

CASE REPORT

Prenatal diagnosis of trisomy 6q25.3-qter and monosomy 10q26.12-qter by array CGH in a fetus with an apparently normal karyotype

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Funding Information

No funding information provided.

Received: 16 January 2014; Revised: 7
September 2014; Accepted: 15 September
2014

Clinical Case Reports 2015; 3(2): 92–95

doi: 10.1002/ccr3.162

Introduction

A 29-year-old G2P1001 (currently pregnant second time and had one previous full-term living child) female was referred to the Center for Medical Genomics at the Magee Womens Hospital after the first trimester screening for Down syndrome, adjusted for age, trisomy 21 risk of 1:16, and a trisomy 18 risk of 1:49. A three-generation family pedigree did not reveal history of birth defects, intellectual disability, or recurrent miscarriages. Fetal ultrasound was performed at 13 weeks of gestation and demonstrated a simple fetal pelvic cyst measuring 12 × 7 × 9 mm and an enlarged fetal bladder. The patient declined chorionic villi sample (CVS) analysis. Follow-up ultrasound at 16 weeks of gestation revealed a persistently enlarged, thick-walled fetal bladder, echogenic kidneys, bilateral pyelectasis measuring 6 mm in anterior to posterior direction for each kidney, two-vessel cord, septated cystic hygroma arising

Key Clinical Message

We present the prenatal case of a 12.5-Mb duplication involving 6q25-qter and a 12.2-Mb deletion encompassing 10q26-qter diagnosed by aCGH, while conventional karyotype showed normal results. The genotype–phenotype correlation between individual microarray and clinical findings adds to the emerging atlas of chromosomal abnormalities associated with specific prenatal ultrasound abnormalities.

Keywords

Array CGH, deletion 10q, duplication 6q, fetal ultrasound, prenatal diagnosis, unbalanced translocation.

from the posterior neck, oligohydramnios with an amniotic fluid index (AFI) of 53 mm, and thickened placenta at 31 mm (Fig. 1). The fetal facial profile appeared normal. Amniocentesis performed at 16 weeks and 5 days of gestation showed a normal male karyotype. Based on the presence of multiple fetal anomalies on ultrasound, fetal DNA was extracted from the cultured amniotic fluid sample using the Puregene Genomic DNA Purification Kit (Qiagen, Valencia, CA), and studied by whole-genome oligonucleotide Comparative Genomic Hybridization (aCGH) microarray analysis using a custom 135 K feature platform (designed by Signature Genetics Laboratories, Spokane, WA; manufactured by Roche NimbleGen, Madison, WI). Array CGH analysis revealed a 12.57 million base pairs (Mb) gain in the 6q25.3-qter region and a 12.24-Mb loss within the 10q26.12-qter (arr[hg18] 6q25.3q27 (158,171,843-170,743,204)×3, 10q26.12q26.3(123,017,596-135,253,240)×1 (Fig. 2A and B). The

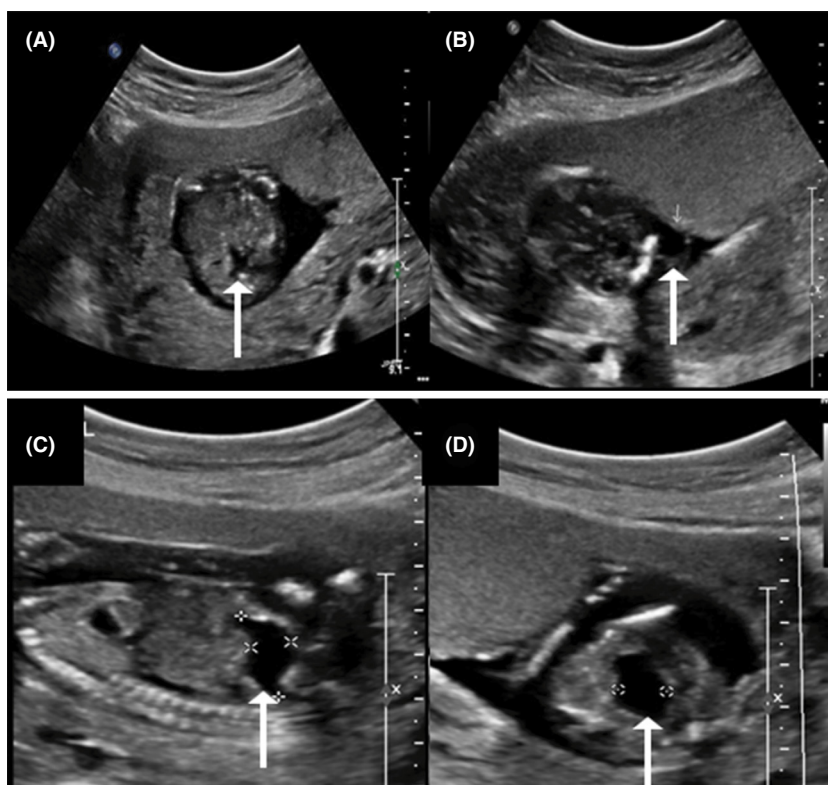


Figure 1. Fetal ultrasound at 16 weeks of gestation. (A) Fetal kidneys with pyelectasis. (B) Multiplanar image showing cystic hygroma. (C) Ultrasound image depicting dilated bladder. (D) Multiplanar image showing dilated bladder.

12.5-Mb terminal 6q duplication caused trisomy for 46 OMIM genes, and the 12.2-Mb terminal 10q deletion caused monosomy for 49 OMIM (Online Mendelian Inheritance in Man database: www.omim.org) genes. Confirmatory fluorescence *in situ* hybridization (FISH) analysis with 6q and 10q subtelomere-specific probes (Abbott Molecular, Des Plaines, IL) showed a derivative chromosome 10 resulted from an unbalanced translocation between the distal 6q and 10q (Fig. 2D). Assessment of parental chromosomes 6q and 10q by FISH analysis was normal, implying a *de novo* chromosomal abnormality in the fetus (46,XY.ish der(10)t(6;10)(q25.3;q26.12)(RP11-665C2+,RP11-702C24-)dn. After extensive genetic counseling, the patient elected to terminate the pregnancy. Autopsy confirmed significant pyelectasis of one kidney with prominent glomerulocystic changes and dysplastic changes in the other kidney. A right foot talipes varus and bulbous tips of all digits were also present. Postmortem placental examination also revealed a two-vessel cord.

This study demonstrates a *de novo* chromosomal aberration involving a 12.57-Mb duplication at 6q25.3-qter and a 12.24-Mb deletion at 10q26.12-qter associated with multiple structural abnormalities on fetal ultrasound. This is the first prenatal case of 6q25.3-qter segmental trisomy

diagnosed with the use of aCGH. 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, however, the 10q deletion and 6q duplication regions were greater than 10 Mb and had seemingly normal G-banding patterns (Fig. 2C). We present an example in which karyotype analysis failed to detect a derivative chromosome 10, where a 12.24-Mb 10q terminal segment has been replaced by a 12.57-Mb segment from the terminal 6q. In our case, two rearranged segments are of similar size, ~12 Mb; and both 6q25–q27 and 10q26.1–q26.3 segments embrace a single G-positive band, thus the exchanged chromosomal regions have similar G-banding pattern. Therefore, a derivative chromosome 10 appeared to have the expected size and G-banding pattern as a normal chromosome 10. Multiple regions in human karyotype have similar banding patterns, and thus rearrangements involving alike segments will remain undetected even by high-resolution karyotype analysis, unless molecular technique such as aCGH is used.

Pure trisomy of the distal 6q is a very rare event with only a few cases described in the literature. Since the first description by de Gouchy et al. [1], the duplication of

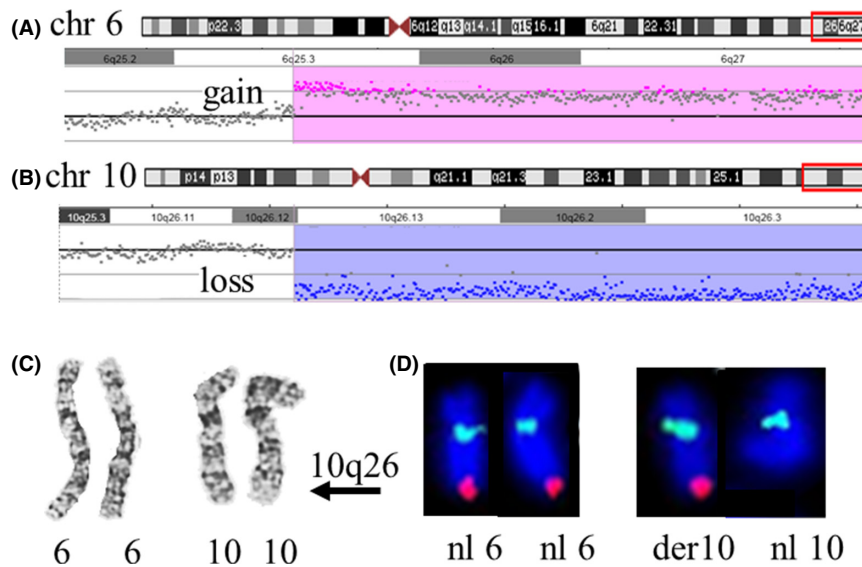


Figure 2. The results of cytogenetic analysis of the fetus. (A) Idiogram of chromosome 6 and microarray plot showing a 12.57 Mb gain involving the distal 6q region (pink-shaded area). (B) Microarray plot demonstrating a deletion in the terminal long arm of chromosome 10. Top, idiogram of chromosome 10 with a deleted region shown by a red rectangle. Below, a magnified view of the 10q26.12-qter terminal deletion (blue shaded area). (C) Partial G-banded karyotype showing chromosome 6 and 10 homologues. (D) Fluorescence *in situ* hybridization (FISH) analysis with a 6q subtelomere-specific probe (red), showing an additional 6qter signal present on the derivative chromosome 10. FISH analysis with a 10q subtelomere-specific probe is not shown.

the distal 6q has a well-recognized phenotype. Common phenotypic features among children with 6q25-qter partial trisomy include cranial anomalies, facial dysmorphism (slanting palpebral fissures, telecanthus, micrognathia, carp-shaped mouth), anterior webbing of the neck, cardiac anomalies, and joint contractures; and profound psychomotor retardation [1–3]. Prenatal diagnosis of trisomy 6q22.2qter was first reported in 1997 after ultrasound findings of cerebellar vermis, thick nuchal folds, bilateral hydronephrosis, ascites, bilateral clubfeet, distal arthrogryposis, atrial septal defect, patent ductus arteriosus, and ambiguous genitalia were identified [4]. All ultrasound findings with the exception of the absent cerebellar vermis were confirmed postnatally. The 6q22-qter duplication region in that case was substantially larger than our presentation.

Partial deletion of the long arm of chromosome 10 is a relatively frequent cytogenetic finding. There are now over 100 patients described in the literature [5–9]. Most cases of terminal 10q deletion have a breakpoint around 10q26 occurring either as *de novo* or as familial translocation with variable phenotypic features [5]. 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 [5, 6, 9]. In our case, ultrasound persistently detected urinary tract anomalies that have been associated with monosomy 10q26 [7].

Array comparative genomic hybridization (aCGH) has been used to define the 600-kb critical region at 10q26. This region includes *DOCK1* and *C10orf90* genes, thought to be important determinants of craniofacial, urogenital, and neuropsychiatric phenotypes [9]. Both *DOCK1* and *C10orf90* genes were deleted in our fetus. The distal 10q region is known to be the critical for the internal and external development of the urogenital organs [7]. Haploinsufficiency of *PAX2* (10q24.3-q25.1), *GFRA1* (10q25.3), and *FGFR2* (10q26.12) genes was proposed to result in abnormal male genital development. Terminal 10q deletions have also been associated with complete sex reversal and gonadal dysgenesis, imperforate anus, and ambiguous genitalia [8]. In our case, the 10q deletion caused haploinsufficiency for the *FGFR2* gene and urinary tract abnormalities were observed, however, genitalia were not ambiguous and anogenital defects were not found on fetal ultrasound. Ultrasound at 13 and 16 weeks detected structural defects, including urogenital abnormalities (enlarged bladder, echogenic kidneys, bilateral pyelectasis),

in addition to the septated cystic hygroma, consistent with features seen in patients with terminal 6q25-qter duplications and 10q26-qter deletions.

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 [10–12]. Most microarray findings have been correlated with postnatal phenotypes, and there is a distinct need to build a database of microarray findings with prenatal ultrasound phenotyping. Our case demonstrates the utility of microarray in detecting a complex chromosomal imbalances that presented with nonspecific findings of fetal pelvic cyst and an enlarged fetal bladder in the first trimester followed by second trimester ultrasound that detected thick-walled fetal bladder, echogenic kidneys, bilateral pyelectasis, two-vessel cord, septated cystic hygroma arising from the posterior neck, and oligohydramnios. Facial dysmorphism, ambiguous genitalia, joint contractures, cardiac abnormalities, and syndactyly were not detected in our case. The use of aCGH in prenatal diagnosis can elucidate the genetic etiology in fetuses with ultrasound abnormalities and 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 and this case report will add to the emerging atlas of chromosomal abnormalities associated with specific prenatal ultrasound findings.

Conflict of Interest

None declared.

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