Case Report

Novel *COL1A1* Gene Mutation (R1026X) of Type I Osteogenesis Imperfecta: A First Case Report

Sathit Niramitmahapanya MD*, Thitinun Anusornvongchai MD*,
Sarinee Pingsuthiwong MSc**, Veerasak Sarinnapakorn MD*,
Chaicharn Deerochanawong MD*, Thongkum Sunthornthepvarakul MD*

** Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand*
*** Division of Medical Genetics and Molecular Medicine, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

A 22-year-old Thai man with blue sclera, normal height and absence of deformity sustained an open fracture at the right talus and talo-navicular dislocation while playing in a volleyball match. The patient had a history of several fractures of his elbows, wrists and ankles from minor impacts. Novel COL1A1 nonsense mutation (c.3202 C→T), a C to T transition at position 3,203, resulting in arginine to stop codon at codon 1026 (R1026X) mutation in exon 42 was found, and this is the first case reported in the literature.

Keywords: *Osteogenesis imperfect (OI), COL1A1 nonsense mutation, Thai*

J Med Assoc Thai 2013; 96 (Suppl. 3): S100-S103
Full text. e-Journal: *http://jmat.mat.or.th*

Osteogenesis imperfecta type I (OI type I, OMIM 166200)[1] is characterized chiefly by multiple bone fractures, usually resulting from minimal trauma. Affected individuals have blue sclera, normal teeth, and normal or near-normal stature. OI is a congenital disease, meaning it is present at birth. It is frequently caused by defects in the gene that produces type 1 collagen, an important building block of bone. There are many different defects that can affect this gene, and the severity of OI depends on the specific gene defect. OI type I is a dominantly-inherited, generalized connective tissue disorder characterized mainly by bone fragility and blue sclera. The severity of OI varies, ranging from perinatal lethality to a very mild phenotype. Even though several reports have identified the mutation[2-4], the vast majority are missense point mutations that convert codons for the obligate glycines in the triple helix of type I collagen to codons for amino acids with bulkier side chains[5-7]. The transcription products of such a *COL1A1* gene are usually unstable and subjected to degradation via nonsense-mediated mRNA decay pathways (NMD). The NMD is a universal phenomenon and describes the degradation of mRNA transcripts that contain premature termination signals[8]. The aim of this report is to present novel mutation of *COL1A1* gene mutation (c.3203 C→T, arginine to stop codon) as the cause of premature termination of the synthesis of pro-alpha-1(I) associated osteogenesis imperfecta type I in a Thai patient.

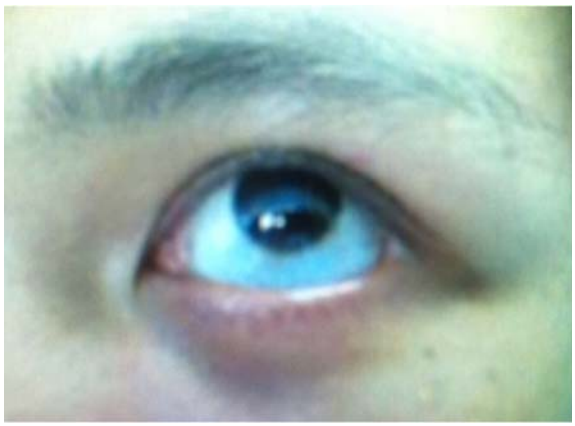

Fig. 1 The blue sclera of proband type I OI

Case Report

A 22-year-old man was referred from a local hospital with an open fracture of the right talus with subtalar joint and talo-navicular dislocation. He had been injured during a volleyball match. His history reported normal pubertal development, normal diet and

Correspondence to:
Niramitmahapanya S, Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University, 2 Phyathai Road, Ratchathewi, Bangkok 10400, Thailand.
Phone: 0-2354-8108 ext. 5101
E-mail: maisathit@hotmail.com

exercise, and no fatigue or chronic diarrhea. His past medical history was notable for multiple fractures of elbows, wrists and left ankle as a result of minor trauma. On physical examination, his general appearance seemed normal; he was of normal height and had no deformities. Blue sclera was identified in both eyes (Fig. 1) and normal hearing was revealed by audiograms. Unfortunately, his paternal family history could not assessed because he had had no contact with his father since birth. His maternal family history was normal, with nobody in this family having symptoms like his.

He was extensively investigated with complete blood count (hemoglobin 13.2 gm/dL, hematocrit 42.0%, white blood cell count 10,800/µL, neutrophil 57.0%, eosinophil 11.0%, monocyte 8.0%, lymphocyte 22.0%, platelet 246,000/mm^3); serum electrolyte (sodium 139 mEq/L, potassium 3.8 mEq/L, chloride 100 mEq/L, bicarbonate 31 mEq/L, calcium 9.4 mg/dL, magnesium 2.1 mg/dL, phosphate 4.4 mg/dL and BUN/creatinine 9/0.9 mg/dL) and endocrinology test (TSH = 1.87 mIU/L (0.27-4.2), FT3 = 3.14 pg/ml (2.5-4.3), FT4 = 1.59 ng/dl (0.93-1.7), Testosterone = 10.8 nmol/L (9.9-27.8), iPTH = 21pg/dl (15-65) and 25 OH Vitamin D3 16.84 ng/ml (> 30)). Vitamin D deficeincy was the only abnormal laboratory result.

Radiology showed a fracture of the right talus with subtalar joint and talo-navicular dislocation (Fig. 2A). *COL1A1* gene was done from leukocyte blood mutation at exon 42 by direct seqeuncing method. PCR product was shown c.3203 C→T substitution arginine by stop codon at position 1026 (R1026X) in Fig. 3.

This patient's fractuers were managed by open reduction and internal fixation with K-wire fixation and medial malleolus osteotomy, and the tendon was repaired (Fig. 2B) with a slab. For medical management of OI, calcium, vitamin D and bisphosphonate are used. Calcium intake is recommended for osteoporosis at 1-2 g/day to slow bone loss. Vitamin D 400 IU/day may be increased to up to 2,000 IU/day depending on the vitamin D deficiency status of the patient. Calcium and vitamin D increase bone mass, decrease seasonal bone loss, and can decrease the incidence of fractures.

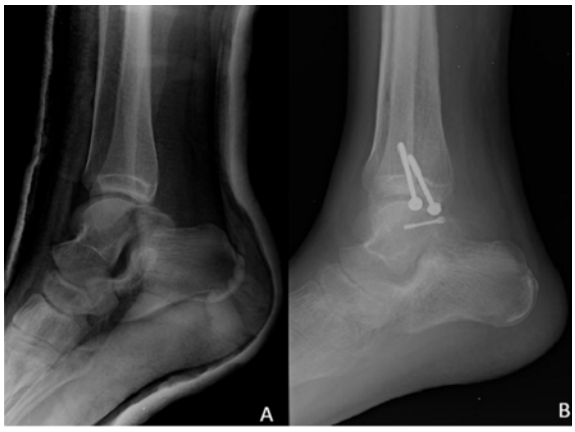

Fig. 2 Film right ankle and foot; A) fracture of right talus with subtalar joint and talo-navicular dislocation, B) internal fixation with K-wire fixation and medial malleolus osteotomy and repaired tendon

Discussion

The critical roles of fragility fractures were identified with the diseases that are caused by mutations on genes coding them, among which are osteogenesis imperfecta, Ehler-Danlos Syndrome, familial hyperparathyroidism, and osteomalacia. In this case, the authors focused on presenting the most prevalent diseases characterized by extremely fragile bone, reduction of bone mass, and blue sclera known as osteogenesis

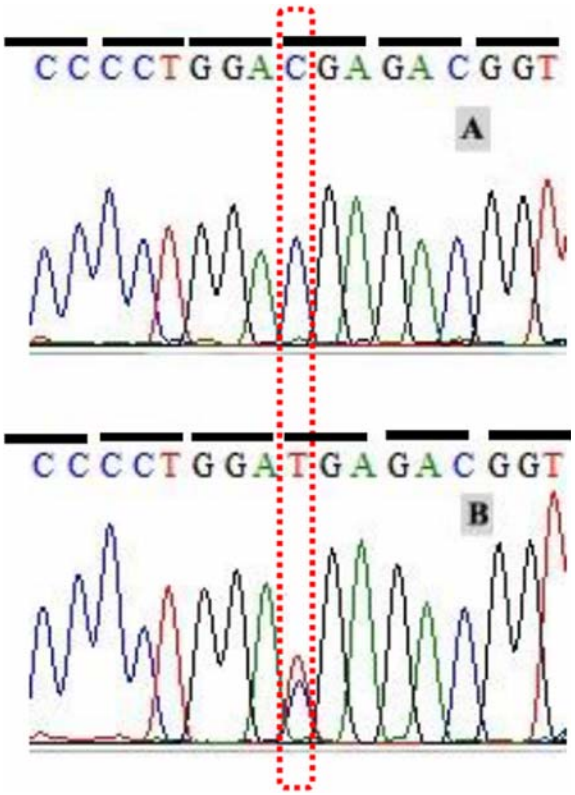

Fig. 3 Direct seqeuncing of *COL1A1* gene mutation; A) from control subject, B) from this patient. In red dot shape that showed T > C in 1026 exon 42 of *COL1A1* change Arg to stop codon in heterozygote type I osteogenesis imperfecta patient

imperfecta.

Over 850 different mutations have already been identified. Most of them are point mutations in one of the two type I collagen genes (*COL1A1* and *COL1A2*) that cause glycine substitutions in the collagen polypeptide[9]. Although no reliable genotype-phenotype correlations have been found, *COL1A1* mutations produce a premature stop codon often associated with Type I OI[10]. The missense point mutation occurring at glycine codon tends to result in a lethal phenotype, while the mutation creating a premature stop codon often leads to a mild, type I phenotype[6].

The nonsense mutation in the present study, R1026X, could cause one α1 (I) allele to be functionally void. The transcription products of such a *COL1A1* gene are usually unstable and subjected to degradation via nonsense-mediated mRNA decay pathways (NMD), ultimately producing a truncated protein. The NMD is a universal phenomenon and describes the degradation of mRNA transcripts that contain premature termination signals[8]. A recent study[11] described 13 known nonsense mutations at the collagen domain of *COL1A1*: R42X, R75X, R183X, R237X, R294X, R420X, E500X, R519X, Q644X, R704X, Q779X, R848X and R963X. Two have been found at the COOH-terminal domain: W1269X, W1325X.

The mutation analysis of OI is a labor-intensive, expensive process due to the "private" nature of offending mutations and their nonclustered distribution in considerably-sized genes[12]. To confirm this mutation, the authors double-checked by direct sequencing of this mutation in forward and reverse PCR products. This mutation could be the cause of the clinical presentation of this patient. Even though the authors did not explore his family history for the reason given above, this is an important data for future genetic counseling in his family.

Conclusion

The present case report is the tenth report in the literature of nonsense mutation converting an arginine codon to a premature stop codon. This is the first case of nonsense mutation in exon 42 of *COL1A1* gene in an OI case. This report suggests that close attention should be paid to arginine codons when screening the *COL1A1* for mutations.

Potential conflict of interest

None.

References

1. Byers PH. Osteogenesis imperfecta. In: Royce PM, Steinmann B, editors. Connective tissue and its heritable disorders: molecular, genetic, and medical aspects. New York: Wiley-Liss; 1993: 317-50.
2. Yang Z, Ke ZF, Zeng C, Wang Z, Shi HJ, Wang LT. Mutation characteristics in type I collagen genes in Chinese patients with osteogenesis imperfecta. Genet Mol Res 2011; 10: 177-85.
3. van Dijk FS, Huizer M, Kariminejad A, Marcelis CL, Plomp AS, Terhal PA, et al. Complete COL1A1 allele deletions in osteogenesis imperfecta. Genet Med 2010; 12: 736-41.
4. Byers PH, Steiner RD. Osteogenesis imperfecta. Annu Rev Med 1992; 43: 269-82.
5. Korkko J, Kuivaniemi H, Paassilta P, Zhuang J, Tromp G, DePaepe A, et al. Two new recurrent nucleotide mutations in the COL1A1 gene in four patients with osteogenesis imperfecta: about one-fifth are recurrent. Hum Mutat 1997; 9: 148-56.
6. Korkko J, Ala-Kokko L, De Paepe A, Nuytinck L, Earley J, Prockop DJ. Analysis of the COL1A1 and COL1A2 genes by PCR amplification and scanning by conformation-sensitive gel electrophoresis identifies only COL1A1 mutations in 15 patients with osteogenesis imperfecta type I: identification of common sequences of null-allele mutations. Am J Hum Genet 1998; 62: 98-110.
7. Benusiene E, Kucinskas V. COL1A1 mutation analysis in Lithuanian patients with osteogenesis imperfecta. J Appl Genet 2003; 44: 95-102.
8. Willing MC, Deschenes SP, Slayton RL, Roberts EJ. Premature chain termination is a unifying mechanism for COL1A1 null alleles in osteogenesis imperfecta type I cell strains. Am J Hum Genet 1996; 59: 799-809.
9. Glorieux FH. Osteogenesis imperfecta. Best Pract Res Clin Rheumatol 2008; 22: 85-100.
10. Rauch F, Glorieux FH. Osteogenesis imperfecta. Lancet 2004; 363: 1377-85.
11. Liu W, Gu F, Ji J, Lu D, Li X, Ma X. A novel COL1A1 nonsense mutation causing osteogenesis imperfecta in a Chinese family. Mol Vis 2007; 13: 360-5.
12. Gat-Yablonski G, Ries L, Lev D, Goldman B, Friedman E. A missense mutation in ColA1 in Jewish Israeli patient with mild osteogenesis imperfecta, detected by DGGE. Hum Genet 1997; 101: 22-5.

รายงานผู้ป่วยการกลายพันธุ์จีน COL1A1 (R1026X) ในผู้ป่วย Osteogenesis Imperfecta ชนิดที่ 1

สถิตย์ นิรมิตรมหาปัญญา, ฐิตินันท์ อนุสรณ์วงศ์ชัย, สาริณี ปิงสุทธิวงศ์, วีระศักดิ์ ศรินนภากร, ชัยชาญ ดีโรจนวงศ์, ทองคำ สุนทรเทพวรากุล

ผู้ป่วยชายไทยอายุ 22 ปี ตรวจร่างกายพบขอบตาสีฟ้า ความสูงปกติไม่พบความผิดปกติของกระดูก มาโรงพยาบาลด้วยกระดูกเท้าแตกและกระดูกข้อเท้าเคลื่อนจากการแข่งขันวอลเลย์บอล โดยผู้ป่วยมีประวัติกระดูกหักหลายครั้งทั้งข้อศอก ข้อมือ และข้อเท้า จากแรงกระทบเพียงเล็กน้อย ตรวจพบการกลายพันธุ์แบบ nonsense ของจีน COL1A1 จากการเปลี่ยนตำแหน่งของเบสไซโตซีนเป็นไทมีน ที่ตำแหน่งเบส 3,203 ทำให้เปลี่ยนกรดอะมิโนอาร์จินีนเป็นรหัสหยุดที่ตำแหน่ง 1,026 ของกรดอะมิโนใน exon ที่ 42 ของจีน COL1A1 ในผู้ป่วย osteogenesis imperfecta ชนิดที่ 1 เป็นครั้งแรก