X-Linked Hypophosphatemia

Synonyms: XLHR, X-Linked Hypophosphatemic Rickets, X-Linked Vitamin D-Resistant Rickets

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Summary

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Disease characteristics. The phenotypic spectrum of X-linked hypophosphatemia (XLH) ranges fromisolated hypophosphatemia to severe lower extremity bowing. XLH frequently manifests in the first two years of life when lower extremity bowing becomes evident with the onset of weight bearing; however, it sometimes is not manifest until adulthood as previously unevaluated short stature. Additionally, in adults enthesopathy (calcification of the tendons, ligaments, and joint capsules) may be the initial presenting complaint. Persons with XLH are prone to spontaneous dental abscesses; sensorineural hearing loss has been reported.

Diagnosis/testing. Low serum phosphate concentration and reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR) are characteristic. Additionally, the normal physiologic response to hypophosphatemia of an elevation of 1,25 $(OH)_2$ vitamin D is absent. Serum calcium and 25-hydroxy vitamin D are within the normal range; parathyroid hormone is normal to slightly elevated. Alkaline phosphatase is characteristically elevated in children, especially during periods of rapid growth, and usually returns to normal in adulthood regardless of treatment. Molecular genetic testing of *PHEX*, the only gene in which mutations are known to cause XLH, is available clinically.

Management. *Treatment of manifestations:* Pain and lower extremity bowing improve with frequent oral administration of phosphate and high-dose calcitriol. Children are generally treated from the time of diagnosis to the cessation of long bone growth. The role of pharmacologic treatment in adults is less clear; such treatment is generally reserved for individuals with symptoms (e.g., skeletal pain), biochemical evidence of osteomalacia, and/or recurrent pseudofractures or stress fractures, and those preparing for elective orthopedic surgery. Persistent lower limb bowing and/or torsion resulting in misalignment of the lower extremity may require surgery.

Prevention of primary manifestations: Frequent oral administration of phosphate and high-dose calcitriol to minimize bowing of long bones during growth. Good oral hygiene with flossing, regular dental care, and active preventive strategies to prevent dental abscesses.

Surveillance: For individuals on phosphate and calcitriol therapy: (1) quarterly monitoring of serum concentrations of phosphate, calcium, creatinine, alkaline phosphatase, intact parathyroid hormone; and urinary calcium, phosphate, and creatinine for evidence of hyperparathyroidism and increased renal phosphate or calcium excretion; (2) routine lower extremity x-rays to assess skeletal response to treatment; (3) annual renal ultrasound examination to assess for nephrocalcinosis if urinary calcium is normal; (4) dental follow up twice a year.

Agents/circumstances to avoid: Treatment with doses of phosphate exceeding 70 mg/kg/day; treatment with phosphate without calcitriol because of the increased risk of hyperparathyroidism; treatment with high doses of calcitriol or calcitriol without phosphate because of the increased risk of hypercalcemia, hypercalciuria, and nephrocalcinosis.

Evaluation of relatives at risk: Biochemical testing or molecular genetic testing (if the *PHEX* mutationhas been identified in the family) of newborns at risk to ensure early treatment for optimum outcome.

Pregnancy management: Continue phosphate and calcitriol treatment throughout pregnancy; monitor urinary calcium to creatinine ratios to detect hypercalciuria early.

Genetic counseling. X-linked hypophosphatemia is inherited in an X-linked dominant manner. Anaffected male passes the disease-causing mutation to all his daughters and none of his sons; an affected female passes the disease-causing mutation to 50% of her offspring. Offspring who inherit the mutation will be affected, but because of the great intrafamilial variation, severity cannot be predicted. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation in the family has been identified.

Diagnosis

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Clinical Diagnosis

The diagnosis of X-linked hypophosphatemia (XLH) is based on clinical findings, radiographic findings, biochemical testing, and family history.

Clinical findings of rickets that often prompt consideration of XLH are:

- **In children.** Progressive lower extremity bowing with a decrease in height velocity after the child starts ambulating and the characteristic clinical signs of rickets: rachitic rosary, craniotabes, Harrison's groove, and epiphyseal swelling
- **In adults.** Musculoskeletal complaints, stress-fractures, dental abscesses, and/or the diagnosis of XLH in an offspring

Radiographic findings. In children: the metaphyses may be widened, frayed, or cupped; sometimes rachitic rosary or beading of the ribs results from poor skeletal mineralization leading to overgrowth of the costochondral joint cartilage. Although involvement of the metaphyses of the lower limbs is typical, any metaphysis can be involved.

Testing

The two main laboratory findings characteristic of XLH are:

- **Low serum phosphate concentration.** Normal phosphate concentrations vary with age with higher values observed in infants; therefore, it is important to use the age-related values. One widely used data set is reviewed in Table 1. Several studies have reported the normative data for age-related serum phosphate values [reviewed by Meites 1989].

Table 1. Age-Based Normal Serum Phosphate Reference Intervals

Age	mg/dL	mmol/L
0-5 days	4.8-8.2	1.55-2.65
1-3 yrs	3.8-6.5	1.25-2.10
4-11 yrs	3.7-5.6	1.20-1.80
12-15 yrs	2.9-5.4	0.95-1.75
>15 yrs	2.7-4.7	0.90-1.50

Lockitch et al [1988]

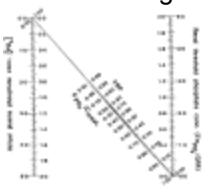
- **Reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR).** Historically, the calculation of TmP/GFR has relied on the nomogram-based method described by Walton and Bijvoet [1975] (Figure 1). In order to use the nomogram, the tubular resorption of phosphate (TRP) must first be calculated as follows:

  $TRP = 1 - [(urine_{phosphate} / plasma_{phosphate}) / (plasma_{creatinine} / urine_{creatinine})]$

  When the TRP is less than 0.86, the TmP/GFR can be calculated directly as follows:

  $TmP/GFR = TRP \times Plasma_{phosphate}$

  The age-related reference ranges for the TmP/GFR are shown in Table 2 [Payne 1998].



Figure

Figure 1. Nomogram from Walton & Bijvoet [1975] for calculation of the tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR) utilizing the plasma phosphate concentration and the calculated tubular resorption of phosphate:(more...)

Table 2. Age-Based Normal TmP/GFR Reference Intervals

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
25-35 yrs	Female	2.4- 3.6	0.96-1.44
45-55 yrs	Male	2.2- 3.4	0.90-1.35
45-55 yrs	Female	2.2- 3.6	0.88-1.42
65-75 yrs	Both	2.0- 3.4	0.80-1.35

Payne [1998]

Note: For the calculation of the TRP the urine should be collected as an untimed urine after an overnight fast.

Other laboratory findings include:

- Normal serum calcium and 25 OH vitamin D. Note: If the serum 25 OH vitamin D concentration is low, vitamin D levels need to be replete before the diagnosis of XLH can be confirmed by laboratory testing.
- Inappropriately normal serum calcitriol concentration in the presence of hypophosphatemia
- Normal parathyroid hormone level; however, it may be minimally elevated in some individuals.
- Absence of glycosuria, bicarbonaturia, proteinuria, or amino aciduria

Molecular Genetic Testing

Gene. *PHEX* (phosphate regulating endopeptidase homolog, X-linked) is the only gene in which mutations are known to cause XLH.

Clinical testing

- **Sequence analysis** of the 22 exon coding region and intronic borders of *PHEX* detected mutations in 57%-78% of individuals with the clinical and biochemical diagnosis of XLH [Holm et al 1997, Dixon et al 1998, Ichikawa et al 2008, Gaucher et al 2009, Ruppe et al 2011]. Some of the reports suggest a lower rate of mutation detection in simplex cases (i.e., a single occurrence in a family); however, this has not been clearly documented.
- **Deletion/duplication analysis.** Two studies utilized multiplex ligation-dependent probeamplification (MLPA) to detect deletions and duplications [Clausmeyer et al 2009, Morey et al 2011]. Of note, using both exon sequencing and MLPA analysis, Morey et al [2011] detected mutations in 100% of their cohort of 36 unrelated families. In contrast, the Clausmeyer study (which also utilized both techniques) failed to find a mutation in a subset of individuals tested.

Table 3. Summary of Molecular Genetic Testing Used in X-Linked Hypophosphatemia

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]	Test Availability
PHEX	Sequence analysis	Sequence variants [2]	Near 100% [3, 4]	Clinical Testing
	Deletion /duplicationanalysis [5]	Deletion / duplication of one or more exons or the whole gene		

Test Availability refers to availability in the GeneTests™ Laboratory Directory. *GeneReviews* designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

1. The ability of the test method used to detect a mutation that is present in the indicated gene

2. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations; typically, exonic or whole-gene deletions/duplications are not detected.

3. In a male, lack of amplification by PCRs prior to sequence analysis can suggest a putative deletion of one or more exons; confirmation may require additional testing by deletion/duplication analysis. In a heterozygous female, sequence analysis of genomic DNA cannot detect deletion of one or more exons or an entire X-linked gene.

4. Morey et al [2011]

5. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; a variety of methods including quantitative PCR, long-range PCR, multiplex ligation-dependent probeamplification (MLPA), or targeted chromosomal microarray analysis (gene/segment-specific) may be used. A full chromosomal microarray analysis that detects deletions/duplications across the genome may also include this gene/segment. See array CGH.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.
Information on specific allelic variants may be available in Molecular Genetics (see Table A. Genes and Databases and/or **Pathologic allelic variants**).

Testing Strategy

To confirm/establish the diagnosis in a proband

- Laboratory testing reveals low serum phosphate concentration with a reduced TmP/GFR based on normative values for age.
- *PHEX* molecular genetic testing (sequence analysis followed by deletion/duplication analysis as needed) can be used to confirm the diagnosis, but is not required to establish the diagnosis in the presence of the characteristic biochemical findings.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Note: It is the policy of *GeneReviews* to include in *GeneReviews*™ chapters any clinical uses of testing available from laboratories listed in the GeneTests™ Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *PHEX*.

Clinical Description

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Natural History

The clinical presentation of X-linked hypophosphatemia (XLH) ranges from isolated hypophosphatemia to severe lower extremity bowing. The diagnosis is frequently 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.

Skeletal abnormalities. Individuals with XLH commonly present with short stature and lower extremity bowing (valgus or varus deformities).

Adults with XLH have a significantly reduced final height with a standard deviation score (SDS) of -1.9 in comparison to reference standards. The patients appear disproportionate, with leg length scores (-2.7) being significantly lower than those for sitting height (-1.1) [Beck-Nielsen et al 2010].
In a longitudinal study that assessed growth in children prior to and during treatment, Zivicnjak et al [2011a] found that untreated children had disproportionate total height (-2.48 SDS) to sitting height (-0.99 SDS); lower leg length was -2.90 SDS. During treatment there was an uncoupling of growth between the trunk and the legs: the difference between SDS sitting and lower leg length became more pronounced as the subjects grew.
Jehan et al [2008] described changes in growth that are associated with different vitamin D receptor promoter haplotypes, providing a possible explanation for some of the clinical variability observed in XLH.
In adults, calcification of the tendons, ligaments, and joint capsules, known as enthesopathy, can cause joint pain and impair mobility [Polisson et al 1985]. Increased osteophyte formation with spinal hyperostosis and arthritis or fusion of the sacroiliac joints can also lead to pain and compromised mobility. Enthesopathy of vertebral ligaments has been reported as well [Beck-Nielsen et al 2010], including a case report of spinal cord compression and paraplegia following calcification of the ligamenta flava [Vera et al 1997].

A radiologic survey of 38 untreated adults revealed flaring of the iliac wings, trapezoidal distal femoral condyles, shortening of the talar neck and flattening of the talar dome [Hardy et al 1989]. Looser's zone or pseudofractures that may be symptomatic or asymptomatic were seen commonly and have been reported to occur at any age.

Cranial structures. Cranial abnormalities include frontal bossing, craniosynostosis, and Chiari malformations. A detailed cephalometric study revealed an increased head length, a 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]. The incidence of Chiari malformations, which may cause headache and vertigo, has not been determined.

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 for abscess formation [Baroncelli et al 2006].

Hearing loss. Sensorineural hearing loss has been reported; the actual prevalence of hearing loss is not known. 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.

Genotype-Phenotype Correlations

Several studies have evaluated genotype-phenotype correlations in XLH.

- The largest study, which involved 59 persons, correlated dental and hearing defects with mutations in exons near the 5' (or beginning) of the gene and increased head length with mutations in exons near the end of the gene [Popowska et al 2001].
- Two studies suggested a correlation between more severe bone disease (defined by the severity of bowing and a history of osteotomies) and truncating mutations [Holm et al 2001] or mutations in the c-terminal portion of *PHEX* [Song et al 2007].
- A study by Morey et al [2011] showed that clearly deleterious *PHEX* mutations (defined as nonsense mutations, insertions or deletions, and splice site mutations leading to premature stop codons) had lower tubular resorption of phosphate and lower calcitriol levels when compared to plausibly deleterious mutations (missense changes or in-frame deletions).

Penetrance

Despite a wide degree of clinical variability in XLH, penetrance is often said to be 100% by age one year [Auricchio et al 2008].

One instance of discordance for XLH in monozygotic twin girls was reported by Owen et al [2009]: at age 19 months the girls were diagnosed with XLH based on biochemical findings and family history; no*PHEX* mutation was identified in either twin. One twin was significantly shorter than the other twin (length: -1.3 vs -0.4 SD). The shorter twin had marked bilateral genu varum compared to mild genu valgum in the other twin. The authors proposed that non-pentrance resulted from discordant X-chromosome inactivation with nonrandom lack of *PHEX* expression in critical tissues.

Anticipation

Anticipation has not been reported in XLH. In fact, one study reported milder skeletal and dental disease in younger generations, which the authors speculated could be attributed to non-genetic factors such as earlier age of diagnosis, earlier age at evaluation, and improved treatments [Holm et al 2001].

Nomenclature

X-linked hypophosphatemia (or its common abbreviation, XLH) is the current and preferable term.

Other terms that have been used:

- X-linked hypophosphatemic rickets (XLH)
- Hypophosphatemic rickets

- X-linked dominant (XLHR)
- X-linked rickets (XLR)
- Vitamin D-resistant rickets
- X-linked (VDRR)
- Hypophosphatemic vitamin D-resistant rickets (HPDR),
- Phosphate diabetes
- Familial hypophosphatemic rickets

Prevalence

The incidence of XLH is 3.9-5 per 100,000 live births [Davies & Stanbury 1981, Beck-Nielsen et al 2009].

Differential Diagnosis

Go to:

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

X-linked hypophosphatemia (XLH) shares clinical findings, radiographic findings, and biochemical profile with other genetic and acquired disorders of renal phosphate wasting.

Table 4. Disorders of Renal Phosphate Wasting without Hypercalciuria

Disorder	Defect	Phenotype OMIM Number	Gene/Locus OMIM Number
XLH	*PHEX* mutation	307800	300550
ADHR	*FGF23* mutation	193100	605380
ARHR1	*DMP1* mutation	241520	600980
ARHR2	*ENPP1* mutation	613312	173335
TIO	Mesenchymal tumor		

XLH = X-linked hypophosphatemia

ADHR = autosomal dominant hypophosphatemic rickets

ARHR1 = autosomal recessive hypophosphatemic rickets 1

ARHR2 = autosomal recessive hypophosphatemic rickets 2

TIO = tumor-induced osteomalacia

Autosomal dominant hypophosphatemic rickets (ADHR). Clinical and biochemical features are similar to those of XLH. The incidence of ADHR is unknown. It is much rarer than XLH: the number of reported kindreds is in the 100s. In some instances onset of ADHR is delayed and, rarely, the phosphate wasting resolves later in life [Econs & McEnery 1997]. Mutations in *FGF23* are causative (Table 3). ADHR results in the stabilization of the full-length active form of the protein leading to prolonged or enhanced FGF23 action.

Autosomal recessive hypophosphatemic rickets (ARHR) is an extremely rare form of hypophosphatemic rickets caused by mutations in *DMP1* (ARHR1) [Feng et al 2006, Lorenz-Depiereux et al 2006] or *ENPP1* (ARHR2) [Lorenz-Depiereux et al 2010, Levy-Litan et al 2010] (Table 4). To date only a few kindreds have been identified.

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia (OOM), is a paraneoplastic syndrome in which secretion of FGF23 by slow-growing mesenchymal tumors known as 'phosphaturic mesenchymal tumors, mixed connective tissue type' results in biochemical features like those of XLH [Folpe et al 2004]. Although the majority of individuals with TIO are adults, TIO can occur at any age. Over 300 affected individuals have been reported [Chong et al 2011]. Adults frequently have progressive muscle and bone pain; children have the skeletal deformities and growth retardation observed in XLH. Treatment relies on localization and resection of the tumor.

Other disorders that have similar biochemical profiles to XLH and have distinguishing clinical features include:

- **McCune Albright syndrome,** characterized by fibrous dysplasia of the bone, precocious puberty, and *café au lait* lesions. The hypophosphatemic rickets observed in McCune Albright syndrome are associated with overproduction of FGF23 by the fibrous dysplastic bone resulting in renal phosphate wasting [Riminucci et al 2003].
- **Linear nevus sebaceous syndrome** (or epidermal nevus syndrome), characterized by multiple cutaneous nevi with radiologic evidence of fibrous dysplasia. The hypophosphatemia that is frequent in this disorder is biochemically indistinguishable from that seen in XLH. FGF23 is also implicated as the cause of the phosphate wasting in this disorder [Hoffman et al 2005].

Hypophosphatemic disorders associated with increased 1,25$(OH)_2$ vitamin D and hypercalciuria (rather than the inappropriately normal 1,25$(OH)_2$ vitamin D that is seen in XLH) include:

- Hereditary hypophosphatemic rickets with hypercalciuria (HHRH), caused by mutations in*SLC34A3* (OMIM 241530)
- Hypophosphatemic nephrolithiasis/osteoporosis 1 and 2 (NPHLOP1, OMIM 612286 and NPHLOP2, OMIM 612287) caused by mutations in *SLC34A1* (OMIM 182309) and *SLC9A3R1*(OMIM 604990), respectively
- Hypophosphatemic rickets, X-linked recessive (OMIM 300554) caused by mutations in *CLCN5*(OMIM 300008)

Renal phosphate loss can also be seen in **Fanconi syndrome,** in which the proximal renal tubule transport of many different substances can be impaired. Fanconi syndrome is differentiated from XLH by the presence of glycosuria, bicarbonaturia, and/or amino aciduria.

The rachitic skeletal changes of nutritional and hereditary forms of rickets are indistinguishable. These types of rickets can be distinguished by biochemical testing: in hypophosphatemic rickets, serum concentrations of 25 OH vitamin D and calcium are normal, whereas in vitamin D-deficient rickets the 25 OH vitamin D serum concentration is low and the calcium concentration may be low or normal. The different forms of hypophosphatemic rickets are distinguished by the presence of hypercalciuria or elevated 1,25(OH)2D. Mode of inheritance and molecular genetic testing help distinguish the different forms of hereditary hypophosphatemic rickets without hypercalciuria (of which XLH is the most common).
Note to clinicians: For a patient-specific 'simultaneous consult' related to this disorder, go to SimulConsult®, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

Management

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Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with X-linked hyposphatemia (XLH), the following evaluations are recommended:

Children

- A lower extremity x-ray (teleoroentgenogram), and x-ray of the wrists to assess the extent of skeletal disease
- Bone age measurement to evaluate growth potential
- Dental examination
- Hearing evaluation
- Craniofacial examination

Adults

- X-ray of skeletal sites with reported pain to assess for possible enthesopathy or stress fractures
- Dental examination
- Hearing evaluation

Individuals of any age. Evaluation of those with headache and vertigo for Chiari malformation

Treatment of Manifestations

Pharmacologic treatment focuses on improving pain and correcting bone deformation

In **children**, treatment generally begins at the time of diagnosis and continues until long bone growth is complete.

Treatment for most children consists of oral phosphate administered three to five times daily and high-dose calcitriol, the active form of vitamin D. Treatment is generally started at a low dose to avoid the gastrointestinal side effects of diarrhea and gastrointestinal upset. The doses are then titrated to a weight-based dose of calcitriol at 20 to 30 ng/kg/day administered in two to three divided doses and phosphate at 20 to 40 mg/kg/day administered in three to five divided doses [Carpenter et al 2011].
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/day (up to a maximum dose of 3.0 µg daily) along with the phosphate [Auricchio et al 2008]. The two different regimens have not been compared.
The doses are adjusted based on (1) evidence of therapeutic success, including reduction in serum alkaline phosphatase activity, changes in musculoskeletal examination, improvement in radiographic rachitic changes, and, when possible, improved growth velocity; and (2) evidence of therapeutic complications, including hyperparathyroidism, hypercalciuria, and nephrocalcinosis (see Prevention of Secondary Complications). Note: Normalization of the serum phosphate concentration is not a therapeutic goal as normal serum phosphate concentration frequently indicates overtreatment and increases the risk for treatment-related complications.

After growth is complete, lower doses of the medications can be used to reach the treatment goals.

In **adults**, the role of treatment has not been well studied; treatment is generally reserved for individuals with symptoms, such as skeletal pain, upcoming orthopedic surgery, biochemical evidence of osteomalacia with an elevated alkaline phosphatase, or recurrent pseudofractures or stress fractures [Carpenter et al 2011]. The calcitriol doses that are frequently employed in adults are in the range of 0.50 to 0.75 µg daily; the phosphate is given as 750 to 1000 mg/day in three to four divided doses. As with children, the phosphate dose is slowly titrated to avoid gastrointestinal side effects: starting dose is 250 mg/day and titrated up by 250 mg/day each week until the final dose is reached.

Orthopedic treatment. Despite what appears to be adequate pharmacologic therapy (see following Note:), some individuals have persistent lower limb bowing and torsion, which may lead to misalignment of the

lower extremity. In these individuals, surgical treatment is frequently pursued. No control trials of the different surgical techniques have been undertaken; the literature consists of case series.

Note: Poor compliance with pharmacologic therapy during childhood and the teen years may be one factor for persistent lower limb deformities.

In prepubertal children who have not yet reached their peak growth velocity (generally before age 10 years), stapling or toggle plate insertion can be considered as a minimally invasive method of reversible hemi-epiphysiodesis [Novais & Stevens 2006]. Note: The risk with this procedure is prematurely stopping growth.
In older children and adults, surgical techniques reported include distraction osteogenesis by external fixation, acute correction by external fixation with intramedullary nailing, internal fixation with intramedullary nailing, and acute correction intramedullary nailing [Petje et al 2008, Song et al 2006].

Additionally, total hip and knee arthroplasty is sometimes required because of degenerative joint disease and enthesopathy.

Dental treatment. Because individuals with XLH are susceptible to recurrent dental abscesses which may result in premature loss of decidual and permanent teeth, good oral hygiene with flossing and regular dental care and fluoride treatments are the cornerstones of prevention. Pit and fissure sealants have been recommended but have not been well studied.

Sensorineural hearing loss has been reported in persons with XLH. No studies have evaluated treatment options in these patients. See Hereditary Hearing Loss and Deafness Overview, Management.
Other therapies. Human growth hormone has been used to stimulate growth in persons with XLH. Although HGH therapy is theoretically beneficial because of its potential to enhance renal phosphate reabsorption, early clinical trials have not shown consistent improvement in height attained. However, the two recent studies suggest that longitudinal/linear growth improves with growth hormone treatment [Makitie et al 2008, Zivicnjak et al 2011b].

Prevention of Primary Manifestations

See Treatment of Manifestations, **Pharmacologic treatment**.

Prevention of Secondary Complications

Hyperparathyroidism is associated with treatment for XLH. Rarely hyperparathyroidism is present at the time of diagnosis; most often it occurs secondary to high phosphate doses and may proceed to tertiary hyperparathyroidism. In order to monitor for these complications, intact parathyroid hormone, serum calcium concentrations, and TmP/GFR should be measured quarterly (see Surveillance).
If secondary hyperparathyroidism is identified, either the calcitriol dose may be increased 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. Only a few case reports of the use of cinacalcet in children are available.

If tertiary hyperparathyroidism is identified, surgical evaluation is warranted.

Hypercalcemia and hypercalciuria may also complicate long-term treatment for XLH and is associated with high calcitriol doses. Serum calcium concentrations and urine calcium/creatinine ratio should be monitored quarterly (see Surveillance). If hypercalcemia or hypercalciuria is detected, the calcitriol dose should be decreased.
Nephrocalcinosis, reported in persons medically treated for XLH, may occur independent of hypercalcemia and hypercalciuria detected on laboratory evaluation. A baseline renal ultrasound examination should be performed at the start of treatment. The frequency of renal ultrasound examination to monitor for the development of nephrocalcinosis is not established; one- to five-year intervals have been recommended [Auricchio et al 2008, Carpenter et al 2011].

Surveillance

Periodic clinical evaluation to assess for disease progression, treatment response, and therapeutic complications is indicated.

For individuals on calcitriol and phosphate therapy the following are recommended:

- Quarterly monitoring of the following: serum concentrations of phosphate, calcium, and creatinine; alkaline phosphatase level; intact parathyroid hormone level; and urinary calcium, phosphate and creatinine to identify and thus prevent therapeutic complications
- Intermittent monitoring of lower extremity x-rays (teleoroentgenograms) to assess skeletal response to treatment. The frequency has not been well established.
- Annual renal ultrasound examination to assess for nephrocalcinosis. Note: The frequency has not been well established.
- Dental follow up twice a year (as for children and teenagers with a high risk for caries)

Agents/Circumstances to Avoid

It is recommended that treatment with unopposed phosphate (without 1,25$(OH)_2$ vitamin D) be avoided as this is felt to increase the risk of hyperparathyroidism.
Although 1,25$(OH)_2$ vitamin D has been used as a single agent, this use is felt to increase the risk of hypercalcemia, hypercalciuria, and nephrocalcinosis.

Evaluation of Relatives at Risk

Testing of at-risk children is warranted to ensure early diagnosis and early treatment for optimum outcome. Evaluation can be accomplished by:

- Molecular genetic testing if the *PHEX* mutation has been identified in the family
- Biochemical testing. Infants with initially normal test results require reevaluation every two to three months until at least age one year.

As XLH is X-linked dominant, heterozygote females may be affected to the same degree as males; thus, no role has been established for screening asymptomatic adult family members.
See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

No data are available on the use of phosphate and calcitriol in pregnant women who have XLH. Most women with XLH who are on active 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.

Therapies Under Investigation

Currently, a novel therapeutic agent KRN23 is under investigation for XLH. This is a recombinant human monoclonal antibody targeting FGF23. (See Molecular Genetics.)
Search clinicaltrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.
See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Genetic Counseling

Go to:

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

X-linked hypophosphatemia is inherited in an X-linked dominant manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disease nor will he be a carrier of the mutation.
- In a family with more than one affected individual, the mother of an affected male is affected.
- If a male is the only affected family member (i.e., a simplex case), the mother may also have the mutation or the affected male may have a *de novo* mutation.
- If the disease-causing mutation found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo*mutation in the proband. Somatic and germline mosaicism has been reported in a male who transmitted the *PHEX* mutation to only one of his two daughters [Goji et al 2006].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutationinclude biochemical assessment with serum phosphate, serum creatinine, and TmP/GFR measurement. Molecular genetic testing can be considered if biochemistry is abnormal. 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 historycannot be confirmed until biochemical or molecular genetic testing is done on at-risk relatives [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 has a *PHEX* mutation, he will transmit the disease to all of his daughters and none of his sons.
- If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Offspring who inherit the mutation will be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if thedisease-causing mutation cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low.
- Somatic and germline mosaicism has been reported in a male who transmitted the *PHEX*mutation to only one of his two daughters [Goji et al 2006].

Offspring of a male proband. Affected males pass the disease-causing mutation to all of their daughters and none of their sons.

Offspring of a female proband. Affected females pass the disease-causing mutation to 50% of their offspring.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* mutationarose, information that could help determine the genetic risk status of the extended family.

Carrier Detection

The disorder is inherited in an X-linked dominant fashion with essentially 100% penetrance. This leads to disease in all females who are heterozygous for the *PHEX* mutation.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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 is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing mutation of an affected family member must have been identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions which (like X-linked hypophosphatemia) do not affect intellect and have treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although decisions about prenatal testing are the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Note: It is the policy of *GeneReviews* to include in *GeneReviews*™ chapters any clinical uses of testing available from laboratories listed in the GeneTests™ Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Molecular Genetics

Go to:

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 Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
PHEX	Xp22.2-p22.1	Phosphate-regulating neutral endopeptidase	Catalogue of Somatic Mutations in Cancer (COSMIC) PHEXdb Locus Database	PHEX

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, click here.

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

300550	PHOSPHATE-REGULATING ENDOPEPTIDASE HOMOLOG, X-LINKED; PHEX
307800	HYPOPHOSPHATEMIC RICKETS, X-LINKED DOMINANT; XLHR

Molecular Genetic Pathogenesis

The function of the protein produced by *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.

Mutations in *PHEX* lead to increased serum levels of 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 produced by bone lineage cells, causes 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 α hydroxylase enzyme and upregulation of the 24 hydroxylase enzyme leading to impaired 1,25$(OH)_2$ vitamin D synthesis and increased degradation [Shimada et al 2004]. This dual defect in phosphate metabolism leads to poor bone mineralization and fractures.
It has also been hypothesized that mutations 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 MEPE, DMP1, and OPN may play a role [Addison et al 2008, Martin et al 2008, David et al 2011] in the mineralization defect seen in XLH. The role of this newly described bone-kidney axis in phosphate homeostasis and bone mineralization is an area of ongoing research.
Normal allelic variants. *PHEX* comprises 22 exons; the transcript length is 2861 bp (NM_000444.4).
Pathologic allelic variants. Pathologic mutations include missense, nonsense, deletions, small intra-exonic insertions and deletions, duplications and at splice sites. Mutations have been reported in everyexon, multiple different intronic splice sites, and the 5' UTR. To date nearly 300 pathologic allelic variants have been described. The *PHEX* database (see Table A. LSDB) is dedicated to maintaining information about nucleotide variation found in *PHEX*.
Normal gene product. *PHEX* codes for a 749-amino acid protein (OMIM 300550; NP_000435.3). Although there have been many possible targets for the endopeptidase activity of *PHEX,* its substrate has yet to be discovered. The protein is expressed primarily in cells of bone lineage, including osteoblasts, osteocytes and odontoblasts leading to its importance in phosphate regulation and mineralization of these tissues. While *PHEX* is expressed primarily in cells of bone and teeth lineage, the main protein effects on renal phosphate wasting and impaired vitamin D metabolism occur in the kidney.
Abnormal gene product. Mutations in *PHEX* are considered loss of function mutations. As the function of *PHEX* is unknown, little is known about the function of the abnormal gene product.

Resources

Go to:

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

References

Go to:

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page PubMed

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Chapter Notes

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Author Notes

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