficulty. Of paramount importance is that probands with deletions in mosaicism with 45,X cells should be excluded from phenotypic comparisons. De la Chapelle et al. have described three non-mosaic cases, their case 1 alone having Turner's syndrome stigmata and short stature with most of the X short arm missing. Though this patient menstruated normally, as did their case 2 with an interstitial long arm deletion, case 1 of Davis et al. (1976), with a complete short arm deletion of translocation origin, had primary amenorrhoea. Three other cases with deletions of the distal long arm region had amenorrhoea but normal stature (Table 2). These were case 3 (de la Chapelle et al., 1975), case 2 of the present study, and the case of Van den Berghe et al. (1973). The latter patient was reported as an i(Xp), as was the mosaic patient of Fitzgerald and Donald (1975), but both could be interpreted as X long arm deletions. In the case of Van den Berghe et al., the patient had normal breast and pubic hair development similar to case 2 of the present report. Thus, at present, only broad delineations are possible. For example: (1) Short stature and most of the stigmata of Turner's syndrome are more likely to be associated with short arm X deletion. (2) Normal stature and secondary sexual characteristics combined with amenorrhoea are more likely to be found in deletions of the distal third of the X long arm.

PROPORTION OF DICENTRIC i(Xq)
The proportion of dicentric i(Xq) has been the subject of recent speculation. The view of de la Chapelle and Stenstrand (1974) and Priest et al. (1975) that dicentrics are in the minority has yielded with the documentation of further cases (Howell et al., 1976; Niebuhr and Skovby, 1977; Fujita et al., 1977) to the view that most are dicentric. The difficulty of explaining the presence of two centromeres in a relatively stable chromosome has resulted in a proposal of 'pericentric inversion of centromeric heterochromatin' (Yanagisawa, 1973) to explain the intercentric regions. In the six i(Xq) reported here (cases 5 to 10, Fig. 4), there is twice the normal amount of centromeric heterochromatin (CCH), whether there is clearly a double mass (cases 5 to 8) or a single mass (cases 9 and 10). Priest et al. (1975), in describing three cases, define two types of i(Xq): 'monocentric' and dicentric, but even their 'monocentric' type 1 has a CCH block twice as large as normal. The single cases of Yanagisawa (1973) and Cohen et al. (1975) and the 4 cases of Howell et al. (1976) are all dicentric. Of the 7 cases of Niebuhr and Skovby (1977), 5 are dicentric, one has a C band twice as large as normal, and the last (case 1) has a marginally bigger C band.

De la Chapelle and Stenstrand (1974) describe twice the normal CCH in two i(Xq) cases, and in a further two a C band of ordinary width, though individual C banded Figs. of these cases are not shown. In the 10 cases of Fujita et al. (1977), cases 7 to 10 have two C bands, but in the remainder only in case 4 is the CCH not increased in size in the isochromosome. Therefore, in a total of 36 cases analysed with banding, all but 4 (11%) have two or a double-sized CCH block.

ORIGIN OF i(X)
With the small proportion of i(Xq) cases containing a regular X sized CCH block, and the variety of other i(X) structures, centromeric misdivision in the sense of a break within the centre of the reverse-repeat structure of the centromere can only explain a small proportion of the i(X) structures. Similarly, in the i(Y) cases reported so far there is only one banded case with a single C band (that of Siebers et al., 1973) and this is larger than normal. However, in a patient with Edwards's syndrome described by Larson et al. (1978) there was both an i(18p) and an i(18q) suggesting that in isochromosome formation a breakpoint in the centre of the reverse-repeat structure can occur.

With a similar spectrum of breakpoints in both i(Y) and i(X) and the same phenomenon of incomplete suppression of one centromere giving rise to X monosomic cells, a similar origin is to be expected. Two alternative origins other than centromeric misdivision have been proposed for i(X). These are (1) An exchange event or translocation

between homologues (Therman *et al.*, 1974), analogous to the U type exchanges in plants (Jones, 1969). (2) A G1 chromatid break, replication, and G2 sister chromatid reunion within the chromosome (de la Chapelle *et al.*, 1966).

For X isochromosomes there is evidence of increased paternal age (Polani, 1965), as in case 1, pointing to a paternal event, which makes the first an unlikely explanation with the single male X. Furthermore, a number of factors make any event between homologues unlikely to explain i(Y) origin. In males, of course, there is a single Y and the fathers of i(Y) probands, when described, have been universally 46,XY (not XYY). If i(Y) originated from single 47,XYY cells, then the U type exchange mechanism which occurs at sites of chiasma formation (Jones, 1969) is hardly likely to occur in the heterochromatic Yqh region. A breakpoint within this region has occurred in two i(Y), those described by Morillo-Cucci and German (1971, case 1) and by Giraud *et al.* (1977, case 4). In the absence of any contradictory data, and with the knowledge that sister reunion does occur in broken and rejoined dicentric ring chromosomes at least, the sister reunion mechanism remains at present the model of choice to explain sex isochromosome origin.

ORIGIN OF MOSAICISM WITH 45,X CELLS

The instability of the dicentric i(X) is likely to be responsible for the genesis of mosaicism with 45,X cells, though a difficulty with this view is why X deletions (for example, cases 2 and 4) should also occur as mosaics with X monosomic cells. Perhaps this may become clear when the loci of X inactivation on the X chromosome are mapped. It has been argued that the greater the intercentric distance, the more likely it is that mosaicism will arise in i(X) (Hsu *et al.*, 1977), or other dicentrics (John and Freeman, 1975). However, some of the largest i(X), for example, the end-to-end X fusions reported by Distèche *et al.* (1972) and Therman *et al.* (1974), are non-mosaics. Similarly, in the i(X) reported here, case 1, with the largest intercentric distance, is one of the two non-mosaics. Furthermore, if the i(Xq) are arranged in order of decreasing intercentric distance, as they are in Fig. 4, the occurrence of 45,X mosaicism in blood is 66%, 30%, 80%, 21%, 78%, and 0%, respectively, that is, there is no relationship. A possible alternative explanation for the degree of 45,X mosaicism is the effectiveness of centromeric suppression as measured by the proportion of dicentrics with 'monocentric' morphology. This is very difficult to evaluate in i(Xq) cases, but in i(Yp) cases, where the Y markers are easily identifiable, there could be an inverse, tissue specific relationship (Table 3).

Table 3 *45,X mosaicism in blood and centromeric suppression in small dicentric i(Yp)*

| Authors | % mosaicism | | | % monocentric appearance in 46 cells |
	45	46	47 (2-i[Yp])	
Hsu *et al.* (1974)	17	83	—	100
Case 128/75, reported briefly by Daniel and Lam-Po-Tang (1976)	20	78	2	72
Stevenson *et al.* (1971)	31	69	—	40
Málková *et al.* (1975)	37	63	—	20
Johnston *et al.* (1974)	70	25	3	5

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