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Regular G21-trisomy in 3 sibs from mother with trisomy 21 mosaicism¹

SUMMARY This paper describes a family with 3 affected sibs with regular trisomy 21 Down syndrome. The condition seems to be transmitted from a phenotypically normal mother in whom G-trisomy mosaicism was identified. Giemsa banding depicted trisomy 21 mosaicism in cells from the mother. Chromosomes from the children showed a trisomy 21 in all the cells analysed.

In 1962, Smith *et al.* first described trisomy 21 Down syndrome associated with maternal mosaicism. Subsequently trisomy Down syndrome associated with maternal G-trisomy mosaicism has been reported in at least 12 instances. Aarskog in 1969 described a family with 2 affected sibs and made a review of cases published so far. In 1 of the families of this series the mother gave birth to 3 consecutive children with Down syndrome. Recently Kaffe *et al.* (1974) reported a case of trisomy 21 mosaicism in a

a woman with 2 children with trisomy 21 Down syndrome.

We would like to present a family in which 3 sibs show trisomy 21 Down syndrome. Chromosomes from the mother showed trisomy 21 mosaicism. Giemsa banding performed by the method of Seabright (1971), confirmed the presence of an extra G chromosome in the trisomic cells.

Case reports

The probands, 1 boy and 2 girls, were first seen at the genetics clinic at the ages of 13, 10, and 8, because of findings suggesting Down syndrome. They were the second, third, and fourth of 4 children (Fig. 1). The first one appeared as a normal 18-year-old youngster. Each affected child showed clinical features of Down syndrome such as brachycephaly, epicanthic folds, mongoloid slant of palpebral fissures, low-set dysplastic ears, hypotonia, and typical dermatoglyphs.

The mother was 39 years old when she was seen for the first time in 1975. She was the eldest of a sibship of 6. Her mother was 26 years old and her father 23 years old when she was born. A paternal aunt gave birth to a child with clinical features of Down syndrome at the age of 41. She had 4 uneventful pregnancies, the first one at the age of 19 and the last one when she was 29 years old, and no abortions. Her first pregnancy ended with the birth of a normal boy. Five years later, at the age of 24 years, she gave birth to a boy with typical features of Down syndrome. She became pregnant again at the ages of 27 and 29 years and gave birth to 2 more children, both of them with clinical stigmata of Down syndrome. There was no history of drug ingestion, radiation exposure, or viral infection. Each child belongs to a different father. At the time of the interview in 1977 she was 39 years old. She displayed no stigmata of Down syndrome, and her intelligence was considered normal.

Fig. 1 Pedigree of the family.

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Fig. 2 Partial karyotype of G group chromosomes from the mother with Giemsa banding.

CYTOGENETICS

Chromosome analysis was carried out on 2 different occasions from peripheral leucocyte cultures of the mother. Giemsa banding was performed by the method of Seabright (1971). Mosaicism 46,XX/47,XX+G was found, there being 12 cells with a 47,XX+G karyotype out of 200 cells examined. The 3 affected children showed regular G-21 trisomy in all the cells examined. The oldest child who appeared to be a normal boy was found to have a 46,XY karyotype. The fathers were not available for examination. The extra G chromosome in the trisomic cells was identified by Giemsa banding (Fig. 2).

Discussion

In addition to these 3 members of the present family, there have been, to our knowledge, 12 more reported cases of trisomy Down syndrome in which maternal trisomy 21 mosaicism has been identified. Of these, 9 cases were isolated; we were only able to find 3 reports of trisomy 21 Down syndrome in sibs from phenotypically normal mothers with trisomy 21 mosaicism (Smith *et al.*, 1962; Aarskog, 1969; Kaffe *et al.*, 1974). In all the cases, the phenotypically normal women have given birth to children with trisomy 21 Down syndrome between the ages of 19 and 32. The proportion of trisomic cells has varied from 5 to 29%, and in the cases reviewed by Aarskog (1969), there were only 2 mothers with stigmata of Down syndrome.

Cytogenetic analysis of 14 young mothers, with ages between 17 and 29, from 43 families with children with trisomy 21 Down syndrome has failed to show any abnormal karyotype, with the exception of the present family (personal observation).

Two different mechanisms have been suggested to explain the origin of mosaic trisomy, from a normal zygote containing 46 chromosomes or from an abnormal zygote containing 47 chromosomes. In the first case, mitotic nondisjunction takes place after the first cleavage division of a normal zygote containing 46 chromosomes. Thus, 3 types of cells each with a different chromosome constitution are formed: 45,-21, which is not viable; 46 (normal) and 47,+21. The second mechanism is meiotic non-disjunction

during parental gametogenesis, by which an abnormal zygote containing 47 chromosomes, with a G 21 trisomy, is formed. After the first mitotic division one of the extra chromosomes would then be lost, giving rise to two different cell lines in the new individual. This last theory seems to be more admissible, since it has been observed that the birth of children with trisomy 21 mosaicism is commonly associated with advanced maternal age (Penrose and Smith, 1966). Therefore, an age-dependent factor may be involved in the formation, by primary non-disjunction, of a zygote with an extra chromosome.

According to Penrose (1963), Down syndrome may be classified in two groups, the maternal age-dependent group and the age-independent group. Most of the familial cases will be found in the age-independent group. Trisomy 21 Down syndrome associated with maternal trisomy mosaicism would be placed in the latter group. Thus, trisomy 21 mosaic mothers carry a considerably higher risk of having children with trisomy 21 Down syndrome. In addition to that, their risk of recurrence is greater than would be expected in non-mosaic women, as is suggested from the findings in the present family and those previously reported by Smith *et al.* (1962), Aarskog (1969), and by Kaffe *et al.* (1974).

It must be stressed that after the birth of a mongol child to a young couple, chromosome analysis should be carried out in both parents in order to rule out parental mosaicism.

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