FAMILIAL CASES OF DOWN'S SYNDROME A PSU DIC (21) (q22) AND A ROB (14q21q) IN COUSINS

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Summary A patient is described of a girl aged 6 months with typical features of Down's syndrome. Chromosomal studies revealed a 46,XX, -21,+psu dic(21) (pter→cen→q22 : : q22→pter) karyotype. A maternal cousin also had Down's syndrome. His karyotype was 46,XY,-14,+rob(14q21q).

INTRODUCTION

Familial occurrence of Down's syndrome is rather rare except for those caused by either translocation or mosaicism of one of the parents. Familial aggregation of trisomy 21 or trisomy 21 plus another case due to *de novo* translocation, have been described (Priest *et al.*, 1963; Zellweger, 1968). A sib with two cases of Down's syndrome due to 21q21q "*de novo*" translocation was also described (Schmidt and Nitowsky, 1977).

In the present communication, a family with two cases of Down's syndrome is described. Chromosome studies revealed two different structural rearrangements, a psu dic(21) and a rob(14q21q), both being *de novo*.

CASE REPORT

The proband (M.K.) was a Japanese female. She was the first child of the mother and the father aged 27 and 24 years, respectively, at the time of her birth. The parents were not consanguineous and phenotypically normal. Family history was negative except for a maternal cousin with Down's syndrome (Fig. 1).

The proband was born at term after an uneventful gestation. The birth weight was 2,730 g and the length 47 cm. Physical examinations at 4 months of age

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Fig. 1. Family tree.

Fig. 2. Patient (M.K.) at 4 months of age.

revealed various features of Down's syndrome; growth retardation, upward slanting of palpebral fissures, strabismus, hypertelorism, bilateral epicanthic folds, wide and flattened nasal bridge and general hypotonia (Fig. 2). The mouth was small and kept open most of the time. There was systolic heart murmur on the left sternal border in the 4th intercostal space. The ECG, X-ray films of the chest and ultrasonic cardiography were also suggestive of the presence of congenital heart disease. Cardiac catheterization, however, was not possible because of her sudden death. No simian line was observed on palms. Hallucal patterns were distal loop (r) and tibial loop (1). She died abruptly at 6 months of age after episodes of dyspnea and cyanosis. Autopsy was not granted.

The maternal cousin (T.U.) was the only child of healthy, nonconsanguineous parents. The mother and father were 25 and 34 years old at the time of the delivery. He was born at term and weight 2,950 g. The crown-heel length and head circumference were 45.5 cm and 33.8 cm, respectively. At birth obstetricians made a diagnosis of Down's syndrome based on clinical findings. It was later confirmed by various

Fig. 3. Chromosome No. 21 pair of the proband. nt, no treatment [Giemsa staining]; G, GTG; Q, QFQ; C, CBG; N, NOR [Ag-I method]; d-D, distamycin-DAPI; D, DAPI.

physical findings (e.g., typical facial appearance, general muscle hypotonia and diastasis recti), X-ray examinations (e.g., markedly reduced acetabular and iliac angle) and dermatoglyphic findings obtained by 21 months of age. The latter included R on both right 5th and left 4th fingers, U on 7 finger tips and bilateral high axial triradii (t'').

CYTOGENETIC STUDIES

Proband (M.K.): The standard leukocyte culture revealed a 46,XX,Gq+ karyotype in every cells examined. The Gq+ chromosome had satellites on both of its ends and either of them were involved in a satellite association. Both C- and N-banding (Sumner *et al.*, 1972; Bloom and Goodpasture, 1976) revealed positive material near the end of the long arm in addition to the centromere (the short arm for the latter). Both G and Q staining revealed that the Gq+ chromosome consisted of two no. 21 chromosomes fused together at near the ends of the long arm, points of breakage being at band 21q22 (Fig. 3). The Gq+ chromosome represented, in fact, a dicentric chromosome with one of its centromeres inactivated, the karyotype being 46,XX,-21,+psu dic(21) (pter→cen→q22 : : q22→pter). Distamycin-DAPI staining revealed a large and bright segment on only one of the two ends. Thus the dicentric chromosome was formed through translocation (tdic) rather than isodicentric (idic) rearrangement. Both parents showed normal karyotype. Only the mother's cells were available for distamycin-DAPI staining and neither of no. 21 pair had an enlarged and bright short arm.

The maternal cousin (T.U.) had a 46,XY,-14,+(14q21q) complement. Both parents showed a normal karyotype.

DISCUSSION

When there is either familial translocation or mosaicism involving a 21(s), multiple cases of Down's syndrome are sometimes observed within a sib. On the other hand, it is very unusual to see, if at all, the same caused by *de novo* formation of different types of structural rearrangement in a family.

In the present communication, familial cases of Down's syndrome is described. The proband was a typical example of Down's syndrome based on clinical findings, however, his karyotype was 46,XX,Gq+. Banding studies revealed that the abnormal chromosome was, in fact, dicentric with one of its two centromeres inactivated, *i.e.*, psu dic(21) (pter→cen→q22 : : q22→pter). This particular chromosome was presumably formed during the process of gametogenesis in one of the parents as both of them showed a normal karyotype by the analysis of somatic cells.

One of the maternal cousin was also affected by Down's syndrome. His karyotype was 46,XY,-14,+rob(14q21q). This rearrangement, again, was arisen *de novo* from normal parents. Whether there are any common causes between the two *de novo* rearrangements is not known. It is quite possible that their occurrence is fortuitous.

It has been established that in a dicentric chromosome, one of two centromeres are inactivated, and further, only the active one is positively stained by the Cd staining (Nakagome *et al.*, 1976; Maraschio *et al.*, 1980). In the present case, the dic(21) chromosome assumed a monocentric appearance and only the active centromere was Cd positive. The other was presumably inactivated and became Cd negative. The details of Cd-band study will be described elsewhere.

The present case is trisomic for no. 21 except for a distal part of q22 band (q22→qter) and showed typical features of Down's syndrome in agreement with the literature. According to Hagemeijer *et al.* (1977), the triplication of the 21q22 band is essential for the phenotype of Down's syndrome. On the other hand, the triplication of the most distal end of it may not be necessary (Poissonnier *et al.*, 1976; and Raoul *et al.*, 1976).

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