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# X-Linked Hypophosphatemia

Synonyms: X-Linked Hypophosphatemic Rickets (XLHR); X-Linked Vitamin D-Resistant Rickets; Hypophosphatemic Rickets, *PHEX*-Related

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## Summary

### Clinical characteristics

The phenotypic spectrum of X-linked hypophosphatemia (XLH) ranges from isolated hypophosphatemia to severe lower extremity bowing and/or craniosynostosis, usually involving the sagittal suture with consequent scaphocephaly. XLH typically manifests in the first two years of life with lower extremity bowing due to the onset of weight-bearing; however, it sometimes does not manifest until adulthood, as previously unevaluated short stature. Adults may present with calcification of the tendons, ligaments, and joint capsules, joint pain, fatigue, insufficiency fractures, and impaired mobility. Persons with XLH are prone to spontaneous dental abscesses; sensorineural hearing loss has also been reported. Rarely, individuals with XLH can suffer from spinal stenosis, Chiari I malformation, syringomyelia, and/or raised intracranial pressure.

### Diagnosis/testing

The diagnosis is established in a proband with characteristic clinical, biochemical, and radiographic findings by identification of a hemizygous *PHEX* pathogenic variant in a male proband or a heterozygous *PHEX* pathogenic variant in a female proband on molecular genetic testing.

### Management

*Targeted therapy:* Burosumab, a monoclonal antibody against FGF23. If burosuman is unavailable, conventional treatment with oral phosphate and active vitamin D analogues (alfacalcidol or calcitriol) to improve pain, promote fracture healing, and, in growing children, to correct and/or prevent bone deformation. Dental health may also improve with pharmacologic therapy.

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*Supportive care:* Craniosynostosis treatment by craniofacial specialists; persistent lower extremity bowing and/or torsion resulting in misalignment of the lower extremity may require surgery; total hip or knee arthroplasty as needed for degenerative joint disease; rehabilitation, physiotherapy, and analgesics for musculoskeletal pain; surgical treatment for those with tertiary hyperparathyroidism; good oral hygiene with flossing, regular dental care, fluoride treatments, and sealants to prevent dental abscesses; standard treatment of sensorineural hearing loss; education and psychosocial support; standard treatment of cardiovascular comorbidities; consider physical medicine and rehabilitation, analgesics as needed, and evaluation for sleep apnea in those with fatigue.

*Surveillance:* For individuals on burosumab therapy, regular monitoring of serum concentrations of phosphate, calcium, creatinine, alkaline phosphatase, and intact parathyroid hormone. For those on conventional treatment with active vitamin D and phosphate supplementation, additional testing includes urinary calcium and creatinine to assess for hypercalciuria; periodic renal ultrasound examination to assess for nephrocalcinosis. For all individuals, assess growth and lower limb alignment at each visit throughout childhood; craniofacial examination at each visit throughout infancy; clinical assessment of joint mobility and pain at each visit; imaging of painful areas to assess for calcifications, pseudofractures, and/or insufficiency fractures; dental evaluation every six months; hearing evaluation and evaluation for Chiari I malformation performed based on clinical suspicion; assess psychosocial impact, fatigue, sleep issues, and quality of life at each visit; monitor weight, blood pressure, and cardiovascular risk factors at each visit.

*Agents/circumstances to avoid:* Treatment with phosphate without 1,25-dihydroxyvitamin D, because of the increased risk for secondary hyperparathyroidism. Although 1,25-dihydroxyvitamin D has been used as a single agent, this may increase the risk for hypercalcemia, hypercalciuria, and nephrocalcinosis. Bisphosphonates or osteoporosis medications may cause deterioration of osteomalacia in some individuals.

*Evaluation of relatives at risk:* Molecular genetic testing (if the *PHEX* pathogenic variant has been identified in the family) or biochemical testing of first-degree relatives at risk to ensure early treatment for optimal outcome.

*Pregnancy management:* There is generally no need for additional fetal monitoring or cesarean sections in pregnant women with XLH. Burosumab is not recommended during pregnancy. The benefit of phosphate and active vitamin D analogs in pregnant women who have XLH remains debated. Most women with XLH who are on oral phosphate and active vitamin D therapy at the time of conception are continued on treatment throughout the pregnancy with vigilant monitoring of urinary calcium-to-creatinine ratios to detect hypercalciuria early in order to modify treatment accordingly.

## Genetic counseling

XLH is inherited in an X-linked manner; hemizygous males and heterozygous females are similarly affected. Affected males transmit the *PHEX* pathogenic variant to all of their daughters (who will be heterozygotes and will be affected) and none of their sons. Affected females have a 50% chance of transmitting the pathogenic variant to each child: male and female offspring who inherit the pathogenic variant will be affected. The severity of manifestations can differ among family members who inherit a *PHEX* pathogenic variant; intrafamilial clinical variability does not correlate with the sex of the affected family member. If the *PHEX* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for XLH are possible.

# Diagnosis

For the purposes of this *GeneReview*, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth as it determines clinical care [Caughey et al 2021].

## Suggestive Findings

X-linked hypophosphatemia (XLH) **should be suspected** in an individual with the following clinical, radiographic, laboratory, and family history findings. Note: XLH generally affects males and females similarly.

**Clinical findings in children**

- Clinical signs of rickets resistant to treatment with regular vitamin D
  - Progressive lower extremity bowing
  - Decrease in height velocity after the child starts ambulating
  - Epiphyseal swelling
  - Harrison groove (a horizontal channel at the lower end of the chest caused by the diaphragm pulling the osteomalacic bone inward)
  - Rachitic rosary (visibly prominent costochondral joints)
- Craniosynostosis and/or craniotabes (softening of the skull bone)
- Dental abscesses

**Clinical findings in adults**

- Short stature, sometimes disproportionate with short legs
- Joint pain, enthesopathy, and decreased joint mobility, particularly at the hips, spine (which may cause spinal stenosis), and shoulders
- Insufficiency fractures
- Dental abscesses
- Fatigue, chronic pain, muscle atrophy, weakness [Kara et al 2023], and sleep disturbances
- Sensorineural hearing loss
- Chiari I malformations (mostly asymptomatic in children)

**Radiographic findings**

- Rickets in growing children. Metaphyses may be widened, frayed, or cupped (most often affecting lower limbs, but any metaphysis can be involved); excessive limb bowing in adults may indicate presence of rickets during skeletal growth.
- Rachitic rosary or beading of the ribs from poor skeletal mineralization leading to overgrowth of the costochondral joint cartilage
- Insufficiency fractures
- Looser zones or pseudofractures
- Calcification of the tendons, ligaments, and joint capsules in adults
- Radiographically dense bones (in contrast to nutritional, calcipenic, or vitamin D deficiency-related rickets, or osteomalacia). Diffuse osteosclerosis may be seen particularly in the axial skeleton at the late stage.

**Laboratory findings**

- Low serum phosphate concentration for age (although individuals with milder manifestations may be normophosphatemic [Dahir et al 2022a])
- High alkaline phosphatase (ALP) for age (bone-specific ALP or total ALP in the absence of liver disease) is a biochemical indicator of rickets/osteomalacia.

- **Reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR).** The age-related normal ranges for TmP/GFR are shown in Table 1. The tubular resorption of phosphate (TRP) must first be calculated as follows (see TmP/GFR calculator):
  - TRP = 1 - [(urine phosphate ÷ plasma phosphate) x (plasma creatinine ÷ urine creatinine)]

  In those with TRP <0.86, the TmP/GFR can be calculated directly as follows:
  - TmP/GFR = TRP x plasma phosphate

  Note: Historically, the nomogram-based method described by Walton & Bijvoet [1975] was used to determine the TmP/GFR. However, it may overestimate values in children [Alon & Hellerstein 1994].

**Table 1.** Age-Related Normal Range of TmP/GFR

| Age | Sex | Range (mg/dL) | Range (mmol/L) |
|---|---|---|---|
| Birth | Both | 3.6-8.6 | 1.43-3.43 |
| 3 mos | Both | 3.7-8.25 | 1.48-3.30 |
| 6 mos | Both | 2.9-6.5 | 1.15-2.60 |
| 2-15 yrs | Both | 2.9-6.5 | 1.15-2.44 |
| 25-35 yrs | Male | 2.5-3.4 | 1.00-1.35 |
| | Female | 2.4-3.6 | 0.96-1.44 |
| 45-55 yrs | Male | 2.2-3.4 | 0.90-1.35 |
| | Female | 2.2-3.6 | 0.88-1.42 |
| 65-75 yrs | Both | 2.0-3.4 | 0.80-1.35 |

Based on Payne [1998]
Note: For the calculation of TRP the urine should be collected as an untimed urine after an overnight fast.

### Other suggestive laboratory findings

- Normal serum calcium and 25-hydroxyvitamin D. Note: If the serum 25-hydroxyvitamin D concentration is low, vitamin D levels need to be replete before the diagnosis of XLH can be confirmed by laboratory testing.
- Lack of hypercalciuria (in untreated individuals with XLH). While TmP/GFR is calculated from paired plasma and urine samples, 24-hour urine collections are recommended to assess urinary calcium excretion in continent individuals [Laurent et al 2021].
- Inappropriately normal serum calcitriol (1,25-dihydroxyvitamin D) concentration in the presence of hypophosphatemia
- Secondary hyperparathyroidism (i.e., without hypercalcemia). In one large cohort, 25% of individuals with XLH had secondary hyperparathyroidism [Lecoq et al 2020]. Rarely (approximately ≤10%), individuals with XLH and long-standing secondary hyperparathyroidism develop tertiary hyperparathyroidism (i.e., with hypercalcemia) from parathyroid adenomatous hyperplasia [Savio et al 2004, Lecoq et al 2020]. Hyperparathyroidism is likely promoted by excessive phosphate supplementation, as the consequent transient increase in blood phosphate levels is associated with decreased levels of ionized calcium.
- Absence of hypouricemia, glycosuria, bicarbonaturia, low molecular weight (tubular) proteinuria, or aminoaciduria (presence of any of these should raise suspicion of renal Fanconi syndrome). However, in long-standing XLH, particularly when complicated by nephrocalcinosis, some degree of renal tubular acidosis may be acquired [Seikaly et al 1996].
- Fibroblast growth factor 23 (FGF23) is usually increased in individuals with XLH. However, there is a lack of standardization of FGF23 assays, and results should be interpreted with caution due to preanalytic and analytic issues. Reference ranges are also not universally established, and higher cutoff values are

associated with poor sensitivity [Hartley et al 2022]. An intact FGF23 >27 pg/mL best distinguished between FGF23-dependent and FGF23-independent causes of hypophosphatemic rickets [Hartley et al 2022].

**Family history** is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

**Note: Bone biopsy** is an invasive procedure which is generally **not required** to establish the diagnosis of XLH. Only in diagnostically challenging individuals and in the hands of experts should bone biopsy be considered. Periosteocytic (unmineralized) lesions may be observed in genetic disorders involving osteocytes (which express and secrete FGF23), including XLH [Fratzl-Zelman et al 2022].

## Establishing the Diagnosis

The diagnosis of XLH **is established** in a proband with suggestive clinical findings and typical biochemical and radiographic findings by identification of a pathogenic (or likely pathogenic) hemizygous (in a male proband) or heterozygous (in a female proband) variant in *PHEX* on molecular genetic testing [Ariceta et al 2023] (see Table 2).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *PHEX* variant of uncertain significance does not establish or rule out a diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

### Option 1

**Single-gene testing.** Sequence analysis of *PHEX* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

**Testing for somatic mosaicism.** If no *PHEX* germline pathogenic variant is found, sequence analysis with methods to detect somatic mosaicism may be warranted. Sequence analysis of DNA derived from saliva or skin (whether visibly affected or not) may detect a pathogenic variant not detected in DNA isolated from blood [Goji et al 2006, Owen et al 2009, Lin et al 2020, Pasmant & Pacot 2020]. Note: Sensitivity to detect low-level mosaicism of a somatic pathogenic variant is greatest using massively parallel sequencing (i.e., next-generation sequencing) in tissues other than blood, and in particular will be of high yield when analyzing affected tissues.

**A multigene panel** that includes *PHEX* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4)

Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

### Option 2

**Comprehensive genomic testing** does not require the clinician to determine which individual gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

**Table 2.** Molecular Genetic Testing Used in X-Linked Hypophosphatemia

| Gene [1] | Method | Proportion of Probands with a Pathogenic Variant [2] Detectable by Method |
|---|---|---|
| *PHEX* | Sequence analysis [3] | ~85% [4, 5] |
| | Gene-targeted deletion/duplication analysis [6] | ~15% [4] |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on variants detected in this gene.
*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*4.* Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
*5.* Deep intronic pathogenic variants may be identified by RNA-based analyses (e.g., sequence analysis of PCR-amplified RNA from urine-derived cells) [Grimbly et al 2023].
*6.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

# Clinical Characteristics

## Clinical Description

The clinical presentation of X-linked hypophosphatemia (XLH) ranges from isolated hypophosphatemia to craniosynostosis and/or severe lower extremity bowing. The diagnosis is typically made in the first two years of life, when lower extremity bowing becomes evident with the onset of weight-bearing; however, because of the extremely variable presentation, the diagnosis is sometimes not made until adulthood. Overall, XLH significantly impairs health-related quality of life (more so than, for example, axial spondylarthritis [Che et al 2016]), posing a significant socioeconomic and psychosocial burden [Skrinar et al 2019, Hawley et al 2021, Seefried et al 2021].

**Table 3.** X-Linked Hypophosphatemia: Frequency of Select Features

| Feature | % of Persons w/Feature | | Comment |
|---|---|---|---|
| | Children | Adults | |
| Short stature | 50%-85% | | Percent of persons w/feature is dependent on age, treatment, population, & definition of feature used. |
| Lower limb bowing | 70%-100% | | |
| Bone & joint pain | 50%-80% | 70%-100% | |

*Table 3. continued from previous page.*

| Feature | % of Persons w/Feature | | Comment |
|---|---|---|---|
| | Children | Adults | |
| Enthesopathy | | 70%-100% | Not clinically evident in younger children but develops progressively w/age in all adults, particularly after age 30 yrs |
| Dental complications | 40%-50% | 60%-85% | Incidence becomes progressive w/age. |
| Craniosynostosis | 5%-10% | | Potentially underrecognized |
| Need for surgical interventions | 40%-50% | 60%-95% | Most commonly osteotomies, joint replacement surgery, skull surgery |
| Fractures | | 20%-50% | • Incl insufficiency & pseudofractures<br>• Fractures are not typical in children. |
| Hearing loss &/or tinnitus | 2%-8% | 14%-55% | Actual incidence of hearing loss &/or tinnitus may be higher than reported. |

Based on Skrinar et al [2019], Seefried et al [2021], Herrou et al [2022], Sandy et al [2023]

**Note:** All heterozygous females are affected. The clinical and biochemical features of XLH are the same in females and males. The severity can differ among members of the same family; however, males are not necessarily more severely affected. Only a somewhat more pronounced growth delay and skeletal dysmorphism in hemizygous males has been reported in several studies [Hardy et al 1989, Laurent et al 2021]. Also, preliminary studies suggest that males may need higher doses to achieve similar biochemical disease control during treatment [Filler et al 2023].

## Skeletal Abnormalities

Individuals with XLH commonly present with short stature and lower extremity bowing (valgus or varus deformities). Joint pain and impaired mobility associated with enthesopathy, osteophyte formation, or other radiologic findings can occur.

**Short stature.** In a longitudinal study that assessed growth in children prior to and during treatment, untreated children had disproportionate total height (2.48 standard deviations [SD] below the mean) to sitting height (0.99 SD below the mean); lower leg length was 2.90 SD below the mean [Zivičnjak et al 2011]. During treatment there was an uncoupling of growth between the trunk and the legs: the difference between sitting height and lower leg length became more pronounced as growth progressed.

Adults with XLH have a significantly reduced final height (1.9 SD below the mean). Individuals appear disproportionate, with leg length scores (2.7 SD below the mean) being significantly lower than those for sitting height (1.1 SD below the mean) [Beck-Nielsen et al 2010].

**Lower extremity bowing.** Genu varum or genu valgum can occur. Measurement of both the intercondylar and intermalleolar distance are useful for monitoring.

Lower extremity torsion and rotation may also be seen, particularly at the femur but also at the tibia [Scorcelletti et al 2022].

Insufficient pharmacologic therapy during childhood and adolescence may lead to persistent lower extremity deformities. In addition, some individuals have persistent lower extremity bowing and torsion despite what appears to be adequate pharmacologic therapy. In these individuals, surgical treatment is frequently pursued for misalignment.

**Joint pain and impaired mobility.** In adults, calcification of the tendons (non-inflammatory enthesopathies), ligaments, and joint capsules can cause joint pain and impair mobility [Polisson et al 1985, Herrou et al 2022].

Calcification of vertebral ligaments has been reported [Beck-Nielsen et al 2010, Herrou et al 2023], which may cause spinal stenosis, spinal cord compression, swallowing difficulties, and even paraplegia [Vera et al 1997].

Increased osteophyte formation with spinal hyperostosis and arthritis or fusion of the sacroiliac joints can also lead to pain and compromised mobility. This often mimics ankylosing spondylitis [Dahir et al 2022a].

Looser zones or pseudofractures that may be symptomatic or asymptomatic are commonly seen and have been reported to occur at any age.

Lower limb muscle power and functional capacity are reduced in adults with XLH and are associated with low levels of physical activity [Orlando et al 2022, Kara et al 2023]. However, severe muscle pain and weakness (particularly when it also effects the upper limbs) should prompt consideration of another cause (e.g., tumor-induced rickets/osteomalacia or Fanconi syndrome).

## Cranial Structures

Cranial abnormalities include frontal bossing, craniosynostosis, and Chiari I malformations. A detailed cephalometric study revealed increased head length, decreased occipital breadth, and a low mean cephalic index (the ratio of the maximum width of the head multiplied by 100 divided by its maximum length) [Pronicka et al 2004].

A retrospective study of 44 children reported that 59% had partial or complete fusion of the sagittal suture, 25% showed protrusion of the cerebellar tonsils, although only 5% had neurologic symptoms, and 9% received neurosurgery [Rothenbuhler et al 2019]. In a large online survey, 8% of children and adults reported Chiari I malformations, while 3%-6% underwent cranial surgery [Skrinar et al 2019].

The presentation of craniosynostosis in individuals with XLH tends to manifest slightly later than congenital craniosynostosis and can vary in severity and appearance, making diagnosis difficult and resulting in inconsistent clinical outcomes [Munns et al 2023a].

## Dental Abnormalities

Persons with XLH are prone to spontaneous dental abscesses, which have been attributed to changes in the dentin component of teeth. Irregular spaces with defective mineralization in the tooth dentin have been described [Boukpessi et al 2006]. Panoramic imaging reveals enlarged pulp chambers with prominent pulp horns, leading to susceptibility to abscess formation [Baroncelli et al 2006]. Recurrent dental abscesses may result in premature loss of decidual and permanent teeth. Some studies have suggested that dental health can improve in those treated early with phosphate and active vitamin D; dental health improvement may be more significant in those treated with burosumab [Connor et al 2015, Biosse Duplan et al 2017, Gadion et al 2022, Kato et al 2023].

## Hearing Loss

Sensorineural hearing loss and tinnitus are reported in adults and children; the actual prevalence of hearing loss is not known [Chesher et al 2018, Skrinar et al 2019]. Radiographic evaluation of a small number of persons with XLH and hearing loss showed generalized osteosclerosis and thickening of the petrous bone [O'Malley et al 1988], a finding that has not been evaluated in other cohorts. In some instances, hearing loss has been attributed to bony impingement on the auditory nerve or abnormalities in the ossicles.

## Nephrocalcinosis

Nephrocalcinosis and nephrolithiasis typically develop as a complication of treatment with phosphate and active vitamin D analogs rather than as a primary complication of XLH. Nephrocalcinosis is reported in 25%-60% of individuals with XLH, and nephrolithiasis in about 10%. With the expanding use of burosumab treatment, it is

expected that these complications will become less prevalent [Seefried et al 2023]. Hypercalciuria should be avoided in XLH; hypocitraturia is commonly observed, whereas hyperoxaluria is not [Colares Neto et al 2019, Sandy et al 2023]. Rarely, kidney failure may occur; in those instances, concomitant causes of progressive kidney disease (including underlying genetic causes) should be considered [Nielsen et al 2022].

### Prognosis

One study reported an increased risk of mortality in older adults with XLH (hazard ratio: 2.93; 95% confidence interval: 1.24-6.91) [Hawley et al 2020].

## Genotype-Phenotype Correlations

Several studies have evaluated genotype-phenotype correlations in XLH. Overall, however, there is little consistent evidence for genotype-phenotype correlations in XLH.

- One study involving 59 persons correlated dental and hearing defects with pathogenic variants in exons near the 5' end of *PHEX* and increased head length with pathogenic variants in exons near the 3' end [Popowska et al 2001].
- Some studies suggested a correlation between more severe bone disease (defined by the severity of bowing and a history of osteotomies) and truncating variants [Holm et al 2001, Park et al 2021] or pathogenic variants in the C-terminal portion [Song et al 2007]. However, other studies have not confirmed this [Zhang et al 2019, Ishihara et al 2021, Rodríguez-Rubio et al 2021].
- A study by Morey et al [2011] showed that individuals with nonsense variants, insertions, deletions, and splice site variants leading to premature stop codons had lower tubular resorption of phosphate and lower calcitriol levels than those with missense variants or in-frame deletions.
- c.*231A>G in *cis* with the out-of-frame duplication of exons 13-15 is common in individuals from North America who are frequently undiagnosed with XLH due to normal height and normophosphatemia or misdiagnosed with ankylosing spondylitis [Dahir et al 2022a]. These individuals may also require lower pharmacologic treatment doses.

## Penetrance

Penetrance is 100%. There is no difference between penetrance in males and females.

## Nomenclature

The designated term for X-linked hypophosphatemia in the 2023 revision of the Nosology of Genetic Skeletal Disorders is hypophosphatemic rickets, *PHEX*-related [Unger et al 2023]. Other terms that have been used to refer to X-linked hypophosphatemia include:

- X-linked dominant hypophosphatemic rickets (XLHR)
- X-linked rickets (XLR)
- Vitamin D-resistant rickets
- Hypophosphatemic vitamin D-resistant rickets (HPDR)
- Phosphate diabetes (a more general term referring to renal phosphate wasting conditions)
- Familial hypophosphatemic rickets

## Prevalence

The incidence of XLH is 3.9-5 in 100,000 live births [Davies & Stanbury 1981, Beck-Nielsen et al 2009]. Lower prevalence rates ranging from 1.3 to 1.7 in 100,000 have been reported, which are likely underestimates due to misdiagnosis [Rafaelsen et al 2016, Hawley et al 2020, Sandy et al 2023].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PHEX*.

## Differential Diagnosis

**Nutritional rickets.** The radiographic changes associated with nutritional and hereditary forms of rickets are similar. However, bone appears osteopenic in nutritional, calcipenic, and vitamin D deficiency-related rickets, whereas bone is dense in X-linked hypophosphatemia (XLH). Muscle weakness is often more pronounced in nutritional rickets. Dental abscesses, enthesopathy, and calcification of spinal ligaments appear to be specific to XLH. Hypocalcemic and vitamin D deficiency-related forms of rickets can be distinguished from XLH by biochemical testing:

- In vitamin D-deficient rickets, the 25-hydroxyvitamin D serum concentration is low and the calcium concentration may be low or normal.
- In hypophosphatemic rickets, serum concentrations of 25-hydroxyvitamin D and calcium are normal. Concomitant vitamin D deficiency should be corrected before establishing a diagnosis of XLH.

Note: Genetic disorders of vitamin D metabolism that may mimic nutritional rickets clinically, radiographically, and biochemically (but can be distinguished from XLH on all three domains) include those associated with pathogenic variants in *CYP2R1*, *CYP3A4*, *CYP27B1*, and *VDR* [Laurent et al 2021].

**Hypophosphatemic rickets.** The different forms of hypophosphatemic rickets are distinguished from XLH by the presence of hypercalciuria (untreated XLH is associated with normal urinary calcium) or the presence of elevated 1,25-dihydroxyvitamin D (XLH is associated with low or inappropriately normal serum 1,25-dihydroxyvitamin D) and inappropriately normal or elevated levels of fibroblast growth factor 23 (FGF23) (see Table 4). Mode of inheritance, clinical and radiographic features, and molecular genetic testing further help distinguish the different forms of hereditary hypophosphatemic rickets without hypercalciuria, of which XLH is by far the most common [Laurent et al 2021, Trombetti et al 2022].

**Table 4.** Hereditary Disorders with Renal Phosphate Wasting in the Differential Diagnosis of X-Linked Hypophosphatemia

| Gene(s) | Disorder | MOI | Comment / Key Features |
|---|---|---|---|
| *CLCN5* | Dent disease type 1 | XL | • Hypophosphatemia & hypercalciuria<br>• Suppressed FGF23<br>• 1,25-dihydroxyvitamin D may be ↑, normal, or low due to proximal tubular dysfunction.<br>• Low molecular weight proteinuria |
| *OCRL* | Dent disease type 2; Lowe syndrome | | |
| *DMP1*<br>*ENPP1* [1] | AR hypophosphatemic rickets (OMIM 241520; 613312) | AR | • Renal phosphate wasting w/o hypercalciuria<br>• Extremely rare |
| *EHHADH*<br>*GATM*<br>*HNF4A*<br>*NDUFAF6* | Fanconi renotubular syndrome (types 1-5) (OMIM PS134600) | AD<br>AR | Proximal renal tubule transport of many different substances impaired, incl phosphate, glucose, & low molecular weight proteins |
| *FAM20C* | Raine syndrome, milder form (OMIM 259775) [2] | AR | • Hypophosphatemia<br>• ↓ DMP1 activity leads to ↑ FGF23 production.<br>• Osteosclerotic skeletal changes |

*Table 4. continued from previous page.*

| Gene(s) | Disorder | MOI | Comment / Key Features |
|---|---|---|---|
| *FGF23* | AD hypophosphatemic rickets (ADHR) (OMIM 193100) | AD | • Renal phosphate wasting w/o hypercalciuria<br>• Onset can be delayed; rarely, phosphate wasting resolves later in life.<br>• The full-length active form of the protein is stabilized, leading to prolonged or enhanced FGF23 action.<br>• ADHR is much rarer than XLH. |
| *FGFR1*<br>*INPPL1* | Osteoglophonic dysplasia (OMIM 166250); opsismodysplasia (OMIM 258480) | AD<br>AR | • Severe skeletal dysplasia<br>• Hypophosphatemia & lower than expected 1,25-dihydroxyvitamin D levels<br>• ↑ FGF23 production from abnormal bone |
| *GNAS* | Fibrous dysplasia / McCune-Albright syndrome | Not inherited [3] | • Hypophosphatemic rickets<br>• Fibrous dysplasia of the bone; precocious puberty; café au lait macules<br>• Overproduction of FGF23 by the fibrous dysplastic bone results in renal phosphate wasting. |
| *HRAS*<br>*KRAS*<br>*NRAS* | Cutaneous skeletal hypophosphatemia syndrome [4] (OMIM 163200) | Not inherited [3] | • Hypophosphatemia is frequent & biochemically indistinguishable from that seen in XLH.<br>• Multiple cutaneous nevi; radiologic evidence of fibrous dysplasia<br>• FGF23 is the cause of the phosphate wasting. [5] |
| *KL* | Hypophosphatemic rickets w/ hyperparathyroidism [6] | AR | • Hypophosphatemia; inappropriately normal 1,25-dihydroxyvitamin D level<br>• Hyperparathyroidism<br>• ↑ alpha-klotho & ↑ FGF23 |
| *PTH1R* | Metaphyseal dysplasia, Jansen type (OMIM 156400) | AD | • Very short stature, more pronounced skeletal dysplasia<br>• Hypophosphatemia; hypercalciuria<br>• ↑ 1,25-dihydroxyvitamin D<br>• Osteopenia, prominent nephrolithiasis/ nephrocalcinosis |
| *SLC34A3* | Hereditary hypophosphatemic rickets w/hypercalciuria (OMIM 241530) | AR | • Hypophosphatemia; hypercalciuria<br>• ↑ 1,25-dihydroxyvitamin D<br>• Osteopenia, prominent nephrolithiasis/ nephrocalcinosis |

AD = autosomal dominant; AR = autosomal recessive; FGF23 = fibroblast growth factor 23; MOI = mode of inheritance; XL = X-linked

*1.* *ENPP1* pathogenic variants are associated with generalized arterial calcification of infancy as an allelic disorder.

*2.* Kinoshita et al [2014]

*3.* Caused by postzygotic somatic activating variants

*4.* Also referred to as Schimmelpenning-Feuerstein-Mims syndrome, linear sebaceous nevus syndrome, or epidermal nevus syndrome

*5.* Hoffman et al [2005]

*6.* Brownstein et al [2008]

In addition to the genes listed in Table 4, a variant of unknown significance in *SGK3* was associated with autosomal dominant hypophosphatemic rickets in one report [Cebeci et al 2020]. However, the causal role of this gene has not been confirmed by other studies.

Two studies reported an association between heterozygous variants in *SLC34A1* and *SLC9A3R1* and hypophosphatemic hypercalciuric nephrolithiasis/osteoporosis (NPHLOP) types 1 and 2, respectively [Prié et al 2002, Karim et al 2008]. However, the status of NPHLOP types 1 and 2 as bona fide autosomal dominant disorders is debated [Gale et al 2020]. (Of note, biallelic pathogenic variants in *SLC34A1* cause [autosomal recessive] infantile hypercalcemia type 2.)

**Tumor-induced (oncogenic) osteomalacia or rickets** is an acquired paraneoplastic syndrome associated with secretion of FGF23 by slow-growing mesenchymal tumors known as phosphaturic mesenchymal tumors, mixed connective tissue type. Features include renal phosphate wasting without hypercalciuria, skeletal deformities and growth restriction in children, and progressive muscle and bone pain [Trombetti et al 2022].

**Other acquired causes of FGF23-mediated hypophosphatemic osteomalacia or rickets** include medications including tenofovir and adefovir (which usually also cause renal Fanconi syndrome), frequent intravenous iron therapy with ferric carboxymaltose in persons without kidney insufficiency, and alcohol abuse [Hidaka et al 2021].

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with X-linked hypophosphatemia (XLH), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 5.** X-Linked Hypophosphatemia: Recommended Evaluations Following Initial Diagnosis

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Endocrine** | • Serum & urine calcium & phosphate<br>• PTH, 25-hydroxyvitamin D, creatinine, & alkaline phosphatase (total or bone specific) | |
| **Skeletal** | • Assess growth.<br>• Lower extremity radiograph (teleroentgenogram) & radiograph of the wrists to assess extent of skeletal disease<br>• Consider bone age radiograph to evaluate growth potential.<br>• Craniofacial exam for manifestations of craniosynostosis | In those diagnosed in childhood |
| | • Clinical assessment of joint mobility & pain<br>• Skeletal radiograph survey, esp of skeletal sites w/reported pain or restricted mobility, to assess for joint calcifications &/or insufficiency or pseudofractures | In those diagnosed in adulthood |
| **Neurologic** | Eval of those w/headache, vertigo, or other neurologic symptoms for Chiari I malformation | |
| **Dental** | Dental exam | |
| **Hearing** | Hearing eval | If hearing loss is clinically suspected |
| **Renal** | Renal ultrasound | |
| **Genetic counseling** | By genetics professionals [1] | To inform affected persons & families re nature, MOI, & implications of XLH to facilitate medical & personal decision making |
| **Psychosocial** | Assess for psychological & social support needs. | |

MOI = mode of inheritance; PTH = parathyroid hormone; XLH = X-linked hypophosphatemia
*1.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

Current guidelines recommend multidisciplinary team evaluation and management at tertiary referral centers for persons with XLH, with appropriate attention to transitioning from pediatric to adult care [Haffner et al 2019, Laurent et al 2021, Dahir et al 2022b, Trombetti et al 2022, Munns et al 2023b].

### Targeted Therapy

*In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure.* —ED

The aim of targeted therapy is to improve osteomalacia and rickets (including pseudofractures), improve pain, promote fracture healing in those with fractures or undergoing (planned or unplanned) surgery, or – in children – to stimulate growth and correct/prevent bone deformation [Carpenter et al 2011]. There may be some benefit for dental health as well. At the same time, the goal is to avoid complications of therapy.

**Table 6.** Targeted Treatment of Manifestations in Individuals with X-Linked Hypophosphatemia

| Treatment Class | Mechanism of Action | Specific Drugs | Comments |
|---|---|---|---|
| **Monoclonal antibody** | Target FGF23 to restore renal phosphate reabsorption & ↑ serum concentration of 1,25 dihydroxyvitamin D | Burosumab (Crysvita®) | • In clinical trials, burosumab improved radiographic signs of rickets, lower limb deformity, & height z scores in children compared to phosphate w/active vitamin D supplementation. [1] At 64 wks (but not at 40 wks), a significant improvement in the 6-min walking test was observed.<br>• In adults, burosumab compared to placebo improved joint stiffness & physical function & improved healing of pseudofractures as well as histologic signs of osteomalacia. [2] |
| **Oral phosphate w/ active vitamin D analogs** | Supplementation | Alfacalcidol or calcitriol (vitamin D analogs) | • Referred to as conventional therapy (although superiority of burosumab compared to phosphate w/active vitamin D has now been demonstrated in children). [3]<br>• Aim of therapy is to improve growth & rickets in children. In adults, this treatment may be considered in case of pseudofractures, bone pain, other symptoms (incl dental abscesses), &/or planned surgery.<br>• Biochemically, aim of therapy is to improve circulating phosphate, 1,25-dihydroxyvitamin D levels, & secondary hyperparathyroidism; however, oral phosphate w/active vitamin D analogues aggravates renal phosphate wasting, ↑ urinary calcium excretion w/risk of nephrocalcinosis, & further ↑ FGF23. [4] |

FGF23 = fibroblast growth factor 23

*1.* Carpenter et al [2018], Imel et al [2019], Whyte et al [2019]

*2.* Carpenter et al [2014a], Imel et al [2015], Ruppe et al [2016], Insogna et al [2018], Portale et al [2019], Brandi et al [2022]

*3.* Imel et al [2019]

*4.* Imel et al [2010]

**Burosumab (Crysvita®)** has been approved by regulatory agencies (including FDA, EMA, and others) for the treatment of XLH in children from age one year, adolescents, and adults. Burosumab is a recombinant human

monoclonal antibody (formerly called KRN23) targeting fibroblast growth factor 23 (FGF23) (see Molecular Pathogenesis). It is administered subcutaneously.

In clinical trials, burosumab improved radiographic signs of rickets, lower limb deformity, and height z scores in children compared to phosphate with active vitamin D supplementation [Carpenter et al 2018, Imel et al 2019, Whyte et al 2019]. At 64 weeks (but not at 40 weeks), a significant improvement in the six-minute walking test was observed. In adults, burosumab compared to placebo improved joint stiffness and physical function and improved healing of pseudofractures as well as histologic signs of osteomalacia [Carpenter et al 2014a, Imel et al 2015, Ruppe et al 2016, Insogna et al 2018, Portale et al 2019, Brandi et al 2022].

Any oral phosphate and active vitamin D analog should be discontinued at least one week before starting burosumab, to avoid excessive hyperphosphatemia and ectopic calcifications. Fasting serum phosphate should be targeted in the lower end of the normal reference range for age.

The recommended starting dose in **children** is 0.8 mg/kg of body weight every two weeks, but lower starting doses, such as 0.4 mg/kg of body weight, have been reported [Mughal et al 2023]. Fasting serum phosphate, alkaline phosphatase (ALP), and parathyroid hormone (PTH) is then monitored every two weeks for the first month, followed by monthly measurements for two months (after initiation or dose adjustments), until a steady state is reached. If fasting serum phosphate remains below the reference range for age after four weeks, the dose may be increased stepwise every four weeks by 0.4 mg/kg of body weight increments up to a maximum dose of 2 mg/kg of body weight or 90 mg. If fasting serum phosphate is above the reference range for age, the next dose should be withheld and the fasting serum phosphate monitored every two weeks. Once the serum phosphate is below the reference age for age, burosumab may be restarted at half the previous dose. In two studies, about half of affected children did not achieve a normal serum phosphate level, despite higher burosumab doses compared to those who did achieve normal phosphate levels [Ewert et al 2023, Walker et al 2023]. Yet, overall outcome was similar in both groups, suggesting that normalization of ALP and PTH is at least as relevant as serum phosphate levels. Also, adolescents appeared to require lower burosumab doses per body weight than children [Ewert et al 2023].

In **adults**, the recommended starting dose is 1.0 mg/kg of body weight every four weeks, up to a maximum dose of 90 mg. Fasting serum phosphate should be measured two weeks after the previous dose of burosumab, then monthly for two months, then monitored as appropriate. Dose adjustment is otherwise similar as in children. In some individuals, high peak and low trough phosphate levels may be avoided by (off-label) dosing every two weeks [Marcellino et al 2023].

Injection site reactions may occur. Burosumab is not recommended in individuals with XLH with severe kidney insufficiency, which is commonly characterized by decreased urinary phosphate excretion and consequent normalization of phosphatemia.

There are insufficient human data to support the safety of burosumab in pregnant women. Moreover, in animal studies, mineralization of the placenta, shortening of gestation, and premature birth have been observed. Burosumab was detected in offspring serum, indicating that it crosses the placenta, but there were no teratogenic effects. Still, given these findings, its use during pregnancy is discouraged. It is unknown whether burosumab or its metabolites are present in breast milk. Also, in animal toxicity studies with burosumab, ectopic mineralization due to hyperphosphatemia was observed in multiple tissues and organs, including the kidney, aorta, heart, lung, and the seminiferous tubules of the testes. The clinical relevance of these findings remains unknown. Both pregnancy and burosumab increase 1,25-dihydroxyvitamin D levels, increasing the risk of hypercalcemia and nephrolithiasis.

Burosumab treatment has been associated with increased PTH levels in some individuals; therefore, monitoring PTH levels may be considered. Coadministration of burosumab with calcimimetics is contraindicated due to the

risk of hypocalcemia. Individuals receiving burosumab may develop anti-drug antibodies, which may be associated with declining phosphate levels and may require increased dosing.

**Oral phosphate with active vitamin D analogs** (alfacalcidol or calcitriol) is also called conventional therapy (although superiority of burosumab compared to phosphate with active vitamin D has now been demonstrated in children [Imel et al 2019]). It aims to improve circulating phosphate, 1,25-dihydroxyvitamin D levels, and secondary hyperparathyroidism. However, it aggravates renal phosphate wasting, increases urinary calcium excretion with a risk of nephrocalcinosis, and further increases FGF23 [Imel et al 2010].

In **children**, this treatment usually begins at the time of diagnosis and continues until long bone growth is complete. Starting this treatment earlier (prior to age one year) has been associated with more favorable outcomes [Mäkitie et al 2003]. Treatment for most children consists of oral phosphate administered three to five times daily and high-dose vitamin D analogs. Two different regimens have been used, but they have not been compared [Imel et al 2023]:

- **Low dose.** Treatment is generally started at a low dose to avoid the gastrointestinal side effects of diarrhea and gastrointestinal upset that is often associated with high-dose phosphate supplementation. The doses are then titrated to a weight-based dose of alfacalcidol at 30-50 ng/kg of body weight per day or calcitriol at 20-30 ng/kg of body weight per day administered in two to three divided doses, and phosphate at 20-40 mg/kg of body weight per day administered in three to five divided doses [Carpenter et al 2011].
- **High dose.** Some clinicians favor a high-dose phase of treatment for up to a year. The high-dose phase consists of calcitriol at 50-70 ng/kg of body weight per day (up to a maximum dose of 3.0 µg daily) along with the phosphate [Sabbagh et al 2014].

Doses are adjusted based on (1) evidence of therapeutic success, including reduction in serum ALP activity, improvements in bone deformities, improvement in radiographic rachitic changes and/or pseudofractures, and (in those with open growth plates) improved growth velocity; and (2) evidence of therapeutic complications including secondary hyperparathyroidism, hypercalciuria, and nephrocalcinosis. Note: Normalization of the serum phosphate concentration is not a therapeutic goal with oral phosphate and vitamin D analogs, as normal serum phosphate concentration frequently indicates overtreatment and increases the risk for treatment-related complications. Phosphate levels will also vary with timing of the blood test in relation to the latest phosphate dose. Spreading out the dose in multiple aliquots over the day (or adding it to the drinking water bottle) may help to achieve more stable and sustained phosphate levels.

Initially, during healing of rickets, ALP levels may paradoxically increase. After growth is complete, lower doses of the medications can be used to reach the treatment goals.

Response to oral phosphate and calcitriol treatment is variable. Jehan et al [2008] described differences in growth during treatment that are associated with different vitamin D receptor promoter haplotypes, providing a possible explanation for some of the clinical variability observed in XLH.

A healthy diet with sufficient fluid intake, as well as nutritional calcium intake from dairy products, is recommended. In fact, a pilot randomized control trial in children showed that dairy products in equimolar doses may be more effective and safer than phosphate tablets [Jørgensen et al 2019]. In contrast, calcium supplements are discouraged because they may lower phosphate absorption and increase the risk of kidney stones [Haffner et al 2019]. Phosphate-rich sodas are also not disadvised. **Dietary counseling** should be considered in individuals with XLH to address these points.

In **adults**, the role of phosphate and active vitamin D treatment has not been well studied; treatment is generally reserved for individuals with skeletal pain, upcoming orthopedic surgery, biochemical evidence of osteomalacia with elevated ALP, or recurrent pseudofractures or insufficiency fractures [Carpenter et al 2011]. There are many adults in whom therapy has been discontinued after childhood and completion of growth (often accompanied by

lack of transition from pediatric to adult care and consequent loss of follow up). These adults may experience a paucisymptomatic "honeymoon phase" until developing musculoskeletal pain, stiffness, and mobility problems in later adulthood. It is not known whether long-term treatment in asymptomatic adults could modify long-term outcomes [Shanbhogue et al 2018, Seefried et al 2023].

The doses that are frequently employed in adults are in the range of 0.50 to 0.75 µg of calcitriol and 1 to 1.5 µg of alfacalcidol daily; the phosphate is given is 750-1,000 mg per day, ideally in three to four divided doses. As with children, the phosphate dose is slowly titrated to avoid gastrointestinal side effects, starting at 250 mg per day and titrating up by 250 mg per day each week until the final dose is reached.

Phosphate supplements can be used in various formulations (e.g., Joulie solution, magistral or commercially available capsules, effervescent tablets). Choice of formulation should be determined by the affected individual rather than prescriber preference. Vitamin D analogs can be considered as monotherapy in individuals unwilling to take phosphate. Conversely, the use of phosphate without vitamin D is contraindicated, because phosphate without vitamin D analogs worsens secondary hyperparathyroidism.

**Side effects of phosphate and calcitriol therapy**

- **Gastrointestinal symptoms** (diarrhea, cramps, abdominal pain) are the most common side effects of phosphate therapy. Usually, doses are increased gradually in order to reduce gastrointestinal symptoms.
- **Secondary hyperparathyroidism** can be aggravated by phosphate therapy. If secondary hyperparathyroidism is identified, the calcitriol dose may be increased (provided blood calcium levels and urinary calcium excretion is normal) and/or the phosphate dose decreased.

  A small clinical trial and several case reports have investigated the use of cinacalcet in adults with XLH who have secondary hyperparathyroidism [Alon et al 2008]. No long-term studies have been conducted. The clinical trial (comprising eight individuals ages six to 19 years) involved inpatient monitoring of phosphate, intact PTH, and tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR) after a single dose of cinacalcet; results showed a decrease in intact PTH and an increase in phosphate and TmP/GFR. Another trial with paricalcitol showed it reduced PTH, renal phosphate wasting, and ALP levels, but worsened hypercalciuria [Carpenter et al 2014b]. Given that calcimimetics are associated with a risk of severe side effects such as hypocalcemia and QT interval prolongation, their use should be limited [Haffner et al 2019].
- **Hypercalcemia and hypercalciuria** may also complicate long-term treatment for XLH and is associated with high calcitriol doses or tertiary hyperparathyroidism. Serum calcium concentrations and urine calcium-to-creatinine ratio should be monitored (see Surveillance). If hypercalcemia or hypercalciuria is detected, the calcitriol dose should be decreased.
- **Nephrocalcinosis** may occur independent of hypercalcemia and hypercalciuria detected on laboratory evaluation. Renal ultrasound examination should be used to monitor for nephrocalcinosis (see Surveillance).
- **Cardiovascular risk factors,** particularly arterial hypertension, overweight/obesity with insulin resistance, and metabolic syndrome appear to be more common in children and adults with XLH than in the general population [Zhukouskaya et al 2020, Bloudeau et al 2023]. These associations may be attributed, at least in part, to phosphate therapy (for obesity and particularly arterial hypertension, which might be due to increased sodium intake) [Zhukouskaya et al 2020, Bloudeau et al 2023]. Some studies have reported an increased risk of left ventricular hypertrophy in individuals with XLH [Hernández-Frías et al 2019]. However, other studies have reported no elevated risk of developing hypertension or left ventricular hypertrophy in individuals with XLH [Bouzemane et al 2023].

- Ectopic calcifications have been reported in individuals on conventional therapy, in the absence of hypercalcemia, hyperphosphatemia, or elevations in the product of calcium x phosphate (phosphocalcic product) [Moltz et al 2001, Arango Sancho 2020].

## Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 7). Physical exercise is recommended, although no formal recommendations exist [Laurent et al 2021].

**Table 7.** X-Linked Hypophosphatemia: Treatment of Manifestations

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **Craniosynostosis** | Prompt referral to craniofacial specialist when head shape abnormalities are identified | |
| **Lower extremity bowing & torsion** | "Guided growth" using stapling or toggle plate insertion in prepubertal children prior to peak growth velocity (generally age <10 yrs) | • Consider as a minimally invasive method of reversible hemiepiphysiodesis. [1]<br>• Note: The risk w/this procedure is prematurely stopping growth. |
| | • Surgical treatment may be used in older children & adults w/misalignment.<br>• Treatments may incl distraction osteogenesis (incl Ilizarov surgery) by external fixation, acute correction by external fixation w/ intramedullary nailing, internal fixation w/ intramedullary nailing, & acute correction by intramedullary nailing. | • There are no controlled trials of the various surgical techniques; the literature consists of case series. [2]<br>• Complications of orthopedic surgery are common. [3] |
| **Degenerative joint disease** | Total hip or knee arthroplasty as needed | |
| **Musculoskeletal pain** | • Evaluate underlying causes (e.g., osteoarthritis, insufficiency fractures, osteophytes).<br>• Rehab, physiotherapy, analgesics (paracetamol/acetaminophen, non-steroidal anti-inflammatory drugs, &/or opioids per standard practices in pain medicine) | |
| **Hyperparathyroidism** | • See Targeted Therapy.<br>• If tertiary hyperparathyroidism is identified, surgical eval (parathyroidectomy w/ or w/o auto-reimplantation) is warranted. | Hungry bone syndrome w/profound hypocalcemia is a common side effect following parathyroidectomy in persons w/ XLH. [4] |
| **Dental abscesses** | • Good oral hygiene w/flossing, regular dental care, & fluoride treatments<br>• Pit & fissure sealants | • Pit & fissure sealants have not been well studied.<br>• Treatment in adults w/phosphate & active vitamin D analogs may improve severity of dental disease. [5] In children, burosumab was assoc w/less dental abscesses compared to treatment w/phosphate & active vitamin D analogs. [6] |
| **Sensorineural hearing loss** | Standard treatment | See Genetic Hearing Loss Overview, Management. |
| **Psychosocial / Quality of life** | • Education on XLH, psychosocial support, referral to XLH organizations<br>• Consider dietary counseling. | Consider collaboration w/school or work physicians. |

*Table 7. continued from previous page.*

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **↑ risk of arterial hypertension, obesity, metabolic syndrome** | Mgmt of cardiovascular comorbidities per standard practice | |
| **Fatigue** | • Consider treatment w/physical medicine & rehab.<br>• Analgesics as needed<br>• Consider sleep studies for suspected central or obstructive sleep apnea. | |

*1.* Novais & Stevens [2006]
*2.* Song et al [2006], Petje et al [2008]
*3.* Paludan et al [2022]
*4.* Savio et al [2004]
*5.* Connor et al [2015]
*6.* Gadion et al [2022]

**Growth hormone therapy** has been used in (particularly prepubertal) children with XLH and short stature, because it stimulated growth velocity [Živičnjak et al 2011, Rothenbuhler et al 2017, Ertl et al 2022] and is associated with higher phosphate and 1,25-dihydroxyvitamin D levels, lower PTH and TmP/GFR, and improved muscle strength. However, it does not improve rickets/osteomalacia, and there is concern that it may aggravate skeletal deformities (if mineral homeostasis is not appropriately achieved); furthermore, some but not all studies showed increased adult height [Mäkitie et al 2008, Meyerhoff et al 2018, André et al 2022]. Growth hormone appears to be more effective than burosumab at increasing adult height and can be used in combination with burosumab in some countries [Ertl et al 2022].

**Aromatase inhibitor** treatment (which are used off-label for short stature in children) has only been described in one individual with XLH with advanced bone age [Felipe Queiroz et al 2023].

## Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 8 are recommended.

**Table 8.** X-Linked Hypophosphatemia: Recommended Surveillance

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **For persons on (stable dose of) burosumab for safety & efficacy monitoring** | • Serum phosphate, calcium, & creatinine, ALP, intact PTH<br>• Note: The adequacy of treatment is indicated by normal ALP, intact PTH, & normal (or near-normal) phosphate levels (using age-specific reference values). | Every 3-6 mos in children & every 6-12 mos in adults |
| | Renal ultrasound for nephrocalcinosis | At start of treatment, then every 6 mos for 1st yr, & annually thereafter |
| | Lower extremity radiographs to assess skeletal response to treatment | Consider based on symptoms & physical exam findings (avoid routine radiographs & unnecessary radiation exposure; consider MRI). |

*Table 8. continued from previous page.*

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **For persons on active vitamin D analogs & phosphate therapy to identify & prevent therapeutic complications** | Serum phosphate, calcium, & creatinine, ALP, intact PTH, urinary calcium & creatinine | Every 3 mos |
| | Lower extremity radiographs to assess skeletal response to treatment | Consider based on symptoms & physical exam findings (avoid routine radiographs & unnecessary radiation exposure; consider MRI). |
| | Renal ultrasound exam to assess for nephrocalcinosis | At start of treatment & then consider every 1-5 yrs; however, the recommended frequency has not been well established. [1] |
| **Asymptomatic adults not receiving medical therapy** | 25-hydroxyvitamin D | Consider every 6 mos depending on clinical risk factors for vitamin D deficiency |
| | ALP, creatinine, calcium, PTH | Every 12 mos |
| **Skeletal** | Assessment of growth & lower limb alignment (intercondylar & intermalleolar distance) | At each visit throughout childhood |
| | Craniofacial exam for signs of craniosynostosis | At each visit throughout infancy |
| | Clinical assessment of joint mobility & pain | At each visit &/or annually |
| | Bone age measurement to evaluate growth potential | Consider based on clinical necessity (do not repeat on routine basis). |
| | • Radiographs of painful areas to assess for calcifications, pseudofractures, &/or insufficiency fractures<br>• Note: Knee MRI has shown promise as a tool to monitor disease activity & skeletal response to treatment, which avoids radiation exposure of serial radiographs. [2] | As needed |
| **Neurologic** | Eval of those w/headache &/or vertigo for Chiari I malformation | |
| **Dental** | Dental exam | Every 6 mos |
| **Hearing** | Hearing eval | As needed |
| **Psychosocial / Quality of life** | Assessment of psychosocial needs, fatigue, sleep issues, & quality of life | At each visit |
| **Cardiovascular risk** | Assessment of weight, blood pressure, other cardiovascular/metabolic syndrome risk factors | At each visit as indicated |

ALP = alkaline phosphatase; PTH = parathyroid hormone; TmP/GFR = tubular resorption of phosphate corrected for glomerular filtration rate

*1.* Carpenter et al [2011], Sabbagh et al [2014]

*2.* Zhukouskaya et al [2021]

## Agents/Circumstances to Avoid

It is recommended that treatment with unopposed phosphate (without 1,25-dihydroxyvitamin D) be avoided as this may increase the risk for secondary hyperparathyroidism.

Although 1,25-dihydroxyvitamin D has been used as a single agent, this may increase the risk for hypercalcemia, hypercalciuria, and nephrocalcinosis.

In individuals with fractures, there is no rationale for bisphosphonates or osteoporosis medications, which may cause deterioration of osteomalacia in some individuals [Cundy et al 2020].

**Bone scintigraphy and bone densitometry** are generally **not recommended** for routine use in individuals with XLH. If performed, bone scintigraphy may show increased uptake at metaphyseal sites and sites of insufficiency or pseudofractures [Hardy et al 1989]. Similarly, bone densitometry typically shows high bone density in XLH [Colares Neto et al 2017], but its use is not recommended (unless for differential diagnosis, when other conditions are suspected).

Laboratory measurements of FGF23 may only be considered for diagnostic purposes but are not useful for follow up.

**Bone biopsy** is an invasive procedure that is generally not required to establish the diagnosis of XLH. Only in diagnostically challenging cases and in the hands of experts should bone biopsy be considered. Periosteocytic (unmineralized) lesions may be observed in genetic disorders involving osteocytes (which express and secrete FGF23), including XLH [Fratzl-Zelman et al 2022].

## Evaluation of Relatives at Risk

Testing of at-risk first-degree relatives (male and female infants, children, and/or parents) is warranted to ensure early diagnosis and early treatment for optimal outcome. Evaluation can be accomplished by:

- Molecular genetic testing if the *PHEX* pathogenic variant has been identified in an affected family member;
- Clinical evaluation and biochemical testing consisting of serum phosphorus, creatinine, calcium, ALP, intact PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D concentrations and urine phosphorus and creatinine concentrations. Infants with initially normal test results require reevaluation every two to three months until at least age one year.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

There is no consensus on the use of active vitamin D analogs and phosphate in women during pregnancy. Most women with XLH who are on this therapy at the time of conception are continued on treatment throughout the pregnancy with vigilant monitoring (every 1-2 months) of urinary calcium-to-creatinine ratios to detect hypercalciuria early in order to modify treatment accordingly. Since 1,25-dihydroxvitamin D rises during pregnancy, the risk of hypercalcemia, hypercalciuria, and urolithiasis increases. Those individuals who are not on therapy at the time of conception are generally not started on treatment during pregnancy. While pregnancy and lactation are accompanied by transfer of phosphorus from maternal stores to the fetus and a consequent decline in phosphate levels, the available clinical evidence from untreated mothers is reassuring [Reid et al 1989].

## Therapies Under Investigation

A randomized controlled trial of calcitriol monotherapy (without phosphate) in children is ongoing (NCT03748966).

Randomized trials are evaluating self-adhesive sealants to prevent dental abscesses in XLH (NCT04872907).

In both growing and adult *Hyp* mice (the mouse model of XLH), sclerostin inhibition increased phosphate and reduced FGF23 levels [Carpenter et al 2022]. The sclerostin inhibitor romosozumab is approved for the treatment of women with postmenopausal osteoporosis at increased fracture risk. However, it increases bone density, which is already high in XLH. No clinical data are currently available to support its use in XLH.

Studies have evaluated calcitonin to suppress FGF23. However, randomized trials have been disappointing [Sullivan et al 2018]. Still, the calcitonin receptor might represent a drug target in XLH.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

By definition, X-linked hypophosphatemia (XLH) is inherited in an X-linked manner; hemizygous males and heterozygous females are similarly affected.

## Risk to Family Members

**Parents of a male proband**

- The father of an affected male will not have the disorder, nor will he be hemizygous for the *PHEX* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If the mother of a male proband has more than one affected child and no other affected relatives and if the *PHEX* pathogenic variant identified in the proband cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case):
  - The mother may be a heterozygote or have germline mosaicism; or
  - The mother does not have the *PHEX* pathogenic variant and the affected male has XLH as the result of a *de novo* germline or postzygotic *PHEX* pathogenic variant.
- Molecular genetic testing of the mother (or biochemical testing if the *PHEX* pathogenic variant has not been identified in the proband) is recommended to evaluate her genetic status and inform recurrence risk assessment (see Evaluation of Relatives at Risk). Note: Testing of maternal leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in germ (gonadal) cells only.
- Evaluation of the mother may determine that she is affected but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed without biochemical or molecular genetic testing of the mother [Gaucher et al 2009].

**Parents of a female proband**

- A female proband may have XLH as the result of:
  - A *PHEX* pathogenic variant inherited from either her mother or her father; or
  - A *de novo* germline or postzygotic *PHEX* pathogenic variant.
- Molecular genetic testing of the mother and father of the proband (or biochemical testing if the *PHEX* pathogenic variant has not been identified in the proband) is recommended to evaluate their genetic status and inform recurrence risk assessment (see Evaluation of Relatives at Risk). Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in germ (gonadal) cells only.

- If the pathogenic variant found in a female proband cannot be detected in either parent and parental identity testing has confirmed biological maternity and paternity, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Parental mosaicism has been reported in multiple families with XLH [Goji et al 2006, Lin et al 2020, Pasmant & Pacot 2020].
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed without biochemical or molecular genetic testing of both parents [Gaucher et al 2009].

**Sibs of a proband.** The risk to sibs depends on the genetic status of the parents:

- If the father of the proband is affected and/or is known to have a *PHEX* pathogenic variant, he will transmit a *PHEX* pathogenic variant to all of his daughters (who will be affected) and none of his sons.
- If the mother of the proband is affected and/or is known to have a *PHEX* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Male and female offspring who inherit the pathogenic variant will be affected.
- The severity of manifestations can differ among sibs who inherit a *PHEX* pathogenic variant; intrafamilial clinical variability does not correlate with the sex of the affected family member.
- If the proband represents a simplex case and if the pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of parental germline mosaicism [Goji et al 2006, Lin et al 2020, Pasmant & Pacot 2020].

**Offspring of a male proband.** Affected males transmit the *PHEX* pathogenic variant to all of their daughters (who will be heterozygotes and will be affected) and none of their sons.

**Offspring of a female proband.** Affected females have a 50% chance of transmitting the pathogenic variant to each child. Male and female offspring who inherit the pathogenic variant will be affected.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

If the *PHEX* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for XLH are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While use of prenatal testing is a personal decision, discussion of these issues may be helpful.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **International XLH Alliance**
  www.xlhalliance.org
- **XLH Network**
  **Phone:** 518-350-9541
  **Email:** info@xlhnetwork.org
  www.xlhnetwork.org/
- **MedlinePlus**
  Hereditary hypophosphatemic rickets

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** X-Linked Hypophosphatemia: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *PHEX* | Xp22.11 | Phosphate-regulating neutral endopeptidase PHEX | PHEX database | PHEX | PHEX |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for X-Linked Hypophosphatemia (View All in OMIM)

| | |
|---|---|
| 300550 | PHOSPHATE-REGULATING ENDOPEPTIDASE, X-LINKED; PHEX |
| 307800 | HYPOPHOSPHATEMIC RICKETS, X-LINKED DOMINANT; XLHRD |

## Molecular Pathogenesis

The function of the protein produced by *PHEX*, phosphate-regulating neutral endopeptidase PHEX (PHEX), is unknown. It is expressed predominantly in bones and teeth in osteoblasts, osteocytes, and odontoblasts. The structure of the protein suggests that it is an endopeptidase; however, the substrate for its proteolytic activity is unknown.

Pathogenic variants in *PHEX* lead to increased serum levels of fibroblast growth factor 23 (FGF23) [Jonsson et al 2003, Weber et al 2003]. The etiology of this increase is not understood, as no direct link has been demonstrated between PHEX and FGF23. FGF23, which is normally produced by bone lineage cells in response to high phosphate or 1,25-dihydroxyvitamin D, binds to the FGF receptor 1c with Klotho acting as a coreceptor. Although the events downstream of these receptors remain incompletely understood, this results in hypophosphatemia through internalization of the sodium phosphate IIa and IIc cotransporters from the renal proximal tubule, leading to a decrease in phosphate reabsorption by the kidney and phosphate wasting [Segawa et al 2007, Gattineni et al 2009]. Additionally, FGF23 causes downregulation of the renal 1-alpha-hydroxylase enzyme and upregulation of the 24-hydroxylase enzyme leading to impaired 1,25-dihydroxyvitamin D synthesis

and increased degradation [Shimada et al 2004]. This dual defect in phosphate metabolism leads to poor bone mineralization and fractures. Enthesopathy may represent a biomechanical adaptation to osteomalacia, while impaired 1,25-dihydroxyvitamin D signaling in enthesis may be sufficient to drive the development of enthesopathy [Macica et al 2022, Rana et al 2023].

It has also been hypothesized that pathogenic variants in *PHEX* lead to an increase in direct inhibitors to bone mineralization, referred to as minhibins. The identification and the mechanism of action of these minhibins are unknown; it has been proposed that proteins containing protease-resistant acidic serine-aspartate-rich motif (ASARM peptide) such as those found in matrix extracellular phosphoglycoprotein (MEPE), dentin matrix acidic phosphoprotein 1 (DMP1), and osteopontin (OPN) may play a role in the mineralization defect seen in XLH [Addison et al 2008, Martin et al 2008, David et al 2011, Buck et al 2022]. Indeed, OPN inhibits mineralization, is degraded by PHEX, and contributes to osteomalacia in XLH, independent of hypophosphatemia [Hoac et al 2020]. Some (but not all) studies have suggested an increased risk of left ventricular hypertrophy in XLH, but studies in the *Hyp* mouse suggest that this may be mediated by phosphate supplementation rather than directly by FGF23 [Liu et al 2018].

**Mechanism of disease causation.** Loss of function

**Table 9.** *PHEX* Pathogenic Variants Referenced in This *GeneReview*

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|
| NM_000444.6 | c.*231A>G | -- | See Genotype Phenotype Correlations. |
| NG_007563.2 | Dup exons 13-15 [1] | -- | |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
*1.* Variant designation does not conform to current naming conventions

# Chapter Notes

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