ERKNet
The European
Rare Kidney Disease
Reference Network

european
society for
paediatric
nephrology

WELCOME TO

ESPN/ERKNet
Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: 7 September 2021

Topic: Renal hypophoshatemia

Speaker: Dieter Haffner, Hannover, Germany

Moderator: Tom Nijenhuis, Nijmegen, Netherlands

Disclosures

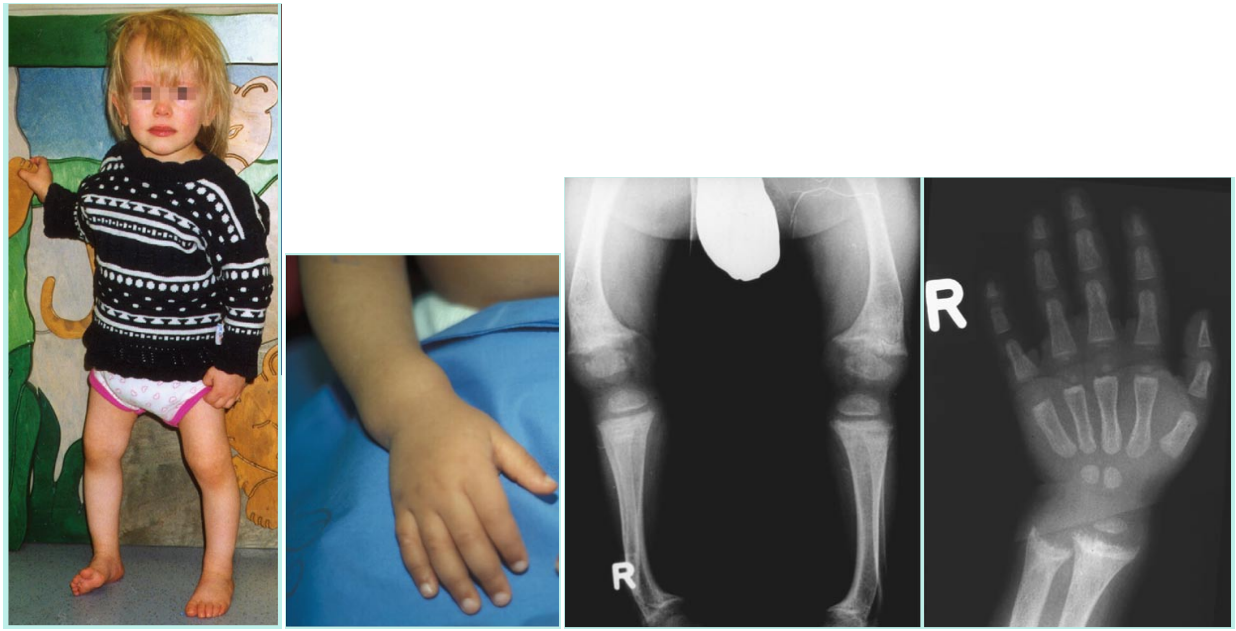
Speaker fees/consultancy: Amgen, Chiesi, Horizon, Kyowa Kirin, Merck-Serono, Pfizer, Sandoz

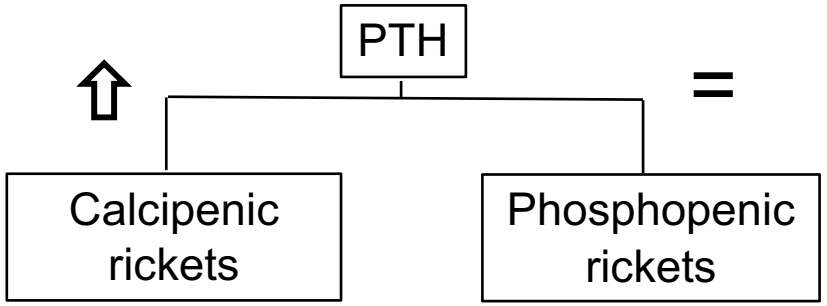
Research grants: Amgen, Kyowa Kirin, Horizon

Diagnostic approach to rickets: calcipenic *versus* phosphopenic rickets

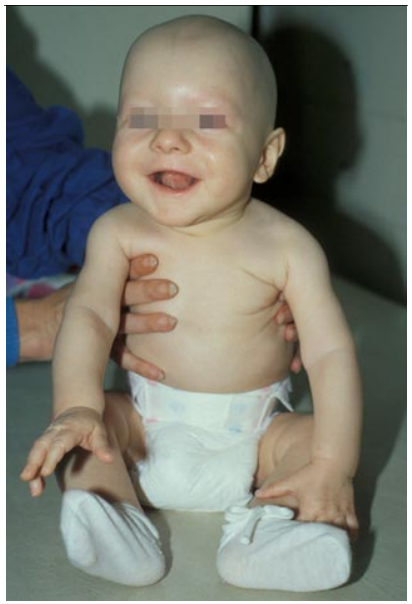
Diagnosis of rickets is based on

- **Clinical presentation:** leg deformities, waddling gait, muscle weakness, short stature, widened wrist..
- **Radiography:** metaphyseal fraying, widening of growth plates, leg bowing
- **Biochemistry:** alkaline phosphatase levels ⇧





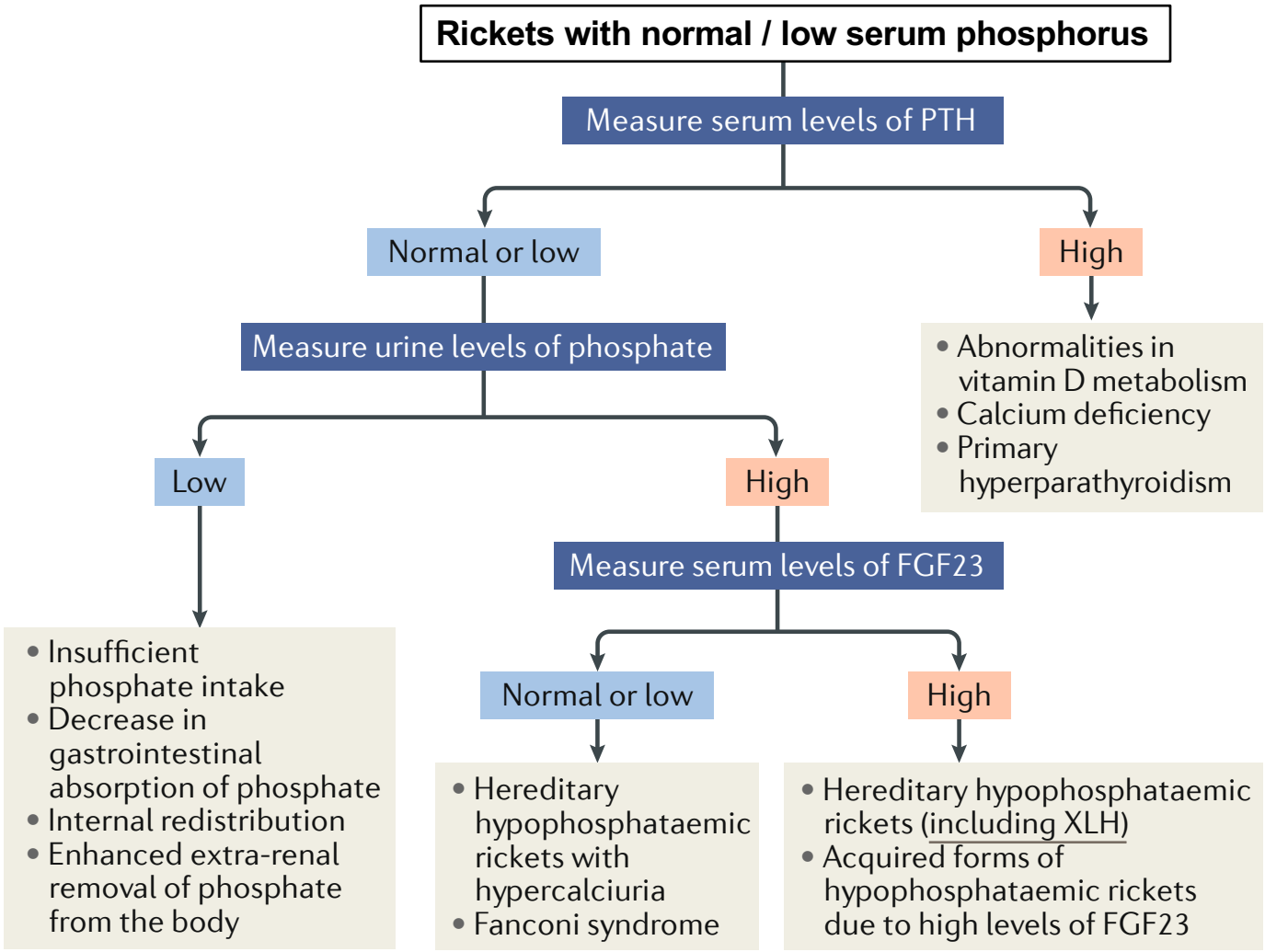
Disorder (abbreviation; OMIM#)	Gene/location	Ca	P	ALP	U_{Ca}	TmP/GFR	FGF23	PTH	25 (OH)D$	1,25 $(OH)_2D$	Pathogenesis
Rickets/osteomalacia with high PTH (calcipen											
Vitamin D deficiency rickets							N	↑↑↑	↓↓	varies	Vitamin D deficiency
Vitamin D dependent rickets type 1A (VDDR1A; OMIM#264700)	*CYP27B1*						N	↑↑↑	N	↓	Impaired synthesis of 1,25 $(OH)_2D$
Vitamin D dependent rickets type 1B (VDDR1B; OMIM#600081)	*CYP2R1/11p15*						N	↑↑↑	↓↓	varies	Impaired synthesis of 25 (OH)D
Vitamin D dependent rickets type 2A (VDDR2A; OMIM#277440)	*VDR*						N	↑↑↑	N	↑↑	Impaired signaling of the VDR
Vitamin D dependent rickets type 2B (VDDR2B; OMIM#264700)	*HNRNPC*						N	↑↑↑	N	↑↑	Impaired signaling of the VDR
Vitamin D dependent rickets type 3 (VDDR3)	*CYP3A4*	↓	↓	↑↑↑	↓	?	?	↑↑↑	↓	↓	Inreased inactivation of 1,25 $(OH)_2D$



Infant with alopecia due to VDDR2A

Haffner D et al, Nat Rev Nephrol 2019
Schnabel D, Haffner D. Monatsschrift Kinderheilkd 2005

MHH Medizinische Hochschule Hannover

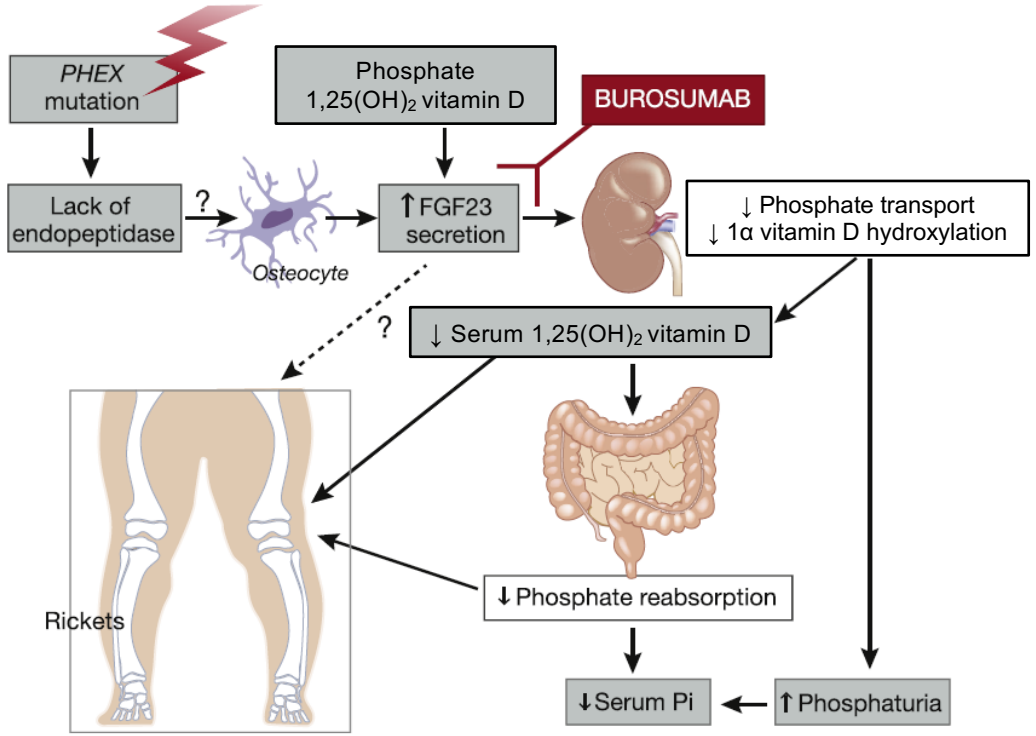


Haffner D et al., Nat Rev Nephrol 2019

X-linked hypophosphatemia

- XLH is the most common cause of inherited phosphate wasting[1]
  - Incidence: 3.9/100,000 live births
  - Prevalence: 1.7–4.8/100,000
- Characterised by renal phosphate wasting (resulting in hypophosphatemia) and reduction in 1,25(OH)$_2$ vitamin D synthesis[1]
- Key clinical characteristics include rickets, disproportionate short stature and osteo- and odontomalacia[1]
- Children usually present with clinical symptoms within the first two years of life, but diagnosis is often delayed due to the diversity of clinical manifestations and the rarity of the disease[1]

Pathophysiology of rickets in XLH[2]



NaPi, sodium–phosphate co-transporter; Pi, phosphate

Poll question 1

CONSENSUS STATEMENT

OPEN

EVIDENCE-BASED GUIDELINE

Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia

Dieter Haffner[1,2], Francesco Emma[3], Deborah M. Eastwood[4,5], Martin Biosse Duplan[6,7,8], Justine Bacchetta[9], Dirk Schnabel[10], Philippe Wicart[8,11,12], Detlef Bockenhauer[13], Fernando Santos[14], Elena Levtchenko[15], Pol Harvengt[16], Martha Kirchhoff[17], Federico Di Rocco[18], Catherine Chaussain[6,7,8], Maria Louisa Brandi[19], Lars Savendahl[20], Karine Briot[8,12,21,22], Peter Kamenicky[8,23,24], Lars Rejnmark[25] and Agnès Linglart[8,24,26,27]*

Abstract | X-linked hypophosphataemia (XLH) is the most common cause of inherited phosphate wasting and is associated with severe complications such as rickets, lower limb deformities, pain, poor mineralization of the teeth and disproportionate short stature in children as well as hyperparathyroidism, osteomalacia, enthesopathies, osteoarthritis and pseudofractures in adults. The characteristics and severity of XLH vary between patients. Because of its rarity, the diagnosis and specific treatment of XLH are frequently delayed, which has a detrimental effect on patient outcomes. In this Evidence-Based Guideline, we recommend that the diagnosis of XLH is based on signs of rickets and/or osteomalacia in association with hypophosphataemia and renal phosphate wasting in the absence of vitamin D or calcium deficiency. Whenever possible, the diagnosis should be confirmed by molecular genetic analysis or measurement of levels of fibroblast growth factor 23 (FGF23) before treatment. Owing to the multisystemic nature of the disease, patients should be seen regularly by multidisciplinary teams organized by a metabolic bone disease expert. In this article, we summarize the current evidence and provide recommendations on features of the disease, including new treatment modalities, to improve knowledge and provide guidance for diagnosis and multidisciplinary care.

Methodology: AAP grading system (2/2)

Aggregate evidence quality	Benefit or harm predominates	Benefit and harm balanced
Level A **Intervention:** well-designed and conducted trials, meta-analyses on applicable populations **Diagnosis:** independent gold standard studies of applicable populations	Strong recommendation (A Strong)	Weak recommendation (B Weak; C Weak)
Level B Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies	Moderate recommendation (B Moderate)	
Level C Single or few observational studies or multiple studies with inconsistent findings or major limitations	Weak recommendation (C Moderate)	
Level D Expert opinion, case reports, reasoning from first principles	(based on low-quality evidence) (D Weak)	No recommendation may be made
Level X Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates	Strong recommendation Moderate recommendation	

AAP, American Academy of Pediatrics.

Diagnosis: children and adults

Children	A diagnosis of XLH should be considered in the presence of: • Clinical and/or radiological signs of rickets • Impaired growth velocity • Serum phosphate levels below age-related reference range associated with renal phosphate wasting, in the absence of vitamin D or calcium deficiency B Moderate
Adults	A diagnosis of XLH should be considered in the presence of: • Lower limb deformities (or history of) • Osteomalacia (clinical and/or radiological signs) – Including pseudofractures, early osteoarthritis and/or enthesopathy In the context of serum phosphate levels below age-related reference range and renal phosphate wasting B Moderate

Haffner D *et al*. *Nat Rev Nephrol* 2019

Clinical and molecular diagnosis: all patients with XLH (1/5)

Diagnosis of XLH is based on the association of clinical, radiological and biochemical assessments

Recommended initial diagnostic work-up

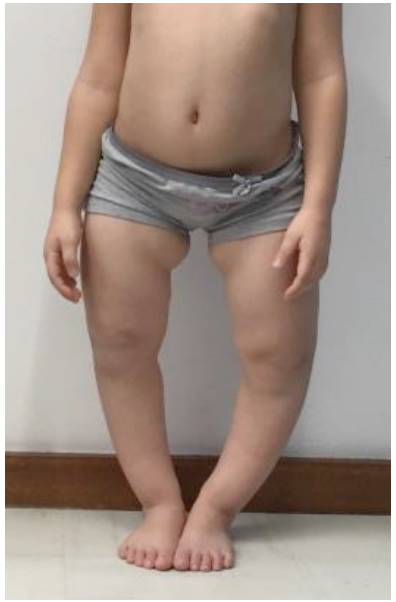
Clinical evaluation:

- Evidence of rickets or growth failure
- Evidence of dental abnormalities
- Signs of craniosynostosis/intracranial hypertension

B Moderate

- Orthopaedic assessment of the musculo-skeletal system should be performed in the presence of lower limb deformity (*varum* or *valgus* or antero-posterior)

C Moderate



Haffner D *et al*. *Nat Rev Nephrol* 2019

Clinical and molecular diagnosis: all patients with XLH (2/5)

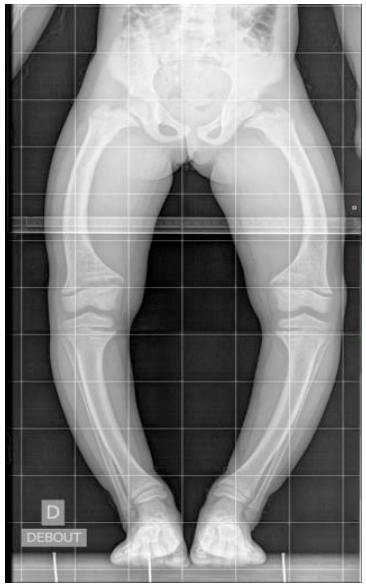
Diagnosis of XLH is based on the association of clinical, radiological and biochemical assessments

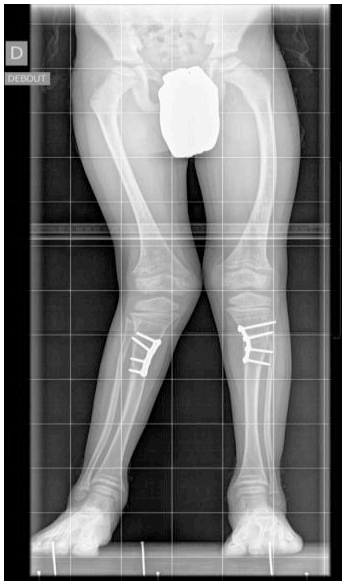
Recommended initial diagnostic work-up

Radiological evaluation:

- Diagnose and grade rickets and osteomalacic lesions

B
Moderate





Haffner D *et al*. *Nat Rev Nephrol* 2019

Clinical and molecular diagnosis: all patients with XLH (3/5)

Diagnosis of XLH is based on the association of clinical, radiological and biochemical assessments

Recommended initial diagnostic work-up

Biochemical tests:

- Serum levels of Pi, Ca, ALP, PTH, 25(OH) vitamin D, 1,25$(OH)_2$ vitamin D, creatinine
- Urinary Ca, Pi and creatinine (spot urine)
  => Calculation of:
  - Renal phosphate threshold concentration (TmP/GFR)
  - Urinary calcium/creatinine ratio

B Moderate

- Exclude non-selective renal tubular phosphate wasting (suggesting renal Fanconi syndrome) by looking for abnormal serum bicarbonate, amino acid, glucose and/or uric acid losses in urines, and low molecular weight proteinuria

B Moderate

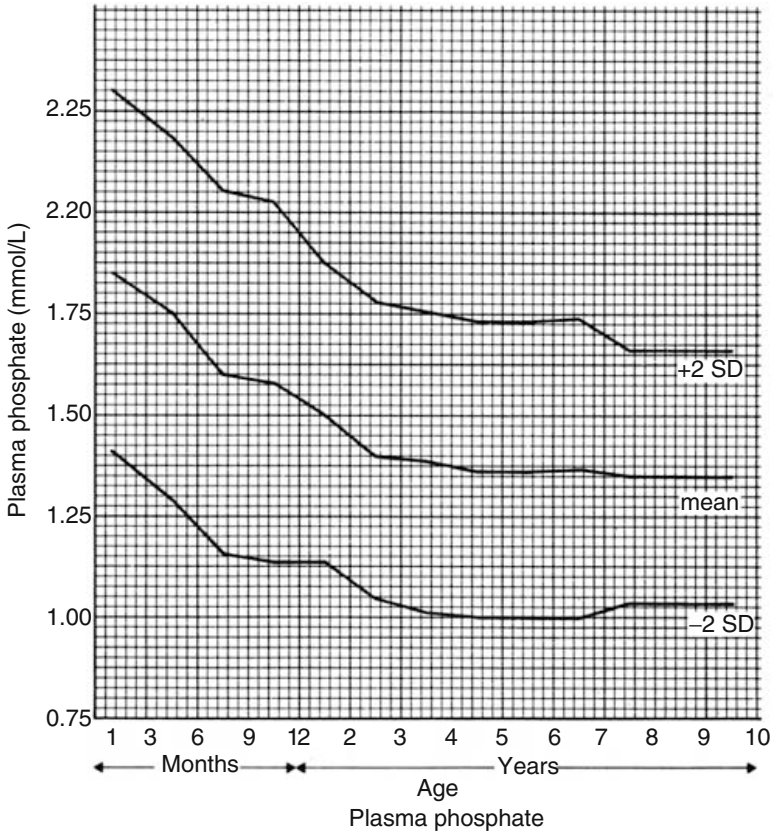
ALP, alkaline phosphatase; Ca, calcium; Pi, phosphate; TmP/GFR, tubular reabsorption of phosphate per glomerular filtration rate.

Biochemical features of XLH (children and adults) (4/5)

	Typical biochemical features of XLH
Serum phosphorus	↓
ALP	↑
TmP/GFR	↓
Serum calcium concentration	Lower normal range
Urinary calcium	Low*
PTH	Upper limit of normal range or slightly elevated
$1,25(OH)_2$ vitamin D	Low or inappropriately normal in the setting of hypophosphatemia
Intact FGF23 (untreated patients)	↑†

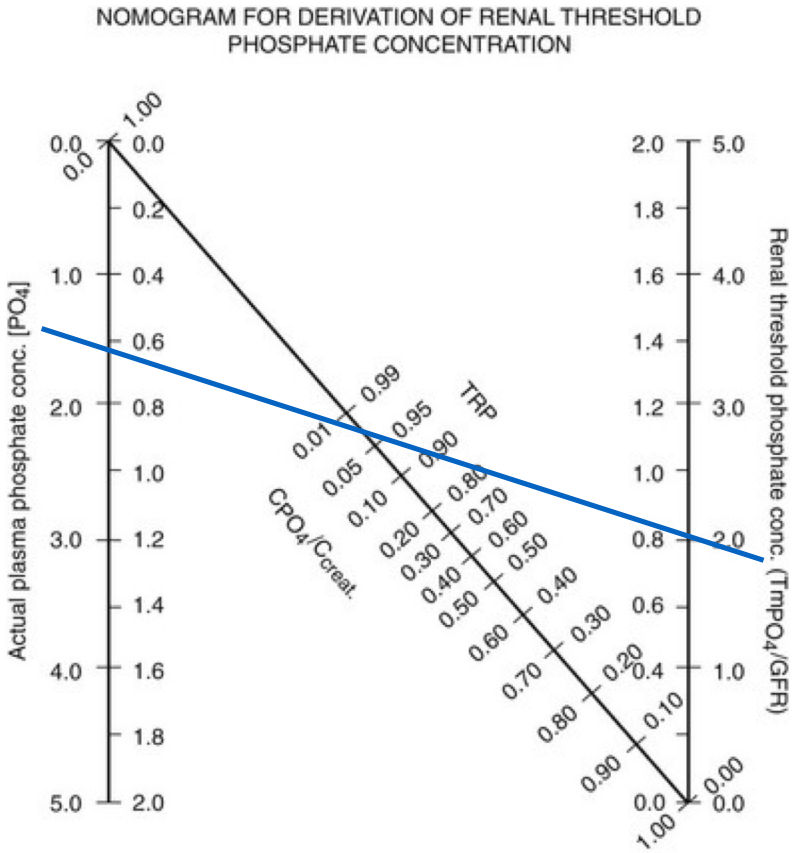
*Due to impaired $1,25(OH)_2$ vitamin D synthesis and decreased intestinal calcium absorption; †Normal levels of FGF23 do not exclude a diagnosis of XLH;
ALP, alkaline phosphatase; TmP/GFR, tubular reabsorption of phosphate per glomerular filtration rate; PTH, parathyroid hormone. Haffner D *et al. Nat Rev Nephrol* 2019

Age dependent normal range for serum phosphorus levels



Holliday, Textbook: Pediatric Nephrology 1998

Calculation of TmP/GFR



Brodehl formula

$TmP/GFR = S_P - (U_P / U_{Cr}) \times S_{Cr}$

Normal range:

0 mo. - 12 mo	1.1 - 2.0 mmol/l
1 yr.- 5 yrs.	1.0 - 1.8 mmol/l
6 yrs. – 12 yrs.	0.97 - 1.64 mmol/l
13 yrs. – 15 yrs.	0.91 - 1.68 mmol/l
> 15 yrs. & adults	0.84 - 1.23 mmol/l

Use 2nd morning urine sample

Take blood sample at the same time

Online calculator available at:
https://gpn.de/service/tmp-gfr-calculator/

Walton & Bijvoet. Lancet 1975;2:309–310

Brodehl et al., Ped Nephrol 1988;2:183-189
Starck et al, Nephron 1986;44:125-128

Clinical and molecular diagnosis: all patients with XLH (5/5)

We recommend confirming the clinical diagnosis of XLH by genetic analysis of the *PHEX* gene in children and adults if feasible

B Moderate

- Negative test result: consider other causes of hypophosphatemia

B Moderate

- If genetic analysis is not available, the presence of elevated plasma intact FGF23 concentrations and/or a positive family history for XLH support the diagnosis

C Moderate

States of elevated FGF23 levels & it‘s diagnostic value

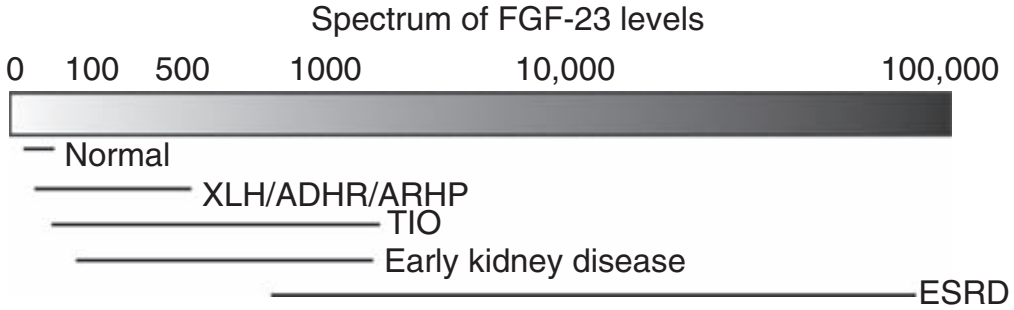
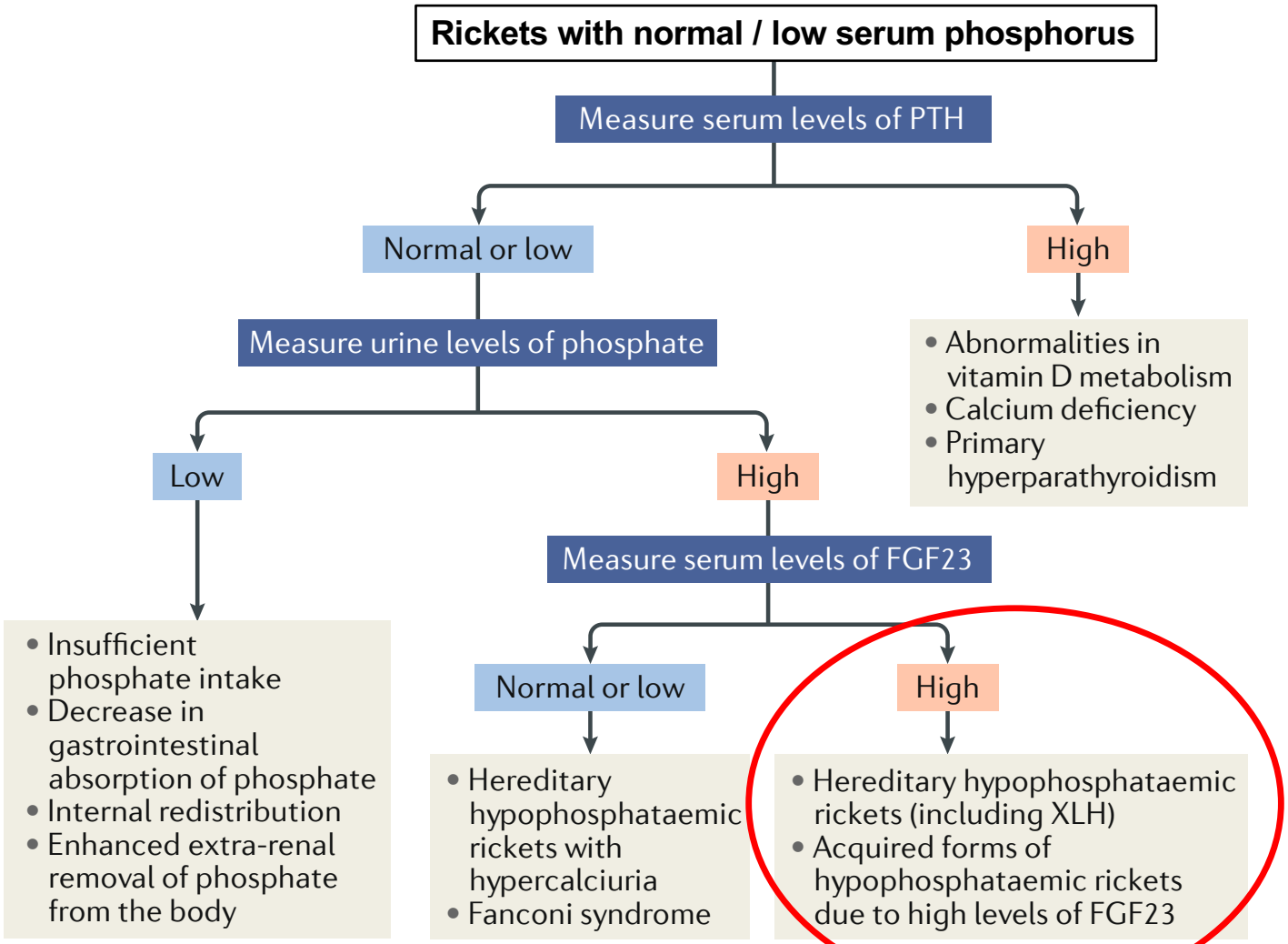


Figure 1 | Spectrum of serum fibroblast growth factor (FGF)-23 levels in early chronic kidney disease and end-stage renal disease (ESRD) as compared with the normal condition and with different disorders affecting FGF-23. ADHR, autosomal dominant hypophosphatemic rickets; ARHP, autosomal recessive hypophosphatemia; TIO, tumor-induced osteomalacia; XLH, X-linked hypophosphatemia. Adapted with permission from Isakova *et al*.[20]

- FGF23 levels are influenced by phosphate intake & vitamin D therapy
- Average intact FGF23 levels in untreated pediatric XLH patients: 84.5 ± 27.4 pg/ml (lowest, 38 pg/ml)
- Proposed cut-off level to diagnose XLH: 30 pg/ml (Kainos assay)



Haffner D et al., Nat Rev Nephrol 2019

Differential diagnoses (4/6)

Disorder (OMIM#)	Gene/location	Ca	P	ALP	U_{Ca}	U_P	TmP/GFR	FGF23	PTH	25 (OH) vitamin D*	1,25 $(OH)_2$ vitamin D	Pathogenesis
Rickets/osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels/signalling												
XLH (OMIM#307800)	*PHEX*/Xp22.1	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑†	N	N‡	↑ FGF23 expression in bone and impaired FGF23 cleavage
ADHR (OMIM#193100)	*FGF23*/12p13.3	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑†	N	N‡	FGF23 protein resistant to degradation
ARHR1 (OMIM#241520)	*DMP1*/4q22.1	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑†	N	N‡	↑ FGF23 expression in bone
ARHR2 (OMIM#613312)	*ENPP1*/6q23.2	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑†	N	N‡	↑ FGF23 expression in bone
ARHR3 (OMIM#259775)	*FAM20C*/7q22.3	N	↓	↑, ↑↑	?	↑	↓	↑, N	N, ↑†	N	N‡	↑ FGF23 expression in bone

*Cave: prevalence of vitamin D deficiency was reported to be <50% in healthy children; †PTH may be moderately elevated; ‡decreased relative to the serum phosphate concentration; ↓ = decreased, ↑ = elevated; ↑↑ = very elevated

1,25$(OH)_2$D, 1,25-dihydroxyvitamin; 25(OH)D, cholecalciferol; ADHR, autosomal dominant hypophosphatemic rickets; ARHR1, autosomal dominant hypophosphatemic rickets 1; ARHR2, autosomal recessive hypophosphatemic rickets 2; ARHR3, Raine syndrome associated; ALP, alkaline phosphatase; Ca, serum calcium; FD, fibrous dysplasia P, serum phosphate; PTH, parathyroid hormone; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate normalised to the glomerular filtration rate; UCa, urinary calcium excretion; U_P, urinary phosphate excretion

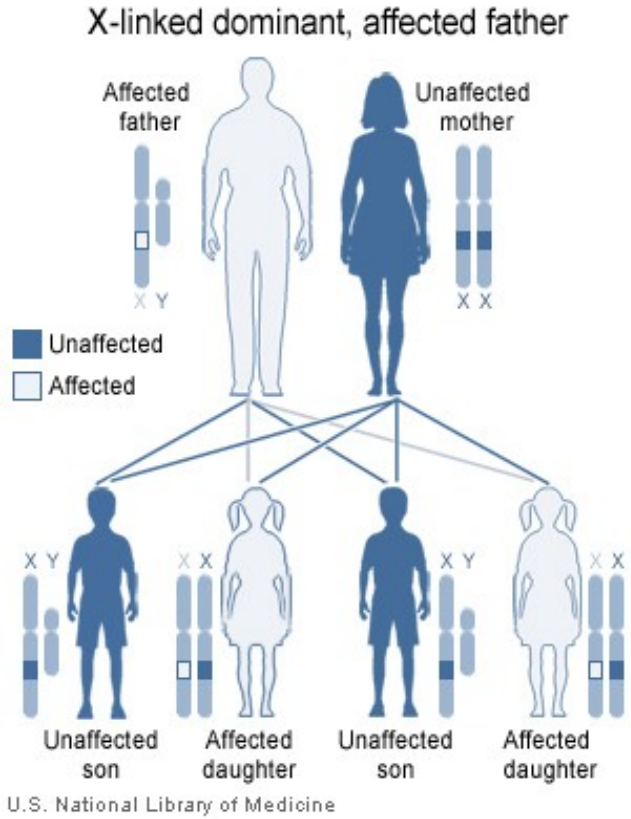
Differential diagnoses (5/6)

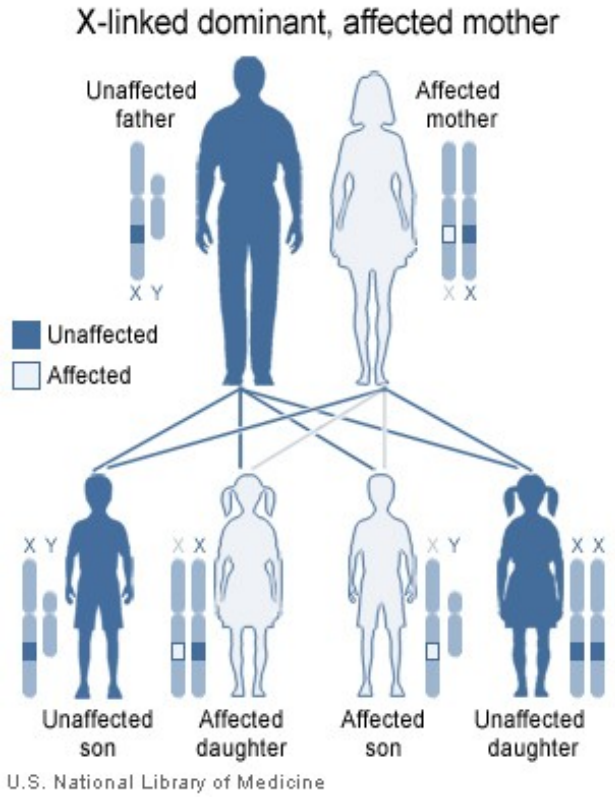
Disorder (OMIM#)	Gene/location	Ca	P	ALP	U_{Ca}	U_P	TmP/GFR	FGF23	PTH	25 (OH) vitamin D*	$1,25\ (OH)_2$ vitamin D	Pathogenesis
Rickets/osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels/signalling (continued)												
Fibrous dysplasia (OMIM#174800)	*GNAS*/20q13.3	N, ↓	↓	↑, ↑↑	↓	↑	↓	N, ↑	N, ↑†	N	N‡	↑ FGF23 expression in bone
Tumour induced osteomalacia	NA	N, ↓	↓	↑, ↑↑	↓	↑	↓	N, ↑	N, ↑†	N	N‡	↑ FGF23 expression in tumour cells
Cutaneous skeletal hypophosphatemia syndrome (SFM; OMIM#163200)	*RAS*/1p13.2	N, ↓	↓	↑, ↑↑	↓	↑	↓	N, ↑	N, ↑†	N	N‡	?
Osteoglophonic dysplasia (OMIM#166250)	*FGFR1*/8p11.23	N	↓	↑, N	N	↑	↓	N	N, ↑†	N	N‡	↑ FGF23 expression in bone
Hypophosphatemic rickets and hyperparathyroidism (OMIM#612089)	*KLOTHO*/13q13.1	N	↓	↑, ↑↑	↓	↑	↓	↑	↑↑	N	N‡	Unknown; translocation of the *KLOTHO* promoter

*Cave: prevalence of vitamin D deficiency was reported to be <50% in healthy children; †PTH may be moderately elevated; ‡Decreased relative to the serum phosphate concentration; ↓ = decreased, ↑ = elevated; ↑↑ = very elevated

$1,25(OH)_2D$, 1,25-dihydroxyvitamin; 25(OH)D, cholecalciferol; ALP, alkaline phosphatase; Ca, serum calcium; P, serum phosphate; PTH, parathyroid hormone; SFM, cutaneous skeletal hypophosphatemia syndrome; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate normalised to the glomerular filtration rate; UCa, urinary calcium excretion; U_P, urinary phosphate excretion

XLH: Mode of inheritance





https://en.wikipedia.org/wiki/X-linked_hypophosphatemia; Winters RW et al Medicene 1958

0013-7227/01/$03.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 86(8):3889–3899

Mutational Analysis and Genotype-Phenotype Correlation of the PHEX Gene in X-Linked Hypophosphatemic Rickets

INGRID A. HOLM*, ANNE E. NELSON*, BRUCE G. ROBINSON, REBECCA S. MASON, DEBORAH J. MARSH, CHRISTOPHER T. COWELL, AND THOMAS O. CARPENTER

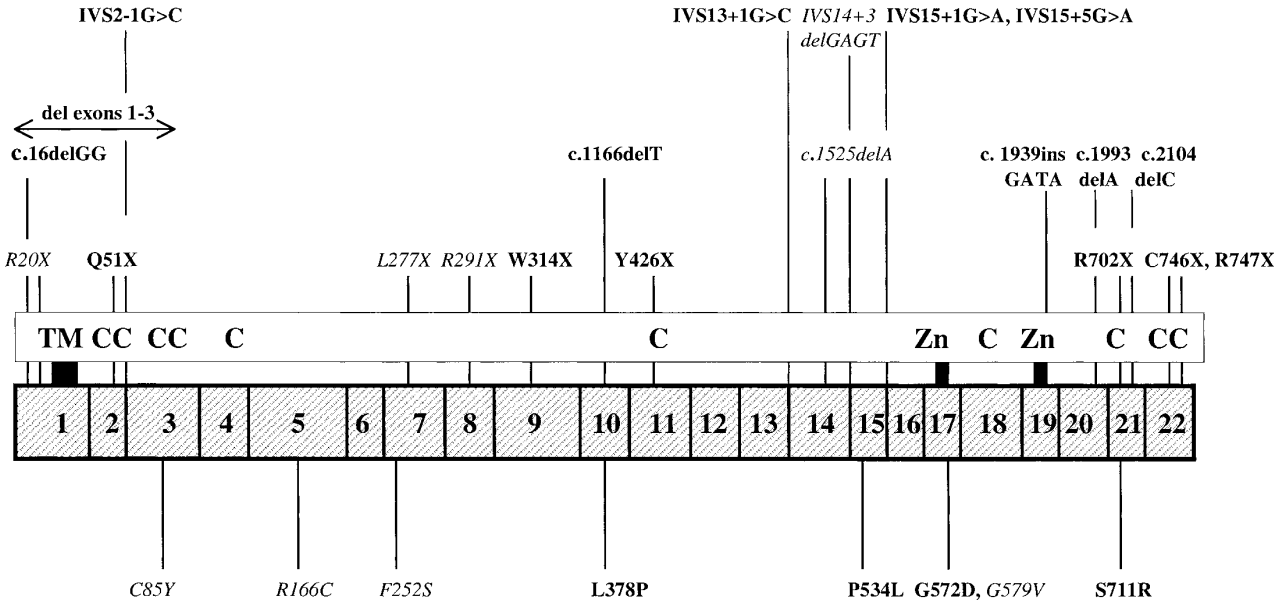


FIG. 1. Diagram of the PHEX gene showing the mutations detected in this study in *bold*, and in the nine patients previously identified (17) in *italics,* in patients with X-linked hypophosphatemic rickets. The *hatched bar* represents the 22 exons of the gene. The predicted transmembrane domain (TM), zinc-binding domains (Zn), and cysteine residues (C) are indicated. Mutations predicted to truncate the protein are shown above the *bar* and missense mutations below the *bar*.

Hum Genet (2009) 125:401–411
DOI 10.1007/s00439-009-0631-z

ORIGINAL INVESTIGATION

PHEX analysis in 118 pedigrees reveals new genetic clues in hypophosphatemic rickets

Céline Gaucher · Odile Walrant-Debray · Thy-Minh Nguyen · Laure Esterle · Michèle Garabédian · Frédéric Jehan

- XLH is caused by mutation in the phosphate-regulating endopeptidase gene (*PHEX*; OMIM-300550) with homologies to Endopeptidase (HYP-consortium 1995)
- 22 exons, no „hot spots“
- *PHEX* mutations have been found in
  - 87% of familial cases
  - 72% of sporadic cases
- No clear genotype-phenotype correlation
- Trend toward more severe skeletal disease in patients with truncating mutations

Follow-up: children with XLH

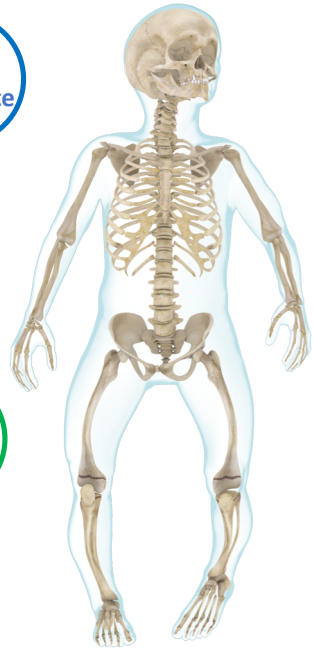
At least every 3 months during the phases of rapid growth (infancy and puberty) or after initiation of therapy
At least every 6 months in patients showing positive response to treatment and/or stable condition

C Weak

Recommended analyses

- Height, weight, head circumference (<5 years), ICD and IMD, and BP
- Measure BMI and annual height velocity

C Moderate



- Search for hearing loss
- Monitor spine deformity and scoliosis, manifestations related to craniosynostosis, Chiari 1 malformation and/or cranial hypertension, and maxillary dysmorphosis

- Record head shape, history of headaches, dental abscesses or maxillofacial cellulitis, bone pain, fatigue, physical function

C Moderate

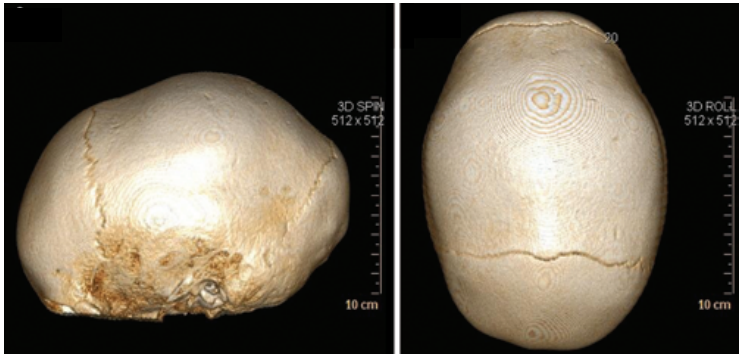
- Perform radiographs* of the left wrist and/or knees if patients:
  - Do not respond well to therapy
  - Worsen in their bone deformity under medical treatment
  - Require orthopaedic surgery
  - Complain of unexplained bone pain
- Or, adolescents with persistent lower limb deformities when they are transitioning to adult care

B Moderate

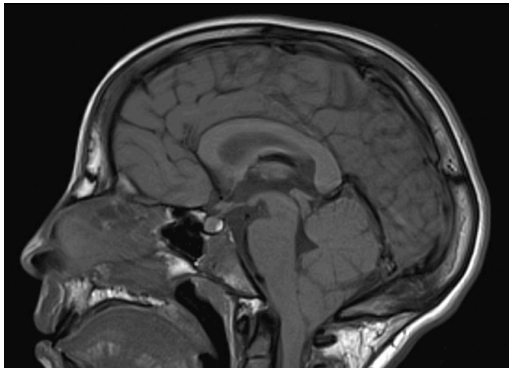
- Assess bone age to evaluate the growth potential >5 years of age in children with growth impairment
- In the presence of lower limb deformity, perform orthopaedic assessment

*Radiographs should be standardised anterior-posterior standing long leg radiographs (utilising low-dose EOS® when feasible) to assess limb deformities, joint alignment, and bone quality. BMI, body mass index; BP, blood pressure; ICD, intercondylar distance; IMD, intermalleolar distance

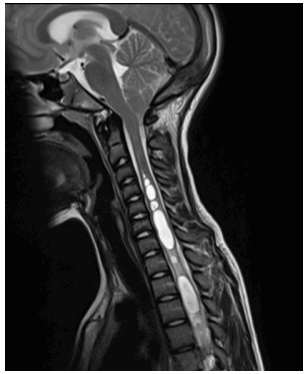
Clinical features of XLH: other symptoms and complications



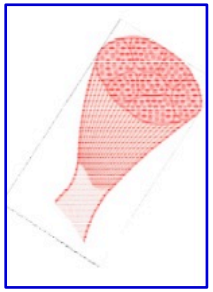
Craniosynostosis



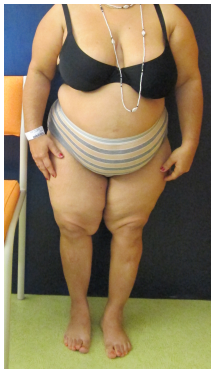
Chiari malformation



Syringomyelia



Impaired muscle function



Weight gain

Craniosynostosis

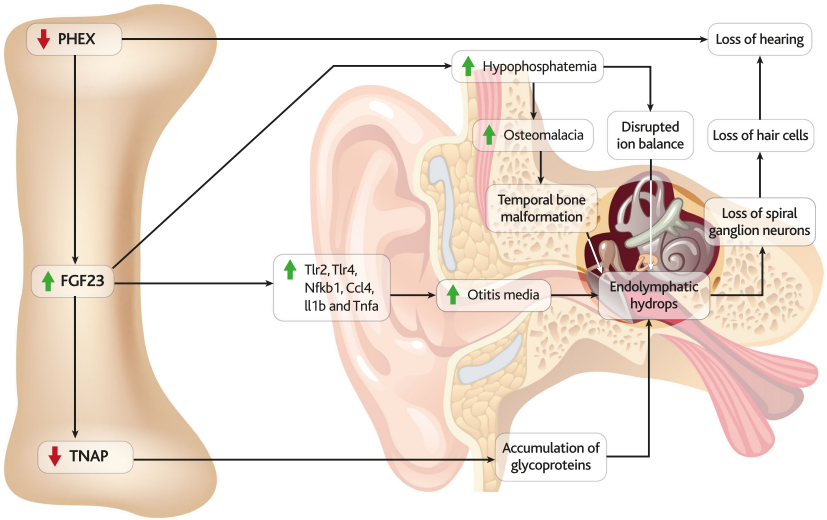
Chiari type I malformation

Syringomyelia, spinal stenosis

Impaired muscle function

Weight gain => CV comorbidity

Hearing loss, tinnitus, vertigo



1. Haffner D et al. *Nat Rev Nephrol* 2019;15:435-456
2. Beck-Nielsen SS et al. *Orphanet J Rare Dis* 2019;14(19):58

Follow-up in all patients with XLH: biochemical recommendations

- Blood:
  - Monitor ALP (total serum ALP in children and BAP in adults), calcium, phosphate, creatinine, PTH, 25(OH) vitamin D
- Urine:
  - Calculate urinary calcium/creatinine ratio in patients receiving conventional or burosumab treatment

B Moderate

In patients receiving burosumab treatment, it is also recommended to:

- Monitor fasting serum phosphate

  together with TmP/GFR

  every 2 weeks during the first month, every 4 weeks for the following 2 months (and thereafter as appropriate)

B Moderate

B Weak

- Measure fasting serum phosphate 4 weeks after dose adjustment

B Moderate

- Measure $1,25(OH)_2$ vitamin D serum levels every 6 months analysed together with the urinary calcium excretion as safety parameters

B Weak

ALP, alkaline phosphatase; BAP, bone-specific alkaline phosphatase; PTH, parathyroid hormone; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate normalised to the glomerular filtration rate

Conventional treatment in children with XLH: recommendations (1/5)

We recommend treating children with overt XLH phenotype with a combination of oral phosphorous (phosphate salts) and active vitamin D (calcitriol or alfacalcidol) as soon as diagnosis is established

B
Moderate

Haffner D *et al. Nat Rev Nephrol* 2019

Conventional treatment in children with XLH: recommendations (2/5)

Phosphorous

- **Infants/pre-school children:** Initial dose: 20–60 mg/kg/day of elemental phosphorous (0.7-2.0 mmol/kg) (adjusted according to improvement of rickets, growth, ALP and PTH levels) — C Moderate
- **Young patients with high ALP levels: frequent administration of phosphorous** (4–6 times per day; lowered to 3–4 times per day when ALP has normalised) — B Moderate
- **Progressive increase in dose (but not >80 mg/kg/day)** to prevent gastrointestinal discomfort and hyperparathyroidism. If present, adjust treatment by decreasing dose and/or increasing the frequency — C Moderate
- **Use lower dose in milder phenotypes** (e.g. infants diagnosed by family screening) — C Moderate

ALP, alkaline phosphatase; PTH, parathyroid hormone

Conventional treatment in children with XLH: recommendations (3/5)

Active vitamin D

- **Initial dose of calcitriol:** 20–30 ng/kg/day
  OR
- **Initial dose of alfacalcidiol**: 30–50 ng/kg/day
  OR
- Treatment can be started empirically at 0.5 µg/day of calcitriol or 1 µg of alfacalcidol (age >12 months) and adjusted based on the clinical and biochemical responses

C Moderate

Native vitamin D

- **Vitamin D deficiency:** Cholecalciferol or ergocalciferol supplements

C Weak

Haffner D *et al. Nat Rev Nephrol* 2019

Poll question 2

Burosumab treatment in children with XLH: recommendations (1/2)

If available, we recommend considering burosumab treatment in XLH children aged 1 year or older, and in adolescents with growing skeletons if:

B
Moderate

- **They have radiographic evidence of overt bone disease**
- **<u>And</u> they are refractory to conventional therapy**
- **<u>Or</u> if they experience complications related to conventional therapy**
- **<u>Or</u> if they are unable to adhere to conventional therapy, presumed that adequate monitoring is feasible**

Haffner D *et al. Nat Rev Nephrol* 2019

Burosumab treatment in children with XLH: recommendations (2/2)

	Treatment administration
Starting dose	• 0.4 mg/kg* every two weeks subcutaneously
Titration	• 0.4 mg/kg increments to raise fasting serum phosphate levels to within the lower end of the normal reference range for age, to a maximum dosage of 2.0 mg/kg body weight (maximum dose 90 mg) • Burosumab should not be adjusted more frequently than every 4 weeks
Monitoring of serum phosphate	• Monitor fasting serum phosphate levels between injections: – During titration period: ideally, 7–11 days after the last injection to detect hyperphosphatemia – After achievement of a steady-state (which can be assumed after 3 months of a stable dose): preferentially, directly before injections to detect underdosing
Other dose recommend-dations	• Withhold dose if fasting serum phosphate level is above the upper range of normal • Burosumab may be restarted at approximately half of the previous dose when serum phosphate concentration is below the normal range
Contra-indications	Do not administer: • Alongside conventional treatment • When fasting phosphate levels are within the age-related normal reference range before treatment initiation • Or in the presence of severe renal impairment

B Moderate

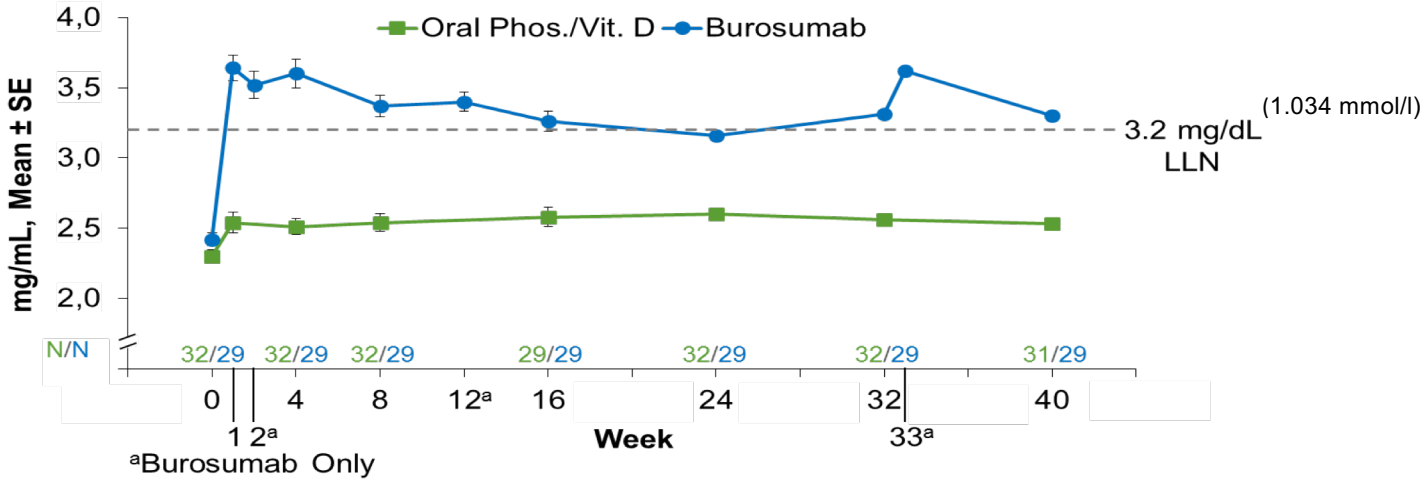
B Weak

B Moderate

*Updated EMA recommendation: 0.8 mg/kg every two weeks subcutaneously

Burosumab versus Conventional Treatment in Children with XLH

UX023-CL301: Improvement in Serum Phosphate



Serum Phosphate	Oral Phos./Vit. D Mean (SD)	Burosumab Mean (SD)
Baseline	2.30 (0.257)	2.42 (0.244)
Week 40*	2.53 (0.339)	3.30 (0.426)
Mean Post-Baselines[b,c]	2.55 (0.291)	3.38 (0.374)
% time in normal range[c]	6.16 (12.175)	68.97 (32.859)

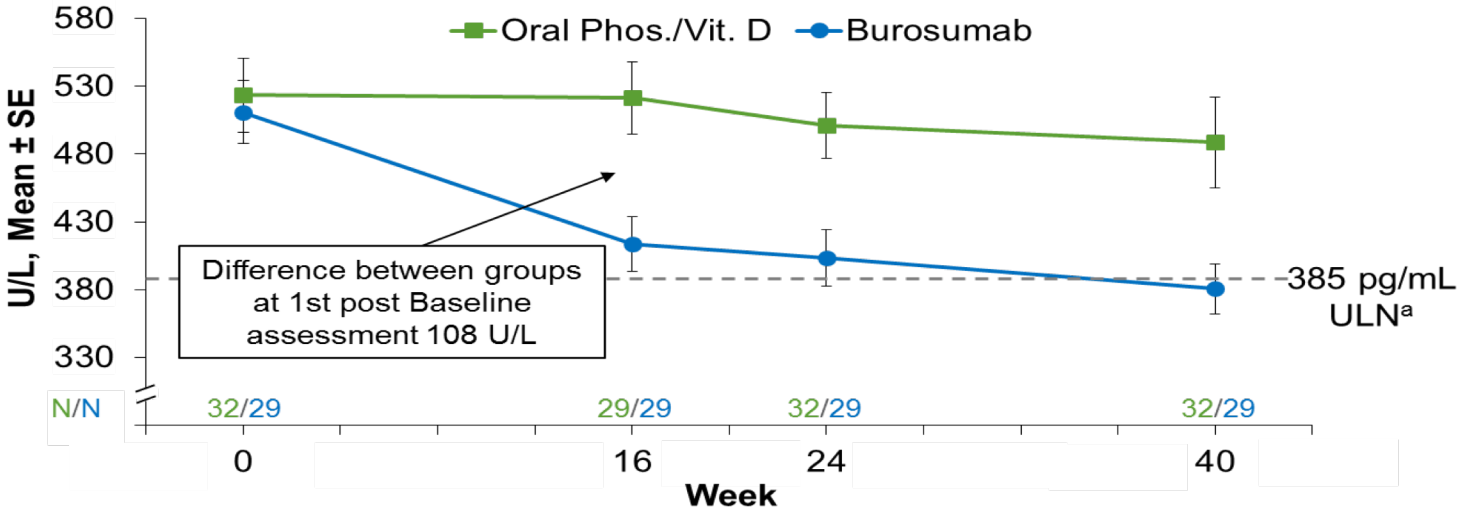
Nilsson O.: FC 10.1, 57zh ESPE Meeting, Athens, Greece, 27.-29. September 2018

*P < 0.0001 for change from baseline at Week 40;
[b]P < 0.0001 for mean change postbaseline from baseline;
[c]Based on data collected at Week 1, 4, 8, 16, 24, 32 and 40, home visits where data only collected for Burosumab group was not included.

Imel EA et al. Lancet 2019; 393:2416-2427

Burosumab versus Conventional Treatment in Children with XLH

UX023-CL301: Improvement in serum alkaline phosphatase



ALP	Oral Phos./Vit. D Mean (SD)	Burosumab Mean (SD)
Baseline	523.44 (154.419)	510.76 (124.903)
Week 40*	488.69 (189.070)	380.76 (99.464)

*P < 0.0001 for change from baseline at Week 40

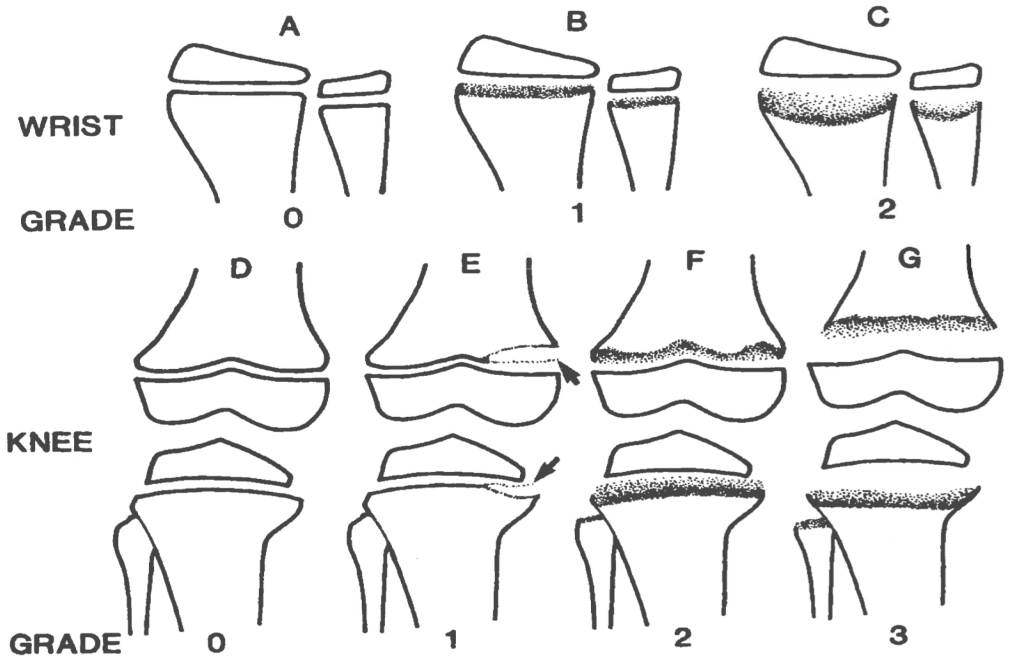
Nilsson O.: FC 10.1, 57zh ESPE Meeting, Athens, Greece, 27.-29. September 2018

[a]Normal range varies depending on sex & age, within males and females ages 1-15, the upper limit ranged from 297 to 385 U/L

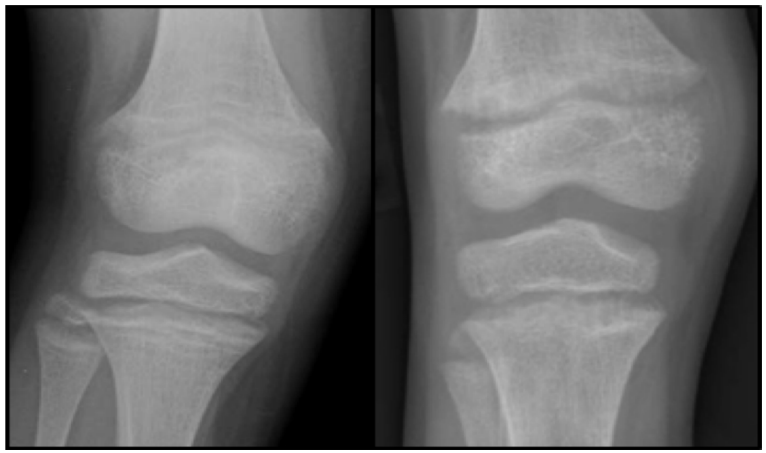
Imel EA et al. Lancet 2019; 393:2416-2427

Rickets severity score (RSS) according to Thacher et al[1]

Values 0–10: Wrist (0–4) + Knee (0–6)



Knee x-ray[2]

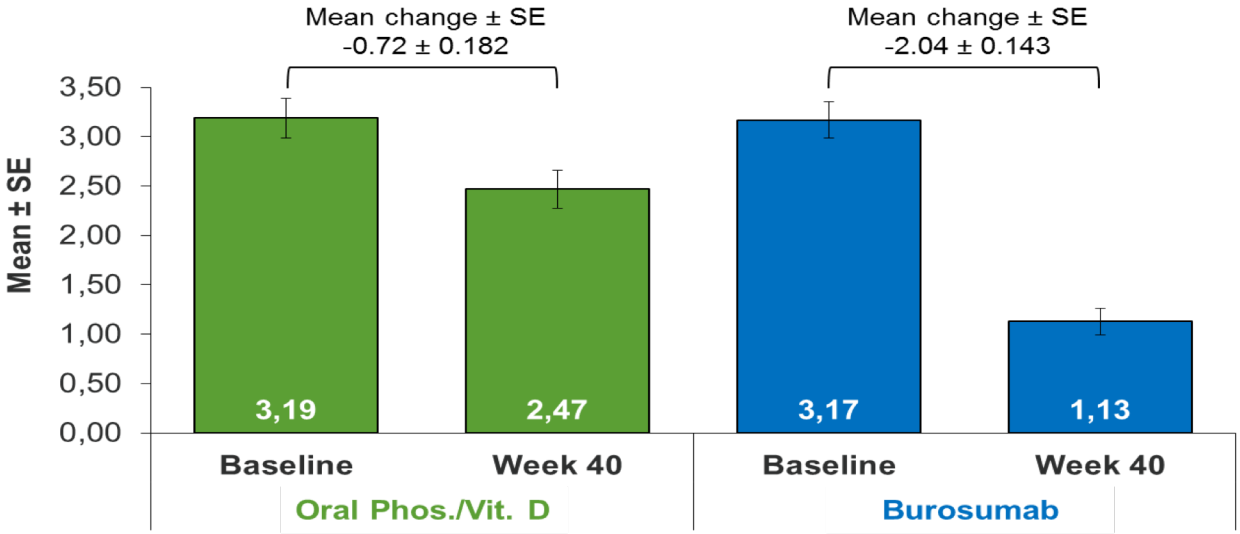


Score 1.0 Score 2.0

1. Thacher T *et al. J Trop Pediatr* 2000;46:132
2. Ultragenyx Pharmaceutical, Inc. UX023-CL201 Compilation of Radiographs for assessment of efficacy

Burosumab versus Conventional Treatment in Children with XLH

UX023-CL301: RSS Total Assessed by Blinded Readers



	Oral Phos./ Vit. D	Burosumab
LS mean change ± SE	-0.71 ± 0.138	-2.04 ± 0.145
Difference (95% CI) Burosumab-Oral Phos./Vit. D	-1.34 (-1.74, -0.94)	
P-Value[a]	<0.0001	

[a]ANCOVA model includes treatment and baseline age stratification as factors and baseline RSS as a covariate
LS = least square mean (mean estimate from a linear model being less sensitive for missing data)

Nilsson O.: FC10.1 , 57th ESPE Meeting, Athens, Greece, 27-29. September 2018

Imel EA et al. Lancet 2019; 393:2416-2427

Medizinische Hochschule Hannover

Guideline will be updated in 2021/22

Current approach in 2021 in most European Centers:
„First line treatment of children with XLH (age > 12 mo.)
either with Burosumab or phosphate/vitamin D depending on the availability“

CONSENSUS STATEMENT

OPEN

EVIDENCE-BASED GUIDELINE

Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia

Dieter Haffner[1,2], Francesco Emma[3], Deborah M. Eastwood[4,5], Martin Biosse Duplan[6,7,8], Justine Bacchetta[9], Dirk Schnabel[10], Philippe Wicart[8,11,12], Detlef Bockenhauer[13], Fernando Santos[14], Elena Levtchenko[15], Pol Harvengt[16], Martha Kirchhoff[17], Federico Di Rocco[18], Catherine Chaussain[6,7,8], Maria Louisa Brandi[19], Lars Savendahl[20], Karine Briot[8,12,21,22], Peter Kamenicky[8,23,24], Lars Rejnmark[25] and Agnès Linglart[8,24,26,27]*

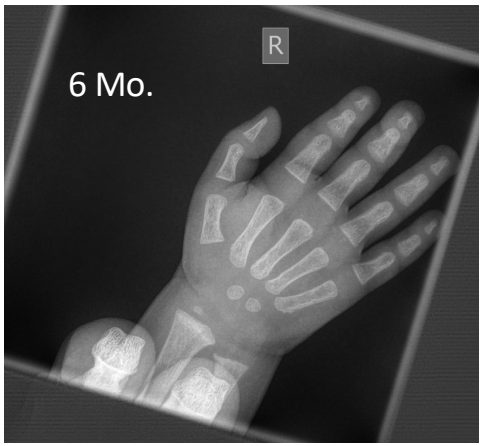
Abstract | X-linked hypophosphataemia (XLH) is the most common cause of inherited phosphate wasting and is associated with severe complications such as rickets, lower limb deformities, pain, poor mineralization of the teeth and disproportionate short stature in children as well as hyperparathyroidism, osteomalacia, enthesopathies, osteoarthritis and pseudofractures in adults. The characteristics and severity of XLH vary between patients. Because of its rarity, the diagnosis and specific treatment of XLH are frequently delayed, which has a detrimental effect on patient outcomes. In this Evidence-Based Guideline, we recommend that the diagnosis of XLH is based on signs of rickets and/or osteomalacia in association with hypophosphataemia and renal phosphate wasting in the absence of vitamin D or calcium deficiency. Whenever possible, the diagnosis should be confirmed by molecular genetic analysis or measurement of levels of fibroblast growth factor 23 (FGF23) before treatment. Owing to the multisystemic nature of the disease, patients should be seen regularly by multidisciplinary teams organized by a metabolic bone disease expert. In this article, we summarize the current evidence and provide recommendations on features of the disease, including new treatment modalities, to improve knowledge and provide guidance for diagnosis and multidisciplinary care.

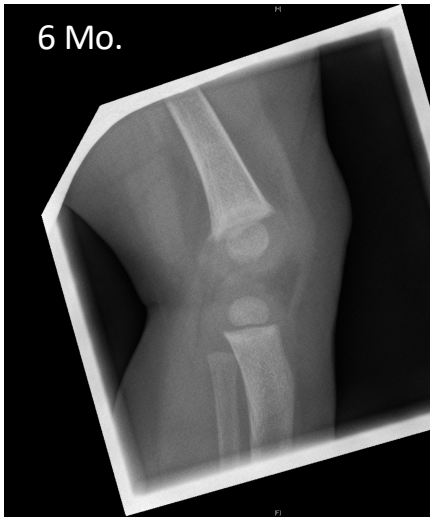
XLH, *PHEX* gene mutation, female

- Age at diagnosis: 0.1 years (father - XLH)
- Age at start of conventional treatment: 0.2 years

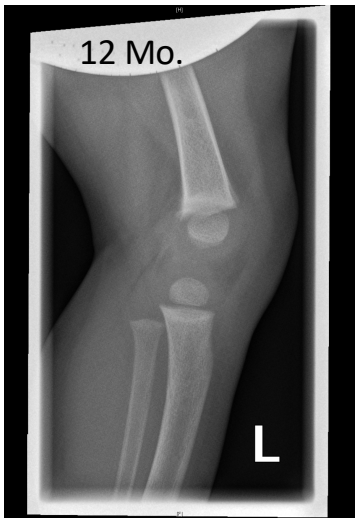
Case report

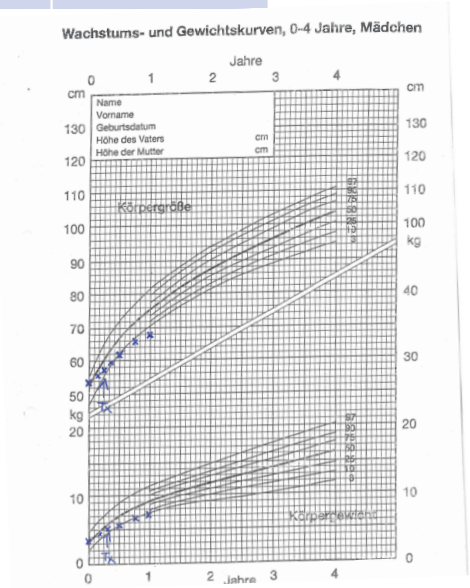
Age (years)	0.1	0.25	0.4	0.6	0.8	1.1
P (mmol/L)	**1.31** (N 1,2-2,1)	1.30 (N 1,2-2,1)	1.07 (N 1,2-2,1)	1.02 (N 1,2-2,1)	1.11 (N 1,1-1,95)	**1.01** (N 1,1-1,95)
AP (U/L)	**169** (N 143-543)	348 (N 134-508)	468 (N 134-508)	429 (N 133-499)	373 (N 128-464)	**375** (N 125-400)
PTH (ng/ml) (N 15-65)	**25**	34	31	37	71	**40**
TRP (N>85)	**85%**		83%			**78%**
TmP/GFR (mmol/l) (N>1.2)	**1.0**		1.0			**0.8**
$U_{Ca/crea}$ (mol/mol) (N<1)	**0.93**	0.58	0.51	0.84	0.18	0.58
P (mg/kg/die)	-	20	20	26	30	Stopped
1 alpha (microg)	-	0.2	0.2	0.4	0.5	2 wk. before





Tibia-deformities
Pain

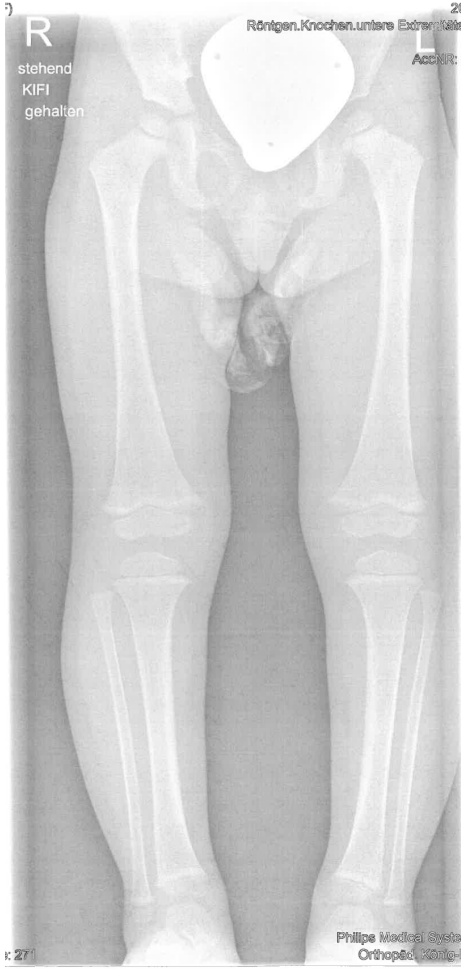


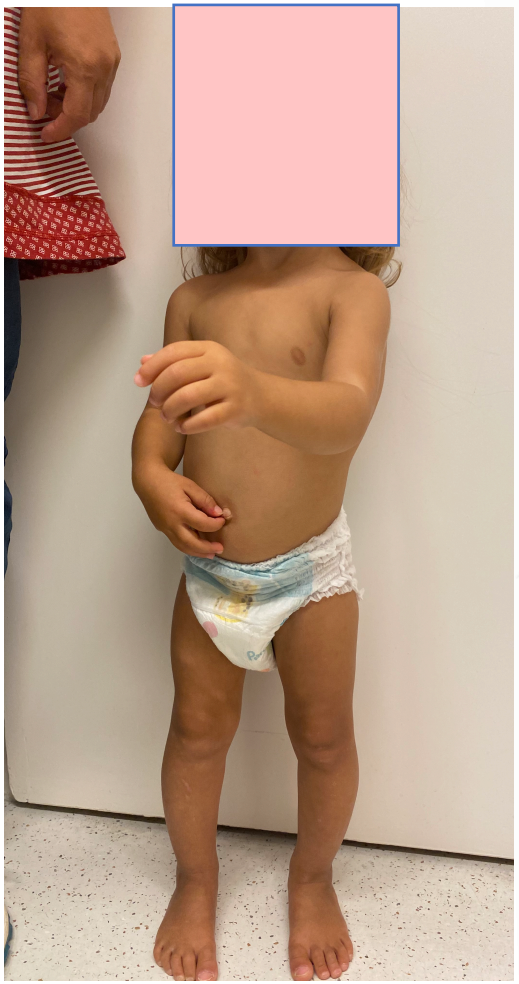


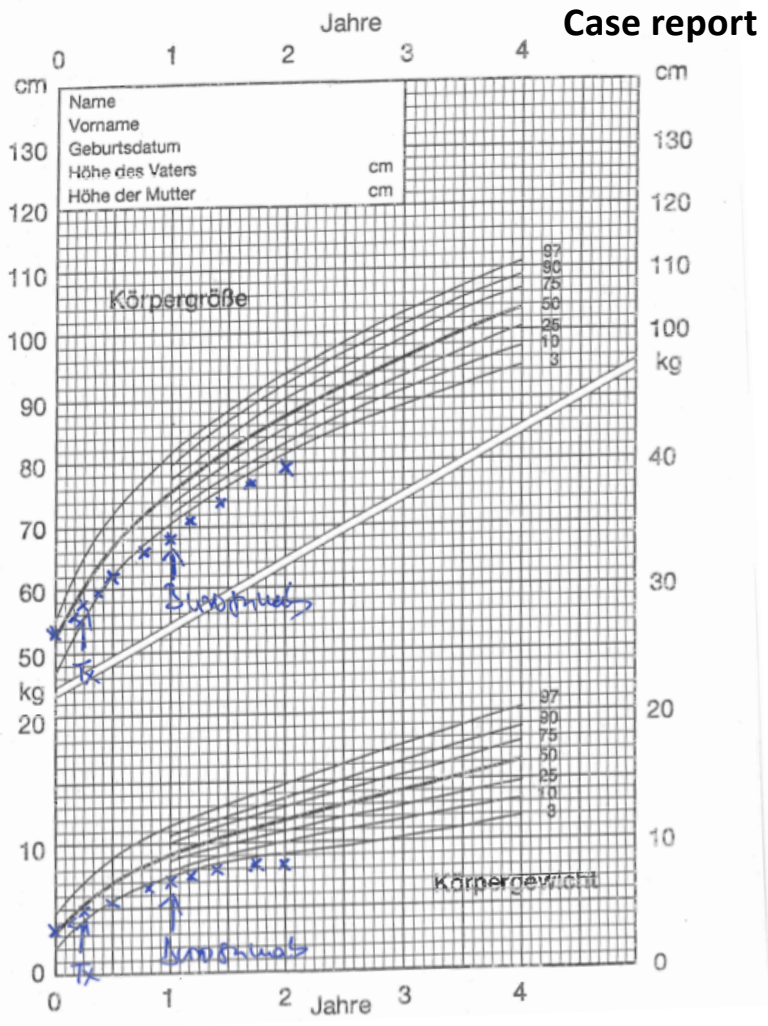
Case report

Age (years)	1.13	1.25	1.40	1.60	1.75	2.0
P (mmol/L)	1,27 (N 1.1-1.95)	1.39 (N 1.1-1,95)	1.33 (N 1.1-1,95)	1.28 (N 1.1-1.95)	1.37 (N 1.1-1.95)	**1.36** (N 1.1-1.95)
AP (U/L)	361 (N 124-433)	374 (N 123-425)	289 (N 123-418)	301 (N 121-404)	266 (N 120-392)	**195** (N 117-349)
PTH (ng/ml) (N 15-65)	38	42	39	56	32	**28**
TRP (N > 85%)	93%	95%	95%	91%	99%	**94%**
TmP/GFR (mmol/l) (N>1.25)	1.25	1.29	1.28	1.27	1,30	**1.31**
$U_{Ca/Krea}$ (mol/mol) (N<1)	0.24	0.30		0.10	0.23	0.19
1,25 Vit. D (pg/ml) (N 47-151)	103				125	**143**
Burosumab (mg/kg)	0.4	0.65	0.62	0.85	0.91	**1.02**

Case report


R
stehend
KIFI
gehalten
Röntgen.Knochen.untere Extrem
Philips Medical Syste
Orthopäd. Klinik




Jahre
0 1 2 3 4
cm
Name
Vorname
Geburtsdatum
Höhe des Vaters cm
Höhe der Mutter cm
Körpergröße
97
90
75
50
25
10
3
130
120
110
100
90
80
70
60
50
kg
20
10
0
kg
40
30
20
10
0
Körpergewicht
Jahre

Growth on burosumab treatment in XLH patients aged 1-4 years

Prior conventional treatment in 13/13 patients (mean duration 16 months)

	Value
Age, years	2·9 (1·2; 1·2–4·9)
Sex	
Male	9 (69%)
Female	4 (31%)
Race	
White	12 (92%)
African American	1 (8%)
Weight Z score	–0·97 (1·16)
Height Z Score	–1·4 (1·2)
Serum phosphorus, mmol/L	0·81 (0·09)
Serum 1,25(OH)$_2$D, pmol/L	108 (42)
Serum 25(OH)D, nmol/L	83·32 (26·36)
Total Thacher Rickets Severity Score	2·9 (1·4; 1·0–6·5)
Conventional therapy	
Received before enrolment	13 (100%)
Duration, months	16 (14; 1–40)
Age at initiation, months	20 (18; 1–54)

Data are mean (SD; range) or n (%). Reference ranges: serum phosphorus, 1·03–1·97 mmol/L; 1,25(OH)$_2$D, 72–287 pmol/L; and 25(OH)D, none reported.

Table 1: **Baseline characteristics**

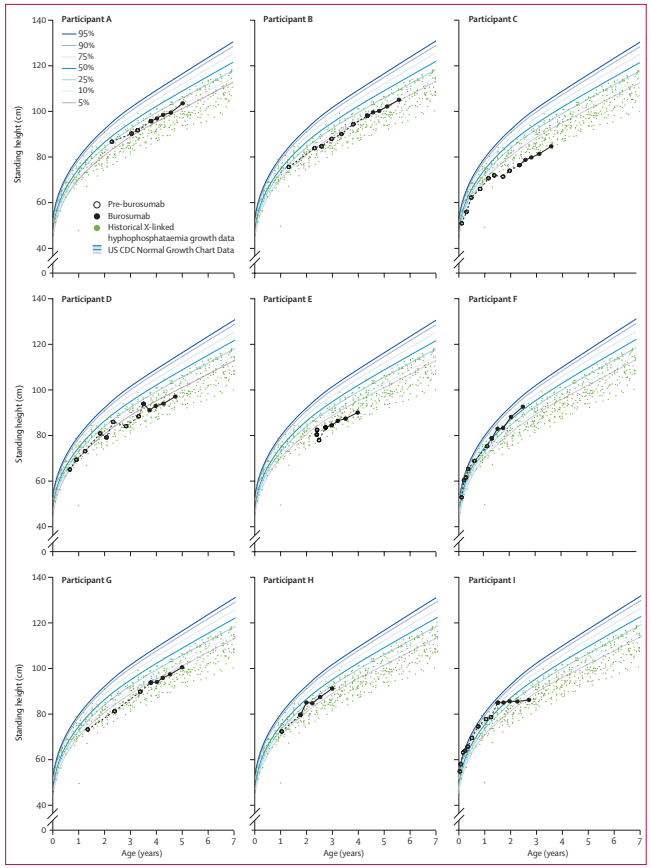


Figure 4: **Individual changes for the nine boys treated with burosumab**
Individual growth data for the nine boys in this study. To smoothly transition recumbent length data to standing height, the reference curves for recumbent length from the CDC and this study were reduced by 0·8 cm, as per CDC guidelines.[21] CDC=US Centers for Disease Control and Prevention.

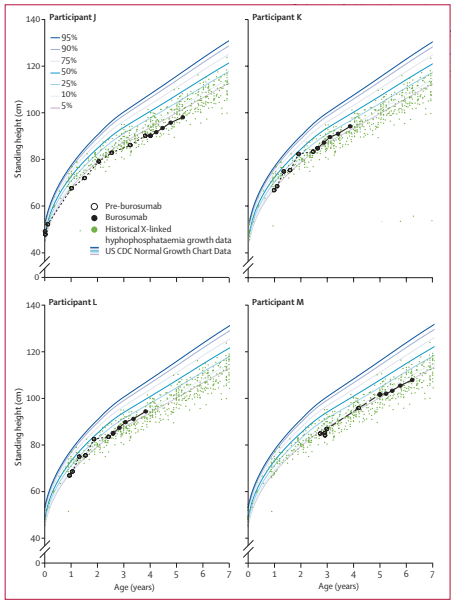


Figure 5: **Individual changes for the four girls treated with burosumab**
Individual growth data for the four girls in this study. To smoothly transition recumbent length data to standing height, the reference curves for recumbent length from the CDC and this study were reduced by 0·8 cm, as per CDC guidelines.[21] CDC=US Centers for Disease Control and Prevention.

Mean height

- Baseline -1.38 SDS (18th percentile)
- 40 weeks -1.65 SDS (13th percentile)
- 64 weeks -1.64 SDS (13th percentile)

Growth on burosumab treatment in XLH patients aged 5-12 years

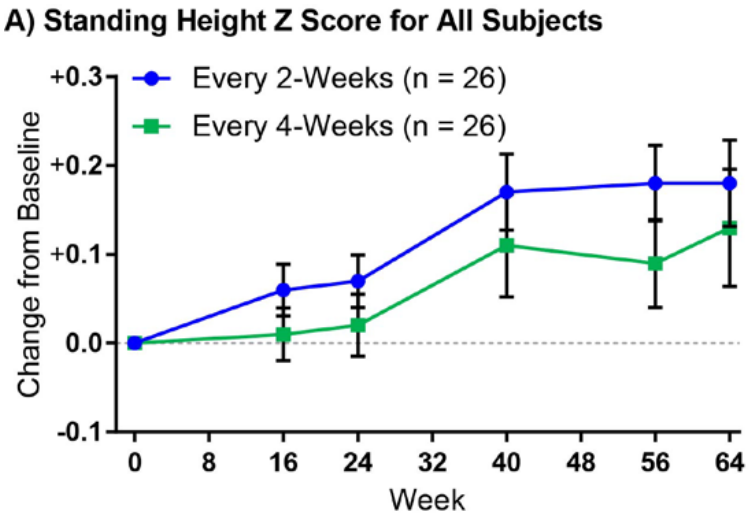
Prior conventional treatment in 96% of patients (mean duration 6.9 years)

Table 1. Demographic and Baseline Clinical Characteristics.*

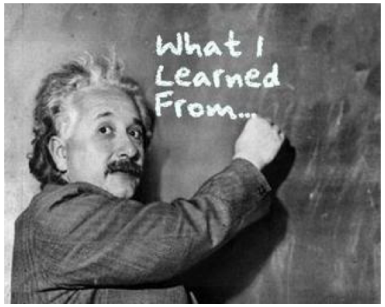
Characteristic	Burosumab Every 2 Weeks (N=26)	Burosumab Every 4 Weeks (N=26)	All Patients (N=52)
Age — yr			
Mean	8.7±1.7	8.3±2.0	8.5±1.9
Range	5–12	5–12	5–12
Male sex — no. (%)	12 (46)	12 (46)	24 (46)
White race — no. (%)†	23 (88)	23 (88)	46 (88)
Weight — kg	31.9±7.9	29.1±10.7	30.5±9.4
Standing height			
z Score	−1.7±1.0	−2.1±1.0	−1.9±1.00
Percentile for age and sex	11.1±13.8	6.2±8.2	8.7±11.5

Table 2. Effects of Burosumab on Height, Physical Functioning, and Patient-Reported Outcomes.

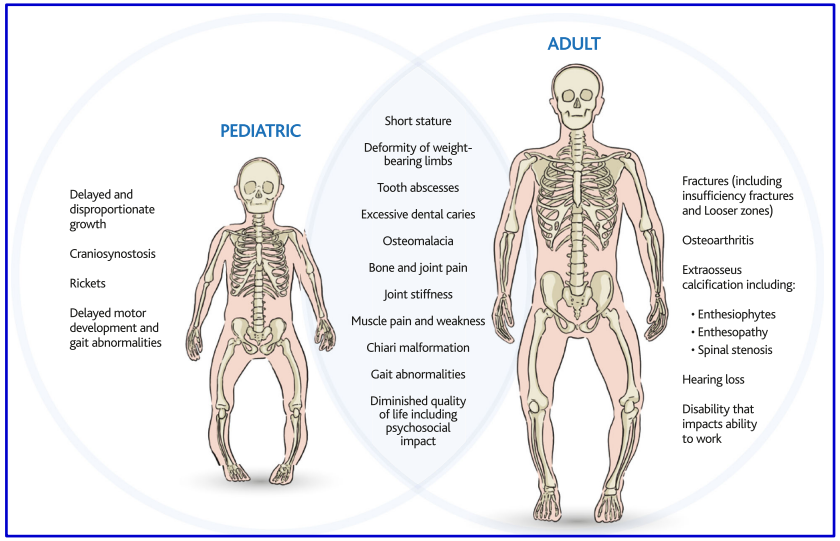
Assessment	Burosumab Every 2 Weeks (N=26)	Burosumab Every 4 Weeks (N=26)	All Patients (N=52)
Standing-height z score*			
Baseline	−1.72±1.03	−2.05±0.96	−1.89±1.00
Week 64	−1.54±1.13	−1.92±0.84	−1.73±1.00
Change from baseline	0.19±0.05	0.12±0.06	0.15±0.04



Conclusions



- **Correct diagnosis of XLH matters**
- Symptomatic treatment:
  - does not cure the disease
  - has limitations and side effects
- Challenges:
  - growth
  - bone deformities
  - recurrent dental infections
  - adherence



- Burosumab is more effective than conventional treatment in children with XLH with respect to healing of rickets and physical functioning (growth?, teeth?, QoL?, enthesopathy?)
- Important to collect the natural history of disease => prospective registries

Thank you for your attention!

Next Webinars

ERKNet Advanced Webinars on Rare Kidney Disorders

Date: **21 September 2021**

Speaker: **Aude Servais**

Topic: **Cystinosis – adult view**

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **05 October 2021**

Speaker: **Martin Konrad**

Topic: **Bartter and Gitelmann syndromes**

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **19 October 2021**

Speaker: **Gema Ariceta**

Topic: **Claudin-related disorders**

Subscribe the ERKNet and IPNA Newsletter and don`t miss Webinars!