Ellis-van Creveld Syndrome: Prenatal Diagnosis, Molecular Analysis and Genetic Counseling

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SUMMARY

Objective: To present the perinatal findings and molecular genetic analysis of two siblings with Ellis-van Creveld (EvC) syndrome.

Materials, Methods and Results: A 33-year-old woman, gravida 3, para 1, was referred for genetic counseling at 18 gestational weeks because of recurrent fetal skeletal dysplasia. Two years previously, she had delivered a 1,316-g dead male baby at 28 gestational weeks with a karyotype of 46,XY, postaxial polydactyly of the hands, thoracic narrowness, endocardial cushion defects, transposition of the great arteries, shortening of the long bones, malposition of the toes, and hypoplastic nails. During this pregnancy, prenatal ultrasound at 18 gestational weeks revealed shortening of the long bones (equivalent to 15 weeks), postaxial polydactyly of both hands, thoracic narrowness, and endocardial cushion defects. The pregnancy was subsequently terminated, and a 236-g female fetus was delivered with a karyotype of 46,XX, postaxial polydactyly of the hands, thoracic dysplasia, endocardial cushion defects, shortening of the long bones, and malposition of the toes and hypoplastic nails. The phenotype of each of the two siblings was consistent with EVC syndrome. Molecular analysis of the *EVC* and *EVC2* genes revealed heterozygous mutations in the *EVC2* gene. 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 was found in the mother and two siblings, and a heterozygous nonsense mutation of c.1195C>T, p.R399X in exon 10 of the *EVC2* gene was found in the father and two siblings.

Conclusion: Prenatal sonographic identification of endocardial cushion defects in association with shortening of the long bones should alert clinicians to the possibility of EvC syndrome and prompt a careful search of hexadactyly of the hands. Molecular analysis of the *EVC* and *EVC2* genes is helpful in genetic counseling in cases with prenatally detected postaxial polydactyly, thoracic narrowness, short limbs and endocardial cushion defects. [*Taiwan J Obstet Gynecol* 2010;49(4):481–486]

Key Words: Ellis-van Creveld syndrome, *EVC*, *EVC2*, prenatal diagnosis, ultrasound

Introduction

Ellis-van Creveld (EvC) syndrome (OMIM 225500), or chondroectodermal dysplasia, is an autosomal recessive ciliary disorder associated with a wide spectrum of developing abnormalities involving the ectoderm, skeleton and heart. EvC syndrome is a relatively rare

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disorder, but is most prevalent in the Amish population [1,2] and in some Arab populations [3] because of consanguinity. The birth prevalence is estimated to be 0.7 per 100,000 of live births in the non-Amish population [4], 5.2 per 100,000 of live births in the United Arab Emirates [3], and 5 per 1,000 of live births in the Amish of Lancaster County, Pennsylvania, USA [5]. EvC syndrome is characterized by short ribs, short limbs, postaxial polydactyly of the hands, polydactyly of the feet (in 10% of cases), ectodermal dysplasia such as dysplastic nails and teeth, sparse hair and an absent gingival sulcus, and congenital heart defects (in 60% of cases) such as a common atrium, atrioventricular septal defects (AVSDs) and patent ductus arteriosus [6,7]. EvC syndrome is caused by mutations in the *EVC* gene (OMIM 604831) [8] or *EVC2* gene (OMIM 607261) [9] that encodes cilia-related proteins Evc or Evc2, respectively. Mutations in the *EVC* gene or *EVC2* gene may also cause Weyers acrodental dysostosis (OMIM 193530), an autosomal dominant disorder characterized by postaxial polydactyly and abnormalities of the lower jaw, dentition and oral vestibule. The Evc and Evc2 proteins are localized in the basal bodies of primary cilia. Evc is a basal body component of hedgehog signaling indispensable for normal endochondral growth and normal transcriptional activation of Indian hedgehog-regulated genes [10]. Both EvC syndrome and Weyers acrodental dysostosis are caused by hedgehog signaling defects in the primary cilia due to mutations in the cilia-related proteins resulting in an aberrant response to the hedgehog ligands [7]. We previously reported perinatal findings of hexadactyly-associated ciliary disorders of Meckel syndrome [11], Joubert syndrome [12], and short rib-polydactyly syndrome (SRPS) [13–16]. We present the perinatal findings and molecular genetic analysis of two siblings affected by hexadactyly and EvC syndrome.

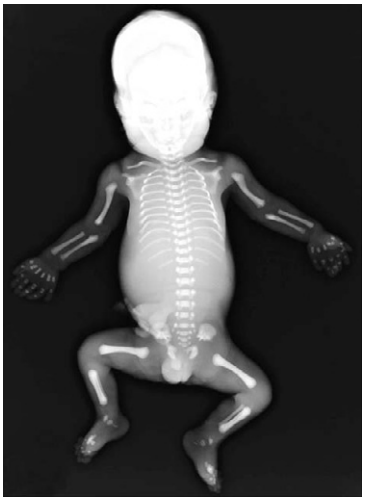

Figure 1. Whole body X-ray of proband 1 at 28 gestational weeks.

Materials, Methods and Results

A 33-year-old woman, gravida 3, para 1, was referred for genetic counseling at 18 gestational weeks because of recurrent fetal skeletal dysplasia. She and her husband were non-consanguineous. She had experienced one spontaneous abortion and delivered a baby with skeletal dysplasia. Two years previously, she had delivered a 1,316-g dead male baby (proband 1) at 28 gestational weeks with a karyotype of 46,XY, postaxial polydactyly of the hands, thoracic narrowness, endocardial cushion defects, transposition of the great arteries (TGA), shortening of the long bones, malposition of the toes and hypoplastic nails (Figures 1–3). During this pregnancy, prenatal ultrasound at 18 gestational weeks revealed shortening of the long bones (equivalent to 15 weeks), postaxial polydactyly of both hands, thoracic narrowness, and endocardial cushion defects (Figures 4–6). The pregnancy was subsequently terminated, and a 236-g female fetus (proband 2) was delivered with a karyotype of 46,XX, postaxial polydactyly of the hands, thoracic dysplasia, endocardial

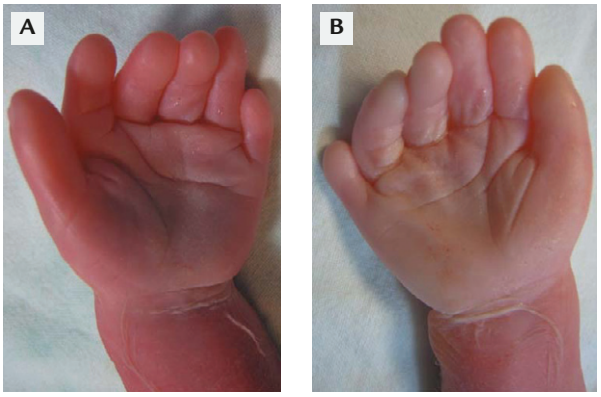

Figure 2. Postaxial polydactyly of the hands in proband 1.

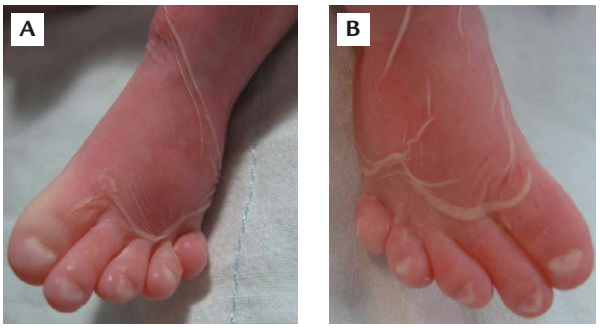

Figure 3. Malposition of the toes with hypoplastic nails in proband 1.