Dic(21;21) in a Down's syndrome child with an unusual chromosome 9 variant in the mother

SUMMARY A child with characteristic clinical features of Down's syndrome and raised red cell SOD-I activity was found to have, in addition to a single chromosome 21, a reverse dicentric tandem translocation of two No 21s with dual NORs and C band regions. The breakpoints on the chromosomes involved in the translocation were at the most distal end of the long arms (21q223). The phenotypically normal mother carried a rare variant of a chromosome 9.

In recent years, the advent of a wide variety of chromosome staining procedures, coupled with the development of techniques for estimating gene dosage, has substantially increased precision in the delineation of chromosomal aberrations. These advances have led, for example, to more detailed correlation between karyotype and phenotype, to new concepts about the existence of latent or inactivated centromeres, and to growing interest in the possible genetic significance of unusual cytogenetic polymorphisms.

We have had the opportunity to study a family which proved to be informative in each of these respects, and present here an account of these observations.

Case report

The proband is the first born child of a mother and father aged 27 and 28 years, respectively, at the time of her birth. The non-consanguineous parents are phenotypically normal and healthy, and they give no family history suggesting chromosomal aberrations, apart, possibly, from the several spontaneous miscarriages represented in fig 1. Other than vaginal

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<th>Hall's 10 best diagnostic signs in newly born Down's syndrome infants</th>
<th>Findings in proband</th>
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<tr>
<td>Oblique palpebral fissures</td>
<td>+</td>
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<tr>
<td>Dysplastic ears</td>
<td>±</td>
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<tr>
<td>Abundant skin on neck</td>
<td>+</td>
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<tr>
<td>Flattened facial features</td>
<td>+</td>
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<tr>
<td>Four-finger palmar crease</td>
<td>+ (bilateral)</td>
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<tr>
<td>Dysplastic middle phalanx of 5th finger</td>
<td>+ (bilateral)</td>
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<tr>
<td>Hyperflexibility</td>
<td>+</td>
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<tr>
<td>Muscular hypotonia</td>
<td>+</td>
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<tr>
<td>Absence of Moro reflex</td>
<td>?</td>
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<tr>
<td>Dysplastic pelvis</td>
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FIG 1 Pedigree of family.

FIG 2 Appearance of proband at 5 months.
bleeding of uncertain amount for several days at about 10 weeks’ gestation, the pregnancy was uneventful and labour began spontaneously at term. This was followed, 14 hours later, by vertex delivery of a slightly cyanosed, hypotonic female infant weighing 2705 g and with an Apgar score of 5. There was no evidence of a cardiac defect. The diagnosis of Down’s syndrome was suspected at birth and chromosomal studies were started.

When seen at the age of 5 months, the general appearance of the child was characteristic of Down’s syndrome (fig 2). Specifically, nearly all the physical signs listed by Hall¹ as being the ten best diagnostic ones in early infancy were present (table). Additional

FIG 3  (a) Chromosomes 21 from 4 cells of proband (GTG banding). (b) Portion of cell from proband (C banding) showing dicentric appearance of translocation chromosome with dark-staining material at each end (arrow). (c) G group chromosomes of proband (NOR staining) showing translocation chromosome with NOR at each end. (d) Portion of cell from proband (NOR staining followed by atebrine fluorescence) showing translocation chromosome (arrow). (e) Variant chromosome 9 from mother (G, G-11, and C banding). Note extra G band in short arm (arrow).
FIG 4  Karyotype of mother (G banding).
findings included reduced head size with occipital flattening and brachycephaly (circumference, 397 mm; length, 133 mm; breadth, 108 mm; cephalic index, 0.81), bilateral epicanthic folds, and height (63 cm) and weight (6·6 kg) both at the 25th centile.

Dermatoglyphic analysis yielded a Walker index\(^a\) of +1·87, a score in the overlap range between Down's syndrome subjects and controls, though more likely to be found among the former. Using the diagnostic index of Reed et al.,\(^a\) with examination of four dermatoglyphic pattern areas, a score of 113 was obtained, which is distinctly within the distribution for persons with Down's syndrome.

**CYTOGENETIC FINDINGS**

Chromosomal examination of the proband and her mother and father was undertaken on peripheral blood lymphocytes. A total of 60, 20, and 14 cells, respectively, were analysed. In addition, 18 fetal cells were examined from amniotic fluid obtained at 16 weeks of the mother's second pregnancy.

In the proband, all cells showed 46 chromosomes, including a single chromosome 21 and another chromosome which, on G banding, was found to be a reverse tandem translocation of two 21s joined together near the telomeres of their long arms (fig 3a). C banding showed the presence of dark staining material at each end of the translocation chromosome (fig 3b), and silver-staining\(^4\) showed a nucleolus organiser region (NOR) also at each end of the chromosome (fig 3c, d). In some cells, a centromere was visible only at one end of the chromosome with the other end open, probably because of centromere inactivation, and here also a C band or silver-stained NOR was recognisable. In all cells analysed, the translocation chromosome was of the same relative size and banding pattern, indicating a high degree of stability. No short structures or chromosome fragments were observed.

In order to establish the breakpoints on the two chromosomes 21 involved in the translocation, the distance between the two centromeres in this translocation chromosome and the length of the long arm of the single chromosome 21 were measured in 16 photographed G banded early metaphase cells. The intercentromere distance of the translocation chromosome (mean = 18·31 units ± 1·40) was twice the long arm length of the single 21 (mean = 8·97 units ± 0·97). This established that the breakpoints were at the very distal end of the long arms of the two chromosomes. It was thus concluded that the karyotype of the proband was 46,XX,−21, + dic(21;21) (pter→q23::q23→pter)\(^{3a}\).

In all the mother's cells examined, an atypically long secondary constriction extending into both arms of chromosome 9 was noted (fig 3e). In this chromo-

some an extra G band was clearly visible in the short arm. The G-11 and C staining secondary constriction was not continuous throughout the centromere. A complete karyotype of the mother is shown in fig 4.

No peculiarities were found in the other maternal chromosomes or in the paternal karyotype. The amniocentesis fetal karyotype showed a normal 46,XY complement with a chromosome 9 variant identical to that in the mother. She subsequently gave birth at term to a phenotypically normal male.

Fluorescent studies and silver staining of the chromosomes from the proband and from her parents were not informative as to the parental origin of the child's extra chromosome 21.

**GENE DOSAGE**

Superoxide dismutase-1 (SOD-1) was measured in the red blood cells of the proband and her parents, using the method of de Chatelet et al.\(^5\) The enzyme level in the proband's cells was similar to the mean level in cells from 15 trisomy 21 patients and more than 50% greater than the mean level in cells from her parents, several other trisomies, and 22 normal controls.\(^8\)

**Discussion**

Identification of the triplicated portions of chromosome 21 in persons with partial trisomy 21, and comparison of the findings with phenotypic manifestations, provides a basis for determining which segments of that chromosome are crucial in the genesis of Down's syndrome. Recent advances in cytogenetic banding techniques have facilitated such studies. Using these techniques, a number of reports have been published (reviewed by Hagemeijer and Smit\(^7\) which provide evidence that trisomy of the distal 21q22 band (though not necessarily the whole of that band) is an essential concomitant of clinically recognisable Down's syndrome. In particular, several cases of inverted tandem translocations of chromosome 21 have been described. The recent well-documented account by Hagemeijer and Smit\(^7\) concerns a retarded child without a characteristic Down's syndrome phenotype who had a similar, but shorter, translocation chromosome than the one recorded here.

In our proband, the cytogenetic findings indicate that the breakpoints on the two chromosomes 21 involved in the tandem translocation occurred at the most distal end of the long arms (21q223), so that at least the q221 and q222 portions of the 21q22 band were present in triplicate. The unequivocal diagnosis of Down's syndrome, on phenotypic grounds, in this child is in keeping with previously reported observations referred to above. As in several other cases, the dicentric chromosome frequently appeared to have
only one functional centromere. This implies some mechanism for centromere inactivation in such chromosomes.

The locus for SOD-1 has been assigned to 21q22.8 These investigators suggested that trisomy for 21q221 is necessary to produce Down's syndrome and that excess SOD-1 is pathogenic for the syndrome. In the context of these observations, the increased activity of SOD-1 in our proband provides additional evidence that band 21q221 is trisomic in her case.

Of interest also in the family described here is the presence of an unusually long secondary constriction extending into both arms of a chromosome 9 in the phenotypically normal mother and brother of the proband. Somewhat similar 'inversions' of chromosome 9 are relatively common9 and there has been considerable debate about their possible deleterious consequences. Frequently, there have been no recognisably adverse phenotypic features in persons carrying such an 'inversion', as was the case in the present instance, though the mother concerned produced a child with a tandem (21;21) chromosome. We have been unable to find any record of a similar association, which suggests that it was coincidental in our family. Whether in fact this is so cannot be established with certainty on the evidence available.

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References


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Ring chromosome 10:
46,XX,r(10)(p15→q26)

SUMMARY Cytogenetic analysis of an 8-month-old Japanese girl with moderate retardation of physical development was performed and a ring chromosome 10, 46,XX,r(10)(p15→q26), was found. She had short stature, mildly stubby nose, antimongoloid slants, and moderately protruding ears. The extremities showed erythrocyanosis, oedema, and pigmentation. Lansky et al1 was the first to describe ring chromosome 10 with a Turner-like phenotype. Only two other cases3 have been reported so far and little is known about this syndrome. This is the report of a fourth case.

Case report

The proband, an 8-month-old Japanese girl, was born on 26.6.75 to a 23-year-old, gravida 1, para 1 mother and a 27-year-old father. The parents were unrelated, healthy, and of normal height and intelligence. At 3 months' gestation, her mother showed signs of threatened abortion and was injected with HCG five times. After 42 weeks of gestation, the patient was delivered spontaneously in breech position. Birthweight was 2500 g and Apgar score was 8 at 5 minutes. The newborn baby appeared normal but had feeding difficulties. At 6 months, she was sent to us because of retarded growth. At that time, her weight, length, head and chest circumference were 5300 g (−2.4 SD), 60.3 cm (−2.4 SD), 38.8 cm (−2.6 SD), and 37 cm, respectively. Her face had a mildly stubby nose, antimongoloid slants, strabismus, and moderately protruding ears (fig 1). Erythrocyanosis, oedema, and pigmentation of both feet, as seen in incontinentia