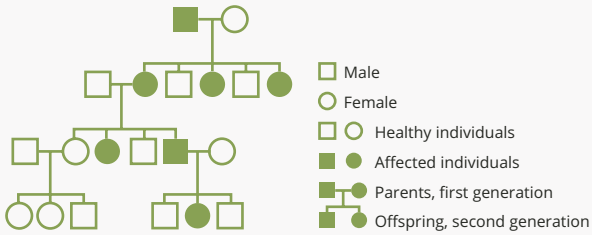
WHAT IS X-LINKED HYPOPHOSPHATAEMIA (XLH)?

XLH is a rare, hereditary, chronic and progressive musculoskeletal disorder, resulting from excess FGF23 production[1-4]

Prevalence

- XLH is estimated to affect approximately 1 in 20,000–1 in 60,000 people[1,4,6]

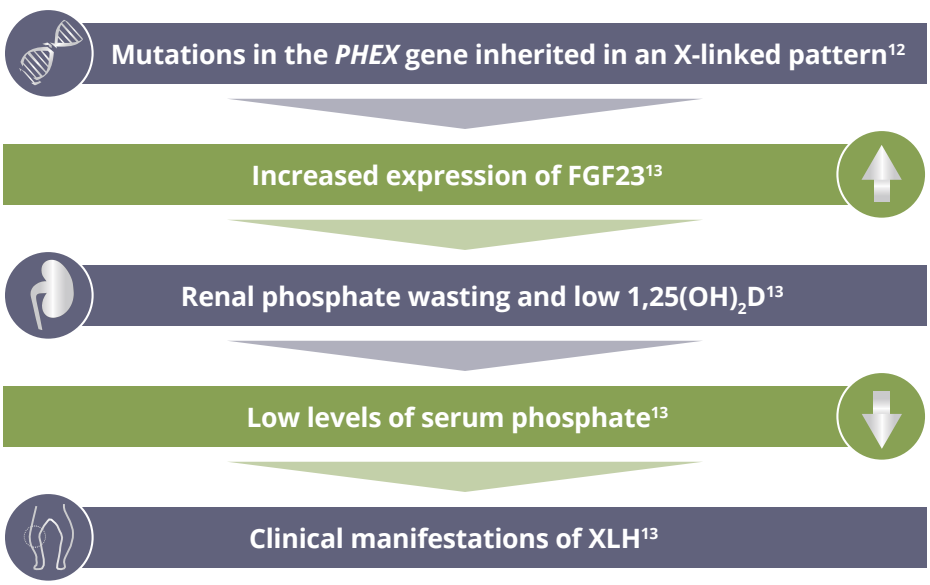
PEDIGREE ANALYSIS



Inheritance

- XLH is inherited in an X-linked dominant pattern and is caused by a loss-of-function mutation in the PHEX gene:[5,7,8]
  - However, in approximately 20–30% of cases XLH occurs spontaneously and there is no family history[9-11]

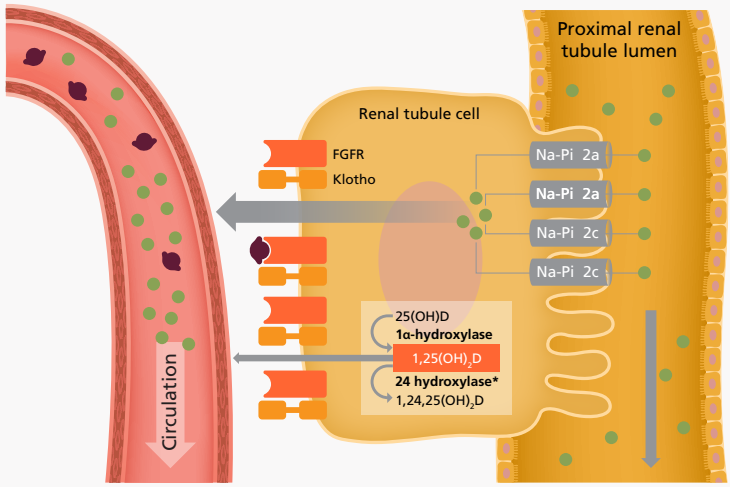
XLH mechanism of disease



Role of FGF23

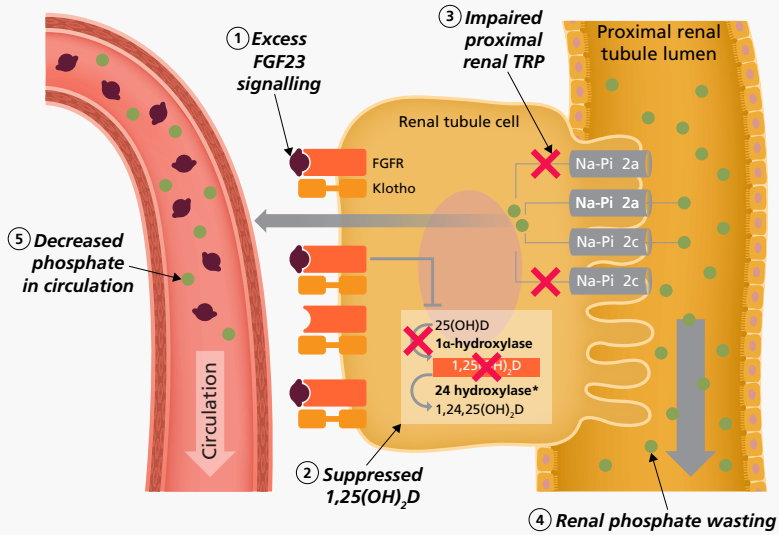
In XLH, excessive levels of FGF23 result in renal phosphate wasting and decreased active vitamin D levels, causing chronic hypophosphataemia[2,3]

FGF23 in **healthy** individuals[3,14-18]

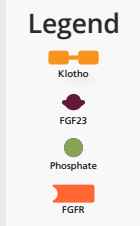


- FGF23 is a bone-derived hormone that regulates phosphate metabolism,[19] which is critical to lifelong skeletal health[16]
- FGF23 regulates serum phosphate levels by decreasing both phosphate reabsorption in the kidneys and $1,25(OH)_2D$ production, leading to decreased intestinal phosphate absorption[2,19]

FGF23 in patients with **XLH**[3,17,20,21]



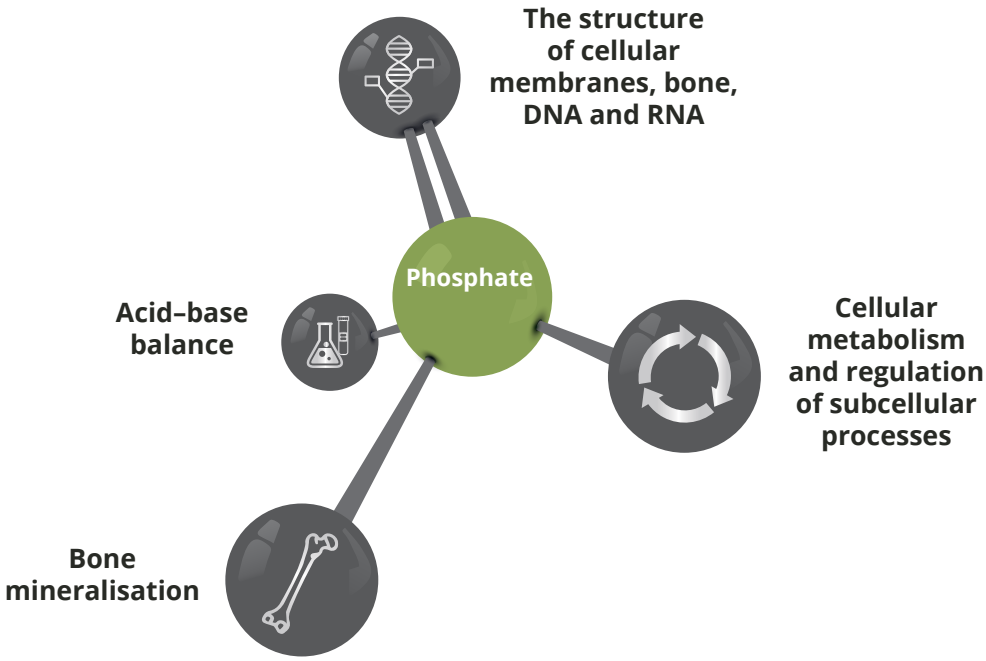
- Excess FGF23 signalling leads to:[2,19]
  - Renal phosphate wasting
  - Suppressed circulating $1,25(OH)_2D$, reducing intestinal phosphate reabsorption
- The resulting chronic hypophosphataemia leads to reduced bone mineralisation and rickets/osteomalacia[3]



*Both $1,25(OH)_2D$ and 25(OH)D are 24-hydroxylated, however $1,25(OH)_2D$ is the preferred substrate

$1,25(OH)_2D$, 1,25-dihydroxyvitamin D; FGF23, fibroblast growth factor 23; PHEX, phosphate-regulating neutral endopeptidase, X-linked; TRP, tubular reabsorption of phosphate; XLH, X-linked hypophosphataemia

Phosphate homeostasis is critical for wellbeing and essential for a wide variety of key biological processes:[16]



- Phosphate requirements change with age and physiological need[22]
- Phosphate homeostasis is highly regulated by 1,25$(OH)_2$D, PTH and FGF23[23]

Clinical presentation[24-28]

Patients can present with a wide spectrum of disease manifestations

XLH is associated with considerable morbidity and reduced quality of life

Paediatric patients	Paediatric and adult patients	Adult patients
Rickets	Short stature	Pseudofractures
Delayed growth	Disproportionate growth	Osteoarthritis
Craniosynostosis	Lower extremity deformity	Extraosseus calcifications including: • Osteophytes • Enthesopathy • Spinal stenosis
	Tooth abscesses	Hearing loss
	Osteomalacia	
	Bone pain	
	Joint pain and stiffness	
	Muscle pain	
	Muscle weakness	
	Chiari malformation	

Functional limitations and quality of life

Paediatric patients	Paediatric and adult patients	Adult patients
Delayed walking	Gait abnormalities	Disability that impacts ability to work
	Walking device use	
	Diminished quality of life including psychosocial impact	

RED FLAG SIGNS AND SYMPTOMS OF X-LINKED HYPOPHOSPHATAEMIA (XLH) IN PAEDIATRIC PATIENTS

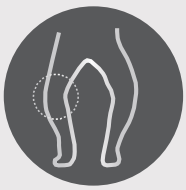
If you see a newborn or infant with a family history of rickets or a phosphate wasting disorder, consider referral. Other red flags for XLH include:

1. BOWING IN LOWER LIMBS

XLH can impair healthy bone mineralisation, leading to rickets and progressive lower limb deformities in children.[3,13,29] Bowing deformities of the leg typically present during the second year of life,[3,13,29] however, appropriate treatment can improve mobility and growth outcomes.[30]

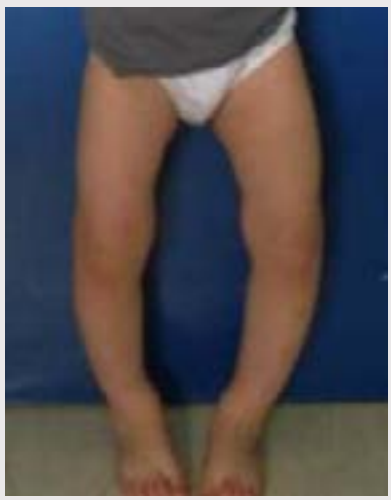
2. DELAYED WALKING WITH A WADDLING GAIT

XLH can impact motor development and mobility.[13,31] During the second year of life, children with XLH typically present with delayed walking and an abnormal, or 'waddling' gait.[13,31]



3. PAIN IN LEGS

Bone, joint and muscle pain are highly prevalent in children with XLH and frequently affect the lower limbs.[31]



Genu Varum in a patient with XLH[32]

4. SHORT STATURE

In XLH, impaired limb growth with relatively preserved trunk growth results in disproportionate short stature. Decreased growth velocity is one of the main clinical symptoms of XLH.[13]

5. ABNORMAL HEAD SHAPE

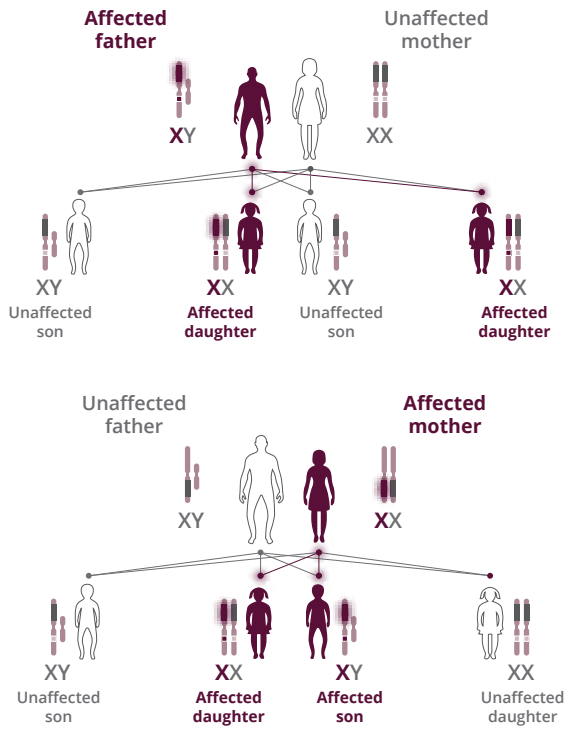
Craniosynostosis is a condition associated with XLH in which one or more of the fibrous sutures in a very young skull prematurely fuses by turning into bone.[13] This may lead to an abnormal head shape in children.

6. DENTAL ABSCESSES

Dental features of XLH include spontaneous dental abscesses that occur in the absence of trauma or dental caries.[33] Impaired dentin mineralisation associated with XLH may contribute to subsequent bacterial penetration and consequent dental abscess despite the absence of carious lesions.[34]

IN THE PRESENCE OF RED FLAG SIGNS OR SYMPTOMS, THE FOLLOWING INVESTIGATIONS AND ASSESSMENTS CAN HELP CONFIRM A DIAGNOSIS OF XLH

Inheritance pattern



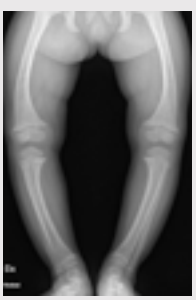
FAMILY HISTORY[13]

- A positive family history can help confirm a diagnosis of XLH
- Any first-generation family member of a patient with XLH should be investigated for XLH; sons of males are not affected
- Mutational analysis of the *PHEX* gene can help in cases with a negative family history

PHYSICAL EXAMINATION

- A detailed clinical evaluation should include evidence of:[13]
  - Rickets
  - Growth failure
  - Dental abnormalities
  - Craniosynostosis

RADIOLOGICAL EXAMINATION



RED FLAG FINDINGS

- Rickets characterised by cupped and flared metaphyses and widened and irregular physes (growth plates) of the long bones[3,13]
- Consider performing radiography of the knees and/or wrists and/or ankles to confirm a diagnosis of rickets[13]

Clinical photos are courtesy of Prof. Natascia Di Iorgi, IRCCS Istituto Giannina Gaslini (Italy)
Legs of a paediatric patient with XLH[13]

BIOCHEMICAL MEASURES

Selected biochemical characteristics of nutritional rickets and XLH[13]

Measure	Nutritional rickets	XLH
Serum Calcium	N, ↓	N
Serum Phosphate	N, ↓	↓
Urinary Phosphate	*Varies*	↑
ALP	↑↑↑	↑(↑↑)
25(OH)D	↓↓, N	N

N, normal; ↓, decreased; ↓↓ markedly decreased; ↑, elevated; ↑(↑↑), might range widely; ↑↑ or ↑↑↑, very elevated.

PEOPLE WITH XLH SHOULD BE URGENTLY REFERRED, DIAGNOSED AND TREATED

Prompt referral, diagnosis and early treatment. Early treatment of XLH is associated with superior clinical outcomes[13]

Care for patients with XLH should be provided by multidisciplinary teams[13,35]

People with XLH may be treated with symptomatic or corrective treatments[24,36]

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KKSG-CRV-15-DEC2021

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