category II¹ resemble the individuals who have triplication for no. 14 (Fig. 2 and 3); thus, cases of 'Snodgrass syndrome, category II' might represent cases of trisomy 14.

In conclusion, our observation of 46,XX/47,XX,+14 mosaicism indicates that trisomy for no. 14 is compatible with life, at least when associated with a normal diploid cell line. Furthermore, phenotypic similarities among patients with triplication of at least a portion of chromosome 14 suggest an associated clinical pattern.

Alice O. Martin, Mary M. Ford, N. T. Khalil,
Karen B. Turk, and M. N. Macintyre

Department of Obstetrics and Gynecology,
Northwestern University Medical School, Chicago,
Illinois; the Department of Pediatrics, Case Western
Reserve University School of Medicine, Cleveland,
Ohio; and Curtiss Clinic, Chagrin Falls, Ohio;
and Department of Anatomy, Case Western Reserve
University School of Medicine, Cleveland, Ohio,
U.S.A.

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- ¹Snodgrass *et al.* (1966) classified cases of D trisomy on the basis of their craniofacial defects. Those in 'category I' were said to have severe prosencephalic defects, e.g. cleft lip, cleft palate, and ocular anomalies. Those in 'category II' were said to be characterized by a large nose with a broad bridge and a bulbous tip, a long upper lip that overhangs the lower lip, an everted lower lip, a large mouth that turns downward at the corners, 'mild' micrognathia, and loose skin folds in the mandibular and periorbital regions.
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Requests for reprints to Dr Alice O. Martin
Laboratory of Human Genetics, Prentice Women's
Hospital and Maternity Center, 333 East Superior
Street, Chicago, Illinois 60611, U.S.A.

45,X/47,XYY mosaicism

SUMMARY This paper describes and discusses the clinical and cytogenetic findings in an infant with an unusual sex chromosome abnormality 45X/47XYY.

There is a wide range of phenotypic and cytogenetic abnormalities in women with primary amenorrhoea: in such patients correlation of genotype with phenotype is extremely difficult. Sex chromosome mosaics are a particularly interesting group in that the cytogenetic diagnosis may be difficult and the management poses complicated problems. Many cases of 45X/46XY mosaicism have been reported (Jackson *et al.*, 1966). A much rarer finding is that of 45X/47XYY mosaicism. Jacobs *et al.* (1961) reported 1 such case in a phenotypic female ascertained during a survey of women with primary amenorrhoea. Another case in a 16-year-old girl with primary amenorrhoea was described by Cooper *et al.* (1962). A third case, the only phenotypic male, was briefly reported by Trowell and Hamilton in 1965. Here we describe a fourth case of 45X/47XYY mosaicism.

Case report

This female infant was born on the 22 November 1973, the second child of healthy unrelated parents. Maternal age at birth was 25 years, paternal age 29 years. Pregnancy of 40 weeks' duration was uneventful and terminated in the normal delivery of an infant weighing 3435 g with an Apgar score of 9. The infant had an enlarged clitoris but no other physical abnormalities were noted. Cytogenetic studies indicated that the infant was an unusual sex chromosome mosaic 45X/47XYY. She was reared as a female but the parents were informed of the chromosome findings. At the age of 3 months the clitoris was noted to have enlarged further, and bilateral inguinal herniae developed. At 9 months of age an episode of obstruction occurred in the left inguinal hernia. This was managed conservatively, but in view of the possibility of recurrence, early investigation of the genitourinary tract was undertaken. Under general anaesthesia the vulvar area was explored and two openings found. The more anterior opening was catheterized and urine obtained. The introduction of radio-opaque dye resulted in a satisfactory outline of a normal bladder. A catheter was then passed into the posterior orifice and a further injection of dye revealed a normal vagina and uterus with tubes on either side. A few days later both inguinal canals were explored under general anaesthesia and the hernial sacs opened. Each sac contained a gonad with part of the broad ligament, the left being smaller than the right. Histological examination of frozen sections taken from each pole of both gonads indicated that testicular tissue was present in all areas. Both gonads were, therefore, removed and the later reports confirmed that they were composed entirely of testicular tissue. The clitoral hypertrophy is to be corrected at a later date.

Cytogenetics

Chromosome examination undertaken at birth because of the ambiguous appearance of the external genitalia revealed the presence of two distinct cell lines in peripheral blood culture. Of the 100 cells examined, 60 had a modal number of 45 chromosomes. No Y chromosome was noted in any of these 60 cells and all lacked one C group chromosome. Forty cells had a modal number of 47 chromosomes and all contained two Y chromosomes. The Y chromosomes were morphologically distinct from the G group chromosomes. Q-banding confirmed the presence of 1 X chromosome and the lack of a Y chromosome in those cells with a modal number of 45 chromosomes and the presence of two Y chromosomes in those cells containing 47 chromosomes. Skin fibroblast culture undertaken at the age of 3 months confirmed the presence of the 2 cell lines. The results of serial leucocyte and skin fibroblast cultures are shown in the Table. In the second leucocyte culture undertaken 14 months after the original investigation, 2 cells with karyotype 46,XY were observed. We do not consider that this finding was the result of random loss of 1 Y chromosome from a 47,XYY cell as the preparations were of high quality with little scatter of chromosomes.

Discussion

Sex chromosome mosaicism is said to be present in 30% of all females with ovarian dysgenesis (Hamerton, 1971a). Mosaicism is generally considered to be the result of an accident in cell division occurring at an early stage in zygotic cleavage. If the error occurs late in cleavage after the establishment of a normal cell line, a multiple cell line mosaic will result (Hamerton, 1971b). There have been several reports of such triple cell line mosaics (Fraccaro *et al.*, 1966). In the present case, only 2 cells in the 400 cells examined had a normal male karyotype. This finding may indicate the presence of a normal male cell line in tissue not examined by us, but the absence of such a cell line in any significant proportion suggests that in the case described the error in cell division occurred soon after cleavage of an XY zygote.

The table sets out the clinical and cytogenetic findings in the present case and the 3 previously reported cases of 45,X/47,XYY mosaicism. It can be seen that correlation of these widely varying findings is extremely difficult.

In our patient, the proportion of the cell lines present in serial leucocyte cultures was reversed over a period of 14 months. Taylor (1968), studying mosaic mongols, also observed that the proportion of

Table Clinical and cytogenetic findings in 4 cases of 45X/47,XXX mosaicism

Case No.	Reference	Age at ascertainment (y)	Clinical findings		Cytogenetic findings						
			External phenotype	Primary sex organs	Tissue cultured	Date	Total cells counted	Chromosome counts			
								<45	45	46	
1	Jacobs <i>et al.</i> (1961)	33	Short stature; neck webbing; female external genitalia with sexual hypoplasia	Laparotomy not done	Blood	Jan. 1961	1000	2	69	4	26
					Skin	Jan. 1961	64	3	60	—	43
2	Cooper <i>et al.</i> (1962)	16	Short stature; female external genitalia; sexual hypoplasia	Absent uterus; blind Fallopian tubes opening directly into vagina; streak gonads in position of ovaries	Blood	1962	50	1	1	—	43
					Skin		60	6	52	—	43
3	Trowell and Hamilton (1965)	29	Short stature; obesity; gynaecomastia; male external genitalia; small testes; Wilm's tumour removed at age of 16 mth	Testicular biopsy (1960) showed tubules lined only with Sertoli cells; well-preserved Leydig cells of normal numbers; absent spermatogenesis	Blood	1965	59	—	37	—	23
4	Present case	Newborn	Enlarged clitoris; ambiguous external genitalia	Normal uterus and Fallopian tubes; normal vagina; gonads attached to broad ligament were composed of testicular tissue	Blood	Nov. 1973	100	—	60	—	48
					Skin	Feb. 1974	100	—	64	—	36
					Blood	Jan. 1975	100	—	31	2	67
					Skin	Jan. 1975	100	—	77	—	25

different cell lines in different tissues varied with increasing age of the subject. Cytogenetic studies performed in later life may, therefore, not accurately reflect the proportion of cell lines present in the embryo, yet it is this admixture which influences sexual differentiation (German, 1970). It could be postulated that in the present case there were sufficient XXX or XY cells in the primordial gonad to activate testicular formation, but that the primitive testes were functionally inert and thus unable actively to impose a male phenotype.

Management of this case began at birth when it was necessary to decide the sex of rearing. Many authors (Schellhas, 1974) stress the high risk of gonadoblastoma developing in patients with gonadal dysgenesis, especially in those patients who, on cytogenetic analysis, have an XY stem line. Laparotomy, which was, therefore, mandatory in this case, was precipitated by the presence of bilateral inguinal herniae, and recurrent abdominal pain. Further management will now consist of an attempt to produce as normal a feminine appearance and function as possible. This will probably necessitate operative intervention to normalise the enlarged clitoris and hormonal therapy to induce a menarche.

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MARIE T. MULCAHY, JOY JENKYN, AND
ALASDAIR MACKELLAR

*Cytogenetics Unit, State Health Laboratory
Services, Perth; and Princess Margaret Hospital
Perth, W.A. Australia*

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Requests for reprints to Dr Marie T. Mulcahy, The Cytogenetics Unit, State Health Laboratory Services, Box F312, G.P.O., Perth, Western Australia 6001.

Reproduction in a woman with low percentage t(21q21q) mosaicism

SUMMARY The birth of a child is described with Down syndrome followed by the conception of a fetus bearing the t(21q21q) chromosome in 100% of their cells in a woman mosaic for the translocation in less than 10% of 2 of her examined tissues and in none of the cells in her peripheral blood. Various hypotheses for explaining the above findings are discussed. The importance of examining as many parental tissues as possible for the detection of low percentage mosaicism is stressed.

Dallaire and Fraser (1964) reported a family in which 3 children in succession had Down syndrome caused by primary trisomy 21. Lymphocyte cultures of the parents were cytogenetically normal, but other tissues were not studied. Recently Nuzzo *et al.* (1975)

reported a similar family. Lymphocyte cultures on the parents were likewise normal, but long-term cultures of maternal skin fibroblasts revealed 0.87% mosaicism for trisomy-21.

Maternal mosaicism (46,XX/47,XX,+21) as a cause of Down syndrome was first reported by Smith *et al.* in 1962 and other cases have since been described (see for example Aarskog, 1969; Kaffe *et al.*, 1974).

Paternal mosaicism for trisomy-21 has also been described (Hsu *et al.*, 1971; Méhes, 1973).

G/G translocation in Down syndrome (Wilroy *et al.*, 1969) has occurred in two sibs. Both parents had normal karyotypes in their peripheral lymphocytes, but no other tissue was examined. Waxman and Arakaki (1966) also reported familial occurrence of G/G translocation. The mother had a normal karyotype in all of her peripheral lymphocytes examined and a 46,XX/46,XX,+F,-G karyotype in 8 out of 27 cells from her skin. She had one normal child and 3 children with clinical Down syndrome. Studies on 2 of the children with Down syndrome showed a G/G translocation. No banding study was performed.

We wish to report a family in which the mother is a low percentage mosaic for a t(21q21q). Blood, skin, ovary, and amniotic fluid were studied. Banding technique was successful in clearly identifying the marker as either an isochromosome for 21q or a t(21q21q) chromosome.

Case report

A 24-year-old gravida II para I phenotypically normal woman was referred for amniocentesis in her 19th week of pregnancy because of a previous delivery of a male infant with Down syndrome. In her second pregnancy chromosomal analysis of cells derived from an amniotic fluid culture revealed a 46,XY,-G,+?(GqGq) karyotype subsequently shown to be 46,XY,-G,+t(21q21q) by trypsin-Giemsa staining technique. The patient, therefore, elected to undergo

Table

Patient	Tissue	Total no. of metaphases	No. of metaphases with marker	Cytogenetic diagnosis
Proband	Peripheral blood	30	0	46,XX
	Skin	50	4	46,XX/46,XX,-G,+?(GqGq)
	Right ovary	30	1	46,XX/46,XX,-G,+?(GqGq)
Proband's husband	Peripheral blood	100	0	46,XY
Proband's first offspring	Peripheral blood	30	30	46,XY,-21,+t(21q21q)
	Amniotic fluid	50	50	46,XY,-G,+?(GqGq)
Proband's fetus	Cord blood	30	30	46,XY,-G,+?(GqGq)
	Heart blood	30	30	46,XY,-G,+?(GqGq)
	Skin	30	30	46,XY,-G,+?(GqGq)
Proband's fetus	Frozen skin	(Banded identification)		46,XY,-21,+t(21q21q)