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PRENATALLY DIAGNOSED PARTIAL TRISOMY 3Q22.2→3QTER, PARTIAL MONOSOMY 11Q25→11QTER AND INTERSTITIAL DELETION 10Q25.1-10Q25.2: A CASE REPORT AND REVIEW OF LITERATURE

DIAGNÓSTICO PRENATAL DE TRISOMÍA PARCIAL 3Q22.2→3QTER, MONOSOMÍA PARCIAL 11Q25→11QTER Y DELECIÓN INTERSTICIAL 10Q25.1-10Q25.2: REPORTE DE UN CASO Y REVISIÓN DE LA LITERATURA

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ABSTRACT

A 19-year-old pregnant woman was admitted to our ultrasound department at 20.4 weeks of gestation. Prenatal sonography identified a fetus with trigonocephaly, an omphalocele protruding out of the abdominal wall, on the right side of the umbilical cord, that contained the liver and bowel, claw hand and bot foot. Amniocentesis revealed an unbalanced chromosome constitution 46,XX,der(11)t(3,11)(q22.2,q24.3) resulting in a deletion of 11q24.3 to 11qter and a duplication of 3q22.2 to 3qter product of a "de novo imbalanced translocation"; the parents' karyotypes were normal. The chromosome microarray results for the proband revealed a 63.07 Mb duplication in the chromosome 3 located at 3q22.2 to terminal 3q29; a 4.08 Mb deletion in the chromosome 11 located at 11q25, and a 5.66 Mb loss in the chromosome 10 located at 10q25.1 to 10q25.2. To the best of our knowledge, this is the first report of this combination of chromosomal abnormalities.

Key words: amniocentesis, chromosome microarray, deletion 10q, deletion 11q, duplication 3q.

RESUMEN

Una embarazada de 19 años ingresó en nuestro servicio de ultrasonido a las 20,4 semanas de gestación. La ecografía prenatal identificó un feto con trigonocefalia, un onfalocele que sobresalía de la pared abdominal, en el lado derecho del cordón umbilical, que contenía el hígado y el intestino, una mano en garra y un pie bot. La amniocentesis reveló una constitución cromosómica desequilibrada 46,XX,der(11)t(3,11)(q22.2,q24.3) que resultó en una deleción de 11q24.3 a 11qter y una duplicación de 3q22.2 a 3qter producto de una "translocación desequilibrada de novo"; los cariotipos de los padres eran normales. Los resultados del microarreglo cromosómico para el probando revelaron una duplicación de 63,07 Mb en el cromosoma 3 ubicado en 3q22.2 a terminal 3q29; una deleción de 4,08 Mb en el cromosoma 11 ubicado en 11q25 y una pérdida de 5,66 Mb en el cromosoma 10 ubicado en 10q25.1 a 10q25.2. Hasta donde sabemos, este es el primer informe de esta combinación de anomalías cromosómicas.

Palabras clave: amniocentesis, *microarray* cromosómico, deleción 10q, deleción 11q, duplicación 3q.

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INTRODUCTION

Trisomy 3q is a very rarely reported chromosomal disorder. In most cases, a duplication of the segment 3q21-qter is included; these duplications being the result of unbalanced segregations of balanced parental translocations involving chromosome 3 (Chen, 2007). Duplication of part of the long arm of the human chromosome 3 causes a distinct and severe syndrome that leads to multiple congenital abnormalities such as growth delay, dysmorphic facial features, microcephaly, intellectual disability, heart defects and structural brain anomalies.

Partial monosomy of the long arm of chromosome 10 is an uncommon chromosomal abnormality accompanied by microcephaly, characteristic facial features and mental retardation. Some cases of this chromosomal defect have been reported to occur with other chromosomal abnormalities (Shapiro *et al.*, 1985; Tsukuda *et al.*, 1996).

Deletions of terminal 11q region are found in individuals with Jacobsen syndrome -JBS- (Sheth *et al.*, 2014). The phenotype may vary with deletion size but the most common features include mild-to-moderate intellectual disability, speech delay, psychomotor delay, congenital heart disease, trigonocephaly, thrombocytopenia, and characteristic facial features.

A 19-year-old pregnant woman was admitted to the ultrasound department in San Luis, Argentina, for pregnancy follow-up. The unborn baby was the firstborn of a non-consanguineous and healthy couple. In the fetal karyotype, an unbalanced translocation between the long arm of chromosomes 3 and 11 was observed, leading to partial monosomy of the long arm of chromosome 11 (11q24.3-11qter); partial trisomy of the long arm of chromosome 3 (3q22.2-3qter) as a result of a "de novo" unbalanced translocation, and interstitial deletion in the long arm of chromosome 10 (10q25.1-10q25.2); parental chromosomes were normal. In the literature, no report of this combination of chromosomal abnormalities was found. The aim of our study was to compare the conventional karyotype with the molecular karyotype at the time of diagnosis, in cases of abnormalities interpreted by classical cytogenetics.

Case report

The present study was carried out in accordance with the guidelines of the Helsinki Declaration. The protocol for the present study was approved by the local Institutional Review Board and written informed consent was obtained from the proband's parents to be enrolled.

MATERIALS AND METHODS

Chromosome preparation and conventional karyotyping

The fetal karyotyping study was performed from amniotic fluid using cell culture with Amnio Max Medium (Gibco, Gaithersburg, MD USA). The cells were incubated for 15 days at 37° C in a humid atmosphere with 5% CO_2, and then treated with colchicine (Aldrich-Sigma, St. Louis, MO, USA). To further identify the chromosomal anomalies, blood from the proband's parents was obtained for karyotyping. Peripheral mononuclear cells were cultured for 72 h at 37° C in RPMI medium 1640 (Gibco, Gaithersburg, MD USA) and stimulated with phytohemagglutinin (Solarbio, Beijing, China) containing fetal bovine serum (Gibco) and then treated with colchicine (Aldrich-Sigma, St. Louis, MO, USA). The ISCN2020 nomenclature was used to describe the karyotype (McGowan-Jordan *et al.*, 2020). Cytogenetic analysis was performed on GTG-banded metaphases from the patients at a resolution of 450 bands according to standard lab protocol. For each patient, the numbers of chromosomes in 30 metaphase mitotic figures were counted and the karyotypes of twenty cells in mitotic metaphase were analyzed by optical microscopy (ZEISS, Germany).

Chromosome microarray

Chromosome microarray was performed in accordance with the manufacturer's protocol. The procedure included genomic DNA extraction, digestion and ligation, PCR amplification, PCR product purification, quantification and fragmentation, labeling, array hybridization, washing and scanning. The array was designed specifically for cytogenetic research to detect the gain or loss of DNA copies associated with chromosomal imbalances. It allows the detection of aneuploidies, deletions and duplications of the loci represented in the microarray. It does not detect balanced alterations (reciprocal translocations, Robertsonian translocations, inversions and balanced insertions) or imbalances of regions not represented in the microarray. Thresholds for genome-wide screening were set at ≥100 kb for gains and ≥50 kb for losses. The platform used was Agilent 180K CGH + SNP.

The detected copy number gains or losses were systematically evaluated for clinical significance by comparing them with values reported in the scientific literature and the following databases: i) Database of Genomic Variants (http://projects.tcag.ca/variation/), ii) DECIPHER (http://decipher.sanger.ac.uk/), iii) ISCA (https://www.iscaconsortium.org/), iv) ECARUCA (http://www.ecaruca.net), v) Online Mendelian Inheritance in Man (OMIM; http://www.ncbi.nlm.nih.

gov/omim) and vi) Clinical Genome Resource (https://www.clinicalgenome.org/).

RESULTS

There was no positive family history. Prenatal sonography at 20.4 weeks revealed trigonocephaly with apparently normal brain structures (Figure 1a), omphalocele protruding out of the abdominal wall on the right side of the umbilical cord that contained the liver and bowel (Figure 1b), claw hand, a condition that causes the fingers to curve in a sustained manner (Figure 1c), and an inwards and downwards deviation of the axis of the foot with respect to the leg, defect known as bot or equinovarus foot (Figure 1d). Counseling was given and amniocentesis was performed after written informed consent form had been obtained.

The results of the cytogenetic examination were shown by chromosome G-banding and karyotype analysis. The fetus presented an unbalanced translocation between the long arm of chromosome 3 and the long arm of chromosome 11, leading to partial monosomy of the long arm of chromosome 11 (11q24.3-11qter) and partial trisomy of the long arm of chromosome 3 (3q22.2-3qter): 46,XX,der(11)t(3,11)(q22.2, q24.3) (Figure 2). The parent's karyotypes were normal; therefore, it was a "de novo" translocation.

Chromosome microarray analysis using a whole genome oligonucleotide array detected three abnormalities in the DNA of this fetus **(Figure 3A)**. Based on microarray analysis, the first abnormality is characterized by a 63.07 Mb copy gain from 3q22.2 through terminal 3q29 (134701427_197771082) **(Figure 3B)**. The second copy change was a 4.08 Mb copy loss from terminal 11q25 (130850244_134928849) (Figure 3c) and the third copy change was a 5.66 Mb copy loss from 10q25.1 to 10q25.2 (107936097_113596588) (Figure 3d).

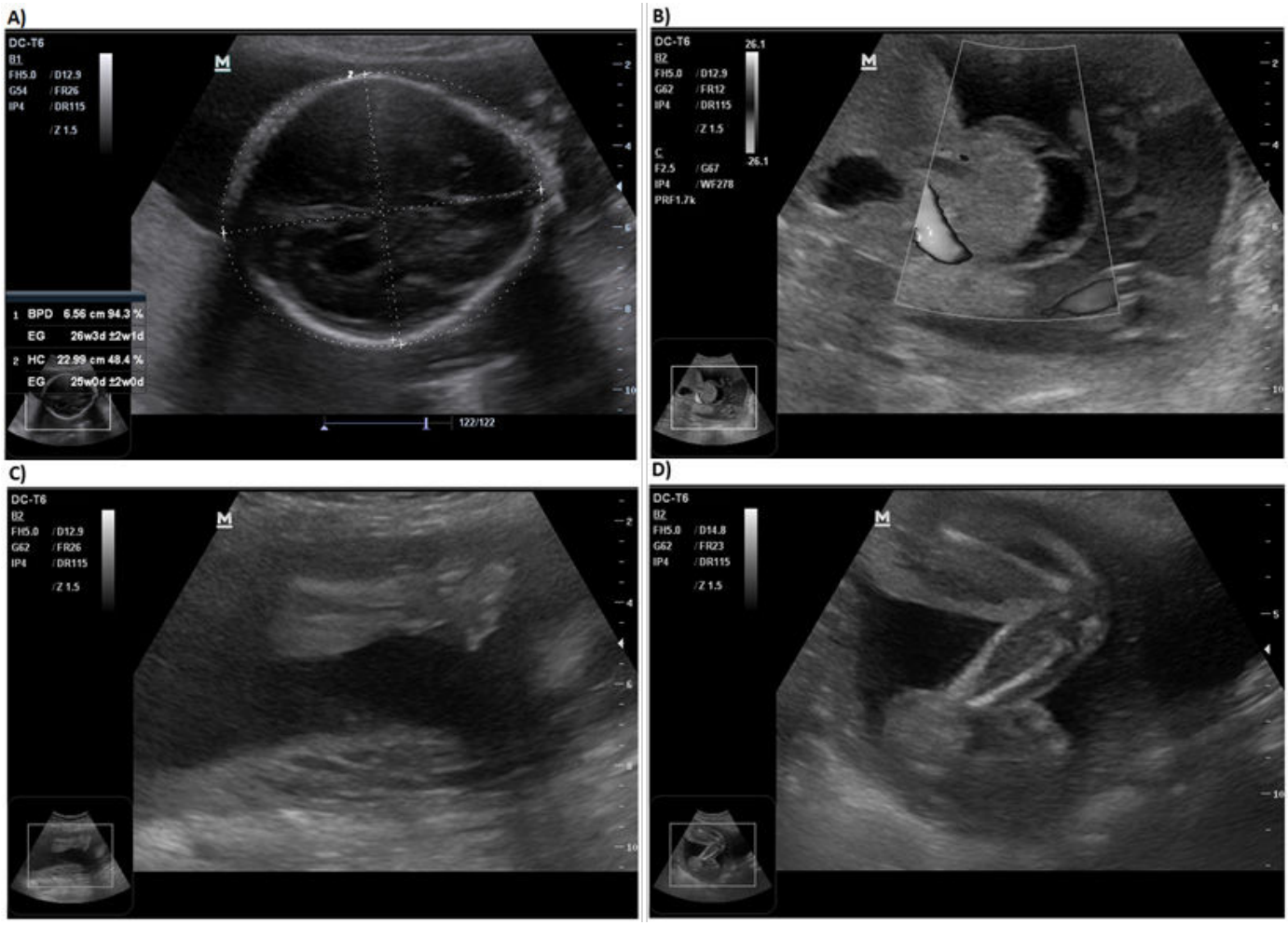

Figure 1. Ultrasonographic view of a) trigonocephaly, b) omphalocele, c) claw hand and d) bot or equinovarus foot.

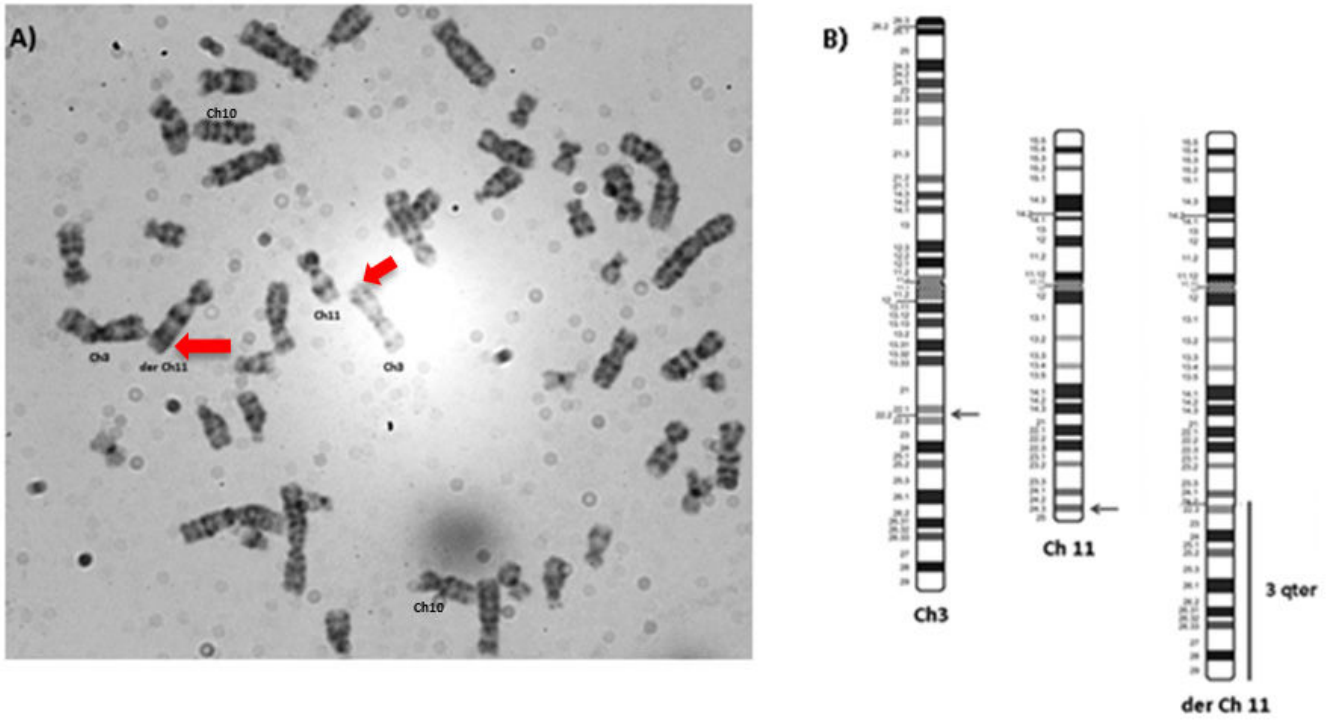

Figure 2. Unbalanced karyotype of the fetus, showing a) partial monosomy 11 and a partial trisomy 3: 46, XX, der (11)t (3,11) (q22.2, q24.3). b) Partial ideogram showing the derivative chromosome 11 resulting from a translocation between chromosomes 3 and 11, and leading to a partial monosomy of the long arm of chromosome 11 (11q24.3-11qter) and a partial trisomy of the long arm of chromosome 3 (3q22.2-3qter). Arrows indicate the breakpoints.

DISCUSSION

In the present case, we report a female fetus karyotype with an unbalanced chromosome resulting in a 11q24.3 to 11qter deletion and a 3q22.2 to 3qter duplication. No reports of this combination of chromosomal abnormalities were found in the literature.

Prenatal sonography revealed trigonocephaly with apparently normal brain structures, omphalocele protruding out of the abdominal wall, on the right side of the umbilical cord, that contained the liver and bowel, claw hand, and an inwards and downwards deviation of the axis of the foot with respect to the leg, defect known as bot or equinovarus foot.

The chromosome microarray results for the proband revealed three copy number changes. First, there is a large copy gain from the long arm of chromosome 3, from 3q22.2 through terminal 3q29. This copy gain is approximately 63.07 Mb in size and contains at least 496 genes which included 262 OMIM genes. Many of the reported 3q copy gains are associated with unbalanced translocations where the corresponding copy loss impacts the phenotype. Copy gains of 3q have been identified in individuals with growth delays, dysmorphic facial features, microcephaly, intellectual disability, heart defects, and structural brain anomalies (de Azevedo Moreira *et al*., 2005; Grossmann *et al*., 2009; Dundar *et al*, 2011; Abreu-González *et al*., 2013; Chen *et al*., 2013; Zhu *et al*, 2013; Lurie, 2016; Dworschak *et al*., 2017).

The present results not only underline the importance of trisomy 3q22.2→3qter but also uncover certain unprecedented clinical features which expand on the current knowledge of the clinical phenotypes of this trisomy syndrome. The limited number of relevant previous studies put a restriction on the clear delineation of the phenotype-karyotype correlation of trisomy 3q22.2→qter.

The second copy number change was a 4.08 Mb deletion of the terminal long arm of chromosome 11, which contains at least 23 genes, including 10 OMIM genes. Deletions of this terminal 11q region are found in individuals with JBS also known as terminal 11q deletion syndrome. JBS is a rare genetic disorder associated with multiple dysmorphic features and occurs in 1 in 100,000 live births with a female predominance of 2:1 (Jacobsen *et al*., 1973; Penny *et al*., 1995; Pivnick *et al*., 1996; Grossfeld *et al*., 2004). JBS occurs due to the loss of contiguous set of genes present at 11q23 with deletion size varying from 7 to 20 Mb but could be as small as 2.9 Mb in some cases (Penny *et al*., 1995; Grossfeld *et al*. 2004; Guerin *et al*., 2012).

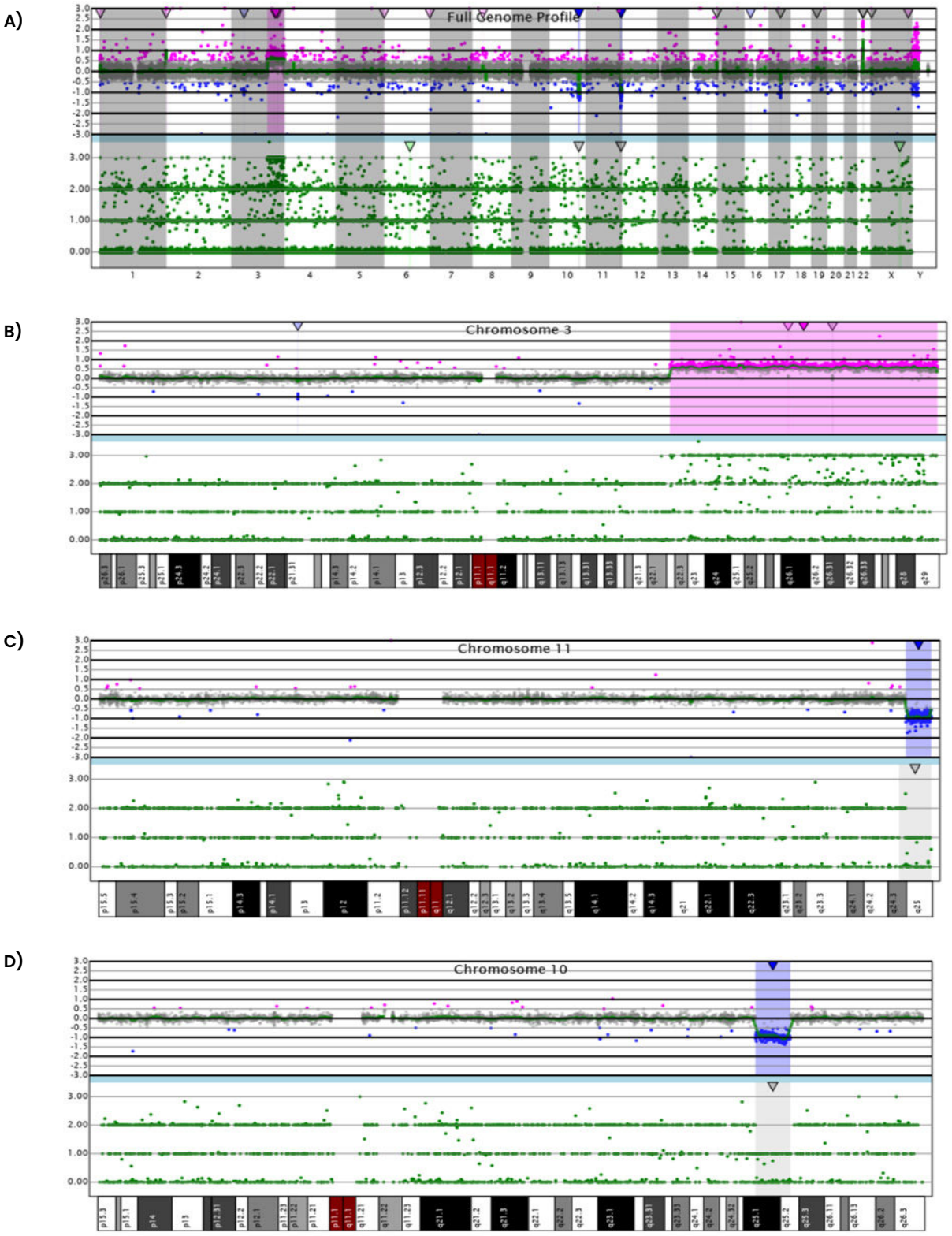

Figure 3. Chromosome microarray showing a) Wole genome data (copy number and SNP data), b) Copy gain from 3q22.2-3qter (associated with unbalanced translocation), c) Copy loss from 11q25-11qter (associated with unbalanced translocation), d) Interstitial 10q deletion. The whole genome plot shows, from chromosome 1 on the left to X/Y chromosomes on the right. Data for each chromosome is plotted from pter->qter. For copy number analysis, the scale is log10, with a normal copy number at zero. Copy losses have a log ratio of approximately -1.0 (a 1:2 ratio between patient and control), with gains of approximately 0.6 (a 3:2 ratio). In blue are shown the deleted regions and in pink the copy gains. The gray probes are normal and the green line shows the moving average of the copy number. Triangles at the top of the graph indicate abnormal regions. The SNP data shows three separate lines, at 0.00, 1.00, and 2.00, displaying the AA, AB, and BB genotypes. A gain of one genotype (due to a gain in copy number) will show data on a fourth line (the 3.00 line), whereas a loss of one genotype (due to a deletion) will show only one genotype, either one allele A or B.

A "de novo" deletion is observed in 85% of patients with JBS, and 15% cases arise as a result of parental translocations (Van Zutven *et al.*, 2009). The phenotype may vary with deletion size, but the most common features include mild-to-moderate intellectual disability, speech delay, psychomotor delay, congenital heart disease, trigonocephaly, thrombocytopenia and characteristic facial features. Occasionally, immunologic and hormonal problems may be present (Bernaciak *et al.*, 2008; Tyson *et al.*, 2008; Mattina *et al.*, 2009; Favier *et al.*, 2015). The implementation of array technology in the clinics has permitted precise characterization of the deletions and detailed genotype–phenotype correlation in cases with JBS.

The last copy number change is a 5.66 Mb deletion of interstitial 10q. There are at least 18 genes in this region including 12 OMIM genes. Partial deletion of the long arm of chromosome 10 is a relatively frequent cytogenetic finding. There are over 100 patients described in the literature (Wilkie *et al.*, 1993; Ogata *et al.*, 2000; Lukusa *et al.*, 2002; Irving *et al.*, 2003; Yatsenko *et al.*, 2009). Most cases of terminal 10q deletion have a breakpoint around 10q26 occurring either as "de novo" or as familial translocation with variable phenotypic features (Irving *et al.*, 2003).

The most striking phenotypic features in patients with the 10q terminal deletions include facial dysmorphism (microcephaly with prominent forehead, triangular face, down slanting palpebral fissures, coarse facial features, bilateral esotropia, epicanthic folds, synophrys, prominent nasal bridge, short philtrum, and small mouth), growth failure and developmental delay, intellectual disability, ophthalmoplegia, syndactyly, congenital cardiac, urinary and anogenital anomalies; however, there is significant heterogeneity in the clinical presentation (Lukusa *et al.*, 2002; Irving *et al.*, 2003; Yatsenko *et al.*, 2009). Cerebral nervous system anomalies such as agenesis of the corpus callosum are reported in partial monosomy 10q. In regard to the visceral anomalies, one third to half of the patients with the partial monosomy 10q syndrome have congenital heart disease such as ventricular septal defect, patent ductus arteriosus, pulmonary stenosis or a coarctation of the aorta (Tanabe *et al.*, 1999; Waggoner *et al.*, 1999).

Interstitial deletions of 10q region similar to the deletion identified in this fetus are relatively rare. Patients with overlapping deletions noted in the DECIPHER database have phenotypes which include developmental delays, behavior abnormalities and facial

dysmorphisms. One of the genes in this 10q region is *SMC3*. Deletions and mutations of *SMC3* are found in individuals with Cornelia de Lange syndrome 3 characterized by dysmorphic facial features, intellectual disability, developmental delay, and occasionally limb malformations (McCandless *et al.*, 2000; Kehrer-Sawatzki *et al.*, 2005; Deardorff *et al.*, 2007; Hillman *et al.*, 2013; Bragin *et al.*, 2014; Gil-Rodríguez *et al.*, 2015;).

The resolution of karyotype analysis in prenatal diagnosis has historically been considered sufficient to detect chromosomal abnormalities in the 5–10 Mb range. In our case, the 10q deletion was 5.66 Mb and had seemingly normal G-banding patterns (Figure 2). In prenatal diagnosis, microarray analysis can unambiguously detect chromosomal imbalances and has substantial advantages by overcoming the limitations of resolution and banding quality that are inherent in conventional karyotype analysis (Wapner *et al.*, 2012; Yatsenko *et al.*, 2013).

In summary, we described the prenatal diagnosis and molecular cytogenetic characterization of a "de novo" partial trisomy 3q22.2→3qter, partial monosomy 11q25→11qter and an interstitial deletion 10q25.1-10q25.2. We demonstrated the usefulness of chromosome microarray in the prenatal identification of a "de novo" chromosome aberration and that the information acquired by molecular cytogenetic analyses was very helpful in genetic counseling.

CONCLUSIONS

Concomitant partial trisomy 3q22.2→3qter, partial monosomy 11q25→11qter and interstitial deletion 10q25.1-10q25.2 is unusual in a clinical context. The coexistence of three copy number changes complicates the clinical symptoms and creates a chimeric disorder marked by characteristics of three chromosomal abnormalities. The use of chromosome microarray in prenatal diagnosis can elucidate the genetic etiology in fetuses with ultrasound abnormalities as well as enable proper genetic counseling management of prenatal care and informed decision making. The differences that can be observed in pre and postnatal phenotypes are important for counseling and further studies regarding phenotypic variability and genotype. Moreover, there is a distinct lack of genotype–phenotype correlation between individual microarray findings; thus, this case report should add useful information to the emerging atlas of chromosomal abnormalities associated with specific prenatal ultrasound findings.

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