Ultragenyx - XLH Website
Content Map

Utility Navigation

- 0.1 Visit the Patient Website

- 0.0 Home/Welcome
  - 1.0 About XLH
    - 1.1 Mechanism of disease
    - 1.2 Prevalence
  - 2.0 Manifestations
    - 2.1 Pediatric manifestations
      - Tab A: Skeletal disease
      - Tab B: Physical function
      - Tab C: Quality of life
    - 2.2 Adult manifestations
      - Tab A: Skeletal disease
      - Tab B: Physical function
      - Tab C: Quality of life
  - 3.0 Diagnosis
    - 3.1 Diagnosis
  - 4.0 Assessment
    - 4.1 Pediatric assessment
      - Tab A: Skeletal disease
      - Tab B: Physical function & quality of life
      - Tab C: Biochemical
    - 4.2 Adult assessment
      - Tab A: Skeletal disease
      - Tab B: Physical function & quality of life
      - Tab C: Biochemical
  - 5.0 Resources
    - 5.1 Resources

Footer Navigation

- ultragenyx.com — Ultragenyx Logo
- kyowa-kirin.com — Kyowa Kirin Logo
- ultragenyx.com — Privacy Policy

Legend

- X.X Content Screen
- Link
- X.X Navigation Label

GLOBAL CONTENT

UTILITY NAVIGATION	
Link	Visit the Patient site [[Links to TK]]
Link	XLH Link logo [[Links to 0.0]]
Tagline	Bringing people and ideas together

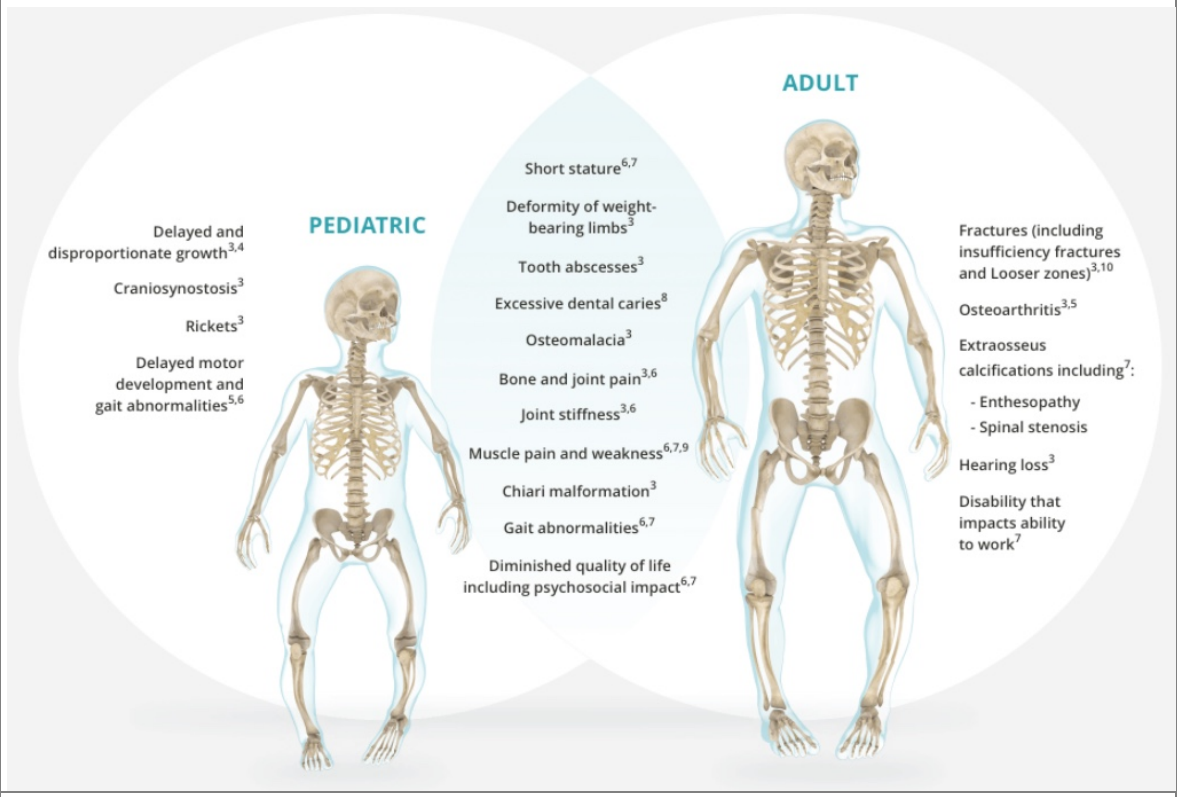
FOOTER	
Global footer copy	This site is intended for US audiences only.
Link	Kyowa Kirin Logo [[links to http://www.kyowa-kirin.com/]]
Link	Ultragenyx logo [links to http://www.ultragenyx.com]]
	Footer contains full site map including links to all pages
Footer site map	**About XLH** Mechanism of Disease Prevalence **Manifestations** Pediatric Manifestations Adult Manifestations **Diagnosis** Diagnosis **Assessment** Pediatric Assessment Adult Assessment **Resources** Resources
Copyright info	© 2017 Ultragenyx Pharmaceutical Inc 12/17 IM/IM-M2/0201 MRCC-KRN23-00016

MAIN NAVIGATION MENU	
1.0	About XLH <opens dropdown menu> Mechanism of disease <Link to 1.1> Prevalence <Link to 1.2>
2.0	Manifestations <opens dropdown menu> Pediatric Manifestations <Link to 2.1> Adult Manifestations <Link to 2.2>
3.0	Diagnosis <Link to 3.1>
4.0	Assessment <opens dropdown menu> Pediatric Assessment <Link to 4.1> Adult Assessment <Link to 4.2>
5.0	Resources <Link to 5.1>

0.0 HOME

Metadata	
Sitemap Number	0.0
Page Name	Home

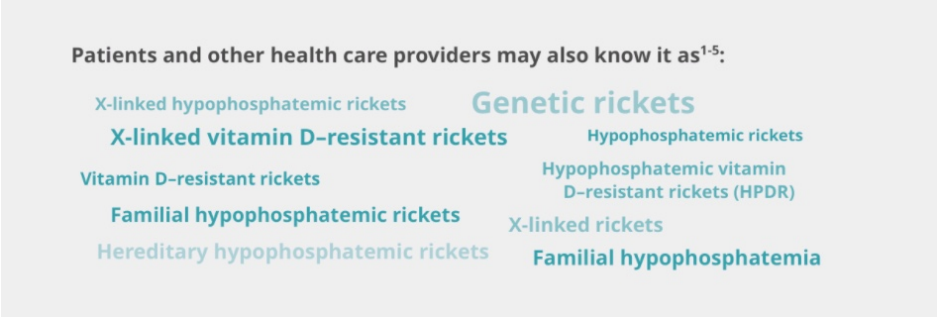
Hero Area	
Headline	**X-linked hypophosphatemia (XLH)**
Subhead	Progressive, chronic, skeletal[1,2]
Body copy	XLH is characterized by renal phosphate wasting, which is caused by excess fibroblast growth factor 23 (FGF23) production[1,2]
Graphic	Image of adult and pediatric skeletons
Onscreen label text in image (not active)	[Left Venn diagram: Pediatric manifestations] Delayed and disproportionate growth[3,4] Craniosynostosis[3] Rickets[3] Delayed motor development and gait abnormalities[5,6] [Middle Venn diagram: Pediatric and Adult] Short stature[6,7] Deformity of weight-bearing limbs[3] Tooth abscesses[3] Excessive dental caries[8] Osteomalacia[3] Bone and joint pain[3,6] Joint stiffness[3,6] Muscle pain and weakness[6,7,9] Chiari malformation[3] Gait abnormalities[6,7] Diminished quality of life including psycholsocial impact[6,7] [Right Venn diagram: Adult manifestations] Fractures (including insufficiency fractures and Looser zones)[3,10] Osteoarthritis[3,5] Extraosseus calcifications including[7]: • Enthesopathy • Spinal stenosis Hearing loss[3] Disability that impacts ability to work[7]

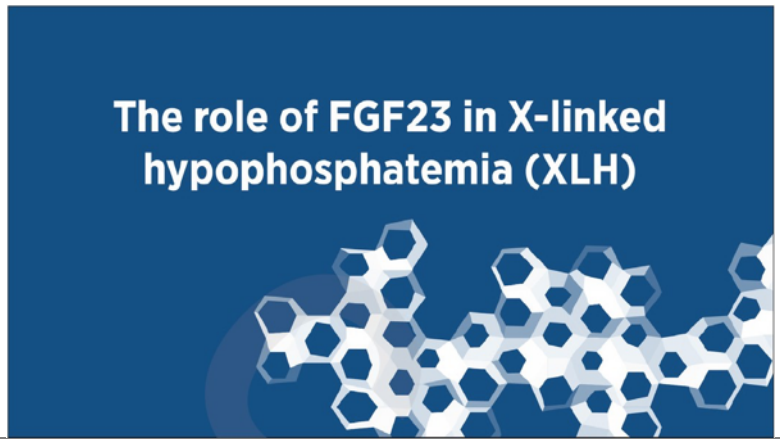
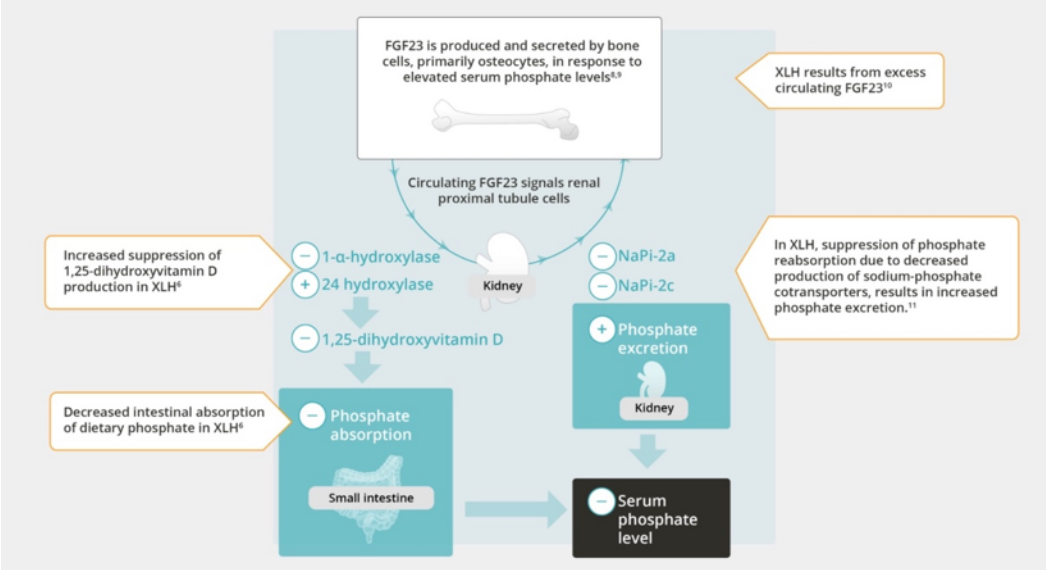
Image	
CTA	**See the lifelong spectrum of XLH**
Button	PEDIATRIC MANIFESTATIONS [Links to 2.1 Pediatric Manifestations]
Button	ADULT MANIFESTATIONS [Links to 2.2 Adult Manifestations]
Callout # 1	**Discover how FGF23 impacts phosphate homeostasis**
Button	WATCH THE VIDEO [Links to 1.1 Mechanism of Disease video]
Callout # 2	**Help improve outcomes through early assessment**
Button	PEDIATRIC ASSESSMENT [Links to 4.1 Pediatric Assessment]
Button	ADULT ASSESSMENT [Links to 4.2 Adult Assessment]
References	1. Martin A, Quarles LD. Evidence for FGF23 involvement in a bone-kidney axis regulating bone mineralization and systemic phosphate and vitamin D homeostasis. *Adv Exp Med Biol.* 2012;728:65-83. 2. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res.* 2011;26(7):1381-1388. 3. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect.* 2014;3(1):R13-R30. 4. Zivičnjak M, Schnabel D, Billing H, et al. Age-related stature and linear body segments in children with X-linked hypophosphatemic rickets. *Pediatr Nephrol.* 2011;26(2):223-231. 5. Che H, Roux C, Etcheto A, et al. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur J Endocrinol.* 2016;174(3):325-333. 6. Linglart A, Dvorak-Ewell M, Marshall A, et al. Impaired mobility and pain significantly impact the quality of life of children with X-linked hypophosphatemia (XLH). Poster presented at: ICCBH 2015 Salzburg, Austria. 7. Skrinar A, Marshall A, San Martin J, Dvorak-Ewell M. X-linked hypophosphatemia (XLH) impairs skeletal health outcomes and physical function in affected adults. Poster presented at: Endocrine Society's 97th Annual Meeting and Expo, March 5-8, 2015. San Diego, CA. 8. Data on file. Ultragenyx, Inc. 9. Veilleux LN, Cheung M, Ben Amor M, Rauch F. Abnormalities in muscle density and muscle function in hypophosphatemic rickets. *J Clin Endocrinol Metab.* 2012;97(8):E1492-E1498. 10. Looser zones. Radiopaedia Web site. https://radiopaedia.org/articles/looser-zones-1. Accessed October 9, 2017.

1.0 About XLH

1.1 Mechanism of disease

Sitemap	
Sitemap Number	1.1
Page Name	About XLH

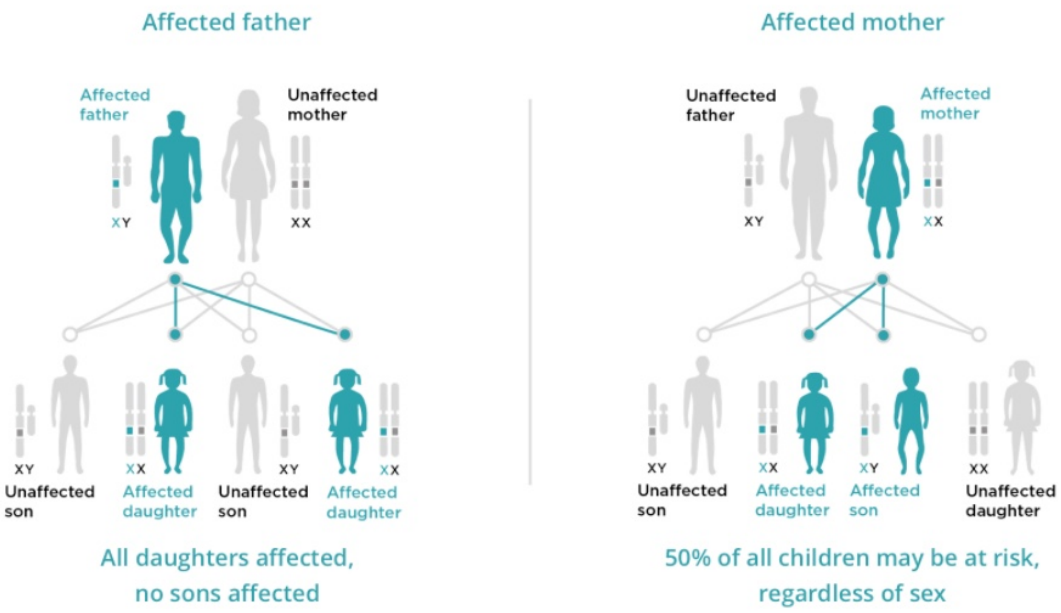
Body	
Page title	**About XLH**
Copy	**XLH is X-linked hypophosphatemia.** **Patients and other health care providers may also know it as[1-5]:** • X-linked hypophosphatemic rickets • Familial hypophosphatemic rickets • Hereditary hypophosphatemic rickets • Vitamin D–resistant rickets • Vitamin D–resistant osteomalacia • X-linked vitamin D–resistant rickets • Hypophosphatemic rickets • Hypophosphatemic vitamin D–resistant rickets (HPDR) X-linked rickets • Genetic rickets • Familial hypophosphatemia
Image	
Headline	**Mechanism of disease**
Video Header	What does XLH look like in action?

Video	
Headline	**Role of FGF23**
Subhead	FGF23 is a protein hormone that regulates serum phosphate levels by suppressing both phosphate reabsorption in the kidney and intestinal absorption of dietary phosphate.[6,7]
Copy	FGF23 is produced and secreted by bone cells, primarily osteocytes, in response to elevated serum phosphate levels[8,9] Circulating FGF23 signals renal proximal tubule cells □ Decreased intestinal absorption of dietary phosphate in XLH[6] □ Increased suppression of 1,25-dihydroxyvitamin D production in XLH[6] □ XLH results from excess circulating FGF23[10] □ In XLH, suppression of phosphate reabsorption due to decreased production of sodium-phosphate cotransporters, results in increased phosphate excretion[11]
Image	
Subhead	**In patients with XLH, excess FGF23 leads to chronic hypophosphatemia caused by renal phosphate wasting and decreased intestinal absorption of phosphate**[1,12,13]
Body	Low serum phosphate concentrations and reduced tubular reabsorption of phosphate corrected for glomerular filtration rate (GFR) are the characteristic laboratory findings in XLH patients[1]
Callout	See the clinical manifestations of XLH in pediatric and adult patients
Callout link # 1	Go to Pediatric Manifestations [Links to 2.1 Pediatric Manifestations]
Callout link # 2	Go to Adult Manifestations [Links to 2.2 Adult Manifestations]

References	1. Ruppe, MD. X-linked hypophosphatemia. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *Gene Reviews*. https://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed October 20, 2017. 2. Hereditary hypophosphatemic rickets. NIH Genetics Home Reference Web site. https://ghr.nlm.nih.gov/condition/hereditary-hypophosphatemic-rickets. Accessed October 11, 2017. 3. Jackson WPU, Dowdle E, Linder GC. Vitamin-D-resistant osteomalacia. *Brit Med J*. 1958:1269-1274. 4. Rickets and osteomalacia. NHS Choices Web site. https://www.nhs.uk/Conditions/Rickets/Pages/Treatment. Accessed October 11, 2017. 5. Familial Hypophosphatemia. National Organization for Rare Disorders Web site. https://rarediseases.org/rare-diseases/familial-hypophosphatemia/. Accessed October 11, 2017. 6. Martin A, Quarles LD. Evidence for FGF23 involvement in a bone-kidney axis regulating bone mineralization and systemic phosphate and vitamin D homeostasis. *Adv Exp Med Biol*. 2012;728:65-83. 7. Schiavi SC. Fibroblast growth factor 23: the making of a hormone. *Kidney Int.*2006;69(3):425-427. 8. Riminucci M, Collins MT, Fedarko NS, et al. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. *J Clin Invest*. 2003;112(5):683-692. 9.Ferrari SL, Bonjour J-P, Rizzoli R. Fibroblast growth factor-23 relationship to dietary phosphate and renal phosphate handling in healthy young men. *J Clin Endocrinol Metab.* 2005;90(3):1519-1524. 10. Che H, Roux C, Etcheto A, et al. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur J Endocrinol*. 2016;174(3):325-333. 11. Gattineni J, Bates C, Twombley K, et al. FGF23 decreases renal NaPi-2a and NaPi-2c expression and induces hypophosphatemia in vivo predominantly via FGF receptor 1. *Am J Physiol Renal Physiol*. 2009;297(2):F282-F291. 12. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res*. 2011;26(7):1381-1388. 13. Penido MG, Alon US. Phosphate homeostasis and its role in bone health. *Pediatr Nephrol*. 2012;27(11):2039-2048.

1.2 Prevalence

Sitemap	
Sitemap Number	1.2
Page Name	Prevalence

Body	
Page Title	Prevalence of XLH
Headline	**XLH is the most prevalent form of heritable hypophosphatemic rickets**[1,2]
Subhead	Hypophosphatemic rickets occurs in 1 in 21,000 to 1 in 25,000 live births[3]
Body Copy	XLH is inherited in an X-linked dominant pattern.[3]
Image title	X-linked dominant inheritance[3]
Image	
Body Copy	However, approximately 20% to 30% of cases arise from spontaneous mutations.[4,5] Along with family history, observing clinical manifestations may be important in identifying XLH.
Callout	See the lifelong and progressive manifestations of XLH
Callout link	Go to Pediatric Manifestations [Links to 2.1 Pediatric Manifestations]
Callout link	Go to Adult Manifestations [Links to 2.2 Adult Manifestations]
References	1. Pettifor JM. What's new in hypophosphataemic rickets? *Eur J Pediatr.* 2008;167(5):493-499. 2. Rafaelsen S, Johansson S, Ræder H, Bjerknes R. Hereditary hypophosphatemia in Norway: a retrospective population-based study of genotypes, phenotypes, and treatment complications. *Eur J Endocrinol.* 2016;174(2):125-136. 3. Ruppe MD. X-linked hypophosphatemia. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *Gene Reviews*. https://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed October 20, 2017. 4. Beck-Nielsen SS, Brixen K, Gram J, Brusgaard K. Mutational analysis of PHEX, FGF23, DMP1, SLC34A3 and CLCN5 in patients with hypophosphatemic rickets. *J Hum Genet*. 2012;57(7):453-458 5. Whyte MP, Schranck FW, Armamento-Villareal R. X-linked hypophosphatemia: a search for gender,

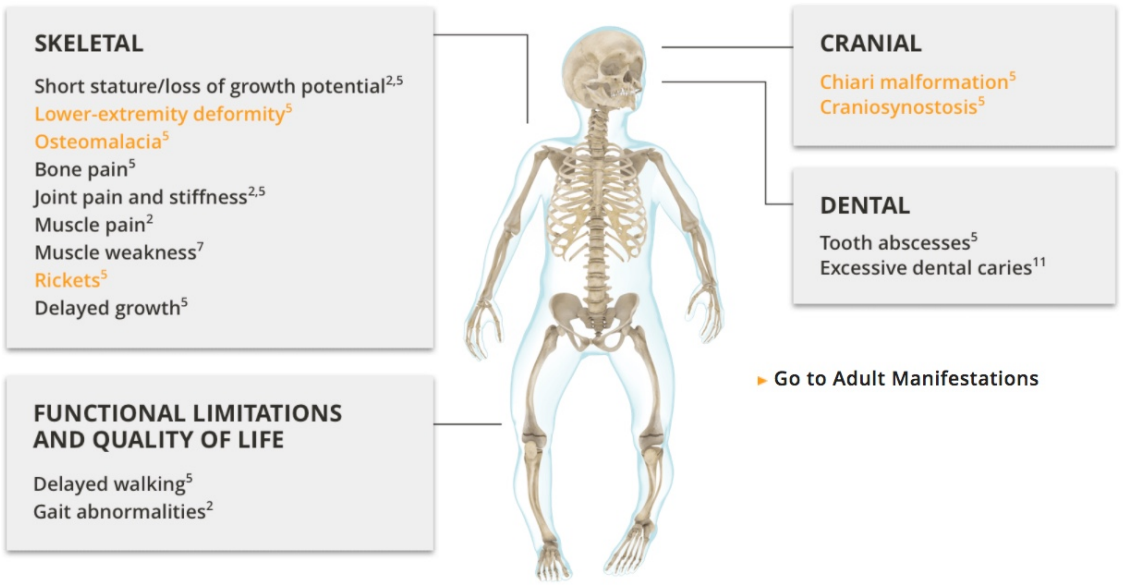
	race, anticipation, or parent of origin effects on disease expression in children. *J Clin Endocrinol Metab*. 1996;81(11):4075-4080.

2.0 Manifestations

2.1 Pediatric manifestations

Sitemap	
Sitemap Number	2.1
Page Name	Pediatric Manifestations
Meta Description	

Body	
Page Title	**Pediatric Manifestations**
Headline	**Clinical manifestations in pediatric patients with XLH**
Subhead	**XLH causes lifelong skeletal disease and can substantially decrease physical function and quality of life**[1,2]
Body Copy	XLH typically presents during the first 2 years of life with progressive lower-extremity bowing, impaired growth after the onset of weight bearing, and the characteristic clinical signs of rickets. Pain, gait disturbances, and impaired gross motor function may also be observed.[3,4]
Body copy	**SKELETAL:** Short stature/loss of growth potential[2,5] Lower-extremity deformity[5] Osteomalacia[5] Bone pain[5] Joint pain and stiffness[2,5] Muscle pain[2] Muscle weakness[7] Rickets[5] Delayed growth[5] **FUNCTIONAL LIMITATIONS AND QUALITY OF LIFE:** Delayed walking[5] Gait abnormalities[2] **CRANIAL:** Chiari malformation[5] Craniosynostosis[5] **DENTAL:** Tooth abscesses[5] Excessive dental caries[11]

Graphic	
Lower extremity deformity pop-up definition	Bowing of weight-bearing bones, especially femurs, manifesting as genu varum and genu valgum.[5]
Osteomalacia pop-up definition	Weakening of bones due to inadequate phosphate, calcium, or vitamin D.[6]
Rickets pop-up definition	Rickets is the softening and weakening of bones in children, usually because of vitamin D deficiency.[8]
Chiari malformation pop-up definition	Structural defects in the cerebellum as a result of brain tissue extending down into the spinal canal.[9]
Craniosynostosis pop-up definition	Premature fusing of skull bone plates.[10]
Link	Go to Adult Manifestations [Links to 2.2 Adult Manifestations]
Tab Subnavigation 1 [Default landing tab]	Skeletal manifestations [Links to 2.1.A Pediatric skeletal manifestations]
Tab Subnavigation 2	Physical function [Links to 2.1.B Pediatric physical function]
Tab Subnavigation 3	Quality of life [Links to 2.1.C Pediatric quality of life]
Persistent callout **[On top of every tab for sections 2.1 and 2.2]**	Due to the lifelong and progressive nature of XLH,[12-16] assessment is recommended
Callout link	Go to Pediatric Assessment [Links to 4.1 Pediatric Assessment]
Callout link	Go to Adult Assessment [Links to 4.2 Adult Assessment]

Tab 2.1 A	
Tab Name	Skeletal manifestations

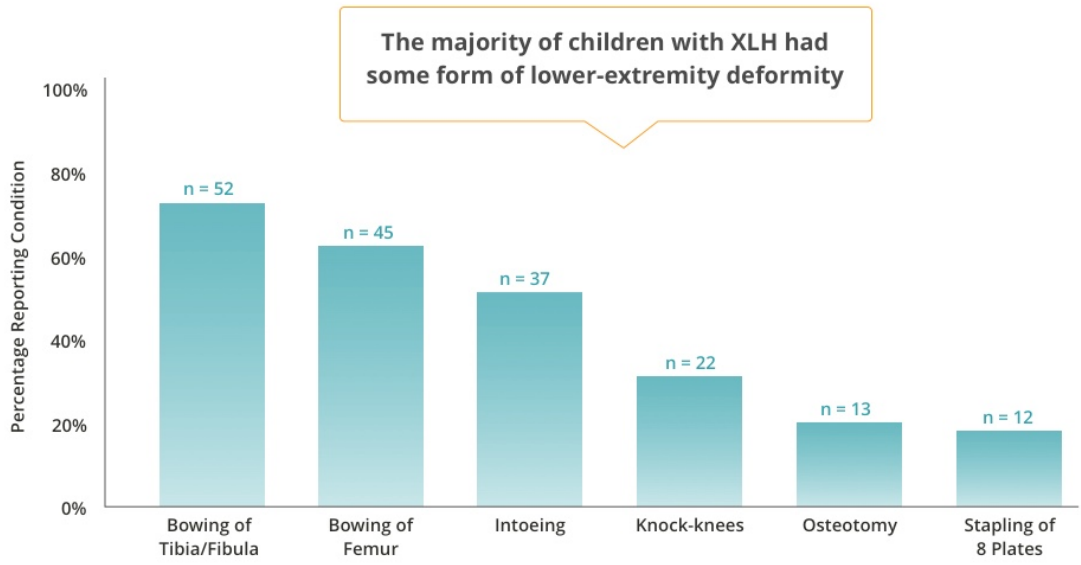
Body	
Tab title	Skeletal manifestations
Headline	**Children with XLH suffer from poor quality of life, impaired mobility, and bone and joint pain.[2]**
Subhead	In addition to skeletal disease and impaired growth, children with XLH may also have dental manifestations of the disease.[2,5]
Jump down link	Go to Growth [jumps to subhead: Growth]
Jump down link	Go to Dental [jumps to subhead: Dental]
Chart title	**In a recent survey of 71 children with XLH, lower-extremity deformities and corrective surgeries were reported in most children younger than 2 years of age[2]**
Chart	
Subhead	**Growth**
Body Copy	Children with XLH are prone to growth impairment, and linear body dimensions are significantly reduced compared to those of healthy children at all ages.[17]
Chart title	**Growth trajectory in pediatric XLH patients compared to non-XLH children aged 2-20[2,5]**

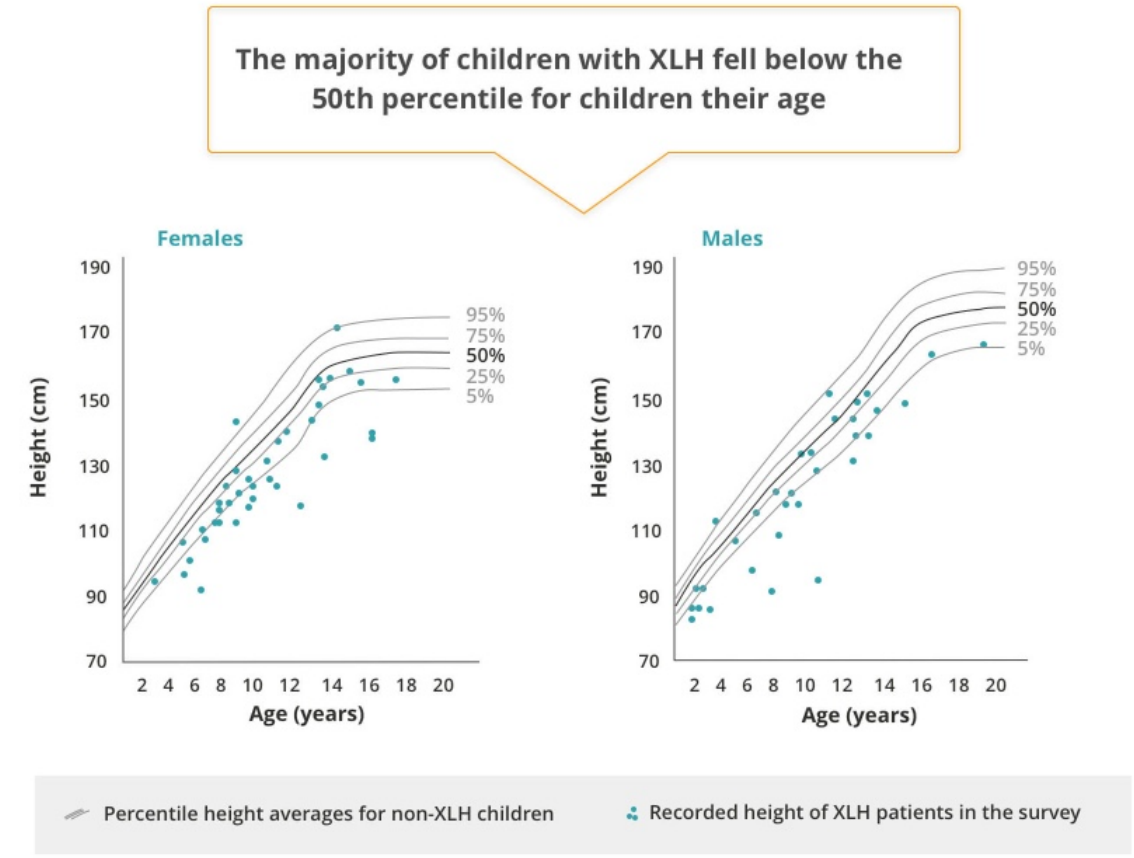
Chart	
Chart title	**Stature, sitting height, and arm and leg length over time in children with XLH versus normal population**[17]

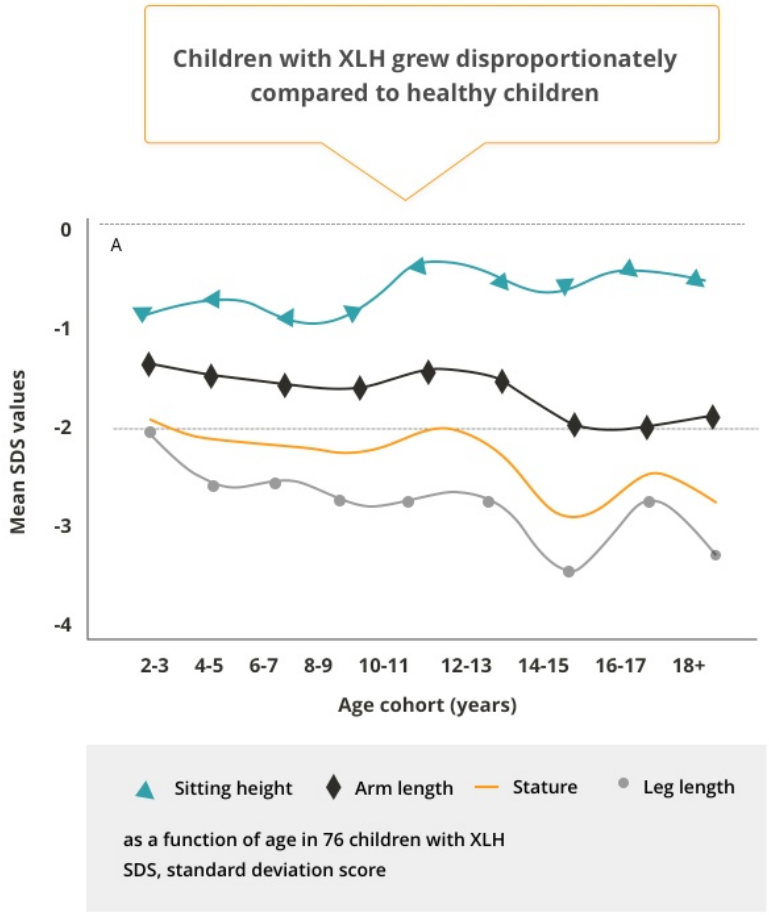
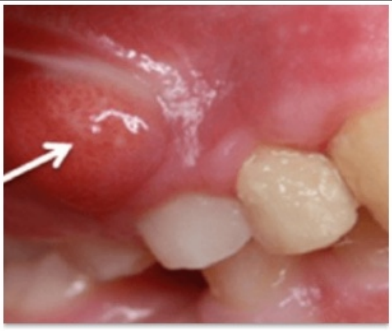
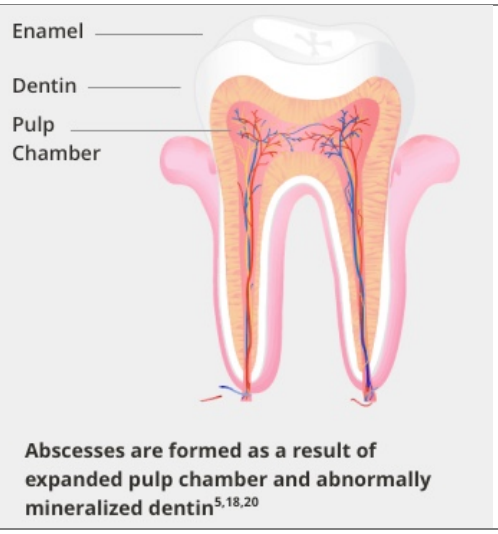
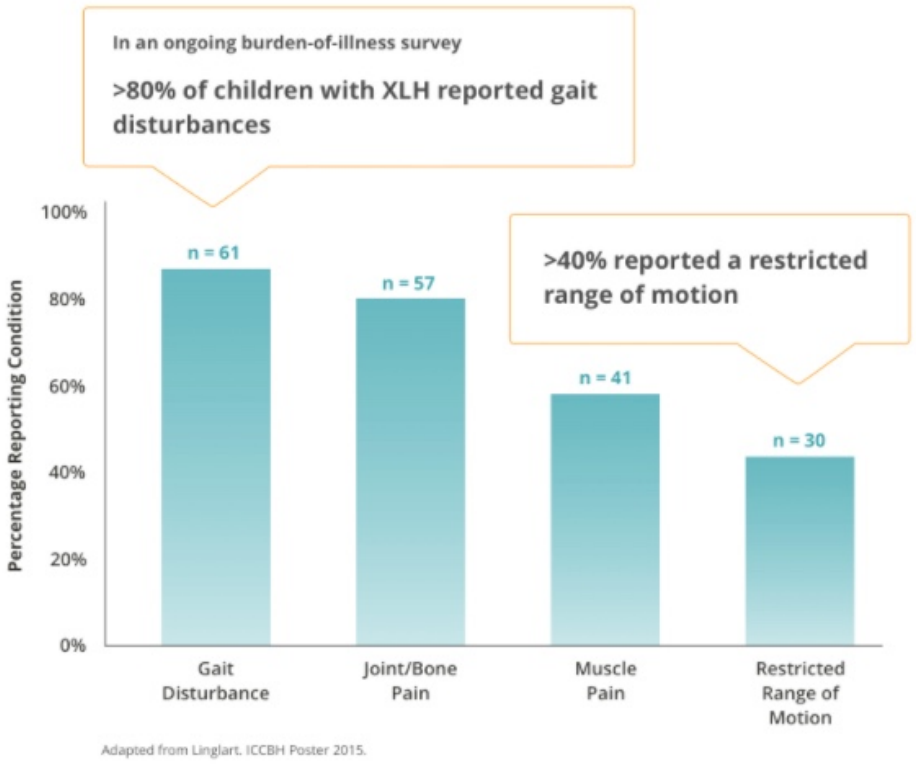
Chart	
Body copy	While linear body dimensions are significantly reduced compared to those of normal children at all ages, there is a strong association between stature and leg length in pediatric XLH patients.[17] Generally, leg length decreases progressively during childhood and adolescence, while sitting height increases significantly during late childhood.[17]
Subhead	**Dental Manifestations**
Body copy	XLH patients can be affected by tooth abscesses in both deciduous and permanent dentition. The disease results in a diminished barrier to the exterior of the tooth, with cracks in the thin enamel, extended pulp horns, and abnormal formation of the dentin, allowing bacteria and infections to enter the tooth pulp chamber without any visible damage to the tooth.[5,18] In an international online survey of parents/caregivers of 90 children with XLH aged 0 to 18 years, it was found that 51% of children had dental abscesses and 24% had excessive caries.[11]

Image	
Image copy	Abscess on a deciduous molar, a dental feature of XLH[19]
Body copy	Spontaneous abscesses appear as a result of bacterial invasion into the expanded pulp chamber via the thin and fissured enamel and abnormally mineralized and malformed dentin[5,18]
Image	

Tab 2.1 B	
Tab Name	Physical function [Middle tab]

Body	
Headline	**Physical function**
Subhead	**Children with XLH can experience diminished mobility and functional limitations[5]**
Copy	In children with XLH, lower-extremity muscle strength and walking ability are substantially decreased relative to non-XLH children.[2]
Chart title	**Commonly reported functional limitations and pain in 71 pediatric XLH patients[2]**
Chart	

Tab 2.1 C	
Tab Name	Quality of life [Bottom right tab]

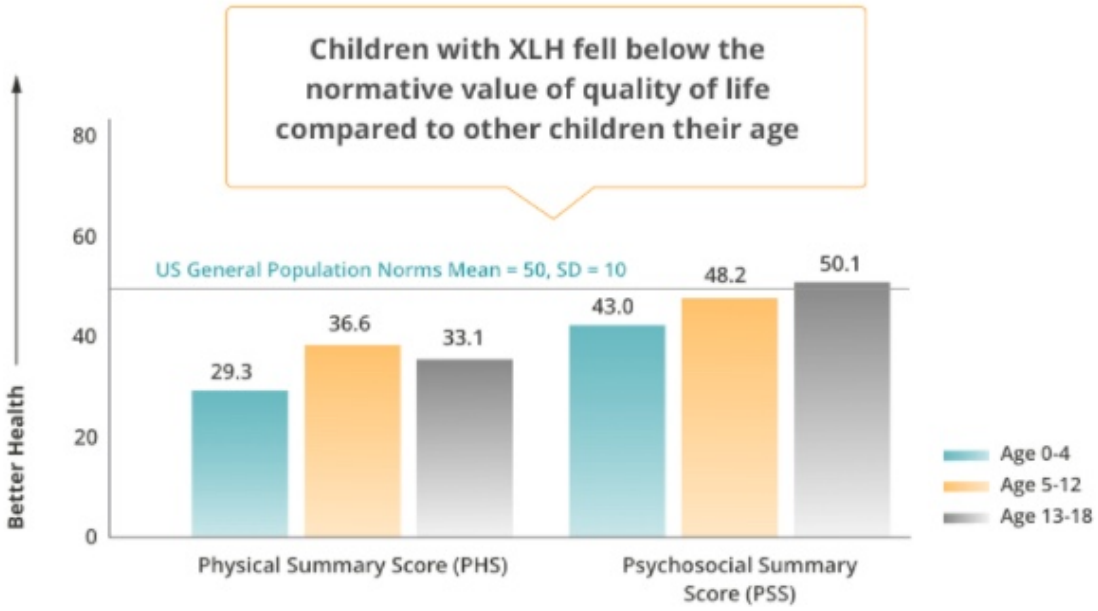
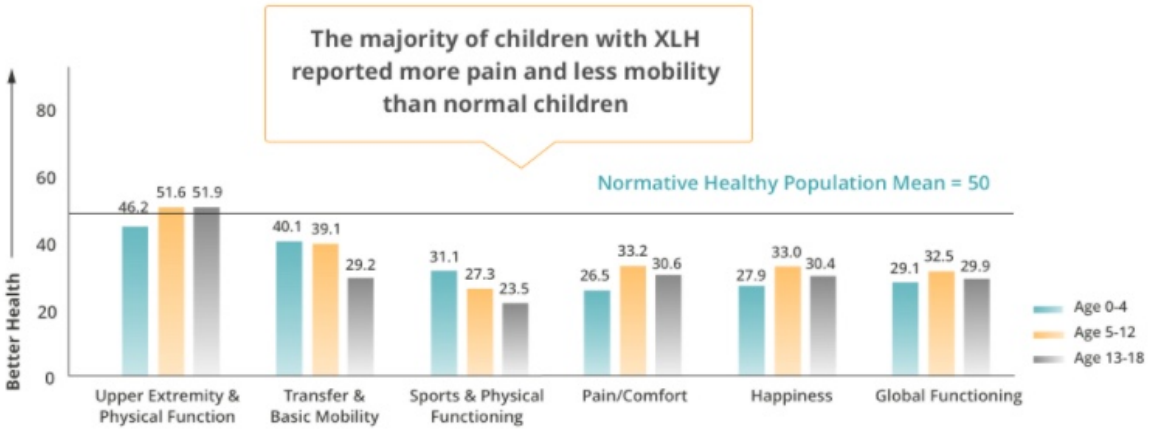
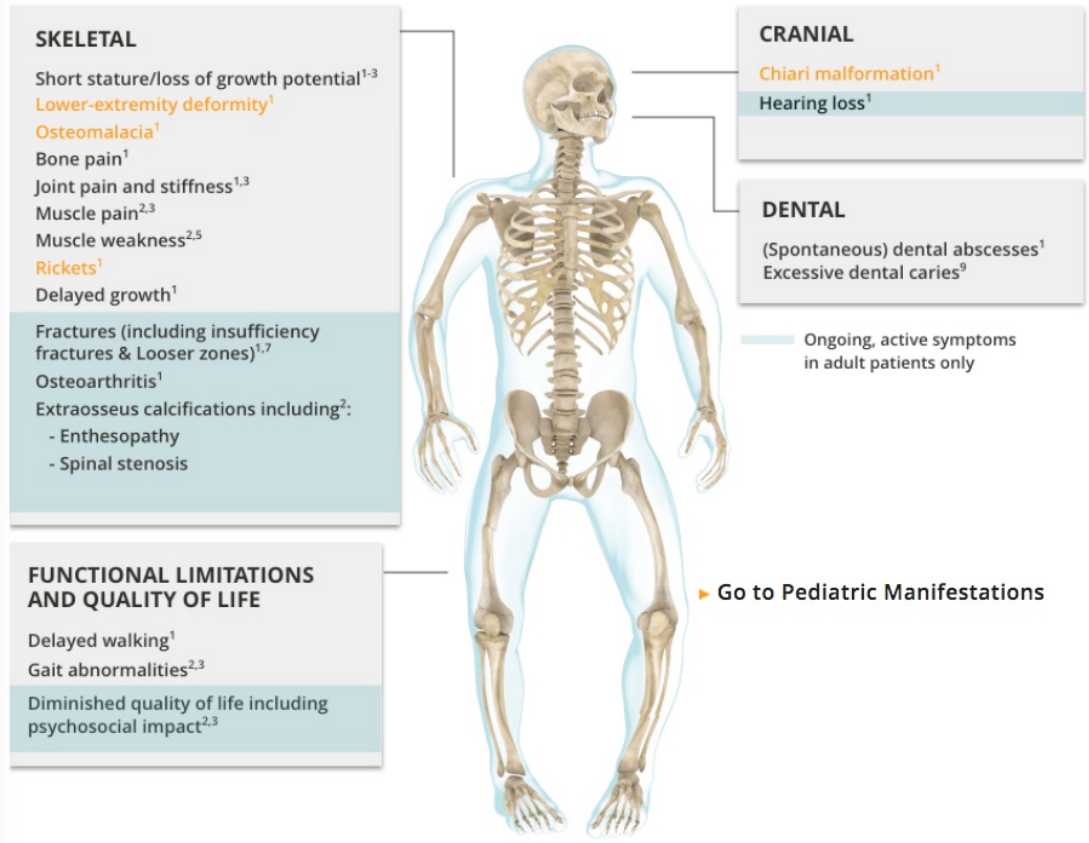
Body	
Headline	**Quality of life**
Subhead	Children with XLH can have impaired quality of life (QOL)[2]
Body copy	Skeletal manifestations of XLH impact physical and psychosocial quality of life in pediatric patients.[2] Added to this, many XLH children experience regular joint pain.[2] Approximately **80% of children** with XLH report knee pain. Pain is also commonly experienced in the[2] ▪ Feet ▪ Hips ▪ Ankles
Chart title	**In an international survey, 71 children with XLH showed below normal results on health-related QOL assessments[2]**
Chart	
Chart title	**Data from the same survey showed children with XLH had heightened pain and impaired mobility relative to normal children[2]**

Chart	
References	1. Carpenter TO. Primary disorders of phosphate metabolism. In: De Groot LJ, Chrousos G, Dungan K, et al, eds. *Endotext [internet]*. South Dartmouth, MA: MDText.com. 2014;1-56. 2. Linglart A, Dvorak-Ewell M, Marshall A, et al. Impaired mobility and pain significantly impact the quality of life of children with X-linked hypophosphatemia (XLH). Poster presented at: ICCBH 2015 Salzburg, Austria. 3. Pettifor JM. What's new in hypophosphataemic rickets? *Eur J Pediatr.* 2008;167(5):493-499. 4. Ruppe MD. X-linked hypophosphatemia. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *Gene Reviews*. https://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed October 20, 2017. 5. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect*. 2014;3(1):R13-R30. 6. Osteomalacia. Medline Plus Medical Encyclopedia. http://medlineplus.gov/ency/article/000376.htm. Updated November 6, 2017. Accessed November 16, 2017. 7. Veilleux LN, Cheung M, Ben Amor M, Rauch F. Abnormalities in muscle density and muscle function in hypophosphatemic rickets. *J Clin Endocrinol Metab*. 2012;97(8):E1492-E1498. 8. Rickets. MedlinePlus Medical Encyclopedia. http:// medlineplus.gov/ency/article/000344.htm. Updated November 6, 2017. Accessed November 16, 2017. 9. Chiari malformation. MedlinePlus Medical Encyclopedia. http://medlineplus.gov/chiarimalformation.htm. Updated December 23, 2016. Accessed November 16, 2017. 10. Craniosynostosis. MedlinePlus Medical Encyclopedia. http://medlineplus.gov/ency/article/001590.htm. Updated November 6, 2017. Accesssed November 16, 2017. 11. Data on file. Ultragenyx, Inc. 12. Skrinar A, Marshall A, San Martin J, Dvorak-Ewell M. X-linked hypophosphatemia (XLH) impairs skeletal health outcomes and physical function in affected adults. Poster presented at: Endocrine Society's 97th Annual Meeting and Expo, March 5-8, 2015. San Diego, CA. 13. Martin A, Quarles LD. Evidence for FGF23 involvement in a bone-kidney axis regulating bone mineralization and systemic phosphate and vitamin D homeostasis. *Adv Exp Med Biol*. 2012;728:65-83. 14. Che H, Roux C, Etcheto A, et al. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur J Endocrinol*. 2016;174(3):325-333. 15. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res*. 2011;26(7):1381-1388. 16. Econs MJ, Samsa GP, Monger M, Drezner MK, Feussner JR. X-linked hypophosphatemic rickets: a disease often unknown to affected patients. *Bone Miner.* 1994;24(1):17-24. 17. Zivičnjak M, Schnabel D, Billing H, et al. Age-related stature and linear body segments in children with X-linked hypophosphatemic rickets. *Pediatr Nephrol*. 2011;26(2):223-231.18. Carpenter TO. New perspectives on the biology and treatment of X-linked hypophosphatemic rickets. *Pediatr Clin North Am.* 1997;44(2):443-466. 19. Opsahl Vital S, Gaucher C, Bardet C, et al. Tooth dentin defects reflect genetic disorders affecting bone mineralization. *Bone*. 2012;50(4):989-997. 20. Picture of the teeth: human anatomy. WebMD. https://www.webmd.com/oral-health/picture-of-the-teeth#1. Updated 2015. Accesssed December 9, 2017.

2.2 Adult manifestations

Sitemap	
Sitemap Number	2.2
Page Name	Adult manifestations

Body		
Page Title	Adult manifestations	
Headline	Clinical manifestations in adult patients with XLH	
Body Copy	Clinical manifestations in adult with XLH arise from[1,2]: • New and continuing symptoms as a result of ongoing, active disease • Unresolved complications of XLH from childhood	
Graphic copy	**SKELETAL:** Short stature/loss of growth potential[1-3] Lower-extremity deformity[1] Osteomalacia[1] Bone pain[1] Joint pain and stiffness[1,3] Muscle pain[2,3] Muscle weakness[2,5] Rickets[1] Delayed growth[1] Fractures (including insufficiency fractures & Looser zones)[1,7] Extraosseus calcifications including[2]: • Enthesopathy • Spinal stenosis **FUNCTIONAL LIMITATIONS AND QUALITY OF LIFE:** Delayed walking[1] Gait abnormalities[2,3] Diminished quality of life including psychosocial impact[2,3]	**CRANIAL:** Chiari malformation[1] Hearing loss[1] **DENTAL:** (Spontaneous) dental abscesses[1] Excessive dental caries[9] _____ Ongoing, active symptoms in adult patients only

Graphic	
Lower extremity deformity pop-up definition	Bowing of weight-bearing bones, especially femurs, manifesting as genu varum and genu valgum.[1]
Osteomalacia pop-up definition	Weakening of bones due to inadequate phosphate, calcium, or vitamin D.[4]
Rickets pop-up definition	Rickets is the softening and weakening of bones in children, usually because of vitamin D deficiency.[6]
Chiari malformation pop-up definition	Structural defects in the cerebellum as a result of brain tissue extending down into the spinal canal.[8]
Link	Go to Pediatric Manifestations [Links to 2.1 Pediatric Manifestations]
Tab Subnavigation 1 [Default landing tab]	Skeletal manifestations [Links to 2.2.A Adult skeletal manifestations]
Tab Subnavigation 2	Physical function [Links to 2.2.B Adult physical function]
Tab Subnavigation 3	Quality of life [Links to 2.2.C Adult quality of life]
Persistent callout **[On top of every tab for sections 2.1 and 2.2]**	Due to the lifelong and progressive nature of XLH,[2,13-16] assessment is recommended
Callout link	Go to Pediatric Assessment [Links to 4.1 Pediatric Assessment]
Callout link	Go to Adult Assessment [Links to 4.2 Adult Assessment]

Tab 2.2 A	
Tab Name	Skeletal manifestations [Bottom left tab]

Body	
Headline	**Skeletal manifestations**
Body copy	Several types of fractures, including **insufficiency fractures and Looser zones,**[10-12] can develop as a consequence of long-term weight bearing on weakened bones.[1] These manifestations commonly result in spontaneous insufficiency fractures in the lower extremities and weight-bearing bones[1]
Pop-up definition for "insufficiency fractures and Looser zones"	Insufficiency fractures are a type of stress fracture that can result from normal stresses on abnormal or weakened bone.[10,11] Looser zones, or Milkman lines, are most frequently associated with osteomalacia, rickets, and weakened bones. These pseudofractures are considered a type of insufficiency fracture.[11,12]
Body Copy	Nearly half of XLH patients reporting ever having fractures, with an average age at first fracture of 26.5[2] **Skeletal manifestations continue into adulthood**[1,2,17] Ongoing, active disease in adults with XLH can cause several skeletal manifestations as a result of osteomalacia, or weakened bone. Reported symptoms of osteomalacia include bone pain, muscle weakness and difficulty walking.
Jump down link	Bone repair and osteomalacia [jumps to subhead: Bone repair and osteomalacia]
Chart title	**Frequency of skeletal and dental impairment in 165 adult XLH patients**[2]

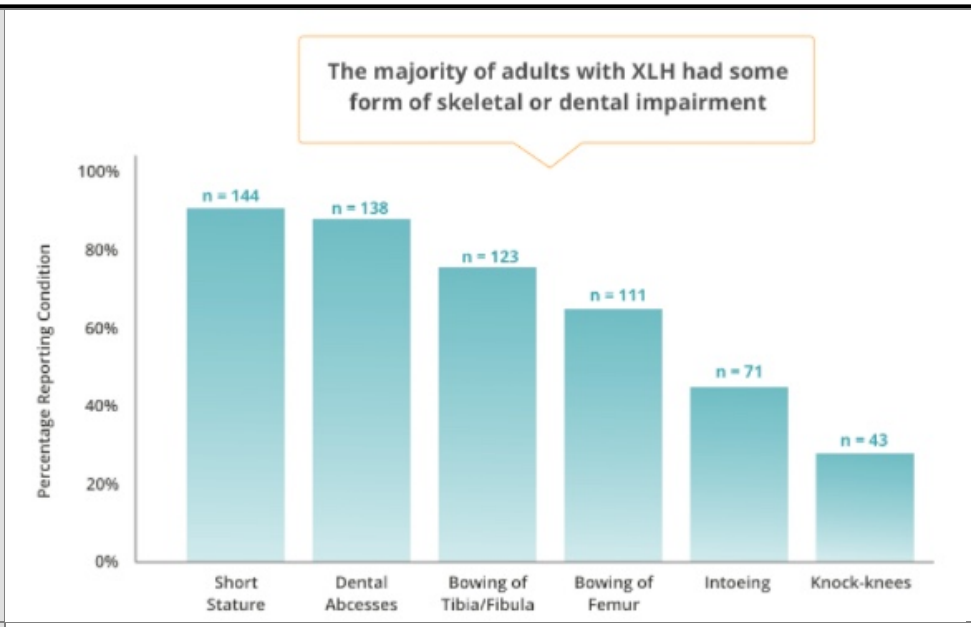
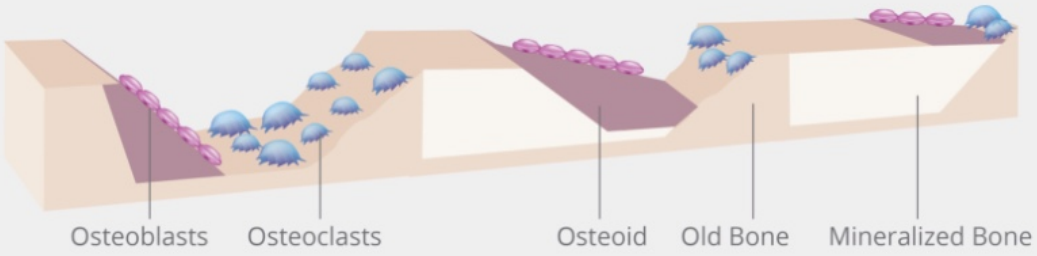
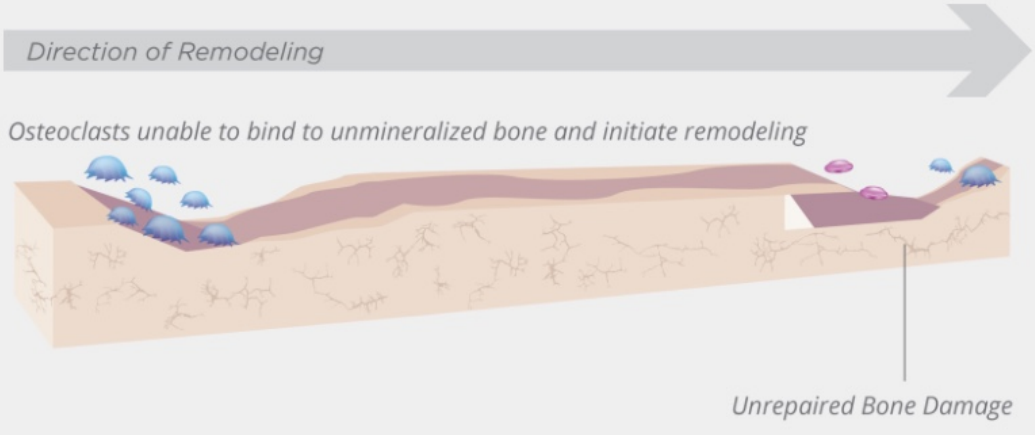
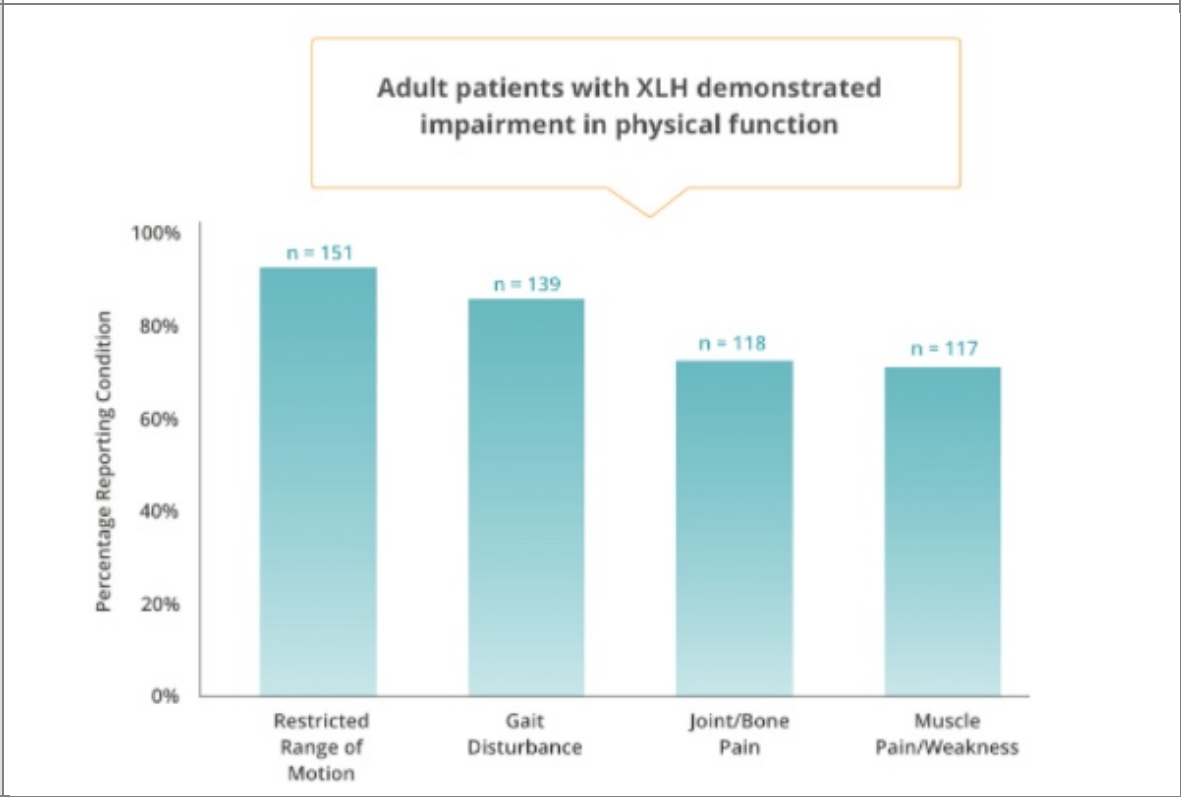
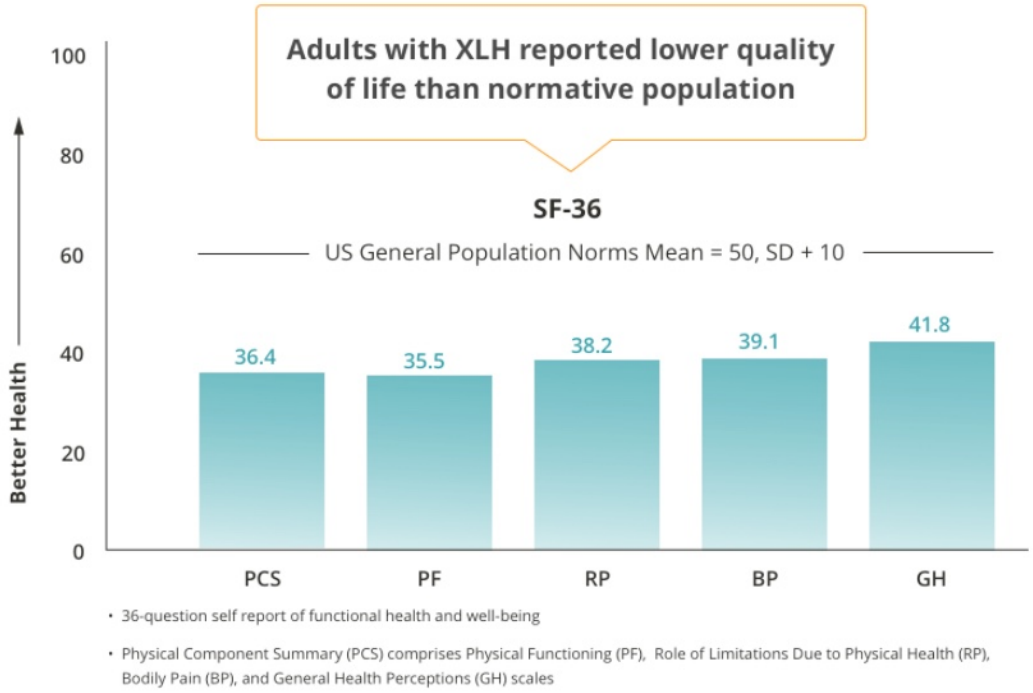
Chart	
Subhead	Bone repair and osteomalacia
Body copy	**Normal Bone Formation**[13,18,19] • Osteoclasts bind and initiate bone remodelling to repair bone damage ○ The mineralization front should normally occupy >80% of the osteoid surface, with a slight decrease in older patients[a]
Image	
	Osteomalacia[13,18-20] • Osteoclasts have reduced ability to bind and initiate bone remodelling on undermineralized bone ○ A mineralization front of <20% represents a definite calcification defect[a]
Image	

Image footnote	[a]Definitive normal values for the measurements made in bone morphometry vary between laboratories.[18]
Static callout	See the clinical manifestations of XLH in pediatric and adult patients
Callout link 1	Go to Pediatric Manifestations [Links to 2.1 Pediatric Manifestations]
Callout link 2	Go to Adult Manifestations [Links to 2.2 Adult Manifestations]

Tab 2.2 B	
Tab Name	Physical function [Bottom middle tab]
Sitemap name	Physical function

Body	
Headline	**Ongoing, active disease in adults with XLH can lead to impaired physical function.[2]**
Body Copy	Adult patients with XLH most commonly report decreased range of motion, especially of the hips, and gait disturbances, as well as pain and the need for walking assistance.[2,14]
Chart title	**Most frequently reported physical function limitations in 165 adult XLH patients[2]**
Chart	

Tab 2.2 C	
Tab Name	Quality of life [Bottom right tab]
Meta Description	

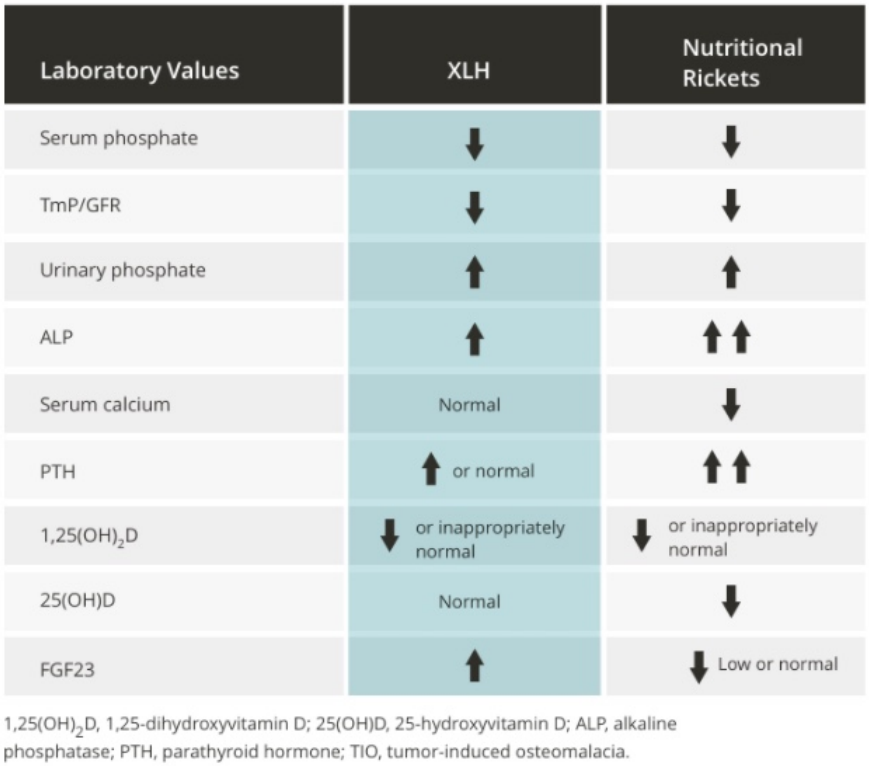
Body	
Headline	**Quality of life**
Subhead	Many adults with XLH have significantly impaired quality of life[2]
Copy	Pain, stiffness, and decreased physical function are the most common contributors to impaired quality of life in adults with symptomatic XLH.[2]
Chart title	**Complications associated with lower quality of life in adult XLH patients[2]**
Chart	
References	1. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect*. 2014;3(1):R13-R30. 2. Skrinar A, Marshall A, San Martin J, Dvorak-Ewell, M. X-linked hypophosphatemia (XLH) impairs skeletal health outcomes and physical function in affected adults. Poster presented at: Endocrine Society's 97th Annual Meeting and Expo, March 5-8, 2015. San Diego, CA. 3. Linglart A, Dvorak-Ewell M, Marshall A, et al. Impaired mobility and pain significantly impact the quality of life of children with X-linked hypophosphatemia (XLH). Poster presented at: ICCBH 2015 Salzburg, Austria. 4. Osteomalacia. Medline Plus Medical Encyclopedia. http://medlineplus.gov/ency/article/000376.htm. Updated November 6, 2017. Accessed November 16, 2017. 5. Veilleux LN, Cheung M, Ben Amor M, Rauch F. Abnormalities in muscle density and muscle function in hypophosphatemic rickets. *J Clin Endocrinol Metab*. 2012;97(8):E1492-E1498. 6. Rickets. MedlinePlus Medical Encyclopedia. http://medlineplus.gov/ency/article/000344.htm. Updated November 6, 2017. Accessed November 16, 2017. 7. Looser zones. Radiopaedia Web site. https://radiopaedia.org/articles/looser-zones-1. Accessed October 9, 2017. 8. Chiari malformation. MedlinePlus Medical Encyclopedia. http://medlineplus.gov/chiarimalformation.htm. Updated December 23, 2016. Accessed November 16, 2017. 9. Data on file. Ultragenyx, Inc. 10. Jackson WPU, Dowdle E, Linder GC. Vitamin-D-resistant osteomalacia. *Brit Med J*. 1958:1269-1274. 11. Insufficiency

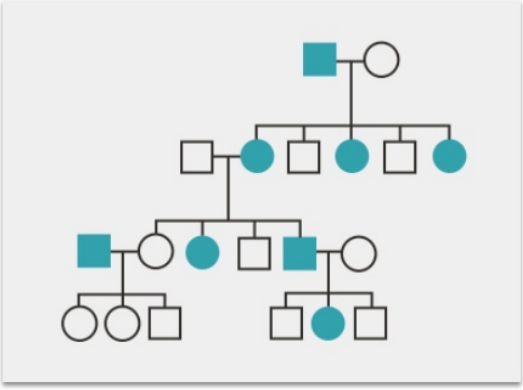
fracture. Radiopaedia Web site. https://radiopaedia.org/articles/insufficiency-fracture. Accessed October 9, 2017. 12. Looser zones. Radiopaedia Web site. https://radiopaedia.org/articles/looser-zones-1. Accessed October 9, 2017. 13. Martin A, Quarles LD. Evidence for FGF23 involvement in a bone-kidney axis regulating bone mineralization and systemic phosphate and vitamin D homeostasis. *Adv Exp Med Biol*. 2012;728:65-83. 14. Che H, Roux C, Etcheto A, et al. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur J Endocrinol*. 2016;174(3):325-333. 15. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res*. 2011;26(7):1381-1388. 16. Econs MJ, Samsa GP, Monger M, Drezner MK, Feussner JR. X-linked hypophosphatemic rickets: a disease often unknown to affected patients. *Bone Miner.*1994;24(1):17-24. 17. Reid IR, Hardy DC, Murphy WA, Teitelbaum SL, Bergfeld MA, Whyte MP. X-linked hypophosphatemia: a clinical, biochemical, and histopathologic assessment of morbidity in adults. *Medicine (Baltimore).* 1989;68(6):336-352. 18. Revell PA. Histomorphometry of bone. *J Clin Pathol.* 1983;36(12):1323-1331. 19. Miller PD. Renal bone disease. In: Orwoll ES, ed. *Atlas of Osteoporosis*. 3rd ed. Current Medicine Group; 2009 . 20. Chambers TJ, Thomson BM, Fuller K. Effect of substrate composition on bone resorption by rabbit osteoclasts. *J Cell Sci*. 1984;70:61-71.

3.0 Diagnosis

3.1 Diagnosis

Page Title	Diagnosis
Headline	Diagnosis
Subhead	A diagnosis of XLH is typically based on clinical and biochemical findings in combination with family history; however, variations in disease presentation can lead to delayed diagnosis or misdiagnosis.[1,2] Molecular genetics can be used to establish a diagnosis, determine if XLH is inherited, and what risk there is to family members.[1]
Jump down link with image 1	Clinical [links to Clinical subhead on same page] 
Jump down link with image 2	Biochemical [links to Biochemical subhead on same page] 
Jump down link with image 3	Family history [links to Family history subhead on same page] 
Subhead	**Clinical**
Body Copy	**In children:** Children with XLH typically present with lower-extremity bowing, impaired growth, and gait abnormalities during the first 1 to 2 years of life. However, diagnosis may occur after the age of 2 or even in adulthood.[1,3]
Image	
Body copy	**In adults:** Adult patients present with joint and bone pain, along with stiffness associated with osteoarthritis and enthesopathy. Nearly half report having had a fracture. The majority of adults with XLH exhibit short stature and lower-extremity deformity.[2,4,5]

Image	
Subhead	**Biochemical**
Body Copy	**If a patient presents with clinical characteristics that resemble rickets, a diagnosis of XLH can be made via biochemical assessment** The main biochemical features of XLH are low serum phosphate levels, inappropriately low or normal 1,25-dihydroxyvitamin D levels, a reduced ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR), and elevated serum FGF23 levels.[1,6,7] • Additional biochemical features of XLH include normal 25-hydroxyvitamin D levels, elevated urinary phosphorus levels, elevated alkaline phosphatase levels, and elevated or normal parathyroid hormone levels[1,7]
Subhead	Phosphate reabsorption[8-15] The TmP/GFR is the ratio of renal tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR)
Chart	
Chart footnotes	1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyviatamin D; ALP, alkaline phosphatase; PTH, parathyroid hormone; TIO, tumor-induced osteomalacia
Static callout	**Biochemical assessment:** Continually assess ongoing disease in children and adults [Links to 4.2.C Adult Biochemical Assessment]

Link	Go to Pediatric Biochemical Assessment [Links to 4.1.C Pediatric Biochemical Assessment]
Link	Go to Adult Biochemical Assessment [Links to 4.2.C Adult Biochemical Assessment]
Subhead	**Family History**
Copy	**Key points:** • Evaluation of at-risk infants and children is warranted to ensure early diagnosis and treatment, which has been shown to improve clinical outcomes[3] • Screening of family members of XLH patients may help to identify previously undiagnosed individuals[16]
Image title	**Pedigree Analysis**
Graphic	
Copy	However, 20% to 30% of cases are spontaneous, and therefore have no family history[17-19]
Static callout	Learn about inheritance and the prevalence of XLH
Link	Go to Prevalence [Links to 1.2 Prevalence]
References	1. Ruppe MD. X-linked hypophosphatemia. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *Gene Reviews*. https://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed October 20, 2017. 2. Econs MJ, Samsa GP, Monger M, Drezner MK, Feussner JR. X-linked hypophosphatemic rickets: a disease often unknown to affected patients. *Bone Miner.* 1994;24(1):17-24. 3. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect*. 2014;3(1):R13-R30. 4. Skrinar A, Marshall A, San Martin J, Dvorak-Ewell M. X-linked hypophosphatemia (XLH) impairs skeletal health outcomes and physical function in affected adults. Poster presented at: Endocrine Society's 97th Annual Meeting and Expo, March 5-8, 2015. San Diego, CA. 5. Hardy DC, Murphy WA, Siegel BA, Reid IR, Whyte MP. X-linked hypophosphatemia in adults: prevalence of skeletal radiographic and scintigraphic features. *Radiology.* 1989;171(2):403-414. 6. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res*. 2011;26(7):1381-1388. 7.Santos F, Fuente R, Mejia N, Mantecon L, Gil-Peña H, Ordoñez FA. Hypophosphatemia and growth. *Pediatr Nephrol.* 2013;28(4):595-603. 8. Payne RB. Renal tubular reabsorption of phosphate (TmP/GFR): indications and interpretation. *Ann Clin Biochem*. 1998;35(pt. 2):201-206. 9. Goldsweig BK, Carpenter TO. Hypophosphatemic rickets: lessons from disrupted FGF23 control of phosphorus homeostasis. *Curr Osteoporos Rep*. 2015;13(2):88-97. 10. Imel EA, Carpenter TO. A practical clinical approach to paediatric phosphate disorders. *Endocr Dev*. 2015;28:134-161. 11.Özkan B. Nutritional rickets. *J Clin Res Pediatr Endocrinol.* 2010;2(4):137-143. 12. Nield LS, Mahajan P, Joshi A, Kamat D. Rickets: not a disease of the past. *Am Fam Physician*. 2006;74(4):619-626. 13. Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. *Endocr Relat Cancer*. 2011;18(3):R53-R77. 14. Jan de Beur SM. Tumor-induced osteomalacia. *JAMA*. 2005;294(10):1260-1267. 15. Halperin F, Anderson RJ, Mulder JE. Tumor-induced osteomalacia: the importance of measuring serum phosphorus levels. *Nat Clin Pract Endocrinol Metab*.2007;3(10):721-725. 16. Beck-Nielsen SS, Brusgaard K, Rasmussen LM, et al. Phenotype presentation of

hypophosphatemic rickets in adults. *Calcif Tissue Int*. 2010;87(2):108-119. 17. Beck-Nielsen SS, Brixen K, Gram J, Brusgaard K. Mutational analysis of PHEX, FGF23, DMP1, SLC34A3 and CLCN5 in patients with hypophosphatemic rickets. *J Hum Genet*. 2012;57(7):453-458. 18. Gaucher C, Walrant-Debray O, Nguyen T-M, Esterle L, Garabédian M, Jehan F. PHEX analysis in 118 pedigrees reveals new genetic clues in hypophosphatemic rickets. *Hum Genet.* 2009;125(4):401-411. 19. Whyte MP, Schranck FW, Armamento-Villareal R. X-linked hypophosphatemia: a search for gender, race, anticipation, or parent of origin effects on disease expression in children. *J Clin Endocrinol Metab*. 1996;81(11):4075-4080.

4.0 Assessment

4.1 Pediatric assessment

Sitemap	
Sitemap Number	4.1
Page Name	Pediatric assessment
Headline	Pediatric assessment
Subhead	Continually monitor pediatric patients
Body copy	Since XLH is a chronic, progressive skeletal disorder,[1-4] continual assessment is needed from childhood through adulthood to monitor the effects.[5] Children should also be asked to identify areas of pain that may not show up during office visits.
Table disclaimer text	**Monitoring and dose adjustment at 3-month intervals are recommended to avoid hypercalcemia, hypercalciuria, nephrocalcinosis, and hyperparathyroidism[5]**
Chart title	**Biochemical assessment should be done at 3-month intervals in children**
Chart	
Static callout appears at top of each tab in section	Excess FGF23 results in the clinical manifestations of XLH for children and adults[4,6,8]
Callout link 1	Go to Mechanism of Disease [Links to 1.1 Mechanism of Disease]
Callout link 2	Go to Pediatric Manifestations [Links to 2.1 Pediatric Manifestations]

Age	Surveillance	Frequency
Infancy	**Blood:** alkaline phosphatases, total calcium, PTH, creatinine	Every 3 months
	Urine (spot): calcium/creatinine	Every 3 months
Childhood	**Blood:** alkaline phosphatases, total calcium, PTH, creatinine	Every 6 months
	Urines (24-h): calciuria, phosphaturia	Every 3 months
	Renal ultrasound	Every year
Puberty	**Blood:** alkaline phosphatases, total calcium, PTH, creatinine	Every 6 months
	Urines (24-h): calciuria, phosphaturia	Every 3 months
	Renal ultrasound	Every year

Callout link 3	Go to Adult Manifestations [Links to 2.2 Adult Manifestations]

Tab 4.1 A	
Tab Name	Skeletal disease [Bottom right tab]

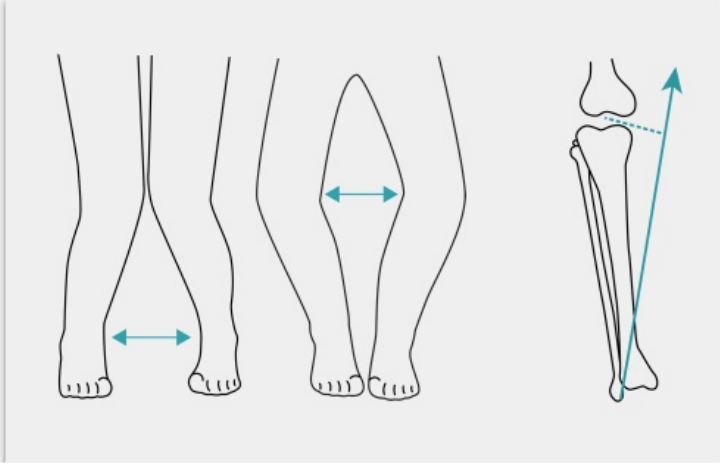
Body	
Headline	**Skeletal assessment for pediatric patients with XLH**
Copy	XLH is chronic, progressive disease, with lower limb deformity, loss of growth potential, and body disproportion increasing with age. Children should be routinely assessed for safety and response to medical treatment.[6,7]
Jump down link	Go to Anthropometric Measurements [Links to Anthropometric Measurements subhead]
Jump down link	Go to Growth [Links to Growth subhead]
Subhead	**Anthropometric measurements**
Copy	To ensure standardized and comparable results, it is recommended that all anthropometric measurements are performed by the same health care provider.[9]
Sub Head	**Tibiofemoral angle**
Copy	The tibiofemoral angle can be clinically assessed by measuring the intercondylar and intermalleolar distances. A variation becomes a deformity when the amount of deviation from normal for that particular age is >2 SD. Response to conventional therapy is defined as a 1-cm decrease in genu valgum or genu varum every 6 months.[5,10]
Copy	Age-related growth and proportion evaluation is comprised of different assessments: standing and sitting height, and arm and leg length.[9] Leg length should be measured as standing height versus sitting height.[9]
Image	

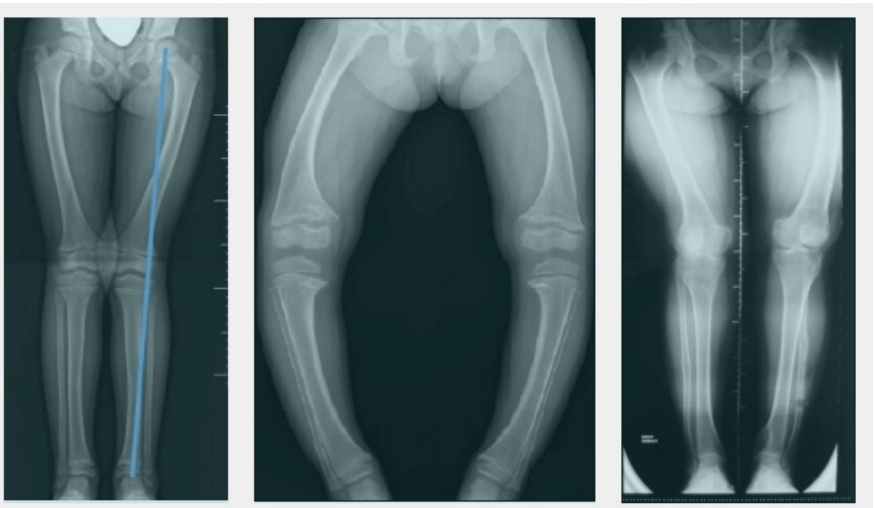
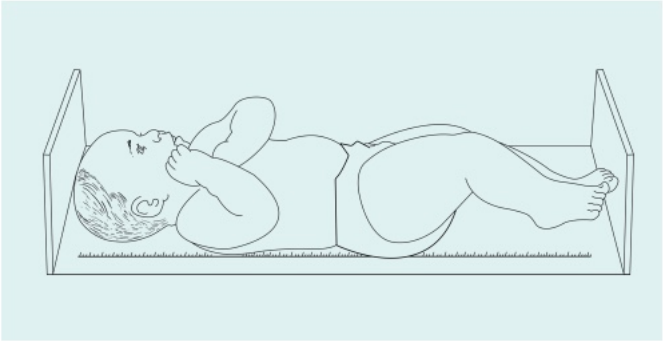
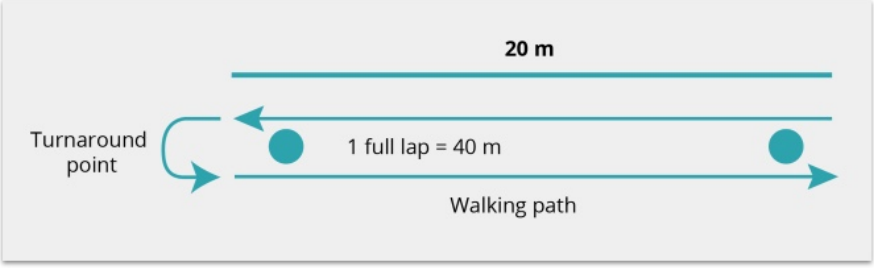
Image	 Left to right: genu valgum, genu varum, and windswept deformity[5,11,12]
Subhead	**Recumbent Length**
Copy	Two people are required to measure recumbent length. The patient's head is positioned on a fixed headboard, while the feet are positioned and the footboard adjusted for measurement. The child is placed supine on the infant board with buttocks and shoulder blades in contact with the board. The child should be measured with minimal clothing. The Frankfort horizontal plane[13] should be parallel to the head and foot boards. The patient's head should be up and their eyes facing forward. Gentle pressure should be applied to the legs to prevent the knees from flexing, while the footboard is adjusted until it rests firmly against the child's heels.
Image	
Subhead	**Growth**
Copy	Children with XLH generally show disproportionate growth, so regular measurement and assessment are important.[9] Height-for-age Z-score: Growth Z-scores reflect the number of standard deviations from age- and sex-matched normal mean values.[14] - Z-scores are based on standard growth references collected from normal children - The WHO recommends cutoff Z-score values of ±2 to define abnormal growth - Short stature is defined as height-for-age Z-scores ≤2 for individuals of the same sex

Chart image	
Copy	Rickets often causes lower-extremity deformity and loss of growth potential.[6] Because of open epiphyses, patients present a significant risk of recurrent bowing at the level of osteotomy or secondary to adjacent epiphysiodesis.[5]

Tab 4.1 B	
Tab Name	Quality of life and physical function [Bottom middle tab]

Body	
Headline	**Quality of life and physical function for pediatric patients with XLH**
Subhead	Several different tools are available to assess quality of life and physical function
Body copy	6-minute walk test (6MWT)
	The 6MWT is a practical, simple test that measures how far a patient can walk in 6 minutes on a flat, hard surface.
In-text hover link	6MWT [Links to: https://www.thoracic.org/statements/resources/pfet/sixminute.pdf]
Image	
Body copy	PROMIS (Patient-Reported Outcomes Measurement Information System)
	PROMIS was developed by the NIH and uses domain-specific measures to assess physical, mental, and social health.
Link	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4371419/
Body copy	SF-10
	The SF-10 for Children™ is a short-form survey that contains items adapted from the CHQ (Child Health Questionnaire) and scored to produce physical (PHS) and psychosocial health (PSS) summary scores.
Link	https://www.caremark.com//portal/asset/CP_SF-10.pdf
Body copy	Pain intensity
	Pain intensity is a self-reported measure of pain intensity developed for children.

Tab 4.1 C	
Tab Name	Biochemical [Bottom left tab]

Body	
Headline	**Measuring**
Copy	The TmP/GFR is the ratio of renal tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR).[6,15-23]
Chart	$TRP = 1 - \left[\left(\frac{urinary\ phosphate}{plasma\ phosphate} \right) \times \left(\frac{plasma\ creatinine}{urinary\ creatinine} \right) \right]$ If TRP ≤0.86, $TmP/GFR = TRP \times plasma\ phosphate$ If TRP >0.86, $TmP/GFR = 0.3 \times \frac{TRP}{1 - (0.8 \times TRP)} \times plasma\ phosphate$
Chart	

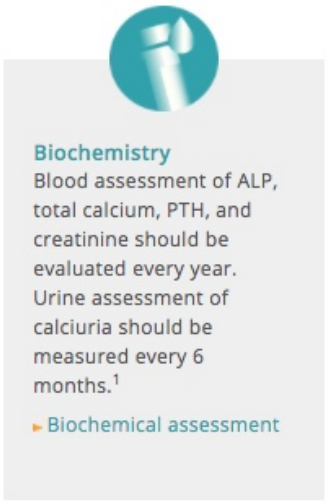
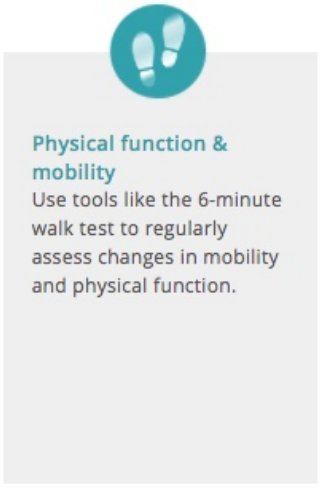
Laboratory Values	XLH	Nutritional Rickets
Serum phosphate	↓	↓
TmP/GFR	↓	↓
Urinary phosphate	↑	↑
ALP	↑	↑↑
Serum calcium	Normal	↓
PTH	↑ or normal	↑↑
$1,25(OH)_2D$	↓ or inappropriately normal	↓ or inappropriately normal
25(OH)D	Normal	↓
FGF23	↑	↓ Low or normal

$1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; PTH, parathyroid hormone; TIO, tumor-induced osteomalacia.

References

1. Beck-Nielsen SS, Brock-Jacobsen B, Gram J, Brixen K, Jensen TK. Incidence and prevalence of nutritional and hereditary rickets in southern Denmark. *Eur J Endocrinol*. 2009;160(3):491-497. **2**. Martin A, Quarles LD. Evidence for FGF23 involvement in a bone-kidney axis regulating bone mineralization and systemic phosphate and vitamin D homeostasis. *Adv Exp Med Biol*. 2012;728:65-83. **3**. Che H, Roux C, Etcheto A, et al. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur J Endocrinol*. 2016;174(3):325-333. **4.** Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res*. 2011;26(7):1381-1388. **5.** Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect*. 2014;3(1):R13-R30. **6**. Ruppe MD. X-linked hypophosphatemia. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *Gene Reviews*. https://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed October 20, 2017. **7.** Pettifor JM. What's new in hypophosphataemic rickets? *Eur J Pediatr*. 2008;167(5):493-499. **8.** Penido MG, Alon US. Phosphate homeostasis and its role in bone health. *Pediatr Nephrol*. 2012;27(11):2039-2048. **9.** Zivičnjak M, Schnabel D, Billing H, et al. Age-related stature and linear body segments in children with X-linked hypophosphatemic rickets. *Pediatr Nephrol*. 2011;26(2):223-231. **10.** Sass P, Hassan G. Lower extremity abnormalities in children. *Am Fam Physician*. 2003;68(3):461-468. **11.** Stevens NM, Hennrikus WL. 3 cases of genu valgum in medically treated X-linked hypophosphatemic rickets. *Austin J Orthop Rheumatol*. 2015;2(3):1-3**. 12.** Gizard A, Rothenbuhler A, Pejin Z, et al. Outcomes of orthopedic surgery in a cohort of 49 patients with X-linked hypophosphatemic rickets (XLHR). *Endocr Connect.* 2017;6(8):566-573**. 13.** Frankfort horizontal plane. Merriam Webster Medical Dictionary Online Web site. https://www.merriam-webster.com/medical/Frankfort%20horizontal%20plane. Accessed October 17, 2017. **14.** de Onis M, Blössner M. *WHO Global Database on Child Growth and Malnutrition.* Geneva, Switzerland: World Health Organization; 1997. **15**. Payne RB. Renal tubular reabsorption of phosphate (TmP/GFR): indications and interpretation. *Ann Clin Biochem*. 1998;35(pt. 2):201-206. **16**. Santos F, Fuente R, Mejia N, Mantecon L, Gil-Peña H, Ordoñez FA. Hypophosphatemia and growth. *Pediatr Nephrol.* 2013;28(4):595-603. **17.** Goldsweig BK, Carpenter TO. Hypophosphatemic rickets: lessons from disrupted FGF23 control of phosphorus homeostasis. *Curr Osteoporos Rep*. 2015;13(2):88-97. **18.** Imel EA, Carpenter TO. A practical clinical approach to paediatric phosphate disorders. *Endocr Dev*. 2015;28:134-161. **19.** Özkan B. Nutritional rickets. *J Clin Res Pediatr Endocrinol.* 2010;2(4):137-143**. 20.** Nield LS, Mahajan P, Joshi A, Kamat D. Rickets: not a disease of the past. *Am Fam Physician*. 2006;74(4):619-626. **21.** Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. *Endocr Relat Cancer*. 2011;18(3):R53-R77. **22.** Jan de Beur SM. Tumor-induced osteomalacia. *JAMA*. 2005;294(10):1260-1267. **23.** Halperin F, Anderson RJ, Mulder JE. Tumor-induced osteomalacia: the importance of measuring serum phosphorus levels. *Nat Clin Pract Endocrinol Metab.* 2007;3(10):721-725.

4.2 Adult assessment	
Sitemap	
Sitemap Number	4.2
Page Name	Adult assessment
Headline	**Adult assessment**
Subhead	Clinical assessment
Copy	To monitor ongoing, active disease, clinical assessment of weight, mobility, and pain should be conducted every year.[1] Radiographic, renal, and biochemical monitoring can be used.
Subhead	**Radiographic**
Copy	Radiographic assessment can help confirm insufficiency fractures and enthesopathies.[2]
Image	 **Radiographic** Radiographic assessment can help confirm insufficiency fractures and enthesopathies.[2]
Subhead	**Renal**
Copy	Renal ultrasound should be conducted every other year.[1]
Image	 **Renal** Renal ultrasound should be conducted every other year.[1]
Subhead	**Biochemistry**
Copy	Blood assessment of ALP, total calcium, PTH, and creatinine should be evaluated every year. Urine assessment of calciuria should be measured every 6 months.[1]

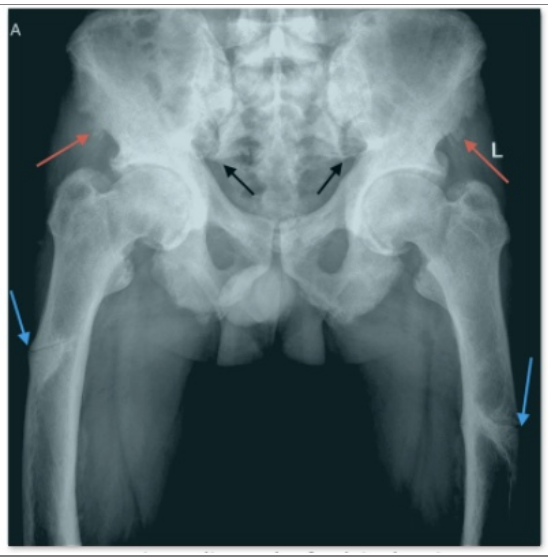
Image	
Link	Biochemical assessment [Links to 4.2.C Biochemical Assessment]
Subhead	**Physical function & mobility**
Copy	Use tools like the 6-minute walk test to regularly assess changes in mobility and physical function
Image	
Subhead	**Continual monitoring of adult patients**
Body Copy	As with pediatric patients, regular monitoring is recommended to avoid hypercalcemia, hypercalciuria, nephrocalcinosis, and hyperparathyroidism.[1]
Chat title	Biochemical assessment, including calcium, PTH, and creatinine, should be done at 6-month to 1-year intervals for adults

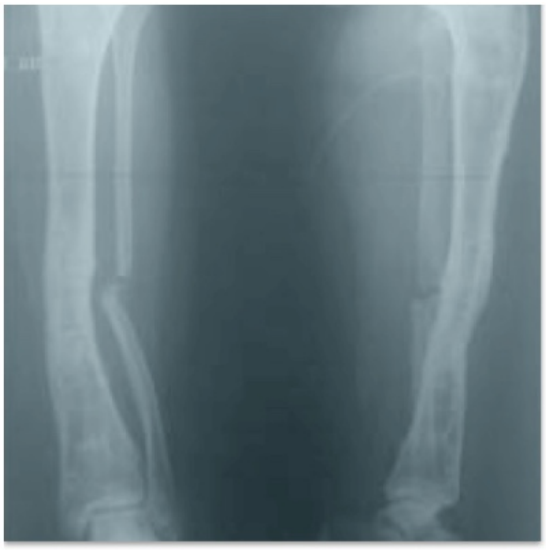
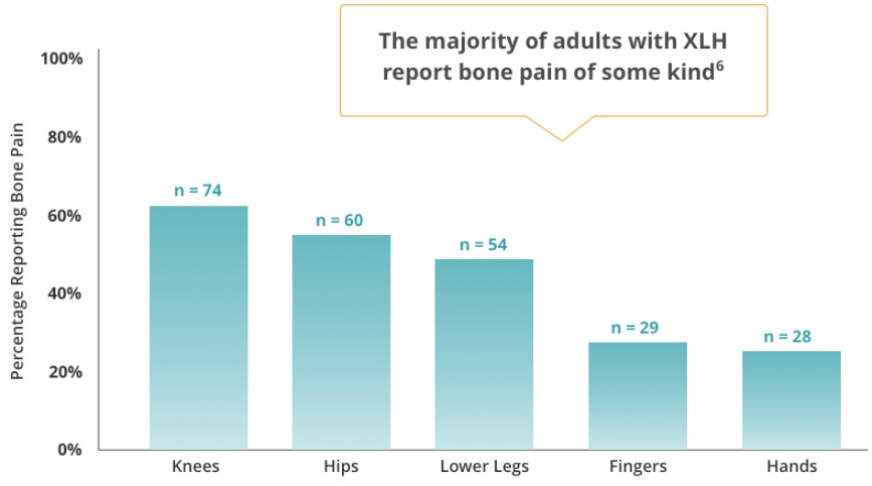
Chart

Age	Surveillance for efficacy and safety	Frequency
Adulthood	**Blood:** bone alkaline phosphatases, total	Every year
	Urines (24-h): calciuria	Every 6 months
	Renal ultrasound	Every other year
Pregnancy	**Blood:** total calcium, PTH, creatinine, 25-OH, vitamin D	Every 3 months
	Urines (24-h): calciuria	Every 3 months
Menopause	**Blood:** bone alkaline, phosphatases, total calcium, PTH, creatinine	Every year
	Urines (24-h): calciuria	Every 6 months
	Renal ultrasound	Every other year

Static callout appears at top of each tab in section	Excess FGF23 results in the clinical manifestations of XLH for children and adults[2-4]
Callout link 1	Go to Mechanism of Disease [Links to 1.1 Mechanism of Disease]
Callout link 2	Go to Pediatric Manifestations [Links to 2.1 Pediatric Manifestations]
Callout link 3	Go to Adult Manifestations [Links to 2.2 Adult Manifestations]

Tab 4.2 A	
Tab Name	Skeletal disease [Bottom left tab]

Body	
Headline	**Skeletal disease**
Subhead	Regular assessment
Copy	Scheduled skeletal assessment of XLH patients is indicated. The frequency of review may vary depending on symptoms and surveillance of therapy.[2]
Jump down link	Bones [Links to Bones subhead]
Jump down link	Joints and ligaments [Links to Joints and ligaments subhead]
Jump down link	Dental [Links to Dental subhead]
Subhead	**Bones**
Copy	**Lower-limb deformity** Height reduction, severity of leg deformity, and number of surgical corrections of leg deformities are indicators of skeletal disease severity.[5] **Osteoarticular symptoms** Pain, reduced physical function, and poor quality of life should trigger assessment of the origin of osteoarticular symptoms via skeletal survey and evaluation of biochemical parameters for evidence of osteomalacia.[1]
Image	
Image caption	Anteroposterior radiograph of pelvis showing calcifications of sacrospinous ligaments (black arrows), tensor fasciae latae (red arrows), along with bowing and lateral cortical fractures of both femurs (blue arrows)[7]
Copy	**Fractures (including insufficiency fractures and Looser zones)[6]** The most common areas of insufficiency fractures are the femurs, feet, and tibiae/fibulae, followed by the hips, hands, and wrists. Indications of insufficiency fractures might include:

	Insufficiency/Looser zones (Milkman zones) • Bone pain and focal tenderness • Worsening deformity Nonunion • Pseudoarthritis **Bone pain**[6] In a survey of 165 adults with XLH, 123 responded to questions about bone pain. Most of these adults experienced some type of bone pain.
Image	
Image caption	Delayed healing of fibula fractures after corrective surgery[1]
Chart	
Copy	**Surgical Interventions** Persistent lower-limb bowing and/or torsion resulting in misalignment of the lower extremity may require surgery. Patients may undergo surgical treatment to straighten the

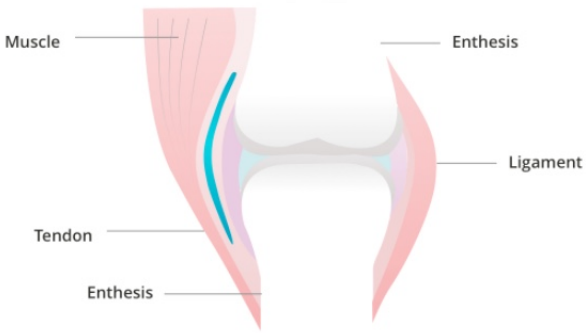
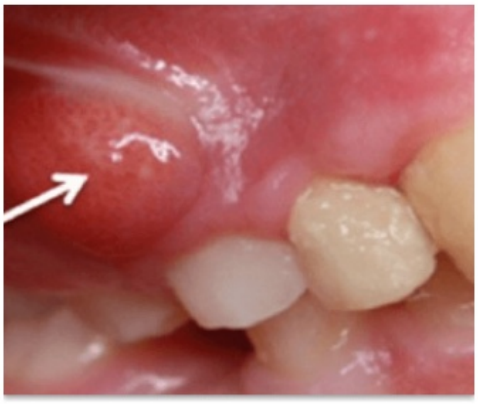
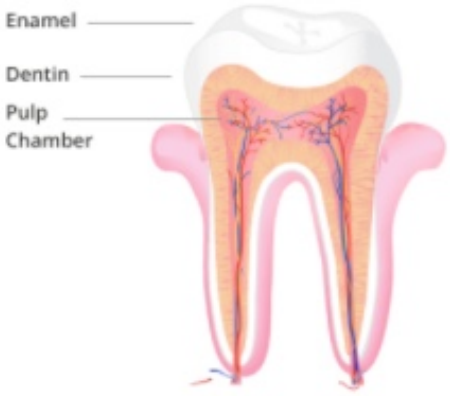
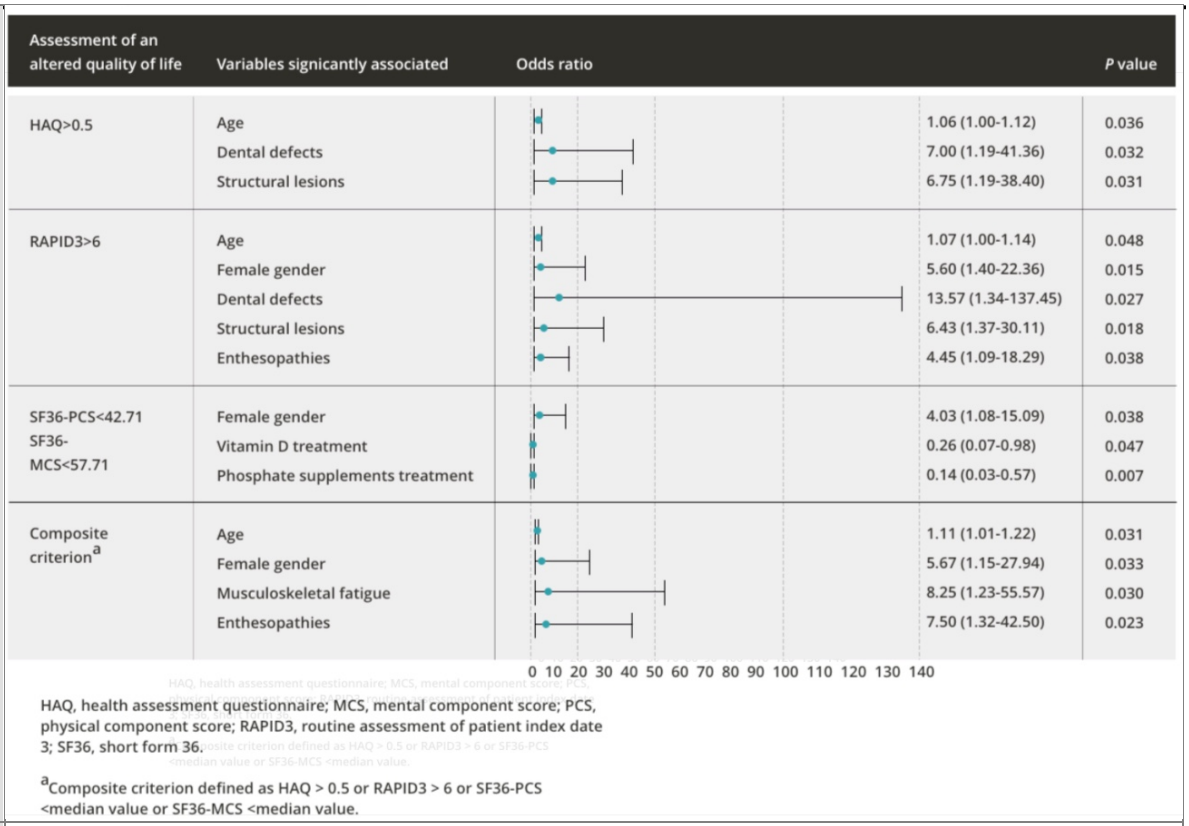
	lower limbs (ie, osteotomy), or they may require hip or knee arthroplasty due to degenerative joint disease and enthesopathy.[2] The aim of current treatment is to improve the symptoms, not to normalize serum phosphate levels.[1]
Subhead	**Joint and ligaments**
Copy	Enthesopathies are predominantly observed in those aged 40+.[5] Enthesopathies are specialized attachments of tendon/ligament to bone resulting from inappropriate mineralization.[8]
Image	
Static callout	See how enthesopathies can affect quality of life
Callout Link	Got to Physical Function and Quality of Life [Links to Quality of Life and Physical Function Tab B]
Subhead	**Dental**
Copy	The dominant dental feature in XLH is the occurrence of spontaneous infection of the dental pulp tissue, resulting in tooth abscesses. In contrast with common endodontic infection, these abscesses develop in teeth without any signs of trauma or decay, affecting both the deciduous and permanent dentition.[1] Adult patients with dental manifestations should be referred to a dental specialist with experience in XLH for a full clinical and radiographic examination. Treatment options for dental abscesses in adulthood include[1]: • Root canal cleaning • Sealing the tooth surface with a dental resin to form a barrier to bacterial penetration

Image	
Image caption	Abscess on a deciduous molar, a dental feature of XLH[9]
Copy	Prevention recommendations include[1]: • Rigorous oral hygiene and preventive procedures • Daily use of fluoride toothpaste adapted to age • Regular fluoride varnish applications at the dental chair
Image	
Image caption	Abscesses are formed as a result of expanded pulp chamber and abnormally mineralized dentin[10,11]

Tab 4.2 B	
Tab Name	Quality of life and physical function [Bottom middle tab]

Body	
Headline	**Quality of life and physical function**
Copy	Quality of life in adults with XLH is affected most negatively by physical function, stiffness, and bodily pain. Impaired quality of life in adult patients may be an indicator of underlying skeletal disease.[6]
Jump down link	Radiographic imaging [Links to Radiographic imaging subhead]
Jump down link	Walking ability [Links to Walking ability subhead]
Jump down link	Dental [Links to Dental subhead]
Jump down link	Other quality of life measurement tools [Links to Quality of life subhead]
Subhead	**Radiographic imaging**
Copy	Radiographic imaging can be used to assess the origin of osteoarticular conditions: physical function, pain, and poor quality of life.
Subhead	**Walking ability**
Copy	6-minute walk test (6MWT): The 6MWT is a practical, simple test that measures how far a patient can walk in 6 minutes on a flat, hard surface.[12]
Subhead	**Dental**
Copy	Dental defects have also been shown to impact quality of life.
Link	See dental assessment [Links to 4.2 Adult Assessment, Skeletal tab, Dental]
Subhead	**Other quality of life tools**
Copy	There are several quality-of-life tools that have been used to assess quality of life in adult XLH patients in studies and clinical trials. They include HAQ, SF-36, RAPID 3, and the composite criterion.
Static Callout	Please see the Resources section for links to download these tools.
Link	Resources [Links to 5.0 Resources page]
Chart title	**Variables associated with worse QOL in adults with XLH using logistic regression**[13]

Chart	
Chart footnotes	HAQ, health assessment questionnaire; MCS, mental component score; PCS, Physical component score; RAPID3, routing assessment of patient index date 3; SF36, short form 36. [a]Composite criterion defined as HAQ > 0.5 or RAPID3 > 6 or SF36-PCS < median value or SF36-MCS < median value.

Tab 4.2 C	
Tab Name	Biochemical [Bottom right tab]

Body	
Headline	**Biochemical monitoring**
Body Copy	**Regular monitoring is recommended to avoid hypercalcemia, hypercalciuria, nephrocalcinosis, and hyperparathyroidism.**
Subhead	**Phosphate reabsorption**
Body Copy	The TmP/GFR is the ratio of renal tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR)[2,14-22]
Image	

Laboratory Values	XLH	Nutritional Rickets
Serum phosphate	↓	↓
TmP/GFR	↓	↓
Urinary phosphate	↑	↑
ALP	↑	↑↑
Serum calcium	Normal	↓
PTH	↑ or normal	↑↑
$1,25(OH)_2D$	↓ or inappropriately normal	↓ or inappropriately normal
25(OH)D	Normal	↓
FGF23	↑	↓ Low or normal

$1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; PTH, parathyroid hormone; TIO, tumor-induced osteomalacia.

Chart footnotes	1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyviatamin D; ALP, alkaline phosphatase; PTH, parathyroid hormone; TIO, tumor-induced osteomalacia
Static callout	See how excess FGF23 results in the clinical manifestations of XLH for children and adults[2-4]
Callout link 1	Go to Mechanism of Disease [Links to 1.1 Mechanism of Disease]
Callout link 2	Go to Pediatric Manifestations [Links to 2.1 Pediatric Manifestations]

Callout link 3	Go to Adult Manifestations [Links to 2.2 Adult Manifestations]
References	1. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect*. 2014;3(1):R13-R30. 2. Ruppe MD. X-linked hypophosphatemia. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *Gene Reviews*. https://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed October 20, 2017. 3. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res*. 2011;26(7):1381-1388. 4. Penido MG, Alon US. Phosphate homeostasis and its role in bone health. *Pediatr Nephrol*. 2012;27(11):2039-2048. 5. Beck-Nielsen SS, Brusgaard K, Rasmussen LM, et al. Phenotype presentation of hypophosphatemic rickets in adults. *Calcif Tissue Int*. 2010;87(2):108-119. 6. Skrinar A, Marshall A, San Martin J, Dvorak-Ewell M. X-linked hypophosphatemia (XLH) impairs skeletal health outcomes and physical function in affected adults. Poster presented at: Endocrine Society's 97th Annual Meeting and Expo, March 5-8, 2015. San Diego, CA. 7. Pal R, Bhansali A. X-linked hypophosphatemia with enthesopathy. *BMJ Case Rep*. 2017;1-2. 8. Karaplis AC, Bai X, Falet J-P, Macica CM. Mineralizing enthesopathy is a common feature of renal phosphate-wasting disorders attributed to FGF23 and is exacerbated by standard therapy in hyp mice. *Endocrinology.* 2012;153(12):5906-5917. 9. Opsahl Vital S, Gaucher C, Bardet C, et al. Tooth dentin defects reflect genetic disorders affecting bone mineralization. *Bone.* 2012;50(4):989-997. 10. Carpenter TO. New perspectives on the biology and treatment of X-linked hypophosphatemic rickets. *Pediatr Clin North Am.* 1997;44(2):443-466. 11. Teeth. Human Anatomy. WebMD Medical Encyclopedia. https://www.webmd.com/oral-health/picture-of-the-teeth#1. WebMD, LLC. 2015. Accesssed December 9, 2017. 12. 6-Minute Walk Test. American Thoracic Society Web site. https://www.thoracic.org/statements/resources/pfet/sixminute.pdf. Accessed November 16, 2017. 13. Che H, Roux C, Etcheto A, et al. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur J Endocrinol*. 2016;174(3):325-333. 14. Payne RB. Renal tubular reabsorption of phosphate (TmP/GFR): indications and interpretation. *Ann Clin Biochem*. 1998;35(pt. 2):201-206. 15. Santos F, Fuente R, Mejia N, Mantecon L, Gil-Peña H, Ordoñez FA. Hypophosphatemia and growth. *Pediatr Nephrol.* 2013;28(4):595-603. 16. Goldsweig BK, Carpenter TO. Hypophosphatemic rickets: lessons from disrupted FGF23 control of phosphorus homeostasis. *Curr Osteoporos Rep*. 2015;13(2):88-97. 17. Imel EA, Zhang X, Ruppe MD, et al. Prolonged correction of serum phosphorus in adults with X-linked hypophosphatemia using monthly doses of KRN23. *J Clin Endocrinol Metab*. 2015;100(7):2565-2573. 18. Özkan B. Nutritional rickets. *J Clin Res Pediatr Endocrinol.* 2010;2(4):137-143. 19. Nield LS, Mahajan P, Joshi A, Kamat D. Rickets: not a disease of the past. *Am Fam Physician*. 2006;74(4):619-626. 20. Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. *Endocr Relat Cancer*. 2011;18(3):R53-R77. 21. Jan de Beur SM. Tumor-induced osteomalacia. *JAMA*. 2005;294(10):1260-1267. 22. Halperin F, Anderson RJ, Mulder JE. Tumor-induced osteomalacia: the importance of measuring serum phosphorus levels. *Nat Clin Pract Endocrinol Metab.* 2007;3(10):721-725.

5.0 Resources

5.1 Resources	
Sitemap	
Sitemap Number	5.1
Page Name	XLH Resources

Body 1	
Page Title	XLH resources
Headline	The resources below have been provided for you and your practice.
Subhead	XLH Information websites
Link	European Society for Paediatric Endocrinology [Links to: https://www.eurospe.org/]
Link	European Calcified Tissue Society [Links to: http://ectsoc.org/]
Link	European Society for Paediatric Nephrology [Links to: http://espn-online.org/]
Link	OMIM® (Online Mendelian Inheritance in Man®) Database of Genes [Links to: https://www.omim.org/]
Subhead	XLH Patient site
Link	XLHlink.com [Links to XLHlink.com]
Subhead	Videos
Copy	Coming soon
Subhead	Downloadable resources
Copy	Coming soon