Case reports

Journal of Medical Genetics, 1984, 21, 216–230

Fragile site at 12q13 associated with phenotypic abnormalities

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SUMMARY A dysmorphic 3 year old boy with severe psychomotor retardation is described. His karyotype was 45,XY,t(13q;14q)rob, fra (12q13). The relationship between fra(12q13) and the clinical picture is discussed.

Constitutional fragility of a number of human chromosomes, often familial, has been described. The breaks are always localised at the same points on the same chromosomes. Sutherland1 reported the factors enhancing or suppressing the frequency of fragile sites on chromosomes from lymphocyte cultures. The significance and aetiology of this phenomenon in man is not yet clear.

A relationship between phenotype and chromosome fragility has been confirmed only in cases of the fragile X. A fragile site at 12q13 has been described by Giraud et al2 and Donti et al.3 Sutherland and Hinton4 documented the existence of fra(12q13) in a kindred in which six members in five generations had this aberration, but without clinical abnormalities.

We have observed a dysmorphic boy with mental retardation and a karyotype 45,XY,t(13q;14q)rob, fra(12q13).

Case report

The proband, a male, was born in July 1980 to non-consanguineous parents, when the mother was 23 and the father 30 years old.

The first pregnancy ended in early miscarriage. In the second pregnancy a male child was delivered before term (weight 1500 g) and subsequently died. A normal male child was born after the proband in August 1982.

The proband, delivered by vacuum extraction, had asphyxia livida, weight 3500 g, length 49 cm, head circumference 34 cm, and Apgar score 8. He was admitted to hospital three times with respiratory infections. Arthrogryposis or cerebral palsy were diagnosed. Seizures with loss of consciousness started in the 16th month. The proband was examined twice, at 16 months and 3 years old (fig 1).

Physical examination at the age of 3 showed: weight 14·5 kg, height 91 cm, square shaped head with a circumference of 49 cm, round face, pro-tuberant forehead, simplified low set ears, deep set eyes, blue irides with Brushfield spots, high palate, small chin, and short broad neck. The hands were clenched until the boy was 3 years old, and the thumbs remained opposed and flexed on the palm.

FIG 1 The proband at 16 months (a, b, c, d) and at 3 years of age (e).
Discussion

The fingers were abnormally long and very small distally. He had a small penis (1 to 1·5 cm) and a small empty scrotum. The lower extremities were hypotonic, the heels were dislocated backwards, and he had long toes with the big toe in dorsal flexion. Reflexes could be elicited symmetrically. There was marked muscular hypotonia and he could hold his head up but could not sit without support. He made sounds but had no words. He still does not follow objects with his eyes and his vision seems to be poor. He cannot grasp things voluntarily. Psychomotor retardation is considerable (estimated IQ around 30 to 35). Contractures of joints or muscles are not evident but there is a stiff and inflexible turgor.

Laboratory Examinations

Radiological examination showed a normal cranium apart from some prominence of the frontal part and oblique anterior fossa. Scapulae and shoulders showed a congenital deformity of the Sprengel type. Maturation of the bones corresponded to age. Biochemical findings were normal and the ocular fundus and EEG were normal.

Cytogenetics

In the first instance, peripheral blood was cultured in TC 199 medium + 20% human AB serum. GTG banding was used for the chromosome analysis. A Robertsonian translocation (13q;14q) was present in all 80 cells examined. In addition, a fragile site at 12q13 was observed in eight cells (10%) (fig 2). In two cells the loss of part of 12q was observed and the whole chromosome 12 was missing in one cell. The father's karyotype was 45,XY,t(13q;14q)rob (30 cells analysed) and the mother's was 46,XX (35 cells analysed).

A further blood culture was set up using the same tissue culture medium but with only 5% fetal calf serum.

The fragile site at 12q13 in the proband's karyotype was more evident and it was seen in eight out of 20 cells (40%). No fragile sites were found in 42 and 51 cells analysed from the father and the mother respectively. The karyotype of the proband's normal brother was 46,XY.

Discussion

There are only few reports of a fragile site at 12q13 associated with phenotypic abnormalities. Giraud et al2 reported two cases of fra(12q13). One was of a boy "with severe mental retardation and multiple complex malformations", and the other was the mother of a malformed infant whose karyotype was normal. No details of the clinical picture of these cases were given.

However, the clinical and cytogenetic findings reported by Donti et al3 are very similar to those of our proband, including a round head, small chin, large low set ears, abnormally long fingers with the thumb opposed and flexed on the palm, and considerable psychomotor retardation. Cytogenetic findings are also similar in both cases, except for the 13q;14q Robertsonian translocation in our proband which was transmitted from the father. In neither case is the fragile 12 familial. Donti et al3 could not compare the clinical picture of their proband with any known syndrome as this was the first well documented case and therefore they could not exclude or confirm the influence of the fra(12q13) on the phenotype.

Although the proband of Donti et al3 and our case were examined at different ages the similarity of the clinical picture is striking. It is possible that the phenotypic abnormalities are caused not just by the presence of the fragile site but by the consequent loss, in some cells, of a large part of 12q. This monosomy may be more frequent in cells of other tissues, such as the brain, disturbing normal development and producing specific clinical features. The stability of the karyotype could be affected by the translocation 13q;14q, thus resulting in a new chromosomal aberration.

References


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Fig 2 Different appearances of chromosome 12 of the proband: (a) without fragile site; (b, c) fragile sites; (d, e) loss of the long arm (12q13→qter).
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doi: 10.1136/jmg.21.3.216

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