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Case Report

Prenatal findings and molecular cytogenetic analyses of a *de novo* interstitial deletion of 1q23.3 encompassing *PBX1* gene

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ABSTRACT

Objectives: To present the prenatal findings and the molecular cytogenetic analyses of a *de novo* interstitial deletion of 1q23.3 encompassing *PBX1* gene.

Case report: A 32-year-old woman (gravida 1, para 0) underwent amniocentesis at 26 weeks' gestation because of constant small fetal kidneys on prenatal ultrasound. Chromosome microarray analysis (CMA) detected a *de novo* deletion of 1.871 Mb at 1q23.3. The deletion encompassed 2 genes of *PBX1* and *LMX1A*. *PBX1* haploinsufficiency had been reported to lead syndromic congenital anomalies of kidney and urinary tract (CAKUT) in humans. Furthermore, at 31 weeks' gestation, borderline oligohydramnios and restricted fetal dimensions were revealed. Ultimately, the pregnancy was terminated at 32 weeks with a 1500-g female fetus presenting polydactyl of left hand.

Conclusions: The shared phenotypes between this case and the previously published prenatal cases demonstrate that loss of function mutation in *PBX1* should be suspicious in fetus with bilateral renal hypoplasia, oligohydramnios and intrauterine growth retardation (IUGR).

Introduction

CAKUT are common finding on fetal ultrasound and present in 3–7 out of 1000 births, accounting for 20–30% of birth defects [1]. CAKUT is the most common cause of end stage renal disease in children, leading to high morbidity and mortality in these patients [2,3]. Though the etiology of most cases is unknown, multiple lines of evidence suggest a strong contribution of genetic defects, such as some copy number variations (CNVs) and monogenic mutations. Furthermore, it was reported that these genetic defects were associated with developmental disorders that develop later in life, especially neurodevelopment diseases, such as autism, schizophrenia, epilepsy, intellectual disability, and others [4,5]. So, identification of the potential genetic defects in fetus with CAKUT is important for prenatal diagnosis and genetic counseling.

Recently, multiple studies demonstrated association of *PBX1* haploinsufficiency with syndromic CAKUT [6–9]. However, little is known about the prenatal phenotype caused by *PBX1* defects. Here, we provide a detailed description of the phenotype in a fetus with heterozygous *PBX1* gene deletion.

Case presentation

A 32-year-old, grvida 1, para 0, woman was referred for genetic counseling and amniocentesis at 26 weeks of gestation because of small fetal kidneys discovered by prenatal ultrasound. She and her 32-year-old husband were normal, healthy and nonconsanguineous, and there was no family history of congenital malformations. In the first trimester ultrasound assessment, the embryo had a normal shape and appearance. Noninvasive prenatal screening at 12 weeks of pregnancy showed normal risk of aneuploidy. Ultrasound at 22^{+6} weeks of gestation showed a small size of right kidney (1.9 cm × 1.0 cm) and blurry left kidney.

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After three weeks, Level III ultrasound at 25^{+5} weeks of gestation revealed that the size of left and right kidneys was 1.51 cm × 0.78 cm and 1.51 cm × 0.98 cm, respectively (Fig. 1). The amniotic fluid amount was normal and other internal organs were unremarkable.

In view of these findings, we decided to perform chromosome microarray analysis (CMA) using the SNP Affymetrix® CytoScan™ 750 K Array (Affymetrix® Inc., Santa Clara, CA, USA) with fetal DNA extracted from uncultured amniocytes. The array has an average space between two oligonucleotides of 4 kb. Scanning was performed by the Affymetrix® GeneChip Scanner 3000 7G (resolution 0.51–2.5 μm). The data analysis was conducted using the Affymetrix® Chromosome Analysis Suite Software (ChAS), version 3.0, hg19. CMA detected a 1.871 Mb heterozygous microdeletion at 1q23.3 with genomic coordinates 163,444,997–165,316,065 (arr [hg19] 1q23.3 (163,444,997-165,316,065)x1), encompassing *PBX1* and *LMX1A* genes (Fig. 2). The deletion was confirmed using custom MLPA probes targeted to *PBX1* gene (Fig. 3). Both parents showed normal copy number at the same region. Thus, the fetal carried a *de novo* microdeletion. Furthermore, no other clinical significant CNVs were identified.

After genetic counseling, the parents selected to temporary continue the pregnancy. However, at 31 weeks of gestation, the size of left and right kidneys was still small (left: 1.64 cm × 0.8 cm, right: 1.70 cm × 0.9 cm). Furthermore, ultrasound revealed borderline oligohydramnios and restricted fetal dimensions: the amniotic fluid index (AFI) was 7 cm, the bi-parietal distance (BPD) was 7.5 cm (−2 SD), the head circumference (HC) was 27.3 cm (−1.68 SD), the abdominal circumference (AC) was 24.3 cm (−2.16 SD), and the femur length (FL) was 5.5 cm (−1.67 SD).

In view of these findings, the parents accepted further genetic counseling and decided to terminate the pregnancy at 32 weeks of gestation at local hospital. The induced aborted fetal was female and weighed 1.5 kg (~10th percentile). No macro phenotypic alterations except polydactyl of left hand were recognized. In compliance with the parents' wishes, neither a fetal autopsy nor photograph was performed.

The ethics committee of Dongguan Maternal and Chindren Hospital approved the study. Informed consent was obtained from participants (husband and wife).

Discussion

Interstitial deletions of the long arm of chromosome 1 described by conventional cytogenetic techniques had showed that patients with proximally located deletions (1q21-q25) presented developmental delay, growth retardation, microbrachycephaly, abnormalities of kidney and urinary tract, and hand anomalies [10,11]. With molecular cytogenetic techniques especially chromosome microarray analysis (CMA), some of patients harboring microdeletions with precise breakpoints were reported, which offered the opportunity to identify *PBX1* as a promising candidate gene associated with renal malformation [12,13]. In 2017, Le Tanno et al. reported several *de novo* microdeletions at 1q23.3-q24.1 locus. Among of these patients, the smallest overlapping region (SRO) focus on *PBX1* gene, which is proposed to be relevant to syndromic CAKUT [6]; In addition, Laurence et al. identified five *de novo* heterozygous loss of function mutations in *PBX1* gene or microdeletions involving the *PBX1* gene in 204 unrelated CAKUT patients [7]. Based on these findings, it provides convincing evidence that *PBX1* gene causes CAKUT by haploinsufficiency mechanism.

PBX1 encodes a transcription factor which promotes protein–protein interaction and plays a crucial role in several developmental processes. In human, *PBX1* is constitutively expressed in human bone-derived cells (HBDC) and is strongly expressed in fetal kidneys and brain [6,14]. Patients with pathogenic *PBX1* variants/microdeletions showed pleiotropic developmental defects similar to those in *Pbx1*$^{-/-}$ mice, including external ear anomalies, abnormal branchial arch derivatives, heart malformations, diaphragmatic hernia, renal hypoplasia and ambiguous genitalia [6–9,15]. Developmental delays and craniofacial dysmorphy were also reported in patients who carried *PBX1* gene mutations and deletions.

In order to analyze the genotype–phenotype relationships, we summarized the genetic changes and phenotypes of 23 patients described so far (See Supplemental Table 1). 16 with loss of function allele showed more phenotypes of CAKUT, hearing impairment and skull anomalies, whereas 7 patients with missense mutation showed more complex phenotypes including cardiac defects, diaphragmatic eventration, and ambiguous genitalia. Difference was also observed in prenatal phenotypes. Among reported patients

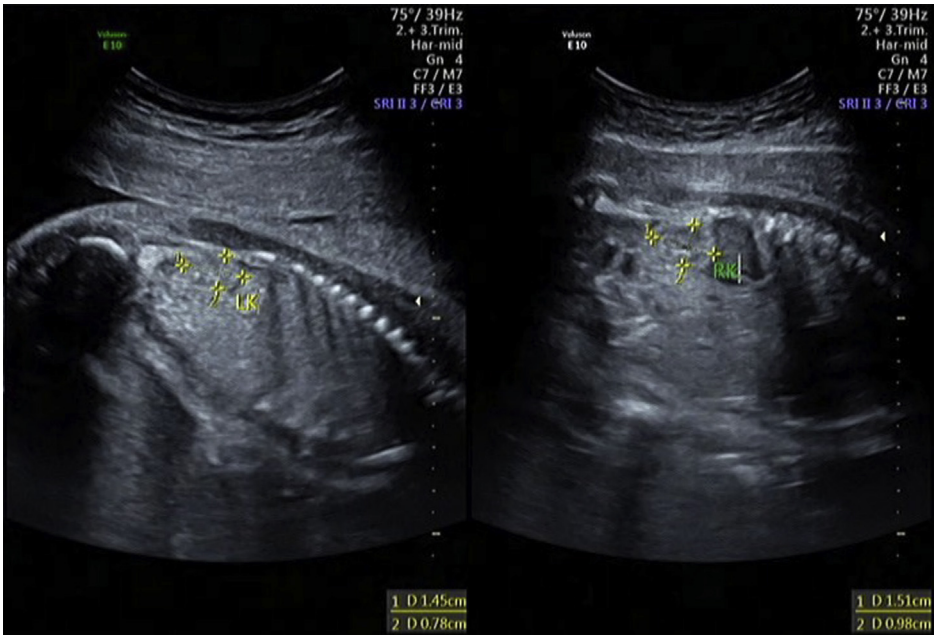

Fig. 1. Sonographic image of the fetus at 25^{+5} weeks of gestation showing bilateral small kidneys (left: 1.52 cm × 0.72 cm, right: 1.51 cm × 0.98 cm).

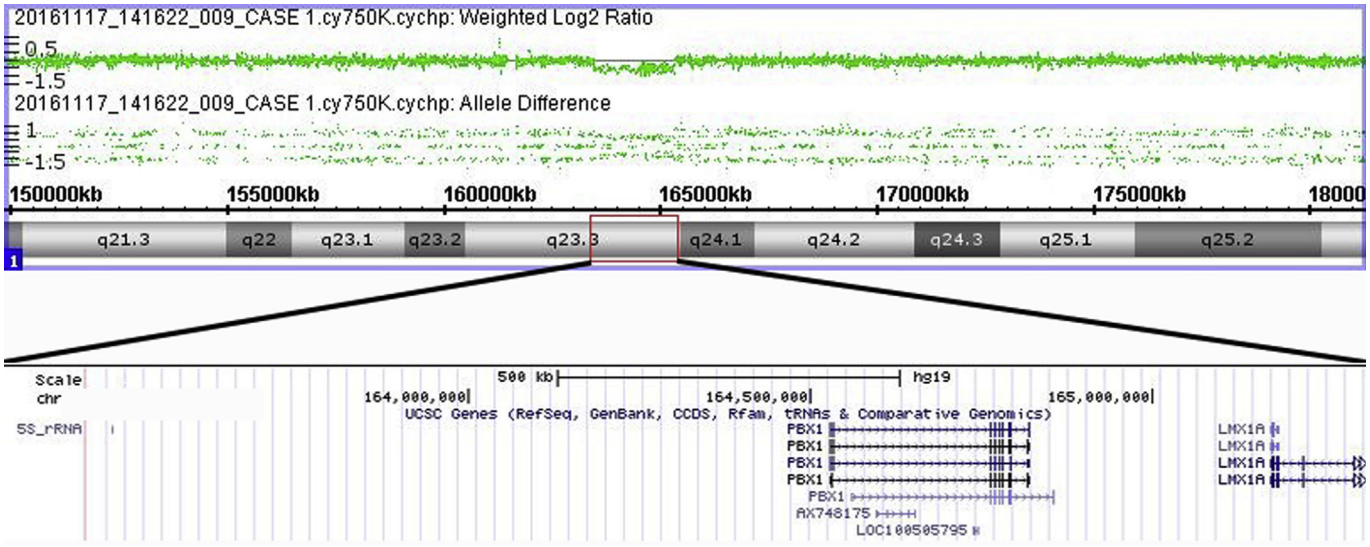

Fig. 2. CMA profile of chromosome 1 showing the deleted region and the corresponding UCSC gene.

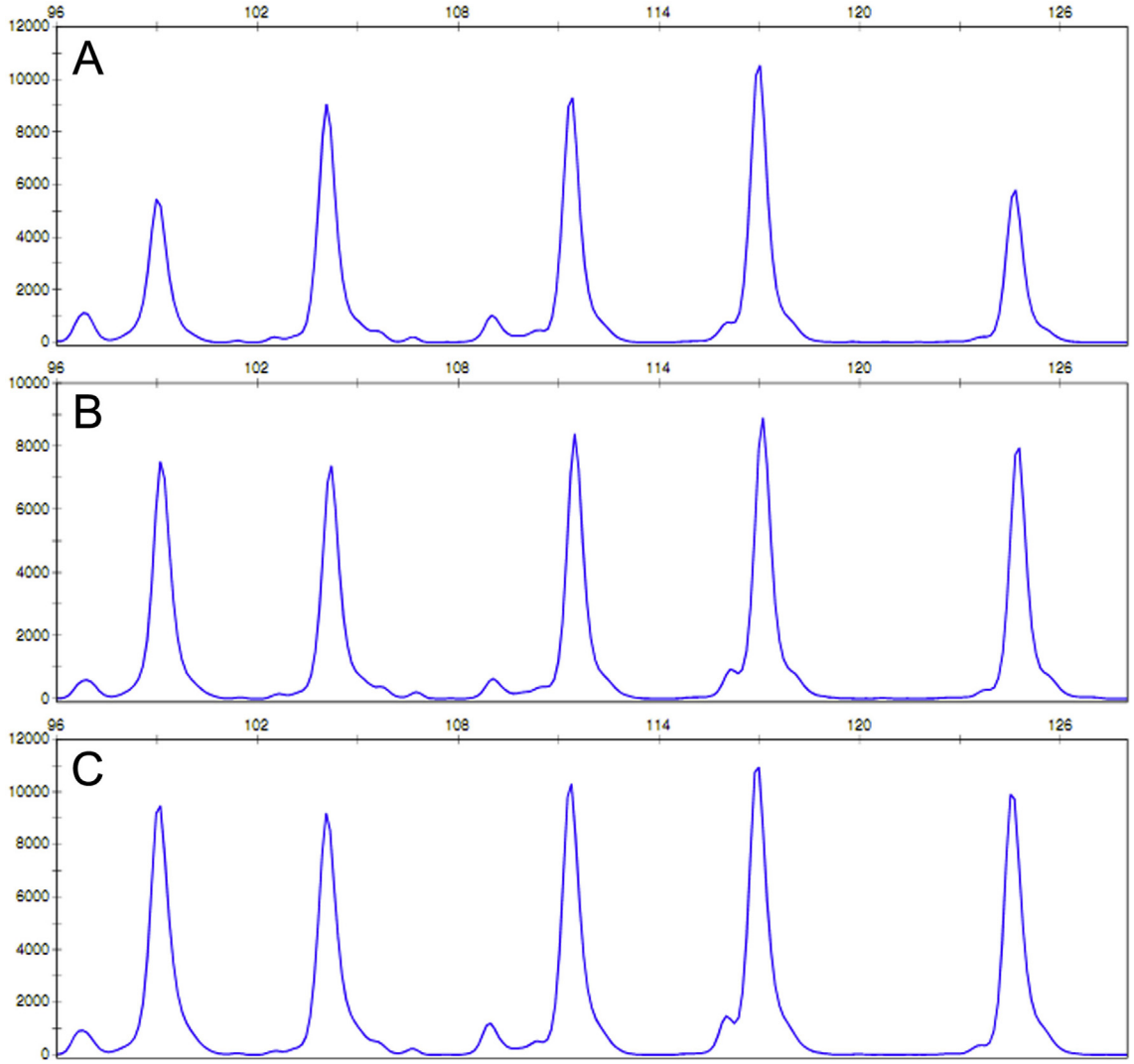

Fig. 3. Custom MLPA results of fetus (A) and parents (B: father; C: mother) confirming *PBX1* deletion. The X-axis represents the probe size and the Y-axis represents the fluorescence intensity. The first and fifth probe presents the *PBX1* exon1 and exon3, respectively; other three are reference probes. ~50% decreased signal in test probes was observed in fetus.

with *PBX1* defects, eight had clinical data during the pregnancies. Four patients with loss of function allele presented bilateral renal hypoplasia, hyperechogenicity, oligohydramnios and IUGR [6,7]. Other four with missense mutation presented with oligohydramnios, increased nuchal folds, unilateral diaphragmatic eventration and bilateral dilated ureters. The phenotypic variability observed in patients may be explained by allelic heterogeneity [9]. Our patient who carried a 1.8-Mb deletion encompassing *PBX1* demonstrated similar phenotypes to those previously reported, especially bilateral renal hypoplasia, oligohydramnios and IUGR. Besides, polydactyly was noticed in our patient, five other patients were also reported to have hand/foot anomaly, so, hand/foot anomaly maybe a characteristic malformation. However, polydactyly was not found in other five patients: three with clinodactyly and two with brachydactyly.

In our patient, another gene *LMX1A,* which encodes an evolutionarily conserved transcription factor with an essential function in neural development, was involved. In developing mouse, *Lmxla* is predominantly expressed in the nervous system and otic vesicles which later become restricted to non-sensory epithelia of the ear. *Lmxla*$^{-/-}$ mouse showed congenital deafness, vestibular defects, and neurological, skeletal, pigmentation, and reproductive system abnormalities [16]. Recently, *LMX1A* missense mutations were identified in patients with autosome recessive or dominant non-syndromic hearing impairment [17,18]. In reported patients with *PBX1* defects, eight had hearing impairments, five of whom had large deletion involving both *PBX1* and *LMX1A*, so, it may remain to determine the role of *LMX1A* in these five patients. However, no genetic changes exclusively affecting *LMX1A* have been reported in patients with anomalies beyond hearing impairment.

In conclusion, we provide a detailed description of the phenotype in a fetus with heterozygous *PBX1* gene deletion. The shared phenotypes between this case and the previously published prenatal cases demonstrate that loss of function mutation in *PBX1* should be responsible for bilateral renal hypoplasia, oligohydramnios and IUGR phenotype.

Conflicts of interest

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

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tjog.2019.01.022.

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