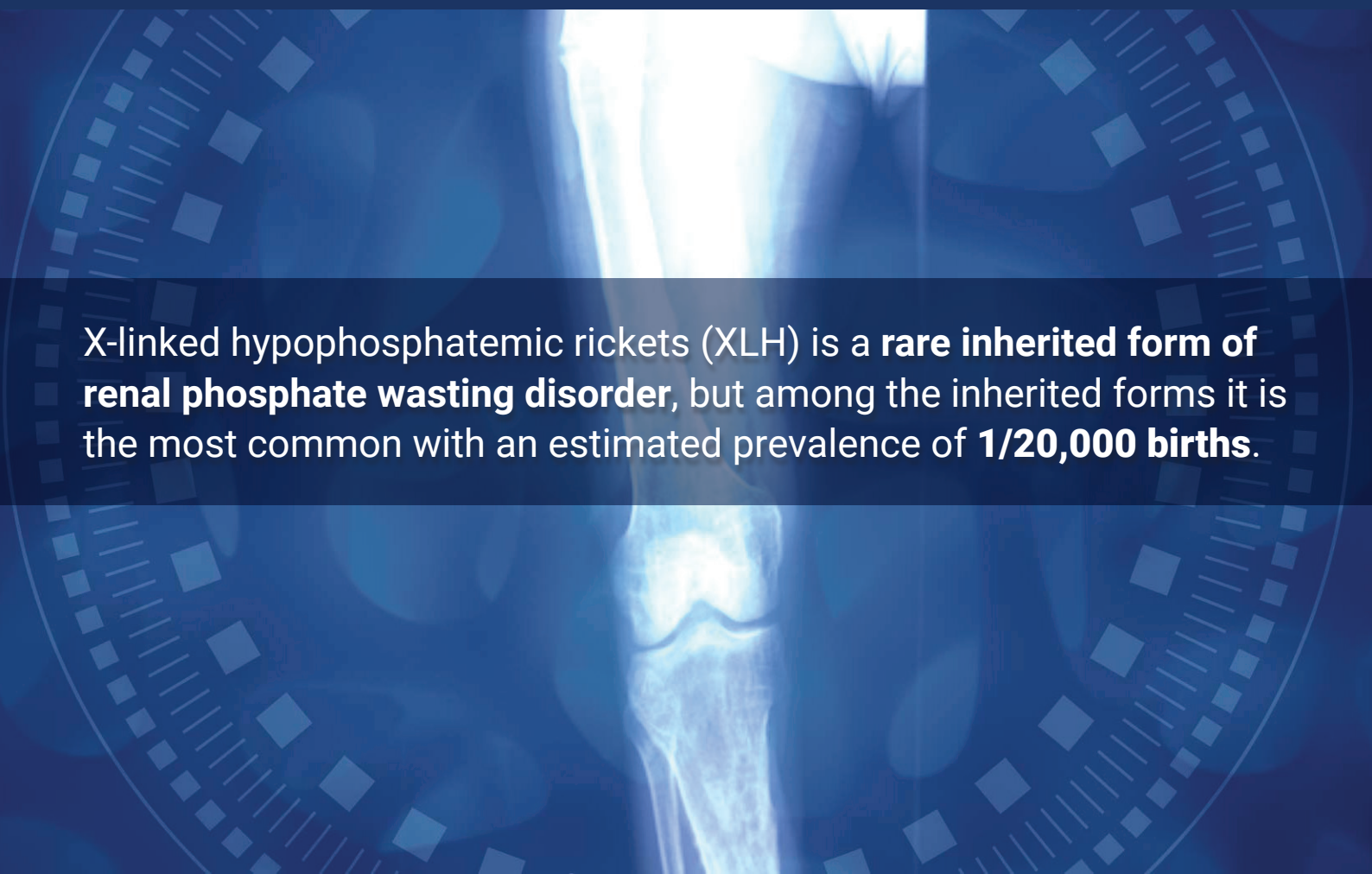


# X-Linked Hypophosphatemia (XLH)

Key information and diagnostic algorithm



X-linked hypophosphatemic rickets (XLH) is a **rare inherited form of renal phosphate wasting disorder**, but among the inherited forms it is the most common with an estimated prevalence of **1/20,000 births**.

# DIAGNOSIS

Diagnosis is based on a consistent medical history, physical examination, radiological evidence of rickets, biochemical exams and a family history suggestive of multigenerational or sporadic occurrence of XLH. Differential diagnosis includes nutritional rickets, metaphyseal dysplasia, and other forms of renal phosphate wasting disorders.

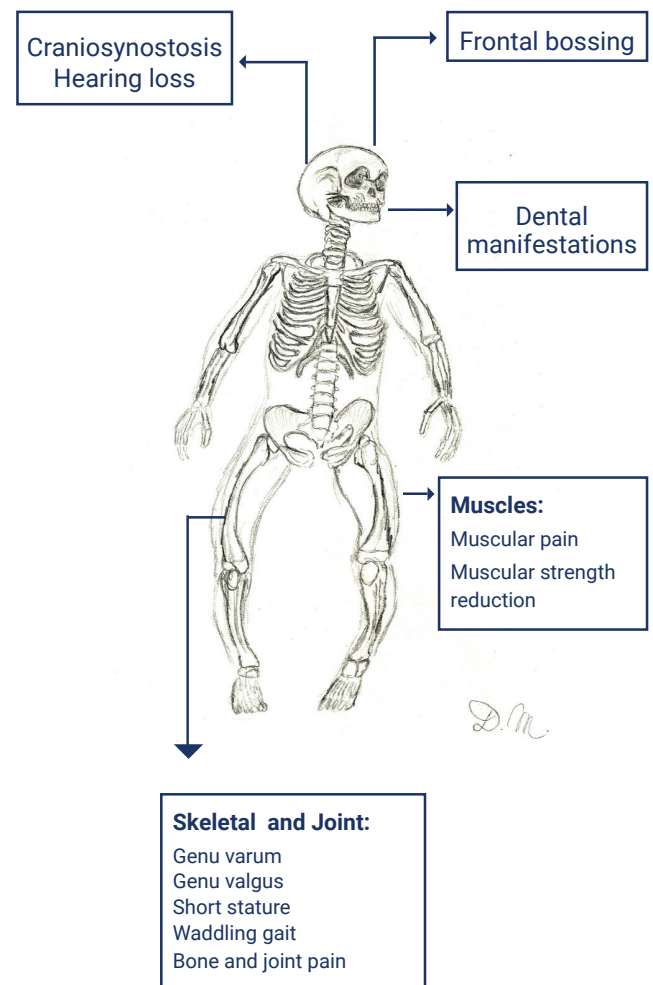
## Clinical Manifestations

### In children

- ▶ rickets, skeletal deformities, bowed legs
- ▶ bone and/or joint pain
- ▶ short stature (decrease in height velocity)
- ▶ cranial abnormalities with frontal bossing, craniosynostosis, increased anteroposterior skull length, hearing loss
- ▶ dental manifestations (abscessed noncarious teeth, enamel defects, enlarged pulp chambers, taurodontism)

### In adults

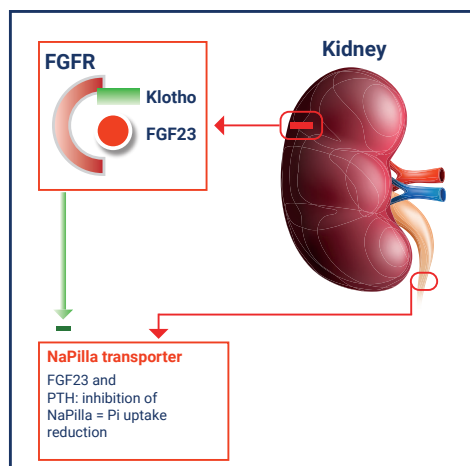
- ▶ bone and joint pain from osteomalacia, pseudofracture, fragility fracture, myopathy, osteoarthritis, enthesopathy
- ▶ bone and/or joint pain
- ▶ short stature (decrease in height velocity)



## Biochemical Features

- ▶ hypophosphatemia
- ▶ renal phosphate wasting, reduced TmP/GFR (tubular maximal reabsorption of phosphate adjusted for glomerular filtration rate)
- ▶ elevated serum alkaline phosphatase
- ▶ low or inappropriately normal levels of  $1,25(\text{OH})_2\text{D}_3$
- ▶ usually normal serum 25-vitamin D [25-(OH) D] level
- ▶ elevated or inappropriately normal levels of serum FGF23
- ▶ normal Ca and PTH (however, secondary hyperparathyroidism is common in this disease, both without treatment with phosphate and as a potential consequence of phosphate treatment)

## PATHOPHYSIOLOGY



Fibroblast growth factor 23 (FGF23) is a hormone primarily secreted by osteocytes/osteoblasts and regulates the phosphate metabolism. Mutations of the PHEX gene, highly expressed in osteocytes and osteoblasts, lead to high FGF-23 levels due to abnormal cleavage of FGF23 leading to hypophosphatemia via impaired phosphate reabsorption in the renal proximal tubules (decreased NPT2a and 2c transporters) and decreased phosphate absorption in the intestines (decreased activity of 1 $\alpha$ -hydroxylase, reducing the renal synthesis of 1,25(OH) $_2$ D $_3$ ).

## TREATMENT

### ► SURGICAL OR ORTHOPEDIC TREATMENT

### ► MEDICATION

- An active form of vitamin D and phosphorus supplement should be prescribed very carefully and taken in association with regular monitoring of blood and urine exams, including PTH and urine calcium levels.
- Humanized monoclonal antibody for FGF23 (burosumab) has been approved for the treatment of XLH in paediatric patients 1 year of age and older. [Crysvita<sup>®</sup> (burosumab) has been approved by FDA and is available since March 2018 in U.S.A. It has also been approved by EMA in the 28 countries of the European Union and in Norway, Iceland and Liechtenstein. The first commercial launch of Crysvita has taken place in Germany in the second quarter of 2018, followed by other European countries].

### Paediatric XLH

Starting dose regimen is 0.8 mg/kg of body weight, administered every two weeks

Dose may be increased up to approximately 2 mg/kg (maximum 90 mg), administered every two weeks to achieve normal serum phosphorus levels

### Adult XLH

Dose regimen is 1 mg/kg of body weight administered every four weeks

### Complications

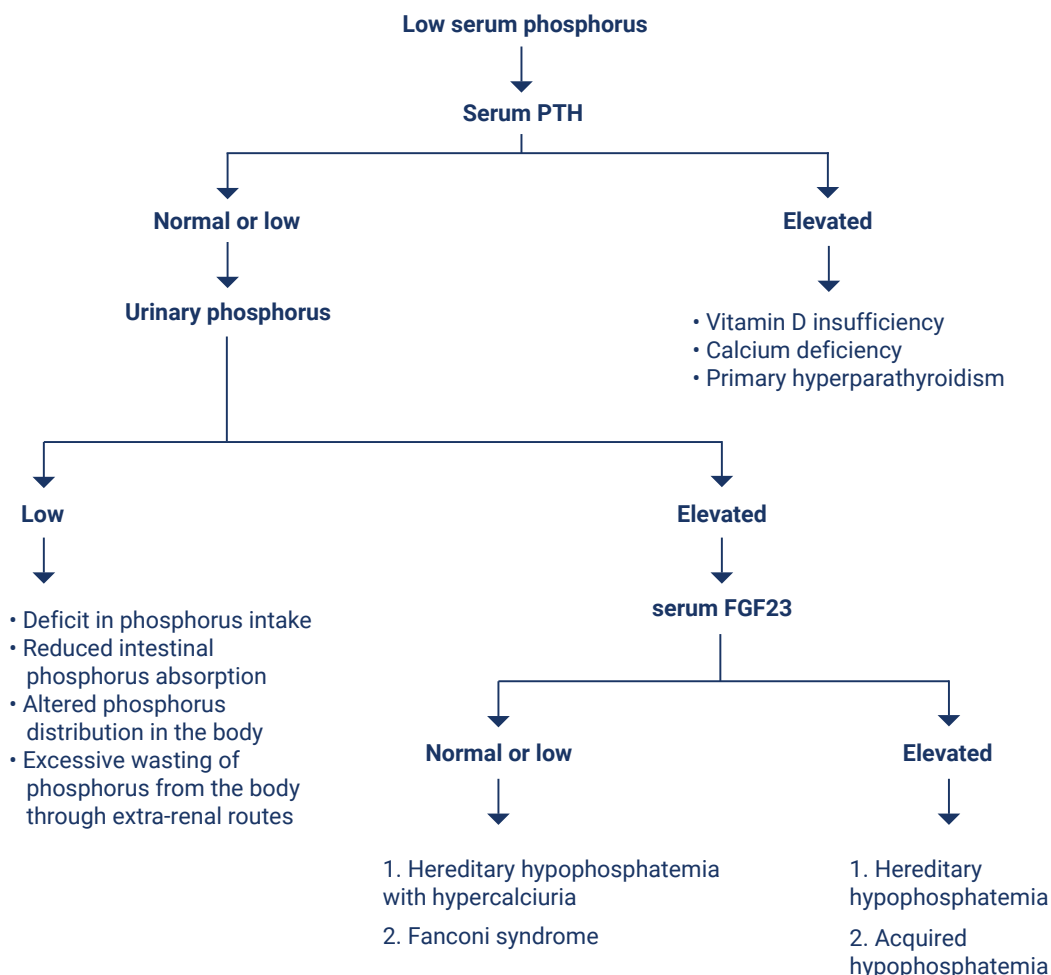
Hypercalciuria-Nephrocalcinosis  
Hyperparathyroidism

# GENETICS



XLH is caused by a variety of inactivating mutations in the PHEX (phosphate regulating endopeptidase homolog X-linked) gene, located on the chromosome Xp22.1, which is expressed in osteocytes and odontoblasts. The PHEX gene codes for a protein which is a transmembrane endopeptidase belonging to the type II integral membrane zinc-dependent endopeptidase family. Alternative splicing results in multiple transcript variants. More than 300 kinds of mutations have been reported. Other genetic and environmental factors may influence the clinical manifestations of this disease. In some cases, a PHEX gene mutation cannot be detected, and sporadic cases are common.

## ALGORITHM FOR THE EVALUATION OF A PATIENT WITH LOW SERUM PHOSPHORUS LEVELS



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