A Boy with XXXXY Sex Chromosomes*

M. C. JOSEPH, JANET M. ANDERS, and ANGELA I. TAYLOR

From the Department of Paediatrics, Guy's Hospital, and the Paediatric Research Unit, Guy's Hospital Medical School

Eight patients with XXXXY sex chromosomes are on record (Fraccaro, Kaijser, and Lindsten, 1960; Miller, Breg, Schmickel, and Tretter, 1961; Fraser, Boyd, Lennox, and Dennison, 1961; Fraccaro, Klinger, and Schutt, 1962; Barr, Carr, Pozsonyi, Wilson, Dunn, Jacobson, and Miller, 1962; Pfeiffer, 1962; Schade, Schöller, and Töberg, 1963). In addition two similar patients with a mosaic pattern have been reported (Anders, Prader, Hauschteck, Schärer, Siebermann, and Heller, 1960; Harnden and Jacobs, 1961). We here describe a further patient with XXXXY sex chromosomes in whom congenital heart disease, mental deficiency, dwarfism, abnormal genitalia, and an unusual facies were present.

Case Report

Family History. Both parents were 32 years old when the patient was born, and both are healthy. He has three maternal aunts and two maternal uncles, all

healthy. All except one aunt are married and have normal children. His father was an only child. There was no consanguinity between his parents or grandparents. His maternal grandmother had 'heart valve disease'. He has one sister aged 4 years who is well.

Patient's History. (J. A., P.R.U. 877). The mother had toxæmia of pregnancy. After a labour lasting 50 hours, the patient was delivered by breech at term and weighed 4 lb. 12 oz. (2154 g.) He was severely shocked and was nursed in an incubator for the first few days following delivery. His subsequent physical and mental progress was slow and at 5 years of age his height and weight were below the third percentile and his I.Q. was 40 (Merrill-Palmer). He has had two attacks of gastro-enteritis and several episodes of bronchitis with wheeze. A cardiac murmur was first heard at the age of 3 months. He has no symptoms referable to his heart except moderate exercise intolerance.

Physical Examination. At 5 years of age the patient (Fig. 1) weighed 28 lb. (12.7 kg.) (less than third percentile) and was 38 in. (95 cm.) tall (less than third percentile). His appearance (Fig. 2 and 3) re-

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FIG. 1. J. A. aged 5 years.

FIG. 2. Facies of J. A. aged 5 years.

FIG. 3. Facies of J. A. aged 5 years.

FIG. 5. Triradii and main lines of the dermal ridges in J. A.

Cytology. The incidence of sex chromatin in oral mucosal cells and cultured cells is shown in Table II. Cells with one, two, and three peripheral sex chromatin masses were observed in both tissues.

Satisfactory blood smears were taken on two occasions. On the first occasion one drumstick was found in 807 polymorphs. On the second occasion two drumsticks were found in 3,300 polymorphs. The reason for the very low incidence on both occasions is unknown but a similar low incidence in an XXXXY patient was reported by Fraccaro *et al.* (1962). No double or other multiple drumsticks were seen.

The results of chromosome counts made on slides prepared from two peripheral blood cultures and a single skin culture are given in Table III. The modal number is 49. The cells with less than this number appeared broken. Analysis of three karyotypes showed five chromosomes in the 21-22-Y group, the majority of cells having a clear Y chromosome, and 18 chromosomes in the X-6-12 group instead of 15 as would be expected in a normal male.

Dr. F. Giannelli labelled the cells from skin culture

with tritiated thymidine during the latter part of the DNA synthetic period and subsequently examined them by autoradiography. Three chromosomes in the X-6-12 group showed differential uptake of tritiated thymidine as compared with the remainder of the chromosome set. Thus, though the X chromosomes cannot be individually identified by morphological means alone, the presence of three additional members of the X-6-12 group together with the finding of three sex-chromatin bodies in a proportion of cultured and oral mucosa cells, and the results of labelling with tritiated thymidine, suggest that the additional members are X chromosomes, giving a chromosome constitution of 2A + XXXXY (A = haploid autosome set).

Discussion

Table IV shows the prominent features in the 8 previously described patients and our own. It can be seen from this Table that these patients have a wide variety of abnormalities. The most

TABLE II

PERCENTAGE DISTRIBUTION OF PERIPHERAL SEX-CHROMATIN MASSES

No. of Peripheral Masses	Oral Mucosa (300 cells)	Cultured Skin (200 cells)
0	33	28
1	29	39
2	27	32
3	11	6

TABLE III

CHROMOSOME COUNTS

Type of Culture	Chromosome Counts					
	46	46	47	48	49	> 49
Blood 1	—	—	—	1	14	—
Blood 2	—	—	—	1*	20	—
Skin	1*	—	2*	4*	49	—

* Broken cells.

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TABLE IV
MAIN FEATURES IN PREVIOUSLY DESCRIBED
PATIENTS AND PRESENT CASE (J. A.)

Features	Present	Absent	Not Reported
Male phenotype	9	—	—
'Dysmaturity'	4	2	3
Dwarfism	3	4	2
Abnormal facies	7	1	1
Squint	3	5	1
Epicanthic folds	3	—	6
Widely set eyes	6	—	3
Down and medial slant of palpebral fissures	4	1	4
Flat occiput	3*	1	5
Cleft palate	2	4	3
Short neck	3	—	6
Abnormal spine	4	1	4
Incurved fifth finger	6	—	3
Radio-ulnar synostosis	5	1	3
Small scrotum	8	1	—
Impalpable gonads	6	3	—
Small penis	7	1	1
Mental retardation	9	—	—
Congenital heart disease	2†	7	—
Dry skin	3	—	6
Retarded bone age	5	—	4
Low iliac index	1	—	8
Abnormal palm prints	1	1	7

* Includes brachycephaly (1).

† Both have patent ductus arteriosus.

consistent features include mental retardation, abnormal facies and genitalia, and skeletal changes.

Maternal and paternal age, parity, gestational age, and birth weights are shown in Table V. Consanguinity, pregnancy, previous history, and illness in sibs do not appear to be significant and have not been included in Table V. The family history of the patient, described by Miller *et al.* (1961), of lymphatic leukaemia in the father, and a paternal aunt and paternal cousin both having regular Down's syndrome, is interesting in view of the association of leukaemia and Down's syn-

TABLE V
SOME GESTATIONAL DATA

Reference	Maternal Age (yr.)	Paternal Age (yr.)	Parity	Birth Order	Gestational Age	Birth Weight (g.)
Fraccaro <i>et al.</i> (1960)	23	29	2	1	Term	2380
Miller <i>et al.</i> (1961)	23	32	3	—	—	—
Fraser <i>et al.</i> (1961)	22	24	3	1	—	—
Fraccaro <i>et al.</i> (1962)	26	29	2	2	Term	3175
Barr <i>et al.</i> (1962) Case 1	25	24	3	1	Term	2550
Barr <i>et al.</i> (1962) Case 2	38	38	4	4	Term	3288
Pfeiffer (1962)	20	23	1	1	Term	1190
Schade <i>et al.</i> (1963)	28	27	2	1	—	3089
Present case	32	32	2	1	Term	2154

FIG. 6. Facies of Case 1 reported by Barr *et al.* (1962).

drome (Krivit and Good, 1957; Stewart, Webb, and Hewitt, 1958; Holland, Doll, and Carter, 1962).

Mental Retardation. All except one patient who was reported as 'probably retarded' and another two as 'retarded' showed severe retardation, the I.Q. figures being 40, 35, 30, 21, and 20.

The Facies. This was definitely abnormal in some way in seven patients. The abnormal features varied, but included epicanthic folds, widely set eyes, and slanting of the palpebral fissures. The occiput was flat in two patients, and in one the head was described as brachycephalic. The facies of our patient closely resembled that of Case 1 reported by Barr *et al.* (1962) (Fig. 6) and, allowing

FIG. 7. Facies of patient reported by Schade *et al.* (1963).

for the age difference, also resembled the patient reported by Schade *et al.* (1963) (Fig. 7).

The Genitalia. These were consistently abnormal, the penis being small, the gonads impalpable, or the scrotum small. In the three specimens examined histologically the testis showed reduction or absence of germ cells (at ages 7 months, 7 years, and 8 years).

Skeletal Changes. The spine showed kyphosis, lordosis, and an extra lumbar vertebra in four patients, and radio-ulnar synostosis in five patients. The latter has also been described in an XXXY male (Ferguson-Smith, Johnston, and Handmaker, 1960). Six of the patients showed incurving of the fifth finger.

Palm and Fingerprints. Details of these are shown in Table I and Fig. 5, and in Fig. A and B in the Appendix. Unlike the patient reported by Fraccaro *et al.* (1962) the number of arches and small loops was not increased and the total ridge counts were near the mean.

Other Features. A striking feature in four patients was their light weight in relation to term, their weights being 2 lb. 10 oz. (1190 g.), 4 lb. 12 oz. (2154 g.), 5 lb. 4 oz. (2380 g.), and 5 lb. 10 oz. (2550 g.) at term. This has been referred to as dysmaturity (Sjöstedt, Engleson, and Rooth, 1958) or intrauterine growth retardation (Warkany, Monroe, and Sutherland, 1961). Other patients with chromosomal anomalies, notably those with trisomy 17-18 (E₁) and 13-15 (D₁) (Paul E. Polani, 1963, personal communication), show this dysmaturity. Congenital heart disease was present in our patient and that of Fraccaro *et al.* (1960), and the anatomical defect was the same, namely patent ductus arteriosus.

Summary

A 5-year-old boy with XXXXY chromosomes is reported. The main features included dwarfism, abnormal genitalia, unusual facies, mental deficiency, patent ductus arteriosus, and radio-ulnar synostosis. These features are compared with those in other reported patients.

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Addendum

Since this paper was completed, an additional patient (N.S., P.R.U. 1528) has been referred by Dr B. Gans to Professor Paul E. Polani. The clinical features were very similar to those of J.A., and he had an identical chromosomal complement. He was the first born of normal parents (father aged 30 years and mother aged 28 years). Gestation was 41 weeks and birth weight 7 lb. 4 oz. (3,288 g.). When seen at 9 years of age, his weight was 46 kg. (more than 97%) and his height 138 cm. (90%). His facies (Fig. 8) was similar to J.A. with widely set eyes, slanting downwards and medially, epicanthic folds, with a wide but otherwise normal bridge of nose. The lower lip was thick. The eyebrows were very arched. The neck was short and broad and there was moderate bilateral webbing. The lower abdomen was prominent and the mons pubis obese;

FIG. 8. Facies of N. S. aged 9 years.

the penis was short. The scrotum was rugose and rather flat. A small soft mass was felt in the right scrotum, but no testis was palpable in the left scrotum. Bilateral radio-ulnar synostosis was present. His I.Q. was about 50. He had a persistent ductus arteriosus, which had been ligated in 1959 by Mr D. Waterston at the Hospital for Sick Children, Great Ormond Street. In summary, this boy resembled the pattern of our patient, J.A., and others previously reported, particularly in respect of facies, mental retardation, genitalia, radio-ulnar synostosis, and type of heart defect. The only three patients with a congenital heart defect (Fraccaro *et al.* (1960) and the two reported here) had the same type, namely patent ductus arteriosus. Data on palm and fingerprints are given in the Appendix (Table B). The mother of this boy had a low total ridge count, and the mother of J.A. had a total ridge count below the average. The other point of note in this child was the small number of drumsticks (1 in 1,000), an observation similar to that found in J.A. Details of his blood groups and those of his mother and sister are shown in Table C in the Appendix.

Appendix

TABLE A

BLOOD GROUPS OF J. A., MOTHER, AND FATHER

Name	ABO	MNS	P ₁	Rh	Lv ^a	K	Le ^a Le ^b	Fy ^a Fy ^b	Jb ^a Jb ^b	Xg ^a
J. A.	B	MsNs	+ ^w	rr	+	—	—	—		+
Mrs A.	A	NsNs	+	R ₂ r	+	—	—	+		+
Mr A.	B	MMS	+	R ₂ r	—	—	—	+		+

TABLE B

RIDGE COUNT OF N. S. AND MRS S. (RADIAL COUNTS ON RIGHT, ULNAR ON LEFT)

	Ridge Counts										Maximal atd Angles		
	Right hands					Left hands					Totals	Right	Left
N. S. Mrs S.	I	II	III	IV	V	I	II	III	IV	V			
	0-0	0-0	0-0	0-0	2-0	0-0	0-0	0-0	0-0	0-0	2	40°	38°
	9-0	0-0	0-0	3-0	7-0	6-0	0-0	0-0	2-0	3-0	30	39°	55°

Note: The bold figures are those used for the total ridge count.

TABLE C

BLOOD GROUPS OF N. S., MOTHER, AND SISTER

Name	ABO	MN	Rh	K	Xg ^a
N. S.	o	MN	R ₁ R ₂	—	+
Mrs S.	o	MM	R ₁ R ₂	—	+
Miss S.	o	MM	R ₁ R ₂	—	+

FIG. A. Dermatoglyphics of mother of J. A.

FIG. B. Dermatoglyphics of father of J. A.