An Extra Small Metacentric Chromosome in a Mentally Retarded Boy

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The presence of morphologically aberrant excess chromosome material in somatic cells has been described in patients with widely differing clinical features. Conclusive identification of this extra material is not possible but may be suggested by the associated clinical condition which could represent the partial expression of one of the established trisomy syndromes. The recording of more data on chromosomally similar cases may eventually help to define more clearly the relation between genotype and phenotype.

We present here a case report of an 11-year-old boy who is clinically abnormal and whose somatic cells contain an extra, small metacentric chromosome.

Case Report

J.J. was born after a normal full-term pregnancy (birthweight 3560 g.). The mother was aged 39, the father 33 years. He showed moderate blue asphyxia and was slow to feed, but there seemed to be no abnormality until he was 11 months old, when he was noted to have a slight squint and was not sitting up. He finally sat at 1 year, walked at 2 years and 9 months, and spoke a few single words only at 3 years and 9 months, though he seemed to understand much of what was said to him.

He was first fully examined at 3½ years, when he had a peculiar facies and a head circumference of 50.5 cm. (10th percentile 49.9 cm.). He dragged the left foot and was ataxic. The IQ on the Stanford-Binet Intelligence test was 54.

During the following 6 years speech became more intelligible. His imbalance and ataxia became more severe and led to frequent falls and some injuries. He tended to be restless and somewhat destructive. An attack of pneumonia and convulsions at the age of 10 brought him to hospital, where a lumbar puncture yielded normal cerebrospinal fluid under normal pressure. Latterly, he has attended an Occupation Centre and seems to improve sociably.

When aged 11 years, he was seen again (Fig. 1). He had moderate microcephaly (circumference 50.5 cm.—10th percentile 52 cm.). The eyes were normally situated and orientated; there were no obvious epicanthic folds (Fig. 2). The ears were normal, the nose was broad and straight, the mouth was small and triangular, and the palate rather high and arched. The hairline showed no abnormalities but there was some degree of webbing of the neck. The thorax was asymmetrical,

FIG. 1. Patient J.J. aged 11 years.

FIG. 2. Patient aged 11 years; note the small head, broad nose, and small triangular mouth and irregular teeth.

FIG. 3. Diagram of the palm print of the left hand. The heavy lines denote dermal ridges, the broken lines the creases.

this being due to a scoliosis. Both testes were undescended and could not be brought down into the scrotum. The limbs appeared normal. The palmar creases and dermal ridge patterns showed no abnormalities (Fig. 3). He walked on a wide base, tended to be ataxic and slightly spastic. Co-ordination was poor especially in the legs, but the tendon reflexes were somewhat exaggerated. The plantar response was normal on the left, but extensor on the right.

X-ray of the back showed wedging of L1 and 2, with partial bony fusion on the right—a partial segmentation abnormality, bilateral cervical ribs, and absent 12th ribs.

The jaw was small, but the dentition was normal though the teeth were overcrowded and irregular.

His IQ on the Stanford-Binet Intelligence test had now dropped to 45.

Family History. The family history is negative except for a mild form of muscular dystrophy in I. 1, II. 1, and III. 3 (Fig. 4), which was not further investigated.

Buccal Smears. In cells from the buccal mucosa taken from the index patient and stained with aceto-orcein, no Barr bodies or small chromatin dots could be found which might be interpreted as a second X chromosome or part of one. No drumsticks or sessile appendages were seen in the neutrophil polymorphs.

FIG. 4. Family tree. The index case is marked with an arrow.

FIG. 5. The karyotype of the patient (IV. 2) showing the extra metacentric chromosome.

Chromosome Studies

(i) *Index Patient.* Peripheral blood specimens were taken on two separate occasions cultured by a modification of the method of Moorhead *et al.* (1960) and processed for chromosome analysis. A specimen of skin was also taken but this failed to grow in culture.

In most of the cells examined, the chromosome count was 47 and the karyotype was that of a normal male with, in addition, an extra metacentric chromosome, smaller than any other chromosome in the set, the arms being about the same size as the short arm of a 17-18 chromosome (Fig. 5). A minority of cells contained 45 or 46 chromosomes. These cells were analysed and chromosome loss from them appeared to be completely random (Table I). There was no evidence of any mosaicism.

(ii) *Relatives.* Specimens of blood were also taken from III. 2, III. 3, IV. 1, and IV. 3, and no chromosome abnormality was found.

Discussion

Morphological assessment suggests that the extra chromosome might represent a deleted supernumerary 17-18 (E) chromosome. The length of the arms approximates most nearly to the short arms of the 17-18 (E) chromosomes or to the distance between the centromere and the site of the secondary constriction of the long arms of that chromosome (Fig. 6). The absence of satellites makes it unlikely that the aberrant chromosome includes any substantial part of the short arms of either the 13-15 or 21-22 chromosomes, nor is it likely to be part of an X chromosome, as neither Barr bodies nor chromatin dots were seen in buccal smears. It is unfortunate that autoradiographic studies were not carried out, as this would probably

TABLE I
CHROMOSOME COUNT DISTRIBUTION

Subject	Chromosomal Counts						Total Counts
	42	43	44	45	46	47	
Index case (IV. 2)	2		2	2	9	19	30
				1	2	22	25
III. 2 (mother)				1	12		13
III. 3 (father)				4	19		27
IV. 1 (half sister)					13		13
IV. 3 (sister)				1	17		18

FIG. 6. The 17 and 18 chromosomes and the extra metacentric chromosomes from three cells compared. The site of the possible constrictions are indicated by arrows.

have established this fact, for it is just conceivable that so much of the X chromosome is deleted in this case as to render such bodies inconspicuous in the resting somatic cells.

The case described in this paper is similar in many respects to 4 cases where the extra small metacentric autosome was present (Frøland, Holst, and Terslev, 1963; Gustavson, Atkins, and Patricks, 1964; Taft, Dodge, and Atkins, 1965; Tamburro and Johnson, 1966). All 5 had some cyanosis or difficulty at birth and moderate to severe mental retardation and hypertonia with spasticity, while 3 of the 5 had microcephaly, a webbed neck, a small triangular mouth, a high arched palate, low-set ears, and squint. All were still alive at the time of reporting. However, in other respects the cases had a diverse clinical picture with only 2, that of Gustavson and his co-workers and ours showing the close resemblance to one another. None the less, in view of the features that they do have in common, it is possible that these 5 cases present the same chromosome abnormality. Further, these features are also seen in the majority of the 94 cases of full 17-18 (E) trisomy shown in Table II. Though these features may be taken as an indication of partial 17-18 trisomy, this could none the less be open to question, as none of these features are an exclusive manifestation of this trisomy. It is of interest that Crawford's case of a 2-month-old girl (1961) who had rather longer arms on the extra chromosome than ours, in fact, showed many more of the features usually associated with the full 17-18 trisomy. It is of course possible that any phenotypic resemblance between these cases is fortuitous and that in each case we are dealing with different chromosome material, or on the other hand, that

there is in fact no relation between the developmental abnormalities and the extra chromosome, as Taft *et al.* (1965) suggest. The two cases of Smith *et al.* (1965), a mother and son, are of interest in so far that neither was phenotypically abnormal, though both had an extra chromosome that seemed identical with that of our case.

It is unlikely that this extra small autosome arose after fertilization, as this would almost certainly have resulted in mosaicism, which was not shown. It must either have already been present in one of the other parent or arisen during meiosis in gamete formation. The former is not the case in our patient or apparently in the other 4, though Gustavson and his co-workers' patient had a sib with 21-22 (G) trisomy. The actual process by which the aberrant chromosome could have arisen in meiosis can only be purely speculative. It could have either resulted after segregation from a reciprocal translocation or perhaps from non-disjunction of a 17-18 chromosome followed by terminal deletion at the site of the secondary constriction. In this connexion it has been suggested by Ferguson-Smith and his co-workers (1962) that there is an increased possibility of chromosome breakage at the site of such secondary constrictions. Probably the most attractive theory, which was also the opinion of Frøland *et al.* (1963) and Gustavson *et al.* (1964), is that the extra chromosome has arisen from a meiotic misdivision through the centromere of a 17-18 chromosome, with the formation of an isochromosome of the short arms.

Summary

A boy with moderate microcephaly, mental retardation, moderate spasticity, a small triangular

TABLE II

COMMON FINDINGS IN PATIENT, 94 CASES OF 17-18 (E) TRISOMY AND 4 CASES WITH AN EXTRA SMALL METACENTRIC AUTOSOME

Clinical Features	Trisomy 17-18 (E) *	Present case	Frøland <i>et al.</i> (1963)	Gustavson <i>et al.</i> (1964)	Taft <i>et al.</i> (1965)	Tamburro and Johnson (1966)
Sex	32.8% male (93)	M	M	M	M	F
Mean maternal age (yr.)	32.8 (91)	39	19	28	NK	NK
Mean paternal age (yr.)	35.9 (80)	33	20	27	NK	NK
Mean gestational length (wk.)	40.6 (75)	40	NK	40	38	38
Mean birth weight (g.)	2370 (89)	3560	2800	3510	3006	2749
Mean age at death	Died at 75 days (82) [†]	Alive at 11 years	Alive at 2 years	Alive at 17 years	Alive at 16/12	Alive at 34/12
Cyanosed at birth	94% (80)	+	+	+	+	+
Failure to thrive	100% (87)	+	+	+	+	+
Mental retardation	100% (57)	(IQ 45)	(IQ 65)	(IQ 22)	(approx. IQ 55)	(No IQ)
Microcephaly	32% (57)	+	+	+	+	+
Prominent occiput	88% (51)	+	+	+	+	+
Hypertonia	87% (69)	+	+	+	+	+
Spasticity	78% (32)	+	NK	+	+	+
Fits	36% (11)	+	NK	+	NK	NK
Ulnar deviation of wrists	67% (46)	+	+	+	+	+
Long arms	—	+	NK	+	NK	NK
Rocker-bottom or flat feet	80% (66)	+	+	NK	NK	NK
Syndactyly	47% (62)	+	+	+	+	+
Short big toes	83% (66)	+	+	+	+	+
Scoliosis	57% (23)	+	NK	+	NK	NK
Webbed neck or loose neck skin	68% (62)	+	+	+	+	+
Asthenic physique	—	+	+	+	NK	NK
Micrognathos	96% (89)	+	+	+	+	+
Small triangular mouth	79% (57)	+	+	+	+	+
High arched or cleft palate	77% (56)	+	+	+	+	+
Low-set ears	89% (91)	+	+	+	+	+
Squint	22% (11)	+	+	+	+	+
Heart malformation	94% (89)	+	+	+	+	+
Renal malformation	60% (68)	NK	NK	NK	NK	NK
Herniae	60% (51)	NK	NK	NK	NK	NK
Meckel's diverticulum	23% (56)	NK	NK	NK	NK	NK
Undescended testes	54% (13)	+	+	+	NK	NA
Family history of chromosome abnormality	NA	—	—	+	—	—
				(Sib Downs)		

NK = not known or recorded; + = present; — = absent; NA = not applicable.

* The percentage frequency of a malformation in 17-18 (E) trisomy was calculated only from cases where the malformation was shown to be present or absent. The number of cases in each instance is given in brackets.

† 12 cases still alive at time of report had a mean age of 3½ years.

Note—The references to the 94 cases on which this Table is based are as follows: Bartolozzi *et al.* (1965); Brodie and Dallaire (1962); Brown, Hale, and Porter (1964); Brown, Patterson, and van Mierop (1962); Brunelli and Rosti (1966); Burks and Sinkford (1964); Butler *et al.* (1965); Cernea *et al.* (1966); Edwards *et al.* (1960); El-Alfi, Bieseke, and Smith (1964); Finley, Finley, and Carte (1963); Ganassi *et al.* (1965); German *et al.* (1962); Gottlieb *et al.* (1962); Grutta *et al.* (1966); Gustavson *et al.* (1962); Hansen *et al.* (1963); Hecht *et al.* (1963); Heinrichs and Allen (1963); Holman *et al.* (1963); Hook and Yunis (1965); Huggert (1966); Koenig, Lubs, and Brandt (1962); Levkoff, Mather, and Eisenstein (1964); Lewis (1964); Ozonoff, Steinbach, and Mamunes (1964); Rohde, Hodgman, and Cleland (1964); Rosenfield *et al.* (1962); Schepens *et al.* (1967); Scherz (1966); Smith *et al.* (1960); Steinberg and Jackson (1963); Taylor and Polani (1964); Taubert, Moszkowski, and Saunders (1966); Tönz *et al.* (1965); Townes, Manning, and DeHart (1962); Townes *et al.* (1963); Townes, De Hart, and Ziegler (1964); Trowell and Hilton (1963); Turner, den Dulk, and Watkins (1964); Uchida, Bowman, and Wang (1962); Voorhess, Vaharu, and Gardner (1962); Voorhess, Aspillaga, and Gardner (1964); Wagshal-Ives and Berman (1963); Walbaum, Breynaert, and Bergeron (1966); Weber *et al.* (1964); Zellweger, Beck, and Hawtrey (1964); Zellweger, Huff, and Abbo (1965).

mouth with a high-arched palate, neck webbing, an asthenic physique, and undescended testes, is described. Dermatoglyphs were normal. An extra small metacentric chromosome, which was interpreted as a presumptive deleted extra 17-18 (E) chromosome or an iso-chromosome of the short arms of chromosome 17 or 18, was found in the index patient but not in his parents or other relatives studied. The findings in the index case are compared with those in other cases with an extra small metacentric chromosome and those in 17-18 (E) trisomy.

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