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ORIGINAL ARTICLE

Evaluation of novel compound variants of *CEP290* in prenatally suspected case of Meckel syndrome through whole exome sequencing

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Abstract

Background: Meckel syndrome (MKS) is a fatal disease characterized by multisystem fibrosis during the prenatal or perinatal period. It has an autosomal recessive genetic pattern and is characterized by meningo occipital encephalocele, polycystic kidney dysplasia, polydactyly, and hepatobiliary ductal plate malformation. Germline variations in *CEP290* have been shown to cause MKS4.

Methods: In this study, a 23-year-old Chinese woman who was 18 weeks pregnant was examined. The pregnancy was terminated due to occipital meningocele and enlarged cystic dysplastic kidney revealed by ultrasonography. In addition, the patient had a history of adverse pregnancy whereby the fetus presented with double kidney enlargement. Karyotype analysis and chromosomal microarray examination (CMA) were carried out using amniotic fluid samples. Whole exome sequencing (WES) was performed using tissue specimens of the aborted fetus.

Results: Karyotype and CMA analyses showed normal results. However, compound heterozygous mutations of *CEP290* c.3175dup and *CEP290* c.1201dup were detected through WES. *CEP290* c.1201dup is a novel heterozygous mutation of *CEP290* that has not been reported previously.

Conclusions: The findings of this study provide information on the correlation between MKS phenotype and genotype in *CEP290*. In addition, these findings indicate that WES is an effective method for detecting genetic causes of multiple structural defects especially those showing normal karyotype and CMA results.

KEYWORDS

CEP290, Meckel syndrome, novel mutation, whole exome sequencing

Meilian Peng and Shuai Han contributes equally to this work.

1 | INTRODUCTION

Meckel syndrome type 4 (MKS4) (MIM# 611134) is an autosomal recessive perinatal fibrotic disease. It is characterized by meningo occipital encephalocele, polycystic kidney dysplasia, and hepatobiliary malformation. Patients with MKS4 die before or shortly after birth and the prevalence of MKS is one in every 140,000 live births worldwide (Frank et al., 2008). MKS is caused by pathogenic variants in at least 14 genes including *CEP290* (MIM*610142), which contribute to cilia formation (Radhakrishnan et al., 2019). Cilia are located on the surface of cells where they maintain the structure and function of several cells including brain cells, kidney cells, and liver cells. Moreover, cilia participate in signal transduction between adjacent cells (Iannicelli et al., 2010; Mougou-Zerelli et al., 2009). Therefore, germline variation in any of the 14 genes affects the structure and function of cilia, thereby causing MKS.

CEP290 is located in the long arm of chromosome 12 and has 54 exons. *CEP 290* encodes a 290-kd centrosome protein (Centrosomal Protein 290, CEP 290) with 13 putative coiled-coil domains, comprising 2479 amino acids and involving in ciliary assembly and ciliary trafficking (Coppieters et al., 2010). As known, more than 100 variants of *CEP290* have been reported, which are mainly associated with Leber congenital anemia (LCA) 10 (MIM#611755) (Valente et al., 2006) and Joubert syndrome 5 (MIM#610188) (Rafalska et al., 2020), and less associated with Senior–Loken syndrome 6 (MIM#610189) (Sayer et al., 2006) and Bardet–Biedl syndrome 14 (MIM#615991) (Leitch et al., 2008). And also, previous fewer studies have demonstrated that mutations in *CEP290* cause MSK4 (MIM#611134) (Brancati et al., 2007; Radhakrishnan et al., 2019). Most of *CEP290*-related diseases-causing mutations are either nonsense, frameshift, or splice-site mutations, and exert a loss-of-function effect on CEP290 protein (Frank et al., 2008; Travaglini et al., 2009).

In this study, compound heterozygous variants of *CEP290* in malformed fetal tissues were investigated through whole exome sequencing (WES). These variants include maternal *CEP290* c.3175dup and paternal *CEP290* c.1201dup. *CEP290* c.1201dup is a novel pathogenic mutation that has not been reported previously.

1.1 | Materials

Informed consent was obtained from all participants enrolled. The study was approved by the Prenatal Diagnosis Ethics Committee of Zhejiang Provincial People's Hospital, China.

What's already known about this topic?

- Mutations in *CEP290* cause MSK4 (MIM#611134), which are rarely reported and exert a loss-of-function effect on CEP290 protein.

What does this study add?

- *CEP290* c.1201dup is a heterozygous novel mutation of *CEP290* reported for the first time, providing information on the correlation between MKS phenotype and genotype.The findings of this study in *CEP290* and indicate that WES is an effective method for detecting genetic causes of multiple structural defects especially those showing normal karyotype and CMA results.

1.2 | Ultrasound scanning and magnetic resonance imaging (MRI)

Ultrasound monitoring and MRI were used to confirm the prenatal diagnosis. In this case, biometric data of the fetal renal as well as data on other abnormalities were collected, analyzed, and compared with normal values.

1.3 | Fetal karyotype and genetic analysis

Amniotic fluid was obtained by amniocentesis under ultrasound guidance. The amniotic fluid samples were used for fetal karyotype and molecular genetic analyses. Karyotype analysis was also conducted using cultured amniotic fluid cells. Fetal genomic DNA was extracted from amniotic fluid leukocytes following guidelines of the QIAGEN QIAamp DNA Blood Mini kit (Qiagen, Hilden, Germany). It was then subjected to chromosomal microarray analysis (CMA). And, fetal genomic DNA was extracted from the aborted fetal tissue following guidelines of the QIAGEN QIAamp DNA Mini kit (Qiagen, Hilden, Germany). Then, it was subjected to the whole exome capture on an Agilent SureSelect Human All Exon V6 Capture (Agilent, California, USA) and high-throughput sequencing on an Illumina HiSeq 2000 (Illumina, Inc., San Diego, CA, USA). We aligned the sequence data to the human reference genome: University of California, Santa Cruz (UCSC) hg19 by using Burrows–Wheeler aligner version 0.7.10: BWA-MEM (version 0.59). Further, we calibrated variants using the Genomic Analysis Toolkit (GATK) and conducted functional annotation using Annovar and SnpEff. And then, the benign variants were filtered with minor allele frequency (MAF) > 1% in the

1000 Genomes data set (1000G) and our internal database. We used Human Gene Mutation Database (HGMD), ClinVar, and Leiden Open Variation Database (LOVD) to annotate the existence of mutation reports. Finally, we performed Sanger sequencing to validate the suspicious variants and confirm the segregation of the identified variants in the affected and unaffected family members. PCR primers were designed as follows: *CEP290* c.3175-F: TGTCAATGGAGGCTGAAGTTTG; *CEP290* c.3175-R: GTTTTCACACTCCAGGTGTTCC; *CEP290* c.1201-F: TCCAATTATGGTAGCTGTCAATGC; *CEP290* c.1201-R: CGTTCCTGTATACCCTGCTGTA. (GenBank reference sequence for *CEP290*: NM_025114.4).

2 | RESULTS

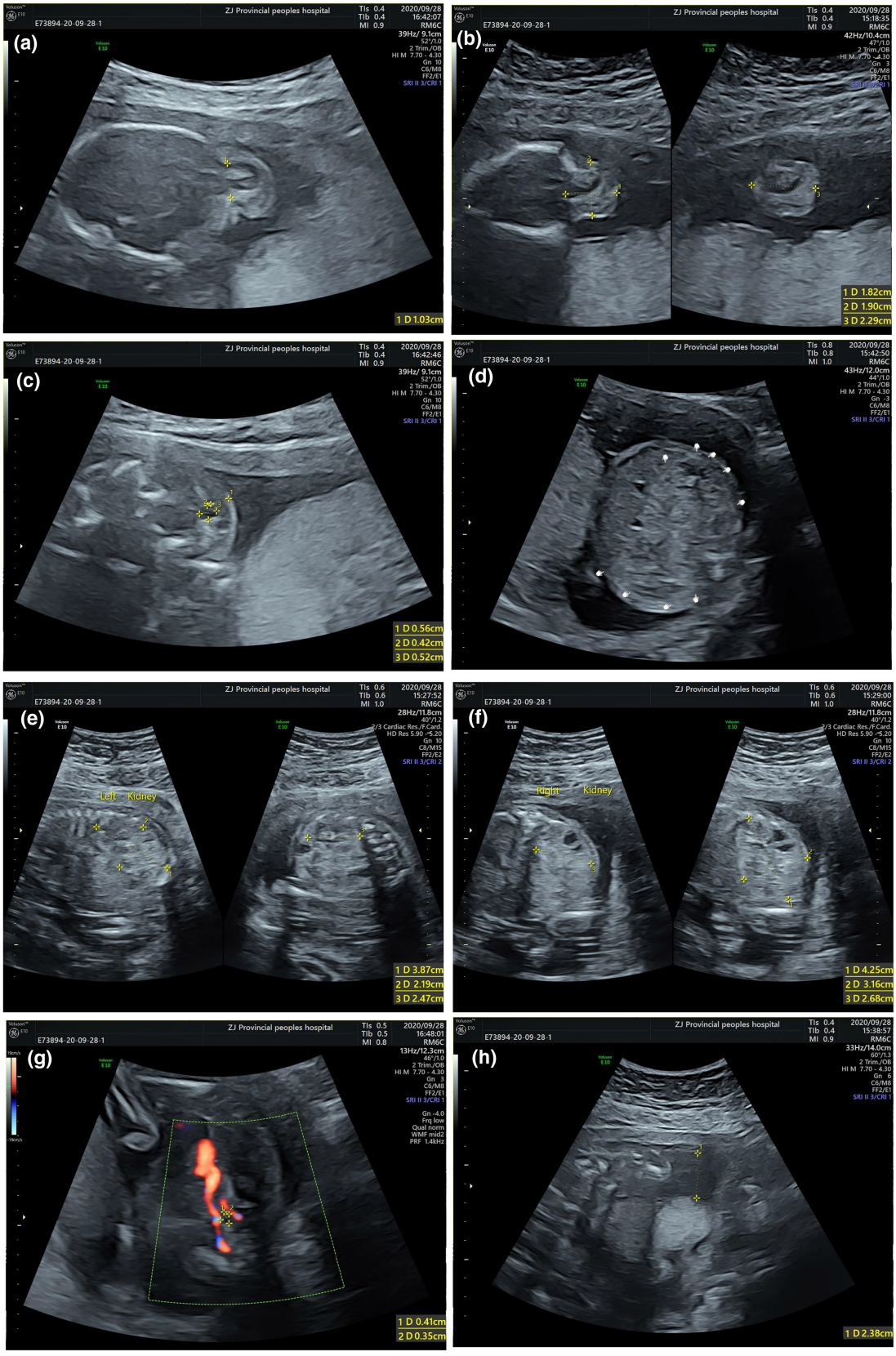
A 23-year-old Chinese woman who was 18-weeks pregnant (gravida 2, para 2) visited the prenatal diagnostic center of our hospital for further examination (Table S1). Because routine nuchal translucency (NT) examination carried out at 12 + 5 weeks of gestation (15th Aug, 2020) showed meningocele in the local hospital. Her last menstrual period occurred on 17th May, 2020. During consultation, we learned that she underwent induced labor at 5-month post-conception because antenatal ultrasonography showed that both kidneys of the fetus were enlarged, 5 years ago, in her first pregnancy. Then, no further genetic testing was carried out for the first fetus. Moreover, no abnormality was observed in peripheral blood karyotype analysis of the phenotypically normal couple. The couple denied they were consanguineous marriage. Then, we carried out fetal ultrasound examination and magnetic resonance imaging (MRI) at 19 + 1 weeks of gestation. Analysis of antenatal ultrasound results showed fetal meningo occipital encephalocele (Figure 1a,b). In addition, the thickness of posterior cervical soft tissue was approximately 0.56 cm, with liquid dark area (Figure 1h). Obvious bilateral kidney enlargement accompanied by many cystic echo regions were seen (Figure 1c–e). No obvious filling bladder was observed (Figure 1f), however, the amount of amniotic fluid was low (AFI: 2.4 cm) (Figure 1g). Moreover, MRI showed fetal multiple malformations, meningoencephalocele (Figure 2a,b), and bilateral polycystic dysplasia kidney (Figure 2c,d).

The couple chose to terminate the pregnancy, finally. Before that, prenatal genetic diagnosis using amniocentesis was performed at 19 + 3 weeks of gestation. Amniotic fluid was collected and used for routine karyotype analysis and CMA. Then, Rivanol was injected. Occipital meningocele and abdominal bulge were founded in the aborted male fetus (Figure 3a). However, cleft lip, palate, and multiple toes were not observed. After obtaining the pregnant woman's consent, the aborted fetal tissue was preserved for DNA extraction. Fetal karyotype analysis did not show any chromosomal structural abnormality. In addition, CMA analysis did not show pathogenic copy number variations (CNVs) in 46 chromosomes. Therefore, WES was performed to further explore the cause of the malformations. Then, one pathogenic and one suspected pathogenic variant were detected: *CEP290* c.3175dup (p.Ile1059fs) and c.1201dup (p.Leu401fs) validating by Sanger sequencing. *CEP290* c.3175dup (p.Ile1059fs), a known variant in Leber congenital amaurosis (Yzer et al., 2012), Joubert syndrome (Sayer et al., 2006), and Meckel syndrome (Baala et al., 2007) causes premature termination of translation. This results in formation of a truncated CEP290 protein with 1068 amino acids instead of the wild-type protein that comprises 2479 amino acids. *CEP290* c.1201dup (p.Leu401fs) is a loss-of-function mutation that leads to the formation of a truncated CEP290 protein with 420 amino acids. *CEP290* c.1201dup (p.Leu401fs) could not be found in the HGMD, ClinVar, and LOVD and was not found in the 1000G and our internal database. In addition, segregation of the identified variants was detected in the couple. This variant existed in a heterozygous state in the mother and father of the fetus (Figure 3b,c).

3 | DISCUSSION

Meckel syndrome (MKS) is a rare and fatal hereditary characterized by multiple congenital malformations. Its clinical features include brain malformation (mainly occipital encephalocele), polycystic kidney, polydactyly, cleft lip and palate, cardiac and genital abnormalities, central nervous system (CNS) malformation, liver fibrosis, and bone dysplasia (Hartill et al., 2017). Most fetuses with MKS die within a few weeks after birth. MKS patients present with polycystic dysplastic kidney, common central nervous system diseases (encephalocele, hydrocephalus, congenital anencephaly, apheresis, and Dandy Walker syndrome), liver hypoplasia, liver fibrosis, polydactyly of limbs (80% of them are posterior type, a few are anteroposterior type), and cardiac malformations (atrial septal defect, aortic coarctation, patent ductus arteriosus, and pulmonary artery) (Logan et al., 2011). Some patients may present with pulmonary hypoplasia, cleft lip and palate, microphthalmos, and micrognathia secondary to oligohydramnios. In addition, genital dysplasia and cryptorchidism are common in male patients.

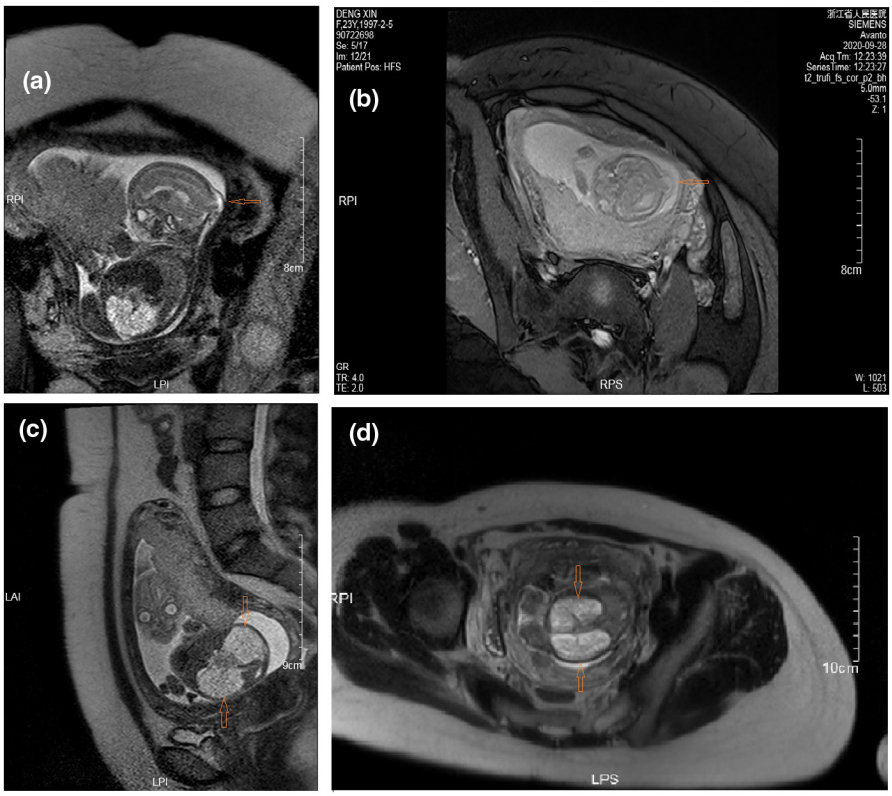
This study examined a 23-year-old pregnant woman with a history of adverse pregnancy and the husband was not a close relative. The second pregnancy was terminated based on the fetal ultrasound and MRI findings. The fetus presented with occipital meningoencephalocele, abnormal



brain, and cystic dysplasia of the kidney. Karyotype and CMA analysis showed no chromosomal abnormalities in the fetus. Therefore, the entire exome was sequenced using fetal genomic DNA extracted directly from fetal muscle tissue. Compound heterozygous mutations of *CEP290* were identified through WES. The mutations included *CEP290* c.3175dup (p.Ile1059fs) and *CEP290* c.1201dup (p.leu401fs). *CEP290* c.1201dup (p.leu401fs) has not been

FIGURE 1 (a) Meningoencephalocele: the echo of posterior occipital skull was interrupted about 1.0 cm, and there was 1.8 cm ×1.9 cm ×2.3 cm bulge, and the echo of brain tissue was seen inside; (b) the aura of fetal skull was irregular; (c) The thickness of the posterior cervical soft tissue is about 0.56 cm, with liquid dark area in it, and the larger one is about 0.42 cm ×0.52 cm; (d–f) Bilateral kidney enlargement: the size of left kidney is about 3.4 cm ×1.9 cm ×2.2 cm, and the size of right kidney is about 3.8 cm ×3.0 cm ×2.6 cm. Parenchymal echo is obviously enhanced. There are many dark areas in the kidney, which are not connected with each other. The larger one is 0.97 cm ×0.61 cm, with sound permeability, and bilateral renal arteries are indistinct; (g) No obvious filling bladder is found. Small dark area appears at the bladder, with the size of about 0.41 cm ×0.35 cm."; (h) Oligohydramnios: biparietal diameter: 3.9 cm, femur length: 3.0 cm, fetal heart rate: 140 beats/min, fetal movement: accessible, placenta: posterior wall GR 0, maximum horizontal segment of amniotic fluid: 2.4 cm

FIGURE 2 (a and b) Fetal posterior occipital projection shadow, consistent with meningoencephalocele changes; hydrocephalus: fetal biparietal diameter is about 41 mm, the midline of brain is in the middle. The lateral ventricle was enlarged and widened, and the shape and signal of brain parenchyma were normal. In the posterior occipital region, the local meninges protruded outwards, with a size of about 11 ×7 mm, and a small amount of brain tissue seemed to be seen in it. There was no abnormal signal shadow in the spinal canal. (c and d) Bilateral polycystic dysplasia kidney may be: the volume of both kidneys in the abdominal cavity increases, and there are multiple small cystic high signal shadows on T2WI



reported previously. Sanger sequencing showed that both the father and mother of the fetus carried one mutation in the heterozygous state. *CEP290* c.3175dup (p.Ile1059fs) was classified as "pathogenic" variant based on the variation interpretation guidelines of American Medical Genetics and genomics (ACMG). *CEP290* c.1201dup (p.Leu401fs) was found to be a frameshift mutation and was classified as "possibly pathogenic" mutation. The two variants are compound heterozygous mutations with high pathogenicity. The novel pathogenic mutation: *CEP290* c.1201dup combined with *CEP290* c.3175dup identified in this study were shown to cause MKS.

Germline variations in *CEP290* rarely cause MKS4 (Frank et al., 2008). Most patients with MKS4 harboring *CEP290* mutations have truncated mutations (Shaheen et al., 2016; Zhang et al., 2020). *CEP290* gene encodes the centrosome protein CEP290 comprising 2479 amino acids. CEP290 is highly tissue specific, and is mainly expressed in embryonic tissues, and not in adult tissues or organs (Tammachote et al., 2009). The expression pattern of CEP290 indicates its important role in embryonic development. CEP290 plays a key role in early and late stages of cilia formation. It is involved in gradual loss of centromere satellites. Furthermore, CEP290 is implicated information of covered ciliary vesicles (CCVs) through transformation of primary ciliary vesicles (PCVs). It plays a role in recruitment of RAB8A into primary cilia and targets and transfers satellite proteins from centrioles to centrosomes (Kobayashi et al., 2014). Sayer et al. reported that CEP290 is located in cilia, centrosome, and nucleus. Expression of CEP290 is cell cycle dependent and it plays an important role in chromosome segregation (Sayer et al., 2006). In kinetochore, CEP290 comprises highly conserved domains and motifs, implying that these domains and motifs have specific domain assembly function in CEP290 (Coppieters et al., 2010). CEP290 has 13 helix domains, including

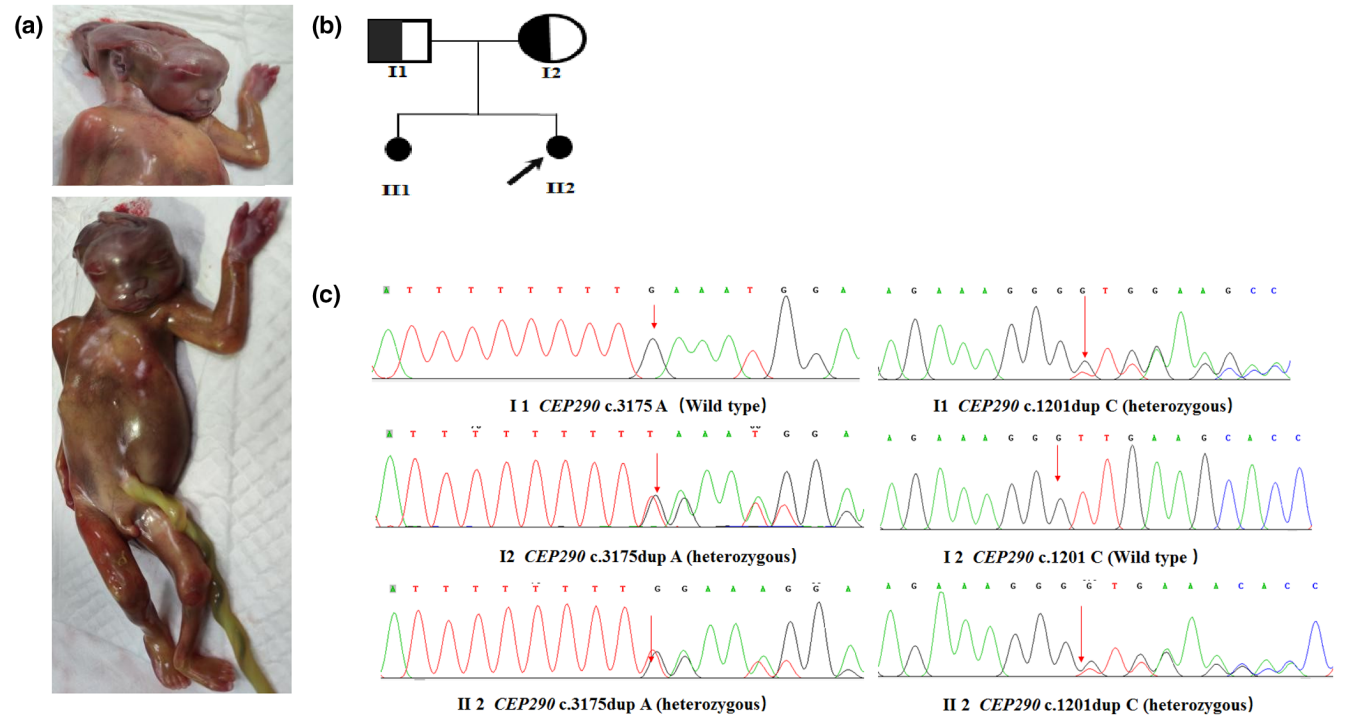


FIGURE 3 (a) Male stillbirth, occipital meningocele, no cleft lip and palate, abdominal bulge, no multiple toes. (b) Pedigree of the family. (c) The sequencing of the proband and his parents

chromosome segregation, ATPase, kinase inducible domain, oncosin homologous domain, nuclear localization signal domain, and ATP/GTP binding domain (Consugar et al., 2007). Furthermore, CEP290 plays a role in N-glycosylation, phosphorylation, tyrosine sulfation, amidation, and N-myristoylation (Dawe et al., 2007). Therefore, germline variations in CEP290 may adversely affect ciliary body and axon transport, resulting in loss of axon guidance and growth, which explain the brain abnormalities observed in MKS4 patients.

Cilia length is instrumental for cilia function and is controlled by intraflagellar transport. Cells sometimes change their cilia length in response to environmental cues, for example, the patients of MKS shows elongated cilia; however, patients of Joubert syndrome manifest less and shortened cilia. Most recently, cilia elongates in response to pro-inflammatory cytokines and thereby, loss of cilia length regulation upon cytokine stimulation is proposed to be a part of the endothelial dysfunction in inflammatory responses-related diseases such as pulmonary arterial hypertension (PAH) (Dummer et al., 2018; Wann & Knight, 2012).

MKS is a rare and highly heterogeneous (both genotype and phenotype) disease. Single gene sequencing or targeted next-generation sequencing does not always identify candidate mutations in MKS patients. When routine karyotype analysis and CMA results are normal and a Mendelian inheritance disease is suspected, WES is performed to further explore the cause of malformations (Dai et al., 2019; Ng et al., 2010). WES can accurately and reliably identify candidate genes and variants of MK disease phenotype, ensuring accurate clinical diagnosis. In addition to routine chromosome examination and gene sequencing of clinical multiple malformation fetus, WES should be performed identify the cause of disease. Moreover, prenatal diagnosis should be carried out to provide pregnant women with favorable genetic counseling. This will ensure a healthy next generation and avoid or reduce birth defects.

This study reports a novel pathogenic mutation-*CEP290* c.1201dup (p.Leu401fs) which causes MKS. In addition, the study shows that WES is an accurate, rapid, and cost-effective tool for genetic analysis of MKS patients.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

This study adhered to the tenets of the Declaration of Helsinki on human subjects and was approved by Prenatal Diagnosis Ethics Committee of Zhejiang Provincial People's Hospital, Hangzhou, China.

AUTHOR CONTRIBUTIONS

Liwei Yang and Yaer Lv designed the study. Meilian Peng and Shuai Han wrote the manuscript. Meilian Peng, Liwei Yang, Juan Sun, Xiaodong He and Yaer Lv undertook collecting samples and collected clinical information. Shuai Han revised the manuscript. All authors reviewed the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

All data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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