Down's Syndrome with 47,XX,+21/47,XX,+mar Mosaicism*

Summary. A four-year-old girl with typical Down's syndrome is described. She has 47,XX,+21 karyotype in skin and lymphocytes and 47,XX,+mar karyotype in some lymphocytes. Autoradiography and fluorescent analyses have failed to identify the +mar chromosome which has the appearance of a 'D' chromosome but which may involve a translocation to a chromosome No. 21. However, the mechanisms of its formation and its significance are not certain.

Fig. 1. Photograph of patient at 1 year showing phenotypic Down's syndrome.

Chromosome mosaicism occurs in about 2% of patients with Down's syndrome, and usually consists of cells with trisomy 21 and cells with an apparently normal karyotype (Carr, 1969). Less commonly, the cell line with trisomy 21 is present with a second cell line that also has an abnormal karyotype. Here we present such an unusual mosaicism (47,XX,+21/47,XX,+mar) in a girl with typical Down's syndrome.

Case Report

The *proposita* is a 4-year-old girl with phenotypic Down's syndrome. She was the fourth pregnancy of a 39-year-old, para 4 gravida 5, Japanese woman and a 35-year-old Caucasian man. Although the mother was tired during the pregnancy, she denied any specific illness and took no medication. The mother's first pregnancy by a previous marriage resulted in a phenotypically normal daughter who is now 14 years old. The mother's second pregnancy was by her present husband and resulted in an unexplained miscarriage at 3 months. Subsequently, she was unable to conceive for 7 years. There are two normal brothers, one a year older and the other 2 years younger than the *proposita*.

The mother had been about 15 miles away from the centre of the atomic bomb explosion in Hiroshima; later she did go into the bombed area and had subsequent epilation of scalp hair. However, she had no nausea, vomiting, oropharyngeal lesions, or petechiae.

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On physical examination at age 4 years, the patient is 95 cm tall and weighs 13 kg (both less than the third centile for her age). Her clinical features (Fig. 1), which are characteristic of Down's syndrome, include brachycephaly, epicanthal folds, mongoloid slant of the palpebral fissures, large tongue, brachydactyly, clinodactyly of both fifth fingers, a simian crease on the right, and generalized hypotonia. In addition, she has a grade IV/VI holo-systolic murmur heard over the lower left sternal border and a grade I/VI apical mid-diastolic rumble. Cardiac catheterization revealed a ventricular septal defect of the AV communis type with a large left to right shunt.

Dermatoglyphic studies of the patient reveal *t* and *r'* palmar axial triradii bilaterally. Digital patterns show whorls bilaterally on the thumbs, fifth fingers and left fourth finger with the rest being ulnar loops. The mother has nine digital whorls and *t* palmar axial triradii; the father has 10 ulnar loops, *t* palmar axial triradii, and a simian crease on the right.

Cytogenetic Studies

Routine chromosome analysis on blood lymphocytes of the *proposita* revealed a modal count of 47 chromosomes. In 21 cells there were five chromosomes in the G group, ie, an extra G-group chromosome and in nine cells there were four chromosomes in the G group and seven chromosomes in the D group, ie, an apparent extra D-group chromosome. A skin fibroblast culture revealed a chromosome count of 47 in 50 cells, all with five chromosomes in the G group and six chromosomes in the D group, ie, 47,XX,+G.

Buccal and hair root sheath sex chromatin counts

FIG. 2. Partial karyotypes of two blood lymphocytes showing the D group and the G group which contain three brightly fluorescing No. 21 chromosomes consistent with the diagnosis of Down's syndrome.

FIG. 3. Fluorescent stained karyotype of a blood lymphocyte showing the brightly fluorescing marker chromosome.

showed a normal female pattern. Tritiated thymidine autoradiographic studies and fluorescent studies using quinacrine mustard on cells with a 47,XX,+G karyotype both indicate 47,XX,+21 (Fig. 2). In the cells with the extra marker chromosome appearing morphologically like a D, autoradiographic studies show three relatively lightly labelled D-group chromosomes, a pattern which is consistent with the labelling of a No. 15 chromosome, and suggests that the karyotype is 47,XX,+15. Fluorescent studies in these cells show this chromosome to be brightly fluorescing in both the long and the short arms without any specific banding (Fig. 3) and only one No. 21 chromosome with prominent short arms (two such chromosomes 21 are seen in the 47,XX,+21 cells), which suggests that

this marker could represent a duplication of the long arms of a No. 21 chromosome. Other alternatives are a No. 13 chromosome, or a translocation of unknown chromosome material to the long arms of a number 21 chromosome.

Results of chromosome studies of the parents and both brothers are normal. Of particular note is that the mother's analysis is normal and shows no evidence of increased chromosome damage.

Galactose-1-phosphate uridyl transferase was elevated in the patient at 31.8 units; the level in the father was 27.4 units and in the mother 22.5 units, both values within normal limits (18–28 units). The patient had normal haemoglobin electrophoresis, serum protein electrophoresis, and leucocyte alkaline phosphatase.

TABLE I
PATIENTS REPORTED WITH DOUBLE AUTOSOMAL TRISOMY

Author	Phenotype	Karyotype
Marks <i>et al</i> (1967)	Down's syndrome without stigmata of E trisomy	47,XY, + G/47,XY, + 18
Zellweger and Abbo (1967)	D and E trisomies	47,XY, + E/47,XY, + D
Warren and Keith (1971)	D and E trisomies	47,XY, + D/47,XY, + E
Porter <i>et al</i> (1969)	Down's syndrome and hypertelorism and opisthotonus	47,XY, + G/47,XY, + D/48,XY, + D, + G
Zellweger and Abbo (1967)	Down's syndrome and E trisomy	46,XY/47,XY, + G/47,XY, + E/48,XY, + G, + E
Garson <i>et al</i> (1969)		47,XX, + D/47,XX, + E/48,XX, + D, + E
Smith <i>et al</i> (1965)	Down's syndrome	47,XX, + G/48,XX, + D, + G
Tolksdorf <i>et al</i> (1965)	Down's syndrome with stigmata of E trisomy	47,XY, + E/48,XY, + E, + G

Discussion

Chromosome studies were undertaken in a patient with typical Down's syndrome because the mother was near Hiroshima at the time of the atomic bomb explosion and because the proposita's parents had a period of reduced fertility before her birth. The 47,XX,+21 karyotype seen in the skin fibroblast cultures and in half of the blood lymphocytes, taken with the typical phenotypic picture of Down's syndrome, makes the interpretation reasonably certain that one cell line has typical trisomy 21. The interpretation of the cell line with the extra marker chromosome is less clear but probably represents extra material attached to the long arm of a chromosome 21. Because this cell line is present only in the lymphocytes, the phenotype does not help to identify this marker chromosome.

A summary of some other patients described with double autosomal trisomy is given in Table I. Because no normal cell line and no cell line with 48 chromosomes containing both trisomic chromosomes has been demonstrated in our patient, it is difficult for a single event to explain the abnormality in our patient. Therefore, more complicated changes will have to be considered. One hypothesis is that our patient began as a regular trisomy 21 and in a lymphocyte precursor a translocation occurred between 2 chromosomes in the G group. In this explanation the centromere of one was lost and the remaining material translocated to the long arms of another G-group chromosome giving the appearance of a D-group chromosome. If this were followed by mitotic non-disjunction, a cell with 47 chromosomes would be produced and a cell with 45 chromosomes with a G-group monosomy would also result and could be lost subsequently. Similarly, some other unrecognized translocation could result in the same chromosomal appearance, and the

limitation of the chromosome change due to lymphocytes would probably not result in any alteration in the Down's syndrome phenotype of the patient.

Because the chromosomal mosaicism in the proposita is limited to the blood lymphocytes, one also has to consider the possibility that the cells with the marker chromosome may represent a pre-malignant or malignant state in view of chromosome changes in neoplastic conditions. At present there is no clinical reason to suspect this possibility, but a long term follow-up may be necessary to rule this out.

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