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Unusual chromosome aberrations in 3 children with Down syndrome

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In 3 children with Down syndrome extremely rare chromosome aberrations were found. In the first patient, the karyotype showed 46 chromosomes with a de novo duplication of the q22-qter segment. This finding supports that the 21q22-qter band was responsible for the characteristic mongoloid features. In the second case, trisomy 21 was present and out of 78 investigated cells, 60 contained a small, supernumerary marker chromosome in addition to trisomy 21. The parents were cytogenetically and clinically normal. In the third case trisomy 21 with inv(10) (p13q22) occurred. The inversion was inherited from the mother with diminished fertility.

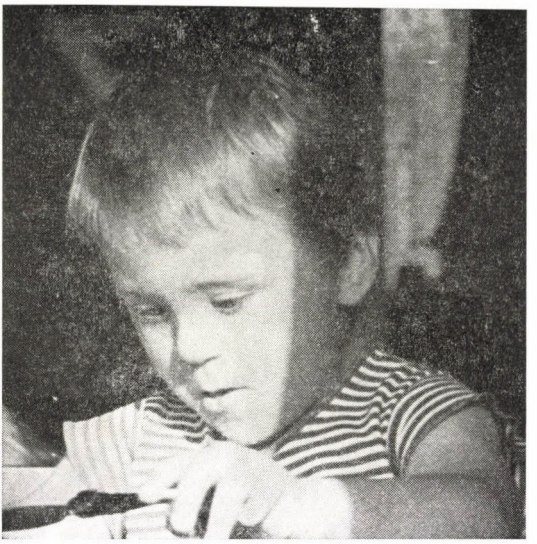
Chromosome aberrations other than regular and Robertsonian translocation trisomy 21 are rare in patients with Down phenotype. The number of observations on trisomy 21 resulting from the fusion of the telomeric regions of the long arms of the two chromosomes 21 amount to about 10 [4, 6, 13, 14, 18, 26, 27, 32, 33]. Trisomy 21 as a result of a parental translocation of chromosome 21 with a non-acrocentric chromosome has been reported by several investigators [1, 2, 5, 11, 12, 15, 16, 17, 19, 20, 21, 24, 29, 35, 36]. Trisomy 21 with other chromosomal imbalance also occurred in some cases; these have been summarized by Schwanitz and Hagner [28].

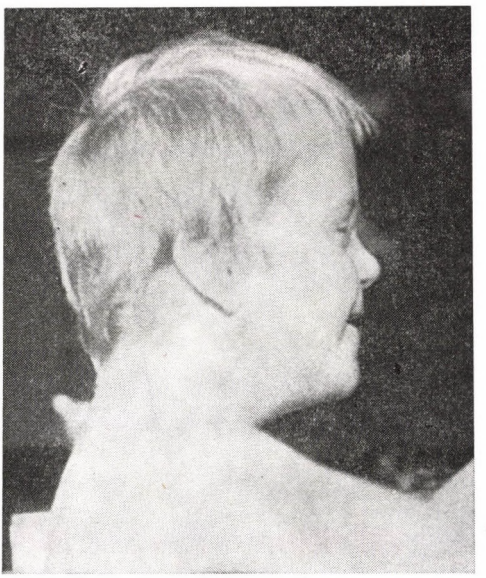
We describe here 3 patients with clinical features of Down syndrome whose karyotypes showed extremely rare aberrations.

Case No. 1

V. H., a female patient (Figs 1 and 2) was referred to chromosome investigation when her mother had become pregnant for the second time.

At birth, her mother was 26 and her father 29 years old. Both are healthy. The patient was born after a normal pregnancy in the 39th week of gestation. Birth weight was 2850 g, length was 54 cm. There was no complication after delivery. Down syndrome was detected clinically in infancy and the baby was sent for chromosome analysis to two different laboratories; both found a normal karyotype. At 3 years of age, the child could not speak, she showed many signs of craniofacial dysmorphia characteristic of Down syndrome including oblique palpebral fissures, epicanthus, flat occiput, flat facial





FIGS 1—2. Patient No. 1 at 3 years of age

profile, small nose and small mouth, short neck, small ears. Her hands were broad, with short fingers, clinodactyly and unilateral transverse palmar crease. An umbilical hernia was also present.

Karyotype analysis of a peripheral blood culture showed 46 chromosomes in the cells and one of the chromosomes 21 was structurally abnormal. The long arms of this chromosome were elongated, as a result of the

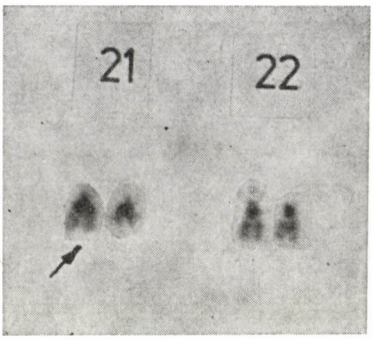


FIG. 3. Patient No. 1. Chromosomes 21—22 from the karyotype

elongation of segment q22-ter (Fig. 3). Duplication of the chromosome segment 21q22-qter has been supposed. The karyotype of the parents was normal.

Case No. 2

The boy Z. M. was 2 years old at the time of chromosome investigation. He was born when the mother was 36 and the father 35 years old. This was the 8th pregnancy of the couple. From the first pregnancy, 16 years before the proband's birth, a normal, healthy boy was born. In the subsequent years, 7 pregnancies were interrupted artificially. The parents are healthy. The mother has a mentally retarded brother, 15 years her junior, who was born when his mother was 39 years of age. The family did not agree to his examination.

Delivery took place after normal pregnancy at term. Birth weight was 3000 g, length was 57 cm. There was no perinatal complication. The patient seemed to be mongoloid, having brachycephaly, flat occiput, flat face,

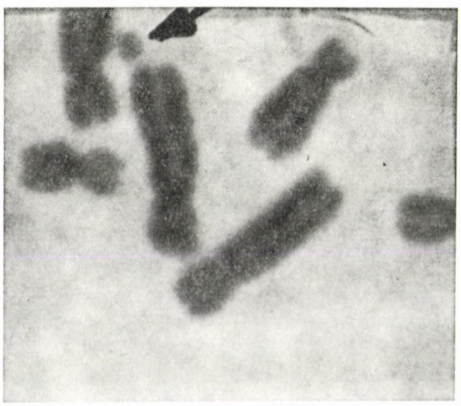


FIG. 4. Patient No. 2. The small marker chromosome in a mitosis

mongoloid palpebral fissures, epicanthus, small nose, small mouth with protruding tongue and a short neck. Hypotonicity and hyperflexibility were also observed, with severe mental retardation.

Cytogenetic investigation of the peripheral blood culture revealed in 60 investigated cells trisomy 21 and, in addition, a minute supernumerary chromosome (Fig. 4). In further 18 cells the marker chromosome was not present. The patient's karyotype was defined as 47, XY, +21/48, XY, +21, +mar; the karyotype of the parents was normal.

Case No. 3

A. B., a gypsy girl, was seen at the age of 3 years. She was born from the third marriage of her mother who was pregnant only twice during a period of 20 years. One pregnancy ended in spontaneous abortion at about the 10th week of gestation. After 17 years, the proband was born from the second pregnancy when the mother was 39 and the father 36 years of age. Both are healthy.

The external appearance of the patient was typically mongoloid. She had no congenital visceral malformation.

Cytogenetic investigation showed a supernumerary chromosome 21 and besides a structurally abnormal chromosome 10 that was stated as inv(10) (p13q22) (Fig. 5). In the maternal karyotype the number of chromosomes was 46; the inv(10) aberration was also present. The father had a normal karyotype.

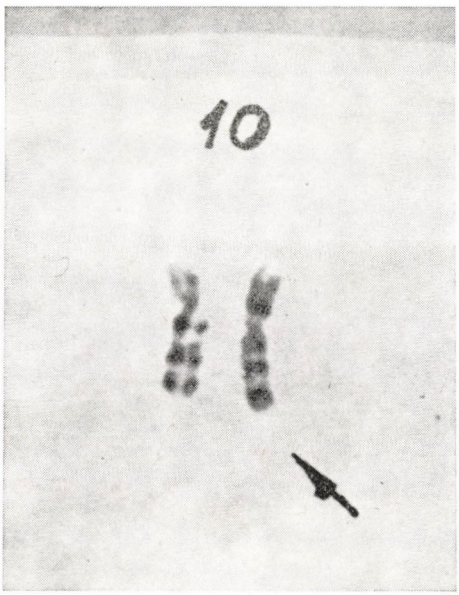


Fig. 5. Patient No. 3. Normal chromosome 10 and its homologous one with pericentric inversion

Discussion

De novo duplication within the same chromosome in abnormal individuals, as in our patient No. 1, has been observed by some authors [8, 10, 31, 32, 34]. Analysing these cases, Vogel et al. [34] stated that the most likely explanation for this aberration type is a translocation between the homologous chromosomes during meiosis. Studying the different cases of partial trisomy 21, several investigators indicated that the trisomy of band q22-qter on chromosome 21 was responsible for the clinical characteristics of Down phenotype [13, 20, 25, 35, 36]. Our observation supports this statement. The rarity of this type of partial trisomy 21 explains why at two previous investigations the karyotype with a chromosome number 46 was declared to be normal although the patient's appearance left no doubt that he had Down syndrome.

Trisomy 21 with a supernumerary minute chromosome was found previously by Calabro et al. [3]. In their case, the small marker chromosome had segregated from the father. In two other cases [22, 23] recurrence of Down syndrome was observed in the investigated families; the subjects with Down syndrome had only trisomy 21, the microchromosome was carried by healthy family members. Ramos et al. [23] assumed the possibility of a connection between the meiotic non-disjunction and the familial occurrence of microchromosomes. In our case, the supernumerary minute chromosome without any modifying effect on the Down phenotype was considered a de novo aberration appearing in mosaic form. Still, we could not exclude an unidentified low rate mosaicism in one of the parents and the absence of the small marker chromosome may have been due to its loss during preparation.

As far as we know, trisomy 21 with inv(10) aberration has not yet been observed in the same subject. This aberration, inherited from the mother, did not alter the mongoloid appearance of patient No. 3. It may have played a role in the diminished fertility of the structurally heterozygote mother. While De la Chapelle et al. [7] concluded that the pericentric inversion of chromosome 10 segregated without consequences, Dutrillaux et al. [9] described a recombinant chromosome 10 in a malformed boy whose mother had inv(10). Recently, inv(10) (p13q22) has been found in our laboratory in a man whose wife had repeated spontaneous abortions. All these data call for further studies definitely to clarify the importance of inv(10).

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