

A 45,XY,5-15-,t(5q15q) Cri-du-Chat Child*

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Translocations involving the B chromosome occur with greater than expected frequency in relatives of cri-du-chat cases, but only rarely in the karyotype of the proband. Thus, De Capoa *et al.* (1967) reported 3 families with presumed or identified balanced translocation carriers and reviewed 5 similar families. In all of these families, the individuals with the cri-du-chat syndrome had a deleted B chromosome short arm as a result of meiotic segregation in a parent. In contrast, only one cri-du-chat case has been reported in which the proband's karyotype had a translocation directly resulting in the deletion of a portion of the short arms of the B chromosome (Wolf *et al.*, 1966). This report describes a second cri-du-chat case with a unique translocation involving chromosomes 5 and 15 and resulting in loss of B short arm material.

Case Report

The patient, a male, was born on 28 June 1967 after a pregnancy of normal length, marked only by slight maternal bleeding in the first trimester. At birth the infant weighed 2430 g. and had no signs of foetal distress. On initial examination the paediatrician noted the abnormal cry and facial features of the cri-du-chat syndrome. He was first seen by us at 12 weeks of age at which time he appeared healthy. He weighed 4425 g., measured 46 cm. in length, with a head circumference of 33 cm. The child was feeding well and had no interval history of illness. Physical examination showed hypotonia, a round face, obvious microcephaly, hypertelorism, epicanthal fold with a slight downward slant of the lateral canthus of the eyes, low-set ears, and micrognathia. No strabismus was evident (Fig. 1). The cry was the typical high-pitched cry of the cri-du-chat syndrome, but there were no obvious oral or pharyngeal anomalies. The chest and heart were normal. The feet appeared normal, and the hands showed incurving of the 5th digit bilaterally with single palmar flexion creases bilaterally. X-ray studies showed a small cranial vault, small mandible, reduced supraglottic air space, and shortening and triangular configuration of the 5th middle phalanx

bilaterally. At the time of the child's birth, the father's age was 33, the mother's 27, and there was an older female sib aged 23 months (Fig. 2). All of these family members were normal. There was no history of congenital malformations in either parent's family.

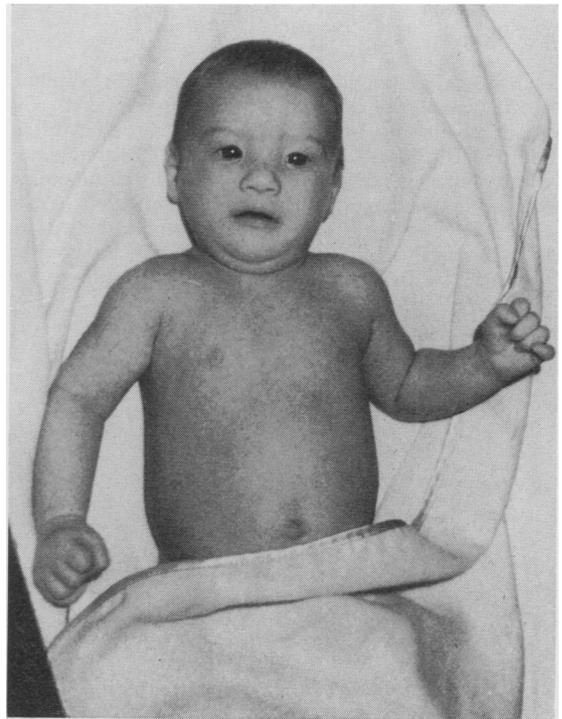


FIG. 1. The proband at age 12 weeks. Note the slight downward slant to the lateral canthus of the eye, micrognathia, and clinodactyly of 5th digits.

Chromosome studies were performed on lymphocyte cultures grown and treated in the standard manner (Hungerford, 1965). The study of the proband showed a modal chromosome count of 45 with a karyotype as shown in Fig. 3. There were only three B group chromosomes and five D group chromosomes, and an extra chromosome was present which had the size and configuration of a No. 2 chromosome. This chromosome was interpreted as a translocation between a B and D

Received 5 December 1969.

* Aided by Grant CE 34 from the National Foundation—March of Dimes.

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chromosome, with loss of all or part of the short arms of the involved B. The translocation chromosome was present in all karyotypes. In addition, 2 of 100 cells examined showed an extra minute chromosome which had the appearance of an acentric fragment. The karyotypes of both parents and the older sib were normal.

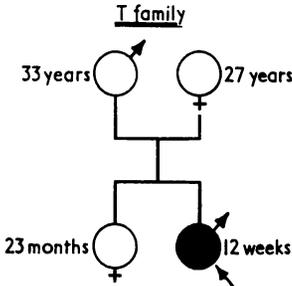


FIG. 2. Pedigree of the T family.

Autoradiographic studies were done using ^3H -thymidine in the lymphocyte cultures at a concentration of $1 \mu\text{Ci/ml}$. of medium for 3 hours, with colchicine added for an additional 3 hours before harvesting. The autoradiographs showed that the translocation chromosome labelled in a manner distinguishable from the No. 2 pair (Fig. 4). Two of the three B chromosomes labelled late and one early. Only one early labelling D chromosome was seen. This is interpreted as showing a translocation between a No. 5 and No. 15 chromosome ($45,XY,5-,15-,t(5q15q)$) (Fig. 4).

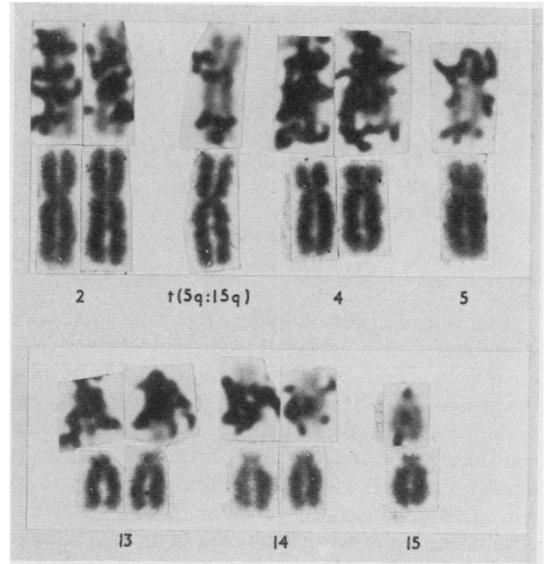


FIG. 4. Autoradiograph of chromosomes 2, $t(5q:15q)$, 4, 5, 13, 14, 15.

Genetic marker studies were performed by Dr. F. H. Allen of the New York Blood Center. The proband was heterozygous at the MN, Duffy, Kidd, Gm, and haptoglobin loci. The results indicated that there were no apparent exclusions to the usual inheritance of the blood groups in the proband or any other member of the family.

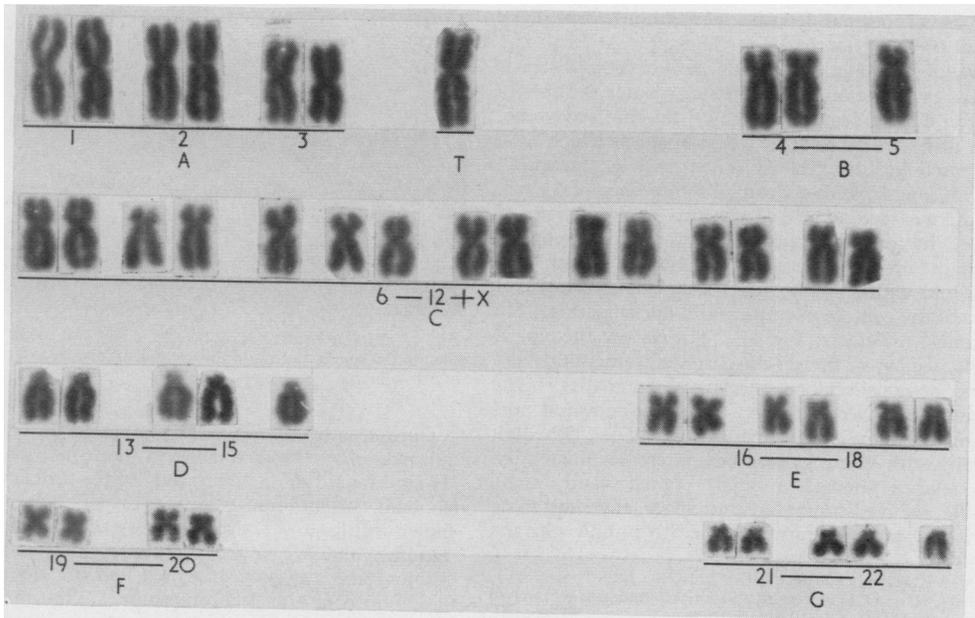


FIG. 3. Karyotype of the proband. Translocation chromosome morphologically resembles a No. 2 chromosome.

Discussion

This infant has most of the typical findings of the cri-du-chat syndrome without having the usual karyotype containing a deleted B chromosome. Instead there is a translocation involving a 5 and 15 chromosome, presumably resulting in loss of all or part of the short arm material of chromosome No. 5. In two karyotypes there was an extra chromosome fragment which was approximately the same size as the short arms of a B chromosome. Because of its small size, it is impossible to tell if it is centric or acentric and its significance is questionable. Since neither parent carried a translocation, it is conceivable that a translocation occurring at meiosis could preserve a minute chromosome fragment of this size in a small number of cells. No other tissues were studied, so the extent of this 'mosaicism' is unknown. However, the patient's clinical manifestations suggest that the fragment is not significantly modifying the cri-du-chat syndrome as presented.

Chromosome translocations apparently occur relatively frequently in families of individuals with the cri-du-chat syndrome. However, most of these are balanced translocations in the carrier, and it is only when the translocation chromosome is segregated at meiosis that the B chromosome deletion syndrome (cri-du-chat) occurs clinically. Of the 7 identified B chromosome translocations in cri-du-chat families, 4 involved D group chromosomes, 2 show t(B;G) and one is a presumed t(B;C) (De Capoa *et al.*, 1967). In the 2 isolated cases reported in which the proband alone possessed the translocation, both involved D chromosomes. In addition, Capotorti has reported a similar t(B;D) with many features of the cri-du-chat syndrome (Capotorti and Ferrante, 1966). The involvement of satellited chromosomes is understandable in the light of their known propensity for association with other satellited chromosomes, centromeres, and secondary constrictions as well as their involvement in other translocation syndromes. It is difficult to understand the involvement of B chromosomes. They do not have particularly marked or constant secondary constrictions and cannot be considered to have areas similar to the satellite areas at least as regards nucleolus organizer regions or ribosomal RNA cistrons. Further it appears that the position of B chromosome breakage before translocation is inconsistent in the cases reported. Wolf and Reinwein's

patient had a t(5;14), giving rise to a chromosome resembling the No. 1 chromosome. Capotorti and Ferrante (1966) did not report autoradiographic studies, but he also had a chromosome resembling a No. 1. Our case had a t(5;15) and the result resembles a No. 2. The difference in arm length between a 15 and 14 or a 15 and 13 chromosome does not explain the difference in appearance of translocated chromosomes. These differences in length could best be explained by a random break in the short arm of the involved B chromosome, with resulting variation in the amount of B short arm deletion. The families reported by De Capoa *et al.* (1967) also showed marked variation in B short arm length which could be similarly explained. Within the limits of clinical observation, this presumed variation in deletion material does not appear to alter significantly the manifestations of the syndrome. Perhaps a critical analysis of a large collection of cases of variable B deletions and translocations after the example set by Magenis, Hecht, and Milham (1968) for the D₁ trisomies might serve to establish better correlation between the clinical and cytogenetic findings in this syndrome.

Summary

A case of a 12-week-old male infant with the phenotypic features of the cri-du-chat syndrome is reported. The karyotype of the child contained only 45 chromosomes with what appeared to be an extra No. 2 chromosome. Autoradiographs of this chromosome showed it to be a t(5q;15q) chromosome with resultant deletion of 5p material. The high incidence of chromosome translocations in cri-du-chat individuals is discussed.

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