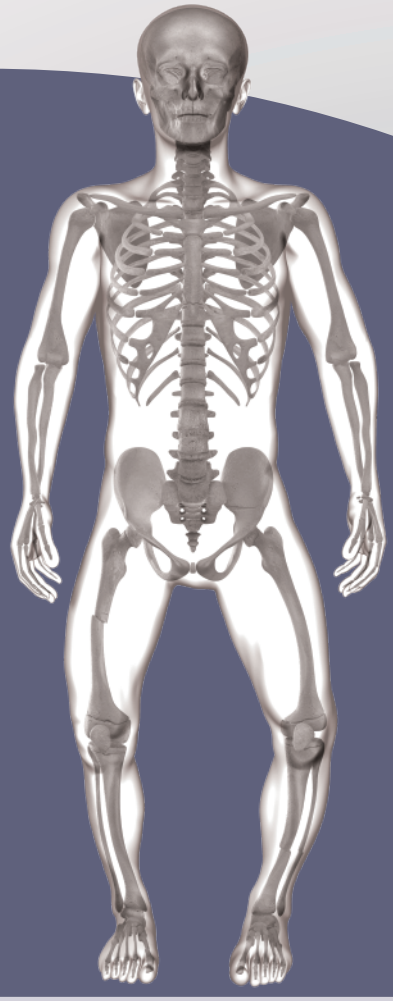
FOR PHYSICIANS

WHAT IS XLH?



ADULT FEATURES[1]

- Short stature
- Deformity of weight-bearing limbs
- Tooth abscesses
- Osteomalacia
- Bone and joint pain
- Joint stiffness
- Muscle pain and weakness
- Chiari malformation
- Gait abnormalities
- Diminished quality of life including psychosocial impact
- Fractures (including insufficiency fractures and Looser zones)
- Osteoarthritis
- Extraosseous calcifications including: Osteophytes, Enthesopathy, Spinal stenosis
- Hearing loss
- Disability that impacts ability to work

As a primary care physician, what should you know about X-linked hypophosphataemia (XLH)?

- XLH is a rare X-linked dominant genetic disorder characterised by renal phosphate wasting.[1] It is the most frequent cause of inherited hypophosphatemia and the most common genetic cause of rickets.[1]
- XLH is caused by mutations of Phosphate regulating Endopeptidase X-linked (PHEX) gene (located at Xp22.1).[1] This results in excess Fibroblast Growth Factor 23 (FGF23) leading to renal phosphate wasting and suppressed circulating 1,25(OH)2D, reducing intestinal phosphate reabsorption.[2]
- The resulting chronic hypophosphataemia leads to reduced bone mineralisation and rickets/osteomalacia.[2]

Suspect XLH in ADULT patients with any of the following signs and symptoms:

"Essential" features for a presumptive diagnosis of XLH in adults[1]

- ☐ Serum phosphate levels below the reference range[a]
- ☐ Renal phosphate wasting[b] – exclude other renal reasons for phosphaturia
- ☐ Short stature[c]
- ☐ Presence/history of pseudofractures, and/or lower limb deformities

a If clinical suspicion exists and serum phosphate levels are normal, 'fasting' serum phosphate test should be conducted
b Assessed by calculating renal tubular reabsorption of phosphate in the fasting state [TmP/GFR and %TRP] based on urinary and serum phosphate and creatinine levels). The normal TmP/GFR for women (by age) are as follows: 0.96–1.44 for 25–35 years, 0.88–1.42 for 45-55 years, and 0.80–1.35 for 65-75 years. The normal TmP/GFR for men (by age) are higher than for women, as follows: 1.00–1.35 for 25–35 years, 0.90–1.35 for 45–55 years, and 0.80–1.35 for 65–75 years[3]
c Disproportionate short stature in severe cases (impaired limb growth with preserved trunk growth)

Additional criteria to support or further confirm the diagnosis of XLH in adults[1]

- ☐ Bone pain, stiffness, reduced functional capacity
- ☐ Recurrent dental abnormalities
- ☐ Radiological signs of osteomalacia, early osteoarthritis and/or enthesopathies
- ☐ Normal serum calcium, normal or elevated PTH, normal or elevated ALP, normal 25-hydroxy vitamin D, low or inappropriately normal 1,25-dihydroxy vitamin D, elevated or inappropriately normal FGF23
- ☐ Positive family history of XLH and/or detection of pathogenic PHEX gene mutations

- If you suspect XLH in an adult patient based on the above criteria, promptly refer the patient to a specialist.
- Prompt referral, diagnosis and optimal treatment in adulthood is associated with improved long term outcomes compared with later treatment onset[4-6]

ALP, Alkaline phosphatase; **PTH**, Parathyroid hormone; **TmP/GFR**, The ratio of the maximum rate of tubular phosphate reabsorption (TmP) to the glomerular filtration rate (GFR); **TRP**, Tubular Reabsorption of Phosphate.

References: 1. Munns CF, *et al.* JBMR Plus. 2023 May 1;7(6):e10744. **2.** Carpenter TO, *et al.* J Bone Miner Res. 2011;26(7):1381-1388. **3.** Payne RB. Ann Clin Biochem. 1998;35:201–6. **4.** Haffner D, *et al.* Nat Rev Nephrol. 2019;15:435-55. **5.** Lambert AS, *et al.* Joint Bone Spine. 2019;86:731-8. **6.** Saraff V, *et al.* Paediatr Drugs. 2020;22:113-21.

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