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,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 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
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-Xamino acid-Yamino acid triplet repeats in the triple helical domain 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 sub-

![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).](image)

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