Available online at www.sciencedirect.com

SciVerse ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology 52 (2013) 152–153

www.tjog-online.com

Research Letter

Prenatal diagnosis of a missense mutation of c.2279G>A, Gly760Glu in exon 37 of *COL1A2* in a fetus with familial osteogenesis imperfecta type IV and favorable outcome

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

[a] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Medicine, Mackay Medical College, New Taipei City, 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 Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan*
[i] *Mackay Medicine, Nursing and Management College, Taipei, Taiwan*
[j] *Department of Obstetrics and Gynecology, School of Medicine, Taipei Medical University, Taipei, Taiwan*
[k] *Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung, Taiwan*
[l] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

Accepted 5 November 2012

A primigravid woman 35 years of age was referred to the hospital for genetic counseling in the second trimester because of advanced maternal age and a positive family history of type IV osteogenesis imperfecta (OI). The woman had a body weight of 56 kg and a height of 145 cm, and her husband had a height of 168 cm. Her husband had normal sclerae, normal stature, dentinogenesis imperfecta, and osteopenia, and he had sustained mild fractures with trauma since childhood. The husband, his 13-year-old daughter (151 cm in height) from a previous marriage, his mother (150 cm in height), and his aunt also had type IV OI. His daughter had multiple fractures of the long bones that required long-term bisphosphonate treatment. Molecular analysis of the husband and his affected family members revealed a G to A change at position c.2279 (c.2279 G > A, GGA > GAA) of the exon 37 in the *COL1A2* gene leading to a change of glycine at codon 760 to glutamic acid (G760E). Prenatal ultrasonographic examination at 19 weeks of gestation revealed a fetus with no skeletal abnormalities and a biparietal diameter (BPD), an abdominal circumference (AC), and a femur length (FL) equivalent to 19 weeks. The woman underwent amniocentesis at 19 weeks of gestation. Cytogenetic analysis revealed a karyotype of 46,XX. Molecular analysis of uncultured amniocytes revealed a missense mutation of c.2279 G > A, pG760E in *COL1A2* (Fig. 1). After genetic counseling of possible phenotypic variability in OI with the parents, the mother elected to carry the pregnancy to term. Prenatal ultrasonography in the third trimester showed shortening of the long bones. At 37 weeks of gestation, fetal ultrasonography showed a BPD of 9.09 cm (36 weeks), an AC of 32.6 cm (38 weeks), a FL of 6.36 cm (33 weeks), a tibia length of 6.0 cm (34 weeks), a fibula length of 5.4 cm (34 weeks), and a humerus length of 5.53 cm (33 weeks). A cesarean section was performed at 39 weeks of gestation, and a 3120-g female baby was delivered with a body length of 48 cm (15–50th percentile). Postnatal radiography showed neither curvature nor fracture of the long bones. She was doing well with no fractures at the age of 1 month.

OI is a genetic disorder of defective collagen synthesis characterized by increased bone fragility, osteopenia, blue sclerae, ligamental and dermal hyperlaxity, dentinogenesis imperfecta, and hearing loss [1,2]. The occurrence of OI in newborns has been estimated to be between one in 20,000 births and one in 60,000 births [3,4]. About 90% of the OI patients have autosomal dominant mutations in the *COL1A1* gene (OMIM 120150) encoding α1 type 1 collagen chain and in the *COL1A2* gene (OMIM 120160) encoding α2 type 1 collagen chain [5]. Type I OI is associated with mutations 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).

http://dx.doi.org/10.1016/j.tjog.2013.01.022

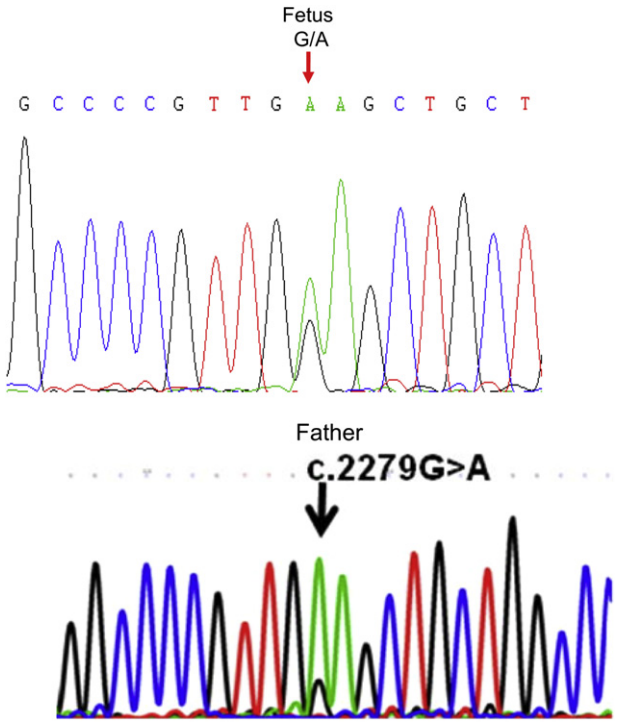

Fig. 1. Molecular analysis of the fetus and the father shows a heterozygous G to A change at position c.2279 (c.2279G > A, GGA → GAA) of the exon 37 in the *COL1A2* gene leading to a change of glycine at codon 760 to glutamic acid (G760E).

COL1A1 mostly because of a null allele caused by a premature stop codon due to deletions, duplications, nonsense mutations, or frameshift mutations, and types II, III, and IV OI are associated with mutations in either *COL1A1* or *COL1A2* mostly caused by glycine substitutions and less frequently caused by splicing defects, deletions, insertions, or duplications [6–11].

We have presented a novel OI mutation in a Chinese family with a dominant inherited form of type IV OI resulting from a heterozygous mutation in *COL1A2*. The present case provides evidence that a glycine substitution by glutamic acid at codon 2279 can result in type IV OI but no a lethal outcome. The substitution of an amino acid for a glycine in the repeating Gly-$X_{\text{amino acid}}$-$Y_{\text{amino acid}}$ triplet repeats in the triple helical domains of the type 1 collagen chains can delay triple-helix formation, permit prolonged access of modifying enzymes, and decrease the thermal stability of the protein [12]. In a study of 290 individual mutations that resulted in substitutions of glycine residues in COL1A2 affecting the α2(I) chain, Marini et al [5] found that about one-fifth (18.9%) (55/290) of all independent glycine substitutions in α2(I) resulted in perinatal lethal type II OI. In their study, substitutions of glycine in α2(I) chains by serine (44%, or 128/290), aspartic acid (15.8%, or 46/290), tryptophan (13.9%, or 40/290), and arginine (10.3%, or 30/290), resulting from mutations in the first position of glycine codons accounted for most of all α2(I) substitutions, and the substitution of glycine by glutamic acid accounted for only 4.9% (14/290) of the cases. Marini et al [5] also found that substitutions of glycine by glutamic acid, aspartic acid, cysteine and arginine had a lethal outcome more often than average for α2(I) chain. The lethal outcomes were in the order of glutamic acid (42.9%, or 6/14), aspartic acid (32.6%, or 15/46), cysteine (24%, or 6/25), and arginine (23.3%, or 7/30). Our case represents a rare occasion and adds Gly760Glu to the list of the substitution of glycine by glutamic acid in the α2(I) chain with a nonlethal form of OI and a favorable outcome.

Acknowledgments

This work was supported by research grants NSC-99-2628-B-195-001-MY3 and NSC-101-2314-B-195-011-MY3 from the National Science Council and MMH-E-101-04 from Mackay Memorial Hospital, Taipei, Taiwan.

References

[1] Rauch F, Glorieux FH. Osteogenesis imperfecta. Lancet 2004;363:1377–85.
[2] Steiner RD, Pepin MG, Byers PH. Osteogenesis imperfecta. In: Pagon RA, editor. GeneReviews [Internet]. Seattle, WA: University of Washington; 1993. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1295/ [accessed 10.08.12].
[3] Key TC, Horger III EO. Osteogenesis imperfecta as a complication of pregnancy. Obstet Gynecol 1978;51:67–71.
[4] Parasuraman R, Taylor MJO, Liversedge H, Gilg J. Pregnancy management in type III maternal osteogenesis imperfecta. J Obstet Gynaecol 2007;27:619–21.
[5] 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.
[6] Chen C-P, Su Y-N, Chang T-Y, Chern S-R, Chen C-Y, Su J-W, et al. Osteogenesis imperfecta type I: second-trimester diagnosis and incidental identification of a dominant *COL1A1* deletion mutation in the asymptomatic father. Taiwan J Obstet Gynecol 2012;51:276–9.
[7] Chen C-P, Lin S-P, Su Y-N, Huang J-P, Chern S-R, Su J-W, et al. Uncomplicated vaginal delivery in two consecutive pregnancies carried to term in a woman with osteogenesis imperfecta type I and bisphosphonate treatment before conception. Taiwan J Obstet Gynecol 2012;51:305–7.
[8] Chen C-P, Su Y-N, Chang T-Y, Chern S-R, Su J-W, Wang W. Identification of a deletion mutation in the short flanking repeat region of exon 44 of *COL1A1* gene in a fetus with osteogenesis imperfecta type II. Taiwan J Obstet Gynecol 2012;51:308–11.
[9] Chen C-P, Su Y-N, Hung F-Y, Chern S-R, Su J-W, Wang W. 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. Taiwan J Obstet Gynecol 2012;51:312–4.
[10] Chen C-P, Su Y-N, Chang T-Y, Huang M-C, Pan C-H, Chern S-R, et al. Osteogenesis imperfecta type II: prenatal diagnosis and association with increased nuchal translucency and hypoechogenicity of the cranium. Taiwan J Obstet Gynecol 2012;51:315–8.
[11] Chen C-P, Lin S-P, Su Y-N, Chern S-R, Lin M-H, Su J-W, et al. Osteogenesis imperfecta type IV: prenatal molecular diagnosis and genetic counseling in a pregnancy carried to full term with favorable outcome. Taiwan J Obstet Gynecol 2012;51:271–5.
[12] Raghunath M, Bruckner P, Steinmann B. Delayed triple helix formation of mutant collagen from patients with osteogenesis imperfecta. J Mol Biol 1994;236:940–9.