WHAT IS X-LINKED HYPOPHOSPHATAEMIA (XLH)?

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

Prevalence | **Inheritance** | **Clinical presentation** | **Role of FGF23**

Prevalence

XLH is a rare disorder

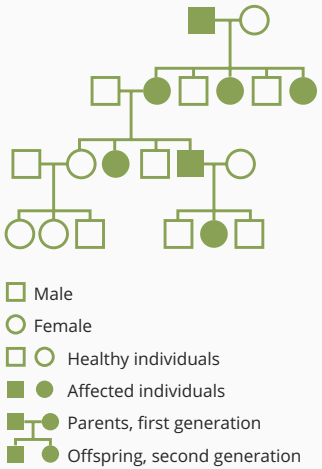
- XLH is estimated to affect approximately 1 in 20,000–1 in 60,000 people[1,5,6]

Inheritance

XLH is inherited in an X-linked pattern in most cases

- 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]

PEDIGREE ANALYSIS

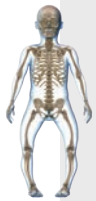


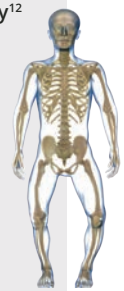
Clinical presentation

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[12]	Short stature[13,14]	Pseudofractures[12]
Delayed growth[12]	Disproportionate growth[15]	Osteoarthritis[12]
Craniosynostosis[12]	Lower extremity deformity[12]	Extraosseus calcifications including:[14] • Osteophytes • Enthesopathy • Spinal stenosis
	Tooth abscesses[12]	Hearing loss[12]
	Osteomalacia[12]	
	Bone pain[12]	
	Joint pain and stiffness[12,13]	
	Muscle pain[13,14]	
	Muscle weakness[14,16]	
	Chiari malformation[12]	





Functional limitations and quality of life

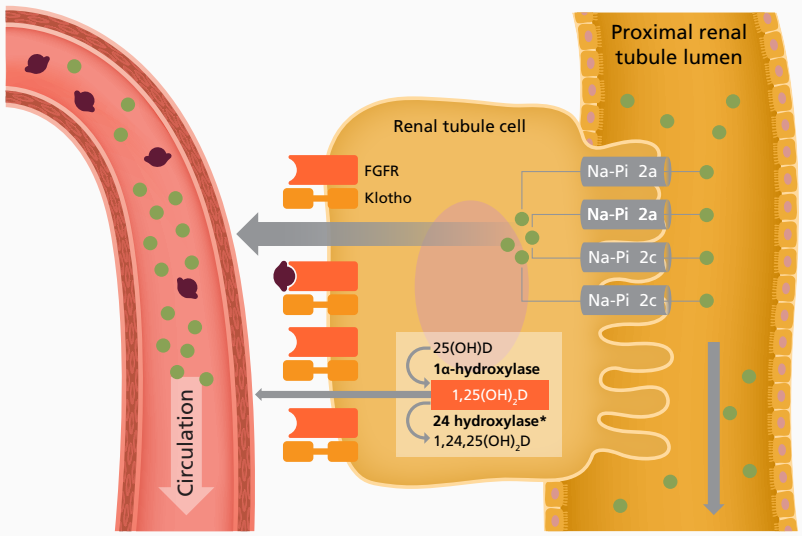
Paediatric patients	Paediatric and adult patients	Adult patients
Delayed walking[12]	Gait abnormalities[13,14]	Disability that impacts ability to work[14]
	Walking device use[13,14]	
	Diminished quality of life including psychosocial impact[13,14]	

KYOWA KIRIN

Role of FGF23

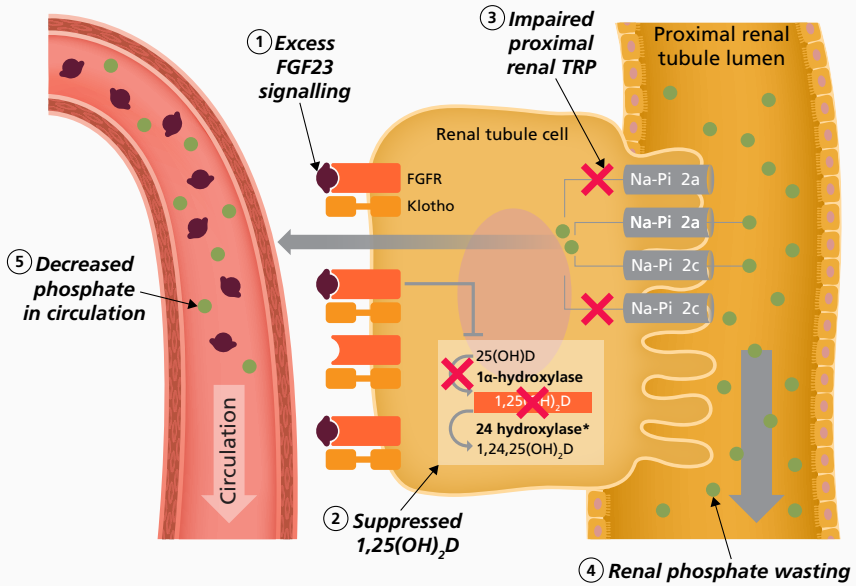
In XLH, excessive levels of FGF23 result in renal phosphate wasting and decreased active vitamin D levels, causing chronic hypophosphataemia[2,3]

FGF23 in healthy individuals[3,17–21]



Legend

FGF23 in patients with XLH[3,20,23,24]



- FGF23 is a bone-derived hormone that regulates phosphate metabolism[22], which is critical to lifelong skeletal health[19]
- 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[2,22]

- Excess FGF23 signalling leads to:[2,22]
  - 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

References:

1. Beck-Nielsen SS, et al. *Eur J Endocrinol.* 2009;160:491–97; 2. Martin A & Quarles LD. *Adv Exp Med Biol.* 2012;728:65–83; 3. Carpenter TO, et al. *J Bone Miner Res.* 2011;26:1381–88; 4. Che H, et al. *Eur J Endocrinol.* 2016;174:325–33; 5. Burnett CH, et al. *Am J Med.* 1964;36:222–32; 6. Rafaelsen S, et al. *Eur J Endocrinol.* 2015;174:125–36; 7. Mumm S, et al. *J Bone Miner Res.* 2015;30:137–43; 8. Gaucher C, et al. *Hum Genet.* 2009;125:401–11; 9. Whyte MP, et al. *J Clin Endocrinol Metab.* 1996;81:4075–80; 10. Rajah J, et al. *Eur J Pediatr.* 2011;170:1089–96; 11. Dixon PH, et al. *J Clin Endocrinol Metab.* 1998;83:3615–23; 12. Linglart A, et al. *Endocr Connect.* 2014;3:R13–R30; 13. Linglart A, et al. ICCBH 2015. Poster P198; 14. Skrinar A, et al. ENDO 2015. Poster SAT-244; 15. Haffner D, et al. *Pediatrics.* 2004;113:e593–6; 16. Veilleux LN, et al. *J Clin Endocrinol Metab.* 2012;97:E1492; 17. Kurosu H, et al. *J Biol Chem.* 2006;281:6120–3; 18. Andrukhova O, et al. *Bone.* 2012;51:621–8; 19. Penido MG, Alon US. *Pediatr Nephrol.* 2012;27:2039–48; 20. Christakos S, et al. *Physiol Rev.* 2016;96:365–408; 21. Bikle DD. *Chem Biol.* 2014:21:319–29; 22. Kinoshita Y, Fukomoto S. *Endocr Rev.* 2018;39:274–91; 23. Huang X, et al. Bone Res. 2013;2:120–32; 24. Quarles LD. *J Clin Invest.* 2008;118:3820–8.

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