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Reproductive failure in a carrier of inv dupl 1(q21.4→q12)

Draga TONCHEVA, Penka GENKOVA, Maria TZONEVA, Tanka LOZANOVA, Elena ANGELOVA, Bogomila MITREVA

Department of Medical Genetics, Medico-Biological Institute Medical Academy, Sofia, Bulgaria

High resolution analysis of the early metaphase and prometaphase chromosomes of the father of a child with malformations and mental retardation revealed inv dupl 1(q21.4 → q12). Almost the same was the aberration in the propositus but with a deletion of the band 1q11.2 : 46,XX, inv dupl 1(q21.4→q12)del 1q11.2. This suggested that the malformations and mental retardation in the child were probably due to the microchromosome anomaly in the euchromatin, connected with the heterochromatin block in the father.

Malformations and mental retardation were observed in a child with extreme amounts of heterochromatin lqh+. Although these data contradicted the view of the innocuous effect of this chromosome polymorphism upon the phenotype, there still remained the problem what kind of chromosome variants create phenotype alterations [1, 3, 4, 7]. High resolution G-banding analysis of early metaphase and prometaphase chromosomes might widen the possibilities of the C and Q banding methods in approaching this problem. In this respect it was of interest to study G-banding patterns of the heterochromatin region (lqh+) in early metaphase and prometaphase chromosomes in a man with reproductive failure.

REPORT OF A CASE

The proband VCV, 18 months of age, was a liveborn female child from a second pregnancy. The child was born before term with 970 g weight and 37 cm length.

The first pregnancy ended with a stillborn male fetus and the third one with a spontaneous abortion accompanied by grave metrorrhagia.

At the time of delivery the mother was 24 years old and the father 26 years old. They denied blood relationship.

The weight gain of the child was slow. Clinical examination revealed severe mental retardation, spastic congenital quadriparesis and microcephaly with temporal depression, small forehead and low hairline (Fig. 1). The tongue was large, the teeth were regularly arranged. A high arched palate and bilateral syndactily of the middle two toes were found.

Neurologic examination revealed muscle hypertony, especially in the legs with contractures of the adductors and Achilles tendons.

Psychologic examination showed anxiety and loss of social adjustment.

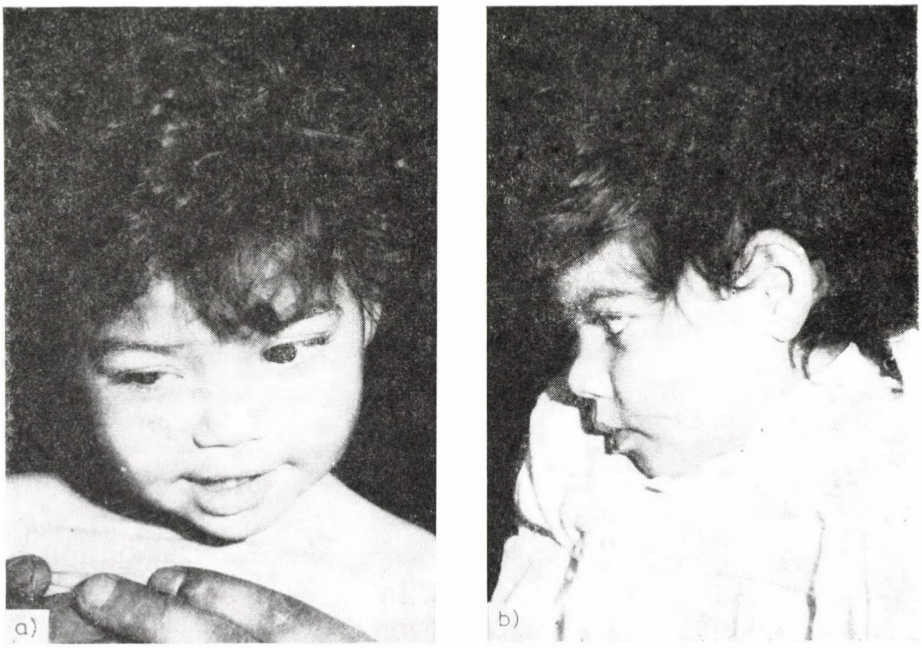

FIG. 1. A and B The proband

Cytogenetic study

Chromosomal study of the parents was performed by means of peripheral blood leukocyte culture. For high-resolution G-banding prometaphase analysis, chromosomes were obtained by a slight modification of the technique of Yunis [10].

The mother's karyotype was 46,XX with normal G-banding patterns. The father's karyotype was 46,XY, lqh+. High resolution G-banding analysis demonstrated an abnormality in one member of the 1st pair of chromosomes: the long arm was 1/3 larger than that of its homologue. The centric heterochromatic region was enlarged and almost doubled, as demonstrated with specific C-banding (Fig 2).

The central part of the chromosome was occupied by a hypochromic band. Thus, the father's karyotype was 46,XY, inv dupl 1(q21.4 → q12) (Fig 3). We suppose that the breakpoint was between lq21.4 and lq21.5. In all stages of chromosomal contraction, clearly demonstrated in the early metaphase and prometaphase, an elongation of band lq11.2 was seen in the derivative chromosome (Fig 4).

Similar was the G-banding pattern of the proband's karyotype, but band lq11.2 was absent in all analysed cells which at 800 G bands differentiation was identified as del lq11.2 (Fig 5). The severe phenotypic anomalies in the propositus probably resulted from an unbalanced rearrangement (karyotype: 46,XX,inv dupl 1(q21.4 → q12)del lq11.2.)

FIG. 2. C-banded 1st chromosome from the father

DISCUSSION

In the father's karyotype, analysis of G-banding of the early metaphase and prometaphase chromosomes revealed inv dupl 1(q21.4→q12). In the proband's karyotype the marker chromosome (lqh+) had lost the band lq11.2, resulting in partial deletion in this region, and affected the phenotype.

Our data correlate with the view that the unusually large heterochromatin variants might affect the phenotype by causing a greater frequency of chromosome rearrangements with genetic imbalance [2, 6, 8, 9, 11].

G-banding prometaphase chromosome analysis in combination with C-banding is a reliable approach to study the problem of chromosomal polymorphism. While the C-banding

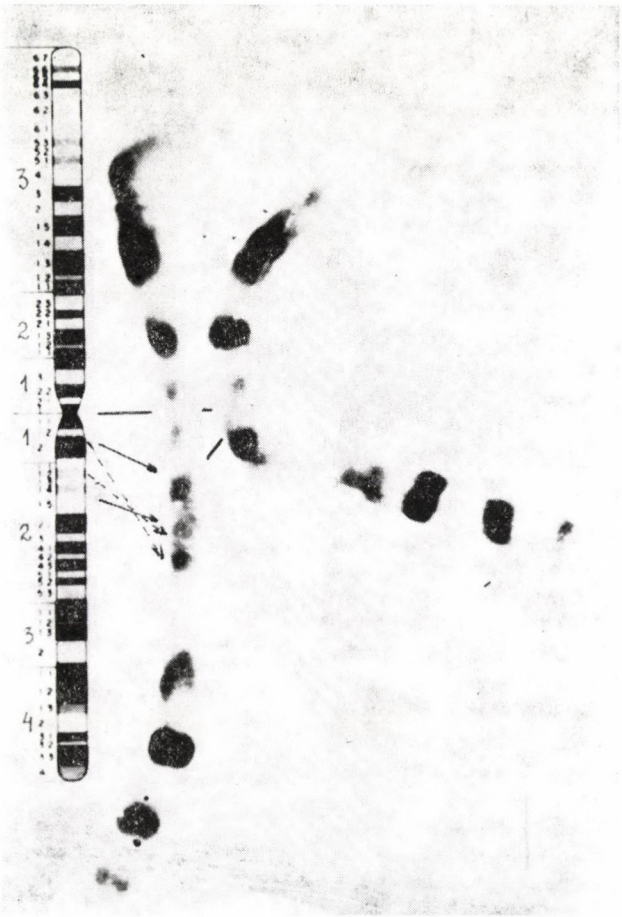

FIG. 3. G-banded 1st chromosome from the father (inv dupl 1/q21.4 q12). Diagram of chromosome illustrating the proposed breakpoints and the resulting inversion [Yunis, 10]

method demonstrates the heterochromatin region as a whole block, the G-banding method of early metaphase and prometaphase chromosomes gives information about the fine structure of these segments.

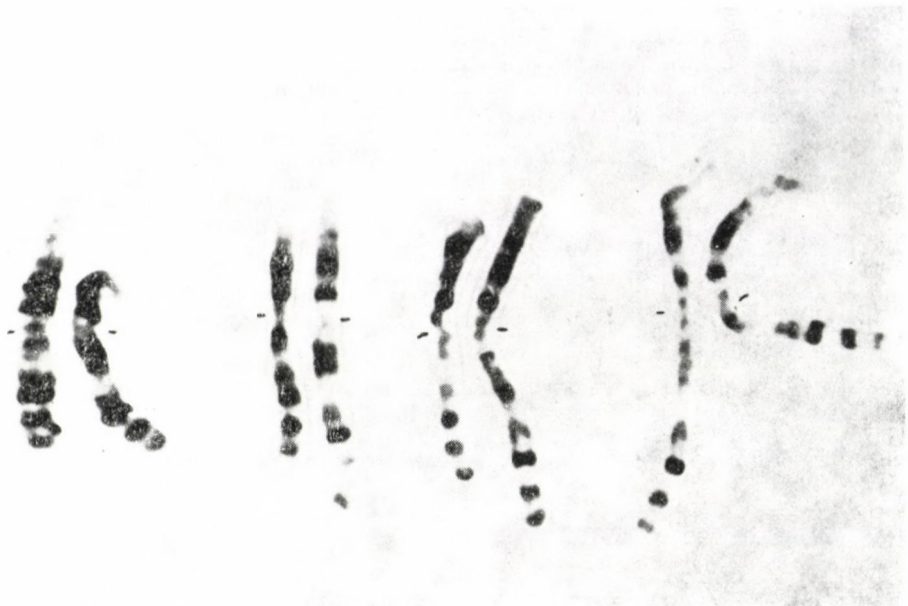

FIG. 4. Early metaphase and prometaphase chromosomes No. 1 of the father after G-banding

FIG. 5. Early metaphase and prometaphase chromosomes No. 1 of the propositus after G-banding

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D Toncheva MD
8 Belo more str
1527 Sofia, Bulgaria