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# X-linked hypophosphatemic rickets: a rare case report

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**X-linked hypophosphatemic rickets (XLHR) is a rare hereditary disease. To date, the diagnosis and treatment of XLHR is still in dilemma due to a lack of cases. In the consensus recommendations for the XLHR proposed in Belgium, next-generation sequencing (NGS) is recommended in several genetic centers for PHEX and other skeletal dysplasia genes. We reported our experiences on the diagnosis and treatment of XLHR. A 17-year-old boy with a body height of 1.3 meters presented to our department with a compound deformity of lower limbs. He showed a visual analogue scale (VAS) of 3, short form 36 questionnaire (SF-36) of 90 scores, and health assessment questionnaire (HAQ) of 23. Laboratory examinations showed increased serum alkaline phosphatase levels (369 U/L) and decreased blood phosphorus levels (0.58 mmol/L). The whole exome sequencing (WES) showed mutation of PHEX gene (NM_000444.6: exon18: c.1853T>G: p.M618R) in the patient and his mother. The patient was finally diagnosed with XLHR. The patient received Ilizarov technique combined with multi-segment osteotomy to correct lower limb deformity. Finally, the patient was able to walk independently and take care of himself without any complications. This may provide a reference for the diagnosis and treatment of XLHR.**

**Keywords:** Case report, multi-segment bone osteotomy and correction, PHEX, X-linked hypophosphatemic rickets.

## INTRODUCTION

Hypophosphatemic rickets (HR) is a disease characterized by impairment of renal tubular phosphate reabsorption, with bone mineralization and hypophosphatemia as the major clinical features[1]. Among them, X-linked hypophosphatemic rickets (XLHR) is the most common subtype with an estimated prevalence of 3.9 per 100,000 live births[2,3]. For the mechanism, XLHR is usually caused by pathogenic variants of PHEX gene and is inherited in an X-linked dominant manner. These variants lead to excessive accumulation of fibroblast growth factor 23 (FGF23), which subsequently induces decreased renal phosphate reabsorption and impaired bone mineralization[4].

In childhood, XLHR can be managed with phosphate supplements and calcitriol, which is proposed to attenuate the bone and muscle injuries[5,6]. Unfortunately, most cases show poor treatment outcome due to delayed diagnosis, together with a lack of drugs to correct the bone deformity and ameliorate the tendon inflammations. In their adulthood, these patients usually present bone pain resulting from bone deformities, microfractures, and osteomalacia. For the adults that have already shown growth completion, the rationale for therapy is directed towards symptomatic osteomalacia, as well as correction of fractures and insufficiency fractures, rather than correcting the phosphate concentration[7-9].

To date, the treatment of patients with residual deformities involves various methods of corrective osteotomy and fixation devices, such as Kirschner wires, plaster cast, epiphysiodesis, and Ilizarov devices[10,11]. In this study, we reported our experiences in treating XLHR using the Ilizarov method. In addition, this is the first time our center has employed whole exome sequencing (WES) to investigate

potential pathogenic genes associated with the onset of XLHR.

## CASE PRESENTATION

*Study design*

A 17-year-old boy with mild intellectual disability and short stature (1.3 meters) presented to our department with refractory fracture and bone pain in the same body part. He presented with lower limb maldevelopment since birth, but no immediate treatment was administered due to financial causes. Then he gradually developed deformity of lower limbs and a waddling gait (Figure 1a and 1b). He underwent an X-ray examination on his lower limbs at the local hospital before presentation, which revealed a compound deformity of lower limbs. Specifically, he exhibited bilateral hip flexion deformity, bilateral femoral varus and anterior angulation deformity, bilateral knee valgus deformity, bilateral patellofemoral subluxation, bilateral tibial valgus and anterior angulation deformity, bilateral ankle valgus deformity, and flat feet (Figure 1c and 1d).

Upon admission, the physical examination revealed crouching gait, skeletal deformities of limbs (especially lower limbs), varus deformity of upper and middle femur (45°), anterolateral angulation deformity (20°), varus of middle and lower tibia (20°), anterior angulation deformity (45°), knee joint flexion deformity (20°) with a flexion and extension of 30°-50°. The other symptoms included blue sclera, unequal bilateral pupils with different sensitivity to light reflex (right, 2 mm, with reduced light reflex; left, 4 mm, with normal light reflex). He showed mild bone pain with a visual analogue scale (VAS) of 3. For the quality of life, he showed a score of 90 in short

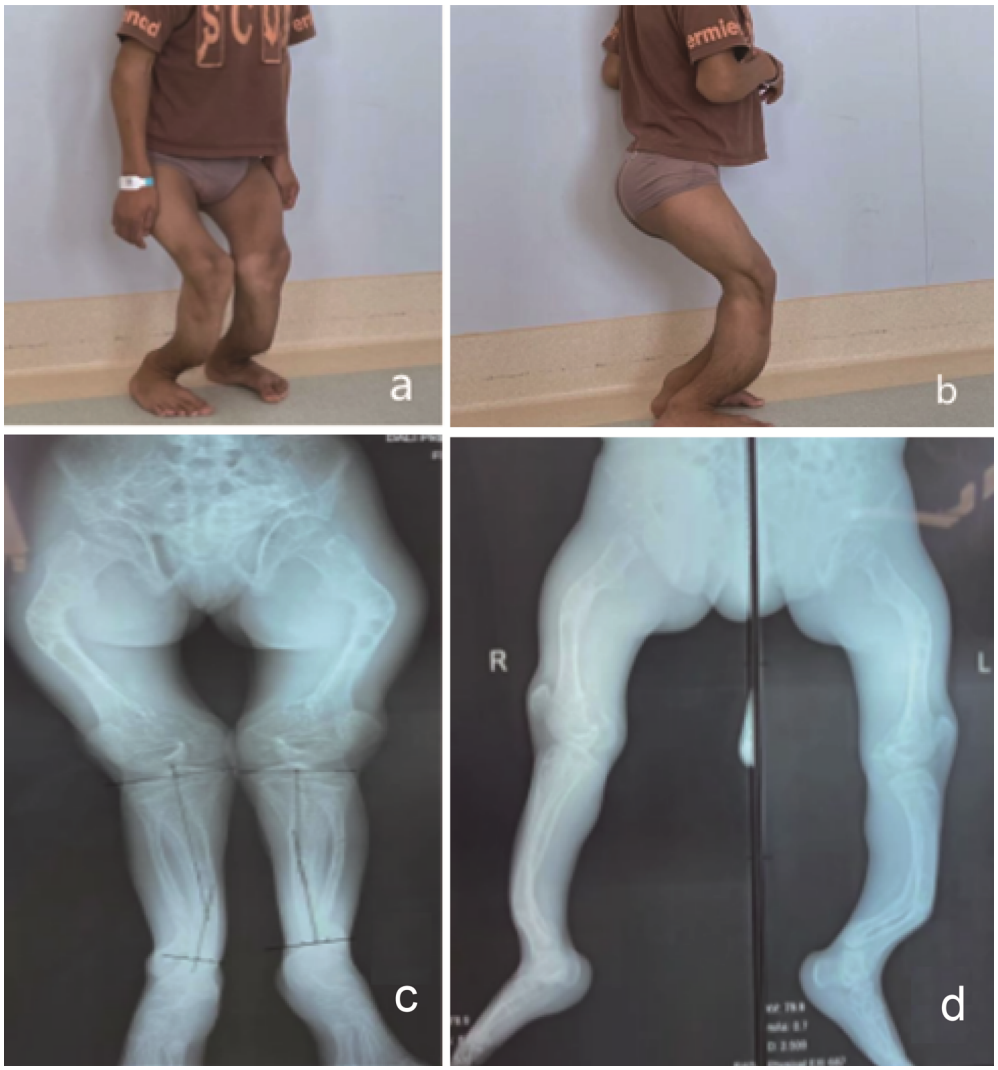


*Fig. 1 — Patient's appearance and X-ray examination results of lower limbs. a, oblique appearance; b, lateral appearance; c, full-length frontal X-ray examination of lower limbs; and d, full-length lateral X-ray examination of lower limbs.*

form 36 questionnaire (SF-36), and a score of 23 in health assessment questionnaire (HAQ). Laboratory examinations after admission showed increased serum alkaline phosphatase (369 U/L; normal range: 45 to 125 U/L), and decreased blood phosphorus (0.58 mmol/L; normal range: 1.1 to 1.3 mmol/L).

The patient's family history included intellectual disability in his father, compound deformities of his mother's lower limbs and difficulty walking, and cerebral palsy in his brother (Figure 2). Genetic testing on the patient and his family was performed by WES. The data were analyzed using the Verita Trekker® variant site detection system and the Enliven® variant site annotation interpretation system. The XLHR-related variants were identified according to the American College of Medical Genetics and Genomics (ACMG) guidelines[12], as well as public databases including Human Phenotype Ontology (HPO), Online Mendelian Inheritance in Man (OMIM), and Genetics Home Reference (GHR). The patient showed mutation of PHEX gene (NM_000444.6: exon18: c.1853T>G: p.M618R). The SNV and InDel diagram of PHEX gene detection showed that the gene of the father and elder brother was normal. However, the mother was heterozygous for the same variant (Figure 3, Table I).

The patient was finally diagnosed with hereditary XLHR based on clinical symptoms and genetic


*Fig. 2 — Mental and healthy status of the patient's parents and elder brother. a, father, mentally retarded; b, mother, compound deformities of lower limbs; c, elder brother, mentally retarded and cerebral palsy.*

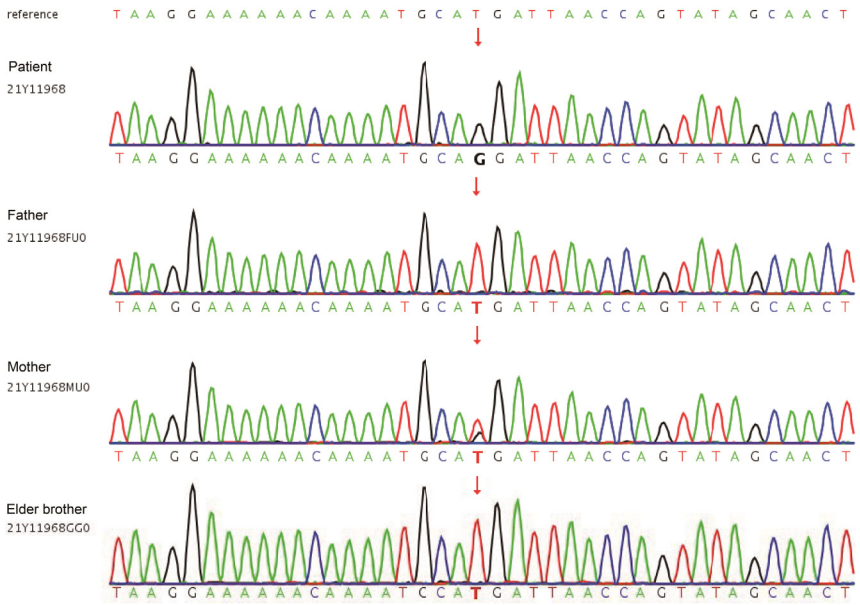


*Fig. 3 — 3 SNV and InDel diagram of PHEX gene detection in the patient and his family.*

**Table I.** — Genetic testing results of the patient, his parents and his elder brother.

| Gene | Mutation site | Gene subregion | HGVS | Mutation type | Heterozygosity |
|---|---|---|---|---|---|
| PHEX | chrX:22221697-22221697 | exon18 | NM_000444.6: c.1853T>G: p.M618R | nonsynonymous SNV | Patient: hemizygotic<br>Father: wild<br>Mother: heterozygous<br>Elder brother: wild |
| Abbreviations: HGVS, Human Genome Variation Society. | | | | | |

testing results according to the guidelines[4,13]. For the treatment, Ilizarov technique combined with multi-segment osteotomy was performed for the correction of lower limb deformities. Owing to the complexity and multiplicity of the deformities, multi-segment osteotomy and corrective external fixation of the compound deformity of right and left lower limbs were performed on September 23, 2021, and October 8, 2021, respectively. One year later, the external fixator was removed, and the femur and tibia were subjected to osteotomy and correction in sequence (Figure 4). Preoperative full-length radiographs of both lower extremities were perfected to depict the anatomical lines of force of the distal and proximal tibial bones for bilateral tibial osteotomy correction. The full-length standing radiographs were reviewed 1 month after surgery, and the threaded rods were adjusted to refine the tibial lines of force. The full-length X-rays of both lower limbs were reviewed again at 6 weeks postoperatively to make sure that the tibial osteotomies were stable and the tibial line of force was good, and then the femoral osteotomies were corrected. On the first postoperative day, the patient ambulated with crutches and bear weight. At the same time, passive flexion and extension exercises of knee, ankle and hip joints were started. After surgery, the adjustment of the threaded rod nut on the angulation side was started, and the daily adjustment of the nut on the external angulation side was gradually adjusted at a rate of 1mm/day. The full-length X-rays of both lower limbs were reviewed weekly, and the changes in the force lines and CORA angles of both lower limbs were measured and recorded to observe the speed of opening of the osteotomized end and the effects of bone growth and healing.

The postoperative VAS, SF-36 and HAQ scores were 3, 85 and 5, respectively. The lack of postoperative VAS change suggests that the patient's baseline pain level remained low, showing that the surgical intervention accomplished the intended corrective outcome without inducing additional pain. The slight decrease in SF-36 scores after surgery may be attributed to the temporary physical burden and lengthy recovery process associated with major orthopedic surgery, which may temporarily affect the patient's postoperative self-perception. The dramatic

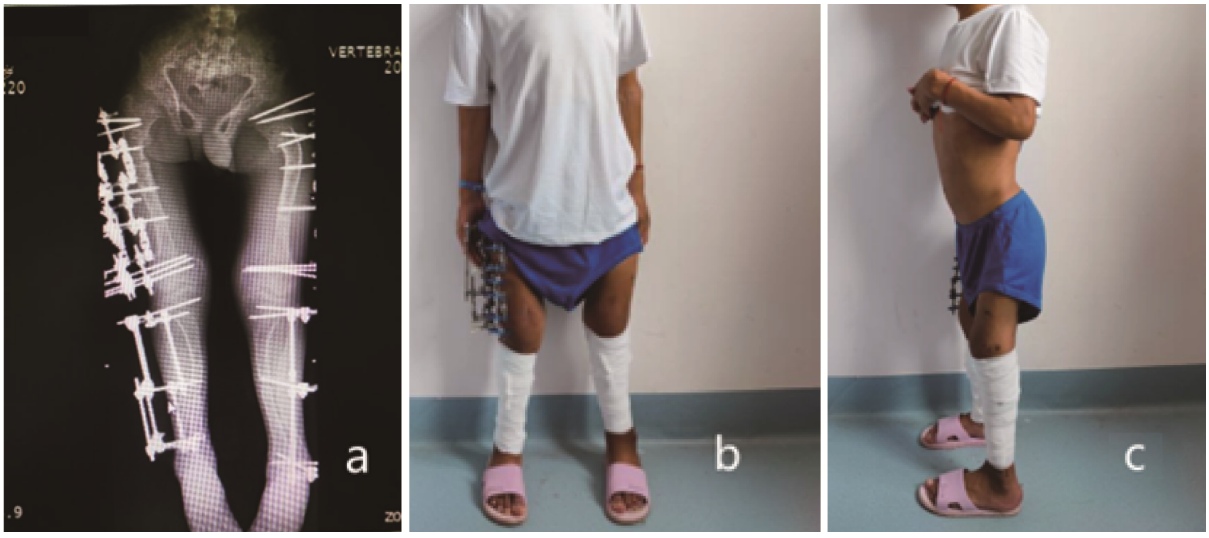


*Fig. 4 — Postoperative full-length X-ray result of the lower limbs and appearance of the patient after removal of part of the external fixator. a, full-length frontal X-ray result of lower limbs.; b, frontal appearance; c, lateral appearance. The femoral CORA angles decreased from 61° on the left and 60° on the right before surgery to 31° on the left and 18° on the right after surgery. The tibial CORA angles decreased from 17° on the left and 34° on the right before surgery to 10° on the left and 16° on the right after surgery.*

decrease in HAQ scores from 23 to 5 highlights the significant functional gain, reflecting a transformative improvement in the patient's daily activities. In addition, the patient's lower limb force alignment was significantly improved after surgery, with bilateral mechanical axis deviation (MAD) approaching normal, mechanical lateral distal femoral angle (mLDFA) and medial proximal tibial angle (MPTA) approaching their ideal values. Moreover, femoral and tibial center of rotation of angulation (CORA) angles were significantly reduced. These findings indicate that osteotomy surgery effectively corrected the complex deformity of both lower limbs (Table II). At 2-year follow-up, the patient had gained 10 cm in height, could walk independently, and led a normal life without any complications.

The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance with the tenets of the Helsinki Declaration, and has been approved by the Ethics Committee of 920th Hospital of Joint Logistics Support Force (Approval No.: 2023-100-01). Informed consent has been obtained from all participants included in this study.

## DISCUSSION

To date, the treatment options for XLHR include symptomatic management, corrective surgery, conventional phosphate supplements and active vitamin D[14]. Contemporary medical options (e.g., targeted anti-FGF23 therapy) would nicely situate the surgical choice in adults with established deformity. Due to the rarity and lack of attention to XLHR in childhood, there is a high risk of misdiagnosis and disease progression in adulthood upon diagnosis. The untreated patients or those with a poor outcome usually show typical symptoms of rickets, including chronic pain, lower limb deformity, and enlarged wrist and ankle metaphysis[15-17]. These symptoms result in a significant financial burden and reduced quality of life for patients[18,19].

In addition, due to the atypical clinical manifestations, XLHR is often misdiagnosed as other similar diseases such as vitamin D deficiency rickets and osteogenesis imperfecta (OI). Especially, XLHR should be distinguished from OI. Clinical manifestations and imaging results are required for diagnosis when genetic or laboratory test results are not available or negative. Although our patient presented with blue sclerae, a common symptom of OI, we excluded OI based on the patient's X-ray results. In addition, next-generation sequencing (NGS) identified a PHEX mutation (exon18: c.1853T>G: p.M618R) in the patient. Ultimately, our case was diagnosed as XLHR. This variant has not been reported in individuals with substantial PHEX-related disease, is not present in population databases, and is not included in the ACMG classification. The in-silico prediction is "Pathogenic Moderate". Regarding segregation, the variant co-segregated with the disease phenotype in the family, as it was identified in the proband's symptomatic mother. This variant has been included in the ClinVar database (Last evaluated: October 31, 2019). Database status is "criteria provided, single submitter". The clinical significance of this variant in ClinVar is "Uncertain Significance".

The pathogenesis of XLHR is closely associated with pathogenic mutations in the PHEX gene. PHEX encodes a zinc-dependent metalloendopeptidase that binds to matrix extracellular phosphoglycoproteins (MEPE) and inactivate the inhibitory effects of these proteins on bone mineralization[20,21]. Mutations in PHEX may lead to increased FGF23 expression[22]. In the renal tubules, FGF23 increases urinary phosphate excretion by downregulating NPT2a and NPT2c. In vitamin D metabolism, FGF23 downregulates CYP27B1, which converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, the active form of vitamin D[22]. Therefore, excess FGF23 leads to phosphaturia, hypophosphatemia, and suppressed vitamin D activity[23,24], ultimately resulting in XLHR[25].

**Table II.** — Changes in key indicators before and after surgery.

| Indicators | Before surgery | After surgery |
|---|---|---|
| MAD | Left side: 10 mm; Right side: 13 mm | Left side: 2 mm; Right side: 2 mm |
| mLDFA | Left side: 88°; Right side: 95° | Left side: 93°; Right side: 90° |
| MPTA | Left side: 98°; Right side: 100° | Left side: 95°; Right side: 92° |
| CORA angles-femur | Left side: 61°; Right side: 60° | Left side: 31°; Right side: 18° |
| CORA angles-tibia | Left side: 17°; Right side: 34° | Left side: 10°; Right side: 16° |
| Because it is a complex deformity, the angle is difficult to measure using standard methods, so the above are approximate angles.<br>Abbreviations: MAD, mechanical axis deviation; mLDFA, mechanical lateral distal femoral angle, MPTA, medial proximal tibial angle; CORA, center of rotation of angulation. | | |

WES is a high-throughput sequencing technique that captures and enriches DNA in the exon region of the whole genome. It can selectively sequence the coding region of the human genome to discover abnormal genes associated with rare and common diseases[26]. WES is more suitable for clinical application compared to expensive whole genome sequencing. To the best of our knowledge, few studies have focused on the application of WES for the screening and diagnosis of XLHR. In the consensus recommendations for the XLHR proposed in Belgium[6], NGS is readily available in several genetic centers in Belgium for PHEX as well as for other skeletal dysplasia genes using a WES-based gene panel. Indeed, some studies proposed that the 3' untranslated region in the PHEX mutations were associated with milder XLH phenotypes[27,28]. In this study, our case was identified to have PHEX gene mutation by WES technique. Besides, his mother showed heterozygous PHEX gene mutation. Our experiences contribute to the diagnosis of XLHR based on the WES technique, which may contribute to the promotion of WES in the diagnosis of such condition.

The clinical symptoms in adults with XLHR include musculoskeletal disorders, dental disorders, pain, and difficulty walking. In a survey in the United States, approximately 65% of adult patients with XLHR underwent orthopedic surgery, including osteotomy (63%), knee replacement (12%), and hip replacement (8%)[29]. The Ilizarov technique is one of the most important tools currently used in bone reconstructive surgery[30]. It involves the application of compressive or distraction forces to bone using an Ilizarov device to achieve bone consolidation, axial alignment, or new bone formation[31]. This process is facilitated by a phenomenon known as distraction osteogenesis[32]. The distraction osteogenesis technique consists of an osteotomy/surgical period, a latent period, a distraction period, and a consolidation period. Previous experiments have shown that ideal conditions include stable fixation, low-energy osteotomy, followed by a latent period of 5-7 days, and a distraction rate of 1 mm per day divided into three to four increments[33]. The main advantages of this approach include the production of viable new bone through distraction osteogenesis and a high healing rate[34]. To our best knowledge, no similar reports on adult XLHR patients are available in mainland China, due to a lack of experiences on the diagnosis of XLHR. In this study, the patient showed compound deformity in lower limbs, whereas conventional open osteotomy orthopedic procedures were insufficient to fully correct such deformities, and it will also bring in great physical trauma and economic burden to the patient. Then, the Ilizarov technique combined with multi-segment osteotomy correction was the most suitable solution for the patient. The patient showed a positive clinical response to the surgery. In the future, long-term follow-up and more cases are needed to verify the effectiveness of the surgery. Furthermore, the Ilizarov frame is not specific to limb deformity corrections and can also be used for soft tissue closure, emphasizing the versatility and modern application of the Ilizarov framework in complex reconstructions[35].

In conclusion, we reported a case with XLHR showing a compound deformity of the lower limbs. WES revealed PHEX gene mutation (PHEX: NM_000444.6: exon18: c.1853T>G: p.M618R) in the patient and his mother. The patient underwent Ilizarov technique combined with multi-segment osteotomy to correct lower limb deformity. Postoperatively, the HAQ score decreased, the height increased by 10 cm, and he was able to walk independently without any complications.

***List of abbreviations:***

ACMG, American College of Medical Genetics and Genomics; CORA, center of rotation of angulation; FGF23, fibroblast growth factor 23; GHR, Genetics Home Reference; HAQ, health assessment questionnaire; HPO, Human Phenotype Ontology; HR, hypophosphatemic rickets; MAD, mechanical axis deviation; mLDFA, mechanical lateral distal femoral angle, MPTA, medial proximal tibial angle; NGS, next-generation sequencing; OI, osteogenesis imperfecta; OMIM, Online Mendelian Inheritance in Man; SF-36, short form 36 questionnaire; VAS, visual analogue scale; WES, whole exome sequencing; XLHR, X-linked hypophosphatemic rickets.

*Ethics approval and consent to participate:* The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research has been approved by the Ethics Committee of 920th Hospital of Joint Logistics Support Force (Approval No.: 2023-100-01).

*Consent for publication:* Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.

*Availability of data and materials:* All data generated or analysed during this study are included in this published article, the raw data can be obtained on request from the corresponding author.

*Competing interests:* The authors declare that they have no competing interests.

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