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Case Report

Detection of a familial 1q21.1 microdeletion and concomitant *CHD1L* mutation in a fetus with oligohydramnios and bilateral renal dysplasia on prenatal ultrasoundChih-Ping Chen^{a, b, c, d, e, f, *}, Jian-Pei Huang^{a, g}, Yi-Yung Chen^a, Schu-Rern Chern^b, Peih-Shan Wu^h, Shin-Wen Chen^a, Wayseen Wang^{b, i}, Chen-Chi Lee^a^a Department of Obstetrics and Gynecology, MacKay Memorial Hospital, Taipei, Taiwan^b Department of Medical Research, MacKay Memorial Hospital, Taipei, Taiwan^c Department of Biotechnology, Asia University, Taichung, Taiwan^d School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan^e Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan^f Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan^g MacKay Junior College of Medicine, Nursing and Management, Taipei, Taiwan^h Gene Biodesign Co. Ltd, Taipei, Taiwanⁱ Department of Bioengineering, Tatung University, Taipei, Taiwan

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ABSTRACT

Objective: We present detection of a familial 1q21.1 microdeletion and concomitant *CHD1L* mutation in a fetus with oligohydramnios and bilateral renal dysplasia on prenatal ultrasound.**Case report:** A 37-year-old, primigravid woman was referred for level II ultrasound examination at 16 weeks of gestation because of oligohydramnios. The parents were phenotypically normal, and there were no congenital malformations in the family. Prenatal ultrasound at 17 weeks of gestation revealed a fetus with fetal growth biometry equivalent to 16 weeks, oligohydramnios with an amniotic fluid index (AFI) of 1.4 cm and bilateral renal dysplasia without sonographic demonstration of bilateral renal arteries. The pregnancy was subsequently terminated, and a 137-g fetus was delivered without characteristic facial dysmorphism. Postnatal cytogenetic analysis of the umbilical cord and parental bloods revealed normal karyotypes. However, array comparative genomic hybridization (aCGH) analysis on the DNA extracted from the umbilical cord revealed a 2.038-Mb microdeletion of 1q21.1-q21.2 encompassing 11 [Online Mendelian Inheritance in Man (OMIM)] genes of *PRKAB2*, *FMO5*, *CHD1L*, *BCL9*, *ACP6*, *GJA5*, *GJA8*, *GPR89B*, *NBPFL4*, *TRN-GTT2-1* and *NBPFL20*. The mother was found to carry the same microdeletion. A missense mutation of c.2353T > G, p.Ser785Ala in *CHD1L* was detected in the umbilical cord. The father was found to carry a heterozygous mutation of c.2353T > G, p.Ser785Ala in *CHD1L*.**Conclusion:** Fetuses with a 1q21.1 microdeletion and concomitant *CHD1L* mutation may present oligohydramnios and bilateral renal dysplasia on prenatal ultrasound.© 2019 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Chromosome 1q21.1 deletion syndrome [Online Mendelian Inheritance in Man (OMIM) 612474] is an autosomal dominant contiguous gene deletion syndrome with a 1.35-Mb deletion

encompassing *PRKAB2*, *FMO5*, *CHD1L*, *BCL9*, *ACP6*, *GJA5*, *GJA8* and *GPR89B*, and can be found in 0.2% of the patients with developmental delay, intellectual disability with or without congenital anomalies evaluated by array comparative genomic hybridization (aCGH) [1,2].

The reported abnormalities in patients with chromosome 1q21.1 deletion syndrome include (1) variable/mild dysmorphic facial features of frontal bossing, deep-set eyes, epicanthic folds, large nasal bridge, long philtrum, highly arched palate and trigonocephaly in more than 75% of the cases; (2) mild-to-moderate

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developmental delay including speech and motor delay in 50–75% of the cases; (3) microcephaly, short stature, intellectual disability and eye abnormalities of microphthalmia, chorior-retinal and iris colobomas, strabismus and cataracts in 25–50% of the cases; (4) attention deficit hyperactivity disorder, congenital heart disease, hypotonia, failure to thrive and seizures in 10–25% of the cases; and (5) autism spectrum disorders, schizophrenia, brain malformations, skeletal abnormalities, genitourinary

malformations and sensorineural deafness in less than 10% of the cases [1–13]. Nevertheless, individuals with chromosome 1q21.1 copy number variations (CNVs) can have a normal phenotype [9,12].

Here, we present detection of a familial 1q21.1 microdeletion and concomitant *CHD1L* mutation in a fetus in a not known at-risk pregnancy associated with oligohydramnios and fetal bilateral renal dysplasia.

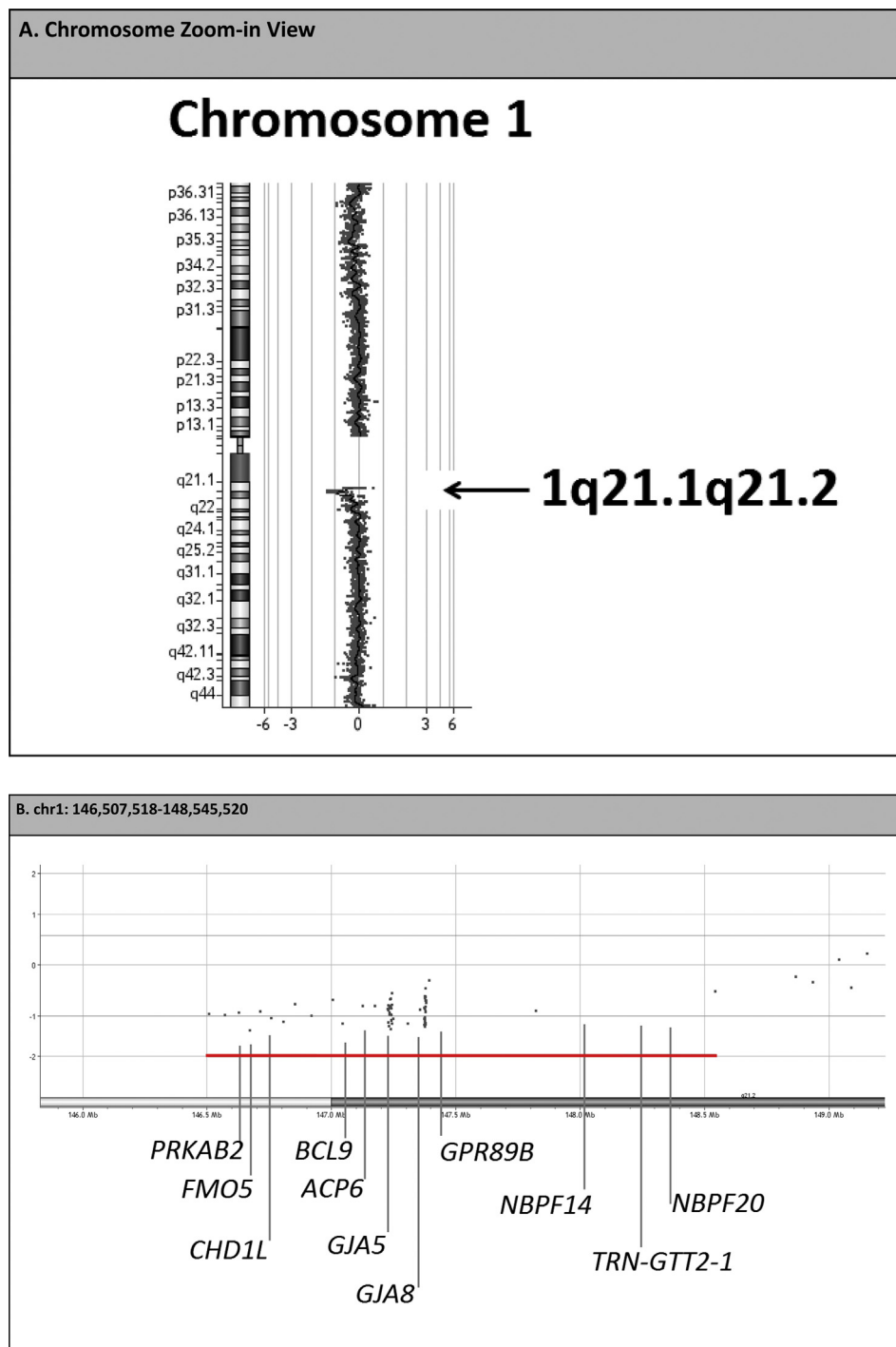


Fig. 1. Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from umbilical cord shows a 2.038-Mb microdeletion of 1q21.1-q21.2 encompassing 11 [Online Mendelian Inheritance in Man (OMIM)] genes of *PRKAB2*, *FMO5*, *CHD1L*, *BCL9*, *ACP6*, *GJA5*, *GJA8*, *GPR89B*, *NBPF14*, *TRN-GTT2-1* and *NBPF20* by SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K Array (Agilent Technologies, Santa Clara, CA, USA).

Case Report

A 37-year-old, primigravid woman was referred for level II ultrasound examination at 16 weeks of gestation because of oligohydramnios. The parents were phenotypically normal, and there were no congenital malformations in the family. Prenatal ultrasound at 17 weeks of gestation revealed a fetus with fetal growth biometry equivalent to 16 weeks, oligohydramnios with an amniotic fluid index (AFI) of 1.4 cm and bilateral renal dysplasia without sonographic demonstration of bilateral renal arteries. The

pregnancy was subsequently terminated, and a 137-g female fetus was delivered without characteristic facial dysmorphism. Postnatal cytogenetic analysis of the umbilical cord revealed a karyotype of 46,XX. The parental karyotypes were normal. Simultaneous aCGH analysis on the DNA extracted from the umbilical cord revealed a 2.038-Mb microdeletion of 1q21.1-q21.2 or arr 1q21.1q21.2 (146,507,518–148,545,520) \times 1.0 [GRCh37 (hg19)] encompassing 11 OMIM genes of *PRKAB2*, *FMO5*, *CHD1L*, *BCL9*, *ACP6*, *GJA5*, *GJA8*, *GPR89B*, *NBPF14*, *TRN-GTT2-1* and *NBPF20* (Fig. 1). aCGH analysis of the parental bloods revealed that the mother carried the same

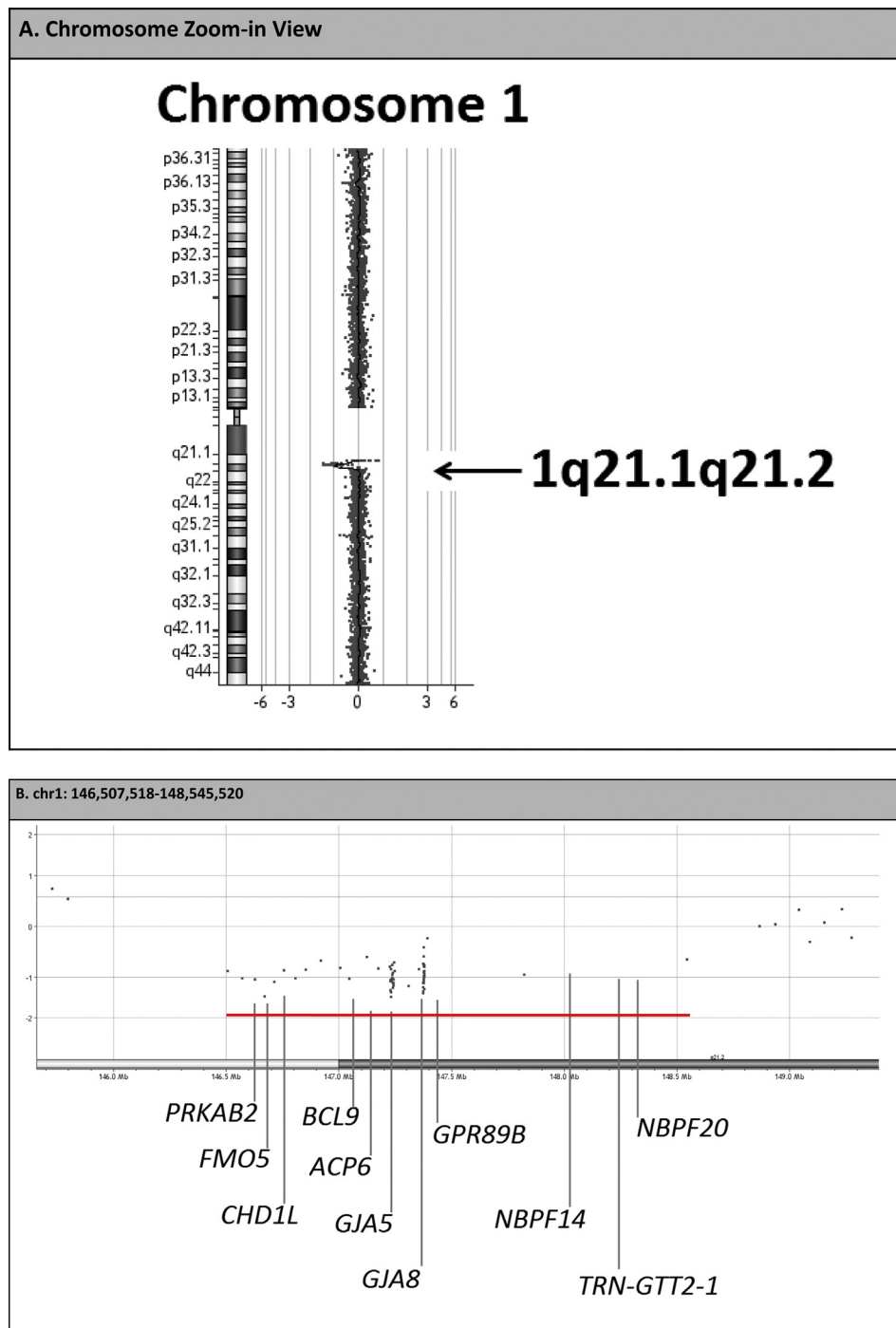


Fig. 2. aCGH on the DNA extracted from maternal blood shows a 2.038-Mb microdeletion of 1q21.1-q21.2 encompassing 11 (OMIM) genes of *PRKAB2*, *FMO5*, *CHD1L*, *BCL9*, *ACP6*, *GJA5*, *GJA8*, *GPR89B*, *NBPF14*, *TRN-GTT2-1* and *NBPF20* by SurePrint G3 Unrestricted CGH ISCA v2, 8 \times 60 K Array (Agilent Technologies, Santa Clara, CA, USA).

microdeletion (Fig. 2). Fluorescence *in situ* hybridization (FISH) analysis on the metaphase umbilical cord fibroblasts confirmed a 1q21.1 microdeletion (Fig. 3). A missense mutation of c.2353T > G, p.Ser785Ala in *CHD1L* was detected in the umbilical cord (Fig. 4). The father was found to carry a heterozygous mutation of c.2353T > G, p.Ser785Ala in *CHD1L* (Fig. 4).

Discussion

Prenatal diagnosis of a 1q21.1 microdeletion in a not known at-risk pregnancy is uncommon [6,14–17]. Liao et al. [6] first reported prenatal diagnosis of the 1q21.1 microdeletion in two fetuses with urogenital anomalies. In their report, the first fetus had absent right kidney, mega-ureter, oligohydramnios and a single umbilical artery on prenatal ultrasound, and a *de novo* 317-kb 1q21.1 microdeletion (144,292,653–144,610,313) encompassing *PDZK1*, *GPR89A*, *CD160*, *RNF115* and *GPR89C*. The second fetus had bilateral renal dysplasia and oligohydramnios on prenatal ultrasound, and a 317-kb 1q21.1 microdeletion (144,292,653–144,610,313) inherited from a father who had a polycystic right kidney. However, the 1q21.1 microdeletions in the two cases reported by Liao et al. [6] are outside the common 1.35-Mb deletion region of the chromosome 1q21.1 deletion syndrome including *PRKAB2*, *FMO5*, *CHD1L*, *BCL9*, *ACP6*, *GJA5*, *GJA8* and *GPR89B*. Papoulidis et al. [14] reported prenatal diagnosis of a 334-kb 1q21.1 deletion in a fetus with thrombocytopenia absent radius (TAR) syndrome, increased nuchal translucency (NT) and short upper limbs. In a study of 115 fetuses with congenital heart disease and investigation, Zhu et al. [15] detected

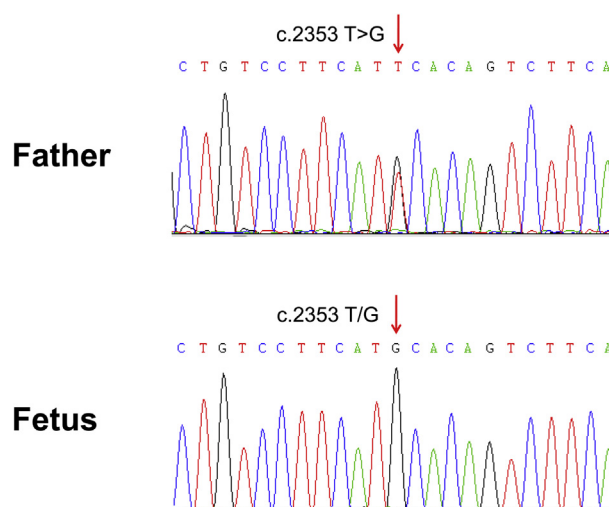


Fig. 4. Mutational analysis on the DNA extracted from the umbilical cord shows a missense mutation of c.2353T > G, p.Ser785Ala in the *CHD1L* gene, and mutational analysis on the DNA extracted from the paternal blood shows a heterozygous mutation of c.2353T > G, p.Ser785Ala in the *CHD1L* gene.

1q21.1 microdeletion by aCGH in a fetus with ventricular septal defect. Chen et al. [16] reported prenatal diagnosis of a familial 1q21.1–q21.2 microdeletion in a fetus with polydactyly of the left foot on prenatal ultrasound. Egloff et al. [17] detected 1q21.1 deletion by aCGH in a fetus with increased NT.

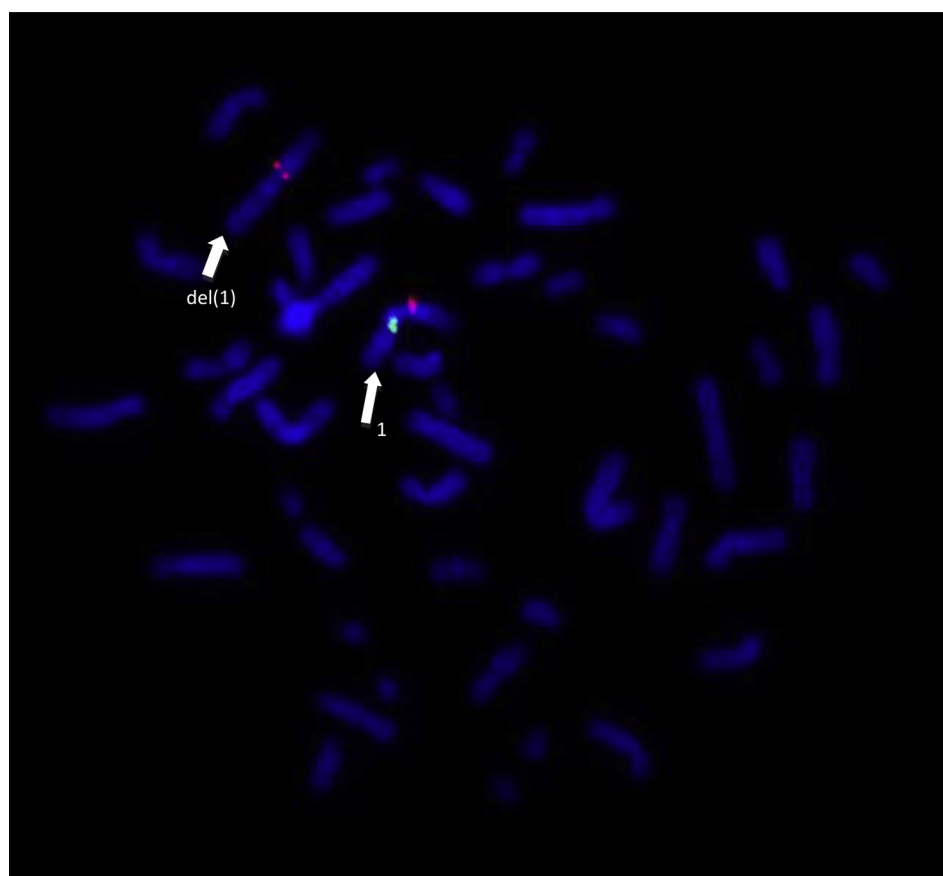


Fig. 3. Metaphase fluorescence *in situ* hybridization analysis on the umbilical cord fibroblasts using the bacterial artificial chromosome (BAC) probes of RP11-441L11 [1q21.1 (146,986,158–146,989,699) (hg19), fluorescein isothiocyanate (FITC), spectrum green] and RP11-254O21 [1q21.3 (99,256,145–99,426,854) (hg19), Texas Red, spectrum red] shows one red signal and one green signal in the normal chromosome 1, and only one red signal and absence of the green signal in the del(1) chromosome with 1q21.1 microdeletion. del = deletion.

Genitourinary abnormalities have been described in patients with the chromosome 1q21.1 deletion syndrome. Klopocki et al. [18] reported genitourinary anomalies including horseshoe kidneys, hypoplasia of uterus and vagina, and renal pelvis dilation in their observation of four patients. Brunetti-Pierri et al. [1] reported small kidneys, hypospadias, pelvic kidney and hydronephrosis respectively in three patients with a 1q21.1 microdeletion. Harvard et al. [5] reported duplex ureter and dilated renal pelvis, and absent left kidney respectively in two patients with 1q21.1 CNVs. Busè et al. [12] reported ectopic urethral meatus and vesicoureteral reflux respectively in two patients with a 1q21.1 microdeletion. In a review of 1q21.1-q21.2 microdeletion cases in DECIPHER database [19], at least five cases (#278626, #280387, #250214, #331384, #268426) had vesicoureteral reflux, one case (#250214) had renal dysplasia, one case (#331268) had renal Fanconi syndrome and two cases (#326602, #285837) had abnormality of kidney. Vesicoureteral reflux is the most common observed genitourinary abnormalities associated with chromosome 1q21.1 deletion syndrome according to the DECIPHER database [19]. However, to our knowledge, bilateral renal dysplasia has not previously been reported in patients with chromosome 1q21.1 deletion syndrome.

The peculiar aspect of the present case is the association of bilateral renal dysplasia and oligohydramnios with chromosome 1q21.1 deletion syndrome. We speculate that haploinsufficiency of *CHD1L* in association with concomitant *CHD1L* mutation may be responsible for the severe urinary tract abnormalities in this case. *CHD1L* (OMIM 613039) encodes chromodomain helicase DNA-binding protein 1-like, which plays a role in chromatin relaxation following DNA damage [20]. Harvard et al. [5] suggested that *CHD1L* and *PRKAB2* play a role in phenotypic variability in 1q21.1 CNVs by sensing and responding to genomic and metabolic stress, and *CHD1L* and *PRKAB2* dysfunction will result in a more severe phenotype in patients who experience more adverse environmental situations during early development. Brockschmidt et al. [21] suggested that *CHD1L* is a new candidate gene for congenital anomalies of the kidney and urinary tract (CAKUT) by their findings that patients with heterozygous missense variants in the *CHD1L* gene demonstrated a CAKUT phenotype. Brockschmidt et al. [21] also found that the *CHD1L* gene was strongly expressed in the human fetal kidney, and the renal fetal expression to renal adult expression ratio was four, which was the highest, compared to all other tissues tested. Brockschmidt et al. [21] suggested that *CHD1L* expression is very important in the developing kidney. In a cohort of 749 individuals from 650 families with CAKUT, Hwang et al. [22] found 12 known dominant disease-causing genes including *SALL1* (9 families), *HNF1B* (6 families), *CHD1L* (5 families), *PAX2* (5 families), *ROBO2* (4 families), *EYA1* (3 families), *RET* (3 families), *GATA3* (2 families), *BMP7* (1 family), *CDC5L* (1 family), *SIX2* (1 family) and *SIX5* (1 family).

In summary, we have presented detection of a familial 1q21.1 microdeletion and a concomitant mutation in the *CHD1L* gene associated with bilateral renal dysplasia. Our case shows that perinatal investigation of embryonic tissues in pregnancy with fetal renal dysplasia and oligohydramnios may elucidate genetic pathogenesis, and the information acquired is useful for genetic counseling.

Conflicts of interest

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

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