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Research Letter

Identification of a deletion mutation in the short flanking repeat region of exon 44 of the *COL1A1* gene in a fetus with osteogenesis imperfecta type II

Chih-Ping Chen [a,b,c,d,e,f,g,*], Yi-Ning Su [h], Tung-Yao Chang [i], Schu-Rern Chern [c], Jun-Wei Su [b,j], Wayseen Wang [c,k]

[a] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[b] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[d] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[e] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[f] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[h] *Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan*
[i] *Taiji Fetal Medicine Center, Taipei, Taiwan*
[j] *Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung, Taiwan*
[k] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

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A 25-year-old, gravida 3, para 1, woman was referred to hospital at 24 weeks of gestation because of short limbs suggesting congenital dwarfism. Her husband was 25 years old. She and her husband were non-consanguineous, and there was no family history of skeletal dysplasias. Prenatal ultrasound at 24 weeks of gestation revealed a fetus with shortening, angulation and a crumpled appearance of the long bones, a small chest with beading of the ribs, skull deformation and hypomineralization of the skull with too-well-seen brain structure (Fig. 1). The measurements of the humerus, radius, ulna, femur, tibia and fibula were 2.91, 2.53, 2.83, 2.71, 2.11 and 1.62 cm, respectively, and all were less than the fifth centile for 24 weeks. The ultrasound findings were consistent with the diagnosis of osteogenesis imperfecta (OI) type II. The pregnancy was subsequently terminated. Cytogenetic analysis revealed a karyotype of 46,XY, and molecular analyses of the *COL1A1* and *COL1A2* genes revealed a *de novo* heterozygous deletion mutation of c.3150_3158delTCCTGGTGC in exon 44 of the *COL1A1* gene that predicts p.1051_1053delProGlyAla (Fig. 2). The parents did not have such a mutation. Postnatal radiograph demonstrated generalized osteopenia, decreased mineralization of the skull, and abnormal tubular bones with thin cortex and shafts, callus formation and fractures (Fig. 3).

OI type II (OMIM 166210) is a lethal form of OI that is characterized by decreased mineralization of the skull and bones, generalized osteopenia, prenatal fractures, and long bone shortening/angulation and callus formation secondary to fractures. OI type II can be inherited in an autosomal dominant pattern with heterozygous mutations in *COL1A1* (OMIM 120150) or *COL1A2* (OMIM 120160) [1]. Most reported *COL1A1* mutations associated with OI type II are missense mutations, and only a few are mutations of splicing, deletions or insertions [1,2]. The present case had a *de novo* heterozygous deletion mutation of c.3150_3158delTCCTGGTGC in exon 44 of the *COL1A1* gene that predicts p.1051_1053delProGlyAla in protein. Such a deletion mutation has been reported to be associated with lethal OI. Pyott et al [3] reported a family with a mosaic mother, two affected infants with lethal OI and a mutation of c.3150_3158del in *COL1A1* that predicts p.Pro1051Gly1052Ala1053del in protein. Our case had a mutation in the short flanking repeat region of three 9-bp (CCTGGTGCT) repeats in exon 44 of *COL1A1*. Bodian et al [1] reported c.3148_3156dupGCTCCTGGT in exon 44 of *COL1A1* that predicts p.1050_1052dupAlaProGly in a case with OI type II. Pace et al [2] reported c.3129_3137del ACCCC CTGG, c.3132_3140delCCCTGGTGC and c.3145_3153 dupGGTGCTCCT, which predict a deletion of proline in 1044, hydroxyproline in 1045 and glycine in 1046; a deletion of hydroxyproline in 1045, glycine in 1046 and alanine in 1047; and a duplication of glycine in 1049, alanine in 1050 and hydroxyproline in 1051, respectively in exon 44 of *COL1A1* in

* Corresponding author. Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

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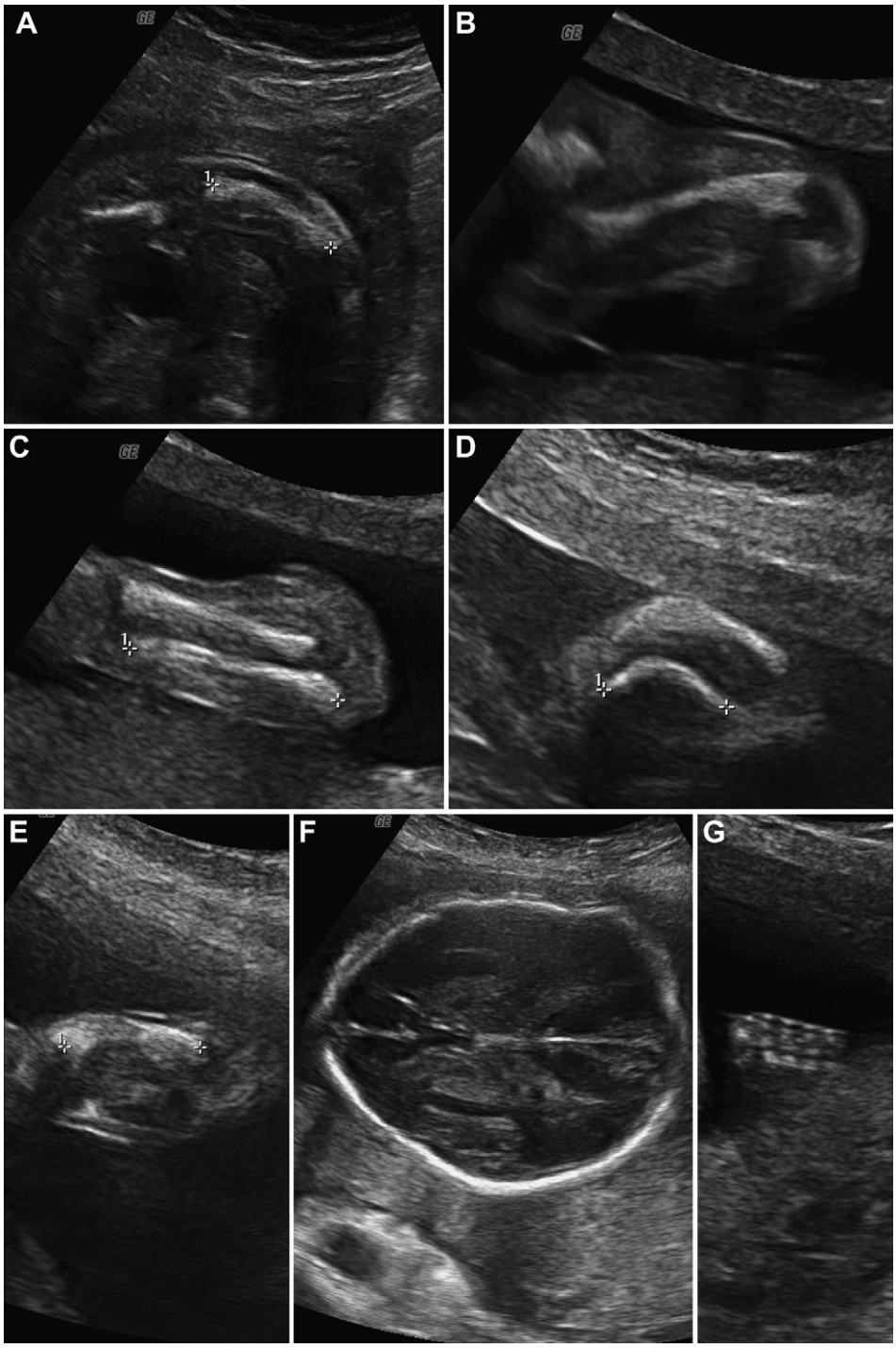

Fig. 1. Prenatal ultrasound at 24 weeks of gestation shows (A) curved femur, (B) humerus with thin cortex and shafts and fracture, (C) radius and ulna with hypomineralization, (D) curved tibia and fibula, (E) curved femur, (F) hypomineralization of the skull with too-well-seen brain structure, and (G) a normal hand with five fingers.

three cases with OI type II. Pace et al [2] suggested that deletions and duplications of Gly-Xaa-Yaa triplet repeats in the triple helical domain of type I collagen chain disrupt helix formation and result in OI. They found replication errors in the repetitive high GC triple helix coding region such as three 9-bp (CCTGGTGCT) repeats in exon 44 of *COLIA1* in three of 11 mutations of deletions or duplications, and all were associated with OI type II. The present case had deletion of proline in 1051, glycine in 1052 and alanine in 1053. The imino acids proline and hydroxyproline are the most common at the Xaa-position and Yaa-position in the collagen triple helix, and the imino acids are important for collagen triple helix formation and stability [2,4–6]. Pace et al [2] suggested that Glycine-Xamino acid-Hydroxyproline repeating units tend to cluster into blocks that correspond to the variation in helical twisting, and the imino acid-rich blocks serve as trimer stabilizing domains of

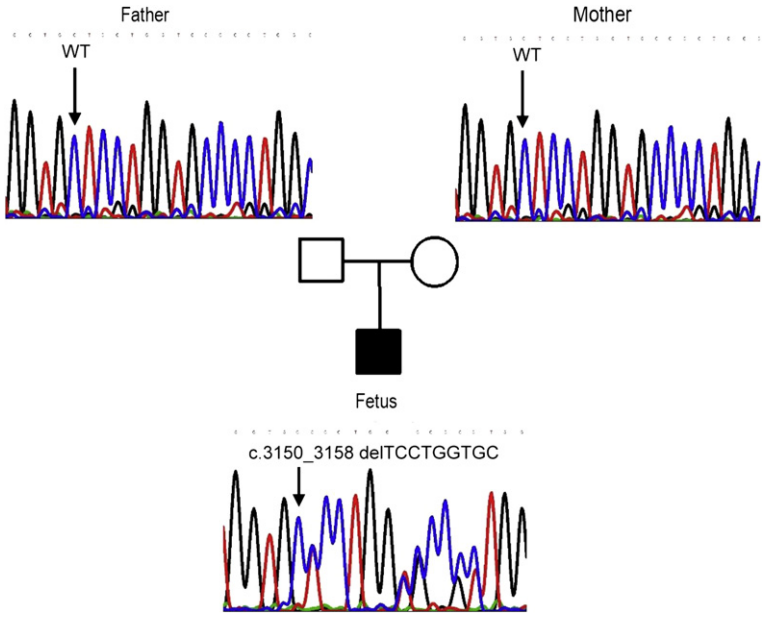

Fig. 2. Molecular analysis of the fetus shows a *de novo* heterozygous deletion mutation of c.3150_3158delTCCTGGTGC in exon 44 of the *COL1A1* gene in the fetus.

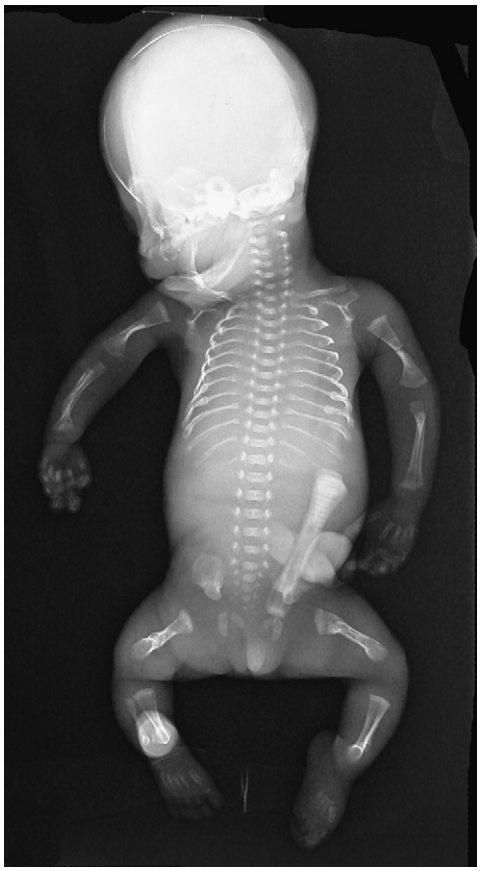

Fig. 3. Postnatal radiograph demonstrates generalized osteopenia, decreased mineralization of the skull, beading of the ribs, and abnormal tubular bones with thin cortex and shafts, callus formation and fractures.

renucleation if helix propagation stalls, whereas the imino acid-poor regions allow increased flexibility of the crystal structure. It is likely that a deletion mutation in the short flanking repeat region of exon 44 will result in lethal form of OI due to deficiency of imino acid-rich blocks and disturbance of the stability of the collagen triple helix. In the present *de novo* case, unequal recombination during meiosis may have led to the deletion. However, in the case reported by Pyott et al [3], the deletion must have occurred as a replication error in mitosis because the index patients' mother was mosaic for the same mutation.

In summery, we present an uncommon in-frame deletion in the short flanking repeat region of Gly-Ala-Pro or CCTGGTGCT 9-bp repeats in exon 44 of *COL1A1*. Our case provides evidence that a deletion in the region of triplet repeats in exon 44 of *COL1A1* may result in a lethal form of OI.

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