CASE REPORT

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X-linked Osteoporosis due to PLS3 Pathogenic Variant: Case Report on Zoledronic Acid Treatment in Siblings

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ABSTRACT

Osteoporosis in children is a rare condition, often associated with genetic factors. Monogenic forms of osteoporosis linked to the X chromosome are often related to mutations in the gene encoding plastin 3 (PLS3). PLS3 is a protein involved in actin bundle formation in the cytoskeleton. We present two brothers with recurrent peripheral fractures and vertebral compression fractures, both associated with low bone mineral density (BMD). The patients shared the same deletion (c.589_590) in *PLS3* on Xq23, which was confirmed by next-generation sequencing. They were treated with zoledronic acid, calcium, and vitamin D, showing optimal improvement in BMD, a reduction in bone fractures, and enhanced quality of life.

Keywords: Bone diseases, Juvenile osteoporosis, PLS3, Zoledronic acid

What is already known on this topic?

Deficiency of PLS3 caused by pathogenic variants will lead to early-onset osteoporosis and bisphosphonate therapy has proven effective in reducing fracture recurrence.

What this study adds?

Our finding expanded the phenotypic spectrum, supporting the theory of scoliosis as a potential phenotype in the patients with PLS3 pathogenic variants.

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Introduction

Osteoporosis is a skeletal disorder characterized by reduced bone mass and impaired bone microarchitecture, leading to increased bone fragility and a higher risk of fractures (1). Pediatric osteoporosis is rare. The diagnosis is established when bone mineral density (BMD) is below a Z-score of -2, accompanied with a significant fracture history, defined as two or more long bone fractures before the age of 10 years, or three or more before the age of 19 years. Notably, the presence of vertebral compression fractures alone is sufficient for diagnosis, even if BMD is within the normal range (1).

Osteoporosis can be classified as primary or secondary. Primary forms are caused by genetic conditions (1), with osteogenesis imperfecta being the most common, occurring in approximately 1 in 15,000 to 20,000 births (2). Over the past decade, pathogenic variants in at least 20 different genes have been identified as potential causes of childhood-onset primary osteoporosis (1). In contrast, secondary osteoporosis is typically associated with chronic systemic diseases or long-term use of medications, such as extended glucocorticoid therapy (3).

X-linked osteoporosis due to pathogenic variants in the plastin 3 *(PLS3)* gene was first described in 2013 and remains an extremely rare condition, with an estimated prevalence of fewer than 1 in 1,000,000 individuals (1). The *PLS3* gene encodes plastin-3, an actin-bundling protein that plays a critical role in cytoskeletal dynamics and bone mineralization. Loss of *PLS3* function has been associated with increased bone fragility, reduced BMD, and recurrent fractures beginning in childhood (4).

Bisphosphonate therapy has demonstrated efficacy in improving BMD and reducing fracture incidence in individuals with X-linked osteoporosis caused by *PLS3* pathogenic variants. Clinical studies have shown significant increases in BMD and vertebral body remodeling after 10 months to 2 years of treatment. Early diagnosis and timely intervention are essential to alter the disease course and prevent progression of osteoporosis (4,5,6).

We report two cases of X-linked osteoporosis caused by a *PLS*3 deletion (c.589_590) on Xq23, confirmed through next-generation sequencing. Both patients were treated with zoledronic acid, calcium, and vitamin D, resulting in marked improvement in BMD, reduced incidence of fractures, and enhanced quality of life.

Case Report

Patient 1

A 12-year-old boy was referred to pediatric endocrinology due to multiple fractures resulting from mild trauma. His first fracture occurred at age 3 years, involving the left elbow, after falling from a tricycle. At age 5 years, he fractured his left humerus after falling from standing height. A third fracture occurred at age 8 years, affecting the right scapula after a collision with a friend while playing. Subsequently, he fractured his left wrist at 10 years old and experienced another fracture of the left humerus at 11 years of age, again due to low-impact trauma.

No complications were noted during birth. He was born at term with appropriate neonatal adaptation, a birth weight of 3500 grams, and a birth length of 51 cm. There is no history of hypoglycemia or jaundice. The patient's neurodevelopment was normal. The mother's height is 177 cm, and the father's height is 172 cm. Accordingly, the mid-parental target height was calculated at 181 cm, with a target height range of 176-186 cm, which corresponds approximately to ±1.9 standard deviation (SD) according to the Colombian C3REF growth reference (5).

On physical examination, all the vital signs were within normal limits. There were no signs of blue sclerae, tooth abnormalities or hypermobility. Anthropometric evaluation showed a weight of 88.6 kg, a height of 178 cm (1.9 SD; C3REF), and a body mass index (BMI) of 27.96 kg/m^2 (+2.32 SD; OMS). Body proportions were harmonious, with no evidence of disproportion (normal upper/lower segment ratio and arm span for height, where assessed). Pubertal evaluation revealed Tanner stage G4P4, with a testicular volume of 15 mL. A notable finding was scoliosis on musculoskeletal examinations. Other systems were unremarkable.

Studies to rule out secondary causes of osteoporosis were performed and yielded normal results, as summarized in Table 1. The evaluation excluded renal and parathyroid disorders, thyroid dysfunction, glucocorticoid excess, hypogonadism, growth hormone deficiency, homocysteinuria, and chromosomal abnormalities, supporting a diagnosis of primary osteoporosis.

Renal and urinary tract ultrasound was normal, and the spine X-ray showed a left-convex scoliotic deviation at T12 and L4 of 18 degrees and at T6 and T22 of 11 degrees with a convexity of 9 degrees. Molecular analysis via clinical exome sequencing identified a hemizygous frameshift variant in the *PLS3* gene: NM_005032.5:c.589_590delTT (p.Leu197GlufsTer39). This variant consists of a two-nucleotide deletion (TT) in exon 6, resulting in a premature stop codon 39 amino acids downstream from the leucine at position 197. The predicted outcome is a truncated protein or, alternatively, non-sense-mediated mRNA decay, aligning with loss-of-function as a disease mechanism in *PLS3*-related disorders.

The variant was classified as likely pathogenic according to the American College of Medical Genetics and Association for Molecular Pathology 2015 guidelines, based on the following criteria: PVS1, indicating null variant in a gene where loss of

Table 1. Biochemical work-up of the two reported cases to rule out secondary osteoporosis

Laboratory test	Reference value	Patient #1	Patient #2
Ionized calcium (mmol/L)	1.24-1.39	1.216	1.3
Phosphorus (mg/dL)	4.1-5.9	5.68	5.78
25-hydroxyvitamin D (ng/mL)	>30	20.9	23
Parathyroid hormone (pg/mL)	10-65	29.3	-
Alkaline phosphatase (UI/L)	141-460	411	-
Karyotype	-	46,XY	-
Homocysteine (umol/L)	12 -15	6.96	6.26
Thyroid-stimulating hormone (uUI/ml)	0.51-5.5	0.67	
Insulin-like growth factor 1 (ng/mL)	99-655	580.08	-
Cortisol (ug/dL)	5-23	5.79	-
Follicle stimulating hormone (mUI/mL)	1,5-12,4	3.06	-
Luteinizing hormone (mUI/mL)	1,7-8,6	4.02	-
Total testosterone (ng/mL)	0.28-11.1	2.91	-
Sodium (mmol/L)	135-148	141.6	-
Urinary calcium (mg/24 h)	100-300	75.4	-
BUN (mg/dL)	5.0-18.0	9.1	-
Creatinine (mg/dL)	0.67-1.17	0.63	0.47

BUN: Blood urea nitrogen

function is a known disease mechanism; and PM2, reflecting its absence from population databases. *In silico* predictive tools further support a deleterious effect, assigning a pathogenicity score of 1.0 (on a scale from 0 to 1), as calculated by two independent algorithms. Although this variant has not been previously associated with clinical phenotypes in the extant literature, the established pathogenicity criteria, corroborating *in silico* predictions, and the patient's clinical presentation collectively support and confirm the diagnosis.

Initial management included calcium supplementation and optimization of vitamin D levels while awaiting completion of the etiological evaluation. Nutritional counseling and exercise recommendations were initiated to optimize weight control and prevent progression of overweight. The first bone densitometry was performed at age 14 years and showed normal results. Since the patient had not experienced any new fractures, clinical follow-up with serial densitometry was pursued. However, over the next two years, a progressive decline in the Z-score was noted. At 16 years old, a third densitometry revealed a BMD Z-score of -0.5 SD in total body less head and -2.4 SD in the lumbar spine (L1-L4), as shown in Table 2**.** Given these findings bisphosphonate therapy was initiated to improve BMD, reduce fracture risk and enhance quality of life.

Intravenous zoledronic acid therapy (0.05 mg/kg/dose) was initiated, administered every six months. No adverse effects related to the medication were reported. After two doses, equivalent to one year of treatment, follow-up bone densitometry showed marked improvement in the BMD Z-scores (Table 2). During follow-up, the patient remained fracture-free, adhered well to treatment, and achieved a final height of 185.5 cm, weight of 85 kg, and BMI of 24.7 kg/m^2.

Table 2. Evolution of bone mineral density (Z-scores) in the two patients, pre- and post-zoledronic acid therapy

Patient	Age (years)	Total body less head (Z-score)	Lumbar spine L1-L4 (Z-score)	Therapy status*
#1	14	0.0	-1.5	Before
	15	-0.8	-1.4	Before
	16	-0.5	-2.4	Before
	17	-0.3	-1.5	After
#2	11	-2.0	-2.7	Before
	13	-0.5	-0.2	After

*: Therapy status refers to bisphosphonate treatment (zoledronate). Both patients showed substantial improvement in lumbar spine and total body BMD Z-scores after therapy, BMD: bone mineral density

Patient 2

This patient is the younger brother of Patient 1. A 10-year-old male patient was referred to pediatric endocrinology for evaluation of secondary hyperthyroidism due to Graves disease, confirmed by the presence of thyroid-stimulating hormone (TSH) receptor antibodies, and was managed with methimazole. He also had a history of recurrent fractures beginning in early childhood. Aged 3 years, he sustained an elbow fracture, followed by right and left cubitus fractures at ages 8 and 9 years, respectively. When he was 10 years old, he presented with a one-month history of severe lumbar pain. Radiographic evaluation revealed a compression fracture at T12, as well as anterior wedging of 50% at T9 and 20% at L4 (Figure 1). Although the exact mechanisms of injury were not documented, the absence of high-energy trauma suggests a fragility-related cause.

The patient weighed 51 kg and was 155.3 cm tall, corresponding to +1.77 SD; C3REF. His BMI was 21.15 kg/m^2 (+1.68 SD; OMS). Physical examination was unremarkable and showed no dysmorphic features, except for scoliosis. Pubertal assessment revealed Tanner stage G2 for genital development and P2 for pubic hair, with a testicular volume of approximately 6 mL. Biochemical evaluation of phosphocalcic metabolism revealed low serum vitamin D levels, prompting initiation of vitamin D supplementation (Table 1). Nutritional recommendations initially provided to his sibling were extended to Patient 2. However, the initiation of regular exercise was initially constrained by underlying vertebral pathology. Given the known familial mutation, targeted analysis next-generation sequencing identified the same pathogenic *PLS3* c.589_590del variant.

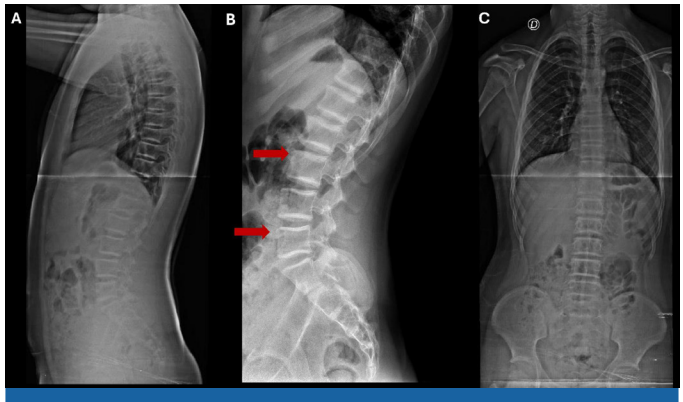

Figure 1. Lateral spine X-ray images of Patient #2 (Panels A and B) prior to treatment show the following findings. (A) Thoracic spine: generalized decrease in bone mineral density. A moderate anterior wedge compression fracture is evident at the level of T9 (arrow). (B) Lumbar spine: diffuse reduction in vertebral radiopacity, also suggestive of decreased bone mineral content. The L4 vertebral body demonstrates a mild reduction in anterior height with a subtle wedge-shaped deformity suggestive of a compression fracture (arrowhead). (C) Anteroposterior radiograph of the thoracolumbar spine showing mild right-convex thoracic scoliosis with compensatory lumbar curvature. Note the subtle anterior height loss and wedge-shaped deformity of the L4 vertebral body (red ellipse)

The first bone densitometry was performed at the age of 11 years and showed abnormal Z-scores for both total body less head and the lumbar spine (L1-L4) (Table 2). The patient was started on intravenous zoledronic acid (0.05 mg/kg/dose). The initial infusion was associated with a mild rash and transient flu-like symptoms, known side-effects of initial zoledronic acid infusion. As expected, subsequent infusions (dose 0.05 mg/kg/dose) were well tolerated without adverse events.

After four doses of zoledronic acid, marked improvement in BMD was observed, with significant increases in Z-scores at both the lumbar spine (L1-L4) and total body less head (Table 2). These improvements were also evident on radiographic follow-up of the vertebral fractures, as described in Figure 2.

Given the trend toward improvement in Z-scores, future doses are scheduled to be reduced to 0.025 mg/kg/dose. Throughout clinical follow-up, the patient has remained fracture-free and has shown continued adherence to and tolerance of bisphosphonate therapy. He was in spontaneous remission of Graves' disease, with negative TSH receptor antibodies and normal thyroid function, having been off methimazole for eight months. At the most recent evaluation, at 13 years of age, his height was 174 cm, with a testicular volume of 15 mL and a bone age of 15 years; his BMI improved to 21.8 kg/m^2 (+0.65 SD, World Health Organization) during follow-up, coinciding with the initiation of regular physical activity.

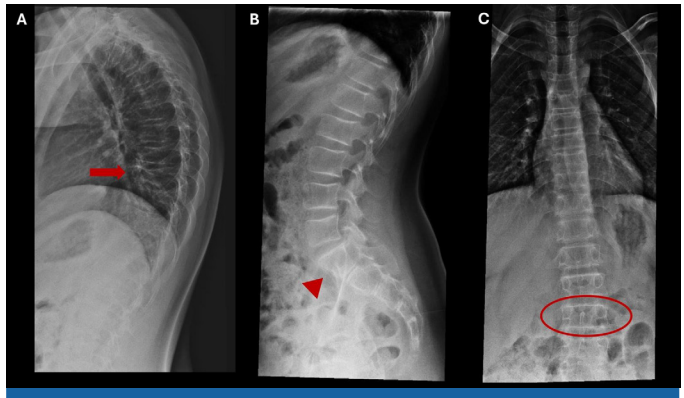

Figure 2. Lateral radiograph (A and B) of the thoracolumbar spine following four doses of zoledronic acid in Patient 2, showing improved bone mineral density and partial restoration of T9 vertebral body height. Diffuse sclerotic lines are observed across multiple vertebral bodies (arrow), consistent with increased bone remodeling activity. Vertebral body contours are well defined, and no new fractures are evident. (C) Anteroposterior radiograph of the spine shows reduction of the previously observed scoliotic curvature

Following confirmation of the diagnosis and in view of the X-linked inheritance pattern, a bone densitometry was performed on the patient`s mother at age 50, showing normal results: lumbar spine (L1-L4) T-score -0.9, BMD 1.073 g/cm^2, and left femoral neck T-score -0.5, BMD 0.962 g/cm^2. Her only relevant history was Graves' disease treated with radioiodine ablation, and she remains euthyroid under levothyroxine replacement. At her current age of 53 years, she has not sustained fractures, spinal radiographs (Figure 3) were normal, and physical examination was unremarkable. Segregation analysis is currently ongoing, and the broader family history is summarized in the pedigree (Figure 3).

Discussion

Various *PLS3* gene variants have been described. Here, we report the cases of two brothers presenting with osteoporosis in hemizygous male affected, manifested by long bone and vertebral compression fractures. A novel hemizygous frameshift variant, NM_005032.5:c.589_590delTT (p.Leu197GlufsTer39), was identified. This variant introduces a premature stop codon 39 amino acids downstream from the leucine at position 197, leading to a truncated protein or non-sense-mediated mRNA decay, and has not been previously reported in the literature.

Consistent with previously reported cohorts, both patients exhibited normal growth and neurodevelopment, and lacked classical extra-skeletal features of osteogenesis imperfecta, such as blue sclerae, dentinogenesis imperfecta, or hearing loss (4). The only notable clinical finding in these siblings was scoliosis, which has also been reported in other patients with *PLS3* mutations. In our experience, scoliosis improved with bisphosphonate therapy, possibly due to vertebral stabilization and reshaping linked to increased BMD (3).

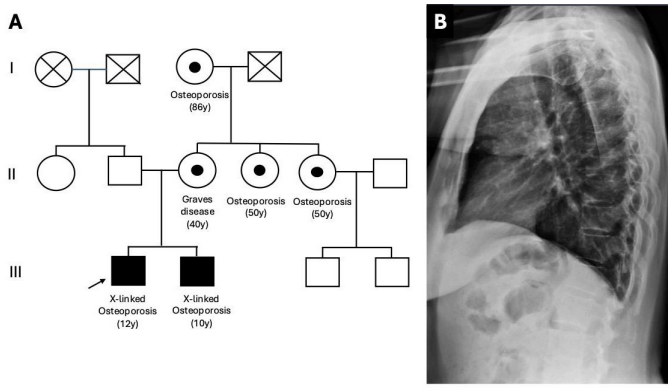

Figure 3. Clinical and radiographic findings in a family with *PLS3*-associated X-linked osteoporosis. (A) Pedigree showing the segregation of the pathogenic *PLS3* variant consistent with X-linked inheritance. (B) Lateral spine radiograph of the mother at age 53 years, showing no evidence of vertebral fractures

Although most patients with PLS3-related osteoporosis do not exhibit extra-skeletal findings, some reports have described variable features, such as pectus excavatum, flat feet, broad and short thumbs, bilateral syndactyly of digits 4-5, and gait disturbances including waddling or clumsiness (7). The reason for this variability remains unclear. It is possible that PLS3 may have a broader role in collagen metabolism or extracellular matrix composition, as similar features have been reported in unrelated individuals with different *PLS3* variants (3,5,7,8).

Heterozygous females carrying *PLS3* variants are generally reported to present with a mild and variable phenotype, most often characterized by normal BMD and absence of fractures, although some cases show reduced bone mass at peripheral sites or skeletal fragility (3,4). No consistent genotype-phenotype correlation has been established, and progression appears to be more strongly associated with age and the degree of BMD reduction than with the specific mutation (3). In the family in our report, the mother, a heterozygous carrier, exhibited normal BMD, no fractures, and no significant clinical findings at 53 years of age, which contrasts with maternal aunts who were diagnosed with osteoporosis around the age of 50 years. This intrafamilial variability illustrates the wide spectrum of phenotypes in heterozygous females, ranging from completely asymptomatic to clinically significant osteoporosis. Taken together, these findings reinforce the suggestion that additional modifiers, including age, hormonal and metabolic factors, and lifestyle, play an important role in shaping bone health in female carriers and highlight the need for individualized longitudinal follow-up, even in apparently unaffected women (3,4).

Optimizing bone health requires a multifaceted approach, including sufficient nutritional intake, regular weight-bearing exercise, and targeted treatment of the underlying condition contributing to skeletal fragility (8). Both of the siblings in this report presented with BMI values above the 95th percentile, highlighting the need to critically evaluate the potential contribution of overweight/obesity to their skeletal phenotype. Although obesity in childhood is often associated with higher absolute BMD values, this increase is not proportional to the greater body mass, resulting in insufficient mineralization to support the excess load and a paradoxical increase in fracture risk (6,7). In Patient 1, insulin-like growth factor-1 and testosterone levels were within the normal range, indicating that endocrine alterations commonly described in obese boys were unlikely to explain the skeletal fragility (6,7). These findings reinforce the suggestion that obesity is not uniformly protective for bone health and, in fact, may act as a confounding factor in the interpretation of densitometry results, particularly in patients with an underlying genetic predisposition, such as the *PLS3* variant.

Bisphosphonates, synthetic analogs of pyrophosphate, are the most extensively studied pharmacologic agents for pediatric osteoporosis. Due to the rarity of this condition, however, clinical trials in pediatric populations remain limited (8). Zoledronic acid, a nitrogen-containing bisphosphonate, inhibits osteoclastic activity by binding to bone hydroxyapatite, thereby reducing bone turnover and preserving skeletal integrity. Clinical trials have shown significant improvements in vertebral body height in patients treated with intravenous bisphosphonates compared to oral formulations (8).

Several studies on patients with *PLS3* mutations have confirmed the effectiveness of bisphosphonate therapy, indicating that younger children may derive greater benefit, likely due to the accelerated accrual of bone mass during these critical developmental stages (4). In Patient 1, although BMD initially improved during adolescence but then declined rapidly, prompting the need for bisphosphonate treatment. This illustrates the importance of early bone densitometry screening and timely intervention to maximize peak bone mass in affected individuals. Both patients exhibited marked improvements in BMD Z-scores after one year of zoledronic acid therapy, reinforcing the value of early diagnosis and initiation of treatment (9).

Advances in molecular diagnostics have significantly improved our ability to identify osteoporosis of genetic origin, particularly in patients where secondary causes and more common primary etiologies, such as osteogenesis imperfecta, have been excluded. Early recognition of clinical signs, such as recurrent low-impact fractures and vertebral deformities, should prompt timely genetic evaluation. Early genetic diagnosis not only facilitates appropriate clinical management but also enables targeted family screening, which is important in X-linked conditions, such as *PLS3*-related osteoporosis. Patients should be closely monitored for early vertebral collapse, and any underlying mineral or hormonal deficiencies should be addressed. Encouraging physical activity and initiating bisphosphonate therapy, when indicated, can positively impact bone health and reduce fracture risk. Continued research into pharmacologic strategies for managing genetically driven osteoporosis remains key to optimizing long-term outcomes.

Ethics

Informed Consent: Informed consent was obtained for the use of patients' medical history and images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: María Camila Velandia-Avendaño, María Paula Sarmiento-Ramón, Concept: María Camila Velandia-Avendaño, María Paula Sarmiento-Ramón, Design: María Camila Velandia-Avendaño, Data Collection or Processing: María Paula Sarmiento-Ramón, Analysis or Interpretation: María Camila Velandia-Avendaño, María Paula Sarmiento-Ramón, Literature Search: María Camila Velandia-Avendaño, María Paula Sarmiento-Ramón, Writing: María Camila Velandia-Avendaño.

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