I. GENETICS

SYNDROME OF 9q LARGE DUPLICATION – CASE REPORT

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Abstract
Partial trisomy 9q represents a rare and heterogeneous group of chromosomal aberrations characterised by various clinical features. Associated clinical features include learning disability and pyloric stenosis.
In this paper we present a 5 months old female patient with different dysmorphic features due to excess of genetic material on the long arm of chromosome 9. This partial trisomy 9q has been analysed in detail to determine the size of the duplication and to characterise the chromosomal breakpoints.
Key words: parial trisomy 9q, cytogenetic analysis

Introduction

Partial trisomy 9q was first described by Turleau et al in 1975 in a 5-years old boy with multiple minor anomalies, short stature, mental retardation, cleft palate, ventricular septal defect and pyloric stenosis. It is a rare and heterogeneous group with respect to the chromosomal region involved in the aberration and the clinical phenotype.

Case report

The female patient was hypotrophic at birth (weight: 1825 g, length: 36 cm) and showed multiple craniofacial anomalies like dolichomicrocephaly (head circumference 30,5 cm, −4 SD below normal). She was born at term as the first child of a young couple, with no noticeable medical records. The parents were not related.

Physical examination at the age of 5 months revealed failure to thrive: weight – 3900 g, length – 55 cm, cranial circumference – 55 cm. The infant was hypotonic with caranio-facial dysmorphy consisting of: frontal between eyebrows haemangioma, small deep-set eyes, horizontal palpebral fissures, slight hypotelorism, prominent cheeks, hooked nose, protruding maxilla, small mouth, thin upper lip with a receding lower lip, mandibular hypoplasia, high-arched palate, retrognathia, low-set ears. She also presented mild webbing of the neck and occipital haemangioma. Her nipples were wide-spaced, arms and legs long and slender. The child presented also hand anomalies (clinodactyly V, camptodactyly, overlapping fingers), long feet, long fingers and toes and abnormal fingerprints with simian crease (figure 3) and extra digital creases.

Growth retardation was apparent during postnatal development (−4 SD). Pictures of the patient at the age of 5 months are shown in figures 1 and 2. The cardiologic evaluation showed a murmur related to atrial septal defect, confirmed by ultrasonography.

The ophthalmologic assessment evidenced: nystagmus, convergent strabismus, bilateral haemangiomas of the palpebral fissueres.

The computerized tomography scan of the head showed symmetrical cerebral atrophy, more severe in the frontal lobes and enlargement of the infratentorial cisterns.

Cytogenetics

Metaphase chromosomes from cultured cells and PHA stimulated peripheral blood lymphocytes of the patient were analysed by standard GTG banding. Chromosome analysis of peripheral blood showed the presence of additional chromosomal material on the terminal region of the long arm of one chromosome 9 in all metaphases analysed (20/20). The computer analyze of the metaphases was performed with the support of the cytogenetic laboratory staff at the Ulleval University Hospital in Oslo and the establishing of the exact chromosomal region involved in duplication required the acquisition of new metaphases. The karyotype of the patient was established to be 46,XX, dup(9)(q13→qter) (figures 4, 5 and 6).

In order to determine whether the chromosomal anomaly was inherited, cytogenetic analysis of the parents were performed, and the karyotypes were normal for both parents.

Fig. 1. Patient's facial dysmorphy – front.

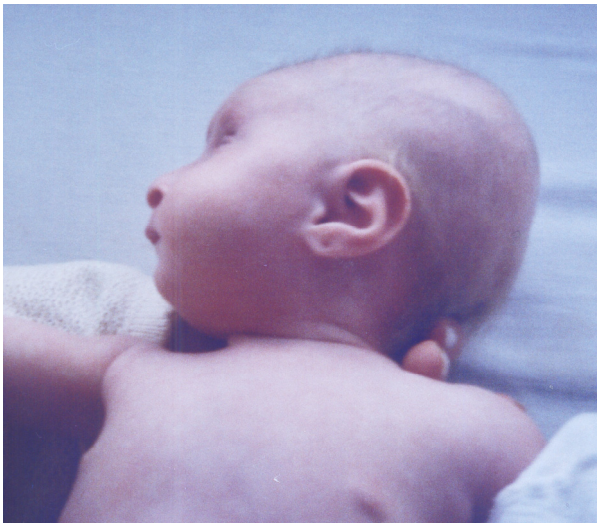

Fig. 2. Patient's facial dysmorphy – lateral.

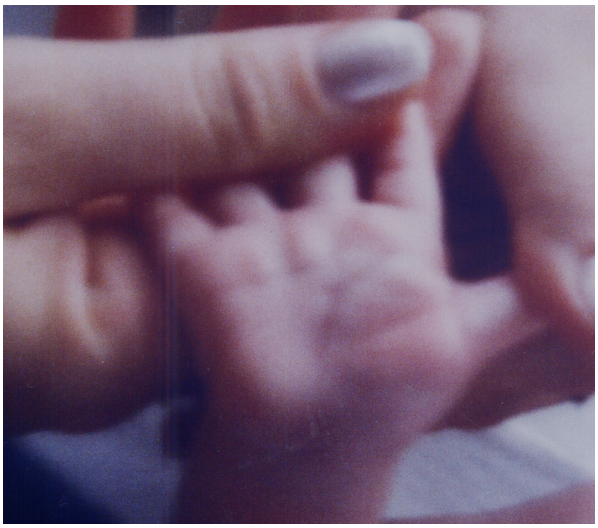

Fig. 3. Simian crease.

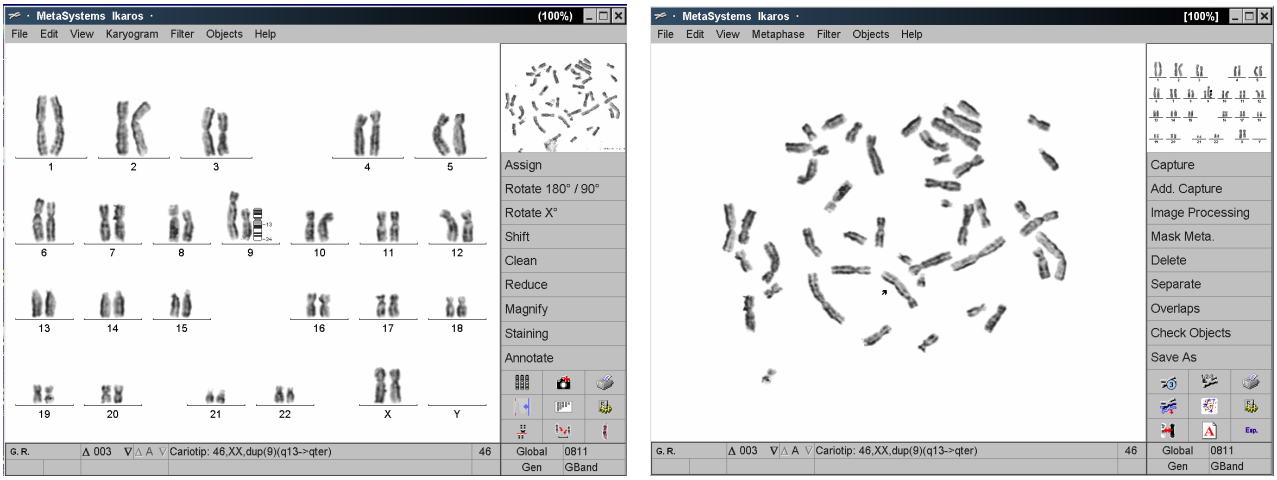

Fig. 4. Karyotype and metaphase of the patient.

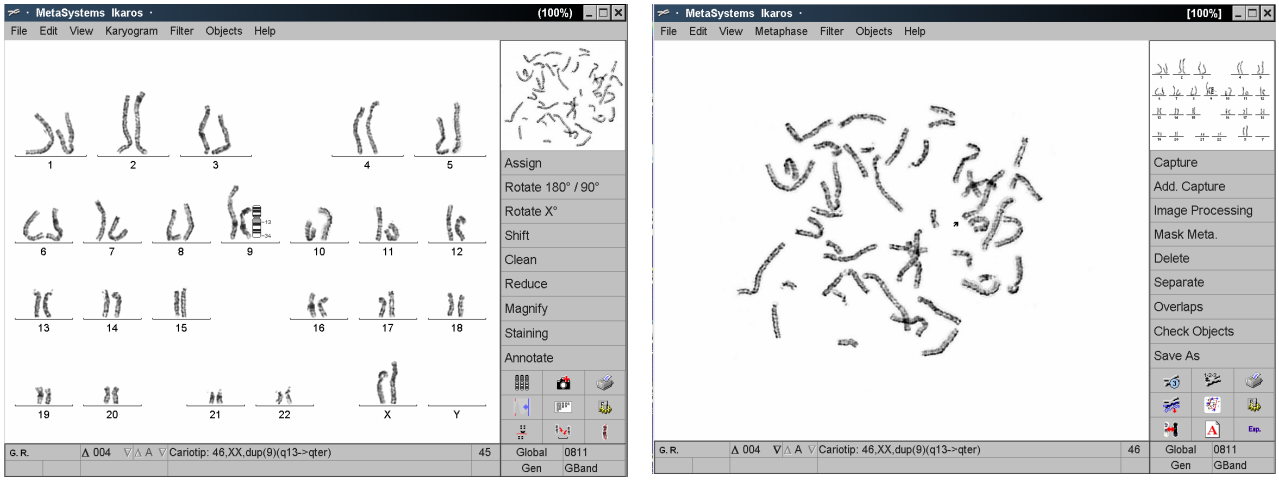

Fig. 5. Karyotype and metaphase of the patient.

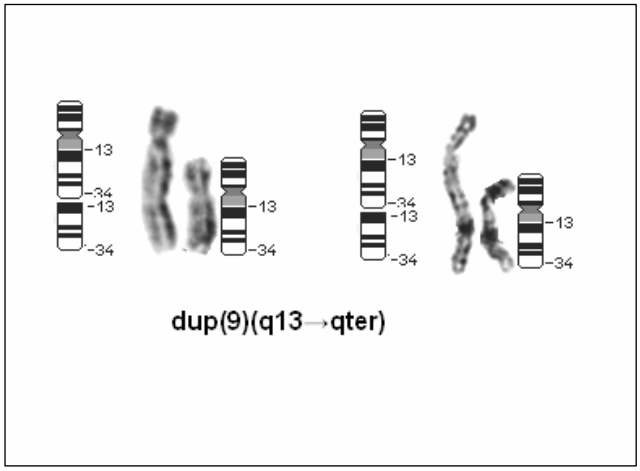

Fig. 6. Ideogram of chromosome 9, dup(9)
and normal chromosome of the pair.

Discussions

We report here on a child with a de novo duplication of the long arm of the chromosome 9.

Whereas the partial trisomy 9p belongs perhaps to the more frequent chromosomal syndromes, the partial trisomy 9q seems to be rare.

The following features reveal the pathognomy of this syndrome: (1) low birth weight and simultaneously normal birth length; (2) the craniofacial dysmorphia consists of deeply set eyes, narrow palpebral fissures, beaked nose, and of receding chin; (3) the mouth typically presents an overlapping upper lip; (4) the ears are low set; (5) the hands reveal abnormally long fingers with persistent flexion and toes also appear abnormally long and, moreover, are abnormally implanted; (6) +/- pyloric stenosis.

The review of all cases of partial trisomy 9q reported in the literature demonstrates that mental retadation, learning disability and facial dysmorphism, +/- pyloric stenosis are characteristic features of this group of chromosomal aberrations. Maraschio et al described the first patient with partial 9q duplication and obvious correlation between pyloric stenosis duplication of distinct parts of 9q in 1998. But, they only included in their study four published cases with partial trisomy 9q without pyloric stenosis even though there are some more. Assuming that 9q22-31.1 is a critical region for pyloric stenosis, there are five published cases corroborating this and at least six cases contradicting this point of view. However, some of the studies contradicting the assumption of Maraschio et al were done in the early days of chromosome banding and exact breakpoints were not verified by FISH studies. On the other hand, the case of Stalker et al from 1993 is well characterised by cytogenetic and molecular cytogenetic techniques. According to

Maraschio et al the duplication in this case spans the postulated critical region for pyloric stenosis in q12-q33, but no pyloric stenosis was reported. Moreover, in cases with complete trisomy 9 there have been no reports of pyloric stenosis. Imprinting could be another possible explanation for the fact that there are cases with duplication in 9q22.1-31. with and without pyloric stenosis. However, no cases with complete trisomy and pyloric stenosis have been described, which could be because all such cases which are viable are mosaic.

Molecular cytogenetic studies were performed in a partial trisomy 9q case with pyloric stenosis. [Anita Heller et al, 2000]. This study postulates that the critical region for pyloric stenosis (9q22.1-q31.1) may be disrupted. For the case reported in this study the region involved in duplication is inverted, therefore only molecular studies can specify whether the inversion that disrupts the gene is the cause for the pyloric stenosis.

In our case, by analysing the banding pattern of the extra chromosomal material on the long arm of chromosome 9, it was appointed as consisiting of 9q13-q34.3 region. Comparing the phenotype and the chromosomal alteration of our patient with similar cases described in the literature, it was striking the fact that such a large region involved in the duplication did not reside in a pyloric stenosis, but the cerebral anomalies present in our case were not reported previously in the literature.

For a thourough establishment of the chromosomal breakpoints the fluorescence in situ hybridization using specific porbes and arrayCGH are to be performed when avaliable for our patient.

The duplication of the arm of chromosome 9 observed in our patient was localized to q13-q34.3 region of the long arm of the same chromosome. Parental karyotypes were normal, indicating a de novo origin for the dup(9) in the proband. However, we cannot exclude the possibility of a gonadal mosaicism for the parents with an unbalanced crossover, this mechanism being the basis of duplication/deletion occurrence.

The correct diagnosis is essential not only for prognosis for the patient but also to ensure accurate estimation of the recurrence risk for the parents.

Documentation of better-characterized cases will contribute to the delineation of this syndrome.

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