

Research Letter

Osteogenesis imperfecta type II: Prenatal diagnosis and association with increased nuchal translucency and hypoechogenicity of the cranium

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A 27-year-old, primigravid woman was referred to hospital for detailed ultrasound evaluation of the fetus because of first-trimester increased nuchal translucency (NT). Her husband was 56 years old. She and her husband were non-consanguineous, and there were no family history of congenital malformations. She had a body weight of 40 kg and a body height of 154 cm and was shorter than her female relatives. Prenatal ultrasound at 13 weeks of gestation revealed an increased NT thickness of 3.8 mm (Fig. 1). Level II ultrasound examination at 15 weeks of gestation revealed nuchal edema; a normal amount of amniotic fluid; short limbs; fracture deformities with angulations of the radius, ulna and tibia; decreased bone density of the cranium; and supervisualization of the intracranial contents suggesting a lethal form of osteogenesis imperfecta (OI) type II (Fig. 2). The measurements of the femur, tibia, fibula, humerus, ulna and radius were 0.97, 0.93, 0.86, 1.51, 1.10 and 1.12 cm, respectively, and all were less than the fifth centile for 15 weeks. The woman underwent amniocentesis at 15 weeks of gestation. Cytogenetic analysis revealed a karyotype of 46,XX. The pregnancy was terminated. Molecular analyses of the *COL1A1* and *COL1A2* genes using denaturing high-performance liquid

chromatography in the fetus revealed a heterozygous mutation in intron 25 of the *COL1A2* gene, or IVS 25+11, C>T or c.1503+11 C>T (Fig. 3). The father did not have such a mutation. However, the mother was mosaic for the mutation (Fig. 3). Postnatal skeletal X-ray confirmed the diagnosis of OI type II (Fig. 4). Two years later, the mother delivered a healthy female baby with a body weight of 3200 g without any skeletal dysplasia.



Fig. 1. Prenatal ultrasound at 13 weeks of gestation shows an increased nuchal translucency thickness of 3.8 mm.

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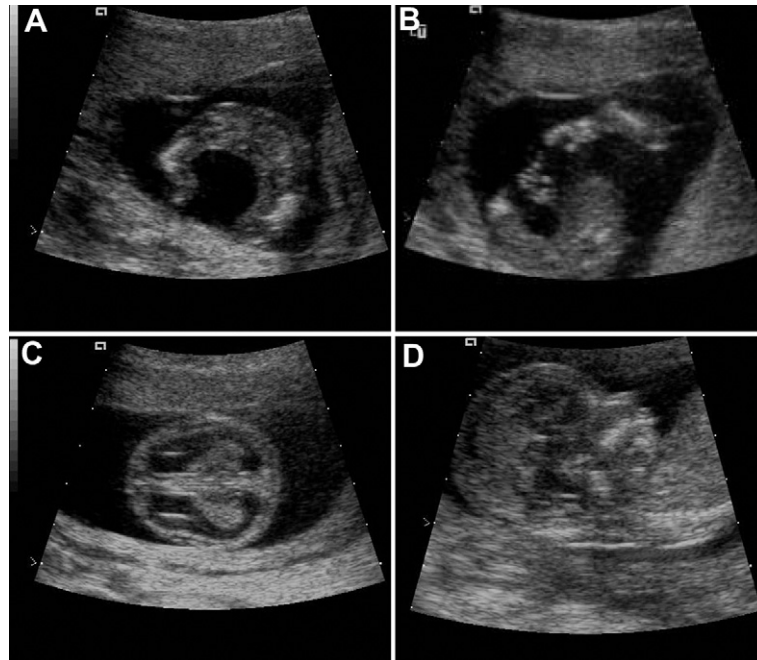


Fig. 2. Prenatal ultrasound at 15 weeks of gestation shows (A) angulation and fracture of the low limbs, (B) fractures of the left forearm, (C) hypoechogenicity of the cranium with supervisualization of intracranial contents and (D) nuchal edema.

OI type II (OMIM 166210) is a lethal form of OI that is characterized by bone hypomineralization and fragility, prenatal fractures, severe bowing of the long bones and perinatal death due to respiratory insufficiency. OI type II is inherited in an autosomal dominant pattern and can be caused by heterozygous mutation in the genes of *COL1A1* (OMIM 120150) or *COL1A2* (OMIM 120160) [1–3]. The present case had a heterozygous mutation in the *COL1A2* gene, and

prenatal ultrasound manifested hypoechogenicity of the cranium, supervisualization of intracranial contents, and fractures and severe bowing of the long bones.

The present case was associated with increased NT in the first trimester. Skeletal dysplasias have been associated with increased NT [4–8]. Reported skeletal dysplasias associated with increased NT include achondrogenesis, OI type II, hypophosphatasia, thanatophoric dysplasia, short rib-polydactyly syndrome, diastrophic dysplasia, Robinow syndrome, achondroplasia, Jarcho-Levin syndrome, cleidocranial dysplasia, campomelic dysplasia, Jeune syndrome and ectrodactyly-ectodermal dysplasia-clefting syndrome [7]. It has been suggested that a narrow thorax with mediastinal compression, reduced movements and alteration of the extracellular matrix due to collagen defects may be responsible for the genesis of increased NT [6,7]. To date, at least eight cases of OI type II associated with increased NT have been reported. Makrydimas et al [9] reported two cases of OI type II with the NT thickness of 3.4 mm and 4.4 mm at 13 and 11 weeks, respectively. Buisson et al [10] reported a case of OI type II with increased NT at 13 weeks. Viora et al [11] reported a case of OI type II with NT thickness of 3.8 mm at 13 weeks. Viora et al [12] reported a case of OI type II with NT thickness of 3.7 mm at 13 weeks. Cho et al [13] reported a case of OI type II with generalized edema and increased NT at 13 weeks. Aerts et al [14] reported a case of OI type II with NT thickness of 4.5 mm at 16 weeks. Hsieh et al [15] reported a case of OI type II with NT thickness of 4.2 mm at 12 weeks. Schönewolf-Greulich et al [16] reported a case of OI type II with NT thickness of 3.2 mm at 13 weeks. Our case additionally adds to the list of cases of OI type II associated with increased NT in early pregnancy.

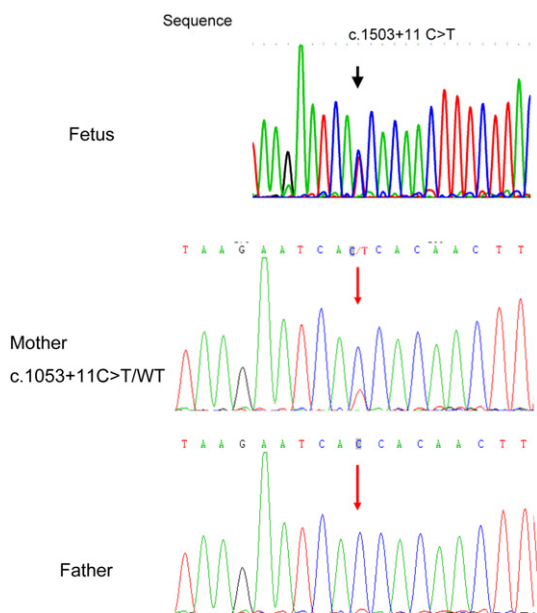


Fig. 3. Molecular analysis shows a c.1503+11 C>T mutation in intron 25 or IVS 25+11 C>T in the *COL1A2* gene in the fetus. The father is normal, but the mother is mosaic for the mutation.

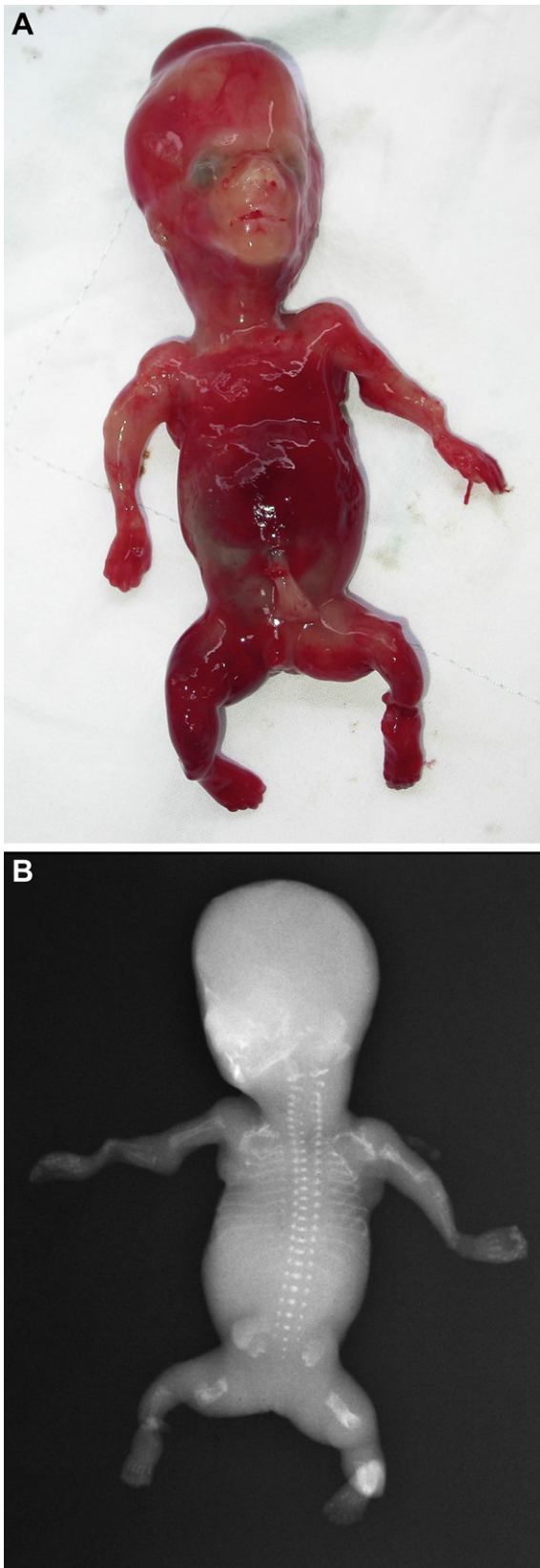


Fig. 4. (A) The fetus at birth and (B) the corresponding roentgenograph.

In the present case, the mother was asymptomatic, and the only phenotypic manifestation was that she was shorter than her female relatives. Pyott et al [17] found that the rate of parental

mosaicism in which a dominant mutation was identified in a first affected child was 16%. Recurrence of lethal OI due to parental mosaicism for a dominant mutation in *COL1A1* or *COL1A2* has been reported [17–19]. Recurrence of lethal OI due to parental mutation for a recessive mutation in *CRTA1* (OMIM 610854), *LEPRE1* (OMIM 610915) or *PPIB* (OMIM 259440) has also been reported [17,20]. Pyott et al [17] suggested a very low risk (<0.1%) of recurrence in the absence of parental somatic mosaicism or recessive inheritance, a risk up to 50% in the presence of parental mosaicism, and a risk of 25% if both parents are carriers of a recessive mutation.

In summary, this report suggests increased NT and hypoechogenicity of the cranium are important early ultrasound adjunctive findings for OI type II.

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