Trisomy 21 mosaicism in two successive generations in a family*

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SUMMARY The occurrence of 46,XX/47,XX,+21 mosaicism in two successive generations implies an aetiological relationship between the 47,XX,+21 cell line of the mother and her daughter.

Case report

The proband is a 20-year-old white female with the typical clinical features of Down's syndrome including upward slanting palpebral fissures, rounded and flat facies, Brushfield spots, epicanthal folds, short stature, and mental retardation. She was evaluated at the age of 20 years by a clinical psychologist who reported her IQ to be 46. No chromosome studies had been performed.

The mother was 24 years of age at the time of the proband's birth, and it was her fourth pregnancy. The first three pregnancies ended in spontaneous abortion by the fourth month of gestation. The fifth and sixth pregnancies were carried to term with delivery of normal females.

CYTOGENETIC STUDIES

A chromosome analysis performed by routine Giemsa staining on the peripheral blood of the affected daughter showed a mosaic form of Down's syndrome (table). Of 100 cells examined, 54% were 46,XX and 41% were 47,XX,+21. A total of 5% of the cells had 45 chromosomes with random loss of different chromosomes.

TABLE *Results of chromosome analyses on various tissues of mother and 3 daughters*

Patient	Tissue	Cells counted	46,XX	47,XX, +21	% trisomic 21
Mother	Blood	101	99	2	1.98
	Skin	92	92	0	0
	Ovary	35	33	2	5.71
Daughter 1	Blood	100	54	41	41.00
Daughter 2	Blood	50	50	0	0
Daughter 3	Blood	50	50	0	0
	Skin	30	30	0	0

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Discovery of mosaicism in the proband prompted chromosome analyses of her sisters, neither of whom displayed features of Down's syndrome. Peripheral blood was examined in both sisters (table). Additionally, chromosomes were examined from cultured fibroblasts from one of the sisters. A normal 46,XX chromosome constitution was observed in each sample.

The mother of the proband showed no features of Down's syndrome, but her poor reproductive history indicated that a chromosome analysis would be appropriate (table). Of the 101 leucocytes examined, 2% were 47,XX,+21. These trisomic cells were the 36th and 54th examined. Finally, cells cultured from an ovarian biopsy performed when the mother underwent abdominal surgery showed a 47,XX,+21 chromosome constitution in 6% of the cells examined.

The proband's father refused a chromosome analysis.

Discussion

There have been numerous examples of a parent who was phenotypically normal or who displayed only minor features of Down's syndrome, and who was found to have a low percentage of 47,XX or XY,+21 cells, producing offspring with standard trisomy 21 Down's syndrome.¹⁻⁵ We are not aware of a previous report of a mosaic child born to a mosaic parent.

Two questions arise from this study. (1) Do the two cell lines observed in the mother's peripheral blood cultures and her ovarian tissue represent true mosaicism or random gain and loss? (2) Did the 47,XX,+21 cell line of the mother contribute to the trisomic 21 cell line of the daughter?

In relation to the first question, the practice of some investigators has been to consider very low

percentage mosaicism to be an artefact. Bochkov *et al*⁶ do not consider subjects in whom a minority cell line represents less than 25% of the total cell population to be true mosaics. Penrose⁷ excluded from the category of mosaics those persons whose minority cell line forms a proportion of less than 10% of the total. Such percentage limits do not take into account the type of tissue sampled.

Although only 2% and 6% of the cells in the peripheral blood and ovarian tissue of the mother in the present case showed the minority cell line, in all such metaphases chromosome 21 was present in triplicate. The quality of the preparations was such that excessive bursting and spreading of the cells did not occur, and in no cells were fewer than 46 chromosomes observed. These observations argue against random gain and loss.

The production of standard trisomy 21 Down's syndrome children by a parent with a low percentage of trisomy 21 cells is not without precedent. Richards⁴ reviewed 17 cases of mosaic parents with affected children. Twelve of these mosaic parents showed 10% or fewer 47,XX,+21 cells in blood or skin or both, and in five of these the trisomic cell line constituted only 2 to 3% of the cell population. Nuzzo *et al*⁸ reported a case in which the mother of an affected child had only 0.87% mosaicism for trisomy 21 in skin fibroblasts.

In relation to the second question, this case implicates the 47,XX,+21 cell line of the mosaic mother in contributing to the trisomic 21 cell line of the mosaic daughter. That 6% of the ovarian cells grown in tissue culture were 47,XX,+21 supports his hypothesis. The ovarian cells examined were fibroblastic and may not accurately reflect the percentage mosaicism present in the oogonial cell line, which may be greater. Recent data concerning the high frequency of prenatal loss in Down's syndrome⁹ would suggest that the mother's three spontaneous abortions could have been trisomic 21 fetuses. However, the three fetuses were not studied.

A child mosaic for Down's syndrome can develop either from a normal zygote or a trisomy 21 zygote in which mitotic non-disjunction occurs during cleavage. Richards,⁴ calculating the proportions of mosaics derived from normal and trisomic zygotes, determined that 52.7% of mosaic parents are derived from normal zygotes, whereas only 19.1% of mosaic children with clinical Down's syndrome are derived from normal zygotes. Thus, the mother in the present case probably originated as a normal zygote. A mitotic non-disjunctional event occurred which produced a trisomic 21 cell line that proliferated into several tissues including reproductive tissue. The mosaic daughter was derived by secondary non-disjunction from a 47,XX,+21 oogonial cell. A

mitotic non-disjunctional event occurred which produced a normal diploid cell line. The absence of appropriate cytological markers and the inability to perform a chromosome analysis on the father prevented a more precise determination of the origin of the daughter's mosaicism.

Although the routine examination of large numbers of cells from different tissues of all parents with Down's syndrome children would be impractical,¹⁰ such procedures would seem to be warranted in familial Down's syndrome or in couples who have had multiple spontaneous abortions and have produced an affected child, even when that child displays a mosaic form of Down's syndrome.

The family presented here suggests that a tendency towards mitotic non-disjunction may be present in some families. This tendency is manifested in mosaic subjects in successive generations and may reflect abnormalities in the genetic control of mitosis. Support of this hypothesis by additional reports of investigations involving large numbers of cells from different tissues in parents of mosaics would have a profound influence on the estimation of recurrence risks of mosaic Down's syndrome.

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