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Taiwanese Journal of Obstetrics & Gynecology 51 (2012) 276–279

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Case Report

Osteogenesis imperfecta type I: Second-trimester diagnosis and incidental identification of a dominant *COL1A1* deletion mutation in the paucisymptomatic father

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Accepted 17 February 2012

Abstract

Objective: To present second-trimester ultrasound and molecular diagnosis for osteogenesis imperfecta (OI) type I in a female fetus and incidental identification of a dominant *COL1A1* deletion mutation in her paucisymptomatic father.
Case Report: A 30-year-old, primigravid woman was referred for genetic counseling in the second trimester because of bowing of the fetal lower limbs. She and her husband were non-consanguineous, and there was no family history of skeletal dysplasias. Prenatal ultrasound at 22 weeks of gestation revealed short and curved right femur and left tibia, and a short left fibula. The lengths of other long bones were normal. The husband was 158 cm tall, had blue sclerae, a history of habitual subluxation and dislocation of bilateral elbows and left knee, and an episode of left ulna fracture, and was not aware of his being affected with OI type I. The woman underwent amniocentesis. Cytogenetic analysis revealed a karyotype of 46,XX. Molecular analysis of the amniocytes revealed a heterozygous deletion mutation of c.1064_1068delCTGGT in exon 17 of the *COL1A1* gene. By genetic testing the husband was found to carry the same mutation. Despite counseling of favorable outcome for OI type I with the parents, the woman elected to terminate the pregnancy. Postnatal skeletal X-ray findings were consistent with OI type I.
Conclusion: Prenatal ultrasound diagnosis of mild forms of OI should include molecular analysis of type I collagen genes in both fetus and parents. Molecular genetic analysis of the family may incidentally identify a collagen gene mutation in the paucisymptomatic affected parent.

Keywords: COL1A1; Osteogenesis imperfecta type I; Prenatal diagnosis

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1028-4559/$ - see front matter
doi:10.1016/j.tjog.2012.04.020

Introduction

Osteogenesis imperfecta (OI) is a group of disorder that is characterized by osteopenia, fractures, short statures, bone deformity, blue sclerae, dentinogenesis imperfecta (DI), progressive, postpubertal hearing loss, and hyperlaxity of ligaments and skin [1,2]. The severity of OI varies in different types ranging from perinatal lethality to individuals with short stature, severe skeletal deformities and multiple fractures to nearly asymptomatic individuals with normal stature, a mild predisposition to fractures and normal life span [2]. OI type I to type IV can be caused by mutations in *COL1A1* or *COL1A2* in an autosomal dominant pattern.

OI type II (OMIM 166210) is the most severe and perinatal lethal form of OI that can be detected by ultrasound after 14 weeks of gestation with sonographic findings of hypomineralization, broad, crumpled and shortened limbs, thin beaded ribs, bowing, angulation or fractures of the long bones, abnormal calvarium and fractures, and clinical findings of undermineralized skull, micromelia of long bones, beaded ribs and severe bone deformity at birth [3]. OI type III (OMIM 259420) is a severe form of OI that can be detected by ultrasound after 18 weeks of gestation with sonographic findings of short limbs, hypomineralized skull, fractures and decreased long bone lengths at 16–18 weeks of gestation, and clinical findings of moderate limb deformity at birth, varied scleral hue, very short stature and DI [3]. OI type IV (OMIM 166220) is a mild form of OI that can be rarely detected by ultrasound after 20 weeks of gestation with sonographic findings of long bone bowing and/or fractures on rare occasions and has clinical findings of normal sclerae, mild/moderate limb deformity with fractures, variable short stature, DI and some hearing loss [3]. OI type I (OMIM 166200) is the mildest form of OI that can be rarely detected by ultrasound after 20 weeks of gestation with sonographic findings of long bone bowing or fractures in rare occasions and has clinical findings of blue sclerae, normal stature, and fractures with little or no limb deformity [3].

Herein we report our experience of prenatal ultrasound diagnosis and molecular analysis of OI type I in the second trimester in a female fetus and incidental identification of a dominant *COL1A1* deletion mutation in her paucisymptomatic father.

Case report

A 30-year-old, primigravid woman was referred to the hospital at 22 weeks of gestation because of bowing of the lower limbs in the fetus. Her husband was 31 years old. She and her husband were non-consanguineous, and there was no family history of skeletal dysplasias. Prenatal ultrasound at 22 weeks of gestation revealed a normal amount of amniotic fluid, a short and curved right femur, a short and curved left tibia, and a short left fibula (Fig. 1). The biparietal diameter, abdominal circumference and the lengths of humerus, radius and ulna were equivalent to 22 weeks. The right femur, tibia, fibula, humerus, radius and ulna were measured 3.97 cm (< mean-2 standard deviation, SD), 3.97 cm, 3.69 cm, 4.16 cm, 3.46 cm and 3.92 cm, respectively, and the left femur, tibia, fibula, humerus, radius and ulna were measured 4.51 cm, 3.50 cm (< mean-2SD), 3.47 cm (< mean-2SD), 4.31 cm,

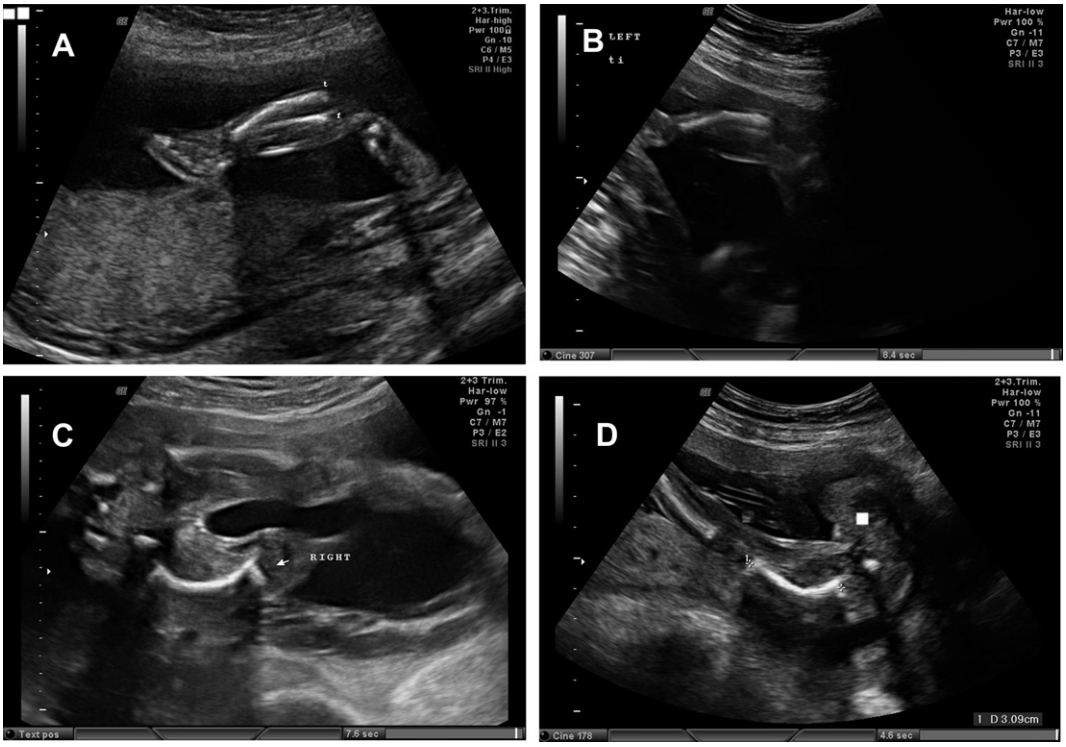

Fig. 1. Prenatal ultrasound at 22 weeks of gestation shows: (A) curved left tibia and straight left fibula; (B) curved left tibia; (C) straight left femur and curved right femur; and (D) curved right femur. f = fibula; t = tibia.

3.50 cm and 3.66 cm, respectively. A non-lethal form of OI type I was tentatively diagnosed. Genetic counseling of the parents revealed that the mother was 165 cm tall, and the father was 158 cm tall. The couple denied any family history of OI. The mother was completely normal. The father was found to have bilateral blue sclerae, a history of habitual subluxation and dislocation of bilateral elbows and left knee, and an episode of left ulna fracture with no bone deformity. The father was paucisymptomatic and was not aware of his being affected with a mild form of OI type I. The woman underwent amniocentesis at 22 weeks of gestation. Cytogenetic analysis revealed a karyotype of 46,XX. Molecular analyses of the amniocytes revealed a heterozygous deletion mutation c.1064_1068delCTGGT in exon 17 of the *COL1A1* gene resulting in a functional null allele (Fig. 2). The mutation caused a frameshift, introducing 6 novel residues at codon 356 and resulting in a premature termination codon (p.G356PfsX7) that removed all the following amino acids of the protein. Molecular analyses of the parental blood also showed that the father carried the same mutation (Fig. 2). Despite counseling of favorable outcome of OI type I with the parents, the mother elected to terminate the pregnancy. Postnatal radiograph demonstrated mildly curved lower limbs in the fetus (Fig. 3).

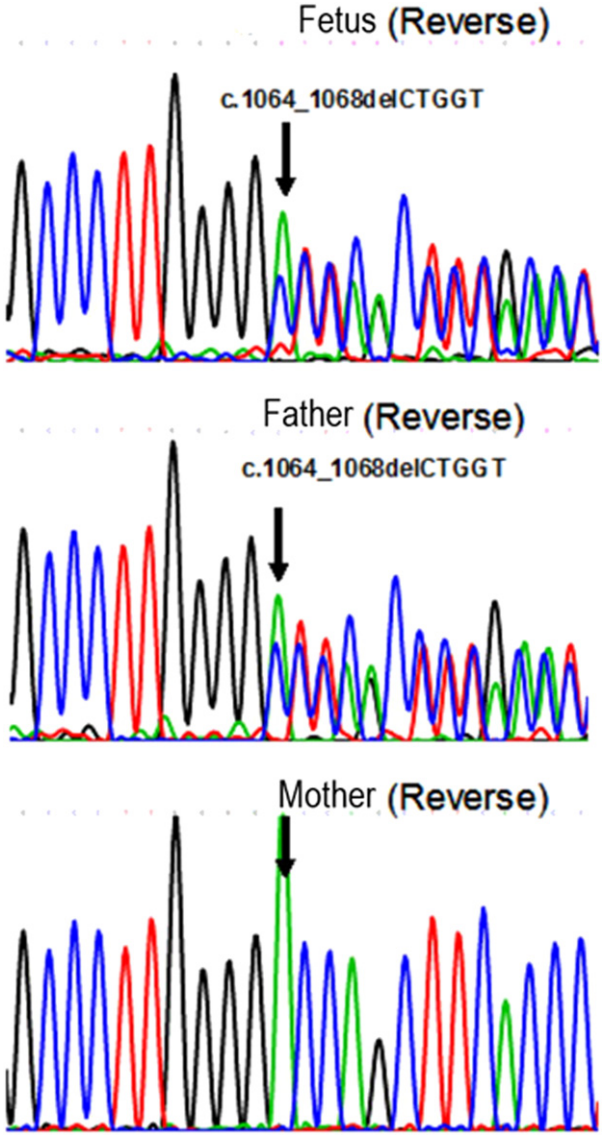

Fig. 2. Molecular analysis of the *COL1A1* gene shows a heterozygous deletion mutation of c.1064_1068delCTGGT in exon 17 in the fetus and the father. The mother was normal.

Discussion

Individuals with OI types II, III and IV generally have structural abnormalities within the triple helix of the type I collagen because of point mutations, insertions, deletions or splice site mutations in either *COL1A1* or *COL1A2*. However, individuals with OI type I usually have decreased synthesis of the structurally normal type I collagen because of a *COL1A1* null allele resulted from mutations within *COL1A1* [4–7]. Mutations that may produce a *COL1A1* null allele include mutations of nonsense, deletions and insertions resulting in a premature stop codon, and mutations of splicing site interfering normal splicing of the *COL1A1* gene [6,8,9]. The present case had a small deletion within the exon 17 of *COL1A1* that causes a frameshift and a premature stop codon, and creates a *COL1A1* null allele. It has been suggested that nonsense and frameshift mutations throughout most of the *COL1A1* gene will result in a "functional null" allele (null allele), which is associated with a mild form of OI type I [5–9]. Such a mutation will lead to both marked reduction in steady-state level of mRNA from the mutant allele and a quantitative decrease in type I procollagen production [6].

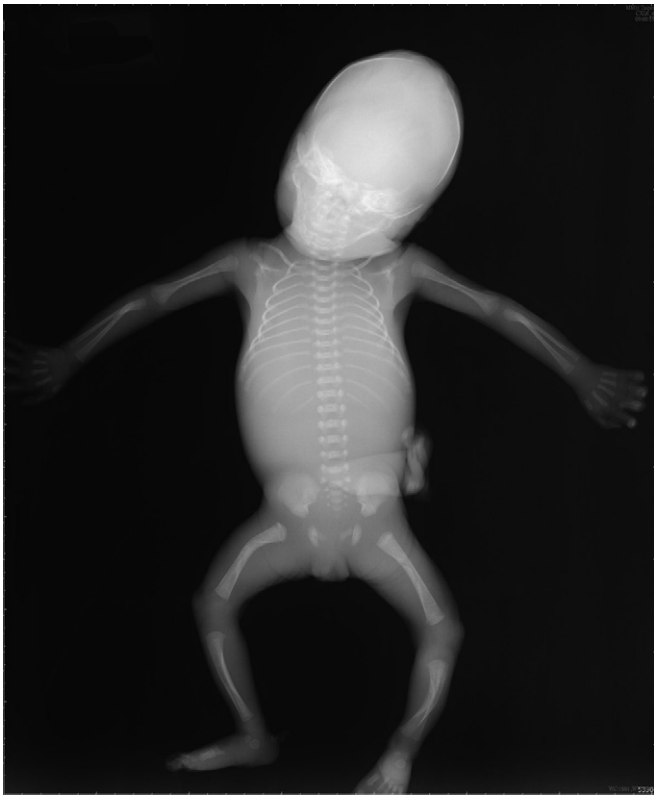

Fig. 3. Postnatal radiograph shows mildly curved lower limbs.

OI type I is very difficult to identify by fetal ultrasound because in OI type I, the limb length is almost always normal, and femur bowing is only rarely apparent after 20 weeks of gestation. Therefore, prenatal molecular diagnosis of OI type I in pregnancies at risk for OI type I may be required. Pepin et al [10] first detected one affected fetus and one normal fetus in two pregnancies at risk for OI type I using molecular techniques instead of biochemical analysis. Pepin et al [10] found that biochemical analysis for OI type I using cultured chorionic villus sampling (CVS) cells is not reliable, and suggested that prenatal diagnosis of OI type I should be limited to molecular diagnosis. Nuytinck et al [11] used *COL1A1* null-allele testing for rapid prenatal diagnosis in a pregnancy with maternal OI type I and found that the fetus would not be affected with OI by the finding that the fetus had inherited a normal *COL1A1* allele in the affected mother. Ries et al [12] reported prenatal molecular diagnosis of R848X in the *COL1A1* gene by CVS in a pregnancy with paternal OI type I. The father was 163 cm tall and had blue sclerae and shortening of the right leg due to poorly healed fracture and osteopenia. The parents elected to carry the pregnancy to term. The affected baby was delivered with a fractured clavicle, bowed right tibia and blue sclerae but had a favorable outcome.

Robyr et al [13] reported three cases of prenatally detected OI with bowed long bones and/or micromelia, and all were associated with paucisymptomatic fathers unaware of the disorder. In the first case, the father had repetitive endorses, marked ligmentous laxity and macrocephaly. In the second case, the father had repetitive endorses and fractures, and unilateral deafness. In the third case, the father had genu varum and kyphscoliosis. Of the three pregnancies, two were terminated, and only one was carried to full term. In a study of 19 cases with OI type I, 10 cases with OI type III and 19 cases with OI type IV, Lin et al [14] found that 84.2% (16/19) of type I patients had a family history of OI compared with none in type III and 36.8% (7/19) in type IV. Since OI type I has the mildest phenotype and the lowest incidence of decreased height, weight and bone mineral density, hearing loss, bone deformity, fractures and walking disability [14], it is very probable that some adults who are affected with OI type I may be unaware of the disorder during genetic counseling.

In conclusion, a fetus with OI may give the first insight into a familial autosomal dominant disorder undiscovered in the parent. We suggest that prenatal ultrasound diagnosis of mild forms of OI should include molecular analysis of type I collagen genes in both fetus and parents. Molecular genetic analysis of the family may incidentally identify a collagen gene mutation in the paucisymptomatic affected parent. The information acquired is helpful for genetic counseling and perinatal management.

Acknowledgments

This work was supported by research grants NSC-97-2314-B-195-006-MY3 and NSC-99-2628-B-195-001-MY3 from the National Science Council, and MMH-E-100-04 from Mackay Memorial Hospital, Taipei, Taiwan.

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