References

[1] Daentl DL, Smith D, Scott C, Hall B, Gooding C. Femoral hypoplasia unusual facies syndrome. *J Pediatr* 1975;**86**:107–11.
[2] Farnsworth PB, Pacik PT. Glossoptotic hypoxia and micrognathia. The Pierre Robin syndrome reviewed. *Clin Pediatr* 1971;**10**:600–6.
[3] Smith JL, Stowe FT. The Pierre Robin syndrome (glossoptosis, micrognathia, cleft palate). *Pediatrics* 1961;**27**: 128–33.
[4] Levinson E, Ozonoff MB, Rayen PM. Proximal femoral focal deficiency (PFFD). *Radiology* 1977;**125**:197–203.
[5] Kelly TE. Proximal focal femoral deficiency anomalad. *Birth Defects* 1974;**10**:508–9.

Requests for reprints to Dr E R Graviss, Department of Radiology, Cardinal Glennon Hospital, 1465 South Grand Boulevard, St Louis, Missouri 63104, USA.

The penta-X syndrome

SUMMARY A child is presented with a 49,XXXXX chromosomal constitution bringing to 12 the total number of children described with this karyotype. Comparison of this child's features with previously reported cases indicates a clinically recognisable specific pattern of malformations referred to as the penta-X syndrome. X chromosome replication studies using BrdU labelling in the patient's cells clearly showed that the four presumably inactive X chromosomes were late replicating but not in a strictly synchronous fashion.

Since 1963, 11 children with a 49,XXXXX karyotype have been reported.[1–11] The purpose of this publication is to describe an additional patient with a 49,XXXXX chromosomal constitution and to report the results of X chromosome replication studies using BrdU labelling in her cells. Comparison of the clinical features of this child with previously reported cases suggests that a 49,XXXXX chromosomal constitution is associated with a specific recognisable pattern of malformations, which has previously been referred to as the penta-X syndrome.

Case report

The patient, a Mexican American female, was born to a 19-year-old gravida 2, para 1 mother and a 20-year-old father. Fetal activity, which started at 4 months, was decreased throughout the remainder of the pregnancy. Delivery after 38 weeks' gestation was uncomplicated. Birthweight was 1785 g and birth length was 42·5 cm. After being in stable condition initially, the infant suffered a dusky spell and at one week of age she developed circumoral cyanosis while feeding. Physical examination at 10 days of age showed a weight of 1800 g, length of 40 cm, and head circumference of 30 cm. The metopic suture was widely separated and the posterior fontanelle measured 3·5 × 2 cm. The hairline was low anteriorly. The inner canthal distance measured 2·2 cm (75th centile). There were external ear malformations consisting of appendages protruding from each tragus (fig 1), prominence of the antitragus bilaterally, and a preauricular pit on the left. There was incomplete development of the eyes manifest by persistence of the primary pupillary membrane and of the hyoid arteries bilaterally. Limb anomalies included decreased supination and pronation of the arms because of radioulnar synostosis, bilateral fifth finger clinodactyly, small hands which measured 5 cm in total length, and overlapping of toes. The digital dermatoglyphic patterns showed radial loops on both thumbs, one arch and three ulnar loops on the fingers of the right hand, and four arches on the left. She had a grade 3/6 systolic murmur at the left sternal border and bilateral rales at the lung bases.

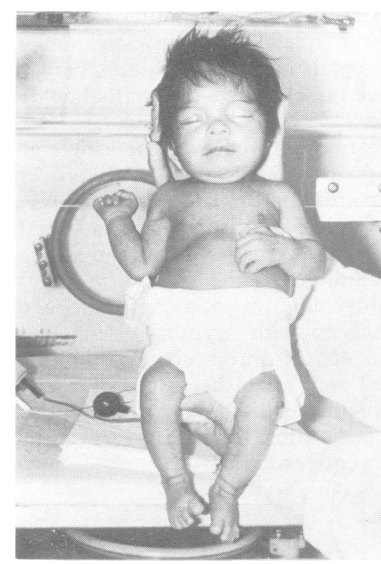

FIG 1 *The patient at 1 day of age. Note the low hair line anteriorly, the ocular hypertelorism, and the appendage protruding from the tragus of the right ear and the prominent antitragus.*

Received for publication 17 November 1979

Chest *x*-ray showed cardiomegaly and increased pulmonary vascularity consistent with mild congestive heart failure, for which she was treated successfully with digoxin and diuretics.

At 3 months of age her length and weight were 47 cm and 2438 g, respectively (both below the 3rd centile). Ophthalmological evaluation at 5 months was normal.

At 10 months of age, her length was 61 cm (height age of 4 months), weight was 4·3 kg (less than the 3rd centile for height age), and head circumference was 39 cm (less than the 3rd centile for chronological age). The anterior fontanelle measured 2 × 2 cm. Muscle tone was slightly increased with scissoring of the lower extremities and flexed arms.

Cardiac catheterisation showed a persistent ductus arteriosus which was surgically ligated. Later cardiac evaluations showed a mild valvular aortic stenosis, mild peripheral pulmonary stenosis, and two small ventricular septal defects.

Development was significantly delayed. At 17 months of age a Vineland Social Maturity Scale was administered, indicating that she was functioning at the level of a 6-month-old child.

Audiology evaluation has revealed a mild hearing loss in the right ear and severe loss in the left.

CYTOGENETICS

The patient's chromosomes were studied in peripheral blood lymphocytes cultured with phytohaemaglutinin for 72 hours (fig 2). All of the 15 metaphases banded with trypsin Giemsa (GTG) banding and 15 cells banded with acridine orange (after BrdU incorporation) R banding showed a 49,XXXXX karyotype. There was no evidence of mosaicism. DNA replication was studied by adding BrdU to the culture 6 hours before harvest. Four of the five X chromosomes were always late replicating; however, the acridine orange banding patterns were not identical, indicating asynchrony between the four late replicating X chromosomes (fig 3). Frequently, two pairs of two identically banded late X chromosomes were observed. A detailed study using pulse labelling with BrdU in different periods of the S phase of the cell cycle was carried out and will be reported elsewhere (Hansen and Francke, in preparation).

The patient's mother had a normal trypsin Giemsa banded karyotype, 46,XX. However, one of 50 cells analysed from her lymphocyte culture had a 47,XXX karyotype. Although this cell may have arisen from non-disjunction during culture, the possibility of 46,XX/47,XXX mosaicism cannot be ruled out. The patient's father had a normal 46,XY karyotype with trypsin Giemsa banding.

A fibroblast culture was established from a skin biopsy taken at 3 weeks of age. Ten metaphases were analysed at passage III with GTG banding. All

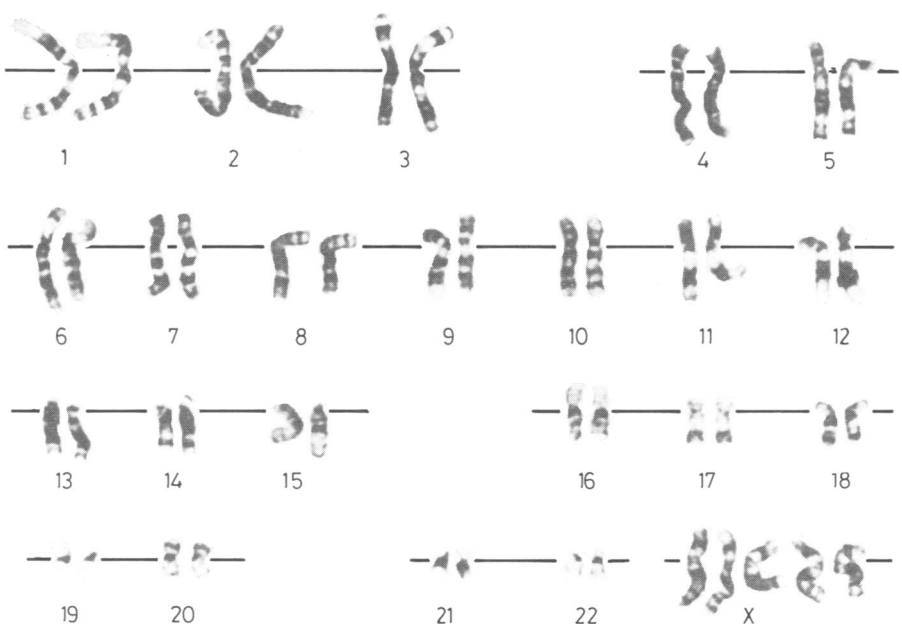

FIG 2 *Patient's karyotype using trypsin Giemsa (GTG) banding: 49,XXXXX.*

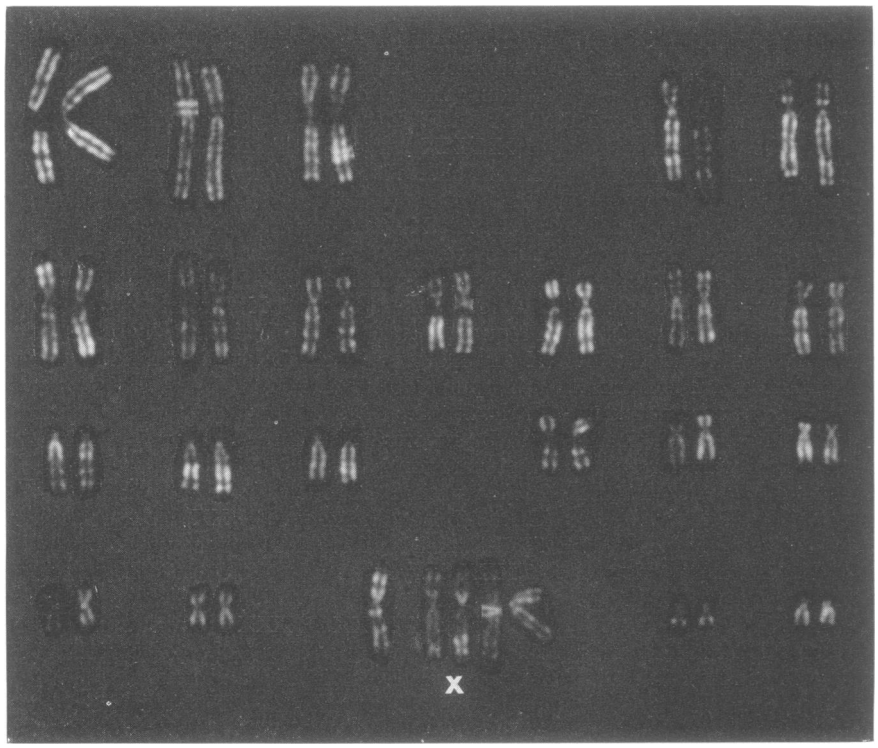

FIG 3 *Patient's karyotype with acridine orange fluorescent staining after BrdU incorporation late in the S phase of the cell cycle. The four late replicating X chromosomes, placed to the right, are clearly distinguishable. Their banding patterns, however, are not identical, suggesting asynchrony of replication.*

of them contained the three supernumerary X chromosomes. In addition, interphase nuclei consistently exhibited a higher number (two to four) of X chromatin (Barr) bodies.

Discussion

The principal features of the penta-X syndrome are set out in the table and illustrated in fig 1.

Growth deficiency was evident in the majority of affected children at the time of birth. Birthweight ranged from 1785 g to 2920 g with an average of 2382 g in the eight children born after a term gestation. Six of the eight patients from whom postnatal growth data are available, and who were followed up past one year of age, had a height and weight below the 3rd centile. Microcephaly, with a head circumference below the 3rd centile for chronological age, was present in six of nine patients in whom data were available. In four of them, the head circumference was also at or below the 3rd centile for height age. Moderate to severe mental deficiency

TABLE *Pattern of malformations in 12 patients with the penta-X syndrome*

	Observed/ evaluated	*Our case*
Performance		
Postnatal growth deficiency	7/9	+
Microcephaly	6/9	+
Developmental delay	9/9	+
Craniofacial		
Ocular hypertelorism	9/12	+
Upward slanting palpebral fissures	7/12	−
Epicanthal folds	6/10	−
Ear anomalies	6/12	+
Dental anomalies*	5/10	+
Short neck	7/12	+
Limbs		
Elbow defects†	5/12	+
Micromelia	3/12	+
5th finger clinodactyly	7/12	+
Low dermal ridge count	7/7	+
Positional foot deformities	9/12	+
Other		
Cardiac defect	5/12	+

*Delayed eruption, decreased number, irregular placement.
†Radioulnar synostosis, elbow subluxations, distended proximal ulna.

manifest by an Intelligence of Developmental Quotient of less than 50 was present in six of the children. One additional child in whom psychological testing was performed had an IQ of 75 and two others were said to be mentally retarded. Although ocular hypertelorism has been described in all but one of the previously reported patients, an increased inner canthal distance has been confirmed by measurement only in our patient. The auricular malformations consisted of preauricular appendages in three children, a preauricular sinus in one, and three children with prominence of the antitragus. One of the children with preauricular appendages also had bilateral hearing loss. Micromelia, although reported in three patients, was confirmed by measurement in only the patient described here. A persistent ductus arteriosus was present in four of the five children with documented cardiac defects. Three of those children developed congestive heart failure within the first year of life and required surgical ligation of the ductus. One child, who probably had an endocardial cushion defect, died of congestive heart failure at 2 5/12 years of age. Two additional children had cardiac murmurs, the aetiology of which were not determined.

Other defects which have been reported, although less frequently, include a simian crease in four, one child with a unilateral iris coloboma, and one with cleft palate. Delayed puberty was noted in the oldest patient, a 16-year-old. She had lack of normal breast development, prepubertal external genitalia, scanty pubic and axillary hair, a small uterus, and a vaginal smear which showed no oestrogen effect.

Four additional patients have been described with chromosome mosaicism including a 49,XXXXX cell line. Two of these, both with an XXXX/XXXXX chromosomal constitution, had a clinical phenotype consistent with the penta-X syndrome.[12 13] The other two, both complex mosaics, have strikingly different clinical phenotypes.[14 15]

We were unable to demonstrate mosaicism, that is the presence of a cell line with less than five X chromosomes, in two different tissues, lymphocytes and skin fibroblasts, from this patient. Thus, there is no evidence for postzygotic non-disjunction of X chromosomes. As has been proposed previously, the most likely mechanism for the production of a 49,XXXXX subject is double non-disjunction of the X chromosome in female meiosis. The finding of a 47,XXX cell in the mother's lymphocytes may be significant, indicating either 46,XX/47,XXX mosaicism or a predisposition for non-disjunction of X chromosomes. The latter hypothetical possibility has also been suggested by the finding of a 49,XXXXX metaphase in the lymphocyte culture from a mother of a subject with a 47,XXX karyotype studied by one of us (UF).

DNA replication studies on lymphocytes and fibroblasts from this patient, using synchronised cultures and BrdU pulses at different stages of the S period, have clearly shown that the four presumably inactive X chromosomes are late replicating, but not in a strictly synchronous fashion. Two of the late replicating Xs had identical patterns which were clearly distinguishable from the identical patterns of the other two late replicating Xs (Hansen and Francke, in preparation). Such asynchrony in the replication pattern of late replicating X chromosomes has rarely been observed in cells containing fewer than five Xs.[16] One might speculate, therefore, that the severe effect of the penta-X chromosome constitution on growth and development compared with clinical findings in triple-X or quadruple-X subjects, is related to the asynchrony of the replicating pattern.

ALAN MONHEIT,* UTA FRANCKE,†
BRIAN SAUNDERS,† AND KENNETH LYONS JONES†
**The Department of Reproductive Medicine, and*
†*the Department of Pediatrics,*
University of California, San Diego School of Medicine, La Jolla, California, USA

References

1 Kesaree N, Wolley PV Jr. A phenotypic female with 49 chromosomes, presumably XXXXX. *J Pediatr* 1963;**63**: 1099–103.
2 Bordy J, Fitzgerald MG, Spiers ASD. A female child with five X chromosomes. *J Pediatr* 1967;**70**:105–9.
3 Zajaczkowska K, Korniszewski L, Wolff-Plodowska A. A case of quintuple-X syndrome (49, XXX). *J Ment Defic Res* 1970;**14**:305–11.
4 Sergovich F, Uilenberg C, Pozsonyi J. The 49, XXXXX chromosome constitution: similarities to the 49, XXXXY condition. *J Pediatr* 1971;**78**:285–90.
5 Yamada Y, Neriishi S. Penta-X (49, XXXXX) chromosome constitution: a case report. *Jpn J Hum Genet* 1971; **16**:15–21.
6 Berger R, Loewe-Lyons S, Derre J, Ortiz MA. Syndrome 49, XXXXX. *Ann Pediatr* 1973;**20**:963–7.
7 Mulcahy MT, Stevens JB. Pentasomy of X chromosome. *Lancet* 1975;**2**:1213–4.
8 Kaufman L, Sekhon GS, Brazy JE, Sivakoff MC, Hatahet G. 49, XXXXX syndrome in a neonate. *Birth Defects* 1975;**11**, No 5:333.
9 Giovannucci-Uzielli ML, Torricelli F, Salvatore Q, Consumi I, Donzelli GP, Seminara S. Corredo cromosomico 49, XXXXX in una bambina con ipoevolutismo psicofisico. *Minerva Pediatr* 1975;**27**:2220–9.
10 Tumba A, Fryns JP, Van Ooteghem G, Van Den Berghe H. Le syndrome 49, XXXXX: a propos d'un nouveau cas. *Union Med Can* 1977;**106**:226–30.
11 Larget-Piet L, Rivron J, Baillif P, *et al.* Syndrome 49, XXXXX chez une fille de 5 ans. *Ann Genet (Paris)* 1978;**15**:115–9.
12 Ricci N, Dallapiccola B, Veutimiglia B, Tiepolo L, Franccaro M. 49, XXXX/49, XXXXX mosaic: asynchronies among the late-replicating X chromosomes. *Cytogenetics* 1968;**7**:249–59.

[13] Cooke P, Black JA, Curtis DJ. Comparative clinical studies and X chromosome behaviour in a case of XXXX/XXXXX mosaicism. *J Med Genet* 1972;**9**:235–8.

[14] Gordon D, Paulsen CA. Premature menopause in XO/XX/XXX/XXXXX mosaicism. *Am J Obstet Gynecol* 1967;**97**:85–90.

[15] Izakovic V, Lukacova M. Short stature and karyotype of mitotic cells in women. *Endokrinologie* 1972;**59**:265–8.

[16] Latt SA, Willard HF, Gerald PS. BrdU–33258 Hoechst analysis of DNA replication in human lymphocytes with supernumerary or structurally abnormal X chromosomes. *Chromosoma* 1976;**57**:135–53.

Requests for reprints to Dr Kenneth Lyons Jones, Department of Pediatrics, University Hospital, H-814-B, 225 West Dickinson Street, San Diego, California 92103, USA.

A case of 47,XY,+der(15),t(3;15)(p25;qll)pat presenting as partial 3p trisomy syndrome with multiple joint contractures

SUMMARY Partial 3p trisomy is a rare chromosomal syndrome which results in a characteristic phenotype. We present a case of partial 3;15 trisomy with clinical features of partial 3p trisomy syndrome and multiple joint contractures.

Partial 3p trisomy syndrome was described originally by Rethoré *et al.*[1] Since her original description of three cases, seven additional cases, characterised by varying degrees of trisomic material for the short arm of chromosome 3, have been reported.[2 3] Aarskog[4] described a child with duplication 3, deletion 18q with the clinical features of partial 3p trisomy syndrome. A female sib born after that publication was found to be similar phenotypically, and on chromosome analysis had duplication 3p, deletion 18q. These children probably represent two additional cases of this rare chromosomal syndrome. We describe a patient with the clinical stigmata of partial 3p trisomy syndrome and multiple joint contractures, who was found to have an unbalanced translocation thought to represent a partial trisomy for the short arm of chromosomes 3 and 15 and a small segment of the proximal long arm of chromosome 15.

Received for publication 5 December 1979

Case report

The proband was a term male born to a 39-year-old gravida 3, para 1, aborta 1, blood type A positive mother. Decreased fetal movements were noted in the last trimester and there was rapid weight gain. Based on the ultrasonographic findings of polyhydramnios in the third trimester, a caesarean section was performed when spontaneous labour occurred. One and five minute Apgar scores were 5 and 7, respectively.

At birth the baby's length was 49·5 cm (10th to 25th centile), weight was 2900 g (10th to 25th centile), and head circumference was 37·75 cm (95th centile). There was frontal bossing with temporal narrowing. The facies was square shaped with prominent cheeks. There were downward slanting palpebral fissures and hypertelorism. The ears were low set. The philtrum was elongated. The mouth was large with down-turned corners. The palate was normal and there was a mild degree of retrognathia (fig 1). No murmurs or organomegaly were detected. The genitalia were hypoplastic with bilaterally undescended testes. There were joint contractures of the elbows, wrists, hips, and knees, and camptodactyly of the fingers and toes. The infant was lethargic with generalised hypotonia. The suck, root, and Moro reflexes were absent.

Nasogastric feeding was started as a result of sucking difficulties. On the third day of life seizure

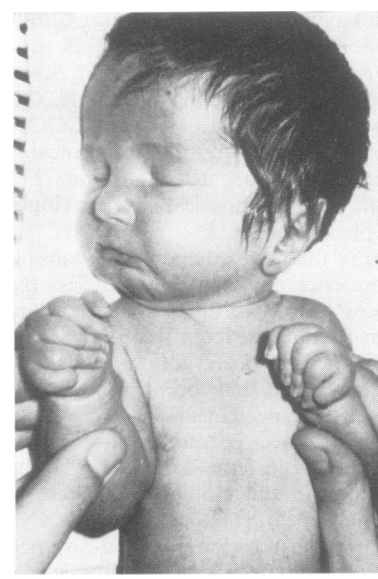

FIG 1 *Patient with partial 3p trisomy syndrome at 2 days of age. Note elbow and finger contractures.*