

Case reports

15-month-old white male. He had psychomotor retardation and severe failure to thrive. His congenital anomalies were microcephaly, bradycephaly, cleft lip and palate, and flat nose.

Thus far, patients with 7q- share only a few features in common, i.e. mental and growth retardation and microcephaly. Hopefully, when more patients with 7q- are identified, a better clinical delineation of this abnormality will be possible.

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Down's syndrome and deletion of short arms of a G chromosome

SUMMARY A woman in a family in which a G group chromosome (No. 21) with deleted short arms (21p-) is present has passed this chromosome to an intellectually deficient son, a normal son, and a daughter with Down's syndrome. Another daughter is chromosomally and phenotypically normal. As in other reports that focus on a concurrence of Gp- chromosomes and Down's anomaly, the possibility is considered that this chromosomal variant may predispose to developmental abnormalities or to non-disjunction, or both.

There are a number of reports of heritable structural variations of the chromosomes being associated with families with both normal and abnormal phenotypes (Gardner *et al.*, 1974; Neu and Kajii, 1969), including familial variants affecting the short arms of the G group chromosomes (Neu and Kajii, 1969;

Neu *et al.*, 1966; Jagiello and Faiman, 1967; Migeon, 1965; Shaw, 1962). Distinct from this functional aspect is the question of the relation between such variants and the occurrence of non-disjunction, a relation which might be inferred to exist in families in which a minor rearrangement and aneuploidy occur together (Neu *et al.*, 1966; Shaw, 1962; Starkman and Shaw, 1967).

At present it is difficult to establish, in any particular instance where they are associated, that the presence of an abnormal phenotype in one sibling or of aneuploidy in another is due to the presence of a small chromosome variant in one of the parents. The genetic and clinical significance of such variants is likely to remain obscure until enough cases are reported for statistical inferences to be made about possible predispositions. This report describes a family in which both clinical abnormalities and aneuploidy are associated with a chromosomal variant.

Case report

A boy aged 6 years 9 months and unable to read was seen at the Child Health Clinic, Hamilton, New Zealand, in 1969. He was the second sibling of Dutch parents, delivered normally after a full-term, normal pregnancy with a birth weight of 4308 g. He was reported to cry well at birth but to suck poorly for three days after delivery. His motor, language, and toilet milestones were slow in appearing and a psychometric assessment at 6 years 4 months indicated an intelligence quotient of 50 to 60.

Investigations for thyroid function; bacterial inhibition tests for metabolic errors; urine amino-acid chromatography; fasting blood sugar; and urea, calcium, and serum proteins were normal. He had a history of normal electroencephalograms and there were no abnormal neurological signs. His hair was fair and, apart from showing mild atopic eczema, he had a normal facial appearance. There was mild clinodactyly of the fifth fingers, which also had rather underdeveloped nails.

Chromosome studies of cultured peripheral leucocytes showed that all cells carried a G chromosome with deleted short arms. Giemsa banding established this chromosome as No. 21 (karyotype 46,XY,21p-) (Fig. 1 and 2). Karyotypic analyses of the mother and older brother showed that they also carried the 21p- chromosome (Fig. 3). Like the index case, both showed mild clinodactyly of the fifth fingers. The father's karyotype was normal as was that of a younger female sibling. The mother's second pregnancy ended in a miscarriage at 11 weeks.

There were no indications of consanguinity but a

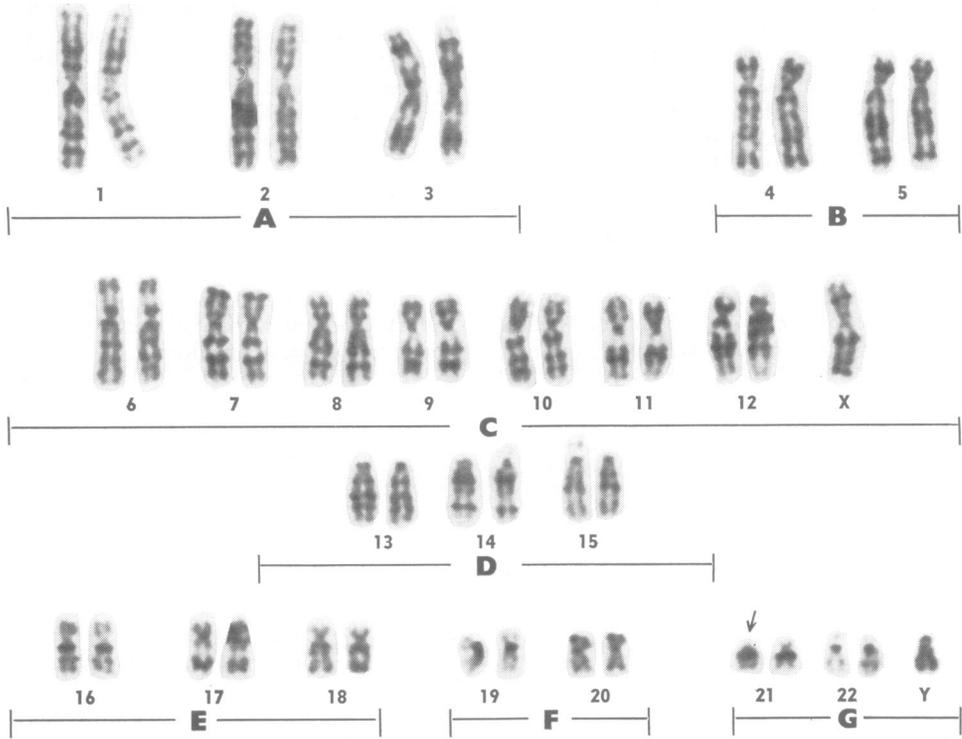


Fig. 1 Giemsa banded karyotype of proband showing 21p- chromosome (arrow).

maternal uncle had exhibited possible mental deficiency. He was reported to attend a sheltered workshop in Holland but to be able to read.

In August 1973 the mother, aged 36, gave birth to a girl with Down's syndrome who had the typical clinical features of this condition (Fig. 3). Chromosome analysis revealed trisomy 21 with one of the 21 chromosomes having deleted short arms.

Discussion

The autosomal variant (21p-) segregating in this family is associated with both normal and subnormal

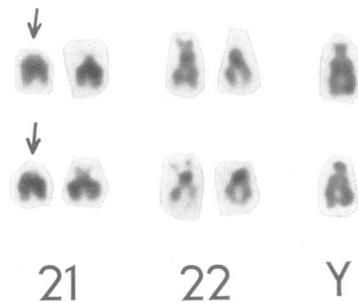


Fig. 2 Partial karyotypes of two cells from proband showing short arm deletions of a No. 21 chromosome (arrows).

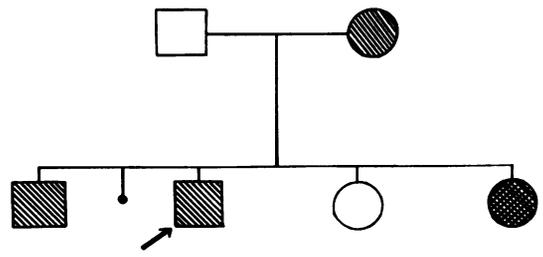
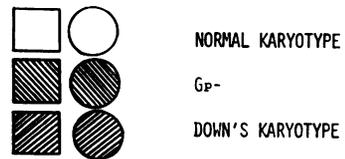


Fig. 3 Pedigree of proband.

(non-Down's) phenotypes, as well as with Down's syndrome. While possibly the two former states reflect the hemizygous expression of allelic variation on the short arms of the paternally-derived 21 chromosomes, direct evidence for a causal relation between variant and pathology (in this case mental deficiency) is lacking. Most other Gp- cases that we are aware of have not involved identification of the variant chromosome, and so are neither corroborative nor contradictory. Thus a number of different diseases have been found in patients and members of their families bearing Gp- chromosomes, including anomalous pulmonary venous return (Migeon, 1965), Albright's syndrome (Šubrt and Brychnáč, 1966), antimongolism (Kelch *et al.*, 1971), and pseudoachondroplasia (Neu *et al.*, 1966). Only one case of mild mental retardation with minor Down's features is reported in association with a Gp- (Shaw, 1962). On the other hand there are also unaffected persons carrying a Gp- in some of these families (Neu *et al.*, 1966; Migeon, 1965; Shaw, 1962) and in other families (Yoshida and Honda, 1969), and population surveys suggest a Gp- frequency in the general population of between 0.1 and 1.0 per 1000 (Nielsen *et al.*, 1974).

The gathering and reporting of families bearing identified Gp- chromosome is also desirable with respect to the possibility of their predisposing to non-disjunction. At least two previous reports have linked Gp- chromosomes and Down's anomaly. Shaw (1962) studied a family in which a woman bearing a Gp- chromosome produced two normal and three Down's syndrome (47,XX or XY,+G) children. Both normal offspring inherited the Gp- as did one of the Down's syndrome cases (Fig. 4). The G chromosomes in the other Down's syndrome cases were normal. The occurrence of the latter indicates that non-disjunction took place in the second meiotic division of oogenesis. The mother in this case had high axial triradii and appeared slightly retarded.

The second previous instance is reported by Neu *et al.* (1966). A woman aged 25 and carrying a Gp- chromosome produced a child with Down's syndrome showing trisomy G with no Gp- chromosome present (Fig. 5). The mother had a single transverse flexion crease on the right palm. The Gp- chromosome was not identified in this family, nor in the Shaw family.

Taken together these two families plus the present family may provide a case for increased susceptibility to non-disjunction in women carrying a G(21)p- chromosome. The physical basis for such a predisposition effect could be understood in terms of the satellite and nucleolar associations with which the short arms of 21 chromosomes are usually in-

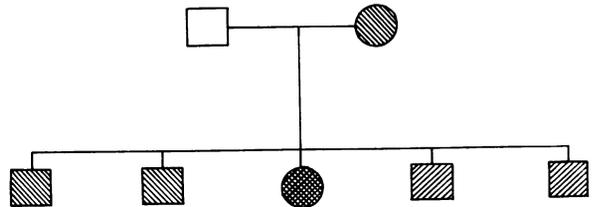


Fig. 4 Pedigree of family reported by Shaw (1962).

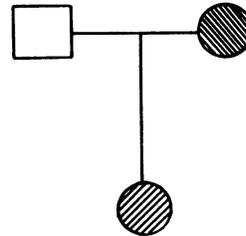


Fig. 5 Pedigree of family reported by Neu *et al.* (1966).

involved. A Gp- chromosome left out of such an association is likely to be especially prone to mis-segregation. The trisomic state resulting from such behaviour, however, is expected to include the Gp- chromosome. This expected result has occurred in the family reported here, and in one case in Shaw's family (Shaw, 1962).

It is more difficult to explain an increased tendency to nondisjunction for the normal 21 homologue in the second meiotic division, an event that is inferred from those Down's offspring with three normal 21 chromosomes. The abnormal Gp- should play no role, unless indirectly through some prior effect produced during the first division.

There are clear indications for hereditary factors (including rearrangements) predisposing to non-disjunction, especially in such organisms as *Drosophila* (Baker, 1975) and maize (Breg, 1969), but also in those human families in which there is a clustering of aneuploid conditions (Breg, 1969; Leary *et al.*, 1975; Soudek *et al.*, 1975; Grell, 1971). A situation in some ways analogous to the one under discussion, and one which tends to support the argument that the presence in a family of a Gp- chromosome concomitant with Down's anomaly is not coincidental, is found in *Drosophila*. Increased non-disjunction has been demonstrated in strains of *D. melanogaster* which carry certain types of rearrangements—namely, the compound autosomes (Baldwin and Chovnick, 1967). These chromosomes are produced by centromere-adjacent breaks in a metacentric

autosome, with subsequent rejoining between two left arms and between two right arms, respectively, of that autosome. Relative to their former positions, the centromeres in such compound chromosomes are effectively terminal or 'exposed.' One consequence of this is a significant increase in the frequency of non-disjunction among such chromosomes (Holm *et al.*, 1967). In the human situation an 'exposed' centromere of a Gp- chromosome would tend to produce irregularities in the normal disjunction of this chromosome and its homologue.

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