46,XY,21qi/46,XY,21p- Mosaicism in a Child with Down's Syndrome

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In the course of cytological investigation of a child with Down's syndrome born to a young mother, we have encountered an unusual type of mosaicism involving a G group chromosome. For the reasons discussed below we believe this case to be an example of 46,XY,21qi/46,XY,21p- mosaicism.

Case Report

The propositus, a 3-year-old white boy, was referred to the Birth Defect Evaluation Center because of a diagnosis of Down's syndrome. Both parents were healthy and 19 years of age. The mother was gravida 1, para 1. The pregnancy was normal, and there was no known exposure to infection, drugs, or x-rays. The birthweight was 2607 g. (5 lb. 12 oz.). There was a history of one episode of pneumonia and frequent upper respiratory infections. He grasped for objects at 1 month, turned over at 5 months, sat with support at 7 months, sat without support at 9 months, and walked at 25 months. He could not speak in sentences and was not toilet trained. There was no family history of Down's syndrome, mental retardation, or any serious birth defects.

On physical examination he was on the 3rd centile for both height and weight. He had the typical facies of Down's syndrome with a square-shaped head, epicanthal folds, mongoloid slant of the eyes, broad nasal bridge, overhanging helix, and absent antihelix of the ears, and a protruding tongue. The hands were short and broad with bilateral clinodactyly; there were no simian lines. The abdomen was somewhat protuberant. The remainder of the physical examination was negative.

Cytogenetic Studies

Chromosome studies of the propositus were done on two samples of blood obtained at different times using a slight modification of the method of Moorhead *et al.* (1960). A skin biopsy specimen was cultured according to Harnden's method (1960). The data are summarized

TABLE
CHROMOSOME COUNTS OF PROPOSITUS

	Chromosome Counts			Total Cells Counted	No. of Cells With Telo-21	No. of Cells With Iso-21
	45	46	92†			
Blood 1	—	100	—	100	88	12
Blood 2	1*	69	—	70	61	9
Skin	1*	63	2	66	3	63

* Includes Group 21-22 with telocentric.
† Endoreduplication.

in the Table. Karyotypes of both skin cells and leucocytes showed 46 chromosomes, with a mixture of two cell types. One line had a metacentric chromosome similar to a member of group 19-20 replacing a member of group 21-22 (Fig. 1). The other line showed loss of the short arm of a member of group 21-22 (Fig. 2). Careful examination of all cells showing the latter abnormality failed to reveal any short arm material on the involved chromosome. Though the possibility exists that a very small short arm may be present on this chromosome, it was presumed to be telocentric. This telocentric chromosome was present in 88% of the leucocytes and in only 5% of the skin cells. Except for the abnormalities noted, the karyotypes of both cell lines were otherwise normal. Chromosome studies of cultured leucocytes obtained from both parents showed no abnormalities.

Discussion

It is possible that the two chromosomal anomalies found in the cells of the propositus arose independently and are unrelated. On the other hand, it seems reasonable to assume that they are related. The cell line with a telocentric chromosome probably had no phenotypic effect. There is evidence from the study of normal persons as well as phenotypically normal carriers of the centric fusion type of translocation that the loss of a short arm from an

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FIG. 1. Metaphase plate with accompanying karyotype of leucocyte of propositus, showing small metacentric (arrow) replacing a member of group 21-22.

acrocentric chromosome may not result in a phenotypic abnormality (Court Brown, 1967).

The metacentric chromosome replacing a G group chromosome in the second cell line of the present case could be a 21/21, a 22/22, or a 21/22 translocation; or it could be an isochromosome for the long arm of a 21 or 22. Because of the clinical features of mongolism the long arm of No. 21 must be present in triplicate. Against the telocentric being derived from one of the above-mentioned

translocations is the relative stability of a centric fusion translocation; conversely, derivation of a centric fusion chromosome from a telocentric is highly unlikely (Therman *et al.*, 1963). If the metacentric represents an isochromosome for the long arm of No. 22, then it must be assumed that all three small acrocentrics in this cell line are No. 21. This would imply non-disjunctions with loss of a No. 22 and a gain of a No. 21, in addition to isochromosome formation. A more likely origin for

FIG. 2. Group 21-22 and Y chromosome from six different leucocytes of propositus, showing loss of short arm from a member of group 21-22.

the metacentric would be an isochromosome derived from a No. 21. Hence, the propositus would be a mosaic, with one cell line effectively trisomic for chromosome 21 and the line with the telocentric effectively normal. Chaudhuri and Chaudhuri (1965), in reviewing reported cases of mongoloid mosaics, note the difficulty in correlating the proportion of cell types and the phenotype in such cases. Also, the proportion of cell types found in cultured cells may not necessarily be the same *in vivo*. From the clinical point of view there was no doubt about the diagnosis of Down's syndrome in the case under discussion.

Chromosomal anomalies similar to those of the present case were found in the D group of a 4-year-old mentally retarded girl with some of the features of the D¹ trisomy syndrome (Therman *et al.*, 1963). Their patient was a mosaic with a mixture of two about equally frequent cell populations found in cultured leucocytes, bone-marrow, and skin cells. Both cell lines had 46 chromosomes: in one line a member of the D group was replaced by a presumed isochromosome for the long arm of a D group chromosome, and in the second line was a telocentric D group chromosome. In effect, their patient was a normal/D trisomy mosaic.

Assuming that the abnormal metacentric of the present case is an isochromosome for the long arm

of No. 21, it may have arisen first and then produced a telocentric 21, or the isochromosome may have originated from the telocentric. Both possibilities have been described in plants (Sears, 1952). Rhoades (1940), in his study of maize plants hyperploid for a telocentric chromosome consisting of the short arm of chromosome 5, showed through the use of mutant genes lying in the telocentric that it was involved in the production of isochromosomes through transverse division of the centromere in meiosis. Therman *et al.* postulate that in their case a telocentric chromosome was formed in a parental gonad, with subsequent transverse division of the centromere and isochromosome formation after the first division of the zygote. A similar sequence of events could have occurred in the case under discussion.

Summary

A 3-year-old boy with Down's syndrome was found to be a mosaic with two cell lines. Both lines had 46 chromosomes: in one a telocentric chromosome 21 was present; in the other line there was an isochromosome for the long arm of No. 21. It is probable that these chromosomal anomalies were related, the most likely sequence being formation of a telocentric No. 21 chromosome in a parental gonad, with transverse division of the centromere of this telocentric and isochromosome formation after the first division of the zygote.

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