XLH LINK

Is it XLH?

X-linked hypophosphatemia (XLH) is a **hereditary, progressive, and chronic** disease that can impact the skeletal, muscular, and dental health of children and adults throughout their lives.[1,2]

Hereditary

XLH is primarily an inherited condition, although up to 30% of cases arise spontaneously.[1]

Progressive

New symptoms of XLH may appear as patients get older and can worsen or change over time.[1]

Chronic

Individuals with XLH can continue to experience symptoms throughout their lives.[1,2]

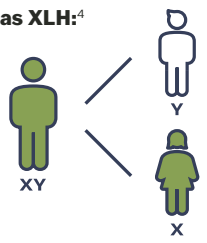
XLH is the most common cause of inherited phosphate wasting.

Genetic background

In XLH, a variant in the *PHEX* gene causes excess FGF23, which results in phosphorus wasting leading to chronic hypophosphatemia.[1] Due to increased FGF23 activity, patients with XLH may experience skeletal defects, muscular dysfunction, and dental abnormalities.[3]

XLH is inherited in an **X-linked dominant pattern**.[1]

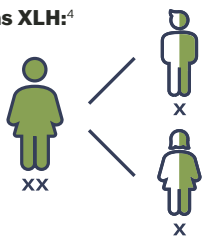
If a father has XLH:[4]



Son 0% chance of developing XLH (X chromosome from mother)

Daughter 100% chance of developing XLH (X chromosome from father)

If a mother has XLH:[4]



Son 50% chance of developing XLH (X chromosome from mother)

Daughter 50% chance of developing XLH (X chromosome from mother)

Accurate and early disease diagnosis can help minimize the lifelong XLH burden on your patients.[1,5]

Family history of XLH

A positive family history with the appropriate X-linked dominant inheritance pattern supports a diagnosis of XLH.[1,2]

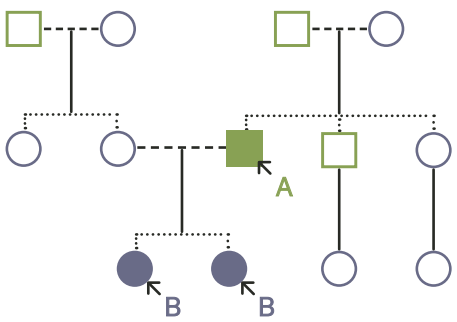
Key points about the XLH inheritance pattern:[4]

- If someone's sibling is affected, their risk of being affected depends on the genetic status of their parents, as outlined below.
- All daughters of an affected father will be affected.
- An affected father will not pass on the *PHEX* variant to any of his sons.
- The children of an affected mother have a 50% chance of inheriting the *PHEX* variant and being affected.

Up to 30% of XLH cases are spontaneous, so it is important ask if your patient has a medical history of short stature, rickets, osteomalacia, osteoarthritis, and dental abscesses, all of which may indicate XLH.[1,4]

Relationship line | **Line of descent** | **Sibling line** | **Male** | **Female** | **Affected individual**

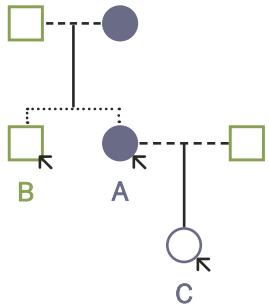
Example A†



A — This affected male had no family history of XLH, until his daughters were born. Although he is an apparently spontaneous case, it is also possible that this patient's mother has undiagnosed XLH, which would put his siblings at risk.

B — All daughters of the affected male would inherit the *PHEX* variant.

Example B[6†]

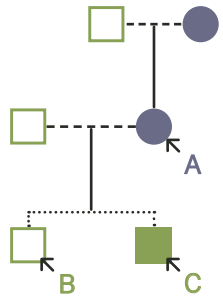


A — This affected female inherited the *PHEX* variant from her mother.

B — This male did not appear to develop XLH. However, his risk would have been 50% (the same risk as his affected sister), due to his mother being affected.

C — This female did not appear to develop XLH. However, her risk would have been 50%, due to her mother being affected.

Example C[6†]



A — This affected female inherited the *PHEX* variant from her mother.

B — Both sons of the affected female had a 50% risk of inheriting the *PHEX* variant from their mother. However, the eldest brother did not inherit it.

C — This affected son will pass XLH to all his future daughters, but none of his future sons.

Guidelines recommend that any first-generation family member of a patient with XLH should be investigated for XLH.[2]

While XLH appears to be completely penetrant, its severity can vary greatly between family members, and there are no clear gender differences.[2]

Screening other family members for XLH can help identify previously undiagnosed individuals.[1]

For example, a parent of a patient with XLH may be undiagnosed due to a milder phenotypic presentation. Therefore, a negative family history cannot be officially confirmed until at-risk relatives are assessed with biochemical or molecular genetic testing.[4]

† Example pedigrees are for illustrative purposes and are not representative of all possible cases.

The importance of diagnosing XLH

The symptoms of XLH are chronic and progressive, and can worsen throughout adulthood.[3] Additionally, misdiagnoses of XLH may lead to increased symptom severity.[2,7]

XLH can often be misdiagnosed as nutritional rickets, Pyle disease, or physiologic bowing.[8] Clinical/radiographic findings, family history, and biochemical tests can help establish a diagnosis of XLH.[2] Additionally, a diagnosis of XLH can be confirmed through genetic testing for variants of the *PHEX* gene.[2]

Genetic counselling and XLH

XLH guidelines recommend that genetic counselling be offered to patients with XLH, especially at the transition from child to adult care and to families planning pregnancies.[2]

Visit **XLHLinkHCP.ca** for more information and resources about XLH!

References: 1. Dahir K, *et al*. X-linked hypophosphatemia: A new era in management. *J Endocr Soc*. 2020;4(12):bvaa151. **2.** Haffner D, *et al*. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol*. 2019;15(7):435-455. **3.** Hamilton AA, *et al*. Whole body, whole life, whole family: Patients' perspectives on X-linked hypophosphatemia. *J Endocr Soc*. 2022;6(8):bvac086. **4.** Ruppe MD. X-linked hypophosphatemia. In: Adam MP, Everman DB, Mirzaa GM, *et al*., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; February 9, 2012. Updated April 13, 2017. https://www.ncbi.nlm.nih.gov/books/NBK83985/ **5.** Glorieux FH, *et al*. Potential influences on optimizing long-term musculoskeletal health in children and adolescents with X-linked hypophosphatemia (XLH). *Orphanet J Rare Dis*. 2022;17(1):30. **6.** Yue H, *et al*. Identification of two novel mutations in the *PHEX* gene in Chinese patients with hypophosphatemic rickets/osteomalacia. *PLoS One*. 2014;9(5)e97830. **7.** Trombetti A, *et al*. Interdisciplinary management of FGF23-related phosphate wasting syndromes: a Consensus Statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia. *Nat Rev Endocrinol*. 2022;18(6):366-384. **8.** Carpenter TO, *et al*. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res*. 2011;26(7):1381-1388.

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Kyowa Kirin