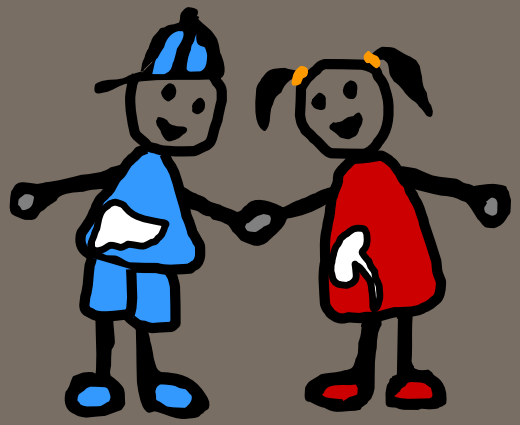
Management of X-linked hypophosphatemic rickets in children and adults

ERKNet
The European Rare Kidney Disease Reference Network

Dieter Haffner
Department of Pediatric Kidney, Liver and Metabolic Diseases
Center for Rare Kidney Diseases



Medizinische Hochschule Hannover

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Disclosures

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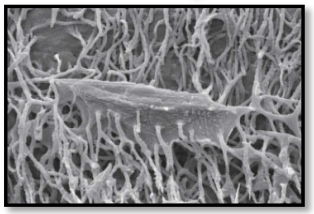
X-linked Hypophosphatemia (XLH)

(Vitamin D-resistant rickets)
(Familial hypophosphatemic rickets)

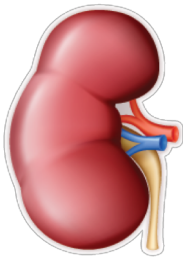
- **Most frequent inherited phosphate wasting disorder, accounting for 80% of cases**
- **Incidence of 1:20,000 individuals**
- **Rickets in infancy resistant to high-dose vitamin D** (Albright, 1937)
- **X-linked dominant inheritance** (1958)
  - NB: negative family history in close to 50% of cases
- **Evidence for humoral basis:**
  - Hypophosphatemia persists after renal transplantation (1974)
  - Kidney cross-transplantation between WT & HYP mice (1992)
- **Caused by mutations in the *PHEX* gene** (1995)
- **Associated with high plasma FGF23 concentrations** (2003)

In XLH excess of FGF23 impairs renal phosphate and vitamin D metabolism

Osteocyte



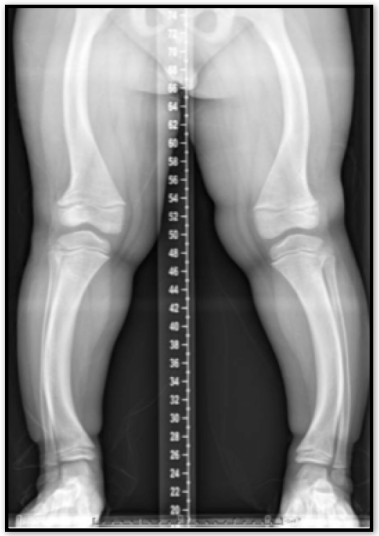
↑ FGF23 secretion



↓ Phosphate transport
↓ Vitamin D production

Diagnosis:
PHEX mutation

- Rickets (↑AP)
- ↓TmP/GFR
- 25(OH)D normal
- +/- pos. family history

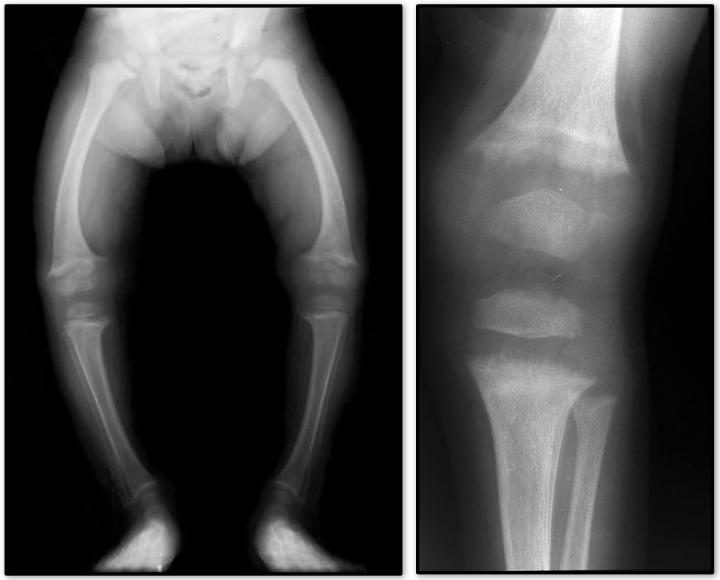


↓ Serum $1,25(OH)_2D$

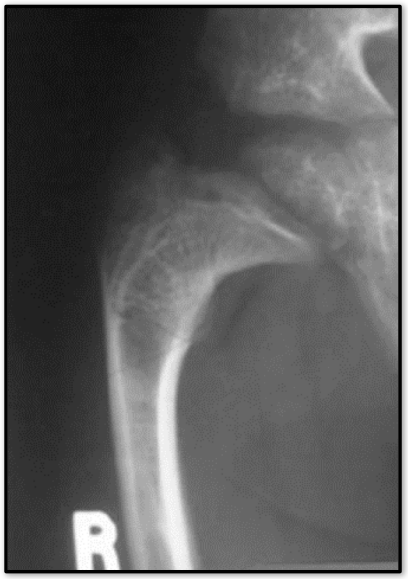
↑ Phosphaturia

↓ Serum Pi

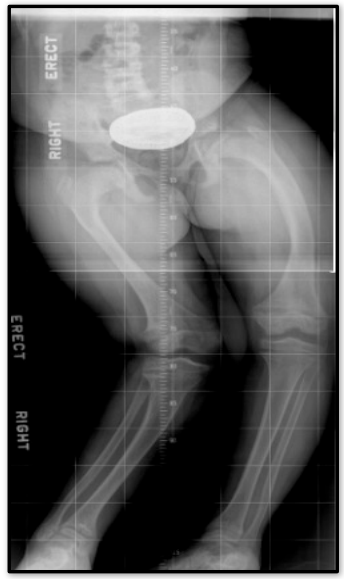
Clinical features of XLH: Rickets and bone deformities



Thick growth plates
Widened knee joints
Wide based gait



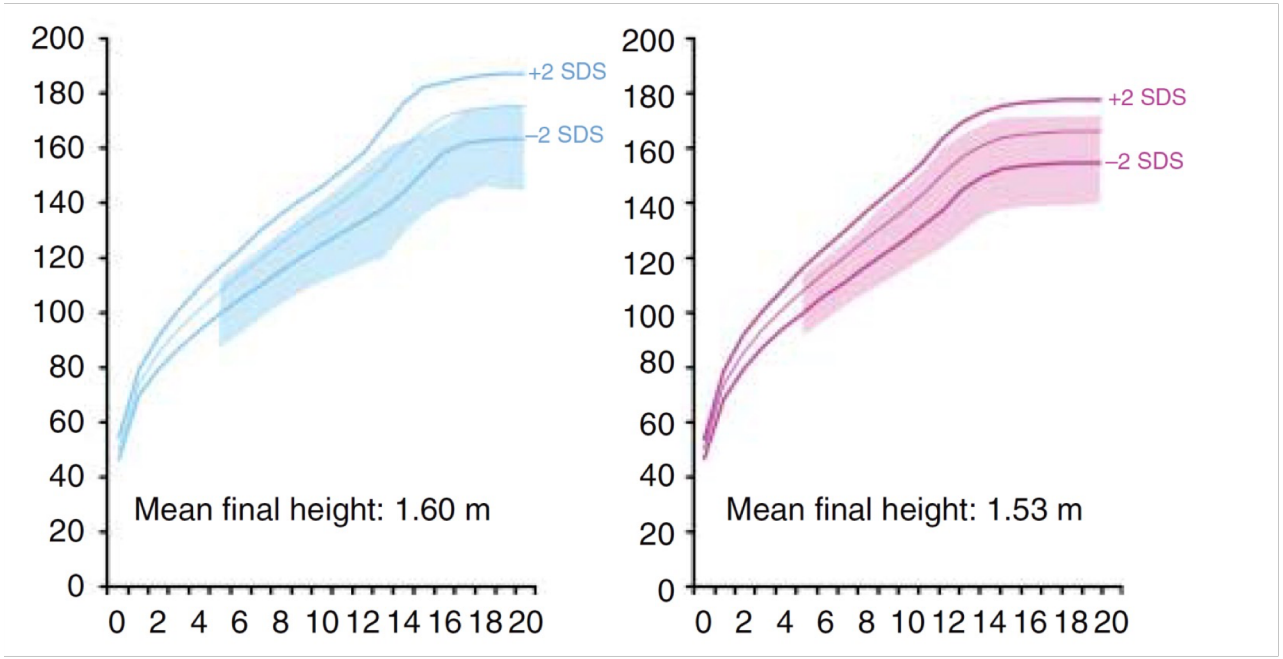
Coxa vara



Genu varus/valgus

Clinical features of XLH: growth retardation

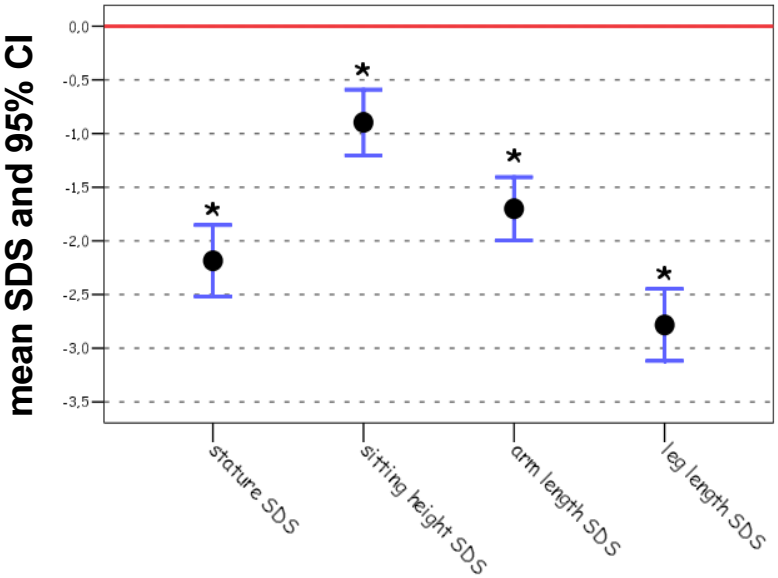
Height < -2.0 SDS in 40% of
“well controlled“ French XLH patients



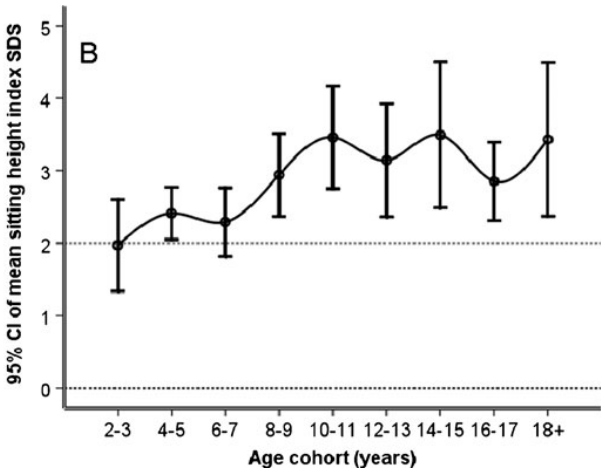
Clinical features of XLH: disproportional growth

German XLH patients on conventional therapy (n=89)

Linear body dimensions



Sitting height index (= body proportions)

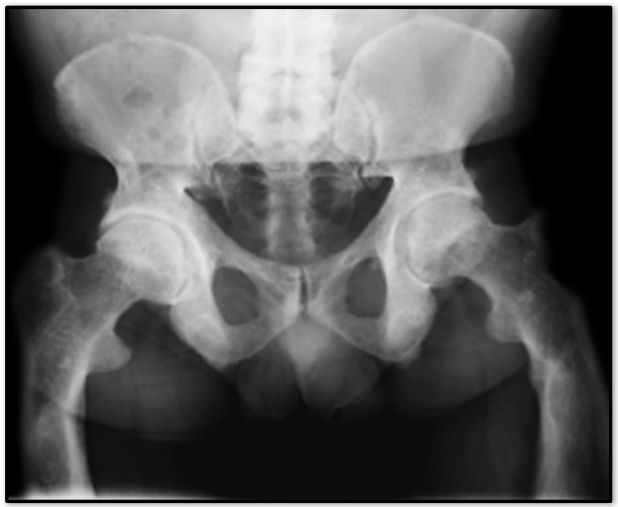


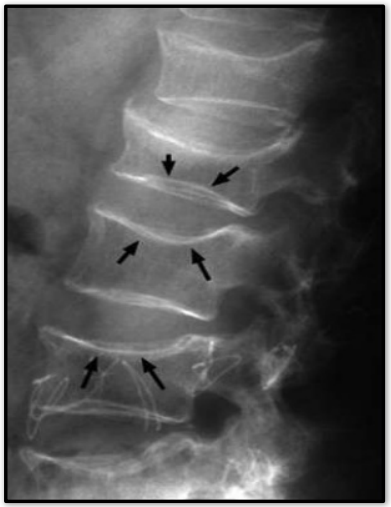
= p<0.001, XLH vs. healthy children

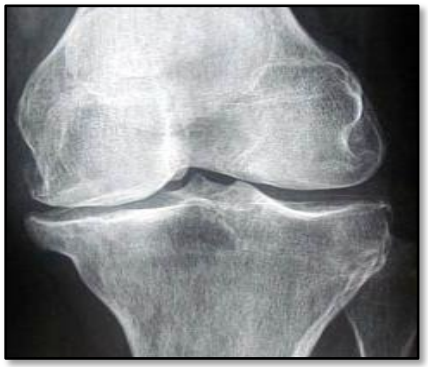
Clinical features of XLH: osteomalacia

Defective mineralization
Bone pain
Pseudofractures (in adults)

Clinical features of XLH: degenerative osteoarthropathy





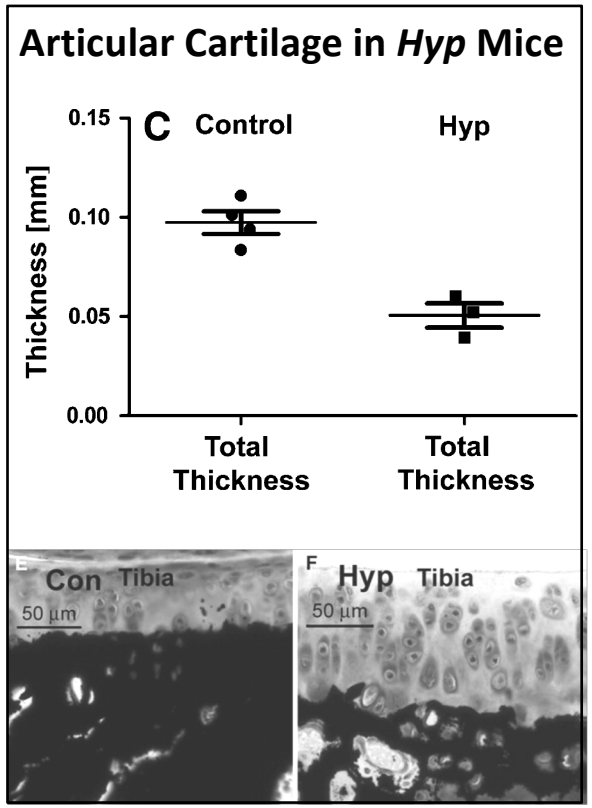


Adults: Ankles 68%

Knee 63%

Sacroiliac 40%

Misalignment & cartilage defect



Liang. Calcif Tiss Int 2011

Clinical features of XLH: enthesopathy

(calcification of tendons & ligaments)

Adults:

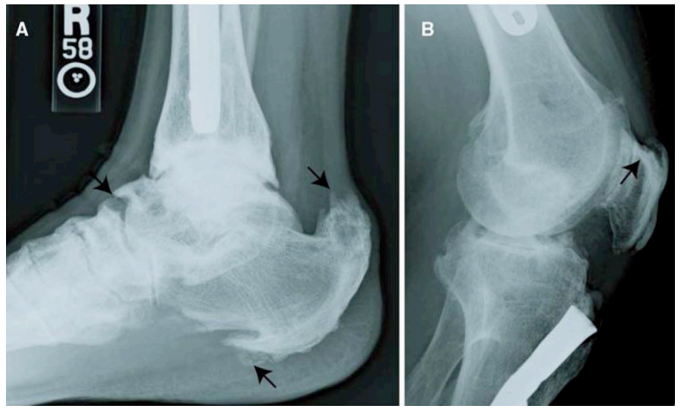
Ankles 74%

Knee 56%

Pelvis 49%

Spine 41%

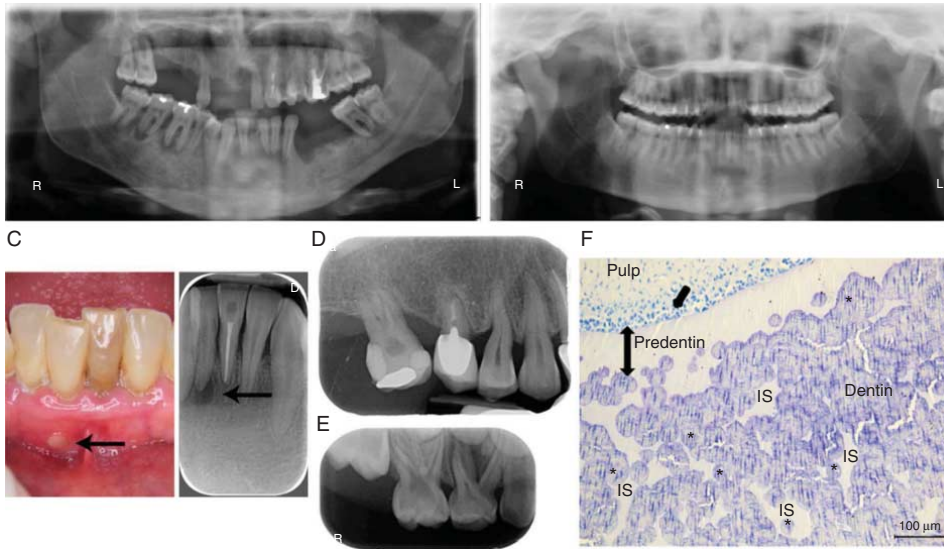
Elbow, hand, shoulder 8-28%



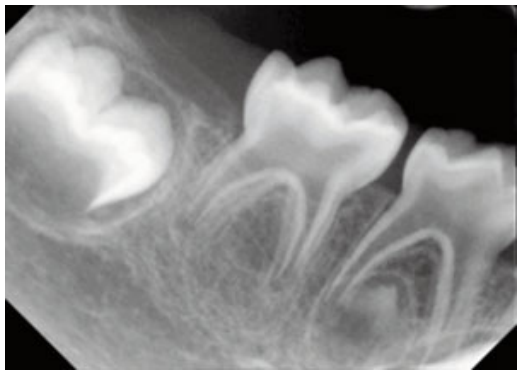
Liang. Calcif Tiss Int 2009

Does not respond to conventional treatment

Clinical features of XLH: tooth abscesses



Agnes Linglart et al, Endocrine Connections 2014



Hypomineralized dentin
Enamel hypoplasia, microdefects
Enlarged pulp chambers

Clinical features of XLH: other symptoms and complications

Craniosynostosis

Chiari malformation

Syringomyelia

Weight gain

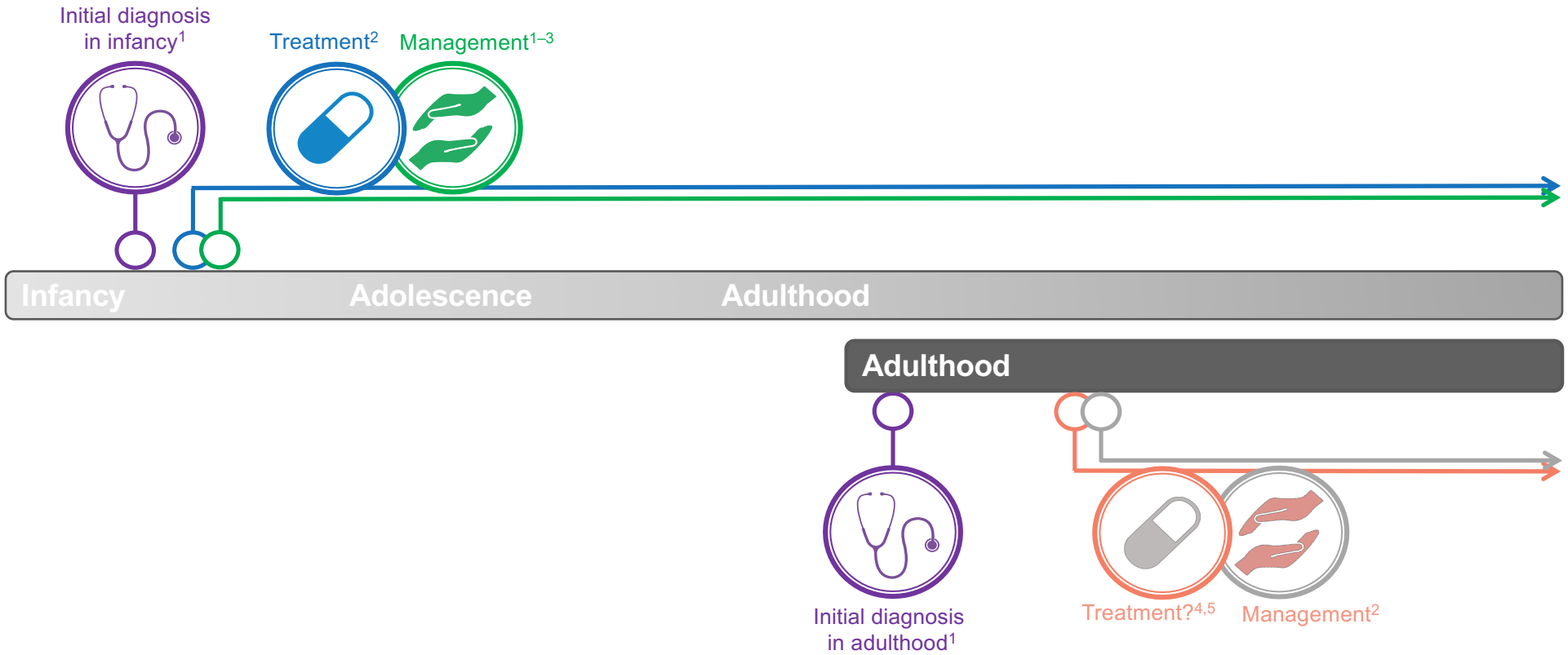
Craniosynostosis

Chiari type I malformation

Spinal stenosis, syringomyelia

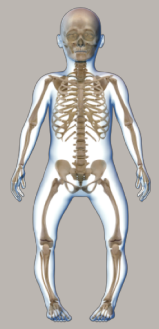
Hearing loss, tinnitus, vertigo

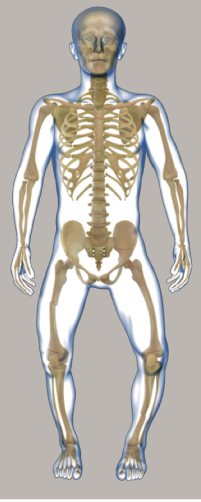
XLH requires lifelong management



Linglart *et al. Endocr Connect* 2014; Carpenter *et al. J Bone Miner Res* 2011
Connor *et al. J Clin Endocrinol Metab* 2015

XLH requires management from a range of specialists

Paediatric patients	Paediatric and adult patients	Adult patients
Rickets	Disproportionate short stature	Pseudofractures
Delayed growth	Lower extremity deformity	
Craniosynostosis	Tooth abscesses	Osteoarthritis
	Dental caries	
	Osteomalacia	Extraosseus calcifications Including • Osteophytes • Enthesopathy • Spinal stenosis
	Bone pain	
	Joint pain and stiffness	
	Muscle pain	
	Muscle weakness	
	Chiari malformation	Hearing loss



Functional limitations and quality of life

Delayed walking	Gait abnormalities	Disability that impacts ability to work
	Walking device use	
	Diminished quality of life	

Symptomatic treatment

Symptomatic treatment:

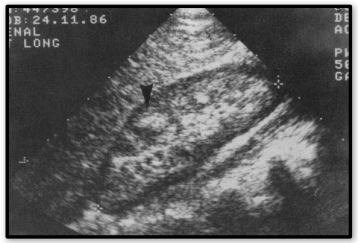
- Oral phosphorus supplements
- Active vitamin D analogues

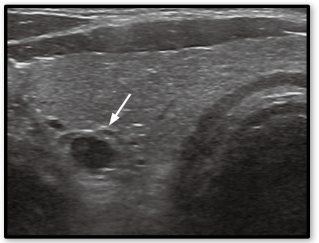
Goals:

- Healing of rickets (AP ≤ 1.5 ULN, improvement of clinical & radiological signs)
- Growth within the lower normal range
- Pain control

Side effects:

- Nephrocalcinosis (30-70%)
- Hyperparathyroidism





Early treatment is associated with better outcome

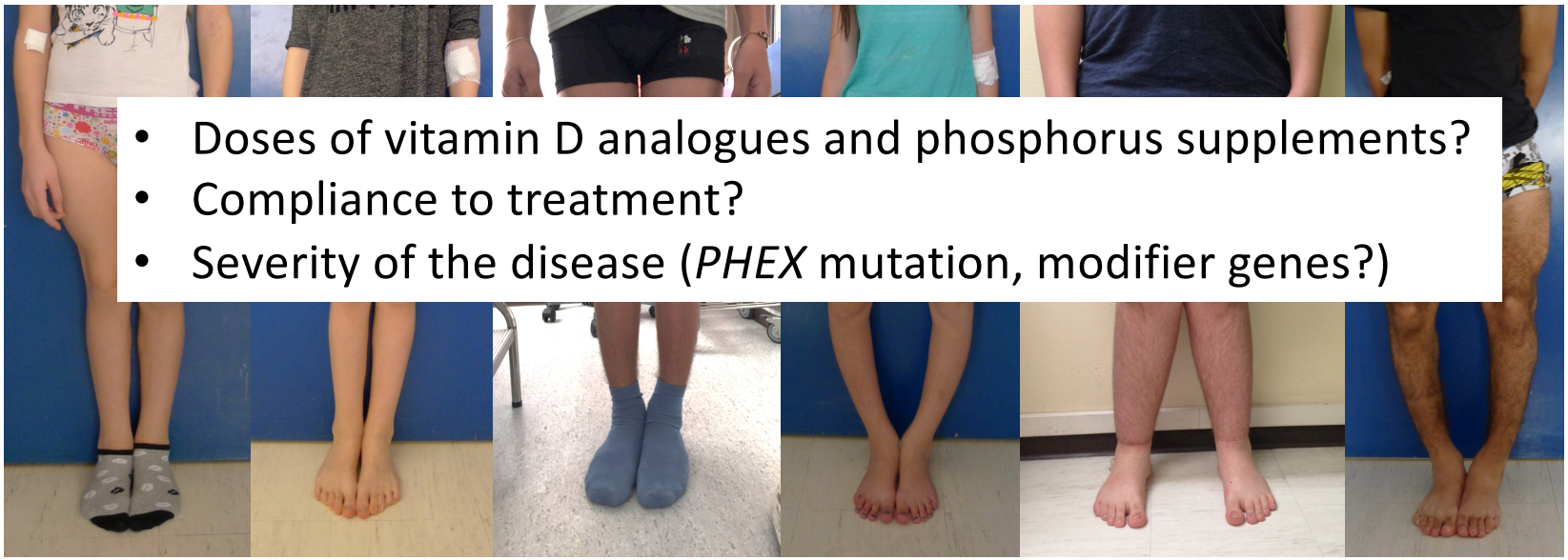
Linglart et al, Endocrine Connections 2014; Carpenter et al, J Bone Min Res 2011
Haffner & Waldegger, Pediatric Kidney Disease 2017; Verge et al, NEJM 1991

Limitations of symptomatic treatment

- **Improves symptoms, but does not cure the disease**
- Variable response among patients
- Risk of side effects
- Promotes a vicious circle:
  both Pi supplementation and active vitamin D stimulate FGF23 serum levels

Bone deformities: need for corrective surgery

	Diagnosis	5 years	10 years	Near adult height
	N=90	N=68	N=58	N=41
Corrective leg surgery	3.3%	3%	6.9%	**31.7%**



- Doses of vitamin D analogues and phosphorus supplements?
- Compliance to treatment?
- Severity of the disease (*PHEX* mutation, modifier genes?)

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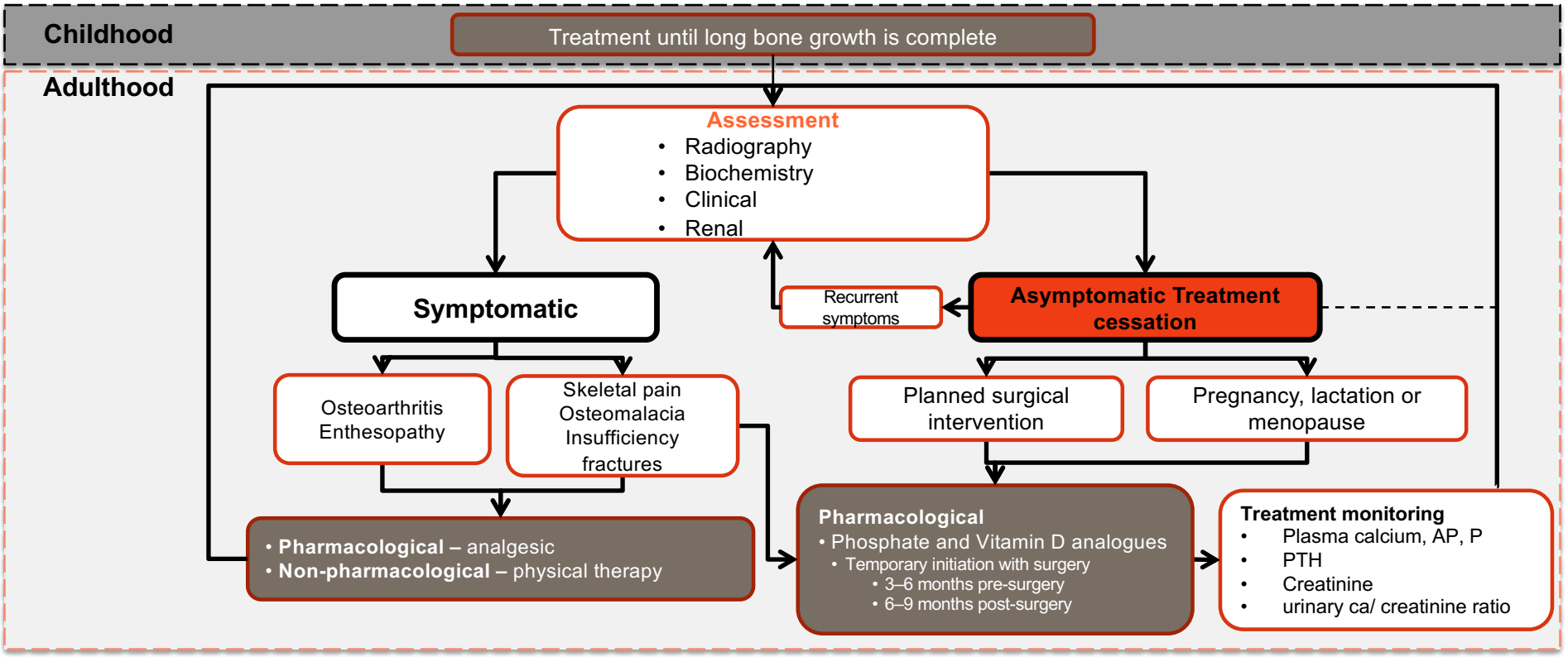
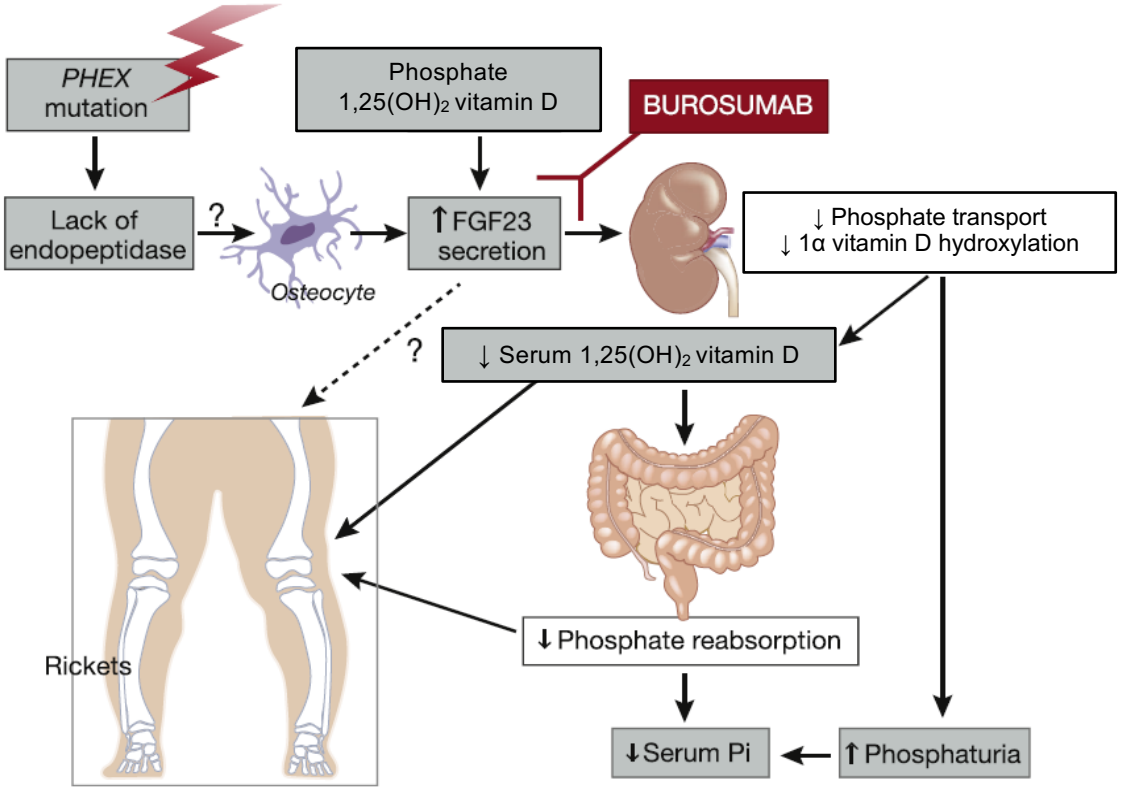
Treatment strategies for adult XLH patients



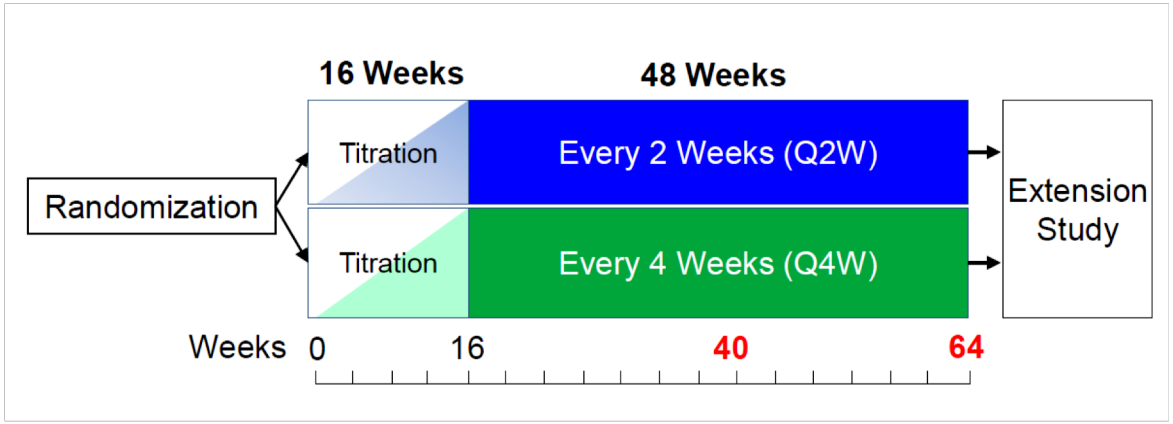
1. **Haffner & Waldegger, Pediatric Kidney Disease 2017**
2. Linglart *et al. Endocr Connect* 2014; 3. Carpenter *et al. J Bone Miner Res* 2011;26:1381
4. Skrinar *et al*. Poster SAT-244. Presented at ENDO 2015, San Diego, USA
5. Sullivan *et al. J Clin Enocrinol Metab* 1992;73:879; 6. Che *et al. Eur J Endocrin* 2016;174:325

Burosumab inhibits serum FGF23



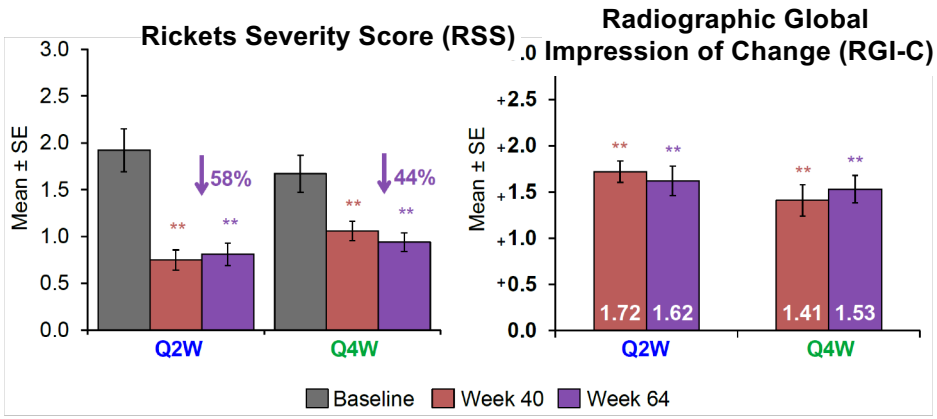
Burosumab for the treatment treatment of XLH

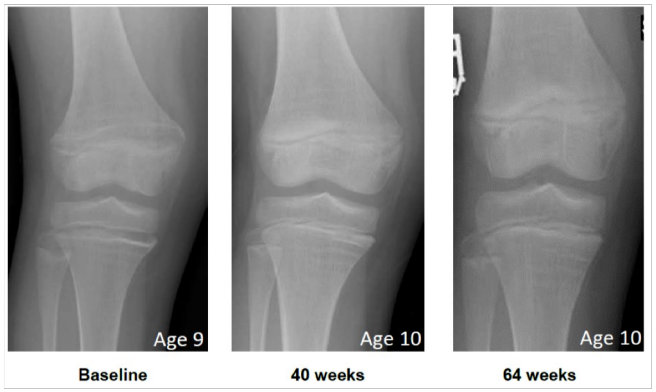
- 52 children (5-12 years) with severe XLH
- 92% (burosumab group) and 100% (controls) being on conventional treatment over a mean period of 7 years
- Conventional treatment was stopped two weeks before start of burosumab



Carpenter T *et al. N Engl J Med* 2018, May 23

Burosumab for the treatment of XLH





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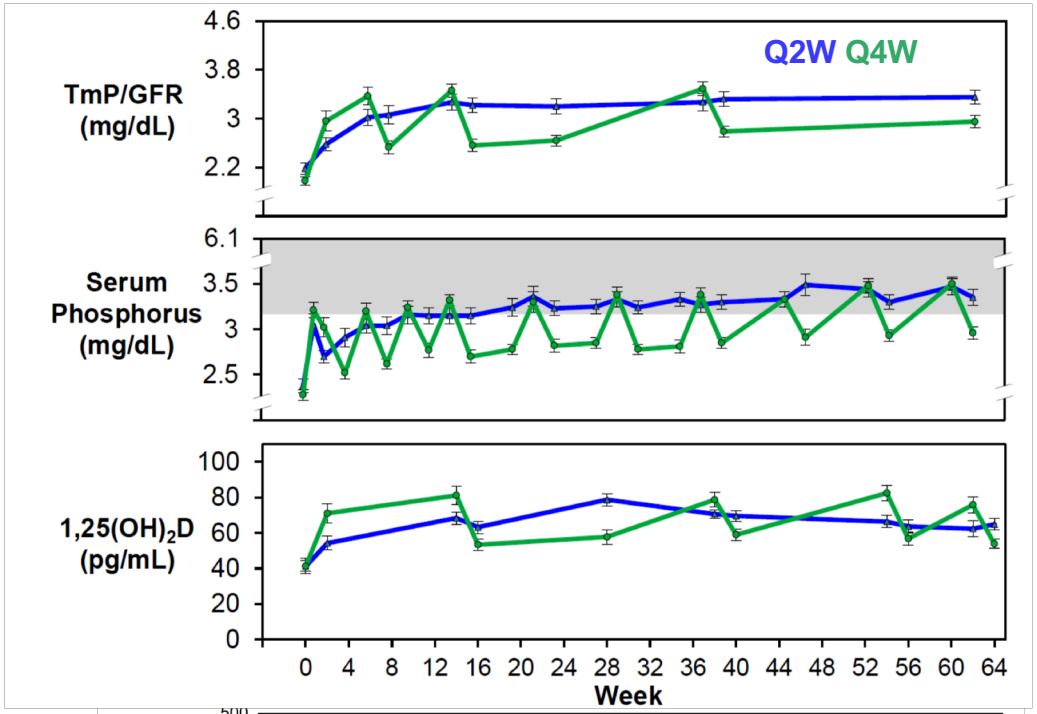

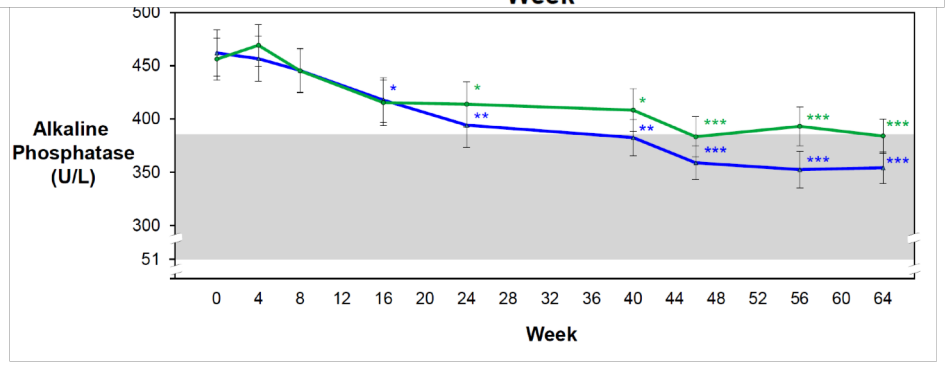

Burosumab for the treatment of XLH

XLH children aged above 1 year and adolescents with growing skeletons
if
they have radiographic evidence of overt bone disease

Conclusions

- **XLH is a severe disease with significant morbidity**
- **Requires lifelong multidisciplinary management**
- Symptomatic treatment:
  - does not cure the disease
  - has limitations and side effects
- Challenges:
  - growth
  - bone deformities
  - recurrent dental infections
  - adherence
- Burosumab is a promising treatment for XLH
- Important to collect the natural history of disease => prospective registries on treated pts.

Growth and comorbidity in children with XLH:

A prospective observational study & national/international registry

German Society for Pediatric Nephrology

German Society for Pediatric Endocrinology

Long-term outcome (conventional / burosemab treatment):

- Growth & body composition
- Musculo-skeletal system
- Teeth, kidney
- CV status
- Quality of life
- Rare complications

Anthropometry
Miroslav Zivicnjak

Ped. Nephrology
Dieter Haffner

Ped. Endocrinology
Dirk Schnabel

Study Nurse
Elene Hammer

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

Dieter Haffner[1,2], Francesco Emma[3], Deborah Eastwood[4,5], Martin Biosse Duplan[6,7], Justine Bacchetta[8], Dirk Schnabel[9], Philippe Wicart[10,11], Detlef Bockenhauer[12], Fernando Santos[13], Elena Levtchenko[14], Pol Harvent[15], Martha Kirchhoff[16], Federico Di Rocco[17,18], Catherine Chaussain[19,20], Maria Louisa Brandi[21], Lars Savendahl[22], Karine Briot[23,24], Peter Kamenicky[25,26], Lars Rejnmark[27] and Agnes Linglart[28,29,30]

[1]Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; [2]Center for Congenital Kidney Diseases, Center for Rare Diseases, Hannover Medical School, Hannover, Germany; [3]Department of Pediatric Subspecialties, Division of Nephrology, Children's Hospital Bambino Gesù – IRCCS, Rome, Italy; [4]Department of Orthopaedics, Great Ormond St Hospital for Children, Orthopaedics, London, UK; [5]Royal National Orthopaedic Hospital NHS Trust, The Catterall Unit, Stanmore, UK; [6]Dental School, Université Paris Descartes Sorbonne Paris Cité, Montrouge, France; [7]AP-HP, Department of Odontology and Reference Center for rare diseases of the metabolism of calcium and phosphorus, Nord Val de Seine Hospital (Bretonneau), France; [8]University Children's Hospital Lyon, France; [9]Center for Chronic Sick Children, Pediatric Endocrinology, Charitè, University Medicine, Berlin, Germany; [10]Necker – Enfants Malades University Hospital, Paris, France; [11]Paris Descartes University, Paris, France; [12]University College London, Centre for Nephrology and Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [13]Department of Pediatrics, Hospital Universitario Central de Asturias (HUCA), Health Service of the Principality of Asturias, SESPA, Oviedo, Spain; [14]Department of Pediatric Nephrology & Development and Regeneration, University Hospitals Leuven,–University of Leuven - KU Leuven; Leuven, Belgium; [15]RVRH-XLH, French Patient Association for XLH, Suresnes, France; [16]Phosphatdiabetes e.V., German Patient Association for XLH, Lippstadt, Germany; [17]Pediatric Neurosurgery, Hôpital Femme Mère Enfant, Centre de Référence Craniosténoses, Université de Lyon, Lyon, France; [18]Centre de Référence Craniosténoses, Neurochirurgie Pédiatrique, Hôpital Femme Mère Enfant, Université de Lyon, Bron Cedex, France; [19]Dental School, Université Paris Descartes Sorbonne Paris Cité, Montrouge, France; [20]AP-HP, Department of Odontology and Reference Center for rare diseases of the metabolism of calcium and phosphorus, Nord Val de Seine Hospital (Bretonneau), France; [21]Metabolic Bone Diseases Unit, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy; [22]Pediatric Endocrinology Unit, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden; [23]Department of Rheumatology, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; [24]INSERM UMR-1153, Paris, France; [25]APHP, Bicêtre Paris-Sud Hospital, Endocrinology Department, Reference Center for Rare Disorders of Calcium and Phosphate Metabolism; [26]Paris-Sud University, Le Kremlin-Bicêtre, France; [27]Dept. of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark; [28]APHP, Reference Center for Rare Disorders of Calcium and Phosphate Metabolism, Platform of Expertise Paris-Sud for Rare Diseases and Filière OSCAR, Bicêtre Paris Sud Hospital (HUPS), Le Kremlin-Bicêtre, France; [29]APHP, Endocrinology and diabetes for children, Bicêtre Paris Sud Hospital (HUPS), Le Kremlin-Bicêtre, France; [30]INSERM U1169, Bicêtre Paris Sud, Paris Sud - Paris Saclay University, Le Kremlin-Bicêtre, France

Haffner D *et al*. *Nat Rev Nephrol* 2019 (accepted)

Thank you for your attention !

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