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

This information has been developed by experts from the XLH Link Working Group, and was initiated and funded by Kyowa Kirin

XLH is a rare, hereditary†, progressive and lifelong disorder characterised by renal phosphate wasting and chronic hypophosphataemia.[1,2]

XLH is caused by mutations in the *PHEX* gene characterised by excess FGF23 activity.[2]

The diagnosis of XLH is frequently delayed, which has a detrimental effect on patient outcomes.[1]

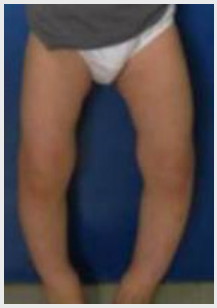
If you see a newborn or infant with a family history of rickets or a phosphate wasting disorder, consider referral. Other red flags for XLH include:

1. DEFORMITIES IN LOWER LIMBS

XLH can impair healthy bone mineralisation, leading to rickets and progressive lower limb deformities in children.[1–3] Bowing or knock knee deformities of the leg typically present during the second year of life,[1–3] however, appropriate treatment can improve mobility and growth outcomes.[4]

2. DELAYED WALKING WITH A WADDLING GAIT

XLH can impact motor development and mobility.[1,5] During the second year of life, children with XLH typically present with delayed walking and an abnormal, or 'waddling' gait.[1,5]



Genu Varum in a patient with XLH[6]

3. PAIN IN LEGS

Bone, joint and muscle pain are highly prevalent in children with XLH and frequently affect the lower limbs.[5]

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.[1]

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.[1] 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.[7] Impaired dentin mineralisation associated with XLH may contribute to subsequent bacterial penetration and consequent dental abscess despite the absence of carious lesions.[8]

THE ABOVE SIGNS AND SYMPTOMS MAY BE CAUSED BY XLH.
IF XLH IS SUSPECTED, REFER TO XLH TREATMENT CENTRES.

†In approximately 20–30% of cases XLH occurs spontaneously and there is no family history.[9-11]
FGF23, fibroblast growth factor 23; *PHEX*, phosphate-regulating endopeptidase homolog on the X chromosome.

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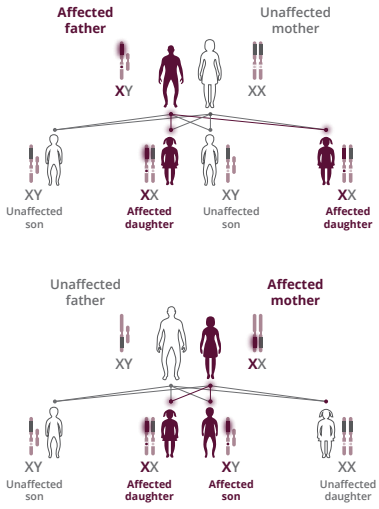
In the presence of red flag signs or symptoms, the following investigations and assessments can help confirm a diagnosis of XLH

Inheritance pattern[12]



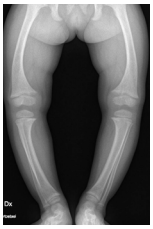
FAMILY HISTORY

- 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
- 20 - 30% of patients may be spontaneous cases of XLH. Analysis of the PHEX gene can help to confirm diagnosis of XLH.†

PHYSICAL EXAMINATION

- A detailed clinical evaluation should include assessing for evidence of:[1]
  - Rickets
  - Growth failure
  - Dental abnormalities
  - Craniosynostosis

RADIOLOGICAL EXAMINATION



Legs of a paediatric patient with XLH

- Consider performing radiography of the knees and/or wrists and/or ankles to confirm a diagnosis of rickets[1]

RED FLAG FINDINGS

- Rickets characterised by cupped and flared metaphyses and widened and irregular physes (growth plates) of the long bones[1,3]

BIOCHEMICAL MEASURES

Selected biochemical characteristics of nutritional rickets and XLH – *see publication for full table*[1]

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.

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†In approximately 20–30% of cases XLH occurs spontaneously and there is no family history.[9-11]

25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; *PHEX*, phosphate-regulating endopeptidase homolog on the X chromosome; XLH, X-linked hypophosphataemia.

References

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