Familial Occurrence of Trisomy 22

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The number of reports describing patients with an extra, small acrocentric chromosome, exclusive of mongolism or XYY, is increasing. Some authors have interpreted their findings as trisomy 22 syndrome (Ferguson and Pitt, 1963; Crawfurd and Lele, 1965) and others as partial D or trisomy 18 (Gustavson *et al.*, 1962; Ishmael and Laurence, 1965; Giorgi *et al.*, 1967). There are also some reported instances of the transmission of an extra, small acrocentric chromosome from mosaic or fully trisomic parents (Koulischer and Perier, 1962; Schachenmann *et al.*, 1965).

We present here a family with two children, both of whom had an extra, small acrocentric chromosome, resulting in five chromosomes in the G group. The clinical picture and dermatoglyphics ruled out mongolism. The normal mother is a mosaic, a few of her cells having the same aneuploidy. A maternal cousin is a mongoloid.

MATERIALS

Case 1

The proband (Fig. 1, *a*) was born in March, 1962, and weighed 2,360 g. The maternal and paternal ages were 18 and 19 years, respectively. The mother's 42-week pregnancy had been characterized by bleeding in the third and seventh months. There was one previous pregnancy, a miscarriage.

An initial diagnosis of Pierre-Robin syndrome had been made at birth because of a large cleft palate, micrognathia, and glossoptosis. Subsequently, 10 hospital admissions were necessary because of failure to thrive, complicated by upper respiratory infections, pneumonia, gastroenteritis, and feeding difficulties.

At the age of 18 months, when chromosome analysis was requested, the proband presented as a slender, undernourished female with a head circumference measuring 40.6 cm and a somewhat flattened occiput. Pertinent physical findings included epicanthic folds, low-set oblique ears, a small right preauricular sinus, and a mandible markedly underdeveloped. The nipples were small and hypoplastic. A simian crease was present on the right hand. The thumbs were low-set, long, and slender, and the fingers, tapered and hyperextensible. The big toes were somewhat shorter than the other toes.

There was a grade 4 systolic murmur over the entire precordium. Hypotonia was generalized, but no specific localizing central nervous system defect was apparent. Though the child was 18 months of age, the peak developmental landmarks achieved

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were at the seven-month level. She reacted to sound and followed objects visually. She was never well enough to withstand surgery for repair of the palate.

She died suddenly in the hospital at age 20½ months, following a course suggesting aspiration. Detailed pathologic evaluation confirmed the clinical impression of atrial septal defect along with a persistent left superior vena cava and aberrant subclavian artery. Failure of adequate growth included proportionate hypoplasia of the brain.

Case 2

A male sib of the proband (Fig. 1, *b*) was born in October, 1964, and weighed 2,660 gm, following a 40-week gestation. The pregnancy was reported as normal. The child did well until approximately 48 hr, when he was noted to experience several cyanotic

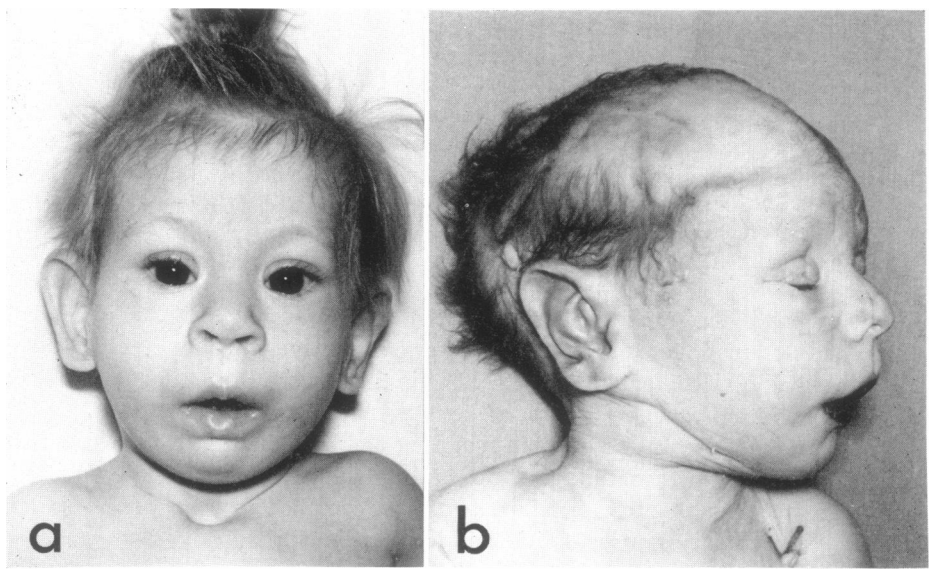

FIG. 1.—Two abnormal members of the family described here: (*a*) Case 1, proband; (*b*) Case 2, sib of proband.

episodes; at the same time, his abdomen became bloated and tense. A laparotomy revealed a perforation in the anterior aspect of the rectum, the etiology of which was never apparent. He experienced several bouts of apnea and died at 4½ days of age.

Physical findings included low-set floppy ears, micrognathia, high palate, epicanthic folds, oblique palpebral fissures, a striking increase in the carrying angle of the arms, some incurving of the fingers, rudimentary toenails, and short big toes. A marked lumbar kyphosis was noted, but there was no abnormality of the individual vertebrae radiologically. A single umbilical artery and fenestration of the valve of the foramen ovale were found at autopsy.

Family History

The mother, an attractive woman of normal intelligence, is the fourth-born in a family of eight (Fig. 2). A sister died at two months with gastroenteritis and no obvious

congenital abnormalities, and a brother died at $3\frac{1}{2}$ months, after a history of vomiting and failure to thrive. A second brother died accidentally at age 24 years. The remaining four sisters are healthy and of normal intelligence. Children of the two older sisters are alive and well. The grandmother died from tuberculosis and breast carcinoma at 36 years. The grandfather recently developed hyperlipemia. A cousin, living in Vancouver, is a mongoloid boy of 14 years (Fig. 2, II-10). The diagnosis of mongolism was confirmed by dermatoglyphic analysis.

The father, second-born in a family of 11, is normal and healthy. There is no known history of any abnormalities on his side of the family.

CYTOLOGY

Leukocyte cultures were prepared from peripheral blood samples obtained from several members of this kindred. At least 100 cells were examined from Case 2, his father, and his mother.

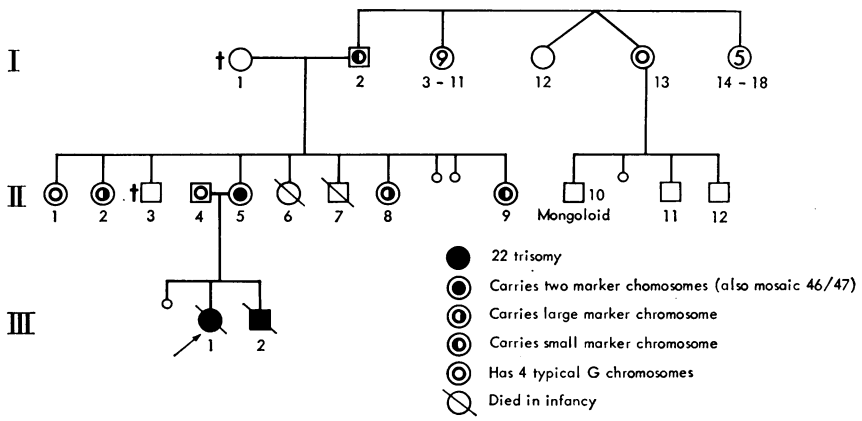

FIG. 2.—Pedigree of present family.

Case 1, the proband, had 47 chromosomes. We had presumed that the extra one was an acrocentric, slightly larger than the G chromosomes but smaller than an 18. No satellite was seen on the short arm. This chromosome was thought at first to be either a D chromosome with a deficiency of part of the long arm or an 18 with parts of both the short and long arms missing. Because of the clinical picture and the presence of arches on many fingers, our first interpretation was partial trisomy 18.

Since cultures from this patient were not too successful, only 50 cells were clear enough for accurate chromosome counting, and detailed analyses could not be carried out.

Case 2, sib of the proband, also had 47 chromosomes, including five small acrocentrics and a Y chromosome (Fig. 3). The same slightly larger nonsatellited acrocentric was present, and association with other satellited acrocentrics was never observed. In addition, one G chromosome appeared smaller than the others and had a longer short arm with a pronounced satellite that often gave it the appearance of a metacentric chromosome (Fig. 4). The other three chromosomes were of the usual G type in appearance.

The father has a normal male karyotype. The four G chromosomes are similar in size and morphology, and all have satellites.

In the mother, among the first 100 cells examined, there were two cells with 47 chromosomes, and both had five chromosomes that fell into the G group. An additional 400 cells were then analyzed from three blood samples taken at different times. In five cells, there were 47 chromosomes, giving a total of 1.4% aneuploids. In all seven aneuploid cells, the five chromosomes in the G group were similar to those of her son. Her diploid cells had the same two marker chromosomes.

The mother's four sisters have 46 chromosomes with the following variation in the

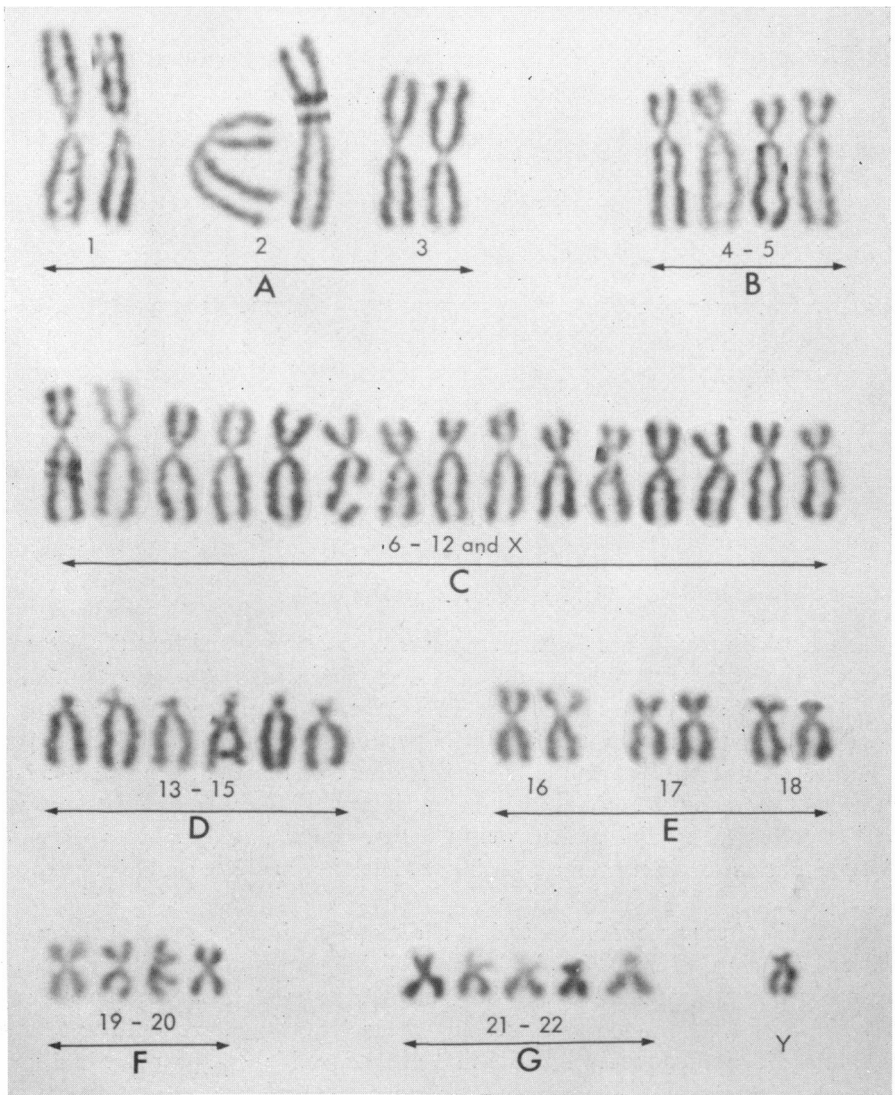

FIG. 3.—Karyotype of Case 2 showing two marker chromosomes in the G group.

morphology of the G group: One sister has four typical G-type chromosomes (Fig. 4, II-1); two have the larger nonsatellited chromosome (II-2, II-8); and one has the small metacentric-like chromosome (II-9). Their father has the small metacentric-like marker chromosome in an otherwise normal karyotype.

A reciprocal translocation was identified in the mongoloid cousin, which resulted in 47 chromosomes, including a GqGq translocation and the tiny reciprocal centric fragment consisting of little more than the two satellites fused together (Fig. 5). The fragment was present in 78 out of 100 cells analyzed. Neither he nor his mother had a marker chromosome. Chromosomal analysis was not carried out on the father because there was no history of consanguinity.

Autoradiography

Autoradiographic studies were carried out on the cells of the mother and her son (Case 2). Tritiated thymidine (1 μc/ml of medium; specific activity, 1.9 c/mmole)

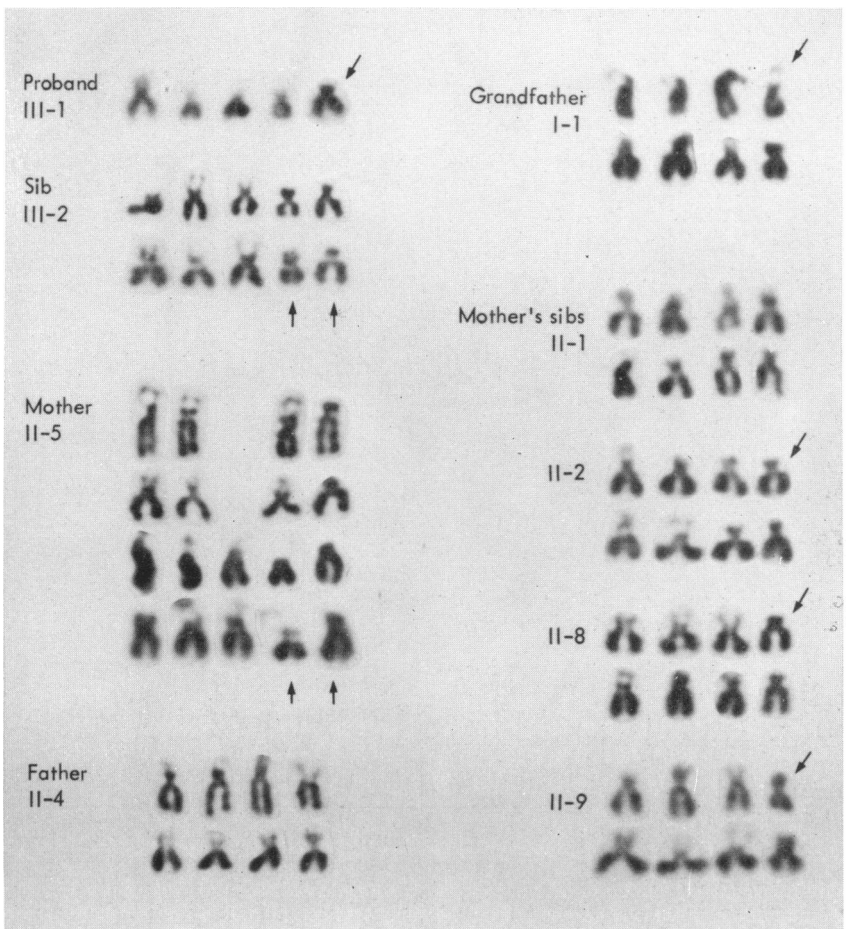

FIG. 4.—G-group chromosomes of proband, sib, parents, and mother's relatives are shown with numbers referring to position on pedigree given in Fig. 2. Arrows indicate the marker chromosomes.

was added to the leukocytes six hours before harvesting. Slides, prepared by the air-dried method (Rothfels and Siminovitch, 1958), were stained with 2% aceto-orcein, and cells with well-spread chromosomes were photographed. The slides were dipped in liquid emulsion and left sealed in the dark for three weeks. Differentially labeled cells were rephotographed. Pictures taken before exposure were screened, and only those cells were used in which, after independent assessment, there was agreement in the identification of the marker chromosomes. The labeling patterns were then examined.

Frequencies of labeled and unlabeled chromosomes from mother and child are given in Table 1. In most of the 16 diploid cells examined from the mother, the two

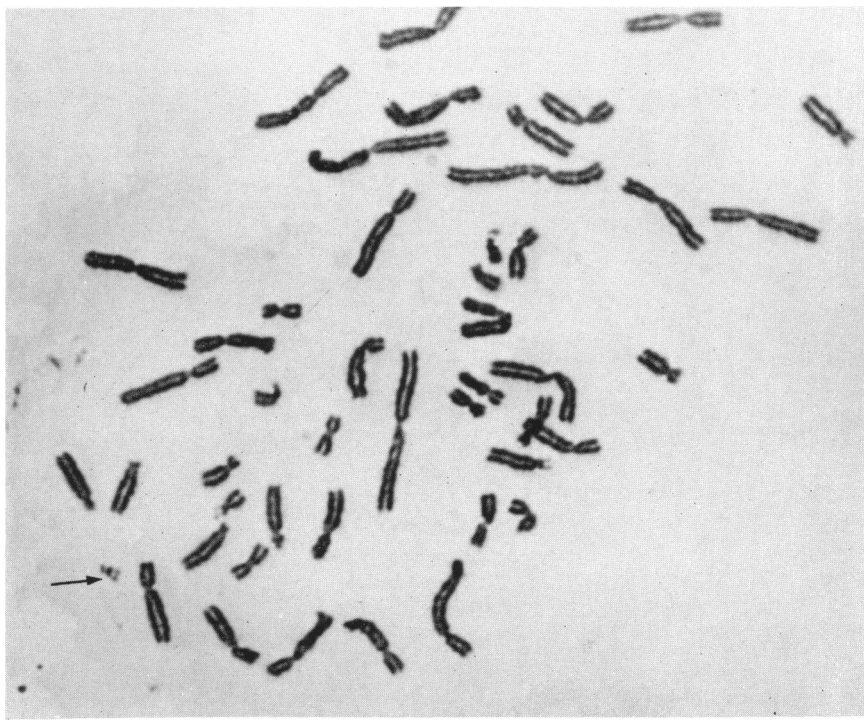

FIG. 5.—Chromosome spread from cell of mongoloid cousin. Note five small metacentrics, three small acrocentrics, and tiny centric fragment.

TABLE 1

RESULTS OF LABELING WITH TRITIATED THYMIDINE

G CHROMOSOMES	HEAVILY LABELED		LIGHTLY LABELED		NOT LABELED	
	Mother	Case 2	Mother	Case 2	Mother	Case 2
Nonmarker I.....	16	19	0	1	0	0
Nonmarker II.....	14	11	1	8	1	1
Nonmarker III.....	.....	2	.....	6	.....	12
Small marker.....	2	1	7	5	7	14
Large marker.....	1	2	4	7	11	11

nonmarker chromosomes were heavily labeled while the two marker chromosomes were lightly or not labeled (Table 2 and Fig. 6). Labeling patterns in the 20 cells from the son agreed with the findings in the mother: two nonmarker chromosomes heavily labeled and the two marker chromosomes lightly or not labeled. Labeling of the third nonmarker chromosome was light or absent.

OTHER INVESTIGATIONS

Dermatoglyphics

The presence of arches on seven fingers of the proband (Fig. 7, *a*) suggested a diagnosis of trisomy 18. Her brother, however, had no arches on his digits (Fig. 7, *b*). In other respects, there was nothing in the dermal configurations to suggest partial trisomy for any of the known aneuploids. On the hands of both children, there were very small loops in the fourth interdigital area high up at the very distal border of the palm. Both parents also have loops in this area, but they are not distally located. The proband had a partial simian crease on the left palm and a full simian on the right, along with a distal crescent crease. Both children and the mother have a loop distal in the hallucal area of both feet, while the father has one loop distal and one loop tibial.

Although the dermatoglyphics do not appear to be remarkable, their importance cannot be evaluated unless a sufficiently large series of trisomic patients with a similar phenotype are printed and frequencies obtained for the various pattern areas. If con-

TABLE 2

LABELING PATTERNS OF G CHROMOSOMES OF MOTHER AND CASE 2

CELL NO.	MOTHER				CASE 2				
	Nonmarkers		Small Marker	Large Marker	Nonmarkers			Small Marker	Large Marker
	I	II			I	II	III		
1	+++	+++	+	N.L.	++	+	+	N.L.	N.L.
2	+++	++	++	N.L.	+++	+++	N.L.	N.L.	N.L.
3	+++	N.L.	+	N.L.	+++	+++	N.L.	N.L.	N.L.
4	+++	++	+	N.L.	+++	+++	N.L.	N.L.	N.L.
5	+++	+++	N.L.	N.L.	+	+	N.L.	N.L.	+
6	+++	+++	N.L.	N.L.	+++	++	+	N.L.	+++
7	++	++	N.L.	N.L.	+++	+++	N.L.	+	+
8	+++	++	N.L.	+	+++	+	+	+	+
9	+++	++	N.L.	+	+++	+++	+++	+	N.L.
10	+++	+	N.L.	+	+++	+	N.L.	+	N.L.
11	+++	++	++	+	+++	+++	N.L.	N.L.	N.L.
12	+++	++	N.L.	++	+++	+	N.L.	N.L.	+
13	+++	+++	+	N.L.	+++	N.L.	N.L.	N.L.	N.L.
14	+++	+++	+	N.L.	+++	+	N.L.	N.L.	N.L.
15	+++	+++	+	N.L.	+++	++	+	N.L.	N.L.
16	+++	+++	+	N.L.	+++	+	N.L.	N.L.	+
17	.....	.....	.....	.....	+++	+	+	+	+
18	.....	.....	.....	.....	+++	++	+	N.L.	+++
19	.....	.....	.....	.....	+++	+++	N.L.	N.L.	N.L.
20	.....	.....	.....	.....	+++	+++	++	+++	+

NOTE.—+++ = very heavily labeled; ++ = fairly heavily labeled; + = lightly labeled; N.L. = not labeled.

sistent similarities are observed, then dermatoglyphics may be of diagnostic value in cases where interpretation of an extra, small acrocentric is cytologically impossible.

Blood Groups and Serum Factors

The blood groups of the two patients and their parents were analyzed by Dr. B. Chown and Miss Marion Lewis of the Rh Laboratory of Winnipeg. Serum factors were determined by Dr. Eloise R. Giblett of Seattle and Dr. A. G. Steinberg of Cleveland. The results are given in Table 3. There is no evidence suggesting that the locus for any of these factors is on the chromosome involved in the trisomy.

DISCUSSION

Among the several reported cases with an extra, small acrocentric chromosome, there are some with similarities in clinical features. In particular, the facial resemblance between our Case 2 and the infant described by Ishmael and Laurence (1965) is striking. Similar cases with features in common are listed in Table 4. A number of

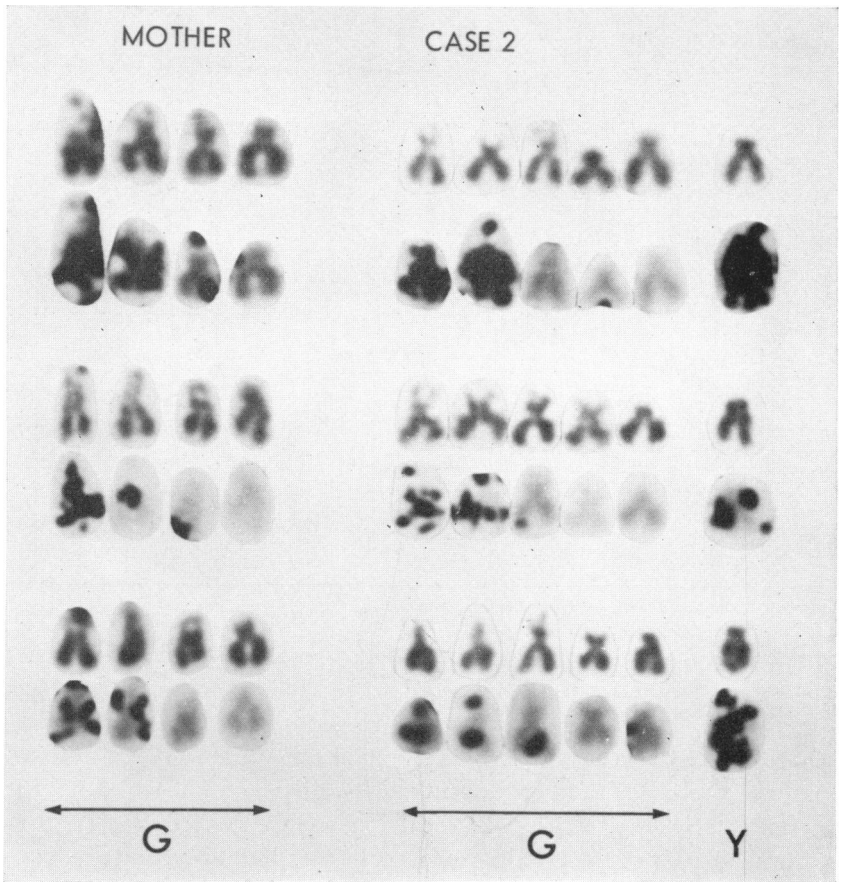

FIG. 6.—Chromosomes of the G group from mother and Case 2 with autoradiographs shown below each chromosome.

these traits, such as low birth weight, mental retardation, low-set abnormal ears, micrognathia, and midline clefts, are shared by many syndromes, including trisomies D and 18. The presence of micrognathia, cleft palate, and accessory auricles or sinuses is suggestive of the first arch syndrome recently reviewed by McKenzie (1966). Chromosomal analyses of the latter syndrome, however, have been reported as normal (Moss *et al.*, 1964). It would thus appear that the region of the first visceral arch is particularly vulnerable to developmental influences. Other reported cases with an

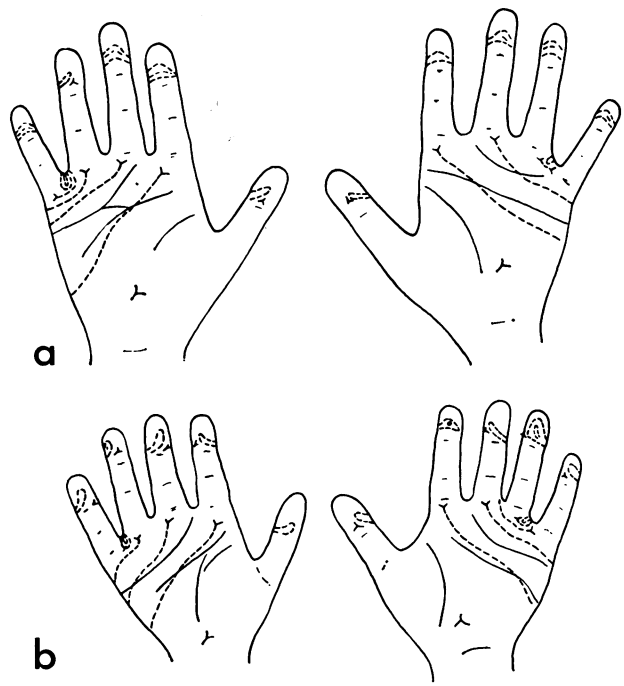

FIG. 7.—Dermatoglyphic patterns of proband (*a*) and her sib (*b*). Note small loop in fourth interdigital area on all four palms.

TABLE 3

BLOOD GROUPS AND SERUM FACTORS

SUBJECT	BLOOD GROUPS												SERUM FACTORS						
	ABO	MSNs	Kell		Lutheran		Duffy		Kidd		Lewis Le^a	Xg^a	Hp	Tf	Gm				Inv (2)
			K	k	Lu^a	Lu^b	Fy^a	Fy^b	Jk^a	Jk^b					1	2	5	6	
Father...	O	MSNs	+	+	−	+	+	+	+	+	+	−	2-2	C	+	+	+	−	−
Mother...	A_1	MSNs	−	+	+	+	+	−	+	+	−	+	2-1	C	−	−	+	−	−
Case 1....	O	NsNs	−	+	−	+	+	+	+	+	−	−	2-2	C	−	−	+	−	−
Case 2....	A_1	MsMs	+	+	−	....	+	−	+	+	−	+	2-1	C	..	..	..	..	.....

NOTE.—All are: C−, Cw−, c+, D−, E−, e+, f+; P+; Kp(a−). Both parents are: Mi(a−); Vw−; Be(a−); (a−)· Wr(a−); Go(a−); Wiel−.

extra, small chromosome, not listed here, have fewer similarities in common or are not described in sufficient detail to allow comparison.

Although it has been demonstrated that the chromosome involved in mongolism is late replicating (Schmid, 1963; Yunis *et al.*, 1965; Fraccaro *et al.*, 1967), some doubts have been cast upon the value of autoradiography in differentiating between chromosomes 21 and 22 (Back *et al.*, 1967; Fraccaro *et al.*, 1967; Hecht and Weleber, 1967) because of the inability to distinguish between them on the basis of relative size or shape. The extra chromosome involved in mongolism has therefore been called no. 21 by definition. The presence of the two marker chromosomes in the mother of our patients was fortuitous. Since there is evidence that homologous chromosomes replicate synchronously, the two early replicating marker chromosomes must be homologous, that is, no. 22. Assuming that the father has made a normal contribution to the

TABLE 4

CLINICAL FEATURES OF CASES WITH AN EXTRA, SMALL ACROCENTRIC CHROMOSOME

FEATURES	GUSTAVSON *et al.* (1962)		FERGUSON AND PITT (1963)	ISHMAEL AND LAURENCE (1965)	PRESENT CASES	
	Case A	Case B			Case 1	Case 2
Birth weight (g)	2,750	3,000	2,495	3,180	2,350	2,650
Micrognathia	+	+	+	+	+	+
Low-set abnormal ears	+	+	+	+	+	+
Accessory auricles, sinuses	+	+	−	+	+	−
Cleft palate	+	+	−	−	+	−
Mental retardation	+	+	+	+	+	?
Hip abnormality	+	−	+	−	+	−

zygote, we can conclude that the extra marker chromosome passed on by the mother makes her son trisomic for chromosome 22.

The aneuploid infant described by Ishmael and Laurence (1965) has one chromosome similar to our small metacentric-like G, while the patients described by Gustavson *et al.* (1962) have the other large nonsatellited one.

It was thought at first that the presence of a mongoloid in this family might have some relevance to our interpretation. However, the chromosomal aberration involved turned out to be a translocation. Since neither the mongoloid nor his mother carried a marker chromosome, thymidine studies were not carried out and it was concluded that the occurrence of mongolism was merely coincidental.

In our kindred, the marker chromosomes are clearly inherited. Segregation of the G chromosomes among the mother and her sibs indicated that both of their parents must have carried one of the marker chromosomes. This conclusion was supported by the demonstration of the small metacentric-like G chromosome in the grandfather. Inheritance of a metacentric-like G chromosome has been shown to occur over three generations in normal families (De la Chapelle *et al.*, 1963; Court Brown *et al.*, 1965) and also among normal and abnormal individuals in other kindreds (Schmid, 1962; Therkelsen, 1964). Other inherited variations in the chromosomes of the D, E, and G groups have been reported by Court Brown *et al.* (1966, p. 91). Ellis (1963) gives evi-

dence of a translocation in vitro producing a small acrocentric chromosome, which, if it had arisen in vivo, could be transmitted as an extra, small acrocentric.

Some interesting conclusions can be drawn from the demonstration of three morphologically different homologous chromosomes in the mother's cells. The extra chromosome could not have arisen after formation of the zygote, since nondisjunction during mitotic division should give rise to two identical chromosomes. It is probable, therefore, that the original zygote was trisomic and loss of the characteristic type G chromosome occurred early in embryonic life. The very small proportion of trisomic cells remaining in her leukocytes is conceivably the result of the selective advantage of normal diploid cells. Since the mother has had no normal offspring, it is possible that her ovarian tissue is mainly trisomic, thus increasing the risk of aneuploidy resulting from abnormal segregation or secondary nondisjunction.

SUMMARY

A family is presented in which two sibs with multiple congenital abnormalities had an extra acrocentric chromosome in the G group. The phenotypically normal mother is mosaic for the same aneuploidy. Morphological and autoradiographic studies indicate that this is an instance of familial trisomy 22. The inheritance of two marker G chromosomes has been traced through this kindred.

A mongoloid cousin has 47 chromosomes with a reciprocal translocation of two G chromosomes.

Clinical comparison with other possible cases of trisomy 22 is presented, along with details of blood groupings, serum factor analyses, and dermatoglyphic studies.

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