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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of chromosome 22q11.2 deletion syndrome associated with congenital heart defects

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ABSTRACT

Objective: To report prenatal diagnosis of 22q11.2 deletion syndrome in a pregnancy with congenital heart defects in the fetus.

Case report: A 26-year-old, primigravid woman was referred for counseling at 24 weeks of gestation because of abnormal ultrasound findings of fetal congenital heart defects. The Level II ultrasound revealed a singleton fetus with heart defects including overriding aorta, small pulmonary artery, and ventricular septal defect. Cordocentesis was performed. The DNA extracted from the cord blood was analyzed by multiplex ligation-dependent amplification (MLPA). The MLPA showed deletion in the DiGeorge syndrome (DGS) critical region of chromosome 22 low copy number repeat (LCR) 22-A~C. Conventional cytogenetic analysis revealed a normal male karyotype. Repeated amniocentesis and cordocentesis were performed. Whole-genome array comparative genomic hybridization (aCGH) on cord blood was performed. aCGH detected a 3.07-Mb deletion at 22q11.21. Conventional cytogenetic analysis of cultured amniocytes revealed a karyotype 46,XY. Metaphase fluorescence *in situ* hybridization (FISH) analysis on cultured amniocytes confirmed an interstitial 22q11.2 deletion.

Conclusion: Prenatal ultrasound findings of congenital heart defects indicate that the fetuses are at increased risk for chromosome abnormalities. Studies for 22q11.2 deletion syndrome should be considered adjunct to conventional karyotyping. Although FISH has become a standard procedure for diagnosis of 22q11.2 deletion syndrome, MLPA can potentially diagnose a broader spectrum of abnormalities, and aCGH analysis has the advantage of refining the 22q11.2 deletion breakpoints and detecting uncharacterized chromosome rearrangements or genomic imbalances.

Introduction

Chromosome 22q11.2 deletion syndrome occurs in approximately one in 4000 births, and is the most common human deletion syndrome. It encompasses a wide spectrum of abnormalities including DiGeorge syndrome [Online Mendelian Inheritance in Man (OMIM) 188400] and velocardiofacial syndrome (OMIM

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192430). Patients with 22q11.2 deletion syndrome can suffer from congenital heart diseases, palatal abnormalities, learning difficulties, immune deficiency, characteristic facial features, and hypocalcemia [1,2]. Individuals with this syndrome have an estimate high rate of 74% of congenital heart disease, including tetralogy of Fallot, ventricular septal defect, interrupted aortic arch, and truncus arteriosus [1,2].

With the advent of ultrasound and molecular genetic technology, many cases with 22q11.2 deletion have been diagnosed in the prenatal period by the use of fluorescence *in situ* hybridization (FISH), multiplex ligation-dependent amplification (MLPA) and array comparative genomic hybridization (aCGH) [3–9]. We present our experience of prenatal diagnosis of 22q11.2 microdeletion syndrome by MLPA and aCGH in a fetus with congenital heart defects.

Case presentation

A 26-year-old, primigravid woman was referred for counseling at 24 weeks of gestation because of abnormal ultrasound findings of fetal congenital heart defects. Her husband was 27 years old. She and her husband were healthy and nonconsanguineous. There was no family history of congenital malformations. She denied any recent infections or exposure to teratogens during this pregnancy. The pregnancy was uneventful until 24 weeks of gestation when Level II ultrasound revealed a singleton fetus with heart defects including overriding aorta, small pulmonary artery, and ventricular septal defect. The amniotic fluid amount and fetal growth were normal. Other internal organs were unremarkable. Cordocentesis was performed for cytogenetic analysis and molecular diagnosis of DiGeorge syndrome. The DNA extracted from cord blood was analyzed by MLPA using the SALSA MLPA P250 DiGeorge Probemix (MRC-Holland, Amsterdam, The Netherlands) according to the manufacturer's protocol. The MLPA showed a deletion in the DiGeorge syndrome (DGS) critical region of chromosome 22 low copy number repeat (LCR) 22-A~C or mlpa 22q LCR22-A~C(P250) × 1. Conventional cytogenetic analysis revealed a normal male karyotype. The parents requested repeated amniocentesis. Repeated amniocentesis and cordocentesis were performed. Whole-genome aCGH on cord blood was performed using a NimbleGen ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA). aCGH detected a 3.07-Mb deletion at 22q11.21, or arr 22q11.21 (18,657,470–21,724,242) × 1 (Fig. 1). The deleted region encompasses 126 genes including 43 OMIM genes: *USP18*, *DGCR6*, *PRODH*, *DGCR2*, *DGCR14*, *TSSK2*, *GSC2*, *SLC25A1*, *CLTCL1*, *DVL1P1*, *HIRA*, *MRPL40*, *UFD1L*, *CDC45*, *CLDN5*, *SEPT5*, *GP1BB*, *TBX1*, *GNB1L*, *TXNRD2*, *COMT*, *ARVCF*, *DGCR8*, *TRMT2A*, *RANBP1*, *ZDHHC8*, *RTN4R*, *DGCR6L*, *GGTLC3*, *RIMBP3*, *ZNF74*, *SCARF2*, *MED15*, *PI4KA*, *SERPIND1*, *SNAP29*, *CRKL*, *LZTR1*, *THAP7*, *P2RX6*, *SLC7A4*, *BCRP2*, and *GGT2*. Whole-genome aCCH analysis on parental bloods revealed no genomic imbalance. Conventional cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,XY. FISH analysis was used for confirmation. Metaphase FISH analysis on cultured amniocytes using Vysis DiGeorge region probe [Vysis, LSI TUPLE 1 (Histone cell cycle regulation defective, s. cerevisiae, homolog of, A (HIRA)) spectrum orange/LSI Arylsulfatase A (ARSA) spectrum green; Abbott Laboratories, Chicago, IL, USA] showed the presence of only one orange signal and two green signals, indicating a deletion of DiGeorge syndrome Tup-like enhancer of split 1 (TUPLE 1) locus at 22q11.2 in the fetus (Fig. 2). The karyotype after FISH analysis was 46,XY.ish del(22)(q11.21)(TUPLE 1−). The fetus had facial dysmorphism of hypertelorism, prominent nasal root, bulbous nasal tip, micrognathia, and low-set ears perinatally.

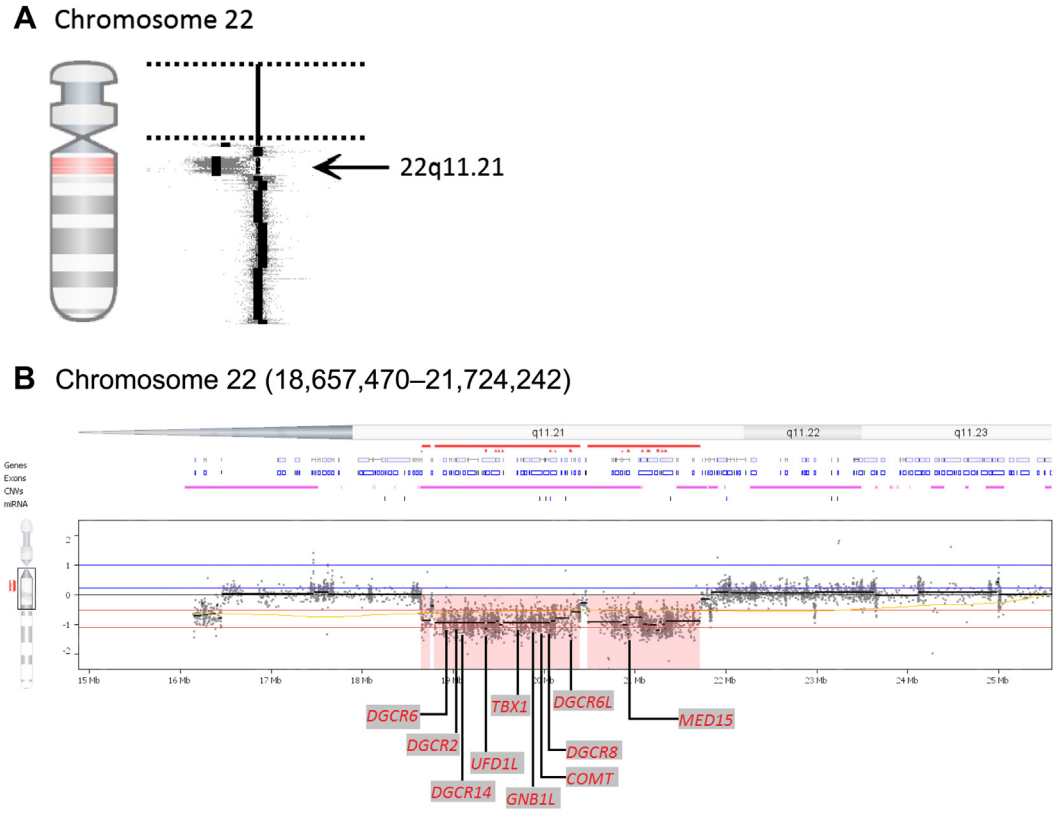

Fig. 1. Whole-genome array comparative genomic hybridization (aCGH) analysis on uncultured amniocytes shows a 3.07-Mb deletion at 22q11.21 or arr [hg 19] 22q11.21 (18,657,470–21,724,242) × 1]. (A) Chromosomal view; (B) zoom-in view.