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Prenatal diagnosis of a partial trisomy 13q (q14→qter): phenotype, cytogenetics and molecular characterization by spectral karyotyping and array comparative genomic hybridization

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ABSTRACT. Partial trisomy 13q is an uncommon chromosomal abnormality with variable phenotypic expression. We report prenatal diagnosis of partial trisomy 13q in a fetus with partial agenesis of the cerebellar vermis, partial agenesis of the corpus callosum, hydrops and polyhydramnios. G-banding karyotyping, spectral karyotyping and array comparative genomic hybridization (aCGH) analysis of fetal blood were performed. Cytogenetic analysis of fetal blood displayed 46,XX,add(4)(q28). The parental karyotypes were normal. A girl was delivered at 34 weeks gestation; she died within 2 h. Autopsy confirmed all the prenatal findings and also showed agenesis of the diaphragm. Spectral

karyotyping identified the additional material's origin as chromosome 13. aCGH was carried out and showed amplification of distal regions of the long arm of chromosome 13 from region 13q14 to qter. This is the first report of a fetus with molecular characterization of a partial trisomy 13q (q14→qter), present as a *de novo* unbalanced translocation at chromosome 4q. This case demonstrates the usefulness of molecular characterization of malformed fetuses for prenatal diagnosis and counseling.

Key words: Partial trisomy 13q; Prenatal diagnosis; SKY; Array comparative genomic hybridization; Corpus callosum agenesis; Dandy-Walker malformation

INTRODUCTION

Partial trisomy 13q is an uncommon chromosomal abnormality, with no well-determined frequency. It has been described as having a variable phenotypic expression. It may result from parental reciprocal translocations, parental pericentric inversions (Chen et al., 2005b) or *de novo* direct duplications (Hall et al., 2007).

We present a case of a partial trisomy 13q prenatally diagnosed on fetal blood, initially detected as a chromosome 4 with an extra genetic material on the long arm and subsequently confirmed to be 13q material with spectral karyotyping and array comparative genomic hybridization (aCGH).

Clinical report

A 19-year-old primigravida woman was referred for prenatal diagnosis and genetic counseling at 28 weeks gestation because of an abnormal sonogram that revealed Dandy-Walker malformation and subcutaneous edema. The sonographic evaluation in our tertiary fetal medicine center showed a single fetus with partial absence of the cerebellar vermis (Dandy-Walker malformation variant) with an enlarged cisterna magna, partial agenesis of the corpus callosum, hydrops, and polyhydramnios. The fetus's heart was morphologically normal at fetal echocardiography. The fetal growth rate was normal for the gestational age.

There was no family history of congenital malformations or genetic disorders. Both woman and her husband were healthy and nonconsanguineous. The mother was tested negative for toxoplasma, parvovirus B19, CMV, herpes, and rubella. Maternal diabetic screening was negative. No atypical antibodies were found in her blood. A cordocentesis was performed at 29 weeks gestation for karyotyping, and the parents gave informed consent for further studies with the fetus blood.

Spontaneous labor began at 34 weeks gestation. A girl was delivered with a birth weight of 3135 g (above 90th percentile), and Apgar scores of 1 and 1 at 1 and 5 min, respectively. The newborn presented bradycardy (66 bpm), cyanosis, hydropsy, hypotony, akinesia, and abdomen distension. She died after 2 h of life.

Neonatal evaluation revealed some dysmorphic features: short neck, low-set ears, nasal bridge hypoplasia, camptodactyly (5th finger at right hand, 4th and 5th fingers at left hand), clinodactyly (4th and 5th fingers, bilateral), and thin umbilical cord.

An autopsy confirmed the prenatal findings of agenesis of the corpus callosum (total) and generalized hydrops. Additional findings were agenesis of the diaphragm and severe pulmonary hypoplasia.

Genetic analysis

Routine cytogenetic analysis of the fetal blood using G-banded metaphase chromosomes at approximately the 500-band level was performed. Extra material of unknown origin attached to band q28 at chromosome 4 was revealed in 20 metaphase spreads studied (Figure 1a). The cytogenetic result was assigned as 46,XX,add(4)(q28). The parental karyotypes performed on lymphocytes were normal.

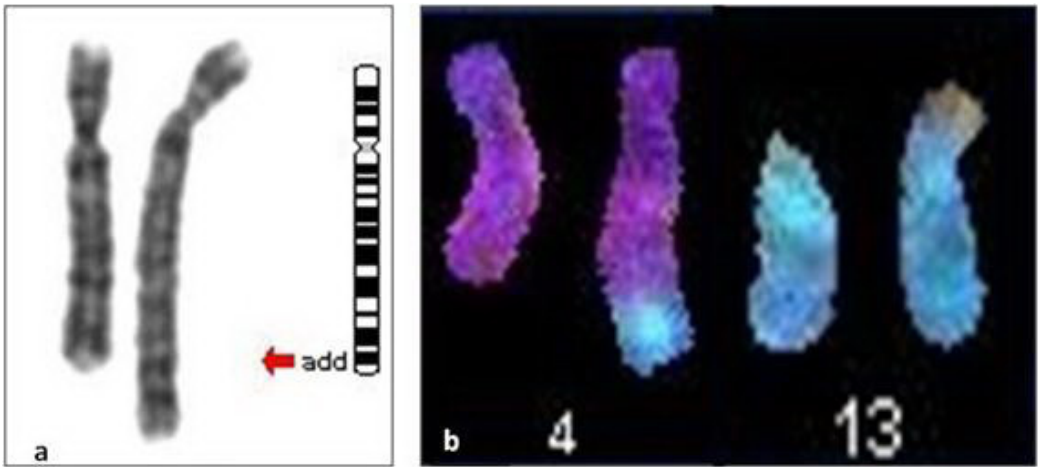

Figure 1. a. G-banded normal and derivative chromosome 4 from the fetus. **b.** Metaphase spread painted for chromosomes 4 and 13 demonstrating the additional material's origin as being from chromosome 13.

Images produced by spectral karyotyping (Applied Spectral Imaging, Inc., Vista, CA, USA) identified the additional material's origin as being from chromosome 13 (Figure 1b). In order to further characterize and refine the size of the translocated segment of chromosome 13, array comparative genomic hybridization was carried out using Constitutional Chip® 4.0 (PerkinElmer Inc., Turku, Finland), comprised of approximately 5000 bacterial artificial chromosome clones, covering the whole human genome with an average resolution of ~650 kb and spotted in duplicate. This molecular technique showed copy number gain of 89 bacterial artificial chromosome clones on the distal regions of the long arm of chromosome 13, from region 13q14 to the terminal segment, with no apparent loss of 4q and 13q material (Figure 2A and B). The proximal breakpoint was located in clone RP11-142D16 (region 13q14.3-13q21.31, mapping 58.98 Mb).

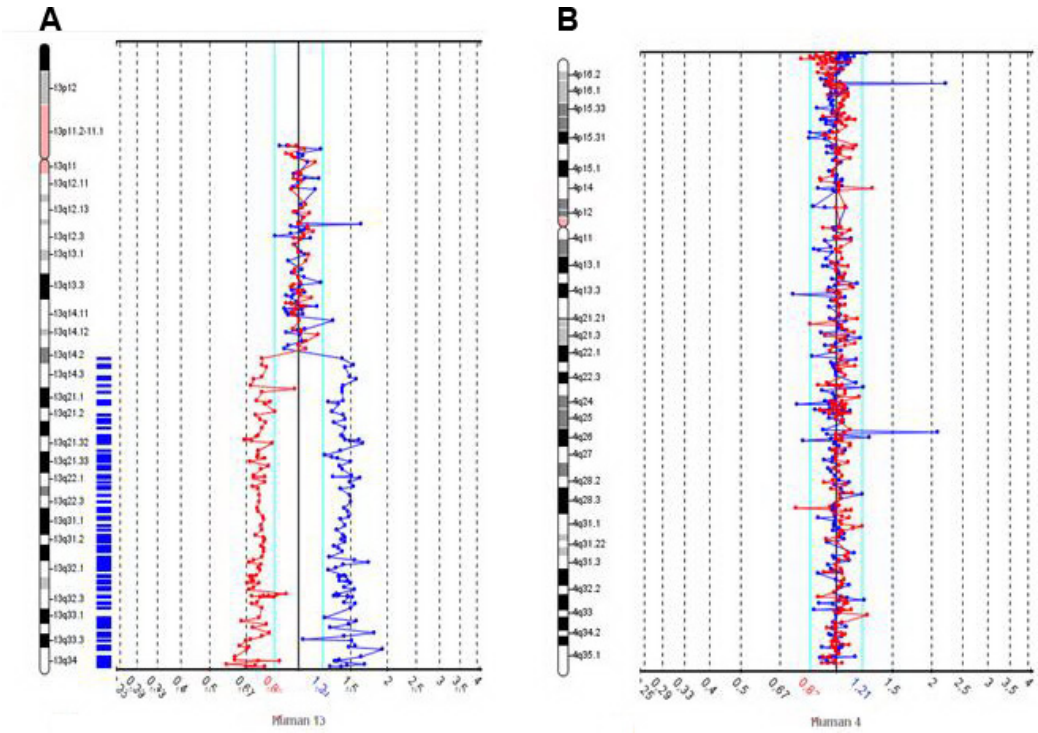

Figure 2. Array comparative genomic hybridization spectral view of chromosome 13 (A) and 4 (B) of the fetus (Constitutional Chip 4.0).

Therefore, based on the knowledge gained from these molecular results, the karyotype of the fetus was reassigned as 46,XX,der(4)t(4;13)(q28;q14).arr 13q14qter (58,974,200-114,005,800)x3 dn.

DISCUSSION

To our knowledge, this is the first report of a prenatal diagnosis with molecular characterization of a partial trisomy 13q (q14→qter) presented as *de novo* direct duplication structurally rearranged at chromosome 4q.

Clinical features seem to be distinctive between the trisomy of the proximal and distal regions of the long arm of chromosome 13 (Tharapel et al., 1986). Partial trisomy 13q has been shown to have both a distinctive (Tharapel et al., 1986) and common (Nikolis et al., 1991) phenotype resembling that of complete trisomy 13. The fetus presented here does not show characteristic trisomy 13 major features. Although the association of congenital diaphragmatic hernia and trisomy 13 has been described, complete bilateral agenesis of the diaphragm is a rare congenital diaphragmatic hernia variant with no previously described chromosomal aberration etiology.

The published cases of partial trisomy 13q helped to delineate the variable phenotype associated with this chromosomopathy (Rivas et al., 1984; Tharapel et al., 1986; Nikolis et al., 1991; Rodriguez de Alba et al., 1999; Chen et al., 2005a,b; Lin et al., 2007; Ribacoba et al., 2008). Common phenotypic features described for partial trisomy 13q are: craniofacial dysmorphism (bushy

eyebrows, long curled eyelashes, prominent nasal bridge, long philtrum, thin upper lip, microcephaly, and hypotelorism), highly arched palate, short neck, hemangioma, hexadactyly, urinary tract/kidney anomalies, umbilical/inguinal hernia, intra-uterine growth retardation, and oligohydramnios. Other phenotypic features in child and adult patients are: psychomotor retardation, hypoacusia, hypochromic anemia, splenomegaly, ocular anomalies, convulsions, and fatty acid disturbances.

This present case involves a trisomy for distal approximate three-quarters of 13q (q14→qter). The proband neonate shares a few characteristic defects with the described ones, such as short neck and low-set ears.

The association of the abnormal sonographic findings noted in the present case (hydrops, agenesis of the corpus callosum and Dandy-Walker malformation) did not correlate with other features previously described in cases involving partial trisomy 13q. This inconsistent phenotype has already been mentioned even when the same region is in trisomy (Tharapel et al., 1986). Even isolated, the abnormal findings have a poor correlation with partial trisomy 13, as noted in the following discussion.

The percentage of chromosomal abnormalities in cases with nonimmune hydrops fetalis has a large range in the recent literature, from 10 to 78% (Russell et al., 2008). The association of fetal hydrops and trisomy 13 as in the present case is rare (Greenberg et al., 1983; Landrum et al., 1986), and in a recent review of 434 fetuses with subcutaneous edema, the authors did not find such association (Beke et al., 2009). Although no loss was found in the present case at chromosomes 4 and 13 breakpoints, the association between terminal 4q deletion and severe hydrops has already been described (Mitchell et al., 1981; Russell et al., 2008). Also, fetal ascites has been described in a case of combination of partial trisomy 13 (13pter-13q12.3) due to maternal reciprocal translocation (Chen et al., 1999).

Our proband fetus presented digital malformations at birth, supporting the current hypothesis that the band 13q32 contains critical genes for digit formation (Brown et al., 1993).

In relation to the structural defects in the central nervous system and the association with partial trisomy 13, three fetuses with enlarged magna cisterna (Nyberg et al., 1991) and one child with corpus callosum agenesis (Marszal et al., 2000) have been published, indicating a possible phenotype-genotype association. Applying a 244-k oligonucleotide-based aCGH, candidate chromosomal regions associated with the Dandy-Walker malformation and agenesis of the corpus callosum were recently delineated as deletions in the 13q32.2-q33.1 and 13q32.3-q33.1, respectively (Kirchhoff et al., 2009). Differently, our fetus showed duplication in these regions.

Parental karyotype was assessed, and due to the excellent banding pattern and high banding resolution we found no need to perform aCGH analysis on these samples. After karyotype analysis of 20 metaphase spreads we could confidently assign normal karyotypes to both parents and indicate that the finding was not inherited but a *de novo* genomic imbalance.

The majority of trisomy 13q cases (>90%) are from maternal origin (Hall et al., 2007), typically due to errors in meiosis I, as in other autosomal trisomies. Many cases are from parental balanced translocations, typically as pericentric inversions. Few cases were described resulting from unequal crossing-over of a paternal pericentric inversion, including trisomy 13q21→qter from paternal inv(13)(p11q21) (Bourthoumieu et al., 2004), trisomy 13q22→qter from paternal inv(13)(p11q22) (Williamson et al., 1980) and trisomy 13q14.1→qter from paternal inv(13)(p12q14.1) (Chen et al., 2005b). One case was described resulting from a paternal translocation involving chromosome Y (46,X,der(Y),t(Yq;13q)pat (Nikolis et al., 1991). Partial trisomy 13q (q14→qter) resulting from a *de novo* duplication, as presented in this case, is very unusual (Rao

et al., 1995; Chen et al., 2005a) and such a partial trisomy involving an unbalanced translocation at chromosome 4 was not found in the consulted literature. Table 1 summarizes some of the structurally rearranged chromosome involved with duplication of chromosome 13q.

Table 1. Structurally rearranged chromosomes involved with duplication of 13q.

13q duplicated region	Other chromosome region involved	References
q32-qter	1q	Rao et al., 1995
q22	3p26	Bonioli et al., 1981
q22-qter	5p	Rodriguez de Alba et al., 1999
q22-qter	5p15	Ribacoba et al., 2008
q12	6p24	Jones et al., 1979
q14-qter	7qter	Martin-Lucas et al., 1982
pter-q12	8p23	Lukusa et al., 1999
q22-qter	8p	Chen et al., 2005a
q21	9p21	Jotterand and Juillard, 1976
q22	15q26	Rivas et al., 1984
pter-q12.3	16p	Chen et al., 1999
q22	18q23	Chu et al., 1994
q22-qter	18q23	Yu et al., 1995
q22-qter	18q	Cekada et al., 1999
q34	21p13	Di Bella et al., 2006
q	Xq	Dries et al., 2003
q14	Yq12	Nikolis et al., 1991
q21-qter	6q21 and 18q22	Quadrelli et al., 2009

As the number of fetuses with this particular condition is not sufficient to define a characteristic prenatal phenotype-genotype correlation, this case with simple duplication of the 13q presented here can contribute for a more precise clinical correlation. The success and accuracy of such correlation depend upon the analysis of sufficient large number of patients with complete phenotypic malformations and molecular description of identical chromosome aberrations.

The molecular characterization of malformed fetuses is important for prenatal diagnosis and counseling. aCGH successfully identified the additional genetic material origin, with its precise location and size, but it cannot describe the specific chromosome organization. This molecular diagnosis can be completed in timely manner, making it particularly suitable for prenatal proposes. Thus, the present case also emphasizes that aCGH may not replace karyotype analysis, but it can complement and extend current methods for a precise prenatal diagnosis and characterization of syndromes.

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