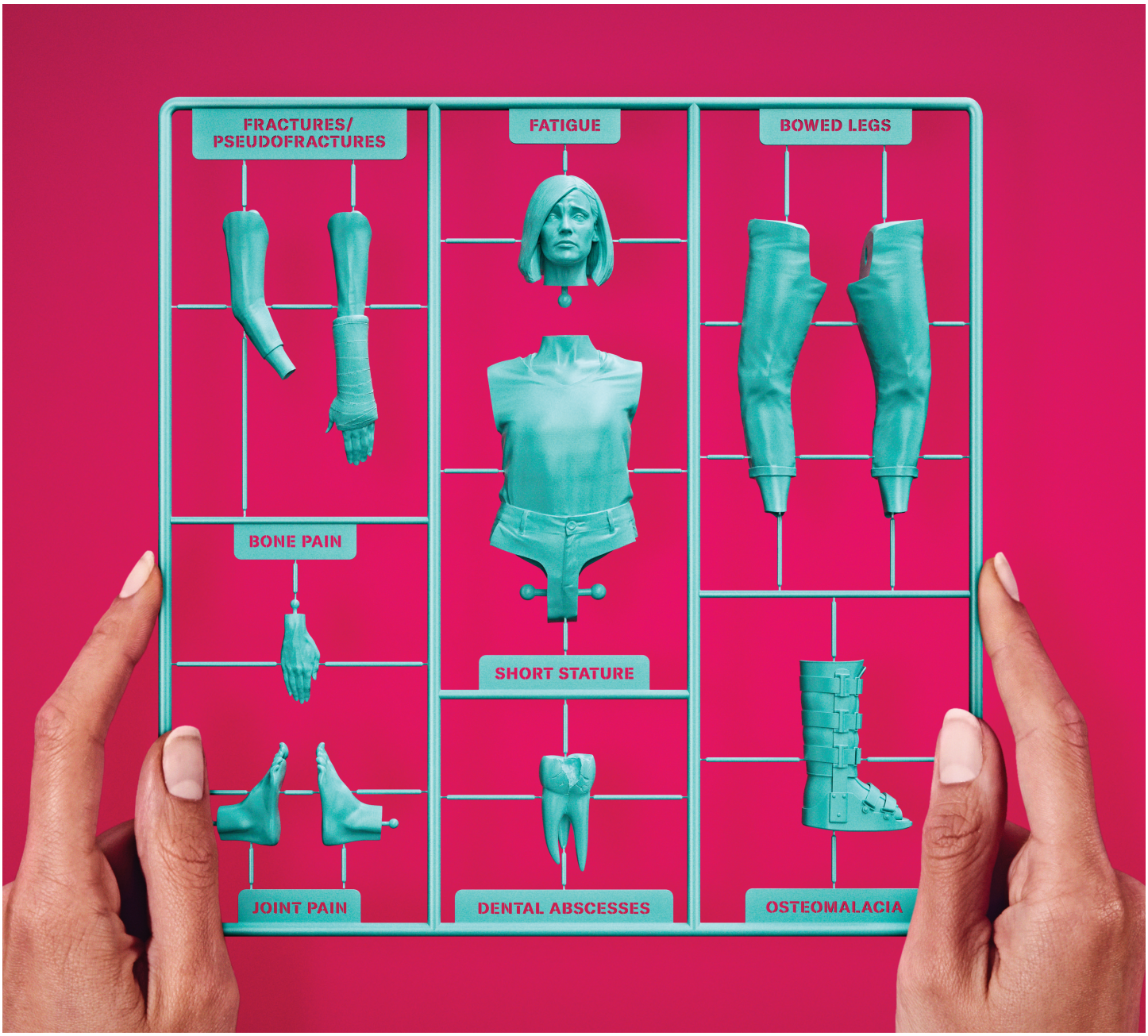
Connect the symptoms.

Is it XLH?

Learn more about X-linked hypophosphatemia (XLH)—a rare, hereditary, chronic, and progressive disease.[1-3]



What is XLH?

XLH is:

Hereditary[2]

Progressive[3]

Chronic[3]

XLH is a **lifelong, progressive disease** characterized by **hypophosphatemia** due to increased fibroblast growth factor 23 (FGF23) activity.[2,3]

- It is considered rare—up to 1 in 20,000 people have it in the US[5]
- Although XLH is primarily an inherited disease, 20% to 30% of cases arise spontaneously[6]
- XLH is the **most common cause of inherited phosphorus wasting** and leads to poor bone mineralization, resulting in rickets and osteomalacia[1,2,4,7]

You and your patients may also know XLH by other names

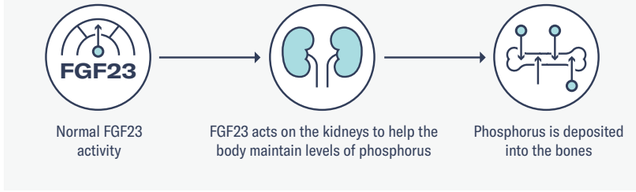
Some of those names may include[2,8,9]:

- Hypophosphatemic rickets
- Familial hypophosphatemia
- Vitamin D–resistant rickets (VDRR) or osteomalacia
- X-linked hypophosphatemic rickets

XLH can progressively impact the skeletal, muscular, and dental health of children and adults throughout their lives and may require long-term management.[2,4,6,7]

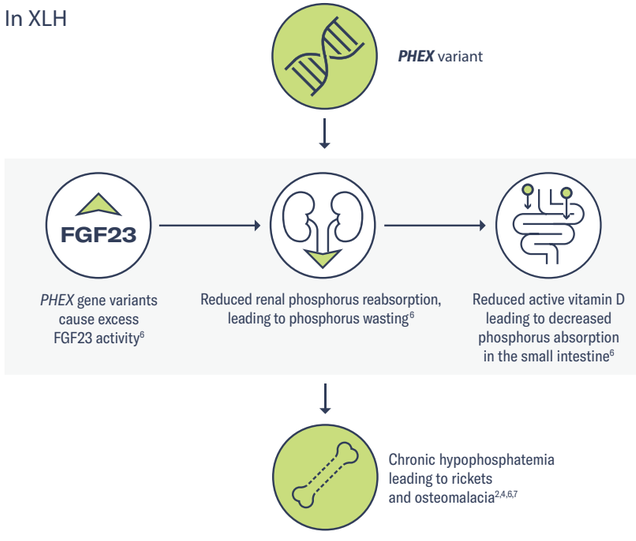
What causes XLH?

In normal homeostasis[1,10]



In normal homeostasis, FGF23 is a protein hormone produced by osteocytes in the bones that regulates serum phosphorus levels.[11]

In XLH



In XLH, a variant in the *PHEX* gene causes excess FGF23, which results in phosphorus wasting leading to chronic hypophosphatemia. This indicator of XLH may lead to skeletal defects, muscular dysfunction, and dental abnormalities.[2,4,7]

Increased FGF23 activity is the underlying cause of chronic hypophosphatemia.[4]

Impact of XLH

XLH causes a substantial lifelong burden[2,3,12]

XLH can affect the entire body. The burden of XLH starts in childhood and may worsen over time. Chronically low levels of phosphorus in XLH may impact bone formation, dental health, muscle functioning, hearing, and energy levels.[2,3,12]

The progressive nature of the disease can leave patients susceptible to[2,3,12]:

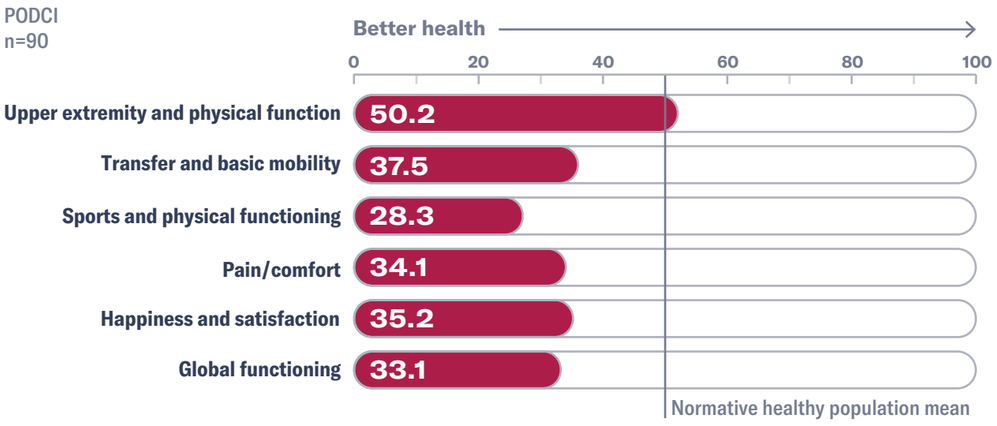
- Delayed growth
- Fractures
- Limited physical functioning
- Pain
- Social and emotional impacts

Effects on physical functioning and mobility in children with XLH

A 2019 survey showed that **children with XLH scored well below the US general population average** for basic mobility, physical functioning, pain/comfort, and happiness and satisfaction.[3]

- Only the mean score for the upper extremity function domain was within normal limits[3]

Functioning and health-related quality of life in children with XLH[3]



Data were taken from a 2019 international burden-of-disease study conducted in 90 pediatric patients with XLH. This component is from an international survey of parents and caregivers of children with XLH that reported below-normal health-related quality of life assessments. The Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument (POSNA-PODCI) score is a parent-reported questionnaire to assess overall health, pain, and ability to participate in normal daily activities, as well as in more vigorous activities associated with children. It contains 7 scales that include upper extremity and physical function, transfer and basic mobility, sports and physical functioning, pain/comfort, happiness and satisfaction, and expectations.[3,13]

Unresolved symptoms can result in long-term consequences[3]

When surveyed about the impacts of XLH:

93% of adult patients reported difficulties with mobility compared to 14% of the general population[14]

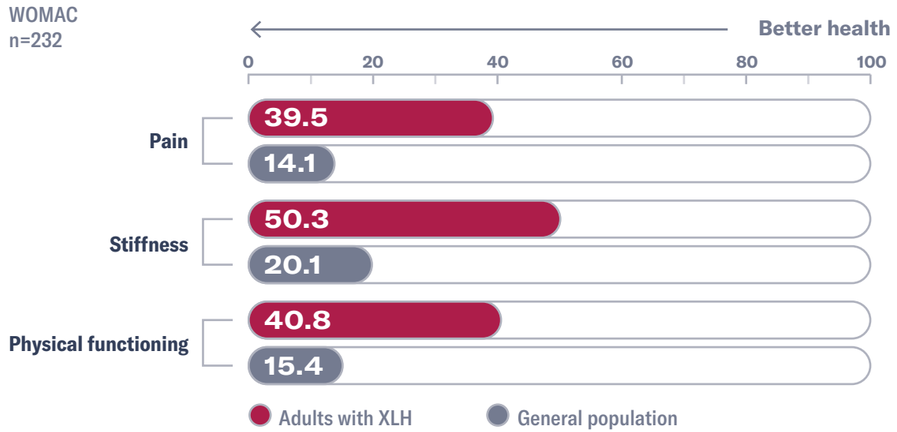
84% of adults believed that over time, their chronic hypophosphatemia had a greater impact and affected more areas of their lives[12]

44% of adult patients reported having a history of fractures or pseudofractures[3]

Effects on physical functioning and mobility in adults with XLH

In adult patients, XLH not only manifests as chronic pain but also can manifest as frequent fractures/pseudofractures and limitations in physical mobility.[3,4,7]

Patient-reported outcomes related to pain, stiffness, and physical limitations in adults with XLH[3,15,16]



Data were taken from a 2019 international burden-of-disease survey conducted in 232 adult patients with XLH. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a questionnaire designed to assess pain, stiffness, and physical function in patients with hip and/or knee osteoarthritis. It has been used among patients with different conditions, including low back pain, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia.[3,17]

Accurate diagnosis and early disease management can help minimize the lifelong XLH burden on your patients.

Symptoms of XLH

Childhood symptoms vary and appear early in life[4,7,12]

Some symptoms manifest as rickets and osteomalacia. Chronically low levels of serum phosphorus negatively impact bone formation, dental development, muscle/nerve function, and energy levels.[4,7,12]

Every patient with XLH is different. A patient does not need to show all of the following symptoms to have XLH.[4]

Skeletal defects

- Rickets[4]
- Osteomalacia[4]
- Lower extremity abnormalities[4] (eg, leg bowing and knock knees)
- Short stature[4]
- Delayed walking[7]
- Bone pain[7]
- Craniosynostosis[2,7]
- Chiari malformations[2,7]

Muscular dysfunction

- Stiffness[3,18]
- Pain[3,18]
- Weakness[3,18]
- Gait disturbances[3]

Dental abnormalities

- Dental abscesses[19]
- Tooth loss[18]

Other symptoms

- Fatigue[19]

Adult symptoms may exist from childhood, but new symptoms may also be experienced in adulthood[1,3,4,7,12]

Most adults with XLH have been living with symptoms since childhood and may develop new complications later in life. Over time, people living with XLH learn to adapt and compensate for chronic pain, fatigue, and muscle dysfunction.[1,3,12]

As a chronic and progressive disease, XLH requires careful monitoring and early management of symptoms.[1,4,7]

Existing symptoms from childhood:

- Osteomalacia[3]
- Lower extremity abnormalities[2,19]
- Short stature[2]
- Skeletal pain[3,20]
- Craniosynostosis[2,7]
- Chiari malformations[2,7]
- Fatigue[12]
- Dental abscesses[7]

Muscular dysfunction:

- Stiffness[3,18]
- Pain[3,18]
- Weakness[3,18]
- Gait disturbances[3]

Symptoms experienced in adulthood:

- Enthesopathy[2,3,7]
- Spinal stenosis[3]
- Osteoarthritis[2,3,7]
- Fractures/ pseudofractures[1,2,7]
- Hearing loss[2,7]

Dental abnormalities:

- Periodontitis[7]

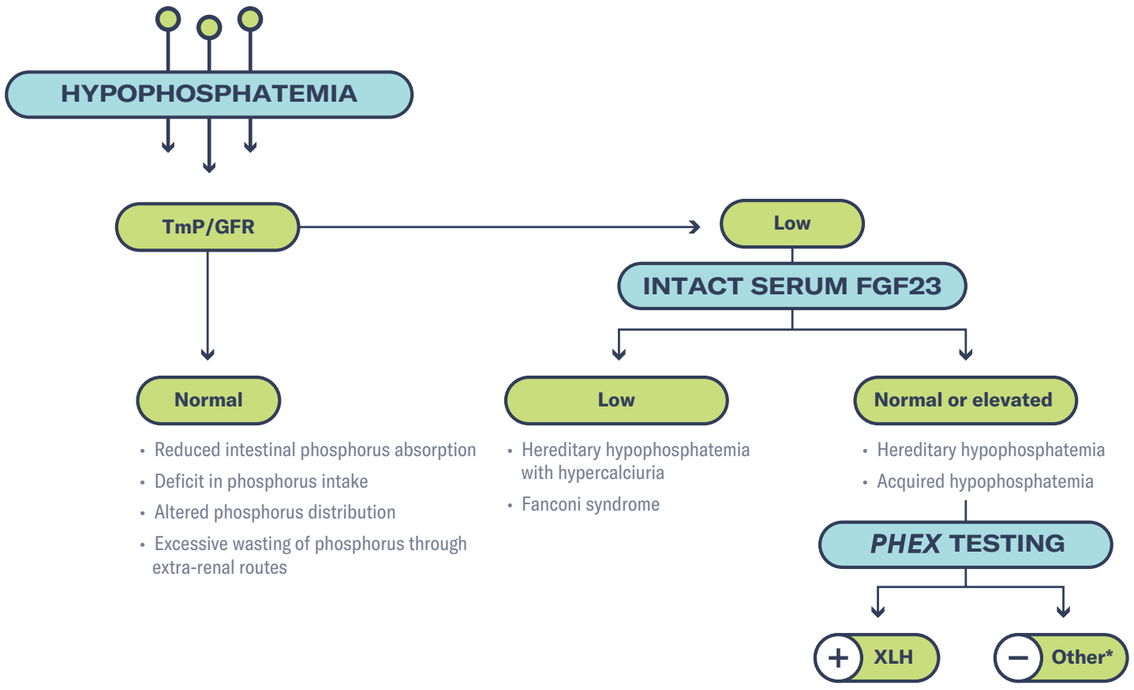
Symptoms of XLH such as chronic pain or fatigue can confound an accurate XLH diagnosis, leading to increased disease burden.[12]

Diagnosing XLH

Establish an accurate diagnosis by testing fasting serum phosphorus levels[2,4,6]

In both children and adults, low serum phosphorus levels are a biochemical finding that can help establish an accurate diagnosis for XLH.[2,4,6]

Evaluating patients with low phosphorus levels[18,21,22]



*Other genetic or acquired forms of hypophosphatemia.

TmP/GFR=ratio of tubular maximum reabsorption of phosphorus to glomerular filtration rate.

XLH is commonly misdiagnosed

Misdiagnosis of XLH may lead to inappropriate disease management, which can lead to increased symptom severity. XLH can be misdiagnosed as nutritional rickets, osteomalacia, hypophosphatasia, Pyle disease, or physiologic bowing.[4,18,19,23]

How to confirm an XLH diagnosis

Family history, clinical findings, and biochemical tests can help establish a diagnosis of XLH. Additionally, a diagnosis of XLH can be confirmed through genetic testing for variants of the PHEX gene.[4,18,19,23]

Predominant clinical findings in children and adults with XLH[2,4,22,24]

Biochemical Test	XLH
Serum phosphorus	↓ Down
$1,25(OH)_2D$	↓ Down or inappropriately normal
25(OH)D	Normal
TmP/GFR	↓ Down
ALP	↑ Up
Serum calcium	Normal
Urinary calcium	Normal to decreased
PTH	Normal to slightly up

$1,25(OH)_2D$=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 phosphorus to glomerular filtration rate.

Prioritize testing your patient's fasting serum phosphorus levels in addition to clinical, radiographic, and other biologic findings in order to accurately diagnose XLH.[2,4]

Managing XLH

XLH management strategies

The progressive nature of XLH may lead to increasing clinical consequences over time. Managing XLH early can interrupt disease progression and help prevent symptoms from advancing.[4,6,12]

Ways to manage XLH[6]:

- Normalizing levels of serum phosphorus to promote the healing of rickets and osteomalacia
- Correcting or reducing bowing of the lower extremities and addressing growth issues (for children)
- Preventing and/or healing of fractures and pseudofractures (for adults)
- Relieving bone, muscle, and joint pain and/or stiffness (for adults)

Other strategies to help manage XLH symptoms[18]:

- Medication and supplements
- Orthopedic interventions
- Physical therapy
- Dental care
- Treatment for hearing loss
- Preventing primary or secondary complications

Actor portrayal

Although XLH is chronic, there are ways to manage the disease and its symptoms.[18]

Comprehensive care for patients

Nonspecific symptoms of XLH lead to a multi-disciplinary approach to achieve diagnosis and treatment. A care team can provide treatment and disease education. This team may include other healthcare professionals such as:

- Orthopedic surgeon[4]
- Genetic counselor[2]
- Nephrologist[6]
- Pediatrician[25]
- Occupational or physical therapists[6]
- Rheumatologist[6]
- General practitioner[6]
- Clinical geneticist[6]
- Pain specialist[25]
- Dentist[6]

Connect the symptoms.

It could be XLH

- XLH is a hereditary, chronic, and progressive disease[2-4]
- Although XLH is chronic, you can help your patients learn ways to manage their disease[3,18]
- Prioritize testing your patient's fasting serum phosphorus to accurately diagnose XLH[2,4]

To learn more about XLH and connect with us, visit XLHLinkHCP.com

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