Clinical Images and Case Reports Journal

Case Report | Vol 8 Iss 3

X-Linked Hypophosphatemic Rickets: A Report of Three Sisters with a Variant in the PHEX Gene with Healthy Parents, One of Them with Two Affected Children

María Beatriz Barrios Escobar[1,4], Hernando Vargas-Uricoechea[2*], Andrea Ramos Díaz[3], Hernán Darío Oviedo Ramos[3] and Alejandro Castellanos Pinedo[3,4]

[1]Universidad del Sinú, Montería 230001, Colombia

[2]Metabolic Diseases Study Group, Department of Internal Medicine, Universidad del Cauca, Carrera 6 No. 13N-50, Popayán 190001, Colombia

[3]Hospital San Jerónimo, Montería 230001, Colombia

[4]Faculty of Medicine, Universidad del Sinú, Hospital San Jerónimo, Montería 230001, Colombia

[*]**Corresponding author:** Hernando Vargas-Uricoechea; Metabolic Diseases Study Group, Department of Internal Medicine, Universidad del Cauca-Colombia. E-mail: hernandovargas@unicauca.edu.co

Received: May 02, 2026; **Accepted:** May 19, 2026; **Published:** June 05, 2026

Abstract

We describe three clinical cases of sisters with X-linked hypophospha-temia (XLH), due to a pathogenic variant in the PHEX gene, born to healthy parents with no genetic findings. One sister has two children affected at an early age, with the same mutation. All three presented with bone symptoms from childhood and did not receive specific treatment. The report emphasizes the importance of early diagnosis, family study, and a multidisciplinary approach in rare inherited disorders of calcium and phosphorus metabolism.

Keywords: X-linked hypophosphatemia; PHEX gene; Hypophosphatemic rickets; X-linked dominant inheritance

Introduction

X-linked hypophosphatemia (X-HL) occurs due to mutations that inactivate the PHEX gene (analog of X-linked phosphate regulating endopeptidase). This gene produces a zinc-dependent metalloproteinase of the M13 family, found primarily in osteoblasts and odontoblasts and, though to a lesser extent, in the lungs, ovaries, testes, and parathyroid glands. Its main function is to regulate the degradation of fibroblast growth factor 23 (FGF-23) [1].

It has a worldwide incidence of 1 in 20,000 births [1,2]. Approximately 20-30% of cases are due to a de novo mutation, meaning there is no family history of the disease [3].

Affected children present with rickets, bone deformities, reduced growth curve, short final height, and dentin defects [1]. Radiographs of the long bones of pediatric patients show decreas-ed mineralization amidst thick sclerotic trabeculae, metaphyseal widen-ing, and bowing of the legs [4]. On the other hand, adults experience osteomalacia, dental abscesses, and forms of ectopic mineralization [1].

Treatment is based on phosphorus supplementation, (40-100 mg/kg/-day), calcitriol (15-60 ng/kg/day, and more recently, Burosumab (a recombinant human immunoglobulin that antagonizes the effects of FGF-23). Burosumab shows promising results in this condition and could be a safe and clinically useful treatment for patients with FGF-23-related hypophosphatemic diseases. This finding could lay the groundwork for establishing a single-agent therapy [5].

Case Presentation

We present the cases of a family residing in a dispersed rural area, con-sisting of healthy parents who had five children: three daughters diag-nosed with X-linked hypophosphatemia, carriers of a PHEX variant iden-tified by genetic testing, and two sons who remain asymptomatic (Figure 1).

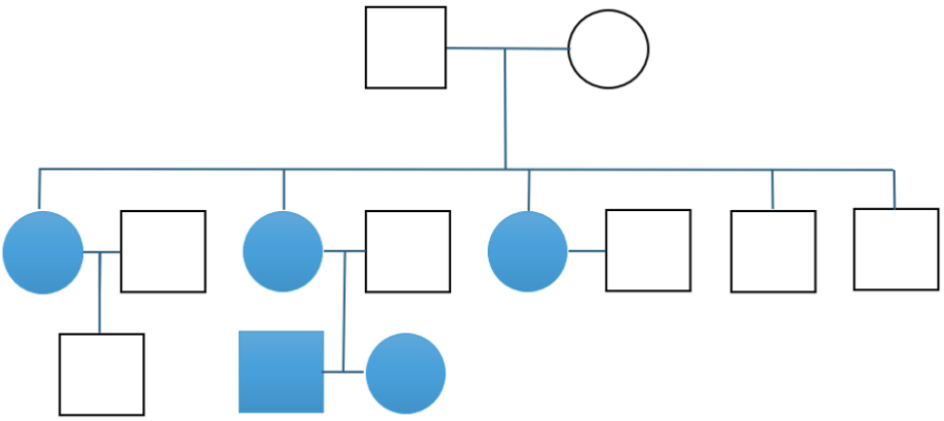
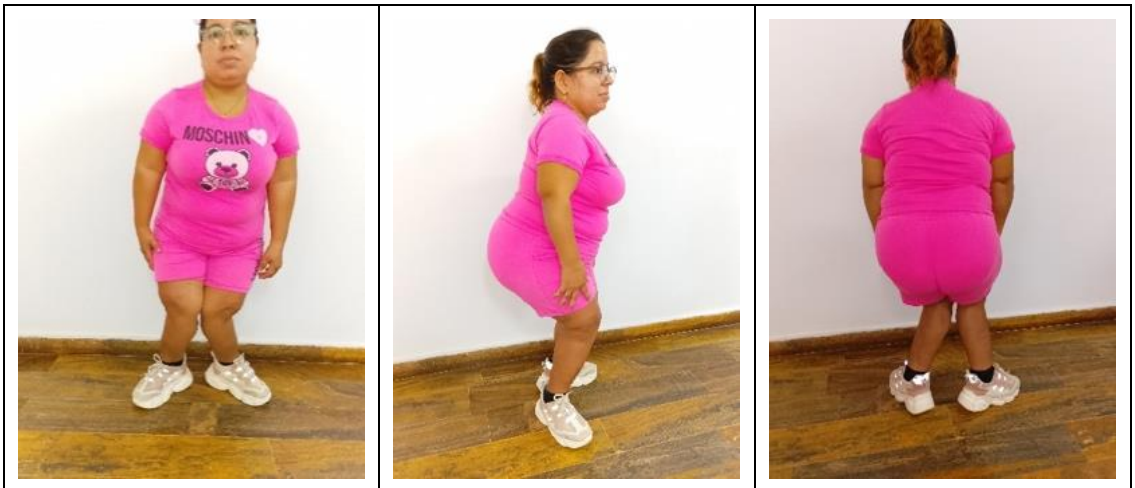


Figure 1: Family Pedigree.

Case 1

A 31-year-old female, born at term to healthy parents, presented with no clinical manifestations until age 4, when she began experiencing progressive valgus deformity in her lower limbs. She did not receive spe-cific treatment. Currently, she presents with pathological short stature, constant leg pain, and functional limitations. Genetic testing confirmed a variant in the PHEX gene. Table 1 summarizes the laboratory results.



1A **1B** **1C**

Figure 1 (A-C): Clinical images of Case 1.

Case 2

A 28-year-old female, sister of the previously described case (Case 1) and second daughter in the family. At birth, she presented no evident pathological findings; however, in early childhood, she began experien-cing symptoms characterized by pain in her lower extremities and pro-gressive development of bone deformities. To date, she has not received any specific treatment or supplementation. Laboratory results are summarized in Table 1.

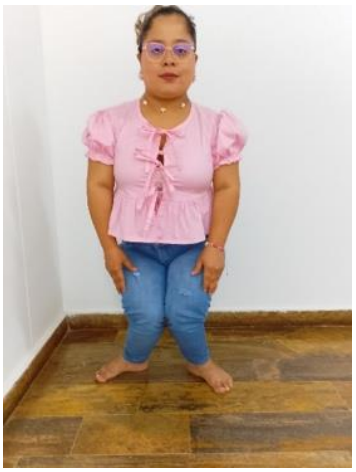
She is the mother of two children (a 7-year-old girl and a 5-year-old boy) who present with limb deformities, a history of recent fractures, and a positive genetic diagnosis for a mutation in the PHEX gene. The clinical management of both will be detailed in clinical cases 4 and 5.

2A **2B** **2C**

Figures 2 (A-C): Clinical images of Case 2.

Case 3

A 26-year-old woman, the third sister of the previous cases. She was asymptomatic at birth; however, at age six she began to exhibit short stature and a progressive valgus deformity.



3A

3B

3C

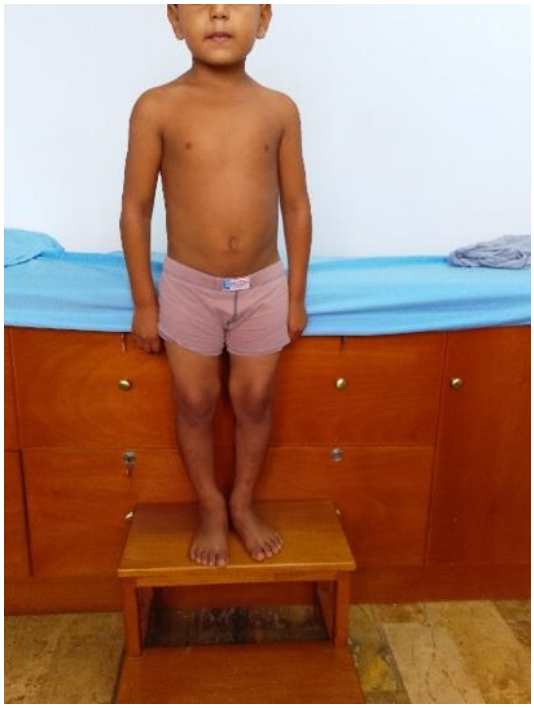
Figures 3 (A-C): Clinical Images of Case 3.

Her genetic testing revealed a variant in PHEX. She has not received treatment and has no children. The results are reported in Table 1.

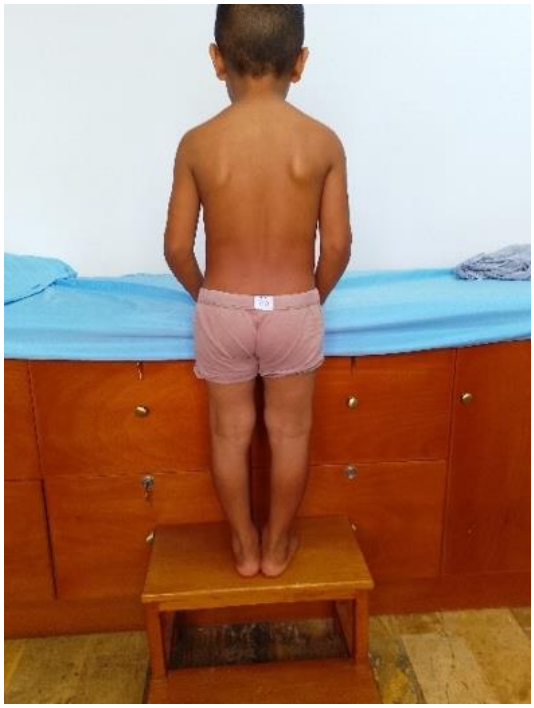
Table 1: Laboratory results (all cases).

Laboratory results	Case 1	Case 2	Case 3	Case 4	Case 5
Vitamin D	35 ng/mL	35 ng/mL	23 ng/mL		19.3 ng/mL
PTH	40 pg/mL	40 pg/mL	48.7 pg/mL		81.9 pg/mL
Creatinine	0.55 mg/dL	0.37 mg/dL	0.50 mg/dL		0.45 mg/dL
Serum phosphorus	1.99 mg/dL	1.99 mg/dL	1.82 mg/dL		2.9 mg/dL
Urinary phosphorus	11.4 mg/dL	1.44 mg/dL			117.45 mg/dL
Serum calcium	1.10 mmol/L	1.26 mmol/L	1.39 mmol/L		10.12

The following are details about both sick children, who are descendants of case 2.



4A



4B

Figures 4 (A-B): Clinical Images of Case 4.

Case 4

A 9-year-old male patient, genetically diagnosed with hypophosphatemic rickets. Genetic testing revealed homozygosity for the PHEX gene. The patient has been treated with Borosumab since the age of 5 and currently presents with short stature and varus deformity.

Case 5

A 6-year-old female patient presented with valgus deformity at age 3. Genetic testing revealed a variant in PHEX. She received Borosu-mab for 2 years, but after a 4-month suspension, she suffered a fracture of her right lower limb.

5A

5B

Figures 5 (A-B): Clinical images of Case 5.

Discussion

Rickets is characterized by an alteration in the normal mineralization of bone tissue and, depending on the cause, is classified into acquired or hereditary forms [2]. Hypophosphatemic rickets comprises a group of inherited disorders, most notably X-linked hypophosphatemic rickets (XLR). X-linked hypophosphatemia (XLR) is caused by mutations that inactivate the PHEX gene (phosphate regulating endopeptidase analog, X- linked). Approximately 460 mutational variants have been documented, of which about 20% may occur spontaneously [1]. In the family analyzed in this case, no family history of clinical manifestations or previous genetic diagnoses were identified, indicating a de novo mutation which may be inherited, as observed in the offspring of patient in case 2.

The loss-of-function mutation of the PHEX gene (3' end deletion) leads to increased FGF-23 production. FGF-23 inhibits the transcription of 1-alpha hydroxylase and is also a phosphaturic hormone that requires the cofac-tor Klotho. PHEX endopeptidases (from Phosphate), regulating gene with Homologies to Endopeptidases on X chromosome and DMP1, control blood levels of FGF-23. This explains the clinical manifestations of growth retardation and of rickets [5].

The diagnosis of RHLX is initially based on clinical suspicion, which arises from the physical examination, where signs compatible with alterations in bone mineralization are detected [6]. This clinical evaluation is complemented by the identification of decreased serum phosphorus in laboratory tests, as well as alterations in the levels of calcium, vitamin D and parathyroid hormone (PTH) [2].

Furthermore, the diagnostic support is reinforced by radiographic evidence of abnormalities in the long bones, characteristics that point toward the diagnosis of hypophosphatemic rickets. Radiologically, there is a loss of definition and sharpness of the distal metaphyseal line with fraying or "unraveling", and pseudo fractures on the lateral aspect of both femurs. Associated with hypophosphatemia, a decrease in TRP and TMP /GRF is observed [1,2]. Definitive confirmation of RHLX is made by detecting pathological variants in the PHEX gene (phosphate regulating endopeptidase analog, X-linked). Identifying a pathogenic variant through genetic testing allows for molecular diagnosis, which is fundamental for therapeutic approaches and family genetic counseling [2].

In summary, the diagnosis of RHLX is made through clinical evaluation, identifying hypophosphatemia, phosphaturia, and radiological findings consistent with rickets, while confirmation is obtained through the detection of a pathogenic variant in the PHEX gene by molecular testing. Early detection and timely initiation of treatment are essential to optimize the patient's prognosis and quality of life [7].

The therapeutic approach for patients with X-linked hypophosphatemic rickets is primarily based on pharmacological supplementation aimed at correcting hypophosphatemia and its clinical sequelae. Traditionally, treatment has consisted of administering oral phosphorus at doses of 40 to 100 mg/kg/day, supplemented with calcitriol at a dose of 15 to 60 ng/kg/day. These measures aim to promote bone mineralization and alleviate the symptoms, resulting from phosphorus deficiency and impaired vitamin D metabolism [5].

In recent years, an innovative biological therapy has been incorporated: Burosumab, a recombinant human immunoglobulin that acts as an antagonist of FGF-23, a key protein in the pathophysiology of this disease. The use of burosumab represents a significant advance, since by inhibiting FGF-23, renal phosphorus reabsorption is improved, resulting in increased serum concentrations of this mineral and the activation of vitamin D [2,8].

In April 2018, the Food and Drug Administration of the United States (FDA) approved the use of a monoclonal antibody (KRN23-Burosumab), targeting FGF-23. That same year, both the European Medicines Agency (EMA) and the FDA extended the approval of burosumab for use in children over six months of age, who showed evidence of moderate to severe rickets, whether in patients who had not received prior treatment or in those with an insufficient response to conventional therapies [2,8]. The recommended starting dose for burosumab depends on the patient's weight: 1 mg/kg if the weight is less than 10 kg and 0.8 mg/kg if it is greater than 10 kg, with a maximum dose of 90 mg. It is administered subcutaneously every two weeks, and the dose may be adjusted as needed to achieve normal serum phosphorus levels.

To date, clinical trials have demonstrated that burosumab has a favorable safety and efficacy profile, showing improvements in linear growth, physical function, and a reduction in both pain and the severity of rickets. Therefore, it is currently considered a key alternative within the management algorithm for patients with X-linked hypophosphatemic rickets [1,8,9].

Even in our country- Colombia- the monoclonal antibody against FGF-23 is not registered with the health system, but it can be imported as a vital medicine that is not readily available, as regulated by Decree 481 of 2004 from INVIMA (National Institute for Food and Drug Surveillance). Approval has been obtained for the use of this newer and more effective therapy compared to traditional treatments [10].

Monitoring patients undergoing treatment for X-linked hypophospha-temic rickets requires periodic evaluation of various biochemical para-meters. Regular monitoring of serum and urine calcium, phosphorus, and creatinine levels is essential to assess metabolic and renal status through-out the course of treatment [2].

Furthermore, alkaline phosphatase is a useful marker for monitoring treatment response. This enzyme is typically elevated before the start of therapy, reflecting increased osteoblastic activity and the bone changes characteristic of the disease. As treatment progresses, alkaline phosphatase levels tend to decrease, which is associated with the improvement of bone lesions and the recovery of the mineralization process [2].

Conclusion

Cases were documented within a family affected by X-linked hypophos-phatemia, in which the mutation in the PHEX gene was confirmed, as well as the presence of a de novo mutation. This finding underscores the importance of performing familial genetic diagnosis, not only to identify the underlying cause of the disease, but also to appropriately guide both the clinical follow-up of at-risk relatives and targeted genetic counseling for the family. The lack of treatment for affected adults highlights the need to strengthen medical education about this condition and to establish early detection programs. These measures would improve access to early diagnosis and, consequently, optimize patient management and prognosis.

Finally, the advances achieved with the introduction of the monoclonal antibody are highlighted, which have shown favorable results and repre-sent an important step forward in the therapeutic approach to the disease.

REFERENCES

1. Guerrero-Tinoco GA, García-Bermejo R, Cardona-Orozco EJ. X-linked hypophosphatemic rickets: A diagnostic and therapeutic challenge. Iatreia. 2021; 34: 280-285.
2. Tascón Arcila JA, Baquero Rodríguez MC, Serrano Gayubo AK, et al. X-Linked Hypophosphatemia: A case report. Revista Ciencias de la Salud. 2024; 22.
3. Forero-Delgadillo JM, Cleves D, Ochoa V, et al. Phex gene mutation in a patient with x-linked hypophosphatemic rickets in a developing country. Application of Clinical Genetics. 2020; 13: 57-62.
4. Bitzan M, Goodyer PR. Hypophosphatemic Rickets. Pediatr Clin North Am. 2019; 66: 179-207.
5. Rabanal CL, Gambini JP. Familial X-chromosome linked hypophosphatemic rickets: Report of a case. Acta Medica Peruana. 2023; 40: 76-79.
6. López-Romero LC, Broseta JJ, Guillén Olmos E, et al. Raquitismo hipofosfatémico ligado al cromosoma X: diagnóstico en la edad adulta y forma paucisintomática. Reumatol Clin. 2021; 17: 116-117.
7. García Vázquez SC, González Polán L, Fernández Sánchez M. Valoración de la calidad de vida de pacientes con raquitismo hipofosfatémico ligado al cromosoma X [Internet]. 2025.

8. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2019; 15: 435-55.
9. Figueredo Arce JD, Polo Castillo AE, Ovalle Villadiego CV. Raquitismo hipofosfatémico ligado al cromosoma X tratado con burosumab. Revista Salud Bosque. 2025; 15: 1-9.
10. Aguilera JGC, Orjuela AM, Meza AI, et al. Consenso de expertos colombianos sobre recomendaciones basadas en evidencia para el diagnóstico, tratamiento y seguimiento del raquitismo hipofosfatémico ligado al cromosoma X (RHLX). 2023.