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Case Report

First-trimester prenatal diagnosis of Ellis–van Creveld syndrome

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Abstract

Objective: To present the perinatal findings and first-trimester molecular and transabdominal ultrasound diagnosis of a fetus with Ellis–van Creveld (EvC) syndrome.

Case Report: A 35-year-old woman was referred for genetic counseling at 13 weeks of gestation because of a family history of skeletal dysplasia. She had experienced one spontaneous abortion, and delivered one male fetus and one female fetus with EvC syndrome. During this pregnancy, a prenatal transabdominal ultrasound at 13^{+4} weeks of gestation revealed a nuchal translucency (NT) thickness of 2.0 mm, an endocardial cushion defect, postaxial polydactyly of bilateral hands, and mesomelic dysplasia of the long bones. Amniocentesis was performed at 13^{+5} weeks of gestation. Results of a cytogenetic analysis revealed a karyotype of 46,XX and that of a molecular analysis revealed compound heterozygous mutations of c.1195C>T and c.871-2_894del26 in the *EVC2* gene. Prenatal ultrasound at 16 weeks of gestation showed a fetus with short limbs, an endocardial cushion defect, and postaxial polydactyly of bilateral hands. The parents decided to terminate the pregnancy, and a 116-g female fetus was delivered with a narrow thorax, shortening limbs, and postaxial polydactyly of the hands.

Conclusion: Prenatal diagnosis of an endocardial cushion defect with postaxial polydactyly should include a differential diagnosis of EvC syndrome in addition to short rib–polydactyly syndrome, Bardet–Biedl syndrome, orofaciodigital syndrome, Smith–Lemli–Opitz syndrome, and hydrolethalus syndrome.

Keywords: Ellis–van Creveld syndrome; *EVC2* gene; prenatal diagnosis

Introduction

Ellis–van Creveld (EvC) syndrome (OMIM 225500), or chondroectodermal dysplasia, is an autosomal recessive ciliopathy that is characterized by short ribs, short limbs, postaxial polydactyly of the hands, polydactyly of the feet (in 10% of the cases), ectodermal dysplasia such as absence of gingival sulcus, sparseness of hair, and dysplasia of teeth and nails, and congenital heart defects (in 60% of the cases) such as a common atrium, an atrioventricular canal defect (AVCD), and patent ductus arteriosus [1,2]. The EvC syndrome is associated with mutations in the *EVC* (OMIM 604831) [3] and *EVC2* (OMIM 607261) genes [4], which are adjacent genes located on chromosome 4p16. Mutations in *EVC* and *EVC2* will result in the formation of truncated proteins and loss of protein function, and such mutations are seen in half of the patients with EvC syndrome [2,5]. Heterozygous mutations in

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exon 22 of *EVC2* have been associated with Weyers acrodental dysostosis (OMIM 193530), an autosomal dominant disorder characterized by postaxial polydactyly and abnormalities of the lower jaw, dentition, and oral vestibule [6–8]. A majority of the reported cases with prenatally detected EvC syndrome are limited to prenatal diagnosis in the second or third trimester with ultrasound findings of shortening limbs, a narrow thorax, hexadactyly of the hands, and congenital heart defects of a common atrium or an AVCD [9–20]. However, prenatal diagnosis of EvC syndrome in the first trimester is very rare. Here, we report a prenatal diagnosis of EvC syndrome in a fetus at 13 weeks of gestation by both ultrasound examination and molecular genetic analysis.

Case report

A 35-year-old, gravida 5, para 2, woman was referred for genetic counseling at 13 weeks of gestation because of a family history of skeletal dysplasia. Her husband was 39 years old. She and her husband were healthy and non-consanguineous. She had experienced one spontaneous abortion, delivered one male fetus and one female fetus with EvC syndrome, and had a 1-year-old healthy daughter. Results of a mutational analysis of the *EVC* and *EVC2* genes of the family revealed a heterozygous deletion mutation of a 26-bp deletion of c.871-2_894del26 encompassing the junction between intron 7 and exon 8 of the *EVC2* gene in the mother and the two affected fetuses, and a heterozygous nonsense mutation of c.1195C>T, p.R399X in exon 10 of the *EVC2* gene in the father, healthy daughter, and the two affected fetuses. During this pregnancy, a prenatal transabdominal ultrasound at 13^{+4} weeks of gestation revealed a nuchal translucency (NT) thickness of 2.0 mm, an endocardial cushion defect, postaxial polydactyly of bilateral hands, and mesomelic dysplasia of the long bones with a humeral length of 0.84 cm (5th–50th centile), a radial length of 0.50 cm (<5th centile), an ulnar length of 0.42 cm (<5th centile), a femoral length of 0.71 cm (5th–50th centile), a tibial length of 0.48 cm (5th–50th centile), and a fibular length of 0.47 cm (<5th centile) (Fig. 1). Amniocentesis was performed at 13^{+5} weeks of gestation. Results of a cytogenetic analysis revealed a karyotype of 46,XX and that of a molecular analysis revealed compound heterozygous mutations of c.1195C>T and c.871-2_894del26 in the *EVC2* gene (Fig. 2). Prenatal ultrasound at 16 weeks of gestation showed a fetus with a biparietal diameter of 3.46 cm (16 weeks), an abdominal circumference of 10.14 cm (16 weeks), a femural length of 1.45 cm (14 weeks), an endocardial cushion defect, and postaxial polydactyly of bilateral hands. The parents decided to terminate the pregnancy, and a 116-g female fetus was delivered with a narrow thorax, shortening limbs, and postaxial polydactyly of the hands (Figs. 3 and 4).

Discussion

The peculiar aspect of this presentation is the ultrasound and molecular diagnosis of EvC syndrome in the first trimester. Venkat-Raman et al [15] suggested that fetuses with EvC syndrome may show increased NT thickness in the late first trimester. However, our case had an NT thickness of 2.0 mm at 13 weeks of gestation and did not show increased NT thickness in the late first trimester. By contrast, our case did show shortening limbs, hexadactyly of the hands, and an AVCD in the first trimester. Dugoff et al [21] first reported first-trimester diagnosis of recurrent EvC syndrome at 12 weeks of gestation by endovaginal ultrasound in a fetus with normal NT thickness, postaxial polydactyly of both hands, mesomelic dysplasia of the limbs, and an atrioventricular septal defect. Our case additionally shows that congenital heart defects and limb deformities associated with EvC syndrome can be detected by transabdominal ultrasound in the late first trimester. Congenital heart defects have been estimated to affect about 60% of the patients with EvC syndrome [22]. In a review of 92 previously reported patients with EvC syndrome, Hills et al [23] found that most of these patients had an AVCD [48 patients (52%)] or a common atrium [42 patients (46%)], and other common heart defects including left superior vena cava [18 patients (20%)], atrial septal defect [15 patients (16%)], ventricular septal defect [15 patients (16%)], and unroofed coronary sinus [8 patients (9%)]. An endocardial cushion defect has been the most common congenital heart defect associated with EvC syndrome. In a survey of 32 cases with EvC syndrome and congenital heart defects, Hills et al [23] found that 88% (28/32) of the cases had an endocardial cushion defect, with 15 of the 28 cases having primary failure of atrial septation resulting in a common atrium. The EvC syndrome is linked to abnormal processing of the hedgehog protein leading to ciliary dysfunction [2]. Goddeeris et al [24] found that intracardiac septation requires sonic hedgehog signaling-dependent cellular contributions from outside of the heart. Sund et al [25] found that EVC and EVC2 proteins coordinately function in cardiac development. The present case was associated with compound heterozygous mutations in the *EVC2* gene and characteristic features of EvC syndrome. Blair et al [26] demonstrated that EVC2 is a positive regulator of the hedgehog signaling pathway and is located at the basal body of primary cilia. They also found that EVC2 interacts with EVC at the cilia membrane, and only EVC2 is present in the cell nucleus, suggesting movement of EVC2 between the cilium and nucleus. Digilio et al [27,28] concluded that AVCD in EvC syndrome is a sign of laterality defect associated with ciliary and hedgehog signaling dysfunction.

Prenatal diagnosis of an AVCD in association with postaxial polydactyly should include a differential diagnosis of short rib–polydactyly syndrome (SRPS), Bardet–Biedl syndrome (BBS), orofaciodigital (OFD) syndrome, Smith–Lemli–Opitz syndrome (SLOS), and hydrolethalus syndrome (HLS) in addition to EvC syndrome [27–31]. SRPS is an autosomal recessive ciliary disorder that is characterized by short ribs, polydactyly, short limbs, and multiple abnormalities of the internal organs including kidneys, heart, liver, pancreas, genitalia, and intestines. There are five types of SRPS: SRPS I (Saldino–Noonan; OMIM 263530), SRPS II (Majewski; OMIM 263520), SRPS III (Verma–Naumoff;

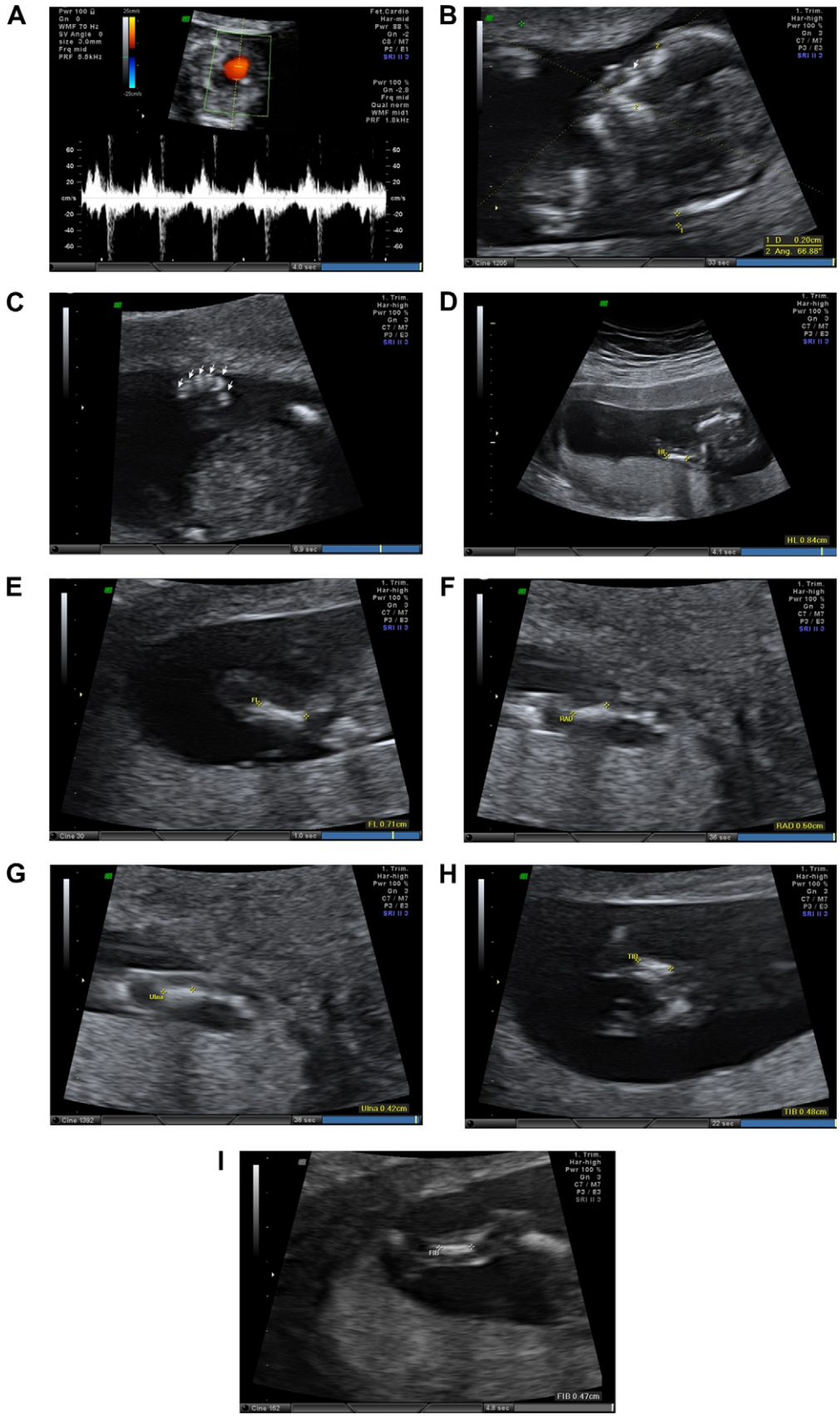

Fig. 1. Prenatal transabdominal ultrasound at 13^{+4} weeks of gestation shows (A) an endocardial cushion defect, (B) a nuchal translucency thickness of 2.0 mm, (C) postaxial polydactyly of the hand, and mesomelic dysplasia of the long bones of (D) humerus, (E) femur, (F) radius, (G) ulna, (H) tibia, and (I) fibula.

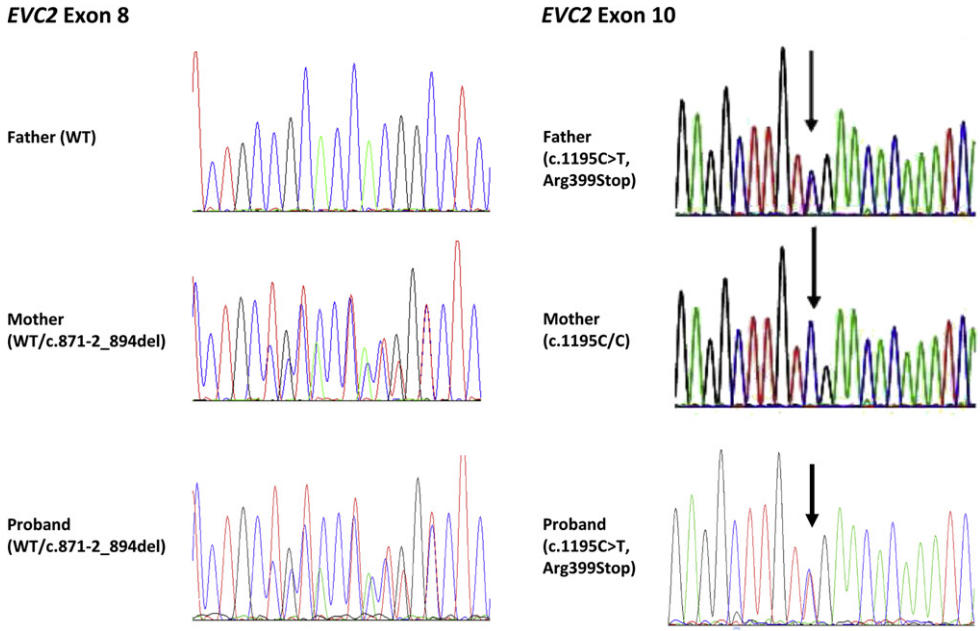

Fig. 2. A molecular analysis of cells in amniotic fluid reveals compound heterozygous mutations of c.1195C>T and c.871-2_894del26 in the *EVC2* gene.

OMIM 263510), SRPS IV (Beemer–Langer; OMIM 269860), and SRPS V (OMIM 614091). These different types of SRPS are a result of a single genetic disorder with variable expressivity and can be caused by mutations in the *IFT80*, *DYNC2H1*, *NEK1,* and *WDR35* genes [5,32,33]. BBS (OMIM 209900) is a genetically heterogeneous autosomal recessive ciliary disorder that is characterized by obesity, retinitis pigmentosa, postaxial polydactyly, urogenital malformations, cognitive deficit, AVCD, dextrocardia, and congenital heart defects. To date, at least 15 types of BBS (BBS1–15) have been reported, and at least nine ciliary function-related genes have been identified (e.g., *CCDC28B*, *C2orf86*, *ARL6*, *PTHB1*, *TMEM67*, *TRIM32*, *CEP290*, *TTC8,* and *MKS1*). The OFD syndrome is characterized by hypertelorism, tongue hamartoma, oral frenula, cleft palate, and postaxial and central polydactyly, and can be inherited in an X-linked dominant or

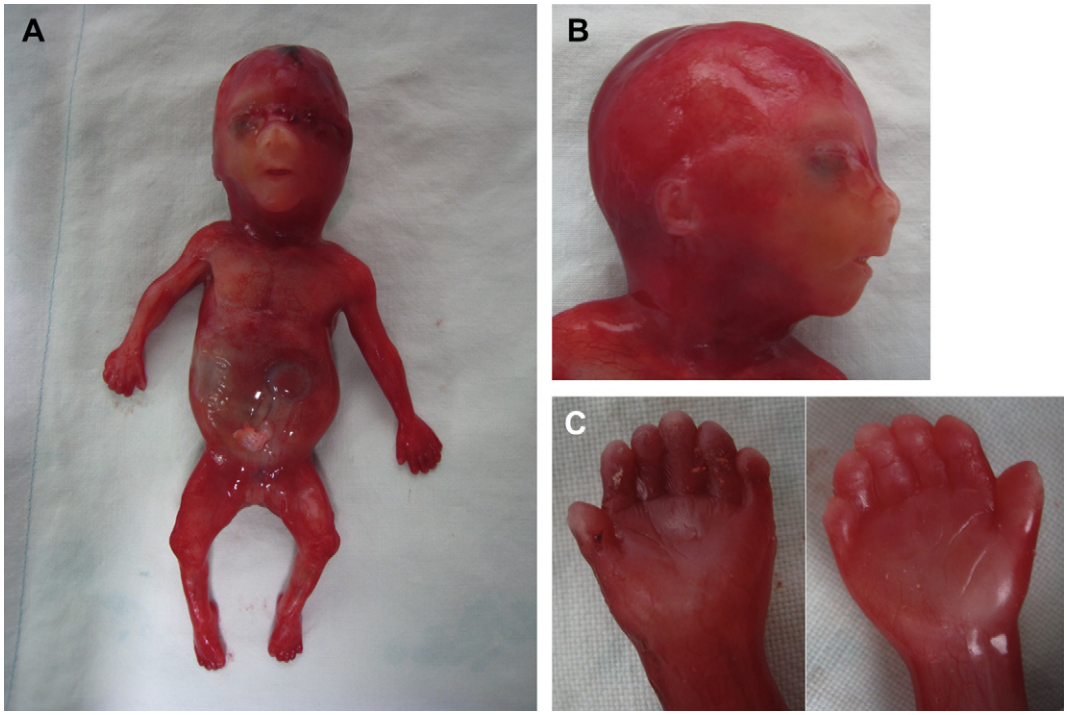

Fig. 3. The fetus at birth. (A) Whole-body view, (B) lateral craniofacial appearance, and (C) postaxial polydactyly of the hands.

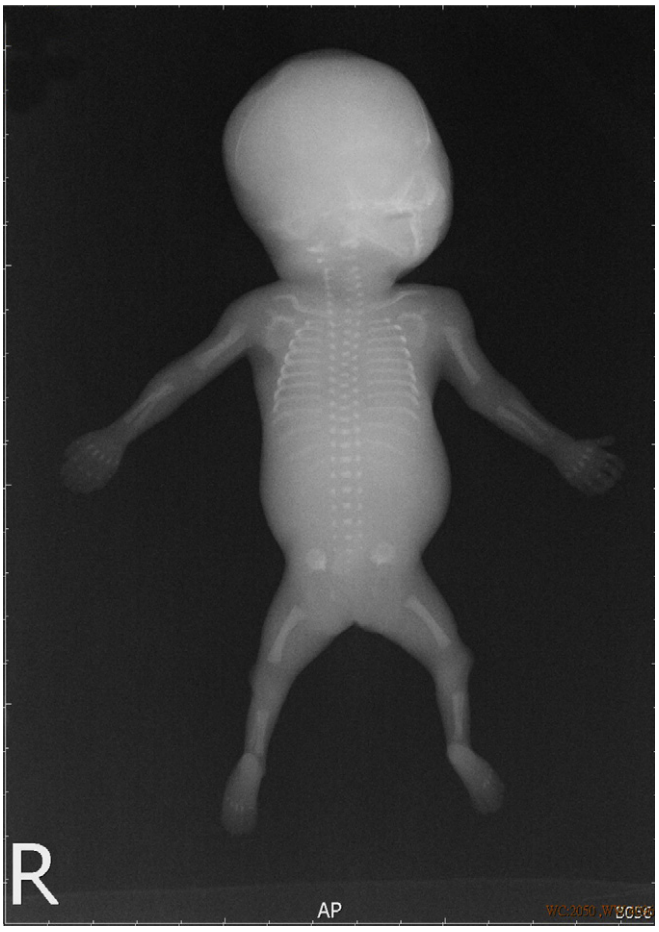

Fig. 4. The corresponding roentgenogram.

autosomal recessive pattern. To date, at least 11 types of OFD syndrome (OFD1−11) have been reported, and at least three genes have been identified [e.g., *CXORF5* (OFD1) and *TMEM216* (OFD6) for cilia basal body, and *TCTN3* (OFD4) for sonic hedgehog signaling pathway]. AVCD is the most common congenital heart defect associated with OFD2, pulmonary stenosis has been reported in OFD4, and AVCD and aortic stenosis have been associated with OFD6 [27,29]. SLOS (OMIM 270400) is an autosomal recessive disorder characterized by facial anomalies, mental retardation, microcephaly, growth retardation, feeding difficulties, cleft palate, postaxial polydactyly, hypospadias and cryptorchidism in male, syndactyly of the second and third toes, and congenital heart defects in 50% of the patients, particularly endocardial cushion defect, hypoplastic left heart, atrial septal defect, patent ductus arteriosus, and ventricular septal defect [34]. SLOS is caused by homozygous or compound heterozygous mutations in *DHCR7*, which is associated with cholesterol synthesis. HLS (HLS1: OMIM 236680 and HLS2: OMIM 614120) is an autosomal recessive disorder characterized by hydrocephalus, micrognathia, postaxial polydactyly of the hands and feet, and congenital heart defects especially AVCD in 50% of the cases [35]. HLS1 is caused by mutations in the *HYLS1* gene, HLS2 is caused by mutations in the *KIF7* gene, and both are considered as ciliopathy [36−38].

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