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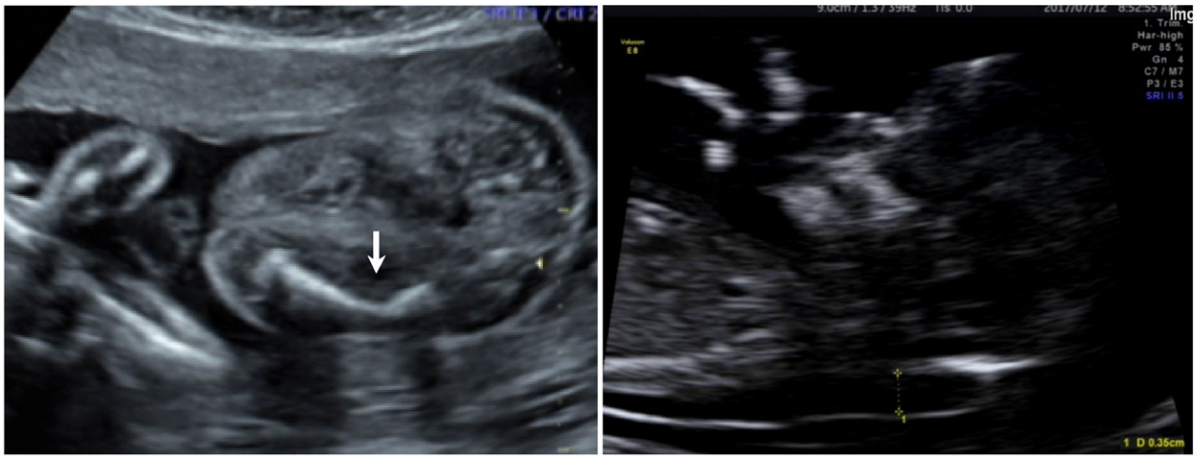
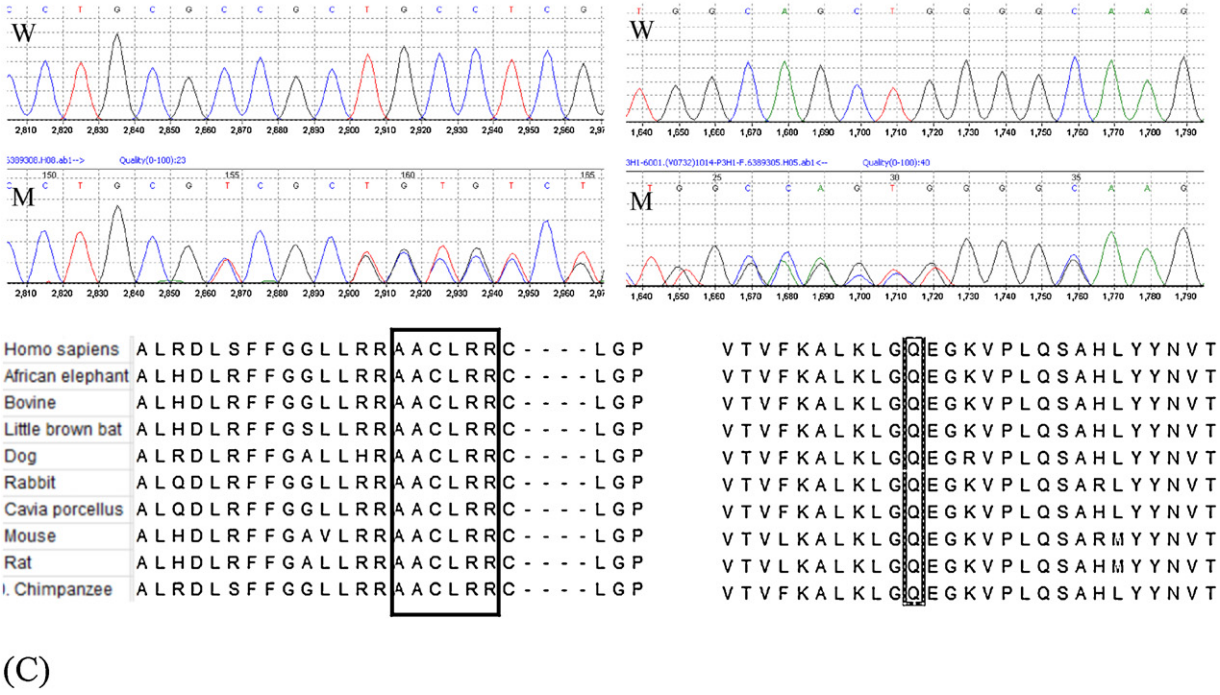
Osteogenesis imperfecta type VIII: Association with increased nuchal translucency and prenatal diagnosis by targeted exome sequencing

Dear Editors

Osteogenesis imperfecta (OI) is a genetically heterogeneous skeletal dysplasia that affects approximately 1 in 10,000–20,000 births [1]. Although most of the time prenatal diagnosis of OI can be confirmed by molecular testing, sonography is still the primary diagnostic modality. Criteria for the prenatal diagnosis of OI using second-trimester sonography include hypomineralization of the skull, early onset of bone shortening, and bowing due to multiple fractures involving long bones. However, the sonographic detection of OI at the first trimestr of pregnancy is challenging. Here we



(A) (B)



(C)

Fig. 1. The prenatal ultrasound, Sanger sequencing data and conservation of the amino acid residues around the variants sites. (A) Bowing of femur at 23 weeks; (B) Increased NT at 12 weeks; (C) Sanger sequencing shows heterozygous c.345_362dup and c.1576delC variants. The box shows changes in the conserved residues.

first report an early prenatal diagnosis of OI type VIII that was confirmed by targeted exome sequencing.

A 34-year-old woman in her second pregnancy came to us for a first-trimester sonographic examination. Her first pregnancy was voluntarily interrupted at 23 weeks' gestation because the fetus was affected by OI with shortening and bowing of long bones (Fig. 1A). At this referral, a detailed scan revealed a crown-rump length of 60 mm with an increased NT (3.5 mm) (Fig. 1B). No other chromosomal markers were observed. Considering the unknown etiology of their first affected pregnancy, which might be caused by a de novo variant, parental gonadal mosaicism, or autosomal recessive inheritance, the couple opted for a two-step testing algorithm after chorionic villus sampling: rapid karyotyping method (QF-PCR) for NT-related common trisomies, followed by microarray analysis and targeted exome sequencing panel for OI.

Both QF-PCR and microarray showed a normal female karyotype. Using targeted exome sequencing of 14 well-known OI-related genes (COL1 A1, COL1 A2, IFITM5, SERPINF1, CRTAP, P3H1, PPIB, FKBP10, SERPINH1, SP7, PLOD2, TMEM38B, BMP1, and WNT1), two novel compound heterozygous variants in the P3H1 gene, NM_022356.3:c.345_362dup; NP_071751.3:p.(Ala117_Arg122dup) and NM_022356.3:c.1576delC; NP_071751.3:p.(Gln526ProfsTer57), were identified in the fetus, and confirmed by Sanger sequencing to be inherited from the father and mother, respectively (Fig. 1C). Both the in-frame and frameshift variants are predicted to be deleterious by bioinformatics programs (SIFT, Polyphen2, and MutationTaster), and have not been reported in the Human Gene Mutation Database (HGMD) and the 1000 genomes database. The molecular results were consistent with the diagnosis of OI type VIII. At the time when the results were available, the woman was 16 weeks pregnant. A repeat scan revealed mildly shortened femurs (fifth centile). The couple elected to terminate the pregnancy. Postmortem examination using X-ray showed affected extremities with popcorn metaphyses and severely under tubulated long bones, thin ribs and mild barrel-shaped chest.

More than 80% of OI cases are due to dominantly inherited variants in *COL1 A1* or *COL1 A2*, which encode the chains of type I collagen. Variants in noncollagen genes are usually associated with recessive forms of OI (type VI-XV) [2]. P3H1 variants are the cause of OI type VIII, a recessive metabolic bone disorder resembling lethal/severe OI [3]. OI has been found to be associated with increased NT. However, almost all of the reported cases are OI type II [4]. Possible mechanisms include mediastinal compression by the narrow thoracic cage, reduced fetal movements due to limb fractures, and an altered composition of the extracellular matrix [5]. Our case is the first report of this association in the OI type VIII case. Since no notable abnormal signs were noted in our case during sonographic scanning, we suspect that altered composition of dermis is the explanation for increased NT. Our report combined with others suggest that an increased NT may be of most use in those families who are at risk of skeletal dysplasia including OI, particularly in the absence of any other sonographic signs in early pregnancy. This study also supports the use of targeted exome-capture sequencing as a cost-effective method in the genetic testing of genetically heterogeneous OI, especially with recessive mode of inheritance.

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