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Short communication

Cystic hygroma and micromelic lower limbs: First-trimester sonographic markers of campomelic dysplasia

Dear Editors,

Campomelic dysplasia (CD) is a rare autosomal dominant skeletal malformation that can be associated with XY sex reversal. It is mainly characterized by facial dysmorphism, bowing of the long bones in the legs, hypoplastic scapulae, 11 pairs of ribs, pelvic malformations and club feet [1]. This condition is often life-threatening in the newborn period. Considering the lethality of this disease, it is extremely important to make an early prenatal diagnosis. We here report a prenatal case of CD detected by specific first-trimester sonographic findings, and confirmed by the identification of a novel *SOX9* variant with exome sequencing.

A 32-year-old nulliparous woman with a dizygotic DCDA pregnancy conceived via IVF was referred to our unit at 12 weeks' gestation for Down screening. Both partners of the couple were healthy and unrelated. Detailed ultrasound showed that one twin had no heartbeat with a CRL of 2.4 cm. The survival twin had a CRL of 54 mm in accordance with 12 weeks. A large cystic hygroma and short lower extremities were noted (Fig. 1). The mildly bowed femur measured 3.7 mm (less than the first percentile). The upper limbs seemed normal. No other obvious anomalies were seen. A presumptive diagnosis of skeletal dysplasia was made, but a precise diagnosis was difficult to achieve with only limited fetal features. Chorionic villus sampling was performed, and chromosomal investigation by microarray and a skeletal dysplasia panel (111 gene) based on targeted exome sequencing were used.

The microarray showed a 46,XX karyotype without pathogenic CNVs. The exome sequencing detected a heterozygous nonsense variant c.1005 G > A (p.W335*) of the SOX9 gene (Fig. 1), which resulted in the formation of a stop codon at position 335 and presumably a truncated SOX9 protein. This variant was not listed in dbSNP, 1000 Genomes and gnomAD databases, and was predicted to be damaging using different bioinformatics tools including Taster, Sorting Intolerant From Tolerant (SIFT), and Polymorphism Phenotyping V2 (PolyPhen-2). This variant was not detected in the parents, suggesting a de novo event. At 17 weeks, another scan revealed a normal biparietal diameter and normal abdominal circumference with increased nuchal fold, shortened and angulated femurs, club feet, ventriculomegaly, micrognathia, ventricular septal defect and persistent left superior vena cava. The parents opted to terminate the pregnancy. Physical examination found a female fetus with facial dysmorphism: short and thick neck, retrognathia, flat nose and low-set ears. The X-ray confirmed the skeletal changes characterized by CD.

Commonly, a prenatal diagnosis of skeletal dysplasia is made using second-trimester anatomic scan [2]. We detect a fetus of CD by identifying cystic hygroma and micromelic lower limbs at 12 weeks. This association has also been found by another study, in which two cases of CD with hygroma colli along with anomalies in the lower limbs were identified by ultrasound at 13 weeks [3]. Indeed, early diagnosis of fetal structural anomalies is possible by first trimester ultrasound. For instance, an early scan performed at 12–13 weeks by a competent sonographer can detect about half of the prenatally detectable structural anomalies and 100% of those expected to be detected at this stage [4]. Unlike other skeletal dysplasias, the problem usually lies exclusively in the lower limbs in the case of CD. This specific feature accompanied by cystic hygroma in early pregnancy may be helpful in defining the correct diagnosis. To confirm the clinical diagnosis, a search for a SOX9 variant would be undertaken. Alternatively, targeted exome sequencing, e.g. a skeletal dysplasia panel, can be chosen. This approach is especially cost-effective in the genetic testing of genetically heterogeneous disorders like skeletal dysplasia [5].

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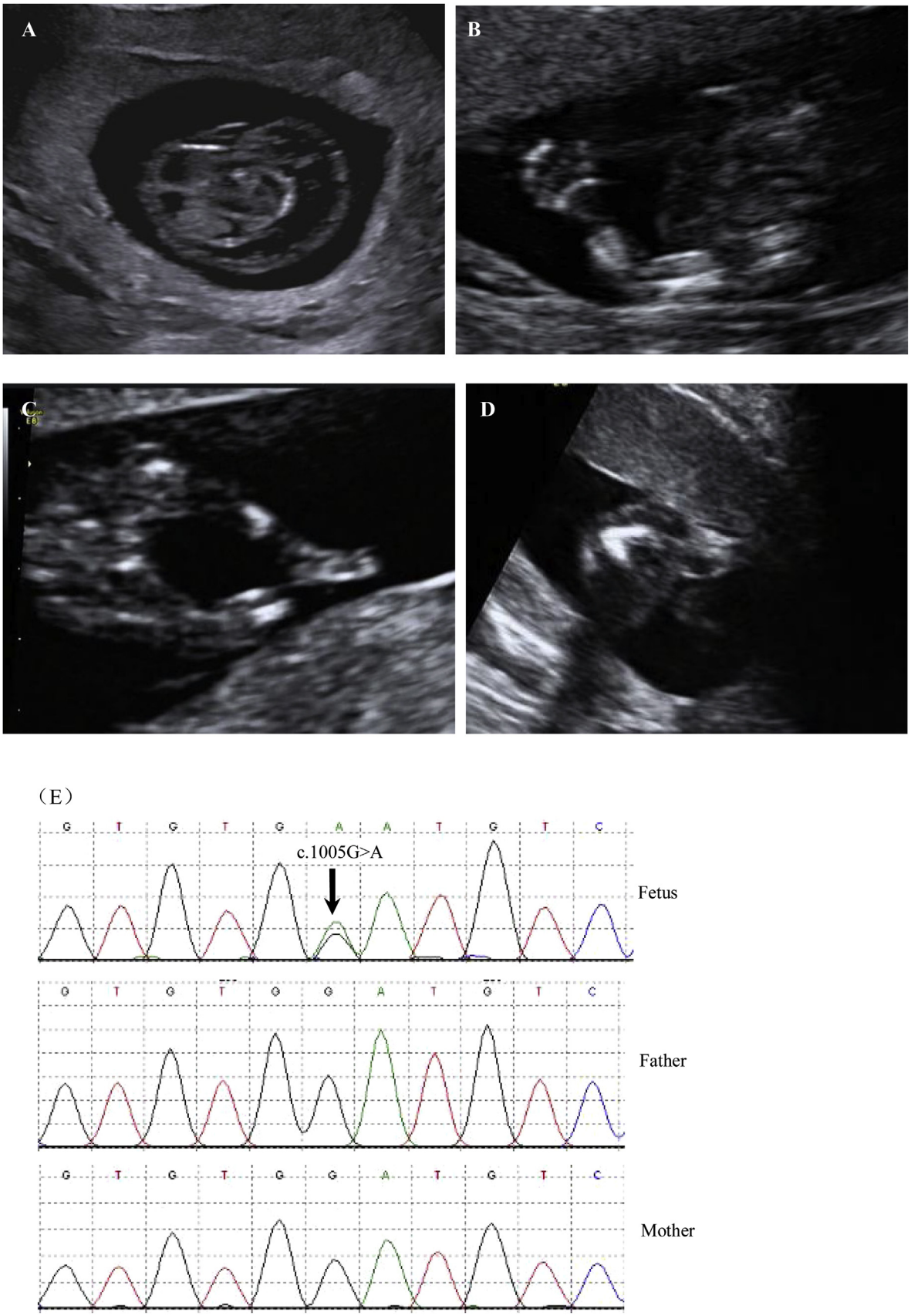

Fig. 1. The prenatal ultrasound and genomic sequencing data of the fetus. (A) Cystic hygroma at 12 weeks; (B) Normal left upper limb at 12 weeks; (C) Short and bowed lower long bones at 12 weeks; (D) Angulated femur at 17 weeks; (E) Sanger sequencing shows a de novo c.1005G > A variant in *SOX9*.

Conflict of interest

The authors report no conflicts of interest.

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