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A Family with a Large Y Chromosome

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It is generally agreed that the Y chromosome shows greater variations in size than other chromosomes (Carr, Barr, and Plunkett, 1961; Bishop, Blank, and Hunter, 1962). In many cases, this variability in length is artefactual (De la Chapelle *et al.*, 1963), in others it may only be an elongation effect (Wennström and De la Chapelle, 1963). Occasionally, however, there is a true addition of chromosomal material to the Y chromosome, resulting either from duplication or from translocation from another chromosome (De la Chapelle *et al.*, 1963).

A review of the cases reported to have a large Y chromosome shows that, so far, there is no uniform or repeatable clinical pattern (Makino and Takagi, 1965) that qualifies for the designation 'large Y syndrome'.

Family Report

The present family, living in Kuwait, Arabia, consists of the two parents (the father 34 years old, working as a barber; the mother 25 years), and three sons, 6½, 5, and 3½ years old. At the time of preparation of this paper, the mother delivered a full-term female with Down's syndrome and cyanotic congenital heart disease; the girl died within 24 hours of birth (Fig. 1).

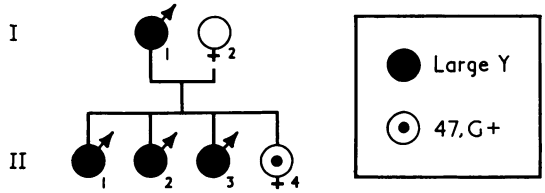

FIG. 1. Family pedigree. See Table I for main clinical features.

The clinical features (Table I), common to all four males in the family, are as follows.

(a) Behaviour disorder, mildest in the father, with hyperkinesia in all three sons, together with a destructive tendency and moderate degree of mental subnormality in two of them. All four showed generalized, non-specific, electroencephalographic changes, with questionable paroxysmal abnormality in the older son, but no history of epileptic fits.

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TABLE I

MAIN CLINICAL FEATURES OF PATIENTS

	I.1	II.1	II.2	II.3
Age (yr.)	34	6½	5	3½
Height (cm.)	185	130	127	107
Skull circumference (cm.)	55	55	52	52
Carrying angle (± 180)	+	+	+	+
External genitalia (large)	+	+	+	+
Behaviour disorder	+	+ +	+	+ +
Mental subnormality	−	+	−	+
EEG abnormalities	+	+	+	+
Serum protein band	+	+	+	+
Sex chromatin (buccal)	−	−	−	−
ABO group	O	B	A	B

(b) All four males showed skeletal overgrowth, as compared to the average stature of the population in the area. The father is 182 cm. in height, muscular, and has a coarse voice. The three boys are well above the 90th percentile curve of height for children of the same ethnic group (Abboud *et al.*, 1957) (Fig. 2). In all four, the increase in height was relatively more in the trunk than in the extremities, resulting in a slightly increased ratio of cephalopubic/total height. An additional skeletal feature in the eldest son is a short second metacarpal bone in both hands.

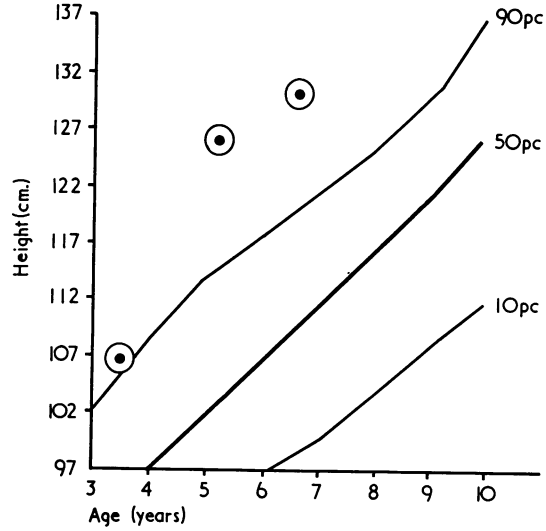

FIG. 2. Heights of the three children compared to those of children from the same ethnic group.

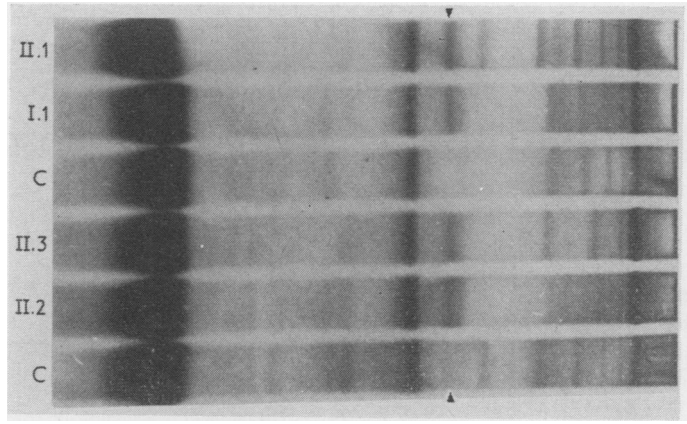

FIG. 3. Acrylamide gel electrophoresis for sera from the father (I.1), the three sons (II.1, II.2, and II.3), and control (c).

(c) The cubital carrying angle is straightened, almost 180°, in all four males.

(d) All four have oversized external genitalia, the youngest boy—3½ years old—has a penis 5 cm. long, with a few hairs on the pubic region. The size of the testicles is also slightly enlarged in the three sons. Urinary 17-ketosteroids in the father were 23 mg./24 hours (control 10–20).

(e) Serum protein electrophoresis (cellulose acetate, barbitone buffer *p*H 8·6) revealed an extra band immediately following the β-globulin, well seen in the father and the three sons, but not in the mother. A study of the sera of the father and the three sons on acrylamide gel showed this band to be a strong representation of a weaker band that is sometimes detected in normal sera (H. E. Sutton, 1968, personal communication) (Fig. 3).

Chromosomal Study

Cultures of peripheral blood leucocytes were prepared from the father, the mother, and the three sons as well as the newborn girl, using a modified technique described elsewhere (El-Alfi, Ragab, and Eassa, 1967). Incubation was maintained for 72 hours, followed by 2 hours' exposure to colcemid (1 μg./10 ml.), hypotonic treatment, fixation in 1:3 acetic-methanol, then flaming. An average of 60 metaphases was examined from each culture. The mother showed a karyotype of 46,XX, with no detectable abnormality. The newborn girl's karyotype was 47,XX,G+ in all cells examined. The

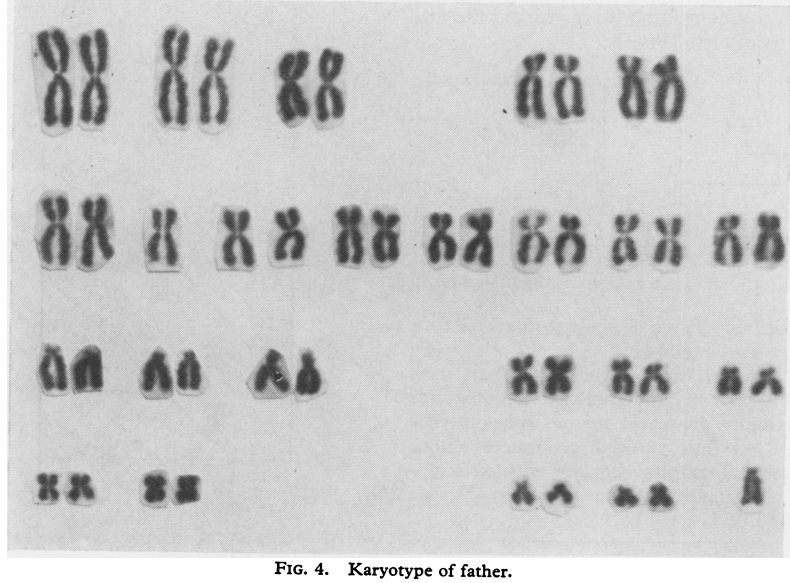

FIG. 4. Karyotype of father.

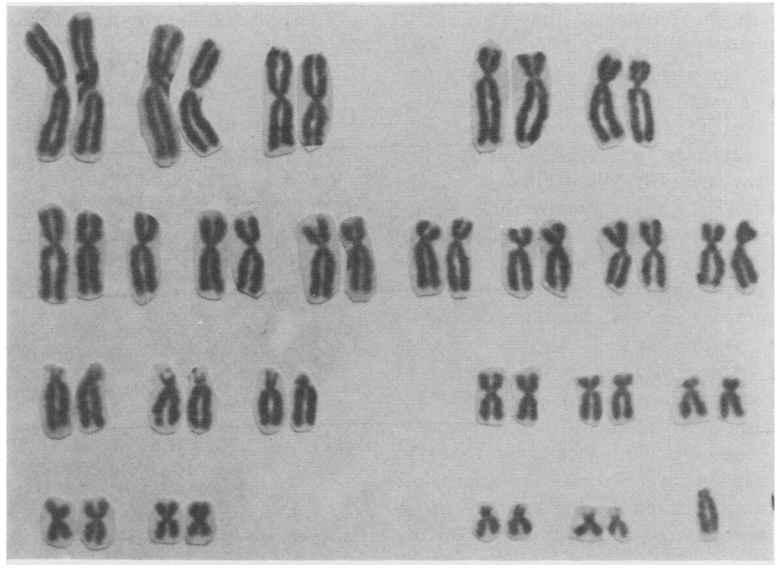

FIG. 5. Karyotype of third son.

father and the three sons had a karyotype of 46,XY with a large Y chromosome in all the cells studied (Fig. 4 and 5). The Y chromosome in all is comparable in length to the 13–15 (D) group of chromosomes, and in most of the metaphases studied the ratio of the length of the Y to the mean length of the D chromosomes ranged between 0·95 and 1·10. The increase in length of the Y chromosome appeared to be all in the long arm (centromeric index 11–12%). In a few plates more than one secondary constriction was suspected on the long arm of the Y, but the usual pattern, however, in the plates where a distinct secondary constriction was seen, was a single secondary constriction situated within the distal third of the long arm.

Discussion

Conclusions drawn by various authors, from some 60 cases of large Y chromosome reported in the literature, point out that the enlargement of the Y chromosome is not essentially correlated to a specific abnormal phenotype (Bishop *et al.*, 1962; Makino and Takagi, 1965). Large Y chromosomes were reported in normal males (Bender and Gooch, 1961; Gripenberg, 1964), as well as in males manifesting various disorders including multiple congenital malformations (Makino and Takagi, 1965), Down's syndrome (Dekaban, Bender, and Economos, 1963), hypogonadism (De la Chapelle and Hortling, 1963), mental retardation (Tonomura and Ono, 1963), etc. More than one-third of the cases reported had a normal phenotype. The large Y chromosome in these cases may be explained either by an elongation of the chromosome, or by assuming that the added or duplicated chromosomal segment has no active genes, for there is general agreement that a major part of the normal Y chromosome carries no active genes (Makino *et al.*, 1963).

On the other hand, the human Y chromosome is thought to influence behaviour, stature, cubital angle, and male genital development (Jacobs *et al.*, 1965; Court Brown, Price, and Jacobs, 1968; *Lancet*, 1965; Patanelli and Nelson, 1961; Muldal and Ockey, 1962). The multiplicity of phenotypes among many of the large Y males might then be explained by the different combinations of genes, added to—or lost from—the Y chromosome, through duplication or translocation (whether from an autosome, or from the X chromosome).

All four males in the family of the present report have a large Y chromosome, together with a uniform clinical picture consisting of behaviour disorder, skeletal overgrowth, straight carrying angle, genital overgrowth, and an abnormal serum protein band. It may be assumed that these clinical manifestations are related to the abnormal large Y chromosome that all four males carry. Some of these manifestations, namely skeletal overgrowth and behaviour disorders, are reported in many 47,XYY males (Jacobs *et al.*, 1965; Court Brown *et al.*, 1968), and could probably be the result, in those cases, of the duplication of the Y chromosome. This clinical resemblance with 47,XYY cases suggests that the large Y chromosome in the present family represents a duplication of a segment of the Y chromosome or possibly a translocation of 2 normal

Y chromosomes in the father, so that effectively the father and sons are all XYY. The band seen on serum protein electrophoresis, being a strong representation of a weaker band occasionally detected in normal sera (H. E. Sutton, 1968, personal communication), might as well be the result of a dose-effect of a gene carried by the Y chromosome.

The birth of a 47,XX,G+ girl in this family raises a question whether there is a relation between the abnormal Y chromosome in the father and the occurrence of non-disjunction. The literature gives several examples of concomitant cases of Down's syndrome and of large Y chromosomes in the same family. Among 63 males with a large Y chromosome reported by various authors (Table II), 21 were either cases of Down's syndrome or phenotypically normal close relatives of cases of Down's syndrome. In addition, in a chromosomal study of the families of mongolism cases, including 7 male propositi and 7 normal male relatives available for study, Dekaban *et al.* (1963) found 3 males with a large Y chromosome. Though these examples might suggest some kind of relation between large Y chromosome and non-disjunction, yet evidence for a direct relation between the two conditions is hard to obtain.

TABLE II

RELATIVES AND CASES OF DOWN'S SYNDROME AMONG 63 MALES WITH LARGE Y CHROMOSOME

Males with Large Y Chromosome			Reference
No. Reported	No. with Down's Syndrome	Phenotypic Normal Relatives*	
21	1	2	Makino and Takagi, 1965
15	1	4	De la Chapelle *et al.*, 1963
6	3	0	Gripenberg, 1964
21	4	6	Others†
63	9	12	

* Mostly parents and sibs.

† Bender and Gooch, 1961; Jacobs and Harnden, 1961; Källén and Levan, 1962; Van Wijck, Tijdink, and Stolte, 1962; Bishop *et al.*, 1962; Gropp *et al.*, 1963; Tonomura and Ono, 1963; Dekaban *et al.*, 1963; Tjio, 1964; Hungerford, 1964; Pfeiffer, Laermann, and Heidtmann, 1967.

Summary

All four males in a family have a large Y chromosome, equal in length to the 13–15 group, and a phenotype showing: (a) behavioural disorder, (b) skeletal overgrowth, (c) straight carrying angle at elbow, (d) genital overgrowth, and (e) abnormal serum protein pattern.

It is suggested that the extra material in the large Y of the present family is probably a duplication of part of the long arm of the Y chromosome.

A girl with a karyotype 47,XX,G+ was born in this family.

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