An Extra Small Metacentric Chromosome in Association with Multiple Congenital Abnormalities*

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Excess genetic material in the form of a small metacentric chromosome, often smaller than a member of the G group, has been reported in a number of cases (Ilberry, Lee, and Winn, 1961; Frøland, Holst, and Terslev, 1963; Uchida *et al.*, 1964; Taft, Dodge, and Atkins, 1965; Gustavson, Atkins, and Patricks, 1964; Crawford and Lele, 1965; Tamburro and Johnson, 1966; Gamstorp, Håkansson, and Lagergren, 1966; Ferrante *et al.*, 1968). In some patients with this small extra chromosome there have been suggestions of which chromosome part was in triplicate, as in the cases described by Stevenson, Patterson, and Goodman (1966), with an isochromosome of the short arms of D, with a C/D translocation (Insley, Rushton, and Jones, 1968), with a G/G translocation (Mukerjee and Burdette, 1966) and with incomplete D trisomy (Ishmael and Laurence, 1965). Also a phenotypically normal mother and her son with oligospermia were found to have an extra small metacentric chromosome (Smith *et al.*, 1965).

In the majority of the cases reported, it has not been concluded which chromosome or chromosome part is in triplicate, but some of the patients with the abnormal chromosome have had features suggestive of Down's syndrome (Ilberry *et al.*, 1961; Dent, Edwards, and Delhanty, 1963; Gustavson *et al.*, 1964; Dekaban and Zelson, 1968).

A child with mental retardation and multiple congenital abnormalities in association with an extra metacentric chromosome which is smaller than a member of the G group is reported here. No conclusion is reached about the origin of the extra chromosome material.

Case Report

An 8-year old Caucasian female (Fig. 1) was referred for evaluation of mental retardation in association with congenital malformations. The mother was 36 years of age at the time of birth of this child who was born prematurely weighing 2040 g. No congenital malformations are obvious in either parent. The propositus first sat up at 22 months of age and first walked at 3 years of age. She weighed 20.4 kg at 8 years of age (less than 10th centile on Stuart scale) and her height of 118.1 cm was also less than 10th centile. Physical examination showed microcephaly with skull asymmetry, small ears with undeveloped pinnae, an epicanthus on the right, marked blepharitis, confluent eyebrows, high arched palate, clinodactyly, flexion of left fifth finger, and scoliosis. By 9 years of age, the scoliosis was marked and there was a beginning cervical kyphosis. Hearing examination did not reveal abnormalities. Psychological evaluation indicates severe mental retardation. Speech development at age 8 years was markedly retarded.

FIG. 1. The proposita.

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TABLE
GENETIC MARKER STUDIES

	ABO	MN	Rh	K	P ₁	Fy ^a	Le ^b	Hp	IgA	IgM	IgG
Proposita	A ₁	MN	R ¹ r	-	+	+	-	1-1	140	132	1820
Mother	A ₁	N	R ¹ r	-	-	+	-	1-1	280	210	1700
Father	A ₂	M	rr	-	+	+	+	2-1	155	132	1150

Radiographic examination showed increase in the trabecular pattern of the ends of the long bones, curvature of distal radii with concavity towards ulna, coxa valga, delayed bone age, rudimentary right first rib, decreased size of iliac bones, and an additional epiphysis at the distal end of the first metacarpal bilaterally.

Cytogenetic Studies. In cells derived by culture of the peripheral leucocytes, the proposita was found to have a karyotype with 47 chromosomes. The extra chromosome appeared to be metacentric and to be smaller than the G chromosomes (Fig. 2). The arms of the abnormal chromosome were interpreted as being longer than the short arms of G chromosomes. Using autoradiography following tritiated thymidine addition to leucocyte cultures, the extra metacentric chromosome was labelled in 3 of 11 metaphase plates studied in detail. In 2 of the 3 plates all chromosomes were labelled except an E chromosome which was concluded to be either a 17 or 18. In the other plates with 9 to 42 labelled chromosomes the extra metacentric was not labelled in any of the plates. Therefore, this extra metacentric chromosome appeared to replicate early in the S phase of the cell cycle in those cells derived by culture of peripheral leucocytes. No satellites were observed on the extra chromosome in any of the 50 plates examined. Karyotypes of mother and father were interpreted as normal.

The Table shows the results of various genetic marker determinations.

Discussion

The most outstanding features of our patient were severe mental retardation, microcephaly, skull

asymmetry, blepharitis, flexion of fifth finger, and scoliosis.

A comparison of the physical features of this patient with other reported patients with an apparently similar extra small metacentric chromosome does not permit the identification of this extra genetic material. The only conclusion from autoradiographic studies was that this metacentric chromosome replicated early in the S phase of the cell cycle.

While the extra chromosome in this patient could not be identified as to origin the karyotype abnormality is likely the aetiology of this child's severe retardation. Perhaps reports of further cases and a comparison of individuals with unusual karyotypes could aid in better classification, diagnosis, and prognostic information in those children with previously undiagnosed multiple malformation syndromes.

Summary

An 8-year-old Caucasian female was found to have an extra metacentric chromosome in association with multiple congenital malformations. This nonsatellited chromosome was smaller than a G chromosome and replicated early. The patient's abnormal features included mental retardation, retardation in growth and development, microcephaly, small ears with undeveloped pinnae, epi-

FIG. 2. E, F, and G chromosomes from 4 karyotypes of the proposita. The extra chromosomes are shown at the right.

canthic fold, blepharitis, confluent eyebrows, high arched palate, clinodactyly, and scoliosis.

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