Haploinsufficiencies of FOXF1, FOXC2 and FOXL1 genes originated from deleted 16q24.1q24.2 fragment related with alveolar capillary dysplasia with misalignment of pulmonary veins and lymphedema-distichiasis syndrome: relationship to phenotype

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Abstract

Objective: We describe a fetus with a 2.12-Mb terminal deleted fragment in 16q associated with alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) and lymphedema-distichiasis syndrome (LDS) and intend to provide a comprehensive prenatal management strategy for the fetuses with ACDMPV and LDS through reviewing other similar published studies.

Methods: The fetus presented a series of diverse structural malformations including congenital cardiovascular, genitourinary and gastro-intestinal anomalies in ultrasound at 23 + 5 weeks of gestation (GA). Amniocentesis was conducted for karyotype analysis and copy number variation sequencing (CNV-seq) after informed consent.

Results: The fetal karyotype was 46,XX, however the result of CNV-seq showed an approximately 2.12-Mb deletion in 16q24.1q24.2 (85220000-87340000) × 1 indicating pathogenicity.

Conclusion: Genomic testing should be recommended as a first line diagnostic tool for suspected ACDMPV and/or LDS or other genetic syndromes for the fetuses with structural abnormalities in clinical practice.

Keywords: ACDMPV, LDS, Haploinsufficiencies of FOXF1, FOXC2 and FOXL1 genes, Multiple-system structural malformations, Prenatal diagnosis

Background
ACDMPV (OMIM 265380) is a rare and deadly disorder characterized by severe respiratory distress and cyanosis with the incidence of 1/100,000 [1]. In addition, about 50 to 75 percent of affected newborns have multiple-system abnormalities such as hypoplastic left heart syndrome (HLHS) and intestinal malrotation [2].
In approximately 80–90% of ACDMPV cases, heterozygous single nucleotide variants (SNVs) or copy number variant (CNV) deletions involving forkhead box F1 (FOXF1, OMIM 601089) in chromosome 16q24.1 have been found [3, 4]. In this report, we describe a fetus featured by a series of diverse structural malformations. Meanwhile, CNV-seq revealed a deleted region in 16q24.1q24.2 related with ACDMPV [5] and LDS [6]. Both ACDMPV and LDS (OMIM 153400) are rarely reported in adults simultaneously in practice because of nearly 100% mortality of the cases with ACDMPV in the newborn period [7]. However, the severity of isolated LDS associated with pathogenetic forkhead box C2 (FOXC2, OMIM 602402) is variable and cannot be predicted, among which the majority have been found in late childhood or adolescence with classical lymphatic abnormalities [8] and the minority have been found in late childhood or adolescence with classical lymphatic abnormalities. Furthermore, we compare the features of our fetus with the reported cases related with 16q24.1q24.2 microdeletion syndromes. We aim to provide a comprehensive prenatal management strategy for the fetuses with ACDMPV and LDS.

Materials and methods

Case presentation

A 28-year-old healthy multigravida woman resorted to prenatal diagnosis medical center of Xuzhou Central Hospital due to abnormal ultrasound results. She had no history of adverse pregnancy and drug usage, and the couple were non-consanguineous. The family has a healthy child. There were not family histories with any serious disorders. Prenatal ultrasound at 23 + 5 weeks of GA showed the following presentations of Fig. 1: (a) pulmonary artery (PA) dilatation; (b) complete atrioventricular septal defect (AVSD); (c) common atrioventricular valve (CAV), foramen ovale closure (FOC), atrial septal defect (ASD), ventricular septal defect (VSD) and right heart enlargement; (d) dilatation of the stomach, esophageal dilation (considering pyloric obstruction); (e) a hypodense mass in the upper pole of the left kidney on December 23, 2022. Amniotic fluid was collected...
for karyotype analysis and CNV-seq after informed consent. Although the fetal karyotype was 46,XX, the result of CNV-seq showed that there was an approximately 2.12-Mb pathogenetic deletion in 16q24.1q24.2 (85220000-87340000) \times 1 \) (Fig. 2) which was confirmed to be de novo after CNV-seq results of the couple were verified. Finally after receiving sufficient genetic counseling, the couple provided informed consent and chose to terminate the pregnancy. This study was approved by Xuzhou Central Hospital Ethics Committee (No. XZXY-LK-20210812-019).

**Methods**

Chromosome analysis was performed on G-band metaphases from amniotic fluid sample according to the laboratory’s standard protocols. The following entire operation process of CNV-seq included extracting uncultured genomic DNA from the sample, constructing DNA libraries, massively sequencing in parallel and conducting the raw sequencing reads following the corresponding operating regulations [12]. Finally, the results of data were assessed according to standards and guidelines of American College of Medical Genetics [13].

**Discussion**

ACDMPV and LDS have been confirmed to be related with the deleted 16q24.1q24.2 fragment until now [5, 14]. In this case, CNV-seq detection showed a 2.12-Mb deleted region in 16q24.1q24.2 containing the following definite pathogenetic genes: FOXF1, FOXC2 and related regulatory genes including forkhead box L1 (FOXL1, OMIM 603252) and FOXF1 adjacent non-coding developmental regulatory RNA (FENDRR). Combined with the abnormal results of multi-system malformations of the fetus such as congenital cardiac, lung, genitourinary and gastro-intestinal anomalies, the diagnosis of ACDMPV and LDS of the fetus was further defined. In addition to our fetus, Table 1 shows the other 10 cases with similar deleted fragment in the 16q24.1q24.2 region with complete information, and the sizes range from 0.9 to 3.5 Mb containing FOXF1, FOXL1 and FOXC2 genes, among which two fetuses were from de novo disease-causing variants of the above genes, four cases from maternal heredity, four cases from unknown origin, three females and seven males are enrolled from five literatures [3, 15–18]. And we present a figure visualizing the deleted regions of 11 cases harboring FOXF1, FOXC2, and FOXL1 according to different versions of the genome map from UCSC Genome Browser Home: (a) cases from C1 to C8 were plotted with HG18; (b) cases from 9 to 11 with HG19 (Fig. 3). As is shown, the deleted sizes of 16q24.1q24.2 fragment are not proportional to the severity of phenotypes, and both cardiac and renal anomalies are the two major manifestations during the fetal period, while the phenotypes of our fetus are the most serious, showing the changes of cardio-pulmonary structure such as PA dilatation, HLHS, complete AVSD, CAV, FOC, ASD, VSD; the upper pyloric obstruction manifestations; a hypodense mass in the left kidney. However, the prime symptoms of neonates after birth are featured by respiratory, gastro-intestinal and genitourinary manifestations. Moreover, the gestational ages of delivery range from 22 to 39+1 weeks, among which three couples opted to terminate the pregnancies at second trimester of pregnancy and all of them died of respiratory diseases and their lifespans ranged from 16 h to 40 days. Therefore, early recognition of ACDMPV and LDS is essential in clinical practice.

The CNV-seq result of our fetus indicated a 2.12-Mb deleted fragment in 16q24.1q24.2 (Fig. 2) including the

![whole genome view](image1)

![chromosome 16](image2)

**Fig. 2** The CNV-seq result of fetus showed a 2.12-Mb deletion in 16q24.1q24.2 (85220000-87340000)
| Cases | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|-------|---|---|---|---|---|---|---|---|---|----|----|
|  | References | 15 | 16 | 16 | 16 | 16 | 16 | 17 | 18 | 3 | Our case |
|  | Genomic coordinates(hg18/hg19) | chr16:84447762-85815086 | chr16:84375076-86275754 | chr16:84275154-85277007 | chr16:84402571-85435712 | chr16:84400199-86403576 | chr16:84400199-86403576 | chr16:85108709-86720212 | chr16:85728812-86831579 | chr16:85863000-87370500 | chr16:85220000-87340000 |
|  | Karyotype | NA | NA | NA | NA | NA | NA | – | – | – | – |
|  | Deletions (del) [Mb] | 1.37 | 1.5 | 2.0 | 0.9 | 1.0 | 3.5 | 1.8 | 1.57 | 1.1 | 1.45 | 2.12 |
|  | Female/ Male | Male | Female | Male | Female | Male | Female | Male | Male | Male | Female |
|  | Inheritance | De novo | Maternal | NA | Maternal | Maternal | De novo | Maternal | NA | NA | NA |
|  | Other pathogenic genes | IRF8; FOXL1 | FOXL1 | FOXL1 | FOX1 | FOXL1 | FOXL1 | IRF8; FOXL1 | IRF8; FOXL1; COX4I1 | IRF8; FOXL1 | FOXL1; IRF8; COX4I1; FENDRR |
|  | Prenatal findings | BH; PE; PHD; HLHS | NA | NA | NA | NA | NA | NA | PH; partial AV defect; BH | Cystic hygroma; fetal hydrolele; hydrophooses; VSD | PH; omphalocle; hydronephrosis and VSD |
|  | Delivery GA (W) | 37 | 28 | 22 | 38 | 37 | NA | NA | 26 | 39 | 4-1 |
|  | Birth Wt (g) | 1091 | 2900 | NA | 3676 | 592.4 | 2920 | NA | 2920 | NA |
|  | Respiratory findings | ACD/MPV | ACD/MPV; PL | – | ACD/MPV; ECOMO dependent | ACD/MPV; LP; hypopnoe; ECOMO dependent | ECOMO dependent | ACD/MPV | ACD/MPV | – | ACD/MPV |
|  | LDS | – | – | – | – | – | – | – | – | – | – |
|  | Cardiac findings | HLHS; PDA; small main PA; VSD; ASD; PDA; PLSVC; CP | PDA | HLHS | TOF; PDA; PPHN | HLHS | IAA; dilated PA; large PDA; small LV; PH | PDA; PPHN | Partial AVC malformation; Small PA | – | – |
|  | Genitourinary findings | Hydronephrosis; hypoprexis; – | Dilated renal pelvices; BH | – | Mild uretero-pelic, colicestasis | Bilateral renal pelvices | – | Bilateral dilatation of the PS with bilateral US | – | – | NA |
|  | Gastrointestinal findings | IM; ectopic cecum and appendix | EA; TSF; ectopic anus | – | DA; AP, imperforate anus | – | – | – | – | Lack of peristalsis | NA |
### Table 1 (continued)

| Cases | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|-------|---|---|---|---|---|---|---|---|---|----|----|
| Other findings | HP; flat nasal bridge; HM; decreased muscle tone | SUA | – | SUA | T11 butterfly vertebra; cleft lip; cleft palate; brachycephaly; SUA | Posterior rib fusions: 10/11 (right side), 9/10 (left side) | – | Intrauterine infection | Low set ears and soft tissue edema of the neck | Coagulopathy; metabolic acidosis | NA |
| LS | 3 days | 1 days | / | 40 days | 15 days | 18 days | 25 days | 16 h | / | 13 days | / |

AP annular pancreas, ASD atrial septal defect, AVC atrio-ventricular canal defect, AVSD atrioventricular septal defect, BH bilateral hydronephrosis, CAV common atrioventricular valve, CP cor pulmonale, DA duodenal atresia, EA esophageal atresia, ECMO extracorporeal membrane oxygenation, ED esophageal dilation, FOC foramen ovale closure, GA gestation, HLHS hypoplastic left heart syndrome, HM holosystolic murmur, HP hypertension, IAA interrupted aortic arch, IM intestinal malrotation, LP left pneumothorax, LS lifespan, LV left ventricle, NA not available, PA pulmonary artery, PDA patent ductus arteriosus, PE pleural effusion, PH pulmonary hypertension, PHD polyhydramnios, PI pulmonary lymphangiectasia, PLSVC persistent left superior vena Cava, PPHN persistent pulmonary hypertension of the newborn, PS pelvicavaliceal system, PVA pulmonary valve atresia, SD dilatation of the stomach, SUA single umbilical artery, TOF tetralogy of Fallot, TSF tracheo-esophageal fistula, US ureteral stenosis, VSD ventricular septal defect, “–” normal
FOX family of transcription factors (FOXFI, FOXL1 and FOXC2), FENDRR, and FOXFI corresponding enhancer region. The FOX transcription factors play critical roles in the process of cellular proliferation, differentiation [19, 20]. FOXFI involves in development of pulmonary alveoli, capillaries and embryonic development of organs associated with airways, gastrointestinal tract and urinary tract in diverse-type cells including capillary endothelial cells, fibroblasts, and peribronchial smooth muscle cells [21, 22]. In epithelial cells of the peripheral lung mesenchyme, sonic hedgehog (SHH) signaling pathway mediated by FOXFI is one of the key pathways regulating formation. Moreover, the interactions between FOXFI-SHH and semaphorins-neuropilin or vascular endothelial growth factor/vascular endothelial growth factor receptor 2 (VEGF/VEGFR2) signaling may result in structural abnormalities of multiple systems, especially the lung, cardiovascular, gastrointestinal and urinary systems [22]. Hence, the haploinsufficiency of FOXFI gene is related with manifestations of lung, gastrointestinal and urinary tracts such as HLHS, duodenal atresia and distal ureteral dilatation [5, 16, 22] because of point disease-causing variant of FOXFI or CNV deletions overlapping FOXFI or the change of its upstream regulatory region located ~270 kb upstream to FOXFI gene (chr16:86178434-86238313, hg19) [4]. In addition, the genetic effects of FOXFI gene inactivation have been confirmed in FOXFI-deficient mice with severe alveolarization and angiogenesis defects, stenosis of esophageal and tracheal, lung repair defects, et al. [16, 23]. In our case, the fetus presenting similar multi-system clinical manifestations may be associated with the haploinsufficiency of FOXFI.

The deleted fragment in our fetus includes the other three genes—FOXC2, FOXL1 and FENDRR. FOXC2 is the key gene of LDS characterized by lymphedema of the limbs and double rows of eyelashes [14, 24], which is essential for lymphatic valve maintenance by regulating lymphatic endothelial cells junctional integrity and cellular quiescence [25]. FOXC2 pathogenic variant has been identified in cases with LDS to impair transcriptional activity and cell proliferation [26] through VEGF-C/VEGFR3 signaling pathway commonly correlated with primary lymphedema, lymphatic valve formation and other lymphatic malformations [27]. The FOXC2-inactivation mice exhibited lymphatic abnormalities, VSD, interrupted aortic arch, et al. [28, 29]. In this report, although the characteristic phenotypes associated with LDS may be atypical in the fetal stage, CNV-seq detection confirms the diagnosis of LDS. Therefore, genetic detection should be recommended as a first-line diagnostic tool for the fetuses with suspected ACDMPV and/or LDS early during the fetal period [30]. In addition, the disease-causing variant of FOXL1 gene is mainly related with gastrointestinal manifestations, as has been confirmed in mice with FOXL1 gene knocked out [31]. Furthermore, FENDRR gene expression has been verified to be regulated both in cis and in trans by FOXFI, indicating
that FENDRR involves in FOXF1-linked diseases including ACDMPV [31]. Therefore, we speculate that the present phenotypes of our fetus resulted from the deleted 16q24.1q24.2 fragment including FOXF1, FOXC2, FOXL1 and FENDRR, and the severity might derive from the integration of multiple genes disease-causing variants of the above four genes. Our fetus has been confirmed with ACDMPV and LDS through CNV-seq detection. In conclusion, this case supports the value of antenatal CNV-seq detection in multiple congenital abnormalities of the fetus. And genetic testing should now be recommend as a first-line diagnostic tool for suspected ACDMPV and/or LDS or other genetic syndromes for the fetuses with structural abnormalities in clinical practice, which may switch traditional histological examination of ACDMPV especially during the fetal period.

Abbreviations
ACDMPV: Alveolar capillary dysplasia with misalignment of pulmonary veins; ASD: Atrial septal defect; AVSD: Atrioventricular septal defect; CNV: Common non-coding regulatory RNA; CNV-seq: Copy number variation sequencing; FENDRR: FOXF1: Adjacent non-coding developmental regulatory RNA; FOX: Forkhead box F1; FOXL1: Sonic hedgehog; VSD: Ventricular septal defect; VEGF/VEGFR2: Vascular endothelial growth factor/vascular endothelial growth factor receptor 2.

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Author contributions
JZ conceived the project. JS designed the molecular approach. BZ, JW, JZ and ML collaborated in the molecular analyses. HT and YS participated in the recruitment, clinical information acquisition of the patient and her families. XW and LG wrote the clinical description and discussion. XW, LG and JZ designed and wrote the first draft with molecular aspects. All authors included in the manuscript.

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Availability of data and materials
The data and materials in the current study were available from the corresponding author upon reasonable request.

Declarations
Ethics approval and consent to participate
All examinations were approved by the ethical standards of the responsible committee. The pregnant woman provided written informed consent for the study.

Consent for publication
Written informed consent for publication and the fetal clinical details were obtained from the couple.

Competing interests
No interests.

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