

HEREDITARY, PROGRESSIVE, AND LIFELONG X-LINKED HYPOPHOSPHATEMIA (XLH)

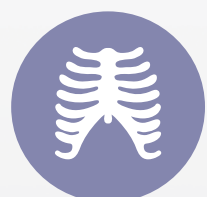


DISEASE OVERVIEW

X-LINKED HYPOPHOSPHATEMIA (XLH) IS A HEREDITARY, PROGRESSIVE, AND LIFELONG DISEASE



XLH is a chronic disease that impacts children and adults throughout their lives¹



Rickets and osteomalacia due to chronic hypophosphatemia result in poor skeletal, muscular, and dental health^{1,2}



XLH is inherited within families, but about 20% to 30% of cases may arise spontaneously³



Prevalence: 1 in 20,000 to 1 in 25,000 live births²

XLH is chronic hypophosphatemia due to increased FGF23 activity resulting in poor skeletal, muscular, and dental health and impaired physical function^{1,2}

XLH is characterized by chronic hypophosphatemia due to increased fibroblast growth factor (FGF23) activity that impacts patients in many ways, resulting in^{1,2}:

- Rickets and osteomalacia, the sources of compounding symptoms in XLH^{1,2}
- Pain and progressive skeletal defects, muscular dysfunction, and dental abnormalities^{1,2}
- Limitations in physical function and mobility^{4,5}

XLH has also been known by patients and health care providers as:

- X-linked hypophosphatemic rickets^{2,6,7}
- Hereditary hypophosphatemic rickets⁸
- Familial hypophosphatemic rickets^{2,6}
- Vitamin D-resistant rickets (VDRR)^{2,6}
- Vitamin D-resistant osteomalacia⁹
- X-linked vitamin D-resistant rickets²
- Hypophosphatemic rickets²
- Hypophosphatemic vitamin D-resistant rickets (HPDR)²
- X-linked rickets (XLR)²
- Genetic rickets⁶
- Familial hypophosphatemia⁶

MECHANISM OF DISEASE

INCREASED FGF23 ACTIVITY — THE ROOT CAUSE OF XLH

In normal homeostasis, FGF23 is a protein hormone mainly produced by osteocytes in the bones to regulate serum phosphate levels.¹⁰



1 INCREASED CIRCULATING FGF23

In XLH, an X-linked dominant genetic variant of the *PHEX* gene causes increased FGF23 activity, which leads to chronic hypophosphatemia^{1,2,10}



2 DECREASED RENAL PHOSPHATE REABSORPTION AND CALCITRIOL PRODUCTION

Increased FGF23 decreases renal phosphate reabsorption, which increases urinary phosphate excretion and decreases calcitriol production^{1,10}



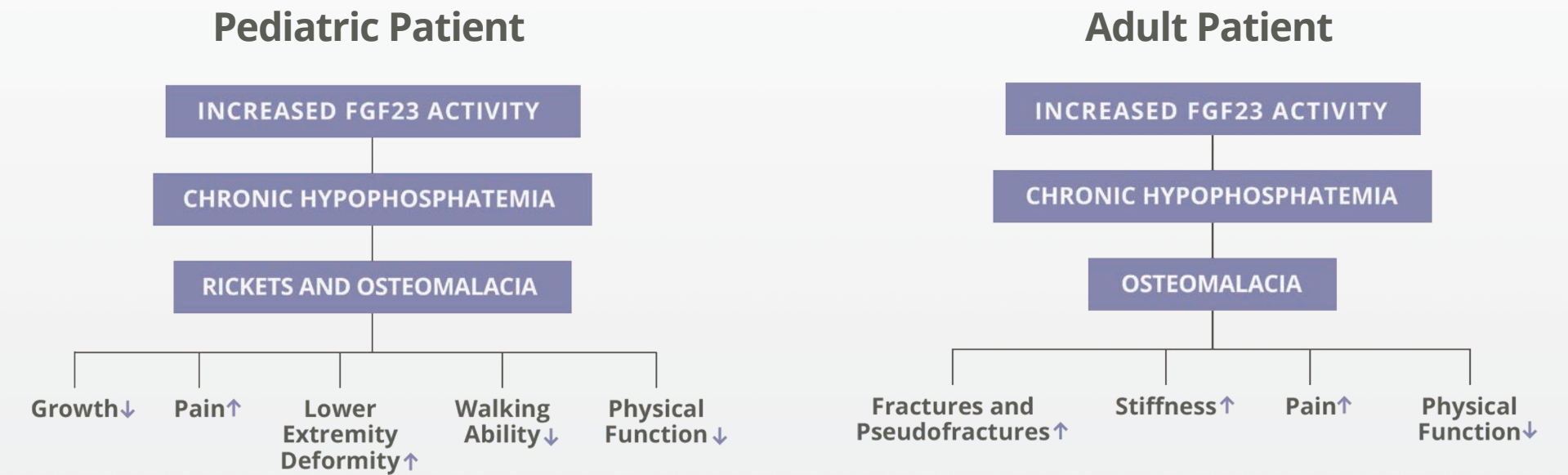
3 DECREASED INTESTINAL PHOSPHATE ABSORPTION

Decreased calcitriol reduces intestinal phosphate absorption^{1,10}

Increased FGF23 activity leads to chronic hypophosphatemia, which manifests as rickets and osteomalacia in children and as osteomalacia in adults

INCREASED FGF23 ACTIVITY IMPACTS YOUR PATIENT

Rickets and osteomalacia due to chronic hypophosphatemia are the underlying sources of compounding skeletal defects, muscular dysfunction, and dental abnormalities.^{1,2,11}



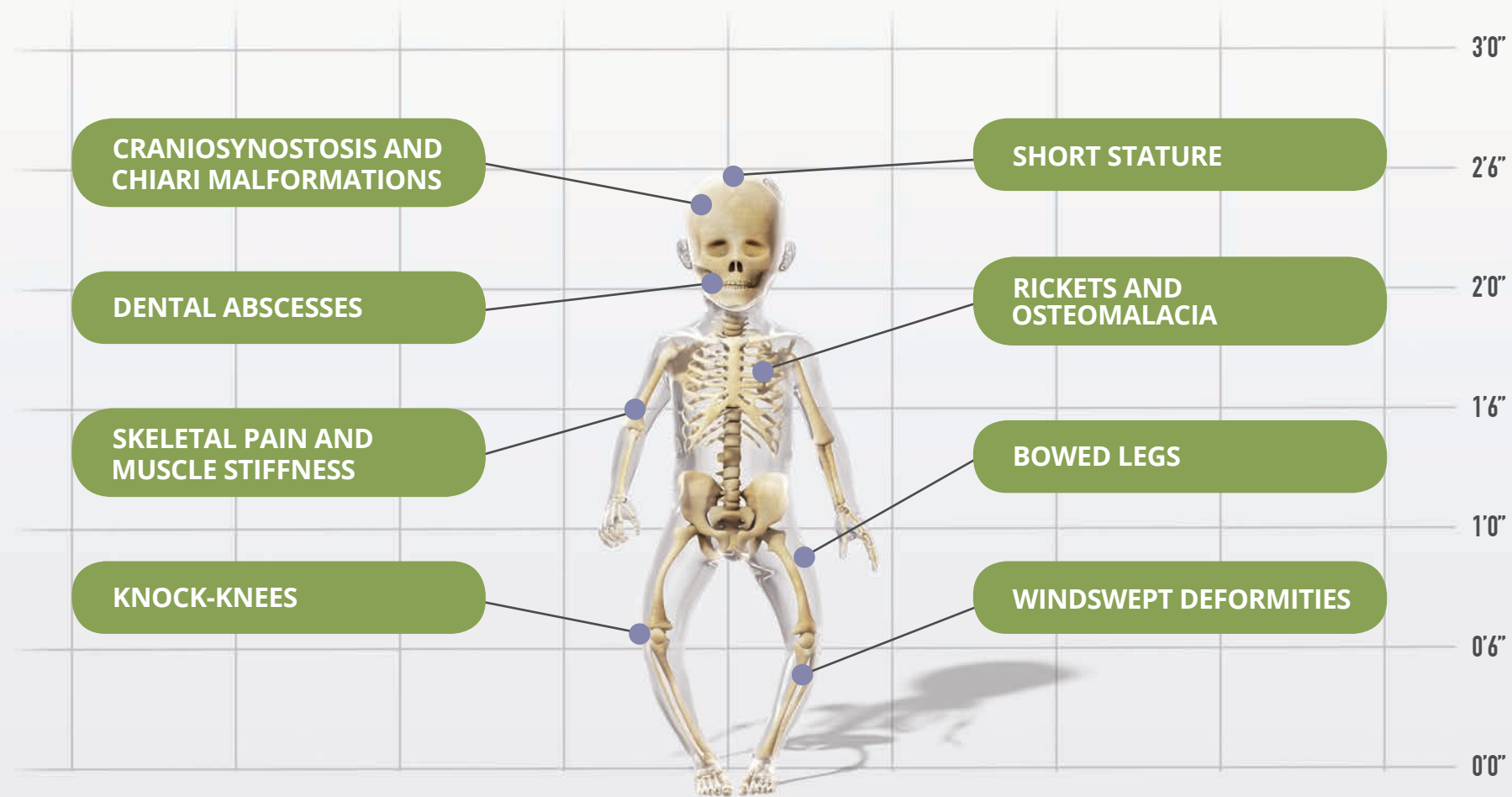
In XLH, increased FGF23 activity is caused by a genetic variation, resulting in lifelong and progressive symptoms from childhood to adulthood

CLINICAL PRESENTATION AND DISEASE PROGRESSION — CHILDREN

XLH IMPAIRS PHYSICAL FUNCTION AND HAS A LONG-TERM NEGATIVE IMPACT ON CHILDREN THAT CAN CONTINUE INTO ADULTHOOD

Rickets and osteomalacia are the underlying sources of symptoms that will progress throughout adulthood and can limit growth and physical function in children with XLH.^{1,2,11}

SIGNS AND SYMPTOMS OF XLH IN CHILDREN^{1,2,6-8,11,12}

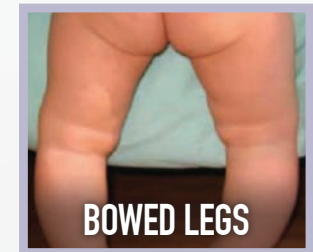


An early and accurate diagnosis of XLH is essential to appropriate disease management

Children can present with symptoms that vary in severity, which may include¹:

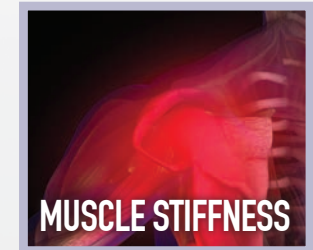
SKELETAL DEFECTS

- Rickets and osteomalacia can lead to lower extremity deformities^{1,2,11}
- Bone and joint pain may accompany rickets and osteomalacia^{2,4}
- Cranial defects such as Chiari malformations and craniosynostosis may also manifest^{2,11}



MUSCULAR DYSFUNCTION

- Muscular dysfunction such as muscle pain, stiffness, and weakness^{4,7,11}
- Muscle weakness can result in gait disturbances^{7,11}



DENTAL ABNORMALITIES

- Dental abscesses^{1,11}
- Tooth loss¹¹

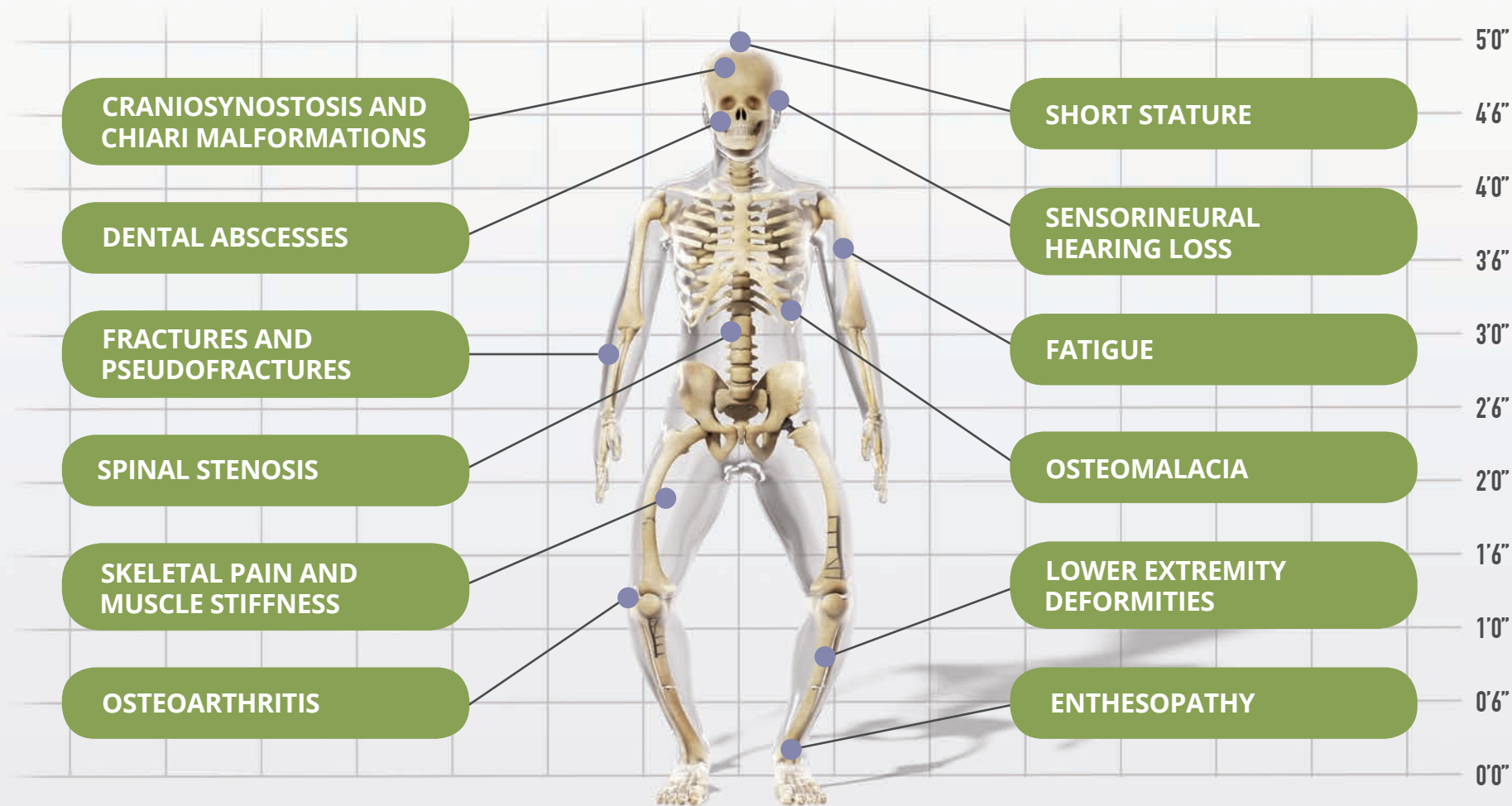


CLINICAL PRESENTATION AND DISEASE PROGRESSION — ADULTS

XLH IMPACTS MOBILITY AND RANGE OF MOTION OF ADULTS AND POSES A BURDEN ON THEIR DAILY LIFE

XLH is not merely a pediatric disease.^{2,7} The lifelong presence of elevated FGF23 activity causes unresolved childhood symptoms to continue to progress into adulthood, paired with new, potentially irreversible symptoms that can appear due to ongoing active disease.^{1,11}

SIGNS AND SYMPTOMS OF XLH IN ADULTS^{1,2,5,7,11}



Osteomalacia continues to be the underlying source of compounding symptoms of XLH⁸

Adults with XLH may not associate their pain with their previous diagnosis and may present with:

SKELETAL DEFECTS

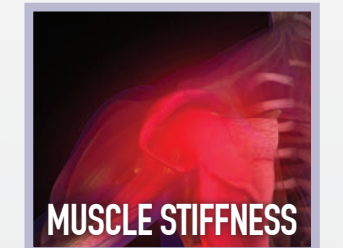
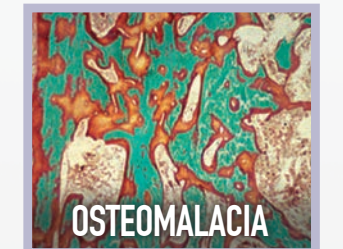
- Bone and joint pain, as well as fatigue, can manifest because of osteomalacia^{2,5,11}
- Pseudofractures and fractures^{1,2,11}
- Short stature and lower extremity deformities^{2,11}
- Enthesopathy or calcification of the tendons^{1,2,11}
- Osteoarthritis^{7,11}

MUSCULAR DYSFUNCTION

- Compounding muscular dysfunction, such as muscle pain, stiffness, weakness, and gait disturbances^{7,11}

DENTAL ABNORMALITIES

- Dental abscesses continue to manifest in adults and may subsequently develop into periodontitis or result in tooth loss¹¹

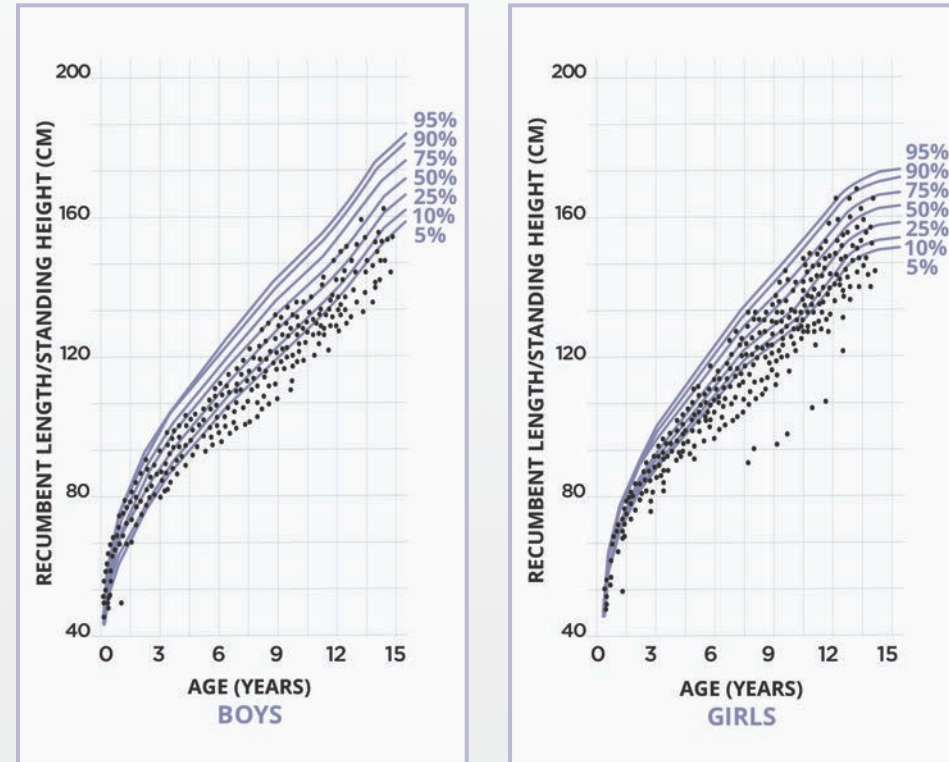


BURDEN OF DISEASE — CHILDREN

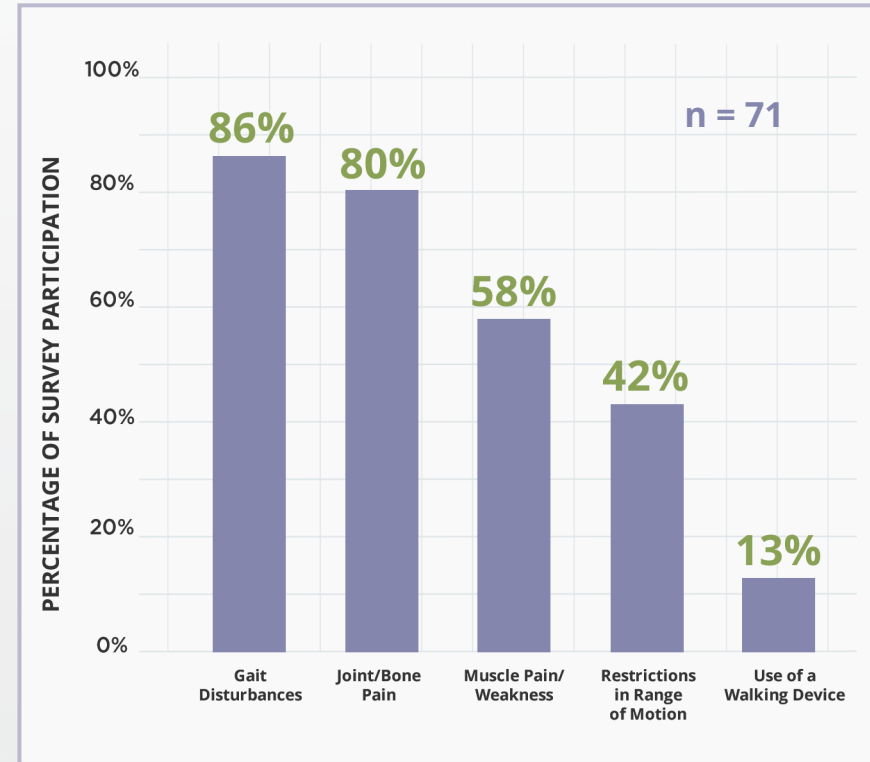
XLH LIMITS GROWTH AND PHYSICAL FUNCTION IN CHILDREN

Rickets, osteomalacia, and lower extremity deformities that result from chronic hypophosphatemia create a significant burden for children, affecting their daily lives.^{4,11}

DELAYED GROWTH RESULTING IN SHORT STATURE^{11,13}



PAIN AND LIMITED PHYSICAL FUNCTION⁴



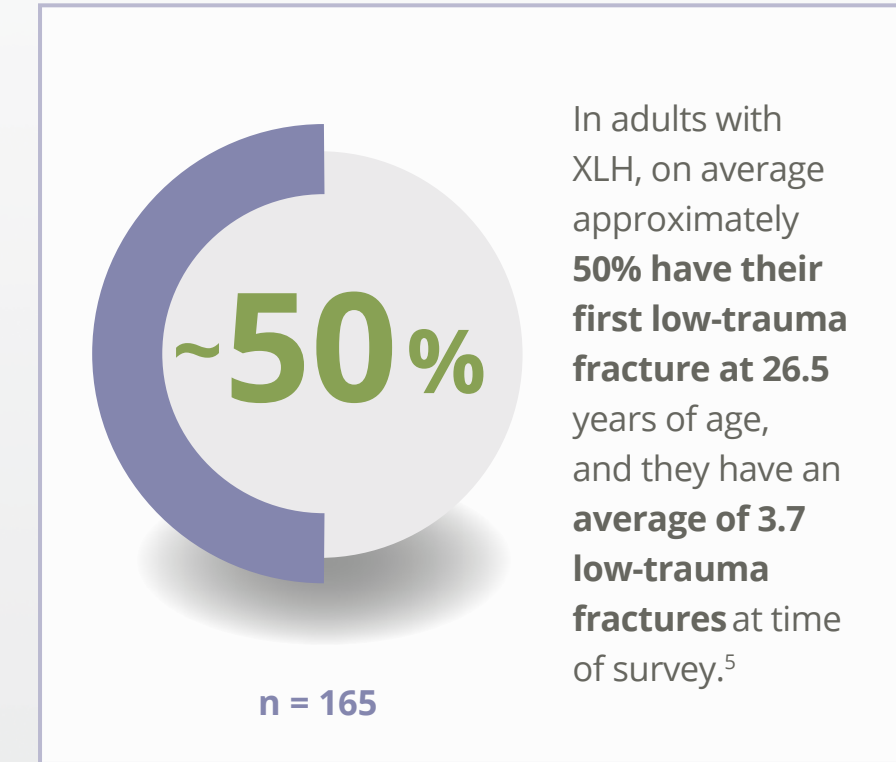
Data taken from a burden-of-disease study conducted in 71 pediatric patients with XLH⁴

BURDEN OF DISEASE — ADULTS

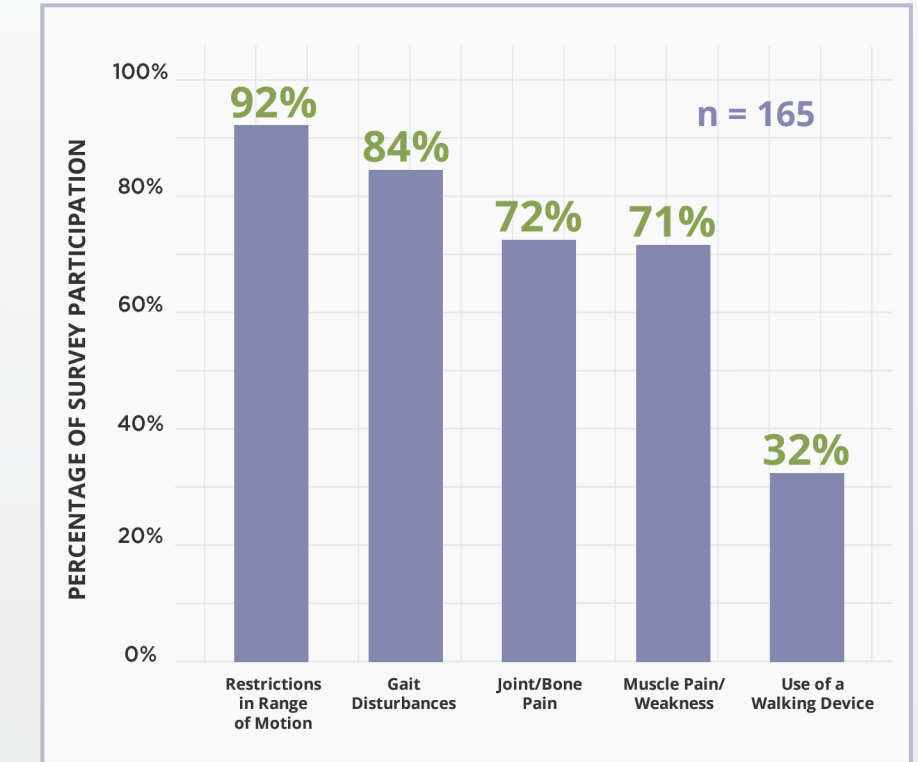
XLH LIMITS PHYSICAL MOBILITY OF ADULTS

The ongoing osteomalacia can result in pain, limitations in range of motion, and even disability.^{5,11}

INCREASED RISK OF FRACTURES AND PSEUDOFRACTURES^{1,2,5}



LIMITED RANGE OF MOTION AND PAIN⁵



Data is taken from an international burden-of-disease study conducted in 165 adult patients with XLH⁵

DIAGNOSIS AND ASSESSMENT

A DIAGNOSIS OF XLH IS TYPICALLY BASED ON CLINICAL AND BIOCHEMICAL FINDINGS IN COMBINATION WITH FAMILY HISTORY

Family history, clinical findings, and biochemical tests can help establish a diagnosis of XLH

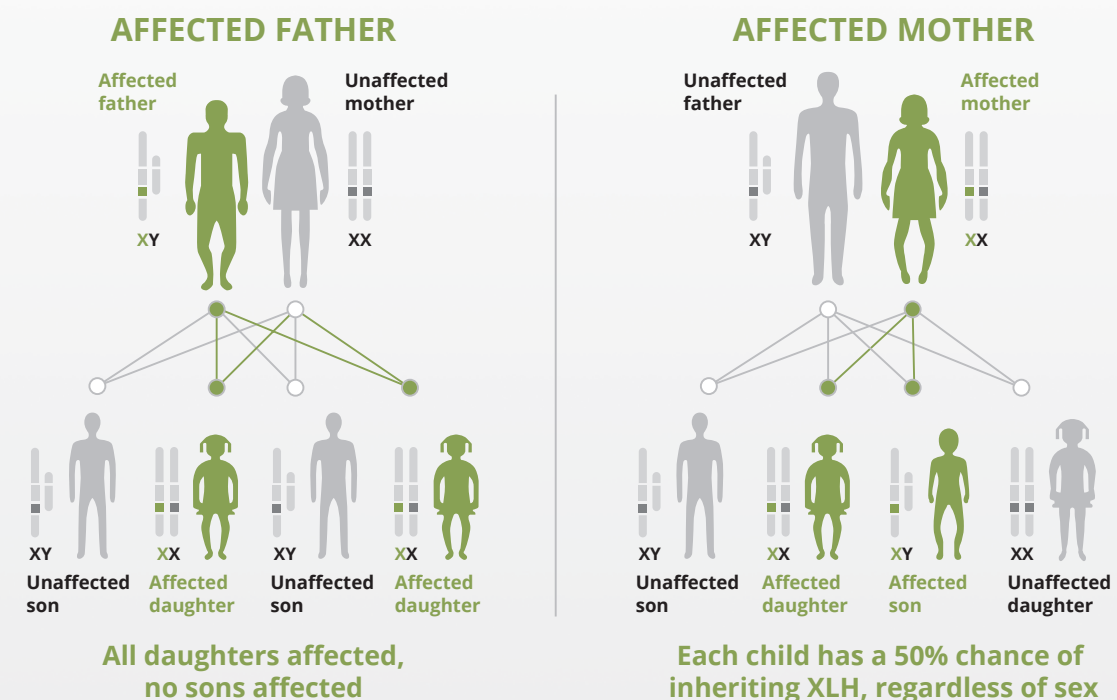
FAMILY HISTORY

WITH KNOWN FAMILY HISTORY OF XLH

XLH is inherited in an **X-linked dominant** pattern.² In a family with a history of XLH, screen for other family members. This can help you identify previously undiagnosed individuals

WITHOUT A KNOWN FAMILY HISTORY

About 20% to 30% of XLH cases are spontaneous.³ Ask about his/her medical history of short stature, rickets, osteomalacia, osteoarthritis, and dental abscesses, which may indicate XLH



A diagnosis of XLH can be confirmed through genetic testing for variants of the *PHEX* gene

CLINICAL FINDINGS

PREDOMINANT FINDINGS IN CHILDREN

Rickets, lower extremity bowing, leg deformities, pain, short stature, and gait disturbances.^{1,2,11} Confirm skeletal findings through radiography.² Other signs and symptoms may also include dental abscesses, craniosynostosis, and Chiari malformations^{2,11}

PREDOMINANT FINDINGS IN ADULTS

Adults with XLH may present with osteomalacia manifesting as bone and muscle pain, enthesopathy, fractures, and pseudofractures. Other signs and symptoms may also include waddling gait, dental abscesses, and hearing loss^{1,2,5,7,11}

BIOCHEMICAL FINDINGS

Include age- and gender-normalized levels of serum phosphorus in metabolic panels for an accurate diagnosis. Low phosphate levels and low TmP/GFR ratio are the most relevant biochemical findings for XLH^{1,2}

Biochemical Test	XLH ^{2,14}
Serum phosphorus	↓
1,25(OH) ₂ D	↓ or inappropriately normal
25(OH)D	normal
TmP/GFR	↓
ALP	↑
Serum calcium	normal
Urinary calcium	normal to ↓
PTH	normal or slightly ↑

Other biochemical tests that may be useful for establishing the diagnosis of XLH include serum alkaline phosphatase (ALP) levels and FGF23 levels. Alkaline phosphatase can be a good marker of skeletal health in children but not necessarily for adults.²

1,25(OH)₂D = 1,25-dihydroxyvitamin D (calcitriol); 25(OH)D = 25-hydroxyvitamin D (calcifediol); ALP = alkaline phosphatase; PTH = parathyroid hormone; TmP/GFR = ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate; XLH = X-linked hypophosphatemia.

XLH RESOURCES FOR YOU AND YOUR PATIENTS



XLHLink - Information, tools, and resources designed for people with XLH, their caregivers, and their health care team
XLHLink.com



The XLH Network - A worldwide community of XLH patients, parents, caregivers, and medical professionals
XLHNetwork.org



Beyond XLH - An online disease-monitoring program for patients with X-linked hypophosphatemia (XLH) and other chronic hypophosphatemic disorders
BeyondXLH.com



NIH Genetic and Rare Diseases Information Center (GARD) - A list of rare diseases and related terms to help people find reliable information
RareDiseases.info.nih.gov



National Organization for Rare Disorders (NORD) - A patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them
RareDiseases.org



Global Genes - A rare disease patient advocacy organization that works to build awareness, educate the global community, and provide connection and resources
GlobalGenes.org

REFERENCES

1. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res.* 2011;26(7):1381-1388.
2. Ruppe MD. X-Linked Hypophosphatemia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017.
3. Gaucher C, Walrant-Debray O, Nguyen TM, Esterle L, Garabedian M, Jehan F. PHEX analysis in 118 pedigrees reveals new genetic clues in hypophosphatemic rickets. *Hum Genet.* 2009;125(4):401-411.
4. Linglart A, Dvorak-Ewell M, Marshall A, Martin JS, Skrinar A. Impaired mobility and pain significantly impact the quality of life of children with X-linked hypophosphatemia. Poster presented at: 7th International Conference on Children's Bone Health; June 27-30, 2015; Salzburg, Austria.
5. Skrinar A, Marshall A, San Martin J, Dvorak-Ewell M. X-linked hypophosphatemia (XLH) impairs skeletal health outcomes and physical function in affected adults. Poster presented at: ENDO 2015; March 5-8, 2015; San Diego, CA.
6. What is XLH? XLH Network Website. <https://xlhnetwork.org/what-is-xlh/>. Updated August 13, 2017. Accessed January 3, 2019.
7. X-linked hypophosphatemia. Genetic and Rare Diseases Information Center (GARD) Website. <https://rarediseases.info.nih.gov/diseases/12943/x-linked-hypophosphatemia>. Updated 2018. Accessed January 3, 2019.
8. Hereditary hypophosphatemic rickets. Genetics Home Reference Website. <https://ghr.nlm.nih.gov/condition/hereditary-hypophosphatemic-rickets>. Updated January 2, 2019. Accessed January 3, 2019.
9. Wang M, Cao X, Cao B. Hypophosphatemic vitamin D-resistant osteomalacia: a case report. *Exp Ther Med.* 2013;6(3):791-795.
10. Martin A, Quarles LD. Evidence for FGF23 involvement in a bone-kidney axis regulating bone mineralization and systemic phosphate and vitamin D homeostasis. *Adv Exp Med Biol.* 2012;728:65-83.
11. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect.* 2014;3(1):R13-30.
12. Al Kaissi A, Farr S, Ganger R, Klaushofer K, Grill F. Windswept lower limb deformities in patients with hypophosphataemic rickets. *Swiss Med Wkly.* 2013;143:w13904.
13. Data on File. Ultragenyx Pharmaceutical.
14. Santos F, Fuente R, Mejia N, Mantecon L, Gil-Peña H, Ordoñez FA. Hypophosphatemia and growth. *Pediatr Nephrol.* 2013;28(4):595-603.

XLH HAS A LIFELONG IMPACT ON PATIENTS

IN PATIENTS WITH XLH, CHRONIC HYPOPHOSPHATEMIA DUE TO INCREASED FGF23 ACTIVITY RESULTS IN POOR SKELETAL, MUSCULAR, AND DENTAL HEALTH AND IMPAIRED PHYSICAL FUNCTION



XLH IS A HEREDITARY, PROGRESSIVE, AND LIFELONG DISEASE



FGF23 IS THE ROOT CAUSE OF XLH



RICKETS AND OSTEOMALACIA ARE THE UNDERLYING SOURCES OF COMPOUNDING AND PROGRESSIVE SYMPTOMS OF XLH



XLH POSES A SIGNIFICANT BURDEN ON THE DAILY LIVES OF CHILDREN AND ADULTS DUE TO IMPAIRED PHYSICAL FUNCTION



FAMILY HISTORY, CLINICAL FINDINGS, AND BIOCHEMICAL TESTS CAN BE USED TO ESTABLISH A DIAGNOSIS OF XLH



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