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Case Report

Prenatal diagnosis of familial 22q11.2 deletion syndrome in a pregnancy with concomitant cardiac and urinary tract abnormalities in the fetus and the mother

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ABSTRACT

Objective: We present prenatal diagnosis of familial 22q11.2 deletion syndrome in a pregnancy with concomitant cardiac and urinary tract abnormalities in the fetus and the mother.

Case report: A 28-year-old woman primigravid underwent amniocentesis at 23 weeks of gestation because of fetal ultrasound findings of aortic stenosis, interrupted aortic arch (IAA), left multicystic kidney, right hydronephrosis and ureterocele. Amniocentesis revealed a karyotype of 46,XX. Simultaneous array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes revealed the result of arr 22q11.21 (18,894,835-21,505,417) × 1.0 [GRCh37 (hg19)] with a 2.611-Mb 22q11.21 deletion encompassing 41 Online Mendelian Inheritance in Man (OMIM) genes including *UFD1L*, *TBX1*, *GNB1L*, *COMT* and *MED15*. aCGH analysis on the DNAs extracted from parental bloods confirmed that the mother carried the same 22q11.21 microdeletion. Level II ultrasound additionally found ventricular septal defect (VSD) and persistent left superior vena cava (PLSVC). Examination of the woman showed short stature, malar hypoplasia, hypertelorism, bulbous nasal tip, prominent nasal root, hypoplasia of nasal wings, right renal agenesis, left ureterovesical reflux and VSD with repair, but normal intelligence and normal neuropsychiatric development. The woman decided to continue the pregnancy, and a 2903-g female baby was delivered at 38 weeks of gestation with left multicystic kidney, right hydronephrosis, dysgenesis of corpus callosum, IAA, VSD, PLSVC, patent ductus arteriosus, patent foramen ovale, atrial septal defect, dilated main pulmonary artery and tricuspid regurgitation. The neonate died at the age of one month.

Conclusion: Prenatal diagnosis of concomitant congenital heart defects and urinary tract abnormalities in the fetus and the parent should raise a suspicion of familial 22q11.2 deletion syndrome.

Introduction

Chromosome 22q11.2 deletion syndrome, occurring in one in 4000–8000 live births [1], is caused by a 1.5–3.0-Mb hemizygous deletion of 22q11.2 with haploinsufficiency of the *TBX1* gene [Online Mendelian Inheritance in Man (OMIM 602054)] at 22q11.21, and includes DiGeorge syndrome (DGS) (OMIM 188400) and

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velocardiofacial syndrome (VCFS) (OMIM 192430) [2–4]. DGS is associated with outflow tract defects, T-cell immunodeficiency, hypocalcemia and hypoplasia of thymus and parathyroid glands [5]. VCFS is associated with velopharyngeal insufficiency, cleft palate, cardiac defects, speech disorders, short stature, microcephaly, typical facial appearance, auricular abnormalities, learning problems, cognitive difficulties and intellectual disabilities [6,7].

With the advent of prenatal ultrasound and molecular genetic technology, prenatal diagnosis of 22q11.2 deletion syndrome is possible [8–20]. Prenatal diagnosis of 22q11.2 deletion syndrome may incidentally detect carrier parents not known to be at risk. The carrier parents may encounter recurrent fetal 22q11.2 deletion syndrome in the subsequent pregnancies, because 22q11.2 deletion syndrome is an autosomal dominant disorder. Therefore, genetic counseling is important under such a circumstance. Here, we present prenatal diagnosis of familial 22q11.2 deletion syndrome in a pregnancy with concomitant cardiac and renal defects in the fetus and the mother.

Case report

A 28-year-old woman primigravid underwent amniocentesis at 23 weeks of gestation because of fetal ultrasound findings of aortic stenosis, interrupted aortic arch (IAA), left multicystic kidney, right hydronephrosis and ureterocele. Her body weight was 74 Kg, and body height was 153 cm. Her husband was 32 years old, and the woman had a past history of congenital heart defects (CHD) and renal disorders. Amniocentesis revealed a karyotype of 46,XX. Simultaneous array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes revealed the result of arr 22q11.21 (18,894,835-21,505,417) × 1.0 [GRCh37 (hg19)] with a 2.611-Mb 22q11.21 deletion encompassing 41 Online Mendelian Inheritance in Man (OMIM) genes including *UFD1L*, *TBX1*, *GNB1L*, *COMT* and *MED15* (Fig. 1). aCGH analysis on the DNAs extracted from parental bloods confirmed that the mother carried the same 22q11.21 microdeletion (Fig. 2). Level II ultrasound additionally found ventricular septal defect (VSD) and persistent left superior vena cava (PLSVC). Examination of the woman showed short stature, malar hypoplasia, hypertelorism, bulbous nasal tip, prominent nasal root, hypoplasia of nasal wings, right renal agenesis, left ureterovesical reflux and VSD with repair, but normal intelligence and normal neuropsychiatric development. The woman decided to continue the pregnancy, and a 2903-g female baby was delivered at 38 weeks of gestation with left multicystic kidney, right hydronephrosis, dysgenesis of corpus callosum, IAA, VSD, PLSVC, patent ductus arteriosus (PDA), patent foramen ovale, atrial septal defect (ASD), dilated main pulmonary artery and tricuspid regurgitation. The neonate died at the age of one month.

Discussion

The peculiar aspect of the present case is prenatal diagnosis of familial transmission of 22q11.2 deletion syndrome. Prenatal diagnosis of 22q11.2 deletion syndrome may incidentally detect a 22q11.2 deletion in the parent. We previously reported familial mosaic 22q11.2 microdeletion at prenatal diagnosis [8]. In that case, prenatal ultrasound showed tetralogy of Fallot (TOF) and thymic hypoplasia in the fetus. Fluorescence *in situ* hybridization (FISH) analysis on metaphase amniocytes showed the result of mos 46,XY.ish del(22)(q11.2q11.2)(D22S553-) [5]/46,XY.ish 22q11.2 (D22S553 × 2) [1] and a ratio of 61 (del.22q11.2)/39 (normal) in 100 interphase amniocytes. After birth, the neonate postnatally manifested hypocalcemia, hypoplasia of the thymus, overriding of the aorta, a large VSD, a small ASD, PDA and hypoplastic pulmonary arteries. FISH analysis on the cord blood showed the result of mos 46,XY.ish del(22)(q11.2q11.2)(D22S553-) [11]/46,XY.ish 22q11.2 (D22S553 × 2) [9] and a ratio of 43 (del.22q11.2)/57 (normal) in 100 interphase cord blood lymphocytes. FISH analysis on the paternal blood showed the result of mos 46,XY.ish del(22)(q11.2q11.2)(D22S553-) [3]/46,XY.ish 22q11.2 (D22S553 × 2) [8] and a ratio of 19 (del.22q11.2)/81 (normal) in 100 interphase lymphocytes. Chen et al. [21] reported a mother with mosaic 22q11.2 microdeletion and recurrent fetal conotruncal defects. One fetus had pulmonary atresia, and the other had TOF and a 22q11.2 deletion. About 90–95% of the patients with 22q11.2 deletion syndrome occur *de novo* [4], and the rest 5–10% can be inherited from asymptomatic or mildly affected carrier parents especially those with mosaicism in the germline (gonadal) form and/or the somatic form [22–25]. Hatchwell et al. [22] reported gonadal mosaic 22q11.2 microdeletion in a non-deleted normal mother who had two affected children inherited from the same maternal chromosome with a 22q11.2 deletion. Kasprzak et al. [23] reported gonadal and somatic mosaic 22q11.2 deletion in a mother who had two sons with 22q11.2 deletion syndrome. Sandrin-Garcia et al. [24] reported recurrent 22q11.2 deletion in two children born from a normal mother who probably had gonadal mosaic 22q11.2 deletion. Patel et al. [25] reported mosaic 22q11 microdeletion in a mother who had two children died of CHD. The mother later experienced intrauterine fetal death, and the heart of the abortus was found to have mosaic 22q11 microdeletion.

In the present case, both the mother and the fetus had severe urinary tract abnormalities in addition to CHD. About 1/3 of patients with 22q11.2 deletion syndrome have genitourinary abnormalities including bilateral or unilateral renal agenesis, dysplastic or cystic kidneys, duplicated collecting system, hydronephrosis,

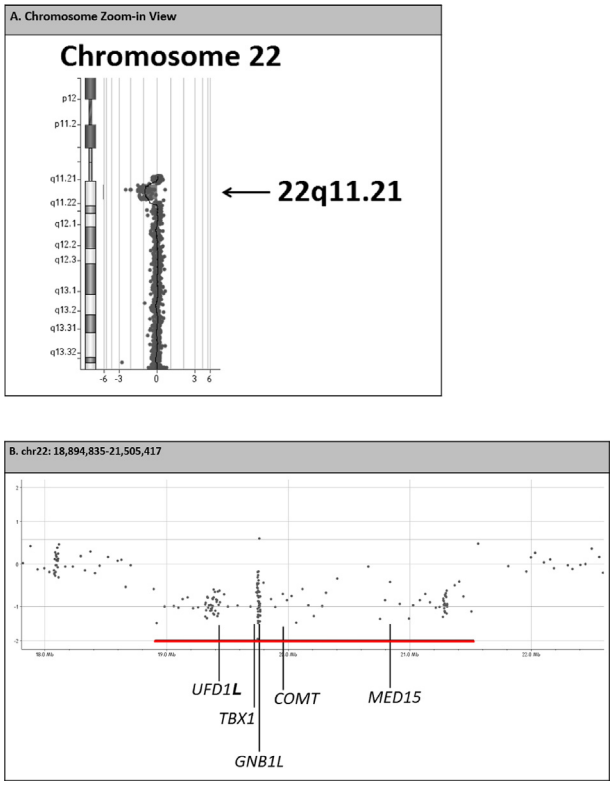

Fig. 1. (A) and (B) Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K (Agilent Technologies, CA, USA) shows a 2.611-Mb 22q11.21 microdeletion encompassing the genes of *UFD1L*, *TBX1*, *GNB1L*, *COMT* and *MED15*.

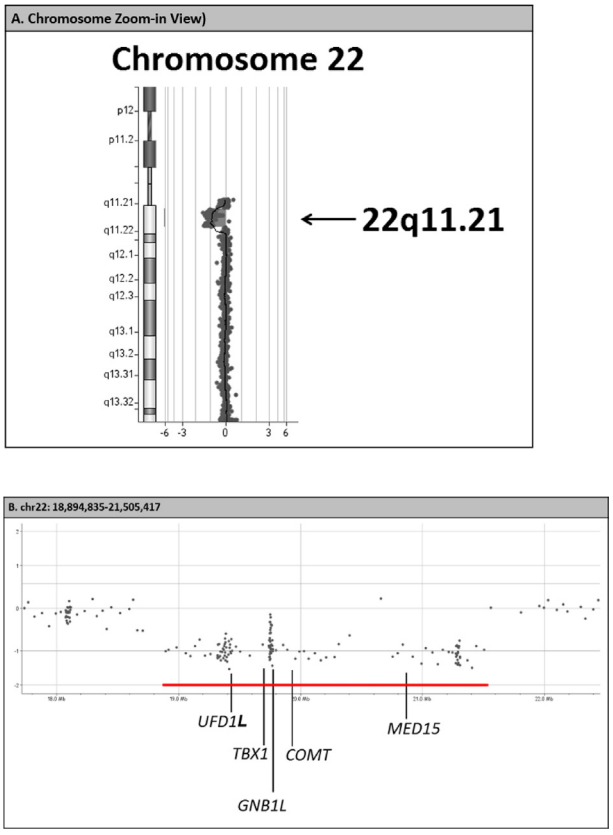

Fig. 2. (A) and (B) aCGH analysis on the DNA extracted from maternal blood using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K (Agilent Technologies, CA, USA) shows a 2.611-Mb 22q11.21 microdeletion encompassing the genes of *UFD1L*, *TBX1*, *GNB1L*, *COMT* and *MED15*.

cryptorchidism, hypospadias, absent uterus or inguinal hernia [4,26,27]. In a study of 42 cases of prenatally detected 22q11.2 deletion syndrome, Schindewolf et al. [14] reported that 95% (40/42) had CHD, and 90% (38/42) had extracardiac findings including central nervous system (38%), gastrointestinal defects (14%), pulmonary defects (7%), skeletal defects (19%), facial dysmorphism (21%), hypoplastic thymus (26%), polyhydramnios (30%) and genitourinary defects (16.6%) such as pyelectasis (5 cases), bilateral ureterocele (1 case) and unilateral multicystic dysplastic kidney (1 case). Devriendt et al. [26] reported that 10.2% (4/39) of 22q11.2 deletion syndrome had urinary tract abnormalities including bilateral obstructive megaureter (1 case), unilateral renal agenesis, (2 cases) and unilateral multicystic kidney, (1 case). Wu et al. [27] reported that 31% (25/80) of the patients with 22q11.2 deletion syndrome had structural urinary tract abnormalities including eight patients with renal agenesis or multicystic dysplastic kidney, four with hydronephrosis and five with vesicoureteral reflux. Goodship et al. [28] reported prenatal sonographic diagnosis of urinary tract abnormalities as a presentation of DiGeorge syndrome in three cases such as a right hydroureter and hydronephrosis with a ureterocele in one case, bilateral multicystic kidneys with associated oligohydramnios in another case and a left multicystic kidney with right renal agenesis and associated oligohydramnios in the third case. The European CATCH22 Consortium Database reported that 49/136 (36%) of the patients with 22q11.2 deletion syndrome had renal ultrasound abnormalities including absent kidneys, multicystic kidneys, obstructive abnormalities and vesicoureteric reflux [28].

The present case had a 2.611-Mb familial 22q11.21 deletion encompassing the genes of *TBX1*, *COMT*, *UFD1L*, *GNB1L* and *MED15*. Mutation or haploinsufficiency of *TBX1* (OMIM 602054) has been associated with DGS, VCFS, conotruncal heart malformations (CTHM) (OMIM 217095) and TOF (OMIM 187500). *COMT* (OMIM 116790) is associated with susceptibility to schizophrenia (OMIM 181500) and panic disorder (OMIM 167870). *UFD1L* (OMIM 601754) polymorphism is associated with schizophrenia [29]. *GNB1L* (OMIM 610778) is associated with schizophrenia and bipolar disorder [30], and autism [31]. *MED15* (OMIM 607372) polymorphism is associated with schizophrenia [32–34].

In summary, we present prenatal diagnosis of familial 22q11.2 deletion syndrome in a pregnancy with concomitant cardiac and urinary tract abnormalities in the fetus and the mother. Prenatal diagnosis of concomitant congenital heart defects and urinary tract abnormalities in the fetus and the parent should raise a suspicion of familial 22q11.2 deletion syndrome.

Declaration of competing interest

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

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