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Case Report

A rare case of partial trisomy 8q24.12-q24.3 and partial monosomy of 8q24.3: Prenatal diagnosis and clinical findings☆

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ABSTRACT

Objective: We describe a rare case of "pure" 8q duplication diagnosed prenatally by conventional karyotyping, that was further characterized by array comparative genomic hybridization (aCGH).

Case report: A 39-year-old, primigravida woman underwent amniocentesis at 23 weeks of gestation because of an abnormal second trimester maternal serum screening for Down syndrome. Conventional cytogenetic analysis demonstrated a karyotype of 46,XX,der(8) (q24.12q24.3) and aCGH identified a duplication of approximately 27 Mb, affecting the distal region of chromosome 8q24.12-q24.3. Parenteral karyotype of both parents was normal and excluded familial translocation or other rearrangements. Although prenatal ultrasound examination showed multiple anomalies the parents decided to keep the pregnancy. The baby was born at 38 weeks of gestation, with an Apgar score of 2. The evolution was unfavorable, and he died within the first 24 h of birth.

Conclusion: Molecular investigations contribute to a more accurate characterization of the patients with these rare duplication, but also for estimating their prognosis.

Introduction

While there are several reported cases of chromosome 8q duplication, yet most of them resulted from balanced translocations or were associated with rearrangements in the genome [1–6]. On the other side, "pure" trisomy is an extremely rare event, with a phenotype that depends on the size of duplication [5]. The most common features include facial dysmorphism (hypertelorism, prominent fronthead, micrognathia, nose and ears anomalies), limb anomalies, cardiac and urinary malformations, growth and developmental delay [1–6].

Although most cases can be diagnosed by cytogenetic analysis alone, molecular investigations have the advantage of adding details that are useful for a more confident genotype–phenotype correlation [6,7].

In the present paper, we describe a rare case of "pure" 8q duplication diagnosed prenatally by conventional karyotyping, that was further characterized by array comparative genomic hybridization (aCGH).

Case presentation

A 39-year-old, primigravida woman underwent amniocentesis at 23 weeks of gestation because of an abnormal second trimester maternal serum screening for Down syndrome, that showed a trisomy 21 risk of 1/135. Consanguinity was denied, and the family history was unremarkable. Conventional cytogenetic analysis demonstrated a karyotype of 46,XX,der(8) (q24.12q24.3) and fluorescence in situ hybridization (FISH) test excluded the existence of an additional translocated chromosome 21 (Fig. 1). Array-CGH was performed using NimbleGen ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA) and identified a duplication of approximately 27 Mb, affecting the distal region of chromosome 8q24.12q24.3(119,488,147–145,984,903)×3,q24.3 (146,056,033–146,293,368)×1 with a microdeletion of the 8q24.3 region (237,336 bp), (Hg 19), (Fig. 2). Parenteral karyotype of both parents was normal and excluded familial translocation or other rearrangements.

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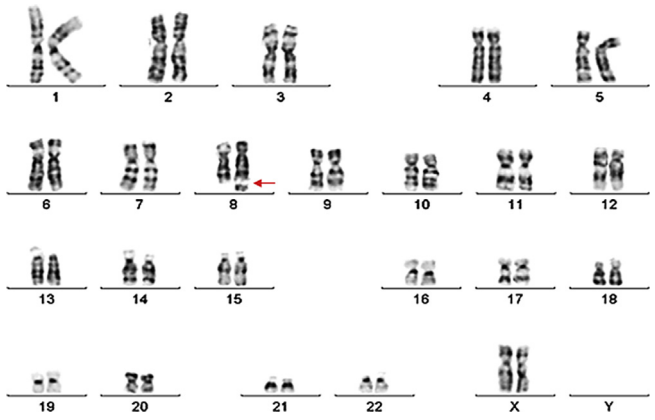

Fig. 1. G–banded chromosomal analysis from amniotic fluid showing a karyotype of 46,XX,der(8) (q24.12q24.3), (red arrow).

Prenatal ultrasound examination showed multiple anomalies including total agenesis of corpus callosum with absent cavum septi pellucidi, hyperechogenic intestines, single umbilical artery, agenesis of ureter and ventriculomegaly (Fig. 3). The parents were informed about the findings and the risk of the pregnancy, but they decided to keep the pregnancy.

The baby was born at 38 weeks of gestation via C-section, with an Apgar score of 2. Birth weight was 2750 g (between 10th and 25th centile), length of 34 cm (25th centile) and head circumference of 29 cm (3rd centile). Clinical examination revealed dysmorphic features including hypertelorism, low set ears, grade II microtia, prominent fronthead, broad nasal bridge, choanal atresia, high-arched submucosal palate cleft and both hands showed simian crease (Fig. 4). Because the baby had anal imperforation, he was immediately transferred to the surgery department. Unfortunately, he died within the first 24 h of birth.

Discussion

In the present paper we describe a case of "pure" partial trisomy of chromosome 8 diagnosed in the second trimester of pregnancy. Parenteral karyotype was normal and indicated a "de novo" chromosome duplication. The structural anomaly of chromosome 8 detected on conventional karyotyping in our patient was confirmed by microarray, that identified a terminal 8q24.12-8q24.3 (chr8:119,200,001–146,364,022) duplication of approximately 27 Mb. The region corresponding to the duplicated segment involves 23 OMIM genes, that probably contributed to the proband's phenotype.

While similar cases of 8q duplication were previously reported, none of them involved the same duplicated segment (8q24.12-8q24.3) identified in our case (Table 1). Concolino et al. described a "pure" de novo duplication of chromosome 8q22.2-8q24.3 and compared their case with other similar ones [5]. They suggested that mental retardation and facial dysmorphism such as hypertelorism, microretrognathia and telecanthus are key features of 8q22.2-q24.3 duplication. Although the duplication identified by them included a larger region than ours, yet there were some similarities between the cases including prominent fronthead, hypertelorism, low seat ears and cardiac anomalies. Our patient lived only few hours after birth, thus we couldn't appreciate his mental status, but since he had agenesis of corpus callosum and microcephalia we believe that he would had developed a grade of mental retardation during his life. Moreover, the duplicated segment found in our patient includes TAF2 gene (OMIM 604912). Halevy et al. described 4 patients with microcephaly, thin corpus callosum and intellectual disability and concluded that the mental disorder of these patients was caused by TAF2 mutation [8]. Comparable results were reported by Najmabadi et al. who performed homozygosity mapping and deep sequencing in 136 families with cognitive disorders. They identified mutation of TAF2 gene in 2 sibs with microcephaly and autosomal recessive mental retardation [9].

Barel et al. reported a syndrome of mental retardation associated with hypotonia and specific dysmorphism caused by the mutation of KCNK9 gene (OMIM 605879) in chromosome 8q24 [10]. Interestingly, this gene was also included in the duplicated segment identified by us and our patient had some common dysmorphic features notably high-arch submucosal cleft palate, broad nasal bridge and ears anomalies.

In addition to the duplicated segment of chromosome 8, we identified a microdeletion of the 8q24.3 region. The 8q24.3 deletion is very rare observed and its characterized by low birth weight, intrauterine growth restriction (IUGR), vertebral anomalies, cardiac and renal defects, dysmorphic features and brain anomalies [11].

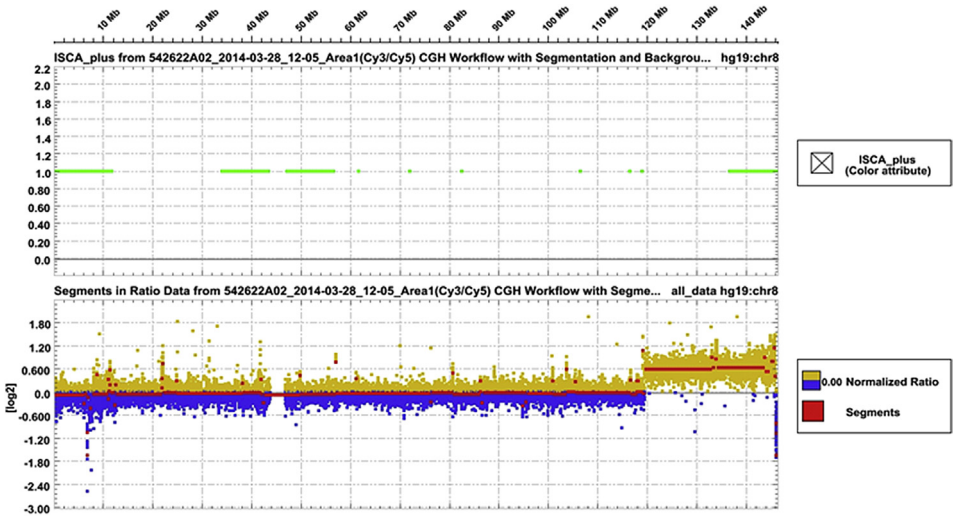

Fig. 2. Comparative genomic hybridization revealing a 27Mb duplication at chromosome bands 8q24.12q24.3(119,488,147–145,984,903) × 3,q24.3(146,056,033–146,293,368) × 1 and a microdeletion of the 8q24.3 region (237,336 bp).

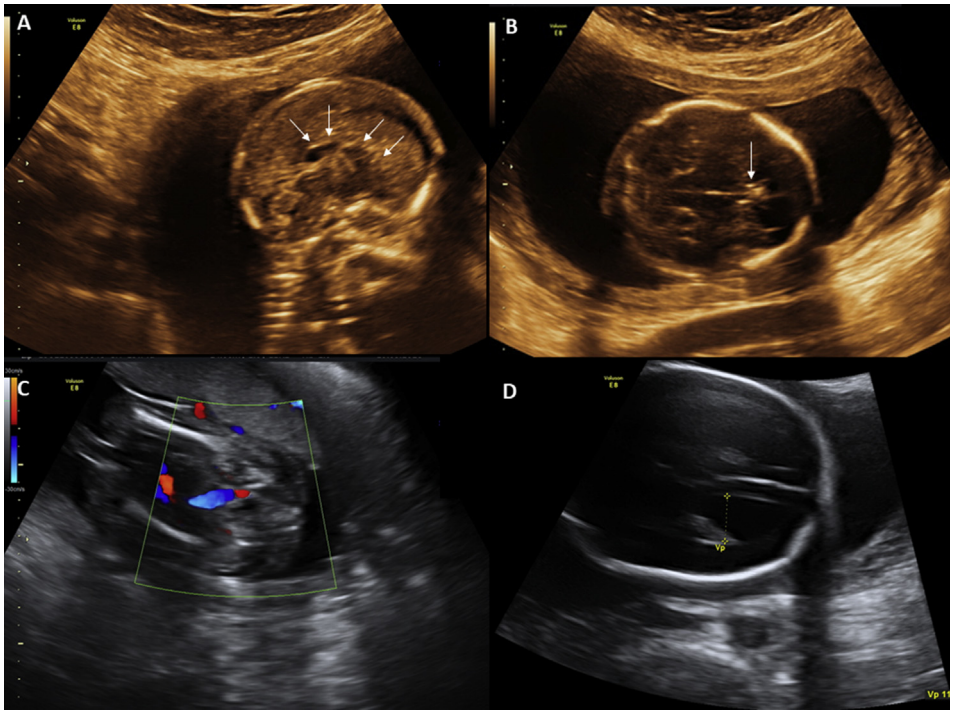

Fig. 3. Ultrasound imaging (2D) revealing complete agenesis of corpus callosum indicated by white arrows (A) and absent cavum septi pellucidi indicated by white arrow (B). Single umbilical artery (C). Mild ventriculomegaly (D).

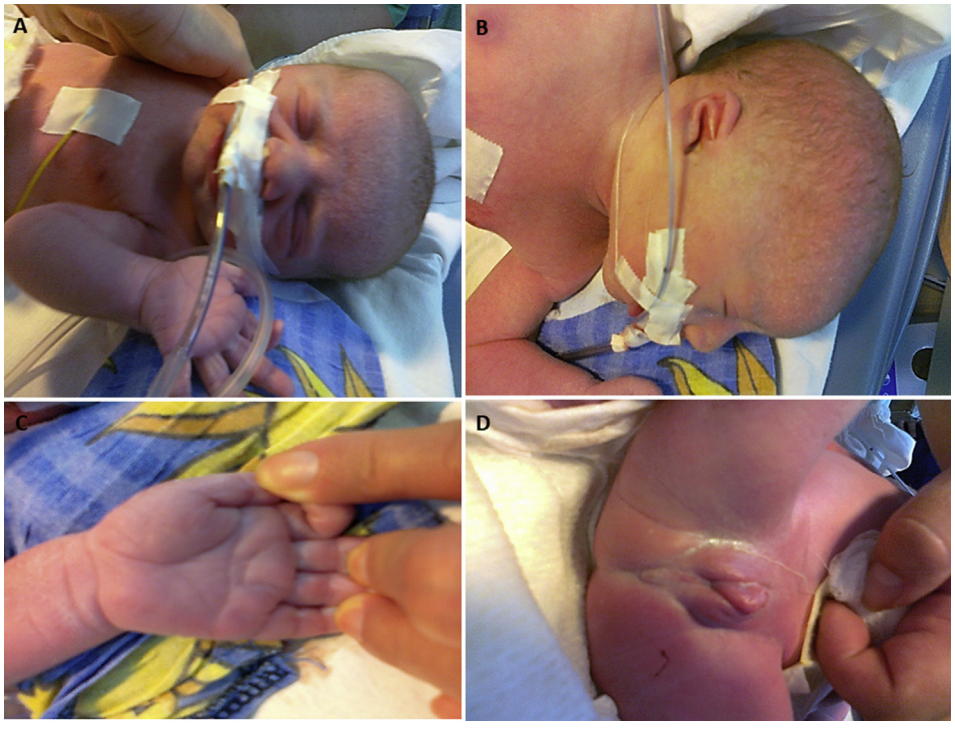

Fig. 4. Dysmorphic features showing hypertelorism, prominent fronthead, broad nasal bridge (A). Low set ears and grade II microtia (B). Simian crease (C). Anal imperforation (D).

The clinical findings of our case match the 8q24.3 phenotype described by Wells et al. including low birth weight, cardiac defect, facial dysmorphism and ears anomalies. Array-CGH has a pivotal role in prenatal detection of this condition [11].

Although the patients with duplication of chromosome 8 share some similar features, the phenotype of each case is related to the size of the duplicated region and the genes included in the affected area. The phenotype differences between patients highlights the variable expressivity of chromosome 8 duplication [5]. Thus, CHG analysis is a key step in such cases, since it adds valuable details that are useful for a more accurate phenotype characterization of each individual and for estimating their prognosis, but also for expanding our knowledge regarding this rare disease.

Table 1
Clinical features of the patients with 8q22-q24 duplication.

Duplicated segment	Present Case	Concoclino 2012	Wheeler 2010
	8q24.12-q24.3	8q22.2-q24.2	8q23.3-q24.21
Facial features			
Hypertelorism	+	+	+
Epicanthal folds	–	–	+
Telacanthus	–	–	+
Microretrognathia	–	+	+
Low set ears	+	+	+
Protruding ears	–	–	+
Microtia	+	–	–
Visual anomalies			
Astigmatism	–	–	+
Keratoconus	–	+	–
Megalocornea	–	+	–
Limb anomalies			
Equinovarus	–	–	+
Distal phalanges hypoplasia	–	+	–
Syndactyly	–	+	–
Simian crease	+	–	–
Birth defects			
Congenital cardiac defects	+	+	–
Bifid uvula	–	–	+
Anal imperforation	+	–	–
Frontal meningocele	–	+	–
Agenesis of corpus callosum	+	–	–
Neurologic anomalies			
Mental retardation	Unknown	+	+
Hypotonia	–	–	+
Hearing loss	–	–	+

Conflict of interests

The authors have no conflicts of interest relevant to this article.

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