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Research Letter

Identification of a *COL1A2* mutation with a deletion spanning coding and intronic sequence in exon 19 and intron 19 in a fetus with osteogenesis imperfecta type II

Chih-Ping Chen [a,b,c,d,e,f,g,*], Yi-Ning Su [h], Fang-Yu Hung [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] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital Hsinchu Branch, Hsinchu, 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 28-year-old, gravida 2, para 1, woman was referred to the hospital at 22 weeks of gestation because of short limbs in the fetus. Her husband was 29 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 fetus with shortening and angulation of the long bones and hypomineralization of the skull and bones (Fig. 1). Fetal biometry showed a biparietal diameter of 5.24 cm (22 weeks), an abdominal circumference of 17.78 cm (22 weeks) and micromelia. The lengths of the long bones were measured as 2.55 cm (17 weeks), 2.56 cm (19 weeks), 2.49 cm (18 weeks), 2.63 cm (18 weeks), 2.45 cm (19 weeks) and 2.39 cm (18 weeks), for femur, tibia, fibula, humerus, radius and ulna, respectively. 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,XX, and molecular analyses of the *COL1A1* and *COL1A2* genes revealed a *de novo* heterozygous coding deletion and splicing mutation of c.1035_1035+2delTGT in exon 19 and intron 19 of the *COL1A2* gene that predicts p.Val345del and an altered splice site of intron 19 and exon 19 skipping (Fig. 2). The parents did not have such a mutation. Postnatal radiograph demonstrated generalized osteopenia, decreased mineralization of bones, and abnormal tubular bones with thin cortex and shafts, callus formation and fractures (Fig. 3).

OI type II (OMIM 166210) is an autosomal dominant perinatal lethal form of OI that is caused by heterozygous mutation in *COL1A1* (OMIM 120150) or *COL1A2* (OMIM 120160), and is characterized by undermineralization; broad, crumpled and shortened limbs; thin beaded ribs; bowing, angulation or fractures of the long bones; normal appearing hands; and deformable calvarium on prenatal ultrasound [1,2].

Mutations in *COL1A2* are predominantly non-lethal (80%) [1,2]. About 60% of reported *COL1A2* mutations are missense mutations that result in substitution for triple helical glycine residues, and the rest are deletions, insertions or splicing defects [2]. In a study of 59 subjects with OI type II and mutations in the type I collagen genes, Bodian et al [2] found that 37 had mutations in *COL1A1* and 22 had mutations in *COL1A2*. In their report, the 37 *COL1A1* mutations included 26 with substitution for a glycine within the Gly-Xaa-Yaa triplet domain of the triple helix, four with altered splice sites, one with exon skipping form a deletion spanning coding and intronic sequence, one with a deletion, one with a duplication, one with an altered single residue in carboxyl-terminal propeptide and others; and the 22 *COL1A2* mutations included

* 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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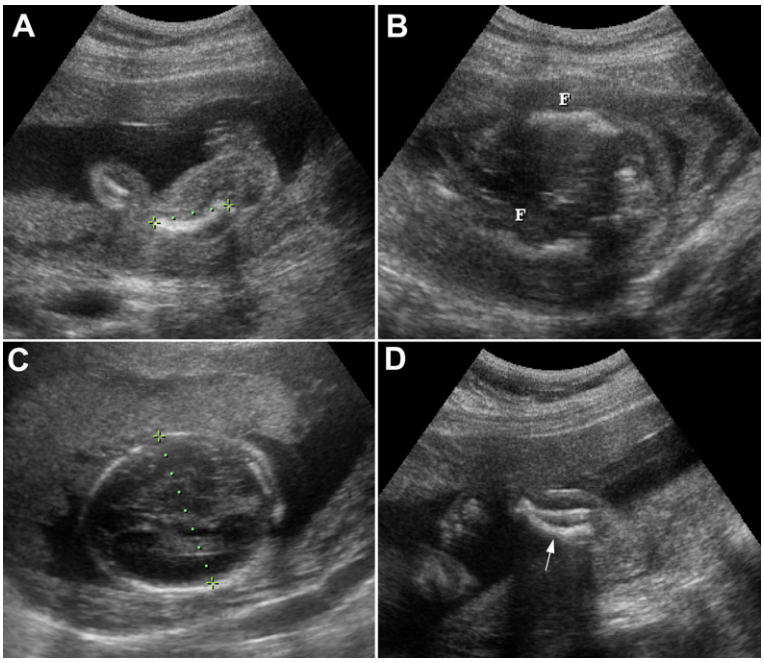

Fig. 1. Prenatal ultrasound at 22 weeks of gestation shows (A) curved femur, (B) curved femurs, (C) hypomineralization of the skull and (D) curved tibia (arrow). F = femur.

13 with substitution for a glycine within the Gly-Xaa-Yaa triplet domain of the triple helix, four with deletions, two with splice-site mutations, one with a duplication, one with a deletion spanning coding and intronic sequence, and one with no resolution. Clinical reports of OI type II associated with both a deletion mutation spanning coding and intronic

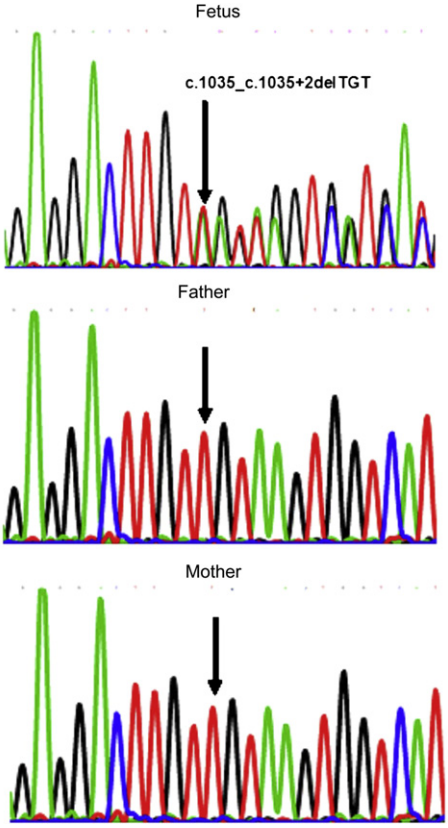

Fig. 2. Molecular analysis of the *COL1A2* gene shows a *de novo* heterozygous coding deletion and splicing mutation of c.1035_1035+2delTGT in exon 19 and intron 19 of the *COL1A2* gene in the fetus.

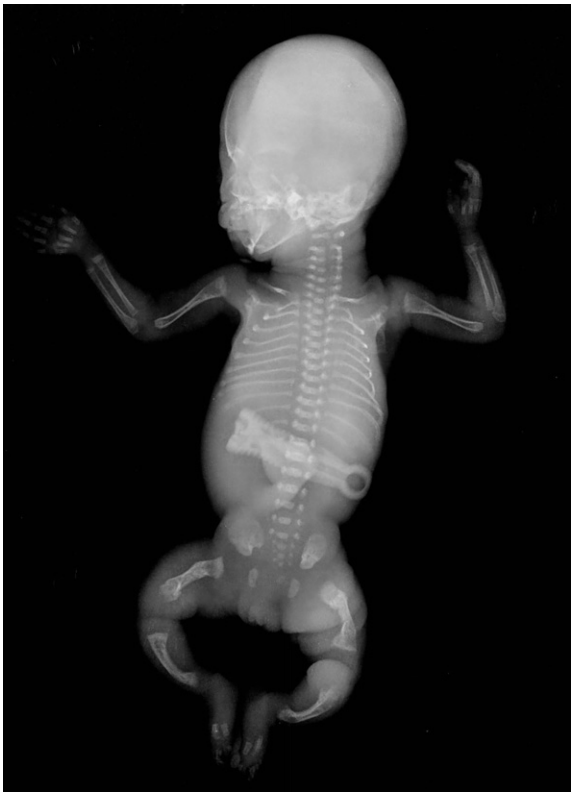

Fig. 3. Postnatal radiograph shows decreased mineralization of bones and abnormal tubular bones with thin cortex and shafts, callus formation and fractures.

sequence in *COL1A2* are very rare. The present case had a *de novo* heterozygous coding and splicing deletion mutation of c.1035_1035+2delTGT in exon 19 and intron 19 of the *COL1A2* gene that predicts p.Val345del and exon 19 skipping. 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.1035_1035+2delTGT in the *COL1A2* gene.

The present case had a mutation at splice donor site. Marini et al [1] found that in *COL1A1* splice-site mutations, mutations at donor sites are equal to mutations at acceptor sites, whereas in *COL1A2* splice-site mutations, mutations at donor sites are four times more common than mutations at acceptor sites. Marini et al [1] reported 11 lethal *COL1A2* splice-site mutations, and all were located in the carboxyl half of the chain, of which ten cases involved exon skipping (exons 28, 30, 32, 33, 34, 37, 42 and 47) and one involved an in-frame deletion in exon 40. Bodian et al [2] reported four lethal *COL1A2* splice-site mutations involving exon skipping (exons 29, 30, 41 and 46). Pyott et al [3] reported three lethal *COL1A2* splice-site mutations involving exon skipping (exons 19, 32 and 35). The present case adds to the list of lethal *COL1A2* splice-site mutations and provides evidence that a *COL1A2* splice-site mutation involving exon 19 skipping can be lethal.

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References

[1] Marini JC, Forlino A, Cabral WA, Barnes AM, San Antonio JD, Milgrom S, et al. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. Hum Mutat 2007;28:209–21.

[2] Bodian DL, Chan T-F, Poon A, Schwarze U, Yang K, Byers PH, et al. Mutation and polymorphism spectrum in osteogenesis imperfecta type II: implications for genotype-phenotype relationships. Hum Mol Genet 2009; 18:463–71.

[3] Pyott SM, Pepin MG, Schwarze U, Yang K, Smith G, Byers PH. Recurrence of perinatal lethal osteogenesis imperfecta in sibships: parsing the risk between parental mosaicism for dominant mutations and autosomal recessive inheritance. Genet Med 2011;13:125–30.