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Short Communication

Molecular cytogenetic characterization of inv dup del(8p) in a fetus associated with ventriculomegaly, hypoplastic left heart, polyhydramnios and intestinal obstruction

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ABSTRACT

Objective: To present molecular cytogenetic characterization of inv dup del(8p) in a fetus with congenital malformations.

Materials and Methods: A 19-year-old, primigravid woman underwent cord blood sampling at 31 weeks of gestation because of prenatal ultrasound findings of polyhydramnios, intestinal obstruction, right ventriculomegaly, and hypoplastic left heart. Preterm precipitous labor and delivery occurred at 32 weeks of gestation. Array comparative genomic hybridization (aCGH), conventional cytogenetic analysis and metaphase fluorescence *in situ* hybridization (FISH) were applied on cord blood lymphocytes. aCGH was also applied on the umbilical cord. Conventional cytogenetic analysis was applied on parental bloods.

Results: aCGH detected an 11.35 Mb deletion in 8p23.3-p23.1 encompassing *SOX7* and *GATA4*, and a 31.99 Mb duplication in 8p23.1-p11.1 in the fetus. Metaphase FISH confirmed inv dup del(8p). The fetus had a karyotype of 46,XX,der(8)del(8)(p23.1) inv dup(8) (p11.1p23.1). Parental karyotypes were normal. A malformed fetus was delivered with facial dysmorphism.

Conclusion: Fetuses with inv dup del(8p) may present central nervous system (CNS) abnormality and congenital heart defect on prenatal ultrasound. Prenatal diagnosis of concomitant CNS and cardiac abnormalities should include a differential diagnosis of chromosome 8p inverted duplication deletion syndrome.

Introduction

The chromosome 8p inverted duplication deletion syndrome caused by inv dup del(8p) is very uncommon and has been found in one in 10,000–30,000 live births [1]. The clinical manifestations of this disorder include mental retardation, facial dysmorphism, central nervous system (CNS) abnormality, hypotonia, orthopedic abnormalities, scoliosis/kyphosis, and congenital heart defects [1–4]. Soler et al [5] first reported prenatal diagnosis of inv dup(8p) with deletion of the distal 8p23 region and duplication of the remaining 8p in a fetus with clubfeet, clenched left hand, subcutaneous edema, and bilateral hydrocephalus. We additionally

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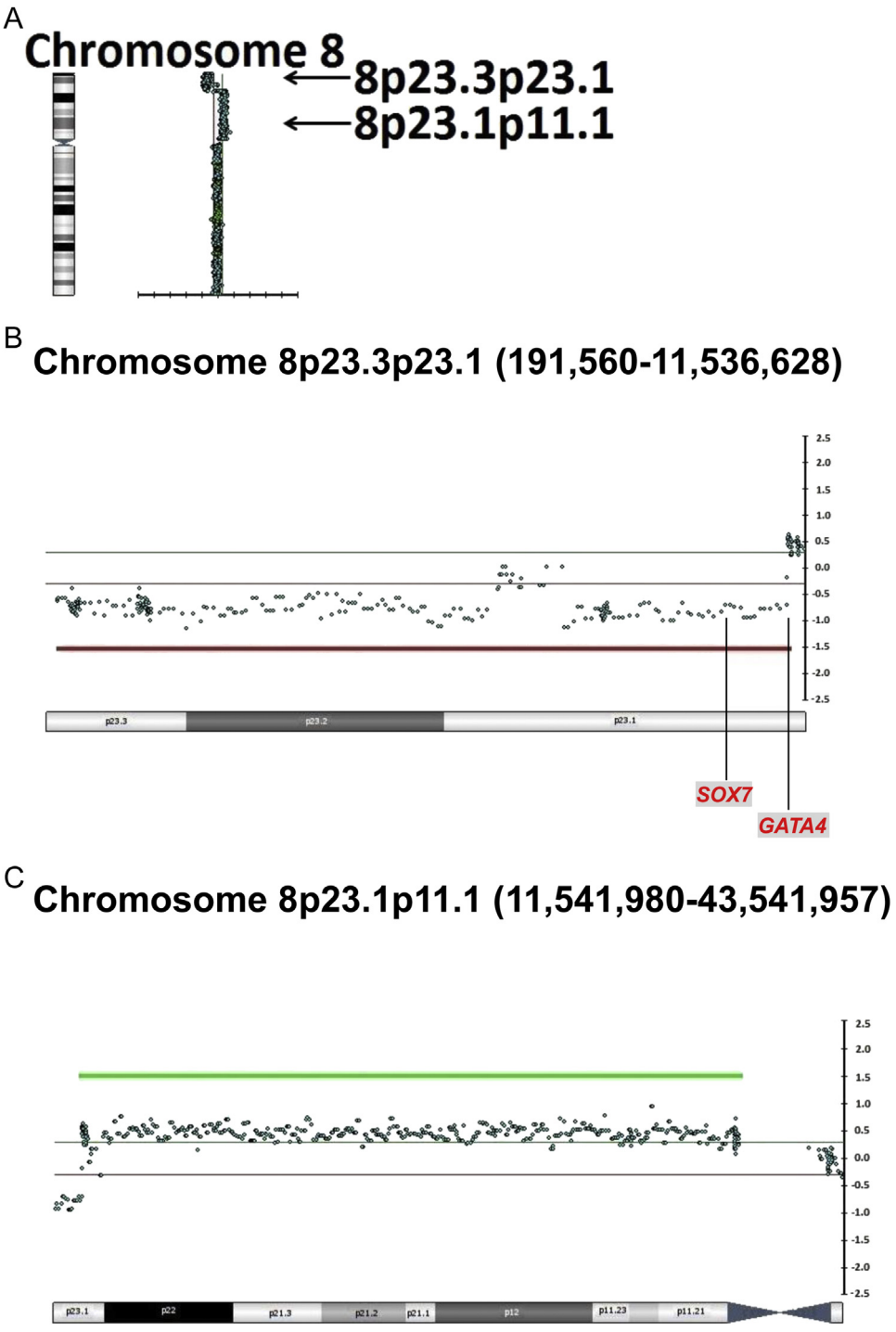

Figure 1. Array comparative genomic hybridization of DNA extracted from the umbilical cord shows (A) an 8p23.3-p23.1 deletion and an 8p23.1p11.1 duplication with (B) an 11.35 Mb deletion in 8p23.3-p23.1 encompassing *SOX7* and *GATA4*; and (C) a 31.99 Mb duplication in 8p23.1-p11.1.

report molecular cytogenetic characterization of inv dup del(8p) in a fetus with ventriculomegaly, hypoplastic left heart, polyhydramnios, and intestinal obstruction.

Materials and methods

Clinical description

This was the first pregnancy of a 19-year-old woman. Her husband was aged 30 years, and there was no family history of congenital malformations. The pregnancy was uneventful until 31 weeks of gestation when right ventriculomegaly, hypoplastic left heart, polyhydramnios, and intestinal obstruction were first noted. She underwent cord blood sampling at 31 weeks of gestation. Preterm precipitous labor and delivery occurred at 32 weeks of gestation. Array comparative genomic hybridization (aCGH), conventional cytogenetic analysis, and metaphase fluorescence *in situ* hybridization (FISH) were applied on cord blood lymphocytes. aCGH was also applied on the umbilical cord. Conventional cytogenetic analysis was applied on parental bloods.

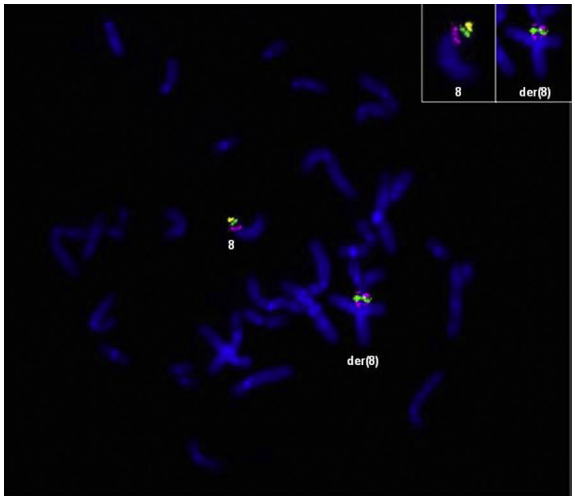

Figure 2. Metaphase fluorescence *in situ* hybridization on cord blood lymphocytes using an 8p23.2-specific probe RP11-656H18 (yellow), an 8p22-specific probe RP11-722B21 (green) and an 8p12-specific probe RP11-893C11 (red), shows a linear order of yellow–green–red in the normal chromosome 8 and an abnormal linear order of red–green–green–red in the derivative chromosome 8 [der(8)], consistent with inv dup del(8p) in the der(8).

Conventional cytogenetic analysis

Routine cytogenetic analysis using G-banding techniques at 550 bands of resolution was performed on parental bloods and cord blood at birth. The samples were subjected to cell culture according to the standard blood cytogenetic protocol.

aCGH

Whole-genome aCGH on the DNA extracted from the cord blood acquired by cord blood sampling at 31 weeks of gestation was performed using the Agilent Human Genome G3 SurePrint 8×60K ISCA Oligonucleotide Microarray (Agilent Technologies, Santa Clara, CA, USA), which has 60,000 probes and a resolution of ~60 kb across the genome. Whole-genome aCGH on the DNA extracted from umbilical cord after delivery was performed using CytoChip ISCA Array (Illumina, San Diego, CA, USA), which has 60,000 probes and a median resolution of 51 kb across the entire genome according to the manufacturer's instruction. The DNA from the cord was extracted through the manufacturer's protocol of a QIAamp DNA Mini kit (Qiagen, Inc., Valencia, CA, USA). Then, 0.65 μg of the extracted DNA was labeled with Cy3 dye while the same amount of normal female genomic DNA (gDNA, G1521; Promega, Madison, WI, USA) was labeled in Cy5 dye as a control. The experiment was performed according to the procedures recommended from Illumina CytoChip Oligo Microarray Reference Guide. The data were represented using BlueFuse Multi software (Illumina).

FISH

Metaphase FISH analysis was performed on cultured cord blood lymphocytes using an 8p23.2-specific bacterial artificial chromosome (BAC) probe RP11-656H18 (2,915,262–3,080,885) [hg 19] (Cy5, yellow spectrum), an 8p22-specific BAC probe RP11-722B21 (12,972,017–13,154,608) [hg 19] (Fluorescein isothiocyanate, green spectrum), and an 8p12-specific BAC probe RP11-893C11 (29,477,207–29,665,027) [hg 19] (Texas red, red spectrum) according to the standard FISH protocol.

Results

The aCGH analysis revealed a result of arr 8p23.3p23.1 (191,530–11,536,657)×1; arr 8p23.1p11.1 (11,545,953–43,541,986) ×3 in the cord blood and a result of arr 8p23.3p23.1 (191,560–11,536,628)×1; arr 8p23.1p11.1 (11,541,980–43,541,957) ×3 in the umbilical cord. The 11.35 Mb deletion region in 8p23.3-p23.1 encompasses *SOX7* and *GATA4* (Figure 1). Metaphase FISH

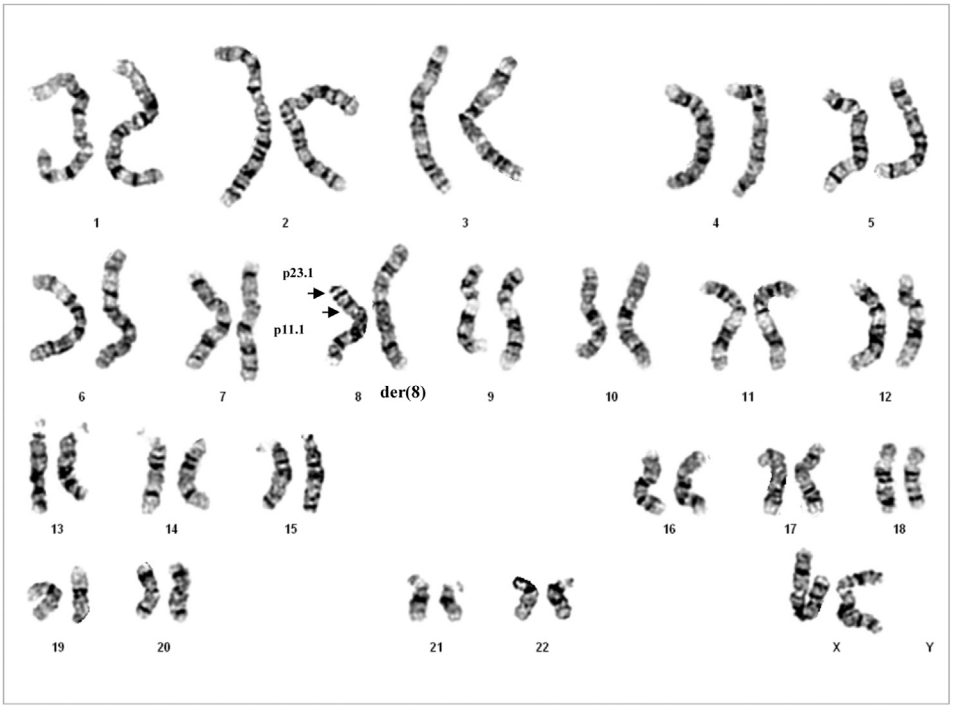

Figure 3. A karyotype of 46,XX,der(8)del(8)(p23.1) inv dup(8)(p11.1p23.1).

analysis showed a linear order of yellow–green–red in the normal chromosome 8 and an abnormal linear order of red–green–green–red in the derivative chromosome 8 [der(8)], indicating the presence of inv dup del(8p) in the der(8) (Figure 2). The karyotype of cord blood lymphocytes was 46,XX,der(8)del(8)(p23.1) inv dup(8)(p11.1p23.1) (Figure 3). A 2142 g female malformed fetus was delivered at 32 weeks of gestation with a body length of 42 cm, facial dysmorphism of prominent forehead, micrognathia, large low-set ears, hypertelorism, a wide nasal base, and a left preauricular tag.

Discussion

The chromosomal rearrangement in this case consists of a deletion of the telomeric region of 8p23.1-pter and an inverted duplication of the rest 8p region of 8p23.1-p11.1. In this presentation, we present the cytogenetic and molecular characterization using aCGH, metaphase FISH, and conventional cytogenetics, and report the prenatal ultrasound findings of ventriculomegaly, hypoplastic left heart, intestinal obstruction and polyhydramnios. Soler et al [5] reported del(8p)/inv dup(8p) in a fetus with hydrocephalus, subcutaneous edema, clubfeet, and clenched hand. Pramparo et al [6] reported del(8p)/inv dup(8p) at chorionic villus sampling in a fetus with hydrops fetalis, atrial and ventricular septal defects, dilated left ventricle and pericardial effusion.

The present case is associated with congenital heart defect and the deletion of *GATA4* and *SOX7*. *GATA4* [Online Mendelian Inheritance in Man (OMIM) 600576] encodes GATA-binding protein 4 which belongs to the GATA-binding proteins that are a group of structurally related transcription factors that control gene expression and differentiation in a variety of cell types. GATA4 is expressed in endodermally derived tissues and the heart [7], and regulates genes critical for myocardial differentiation and function such as *TNNC1* (OMIM 191040), *MYH6* (OMIM 160710), and *NPPB* (OMIM 600295) [8]. Mutations and deletions of *GATA4* have been involved in the etiology of some autosomal dominant congenital heart defects such as testicular anomalies with or without congenital heart disease (OMIM 615542), atrial septal defect 2 (OMIM 607941), atrioventricular septal defect 4 (OMIM 614430), tetralogy of Fallot (OMIM 187500), and ventricular septal defect 1 (OMIM 614429) [9–19]. *SOX7* (OMIM 612202) belongs to SOX proteins that are transcription factors critical for the regulation of diverse developmental processes [20]. SOX7 and GATA4 are competitive activators of *Fgf-3* transcription [21]. *SOX7* has been implicated in congenital heart defects [22] and congenital diaphragmatic hernia [23,24].

The present case is also associated with ventriculomegaly and the deletion of CNS function and development genes such as *DLGAP2* (OMIM 605438), *CLN8* (OMIM 607837), *ARHGEF10* (OMIM 608136), *CSMD1* (OMIM 608397), and *MIR124-1* (OMIM 609327), and the duplication of brain development genes such as *MTMR7* (OMIM 603562), *SGCZ* (OMIM 608113), and *ATP6V1B2* (OMIM 606939).

In conclusion, fetuses with inv dup del(8p) may present CNS anomaly and congenital heart defect on prenatal ultrasound. Prenatal diagnosis of concomitant CNS and cardiac abnormalities should include a differential diagnosis of chromosome 8p inverted duplication deletion syndrome.

Conflicts of interest

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

Acknowledgments

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