Prenatal diagnosis of ventricular septal defect and trisomy 7q11.23q21.3 in two fetuses: A case report

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Genet. Mol. Res. 17 (1): gmr16039878

Received January 02, 2018

Accepted February 18, 2018

Published February 20, 2018

DOI http://dx.doi.org/10.4238/gmr16039878

ABSTRACT. The objective of prenatal diagnosis (PD) is to provide prenatal diagnostic testing services for genetic conditions that enable families to make informed choices consistent with their individual needs and values, and to support them in deal with the outcome of such testing. This case we reported is about two fetuses with ventricular septal defect (VSD) and trisomy 7q11.23q21.3. With Karyotypic analyses, array-SNP and FISH, the trisomy 7q11.23q21.3 of two fetuses inherit from her mother. In her family pedigree, the carriers are all normal, especially heart. Because the defects with diameter is 3.1mm,2.9mm respectively without other abnormal phenotype, so surgery and catheter interventional treatment are both good methods to treat the VSD. Although we didn't advise the woman terminal this pregnancy, the woman need take examinations to observe two fetuses regularity by ultrasound examination in the hospital.

Key words: Prenatal diagnosis; VSD; Array-SNP; FISH; Trisomy 7q11.23q21.3

INTRODUCTION

With technological innovations and the increased accumulation of clinical knowledge, the importance of prenatal diagnosis has also increased in recent times. Invasive amniocentesis and chorionic villus sampling procedures, non-invasive maternal serum screening, and high-resolution ultrasound examination were introduced in the late 1970s and have become the standard for prenatal diagnosis. The main clinical indications for prenatal diagnosis include advanced maternal age for increased risk of Down syndrome, abnormal findings on maternal serum screening, abnormal ultrasound findings, family history of chromosomal or genetic disorders,

history of spontaneous abortion, pregnancy in which the women had previously given birth to children with specific diseases, and recently integrated maternal serum fetal DNA sequencing for aneuploidy screening.

The main diagnostic method used early in pregnancy is cytogenetic analysis, and to some extent, it helps guide the termination of pregnancies in which the child potentially has a serious disease. However, it has a low analytical resolution of about 5–10 megabase (Mb). Various DNA-based molecular approaches have now been introduced to enable rapid prenatal screening and diagnosis, such as fluorescence *in situ* hybridization (FISH), quantitative fluorescence-polymerase chain reaction, multiplex ligation-dependent probe amplification, comparative genomic hybridization array, and single nucleotide polymorphism (SNP) array.

Here we describe a 36-year-old woman whose fetuses have dup (7q21.11-q21.3,15.54Mb) revealed by non-invasive prenatal testing (NIPT). Cytogenetic analysis and array-SNP analysis found that the fetuses both had a derivative chromosomes 4 and trisomy 7q11.23q21.3. Ultrasound examination revealed VSD. We took some measures to search where the derivative chromosomes 4 and trisomy 7q11.23q21.3 came from, and whether VSD was related to the derivative chromosomes 4 and trisomy 7q11.23q21.3.

MATERIAL AND METHODS

Clinical report

A 36-year-old G3P1 woman was referred to us at about 23 weeks of gestation for genetic amniocentesis because non-invasive prenatal testing had shown that her twin fetuses had a 15.54-Mb duplication in 7q21.11-q21.3. We were not sure whether the fetuses shared a chorionic cavity or had two separate ones, because the mother had not received ultrasound examination during early pregnancy. We collected 30 ml amniotic fluid for each foetus for cytogenetic analysis and SNP array analysis. The woman had an older son, aged 7 years. Neither she nor her husband had a history of consanguinity or genetic disease. They did not smoke or drink and had not been exposed to radiation or chemical insult. Routine blood, urine, and liver and renal function analyses were normal for both parents, and electrocardiography and chest radiography showed no abnormalities in their hearts and lungs.

Cytogenetic analysis

Amniocytes were cultured in two lines from 20 ml of amniotic fluid collected from each foetus. Fetal chromosome analyses were performed on metaphasic amniocytes, so amniocytes cultivated for 9–11 days were examined using standard procedures.

Short-term phytohemagglutinin-stimulated peripheral blood lymphocyte cultures were prepared from the blood of the parents, their older son, and the woman's parents by using standard procedures. At least 30 metaphase plates were analyzed for everyone. Karyotyping was performed using an image analyser (CW4000; Leica).

Array-SNP analysis

For SNP array analysis, genomic DNA was isolated from the amniocytes of the two fetuses and the peripheral blood of the woman, her husband, their son, and her parents. The analysis was conducted with a DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA) and a QIAcube automated DNA extraction robot (Qiagen, Hiden, Germany). The samples were adjusted to a final concentration of 50 ng/μl. The HumanOmni1-Quad Chip (Illumina Inc., San Diego, CA) and the Illumina BeadScan genotyping system (Bead station Scanner; Illumina Inc.) were employed to obtain the signal intensities of SNP probes. The chip contains over 1.1 million loci across the human genome. Genome Studio V2011 software was used to analyze the genotypes (human genome builds 37/Hg19 for analysis) and evaluate the experimental quality. The call rates of the samples exceeded 99.5%.

Fluorescence *in situ* hybridization (FISH) analysis

FISH analysis was undertaken on metaphase spreads from the amniocytes, using a chromosome 4p16.3 (2,156,895-2,351,734) probe, a chromosome 7q21.12 (86,802,721-86,975,903) probe, and a chromosome 7p22.3 (1,645,493-1,814,816) probe (VYSIS), according to the manufacturer's instructions. Metaphase plates for each chromosome were analyzed using fluorescence microscopy. At about 29 weeks of gestation, the woman underwent fetal ultrasound examination systematically and routinely.

Ultrasound examination

About 29 weeks of gestation, the woman took fetal ultrasound examination systematically and roundly.

RESULTS

Conventional cytogenetic analysis of the amniocytes demonstrated that both fetuses had the same karyotype, namely, 46, XN,der (4)ins (4?) (q31.3;?) (Figure 1), and SNP array analysis showed that both had trisomy 7q11.23q21.3 (77,283,926-93,528,760) (Figure 2). To identify the origin of the derivative chromosome 4 and trisomy, we recommended cytogenetic and SNP array analyses for the woman and her husband as well. The woman's karyotype was 46,XX,der (4)ins (4;?) (q31.3;?) and she had 7q11.23q21.3 (77,283,926-93,528,760) × 3 (data not shown), but her husband had no genetic anomalies. Simultaneously, her 7-year-old son and her parents also underwent cytogenetic and SNP array analyses. The older son and the woman's mother had the same karyotype and SNP array results (data not shown), while the woman's husband and father had normal findings (data not shown). FISH analysis showed the repetition of the 7q11.23q21.3 insert in the long arm of chromosome 4, indicative of a derivative chromosome 4 (Figure 3). Fetal ultrasound examination showed that both fetuses had VSDs (Φ = 3.1 and 2.9).

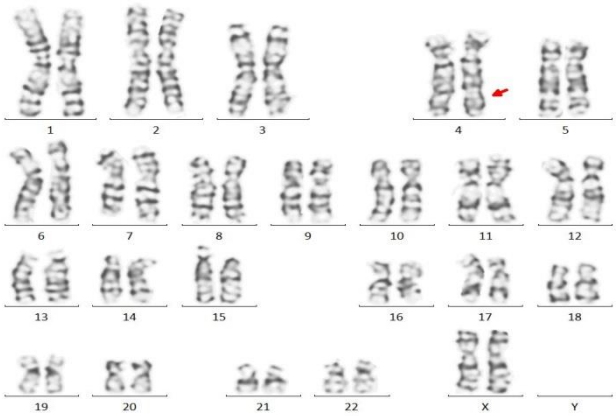

Figure 1. one foetus's karyotype.

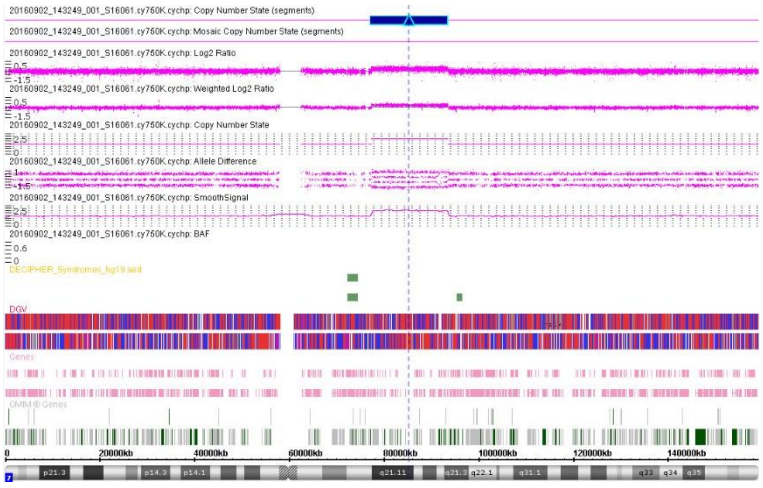

Figure 2. The result of array-SNP: one foetus

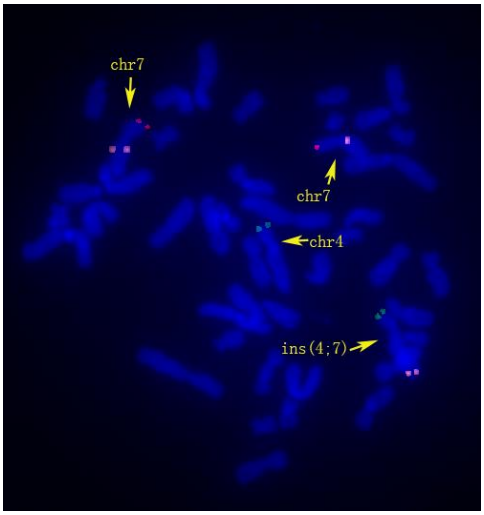

Figure 3. Karyotype of one foetus. Red (7-302) indicates RP11-103I21 7p22.3 (1,645,493-1,814,816); orange (7-370) indicates RP11-1005L 7q21.12 (86,802,721-86,975,903); green (4-81) indicates RP11-89N1 4p16.3 (2,156,895-2,351,734). FISH results obtained using three chromosome painting probes specific for chromosomes 4 and 7 show a derivative chromosome 4 and trisomy 7q11.23q21.3.

DISCUSSION

The frequency of chromosomal abnormalities, whether structural or numerical, is approximately 0.40% (1:250)–0.65% (1:154) in the live-born population (Gilbert-Barnes E, 2006.) Spontaneous abortions and stillbirths are common in the case of chromosomal abnormalities. In terms of numerical abnormalities, deletions and duplications of large fragments can be easily detected by cytogenetic analysis, but microdeletions and microduplications are difficult to identify. However, with the introduction of advanced genomic technologies, such as CGH array, SNP array, and next-generation sequencing, microdeletions and microduplications have become easier to identify. Nonetheless, the significance of the many findings of these new technologies is not known. In other words, several factors must be considered during prenatal diagnosis, and the relevance of tests must be confirmed. Partial duplication of chromosome 7q was first described by Carpentier et al. Several reports have been published in relation to this anomaly, and it is reportedly induced by chromosomal translocations, inversions, and complex rearrangements. (Grace et al), and Serville et al. reported trisomy 7q22-32 in patients with frontal bossing, strabismus, large wide ears, and hypotonia. A study by Vogel et al. found trisomy 7q22 or 7q31-qter in patients with low birth weight, growth, and mental retardation, micrognathia, cleft palate, and ocular conditions like cataracts and colobomata. Harold et al. reported the presence of trisomy 7q32-qter in individuals with low birth weight, developmental and growth delays, hypertelorism, small noses, and very short necks. Similarly, Romain et al. reported trisomy 7q22-q31.2 in individuals with developmental delays, right kidney dysplasia, iron-deficiency anemia, and moderate hearing loss.

A VSD is an abnormal opening in the dividing wall between the ventricles caused by a hypoplastic ventricular septum in the embryonic period. It is a common type of congenital heart defect, with an incidence of about 12%–25% among congenital heart diseases (Porstmann W, 1967). It has been estimated that in China, the annual rate of VSD is 17.3 per 1000 births (Zhao QM, 2013). As VSD is a polygenic inherited condition, it is influenced by genetic factors, environment factors, or both. VSD can appear either as an isolated cardiac defect without other abnormalities referred to as eusemia or with several complex malformations which is usually difficult to cure and can even be fatal. Therefore, prenatal diagnosis of VSD is vital to enable prenatal genetic counselling and provide postpartum assistance.

The aim of our examinations was to determine whether the two fetuses had genetic problems that warranted termination of pregnancy. Cytogenetic analysis showed that both fetuses had a derivative chromosome 4, and SNP array analysis showed that both had trisomy 7q11.23q21.3. Using FISH, we identified the repetitive sequence of 7q11.23q21.3 in the long arms of chromosome 4, indicative of a derivative chromosome 4. To determine the origin of the trisomy 7q11.23q21.3, we performed cytogenetic and SNP array analyses for the woman, her husband, her older son, and both her parents. We found that the fetuses had inherited the trisomy 7q11.23q21.3 from their mother. Fetal ultrasound examination showed that both fetuses had VSD, so we performed physical and intelligence examinations, heart examination for the pregnant woman. Since the findings were normal, it appears that the VSD was unrelated to the trisomy 7q11.23q21.3.

CONCLUSION

We concluded that the VSD had not been caused by the trisomy 7q11.23q21.3. Both fetuses had only VSD, without any other abnormal phenotype, and the defects were of diameter 3.1 and 2.9 mm. Several studies have demonstrated that spontaneous VSD closure occurs more frequently if the defect is small (3–6 mm) than if it is large. Meanwhile, the traditional method of surgery and the new method of catheter intervention are both suitable methods to treat VSDs. Although we did not advise the woman in the present case to terminate the pregnancy, we recommended regular ultrasound examination of the two fetuses at the hospital.

FUNDING

This study was supported by grants from the Medical Technology Breeding Project for PLA's Youth (No. 14QNP004), the Natural Science Foundation of Liaoning (No.2015020423).

ACKNOWLEDGMENTS

We thank all the patients who participated in this study.

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