

Severe cases of osteogenesis imperfecta type VIII due to a homozygous mutation in *P3H1* (LEPRE1) and review of the literature

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Abstract

Background. Osteogenesis imperfecta (OI) is a genetic disorder that causes skeletal fragility, multiple fractures and several extraskeletal disorders. Most cases of OI are caused by mutations in COL1A1/A2. Osteogenesis imperfecta type VIII typically causes a severe and fatal phenotype that presents at birth with severe osteopenia, congenital fractures and other clinical manifestations.

Objectives. We describe the cases of an 11-year-old female and a 9-year-old male with homozygous truncating mutations in *P3H1*. Both cases were born with intrauterine fractures and suffered multiple fractures shortly after birth, requiring multiple operations to correct both fractures and severe scoliosis. The patients have been treated with pamidronate since the age of 2.

Materials and methods. Whole exome sequencing (WES) was performed by Gene by Gene using Twist Bioscience technology. Initially, ~36.5 Mb of consensus coding sequences (targeting >98% of RefSeq and Gencode v. 28 regions obtained from the human genome) was replicated from fragmented genomic DNA using the Twist Human Core Exome Plus kit. The subsequent library was sequenced on the Illumina Novaseq Next Generation Sequencing platform to achieve at least ×20 reading depth for >98% of the targeted bases. Variant annotations and filtering was performed using Ingenuity Variant Analysis software.

Results. We identified a homozygous mutation in the 3rd exon of *P3H1* (c.628C>T/p.Arg210 Ter). Our cases broaden the phenotypic spectrum of OI type VIII as, to the best of our knowledge, these are the first postnatal cases with *P3H1* (c.628C>T/p.Arg210 Ter) mutations published in the literature.

Conclusions. We present the first recorded postnatal cases from unrelated families of OI type VIII, broadening our understanding of the severe, but nonfatal spectrum of clinical phenotype of this recessive form of OI.

Key words: osteogenesis imperfecta, severe, homozygous mutation, *P3H1*, LEPRE1

Background

Osteogenesis imperfecta (OI) is a clinically and genetically heterogeneous skeletal dysplasia that occurs in approx. 1 in 10,000–20,000 births.¹ It is characterized by multiple fractures caused by skeletal fragility and extra-skeletal findings, such as blue sclera, dentinogenesis imperfecta, hearing loss, joint hypermobility, and hyperlaxity.¹ Most OI cases (type I–IV) are associated with heterozygous mutations in *COL1A1* (MIM 120150) or *COL1A2* (MIM 120160), which encode the type I procollagen alpha chain to proalpha1 and proalpha2.¹ Osteogenesis imperfecta type V is caused by heterozygous mutations in *IFITM5* (MIM 614757).²

Osteogenesis imperfecta types VI–XV are inherited in a recessive manner.³ Homozygous truncating mutations in *P3H1* (LEPRE 1) (NM_022356) are responsible for OI type VIII and were first reported in 2007.⁴ The *P3H1* encodes prolyl 3-hydroxylase 1, which forms a molecular complex with cyclophilin B, encoded by the cartilage-associated protein (CRTAP) and peptidyl prolyl isomerase B (PPIB). The *P3H1* is involved in the post-translational modification of collagen in the endoplasmic reticulum and prolyl 3-hydroxylation of specific proline residues (especially a1 (I) Pro986).^{5,6} So far, 48 different mutant *P3H1* alleles have been reported in patients with OI.⁷

Objectives

We describe 2 cases – of an 11-year-old female and a 9-year-old male – with a clinical presentation of severe OI, and identify a homozygous mutation in the 3rd exon of *P3H1* (c.628C>T/p.Arg210 Ter). Our cases broaden the phenotypic spectrum of OI type VIII as, to the best of our knowledge, these are the first postnatal cases with *P3H1* (c.628C>T/p.Arg210 Ter) mutations published in the literature.

Case reports

Case 1

The female patient was 11 years and 7 months of age at the time of the study. She was born from the first pregnancy of a 21-year-old mother. The mother and 27-year-old father of the child were first cousins, Turkish in origin, and had a height of 150 cm and 180 cm, respectively. Neither of the parents had a history of chronic illness or fracture. The patient was an only child, and the mother had no history of stillbirth or miscarriage. Moreover, there was no known familial history of OI or any other bone dysplasia.

The mother's pregnancy was followed up every 4–8 weeks starting from the 8th gestational week, and no maternal medical problems affecting pregnancy were found. She took prenatal vitamins regularly. The ultrasound

performed during the 12th gestational week revealed the fetus had curved and short legs. The amniotic fluid level was normal. The patient was born in the 39th gestational week via normal vaginal delivery without intervention. Her birth weight was 3020 g and height was 47 cm.

Her right upper arm was swollen, and leg movements were reduced on the 1st postnatal day. The patient was evaluated by orthopedic surgeons, and direct radiographic examination was performed. Fractures were detected in the right humeral diaphysis, right clavicle, distal aspect of both the femurs, right proximal tibia, right distal fibula, and left distal tibia. Spinal body fracture was not detected. Chronic changes were detected in the symmetrical, curved and weakened femurs and ribs, suggesting intrauterine fractures.

Pamidronate treatment at a dose of 9.0 mg/kg/year was initiated when the patient was 2 years of age. She underwent a total of 6 operations, 5 of which were for the fractures and 1 for scoliosis, and she has been followed up for the last 3 years, over which she did not sustain any new fractures. The latest bone mineral density (BMD) of the patient was –2.2 SDS (standard deviation score). During follow-up, her calcium, phosphorus and alkaline phosphatase levels were normal, and she was given vitamin D supplements to ensure that her 25-hydroxy vitamin D (25(OH)D) levels were within the normal range.

On physical examination, her height was –7 SDS and weight was –4.7 SDS, according to her age and sex. The patient had normal results for echocardiographic, urinary, hearing and dental examinations, and did not have blue sclera (Table 1). Both femurs had anterolateral curvatures. The patient was able to walk with the help of a walker. Radiographic examinations of the patient demonstrated severe osteopenia, thoracolumbar scoliosis, diaphyseal expansion in the distal humerus and proximal radioulnar metaphyses, trabeculae in the bones, and popcorn-like concentric concentrations (Fig. 1, 1a–f).

No mutation was found in *COL1A1*, *COL1A2*, *CRTAP*, and *SERPINH1* in the initial genetic analyses of the patient. Following the initial investigations, whole exome sequencing (WES) was performed using peripheral blood in the Microgen Genetic Diseases Diagnosis Center, Ankara, Turkey, and a homozygous nonsense mutation (c.628C>T/p.Arg210 Ter) was detected in the 3rd exon of *P3H1*. Mutations in *CRTAP*, *PPIB*, *FKBP10*, *SERPINF1*, *PLOD2*, *SERPINH1*, *SP7*, or *ALPL* were excluded using WES. The patient's mother and father were found to be heterozygous for the same mutation, based on the targeted mutation analyses.

Case 2

The male patient was 9 years and 3 months of age at the time of evaluation. He was born from the 2nd pregnancy of a 30-year-old mother, whose 1st child was a 10-year-old, healthy female at the time of the investigation.

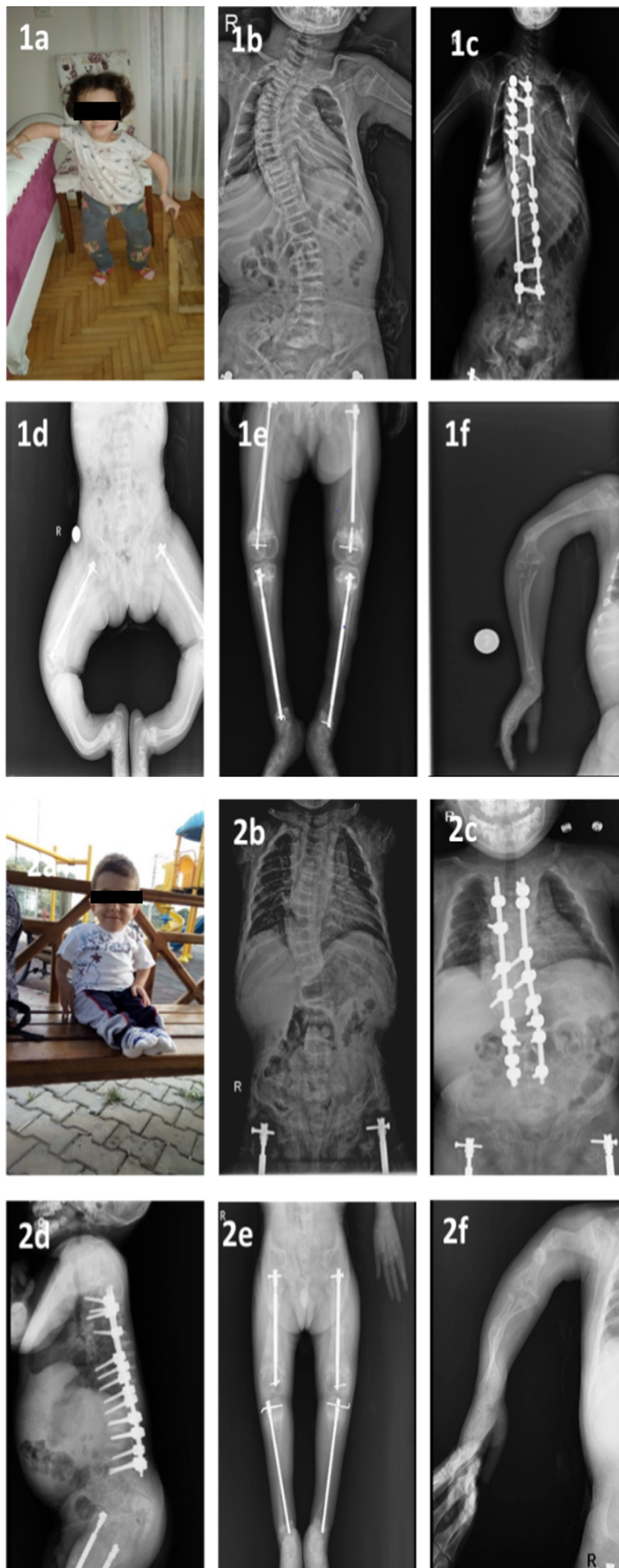


Fig. 1. Autosomal recessive osteogenesis imperfecta (OI) phenotype due to P3H1 mutations (clinical presentation and skeletal graphs). Severe scoliosis, asymmetry of the lower limbs, thin bones, and severe deformities in the femurs, tibias and fibulas were observed. 1a. Clinical pictures of case 1 (11 years and 7 months of age: walks and stands with assistance); 2a. Clinical pictures of case 2 (9 years and 3 months of age: walks and stands with assistance); 1b and 2b. Anteroposterior (AP) view of the thoracolumbar spine on radiography; 1c and 2c. The AP view of thoracolumbar scoliosis on a radiograph taken postoperatively; 1d. Bilateral tibia and fibula showing anterolateral curvatures; 2d. Lateral view of thoracolumbar scoliosis on a radiograph taken postoperatively; 1e and 2e. Postoperative radiographic images showing nailing and healing of the fracture; 1f and 2f. Severe deformities of the upper limbs. Informed consent was obtained from the patients prior to publishing these images

Table 1. Clinical features of the presented cases

Parameter	Case 1	Case 2
P3H1 (LEPRE1) mutation	(c.628C>T/p.Arg210 Ter)	(c.628C>T/p.Arg210 Ter)
Growth data		
birth	term, 3.2 kg	term, 2.8 kg
current age [years]	11	9
weight (SDS)	−4.7	−9
length (SDS)	−7	−6.6
Facial features		
facial shape	triangular	triangular
scleral hue	white	white
dentiogenesis imperfecta	no	no
Hearing loss	no	yes
Phenotype	severe OI, type B progressive	severe OI, type B progressive
Pulmonary functions	normal	moderate restrictive
Echocardiography	normal	normal
Spinal abnormalities	scoliosis, multiple T-L vertebral compression	scoliosis, multiple T-L vertebral compression
Rhizomelia	yes	yes
Bone mineral density score (pre- and post-biphosphonate therapy) (SDS)	−8.1 (pre-therapy) −2.2 (post-therapy)	−9.3 (pre-therapy) −3.7 (post-therapy)

OI – osteogenesis imperfecta; SDS – standard deviation score; T-L – thoracolumbar.

The mother and 35-year-old father were of Turkish origin, not related, and had a height of 157 cm and 175 cm, respectively. Neither of them had a history of chronic illness or fracture. Moreover, the mother had no history of still-birth or miscarriage, nor any known familial history of OI or other bone dysplasia.

The pregnancy was followed up every 4–8 weeks starting from the 6th gestational week, and no maternal medical problems that may affect the pregnancy were found. The mother took prenatal vitamins regularly. The fetus was found to have short legs during an ultrasound in the 12th gestational week. The amniotic fluid level was normal. The child was delivered via cesarean section in the 38th gestational week. His birth weight was 2850 g and height was 48 cm.

The patient had swollen arms and legs on the 1st post-natal day. Orthopedic surgeons evaluated the patient and direct radiographic examination was conducted. Fractures were detected in both, the distal femurs and humeri. Spinal body fractures were not detected.

Pamidronate treatment at a dose of 9.0 mg/kg/year was initiated when the patient was 2 years old. He underwent a total of 11 operations, 10 of which were for fractures and 1 was for scoliosis, and the patient has been followed up for the last 2.5 years, over which time he did not sustain any new fractures. The latest BMD of the patient was −3.7 SDS. During follow-up, the patient's calcium, phosphorus and alkaline phosphatase levels were normal, and vitamin D supplements were administered to ensure that his 25(OH)D levels were within the normal range.

On physical examination, the patient's height was −6.6 SDS and weight was −9 SDS, according to his age and sex. His echocardiographic and dental examinations were normal. However, conductive deafness in the right ear and bilateral nephrolithiasis were detected on the audiological and urinary examination, respectively. He did not have blue sclera, but had frequent pulmonary infections due to restrictive lung disease (Table 1). The patient was unable to walk because of his almost immobile legs. Severe osteopenia, thinning of long bones, marked appearance of epiphysis, and curvatures caused by multiple fractures were observed on radiographic examinations. The ribs were extremely thin and thoracolumbar scoliosis was also observed (Fig. 1,2a–f).

The *COL1A1*, *COL1A2*, *CRTAP*, and *SERPINH1* genes were excluded in the initial patient's 1st genetic analysis. Subsequent WES analyses of the patient demonstrated a homozygous pathogenic variant (c.628C>T/p.Arg210 Ter) in the 3rd exon of the *P3H1* gene (performed at the Microgen Genetic Diseases Diagnosis Center). Mutations in other genes, including *CRTAP*, *PPIB*, *FKBP10*, *SERPINF1*, *PLOD2*, *SERPINH1*, *SP7*, and *ALPL*, were excluded using WES. Sanger sequencing of parental DNA samples revealed that both parents were heterozygous for c.628C>T.

Method of genetic analyses

Whole exome sequencing was performed by Gene by Gene using Twist Bioscience technology (Microgen Genetic Diseases Diagnosis Center). Initially, ~36.5 Mb of consensus coding sequences (targeting >98% of RefSeq and Gencode

v. 28 regions obtained from the human genome) were replicated from fragmented genomic DNA using the Twist Human Core Exome Plus kit (Twist Bioscience, South San Francisco, USA). The subsequent library was then sequenced on the Illumina Novaseq NGS (Illumina, San Diego, USA) platform to achieve at least a $\times 20$ reading depth for $>98\%$ of the targeted bases. Variant annotations and filtering was performed using the Ingenuity Variant Analysis software (Qiagen, Hilden, Germany).

Discussion

The *P3H1* (c.628C>T/p.Arg210 Ter) was first reported by Willaert et al. in a consanguineous Turkish family.⁸ The mother had 2 pregnancies in which the fetuses were found to have genetic mutations, and elective termination was performed at the 20th and 18th gestational week, respectively. To the best of our knowledge, our cases are the first recorded postnatal cases of OI type VIII carrying homozygous *P3H1* (c.628C>T/p.Arg210 Ter) mutation.

The *P3H1* mutations typically have a clinical presentation of severe or fatal OI, and are characterized by rhizomelic short limb, white sclera, severe demineralization of bones, excessive growth retardation, intrauterine fractures, and bulbous expansion of metaphyses.⁴ Similar to typical *P3H1* mutations in literature, our cases also had considerably short stature, severe demineralization, white sclera, and fractures detected at birth. According to the Van Dijk and Sillence criteria, the 2 patients were classified into OI type B group with progressive deformation and severe OI group.⁹ Currently, Willaert et al. is the only publication to present cases with the same mutation.⁸ Their study reported a case of siblings who were electively aborted, and hence there was no data on postnatal physical examination findings. In addition, similar to their findings, intrauterine skeletal dysplasia-associated findings were detected in both of our cases.

Literature on pamidronate treatment in OI type VIII is limited. In a case published by Santana et al., pamidronate treatment was initiated at 7 weeks of age. Although the measurements were made using different equipment in different centers, a good response was obtained with $>300\%$ improvement.¹⁰ Takagi et al. also reported an OI type VIII case in which pamidronate treatment was started at 2 months of age. The patient developed very few fractures and presented a good response.⁵ In both of our cases, pamidronate treatment was started at ~ 2 years of age at a dose of 9.0 mg/kg/year. These patients, who were followed up in different clinics until they presented to our center, had a history of many fractures because of starting the treatment later than the previous cases. In their study, Willaert et al. reported a significant improvement in BMD Z-score (from -11.0 to -6.8) in an OI type VIII case of a six-year-old patient treated with pamidronate.⁸ When our patients presented to our center, their BMD Z-scores were -2.2 SDS and

-3.7 SDS for case 1 and case 2, respectively. This indicated that they responded well to the treatment. They were followed up and did not sustain any new fractures over the last 3 years.

The c.628C>T mutation in *P3H1* was identified as pathogenic.⁸ A significant decrease in *P3H1* mRNA was observed on evaluation of fibroblast samples from fetuses with this mutation, using quantitative polymerase chain reaction (qPCR), as expected with the degradation of mutant transcripts by the nonsense-mediated decay pathway. They found that mRNA expression in the patients' parents, who were heterozygous carriers of these nonsense *P3H1* mutations, was similar to that of the control group. The western blot analysis of fibroblast cell lysates probed with anti-*P3H1* antibody showed that *P3H1* was completely absent in patients and slightly decreased in their parents.

Interestingly, in the review from 2010, Marini et al. reported 17 mutant *P3H1* alleles occurring throughout the gene.⁶ Most of these mutations showed a loss of *P3H1* expression in real-time reverse transcription PCR (RT-PCR) with RNA isolated from the patients' fibroblasts.⁴ Mrosk et al., in their study on genotype–phenotype correlation, found 5 novel pathogenic variants in *P3H1* in 5 cases in an Indian OI cohort. Moreover, they observed a variant that was predicted to affect a donor splice site, resulting in a splicing alteration in another patient.¹¹ Scollo et al. reported a retinal tear in a 9-year-old OI type VIII case with a c.1914 + 1G>A (NM_001243246.1) homozygous mutation in *P3H1*.¹² Furthermore, de Souza et al. reported retinal detachment in a 28-year-old OI type VIII case with a similar mutation (c.1914 + 1G>C (NM_001243246.1)).¹³ However, fundoscopic examinations of our cases were found to be normal.

Fratzl-Zelman et al. performed the first study in the literature on the effect of null mutations in *P3H1* on the patient's bone tissue. They evaluated bone histology and histomorphometry, bone mineralization density distribution, and procollagen 3-hydroxylation measurements in bone and skin tissue in non-lethal OI type VIII.¹⁴ Although the bones sampled from these OI type VIII children resembled those of OI type VII, its distinctive features were bone matrix hypermineralization, extremely thin trabeculae, focal osteoid deposition, and an increase in the proportion of bone with low mineral density.

Li et al. found that *P3H1* mutations had a prevalence of 4.05% in an autosomal recessive OI Chinese cohort, and they reported 3 mutations, including 2 new mutations (c.652G>T; c.1948G>C, c.652G>T; c.2164C>T), and 1 previously reported mutation (c.1466T>C; c.1915-1G>A). The most common clinical manifestations were reported to be gait problems, scoliosis and frequent fractures (fractures ≥ 2 /year) in this autosomal recessive OI cohort, which was similar to our cases.¹⁵ Madhuri et al. found 2 new homozygous duplications in *P3H1* in an Indian OI cohort of 52 patients (c.2131dup (p.Leu711Profs*19) (SCV000987189) and c.1980dup (p.Val661Serfs*33) (SCV000987190)).¹⁶

Progressive deformities, blue sclera, recurrent long bone fractures, rhizomelia, scoliosis/kyphosis, vertebral compression fractures, and wormian bones have been reported in these children, which are similar to the findings in our cases. The researchers have also observed a previously reported variant (c.1346-1G>C) in 5 of their patients, and considered it a recurrent *P3H1* variant in India.

Pepin et al. examined 200 samples from an African population and a neonatal death record of a hospital in Tobago, and they found the prevalence of carriers of the c.1080 + 1G>T mutation in *P3H1* was approx. 1 in 200.¹⁷ During sequence analysis, they found a surprisingly high LEPRE1 allelic diversity in the DNA samples from Tobago. These findings suggested that the milder end of the clinical spectrum may be due to the as yet unidentified missense mutations in *P3H1*. Caudevilla Lafuente et al. reported 1 (fatal) homozygous case in which both parents were heterozygous carriers of the most common variant (c.1080 + 1G>T/IVS5 + 1G>T) in *P3H1* in West African populations.¹⁸ They also reported a case having a previously reported pathogenic heterozygous variant (c.1080 + 1G>T (i5) with c.35T>G (p.Leu12Arg) exon 1, *P3H1*-VUS and c.969C>T (p.Gly323Gly) exon 7, *SERPINF1* gene-VUS). However, this case exhibited a very severe, although nonfatal clinical course. Finally, Tonelli et al. found that the defective chaperone role of the 3-hydroxylation complex was the primary cause of the skeletal phenotype.¹⁹ However, Cabral et al. observed that the functions of the modification complex as a collagen chaperone are distinct from its role as prolyl 3-hydroxylase.²⁰

Limitations


Our study has several limitations. First, we only have 2 cases, although our findings may be useful in clinical practice. Second, we could not study in vivo or in vitro models, and hence, there is a need for further studies in this field.

Conclusions

In conclusion, we reported cases of OI type VIII from 2 unrelated families that are the first postnatal cases in which this mutation was detected, and they presented a more severe, but nonfatal spectrum of the clinical phenotype of this recessive form of OI.

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