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Short Communication

Detection of recurrent transmission of 17q12 microdeletion by array comparative genomic hybridization in a fetus with prenatally diagnosed hydronephrosis, hydroureter, and multicystic kidney, and variable clinical spectrum in the family

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Abstract

Objective: This study was aimed at detection of recurrent transmission of the 17q12 microdeletion in a fetus with congenital anomalies of the kidney and urinary tract.

Materials and Methods: A 35-year-old woman was referred to the hospital at 20 weeks' gestation because of hydronephrosis in the fetus. The mother was normal and healthy. Her second child was a girl who had bilateral dysplastic kidneys that required hemodialysis, and died at the age of 5 years. During this pregnancy, the woman underwent amniocentesis at 18 weeks' gestation because of advanced maternal age. Cytogenetic analysis revealed a karyotype of 46,XY. Prenatal ultrasound showed left hydronephrosis with a tortuous ureter, right hydronephrosis, and increased echogenicity of the kidneys. Fetal magnetic resonance imaging showed right dilated renal calyces, left hydronephrosis, hydroureter, and multicystic kidney. The pregnancy was subsequently terminated. Array comparative genomic hybridization (aCGH) and fluorescence *in situ* hybridization were applied for genetic analysis using umbilical cord, maternal blood, and cultured amniocytes.

Results: aCGH analysis on umbilical cord detected a 1.75-Mb deletion at 17q12 including haploinsufficiency of *LHX1* and *HNF1B*. aCGH analysis on maternal blood detected a 1.54-Mb deletion at 17q12 including haploinsufficiency of *LHX1* and *HNF1B*. Metaphase fluorescence *in situ* hybridization analysis on cultured amniocytes and maternal blood lymphocytes using 17q12-specific bacterial artificial chromosome probe showed 17q12 microdeletion in the fetus and the mother.

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Conclusion: Prenatal diagnosis of recurrent renal and urinary tract abnormalities in the fetus should include a differential diagnosis of familial 17q12 microdeletion.

Keywords: 17q12 microdeletion; *HNF1B*; hydronephrosis; *LHX1*; multicystic kidney

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) occur in three to seven in 1000 births [1–5]. Unilateral dysplastic kidney occurs in one in 1000 and bilateral dysplastic kidneys occur in one in 5000 of the general population [6]. About 10% of the patients with CAKUT have a family history of CAKUT indicating a genetic pathogenesis of these disorders [4–6].

Chromosome 17q12 deletion syndrome (OMIM 614527) is a contiguous gene syndrome caused by 17q12 deletion with clinical phenotypic features including renal cysts and diabetes consistent with maturity-onset diabetes of the young type 5 (MODY5; OMIM 137920) [7–9], Müllerian aplasia/dysgenesis [10,11], autism spectrum disorder and schizophrenia [12,13], and speech delay, learning difficulty, transient neonatal hypercalcemia, and neonatal cholestasis [14].

Here, we present our experience of detection of recurrent transmission of 17q12 microdeletion by array comparative genomic hybridization (aCGH) in a fetus with prenatal ultrasound diagnosis of hydronephrosis, hydroureter, multicystic kidney, and variable clinical spectrum in the family.

Materials and methods

Clinical description

A 35-year-old, gravida 3, para 1, woman was referred to the hospital at 20 weeks' gestation because of hydronephrosis in the fetus. The mother was normal and healthy. She did not have mental disorder, behavior disorder, diabetes mellitus, or genitourinary abnormalities. Her husband was 36 years old. The couple had a healthy 8-year-old daughter. Their second child was a girl who had bilateral dysplastic kidneys that required hemodialysis, and died at the age of 5 years. During this pregnancy, the woman underwent amniocentesis at 18 weeks' gestation because of advanced maternal age. Cytogenetic analysis revealed a karyotype of 46,XY. Prenatal ultrasound showed left hydronephrosis with a tortuous ureter, right hydronephrosis, and increased echogenicity of the kidneys (Fig. 1). The amniotic fluid amount was normal. Fetal magnetic resonance imaging at 21 weeks' gestation showed right dilated renal calyces, left hydronephrosis, hydroureter, and multicystic kidney (Fig. 2). The pregnancy was terminated at 23 weeks' gestation, and a 737-g male fetus was delivered with no facial dysmorphism and abnormalities of male external genitalia.

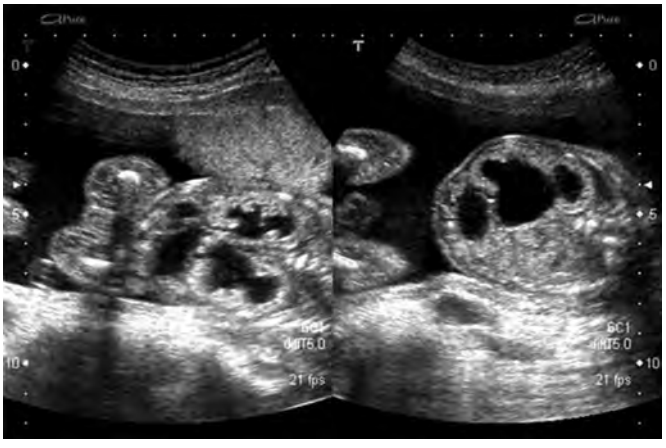

Fig. 1. Prenatal ultrasound at 21 weeks' gestation shows bilateral hydronephrosis, tortuous left ureter, and increased echogenicity of the kidneys.

aCGH

Whole-genome aCGH analysis on the DNA extracted from umbilical cord was performed using NimbleGen ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA). The NimbleGen ISCA Plus Cytogenetic Array has 630,000 probes and a median resolution of 15–20 kb across the entire genome according to the manufacturer's instructions. Parental blood and the healthy elder daughter's blood were also collected, and the samples were subjected to aCGH analysis using the same array kit. The DNA from the cells was extracted first. It was done by following the manufacturer's protocol of the QIAamp DNA Mini kit (Qiagen, Valencia, CA, USA). Then, 0.5 μg of the extracted DNA was labeled with Cy5 dye and compared with an equivalent amount of normal female genomic DNA (G1521; Promega) labeled with Cy3 dye to perform the aCGH experiment. The experiment was performed according to the procedures recommended in the Roche NimbleGen ISCA plus Cytogenetic Array user guide. The data were finally presented using Nexus 6.1 (BioDiscovery, Hawthorne, CA, USA).

Fluorescence in situ hybridization

Metaphase fluorescence *in situ* hybridization (FISH) analysis was performed on cultured amniocytes derived from the stored amniotic fluid and maternal blood using a 17q12-specific bacterial artificial chromosome (BAC) probe RP11-143E18 (dye: Texas red) (35,985,121–36,129,469) and a control 17q25.3-specific BAC probe RP11-388C12 (dye:

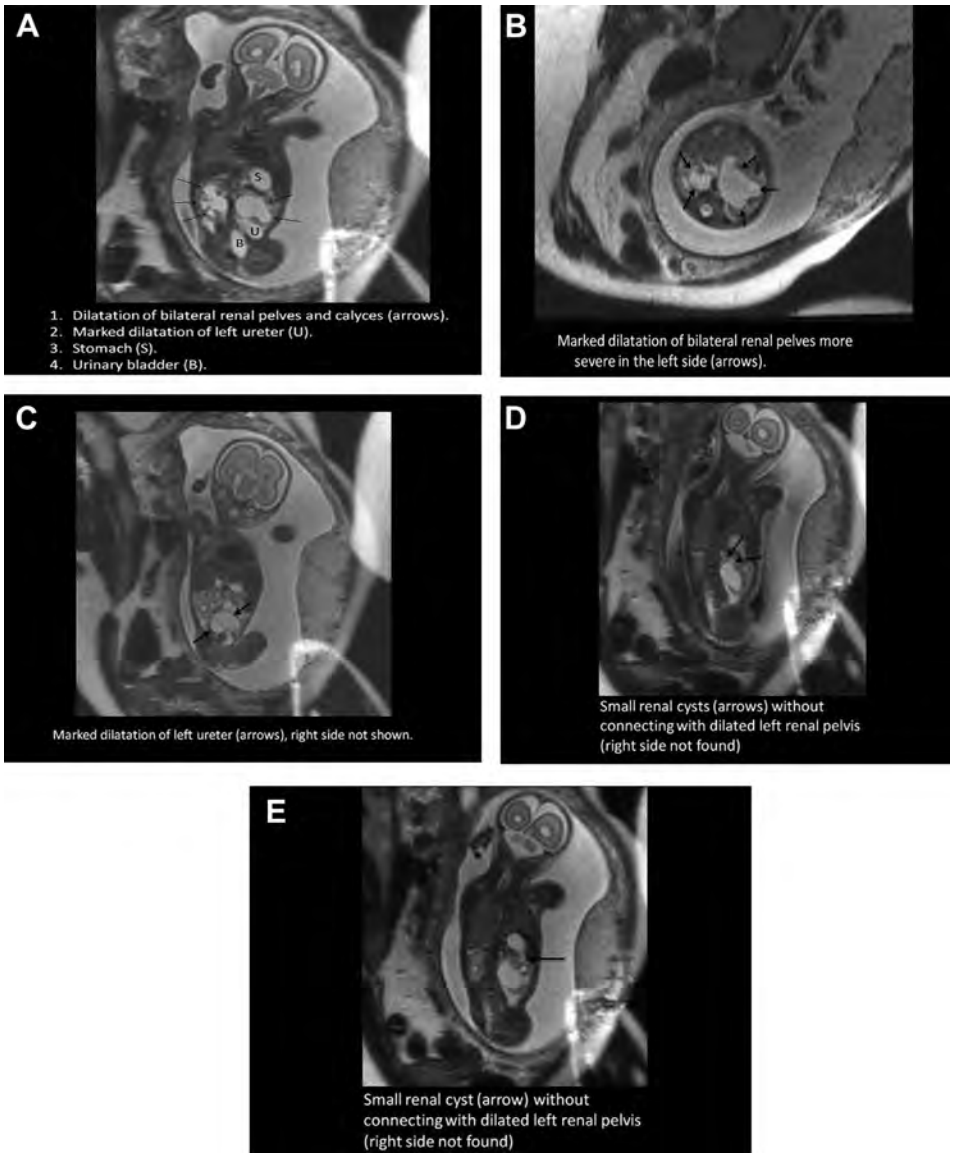

Fig. 2. Prenatal magnetic resonance imaging at 21 weeks' gestation showed: (A) dilation of bilateral renal pelves and calyces (arrows), and marked dilation of left ureter (B = urinary bladder; S = stomach; U = ureter); (B) marked dilation of bilateral renal pelves (arrows) with more severe condition on the left side; and (C–E) small renal cysts (arrows) in the left kidney without connection with the dilated renal pelvis.

FITC, green) (80,606,711–80,718,184) [hg 19] according to the standard FISH protocol [15].

Results

Whole-genome aCGH analysis on the DNA extracted from umbilical cord detected a 1.75-Mb deletion at 17q12, or arr [hg19] 17q12 (34,653,178–36,402,867) × 1 (Fig. 3). The deleted 17q12 region contained 29 genes involving 15 OMIM genes including *LHX1* and *HNF1B*. Whole-genome aCGH analysis on the DNA extracted from maternal blood detected a 1.54-Mb deletion at 17q12, or arr [hg19] 17q12 (34,814,526–36,355,604) × 1 (Fig. 4). The deleted 17q12 region contained 26 genes involving 13 OMIM genes including *LHX1* and *HNF1B*. Whole-genome aCGH analysis on the DNA extracted from paternal blood and the healthy elder daughter's blood showed no 17q12 microdeletion and no other genomic imbalance. Metaphase FISH analysis on cultured amniocytes and maternal blood lymphocytes using 17q12-specific BAC probe showed presence of only one 17q12 signal, indicating 17q12 microdeletion in the fetus and the mother (Fig. 5).

Discussion

The present case is believed to be the first report of detection of recurrent transmission of 17q12 microdeletion in association with prenatally diagnosed hydronephrosis, hydroureter, and bilateral multicystic kidneys in a fetus born to an asymptomatic mother carrying a 17q12 microdeletion. In a study of 62 pregnancies with fetal bilateral hyperechogenic kidneys, Decramer et al [16] found that *HNF1B* gene

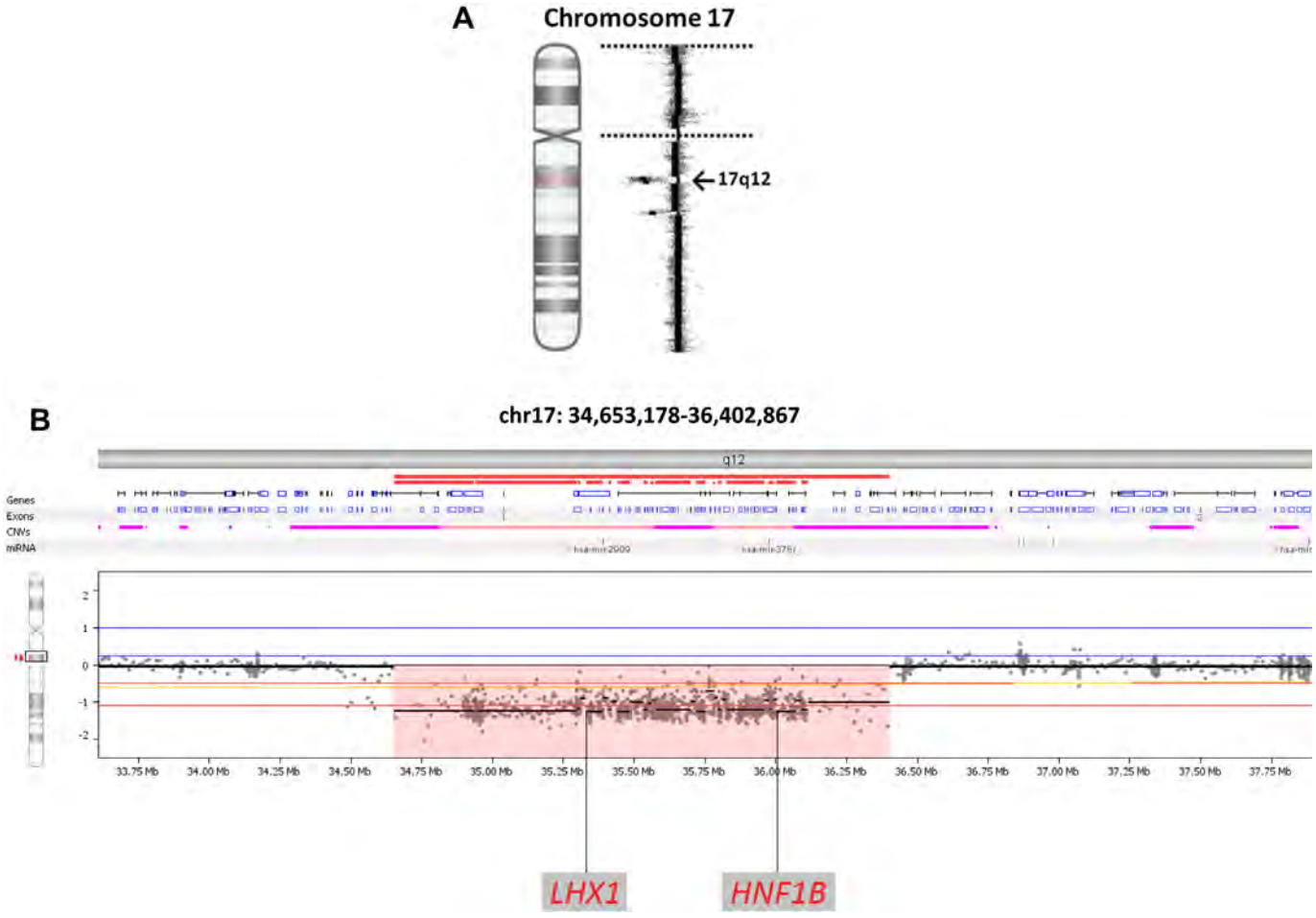

Fig. 3. Array comparative genomic hybridization analysis on the DNA extracted from umbilical cord shows a 1.75-Mb deletion at 17q12, or arr [hg19] 17q12 (34,653,178–36,402,867) × 1. (A) Chromosomal view and (B) zoom in view.

anomalies occurred in 18 of the 62 fetuses (29%), and among the 18 fetuses with *HNF1B* gene anomalies, 15 probands had a complete heterozygous deletion of the *HNF1B* gene. Hendrix et al [17] reported prenatal diagnosis of a 1.52-Mb 17q12 microdeletion encompassing *HNF1B* and *LHX1* with nuchal edema, bilateral echogenic kidneys, and a left-sided diaphragmatic hernia. Mefford et al [8] reported a 1.8-Mb 17q12 microdeletion encompassing *HNF1B* with bilateral multicystic renal dysplasia, bilateral ureteropelvic junction stenosis, atretic right ureter, and hypoplastic bladder. The present case provides evidence that fetuses with a 17q12 microdeletion encompassing *HNF1B* and *LHX1* may prenatally present hydronephrosis and hydroureter in the second trimester, in addition to bilateral hyperechogenic kidneys [16,17] and multicystic dysplastic kidneys [8].

The present fetus had a 1.75-Mb 17q12 microdeletion encompassing *HNF1B* and *LHX1*, and phenotypic abnormalities in the kidney and ureter. HNF1B (OMIM 189907) or transcription factor-2 is a transcription factor that belongs to the homeodomain-containing suprafamily of transcription factors [18]. Heterozygous mutations in *HNF1B* are associated with renal cysts and diabetes syndrome or MODY5, which is an autosomal dominant disorder comprising diabetes occurring earlier than age 25 years, and variable renal and genital tract anomalies [19–31]. Mutations in *HNF1B* are common in women with both uterine and renal abnormalities [32]. 17q12 microdeletion involving *HNF1B* is associated with MODY5 [8,9,28], Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome and Müllerian aplasia/dysgenesis [10,11], and autism spectrum disorder and schizophrenia [12,13]. Thomas et al [33] reported identification of pathogenic *HNF1B* or *PAX2* mutations in 14% of Caucasian patients in a North American cohort of children with renal hypoplasia. *HNF1B* and *PAX2* play key roles in early mouse urogenital tract development [34]. Paces-Fessy et al [34] found that *HNF1B* acts as a modifier of the *PAX2* haploinsufficient phenotype in a mouse model, and suggested that *HNF1B* and *PAX2* cooperate in a common pathway governing both kidney morphogenesis and ureter differentiation. *HNF1B* deficiency is associated with ciliary anomalies in cholangiocytes [35]. Roelandt et al [35] detected 17q12 microdeletion in two patients and *HNF1B* mutation in one patient with ciliary defects in cholangiocytes.

LHX1 (OMIM 601999), also known as *LIM1*, belongs to the *LIM*/homeobox gene family and is essential for head-organizer function, renal, central nervous system and female

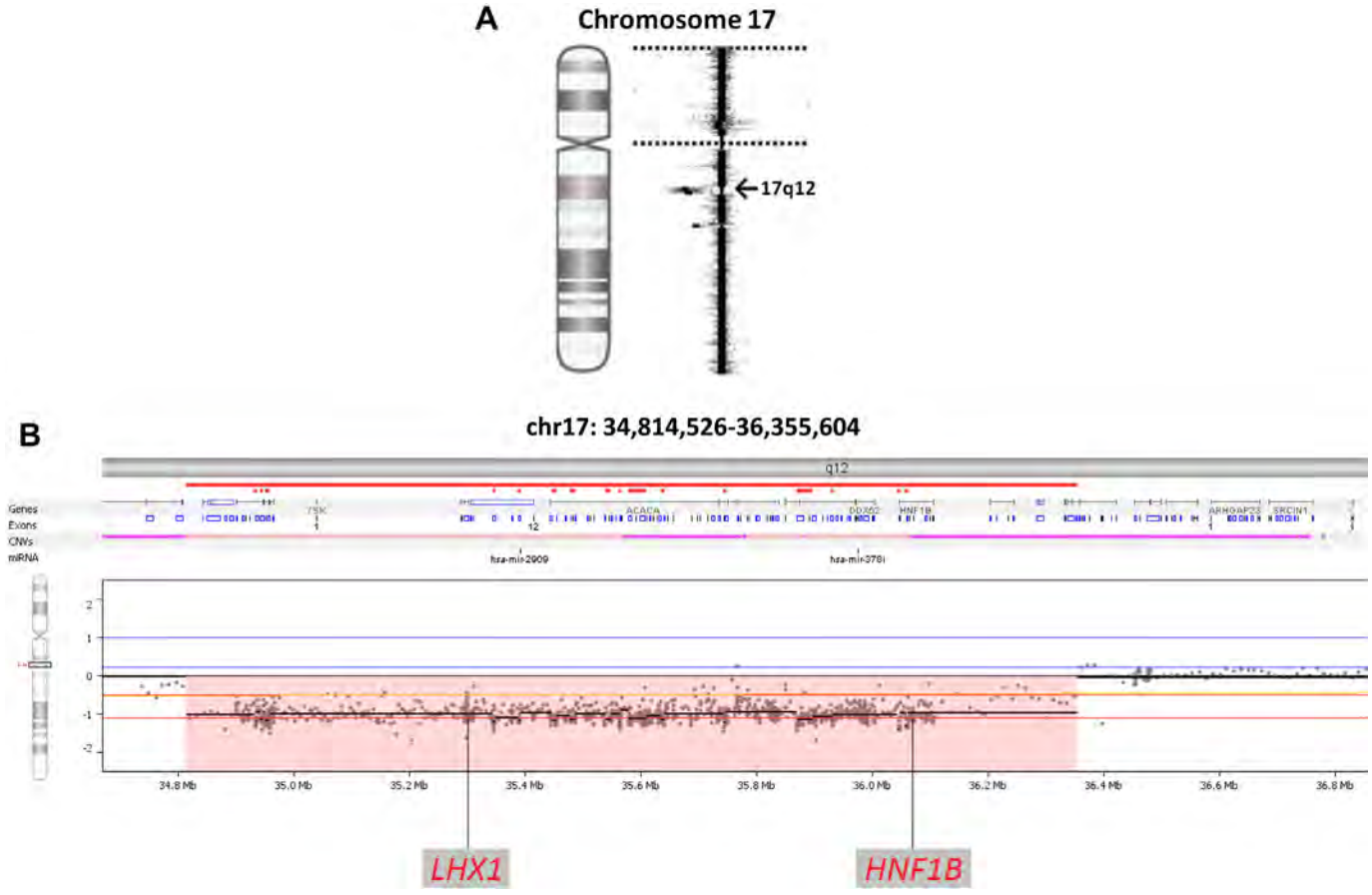

Fig. 4. Array comparative genomic hybridization analysis on the DNA extracted from maternal blood shows a 1.54-Mb deletion at 17q12, or arr [hg19] 17q12 (34,814,526-36,355,604) × 1. (A) Chromosomal view and (B) zoom in view.

reproductive duct development [35–42]. Kobayashi et al [38] found that female *Lhx1*-null mutant mice had ovaries but lacked derivatives of the Müllerian duct including uterus, cervix and the upper vagina. Mutations of *LHX1* are associated with MRKH syndrome [43,44]. In a study of 56 patients with MRKH syndrome, Ledig et al [43] detected 17q12 microdeletion encompassing *LHX1* and *HNF1B* in two patients and a missense mutation in *LHX1* in one patient. Ledig et al [44] additionally detected a frameshift mutation of *LHX1* in a patient with MRKH syndrome and suggested that heterozygous mutations of *LHX1* might be one cause of MRKH syndrome. However, Xia et al [45] performed *LHX1* mutation screening in 96 patients with Müllerian duct abnormalities but found no significant mutation in *LHX1*.

The present case provides evidence for variable clinical spectrum associated with 17q12 microdeletion in the family. In the present case, the carrier mother was asymptomatic, the affected sibling had neonatal bilateral dysplastic kidneys, and the affected fetus had congenital hydronephrosis, hydroureter, and multicystic kidneys. A wide range of phenotypes with considerable variability in expressivity can be observed in the patients with 17q12 microdeletions [8,13,46]. Individuals with nearly identical 17q12 deletions can have variable phenotypic spectrum ranging from prenatally detected renal disease, renal disease detected in childhood, MODY5 diagnosed before age 40 years, to a mild phenotype [8]. Mefford et al [8] suggested that early-onset renal disease is more likely to occur in fetuses with a large genomic deletion of 17q12 than those patients with a mutation in *HNF1B*. Although the carrier mother in this case was asymptomatic at the age of 35 years, she is at risk of diabetes, renal disease and cognitive disorder in the future and should undertake regular metabolic, renal, and mental examinations. The considerable variability in the phenotypic expressivity and the wide spectrum of the disease in the affected individuals with 17q12 microdeletion imply the necessity for genetic counseling of familial transmission in the family members under the circumstance of perinatally detected 17q12 microdeletion in the fetus.

aCGH has the advantages of detection of microdeletions or microduplications in the fetuses with apparently normal karyotype and prenatally detected structural abnormalities as well as familial transmission of the genomic imbalance [47–50]. We suggest that prenatal diagnosis of recurrent renal and urinary tract abnormalities in the fetuses should include a differential diagnosis of familial 17q12 microdeletion.

In summary, we present molecular cytogenetic characterization of recurrent 17q12 microdeletion in a family with

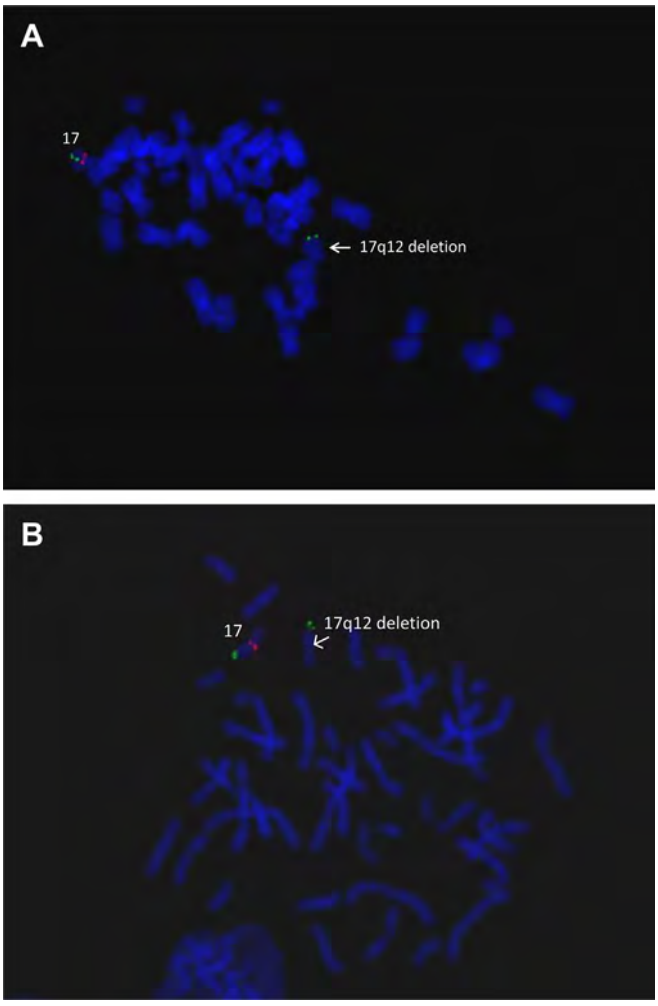

Fig. 5. Metaphase fluorescence *in situ* hybridization analysis on (A) cultured amniocytes and (B) maternal blood lymphocytes using a 17q12-specific bacterial artificial chromosome probe RP11-143E18 (dye: Texas red) (35,985,121−36,129,469) and a control 17q25.3-specific bacterial artificial chromosome probe RP11-388C12 (dye: FITC, green) (80,606,711−80,718,184) [hg 19] shows presence of one red signal and one green signal in a normal chromosome 17, and presence of only one green signal in the aberrant chromosome 17, indicating 17q12 microdeletion.

variable clinical spectrum, and we discuss the genotype−phenotype correlation in this case.

Acknowledgments

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