



*Oktatás, kutatás,  
gyógyítás: 250 éve az  
egészség szolgálatában*

# XLH - from the past to the future

Milestones in the diagnosis and therapy of familial hypophosphatemia

George S Reusz

Department of Pediatrics

Semmelweis University

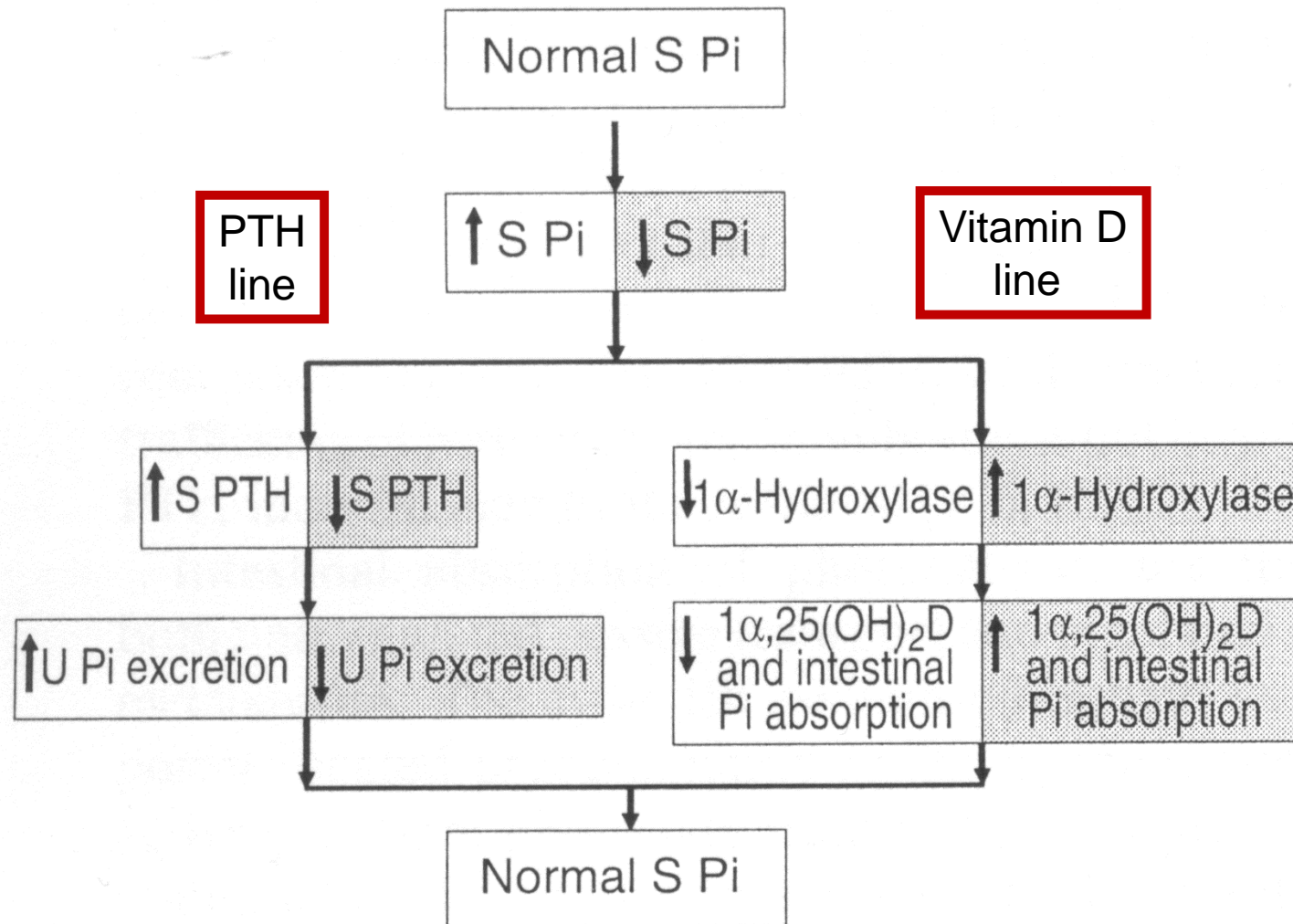
# Outline

- Classical concept of phosphate metabolism
- XLH
  - The clinical spectrum
- Conventional therapy
- Additional data
- XLH, ADHR, OOM, TC
- Unifying concept
- PHEX, FGF23 and hereditary hypophosphatemia
- A new therapy on the horizon

# Outline

- Classical concept of phosphate metabolism
- XLH
  - The clinical spectrum
- Conventional therapy
- Additional data
- XLH, ADHR, OOM, TC
- Unified concept
- PHEX, FGF23 and hereditary hypophosphatemia
- A new therapy on the horizon

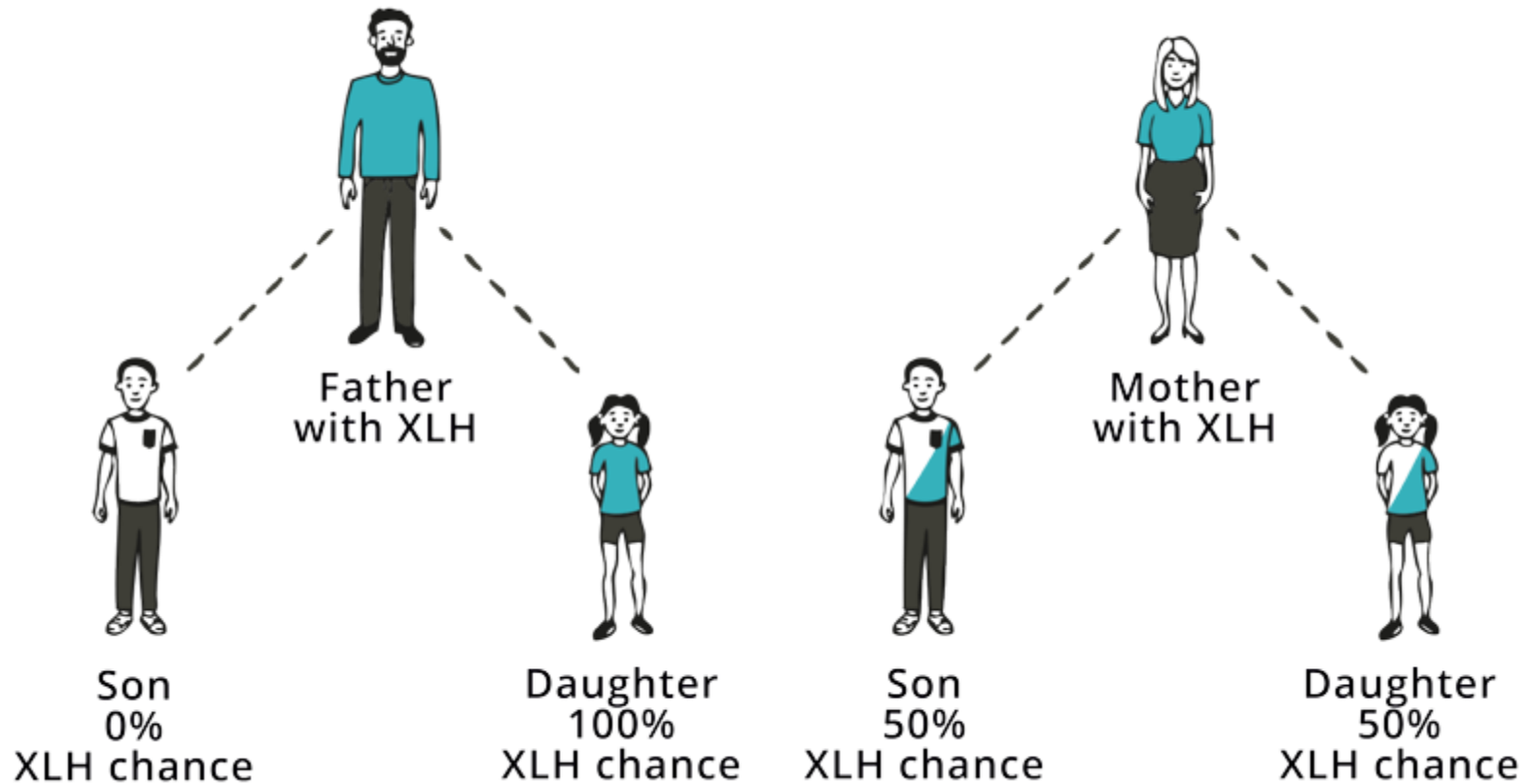
# Phosphate metabolism



# Outline

- Classical concept of phosphate metabolism
- XLH
  - The clinical spectrum
- Conventional therapy
- Additional data
- XLH, ADHR, OOM, TC
- Unifying concept
- PHEX, FGF23 and hereditary hypophosphatemia
- A new therapy on the horizon

# XLH inheritance



# XLH



## XLH

- Isolated tubular phosphate transport defect
- (= absence of other tubular transport disorders: glucose, bicarbonate, amino acids)
- Low serum P level
- Ca, PTH and 1,25 DHVD paradoxically normal
- Abnormal bone metabolism
  - Alkaline phosphatase increased
  - Rickets, disproportionate short stature, later osteomalacia

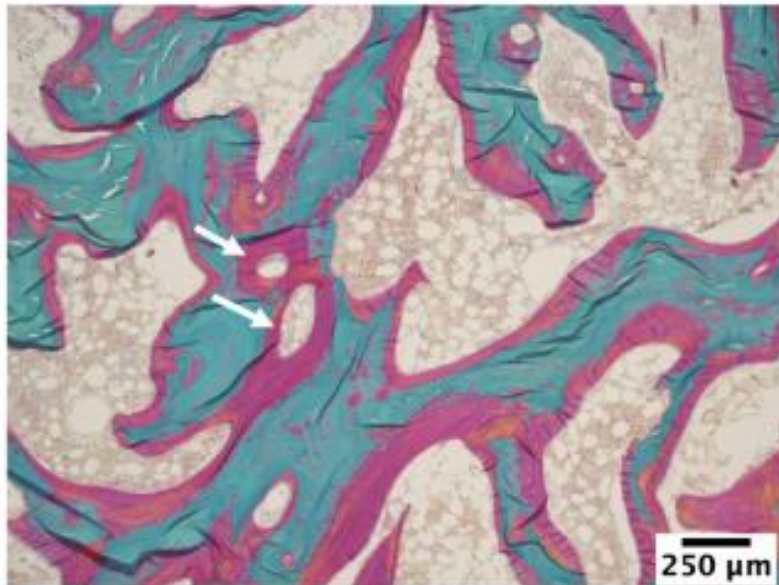


# Alterations of bone material properties in XLH

red = unmineralized matrix (i.e. osteoid), green = mineralized bone

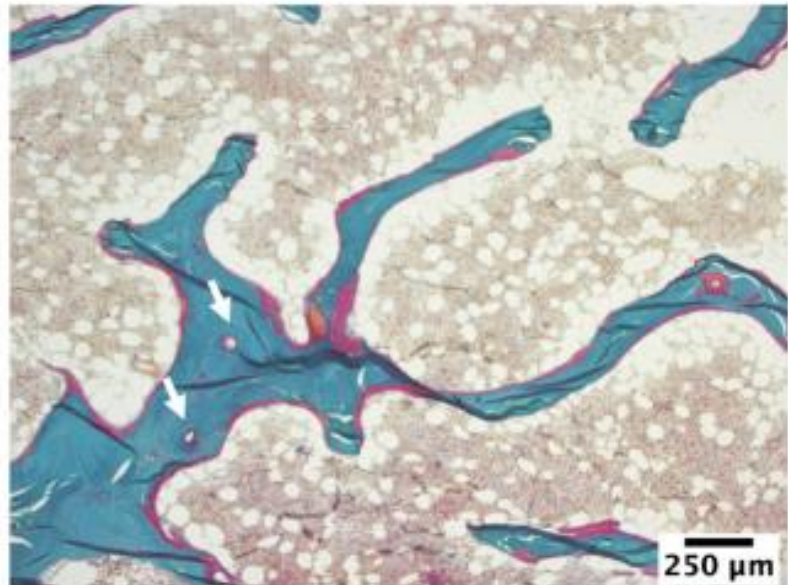
XLH non-treated

A



XLH treated

D



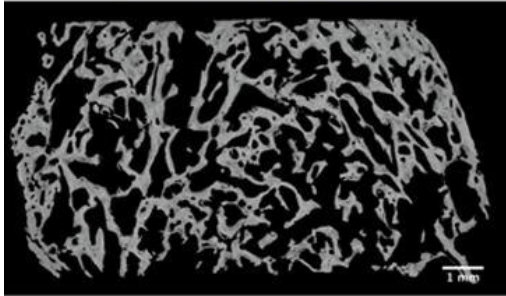
White arrows: areas of mineralized matrix containing red spots (arrow) = area of disorganized woven bone

Red: unmineralized matrix (i.e. osteoid),  
Green: mineralized bone

# XLH

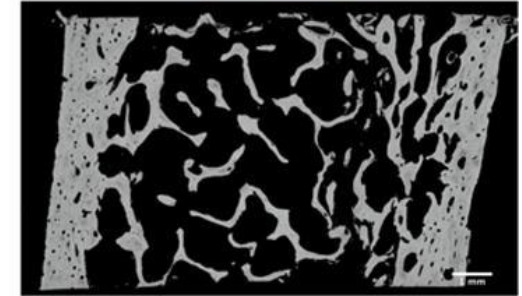
Quantitative backscattered electron imaging (qBEI)

**Late diagnosis & non-treated**

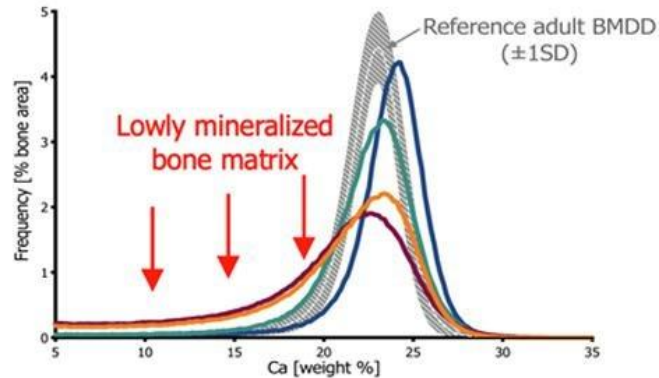


- Only broad osteoid seams ( $> 5\mu\text{m}$ )
- Large hypomineralized peri-osteocytic lesions (quantified by qBEI)

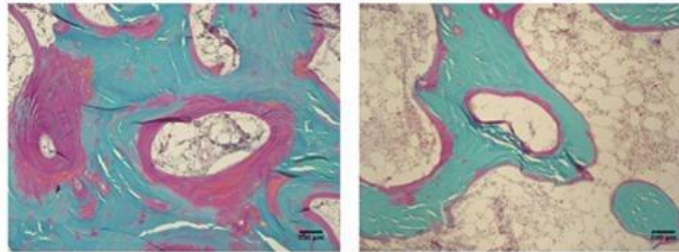
**Early diagnosis & treated**



- Mostly narrow osteoid seams ( $< 5\mu\text{m}$ )
- Smaller hypomineralized periosteocytic lesions (quantified by qBEI)



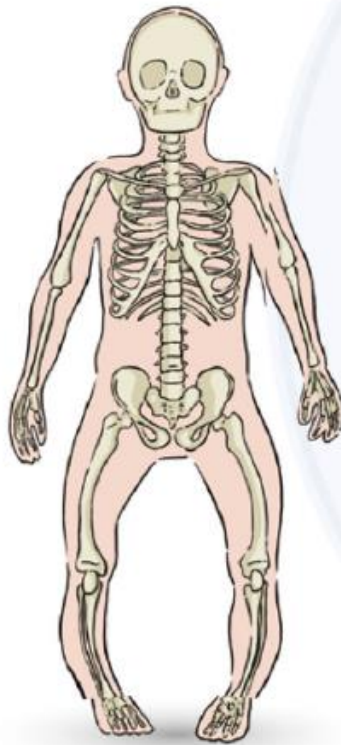
Bone histomorphometry



# XLH – not just the bones

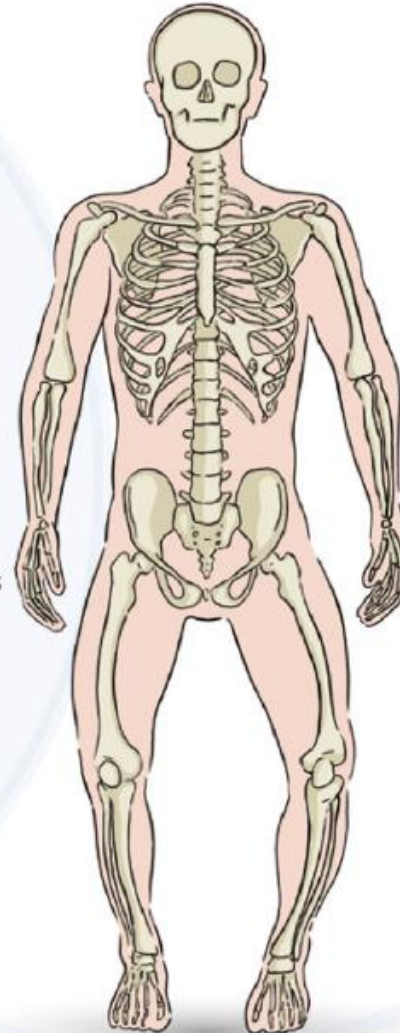
## PEDIATRIC

Delayed and disproportionate growth  
Craniosynostosis  
Rickets  
Delayed motor development and gait abnormalities



## ADULT

Short stature  
Deformity of weight-bearing limbs  
Tooth abscesses  
Excessive dental caries  
Osteomalacia  
Bone and joint pain  
Joint stiffness  
Muscle pain and weakness  
Chiari malformation  
Gait abnormalities  
Diminished quality of life including psychosocial impact

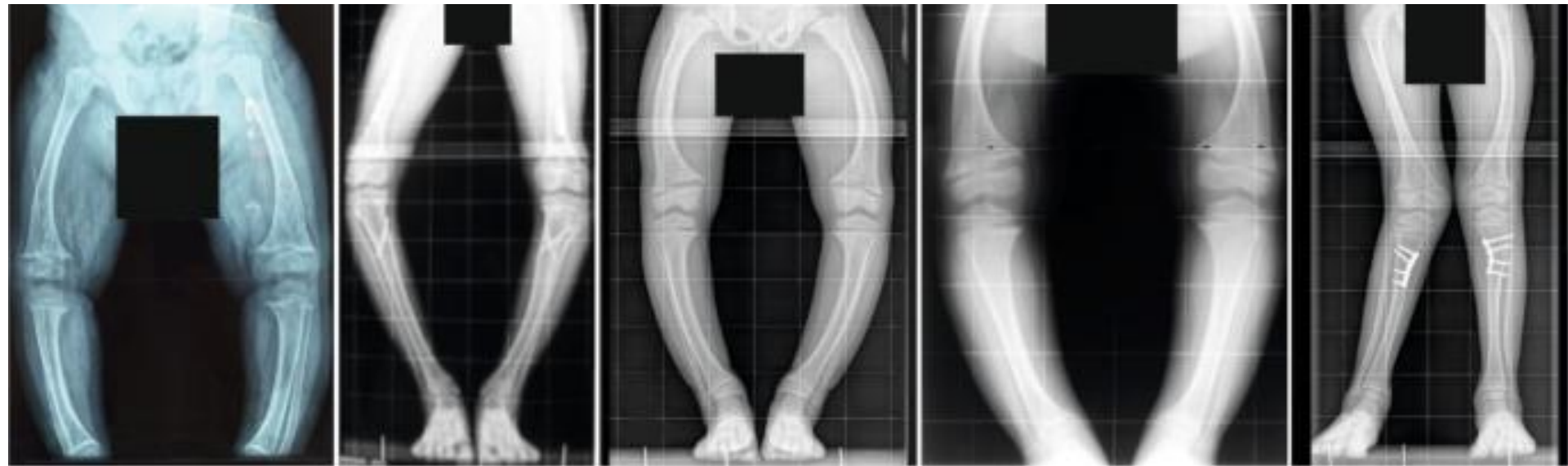


Fractures (including insufficiency fractures and Looser zones)  
Osteoarthritis  
Extraosseous calcification including:

- Enthesiophytes
- Enthesopathy
- Spinal stenosis

Hearing loss  
Disability that impacts ability to work

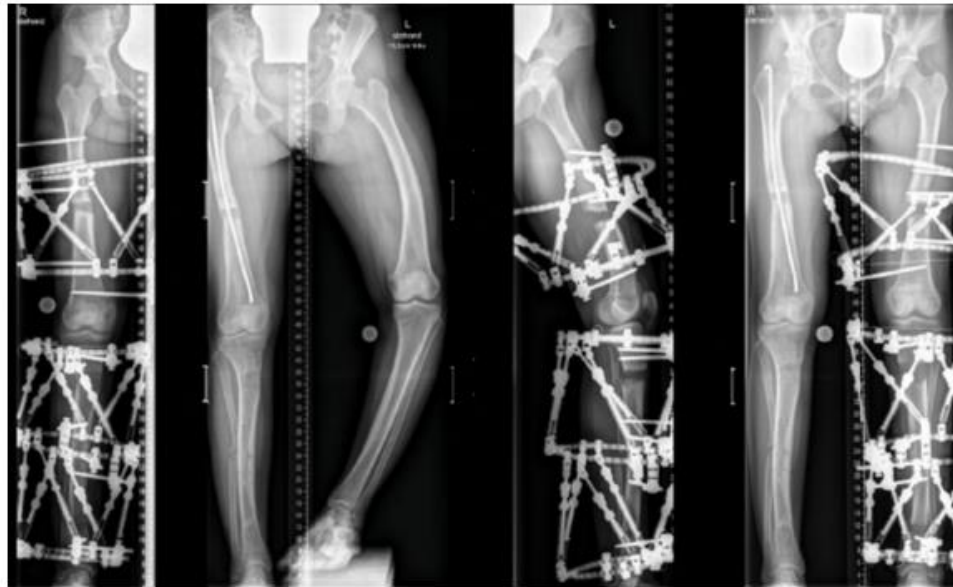
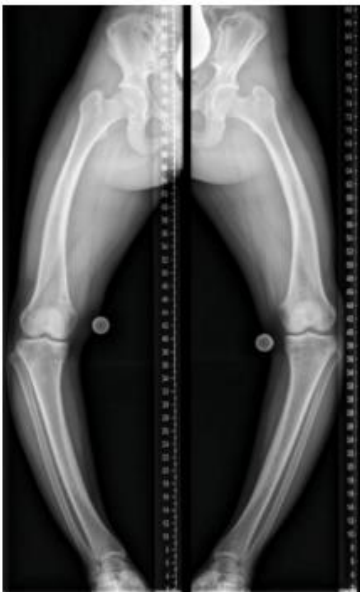
# Bone disease



Haffner D: Nat Rev Nephrol . 2019 Jul;15(7):435-455. doi: 10.1038/s41581-019-0152-5

# Interdisciplinary management of FGF23-related phosphate wasting syndromes

a Age: 16 years

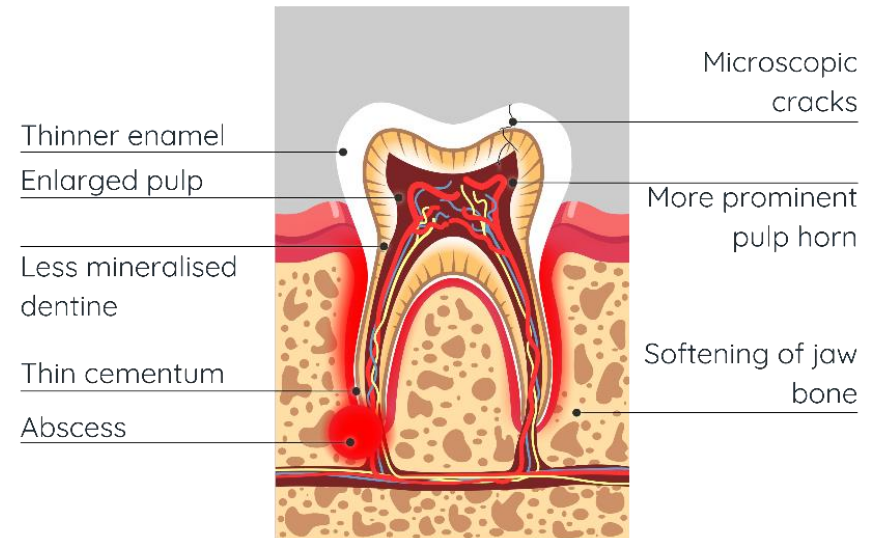
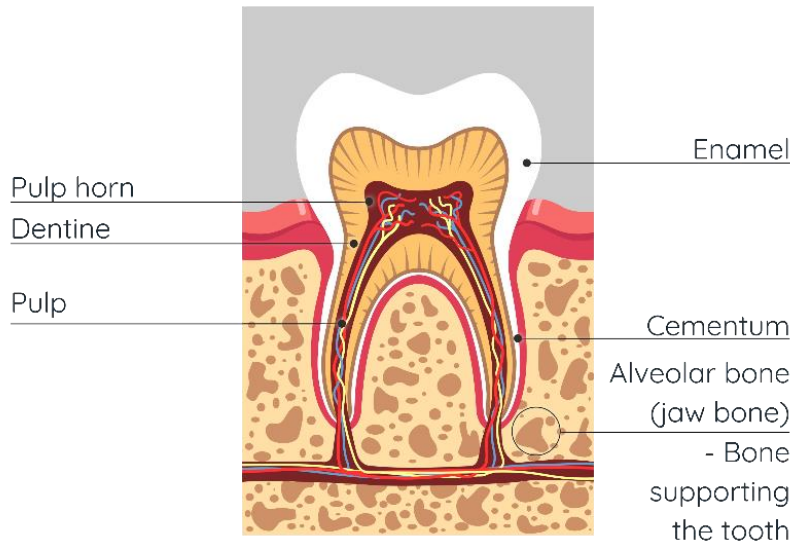


c Age: 25 years



Treombetti A et al: Nat Rev Endocrinol **18**, 366–384 (2022).  
<https://doi.org/10.1038/s41574-022-00662-x>

# Dental manifestations of XLH



Enamel covers the crown of the tooth and acts as a protective barrier; it is a highly mineralised semi-transparent layer.

The enamel is thinner and more prone to being worn down. Microscopic cracks are often present and allow bacteria to enter the pulp without the presence of cavities.

# Dental manifestations of XLH



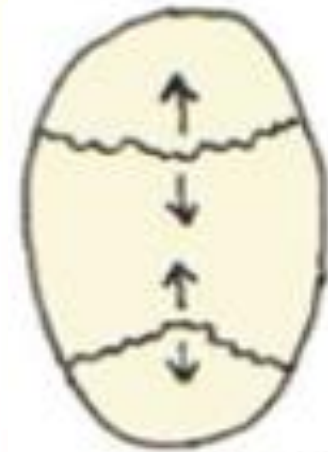
Abscess on a deciduous molar, a dental feature of XLH<sup>12</sup>



Opsahl Vital S et al: *Bone*. 2012;50(4):989-997.

[James M et al: Int J of Implant Dentistry](#)  
volume 5, Article number: 15 (2019)

# Craniosynostosis

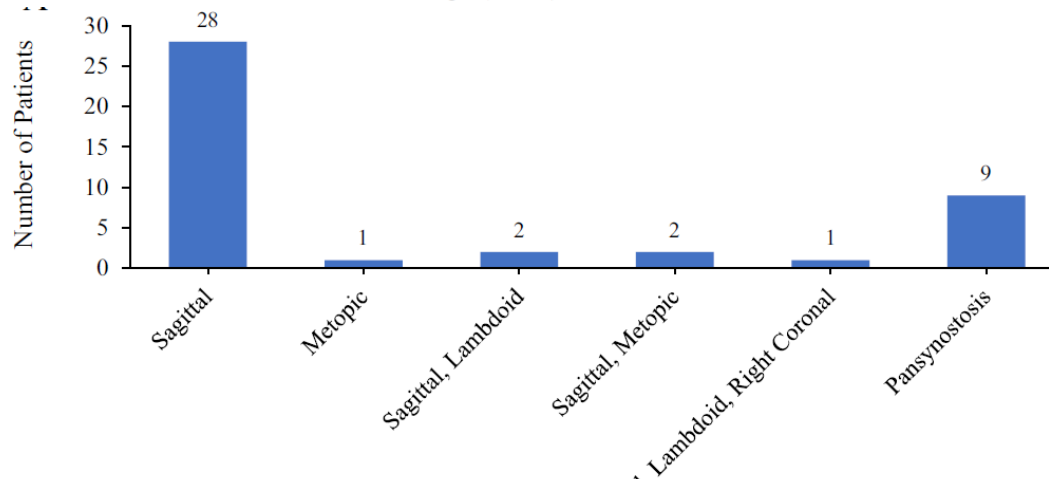
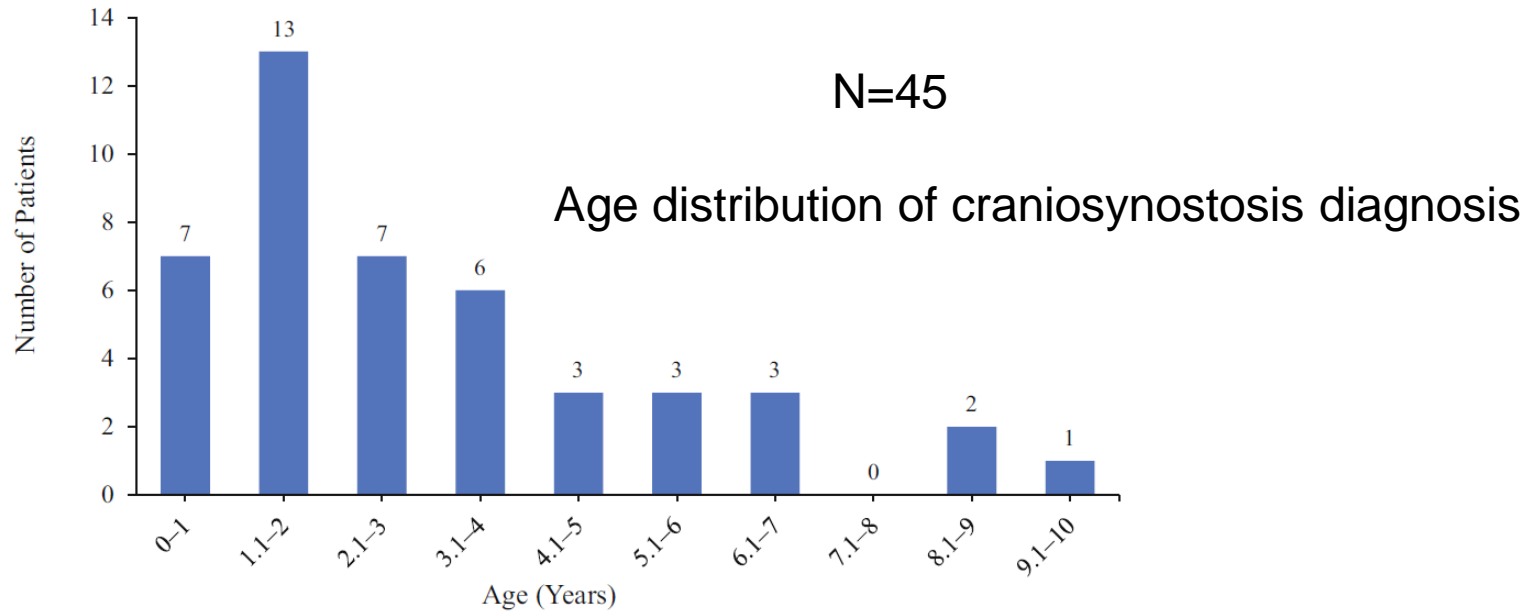


Synostotic  
scaphocephaly

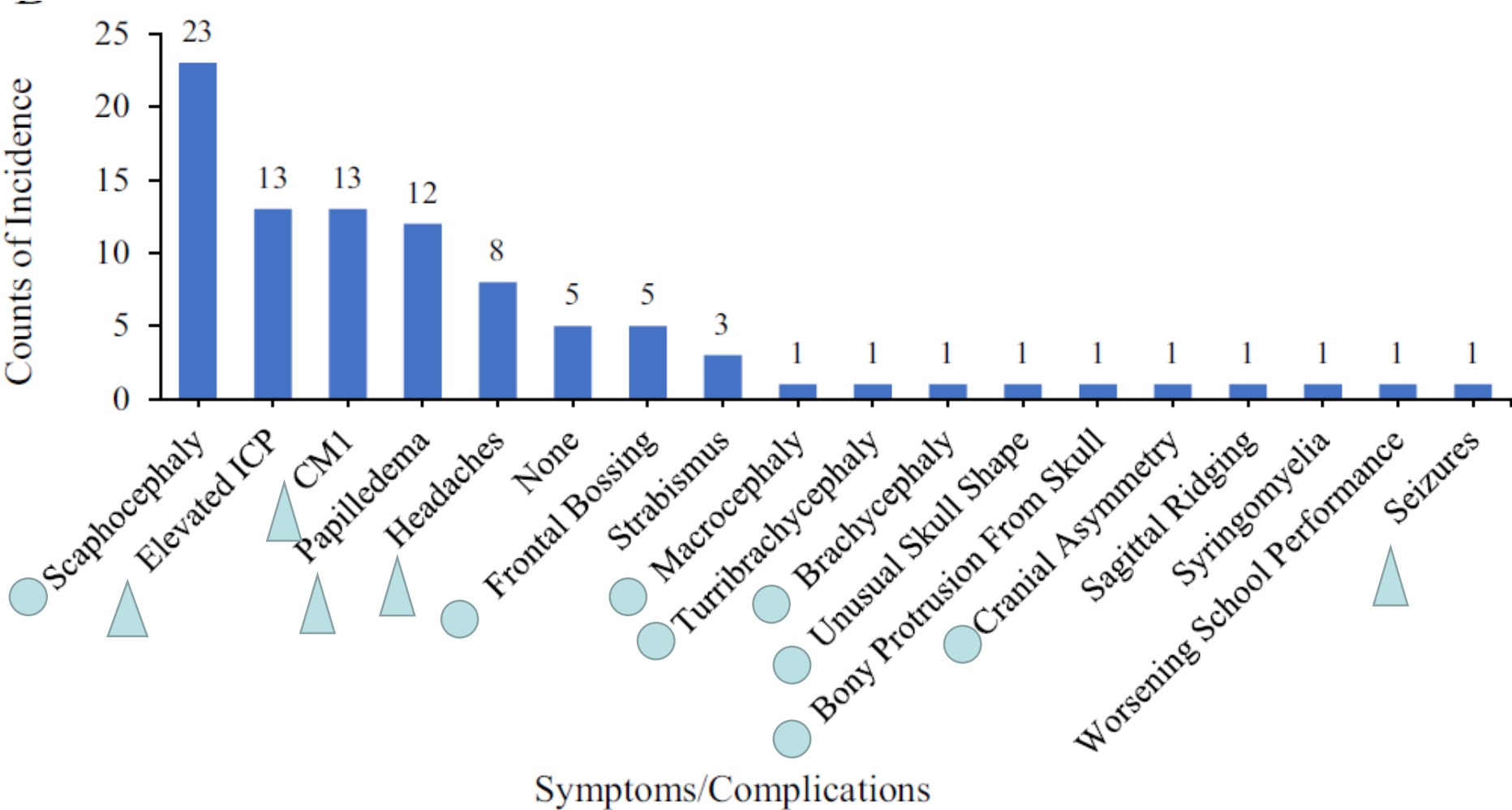
= premature fusion of the bones of the skull

# Age at diagnosis and type of craniosynostosis in XLH

Munns CF et al JBMR Plus. 2023 Mar 14;7(5):e10728. doi: 10.1002/jbm4.10728



# Clinical symptoms due to craniosynostosis in Patients With XLH



# Outline

- Classical concept of phosphate metabolism
- XLH
  - The clinical spectrum
- **Conventional therapy**
- Additional data
- XLH, ADHR, OOM, TC
- Unifying concept
- PHEX, FGF23 and hereditary hypophosphatemia
- A new therapy on the horizon

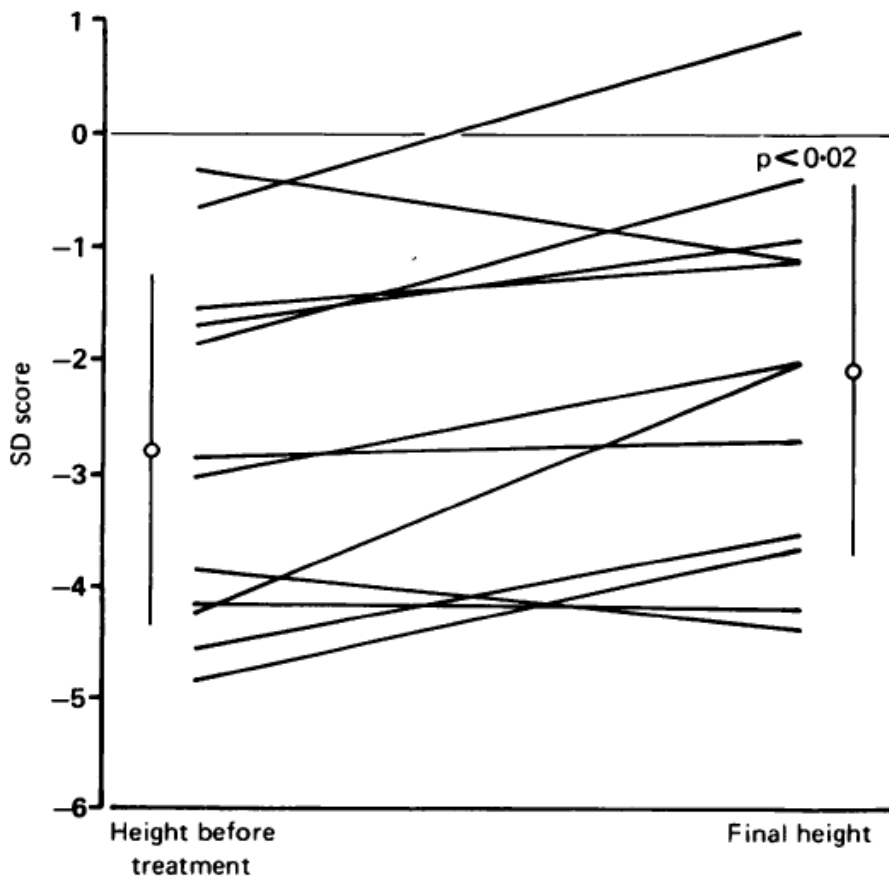
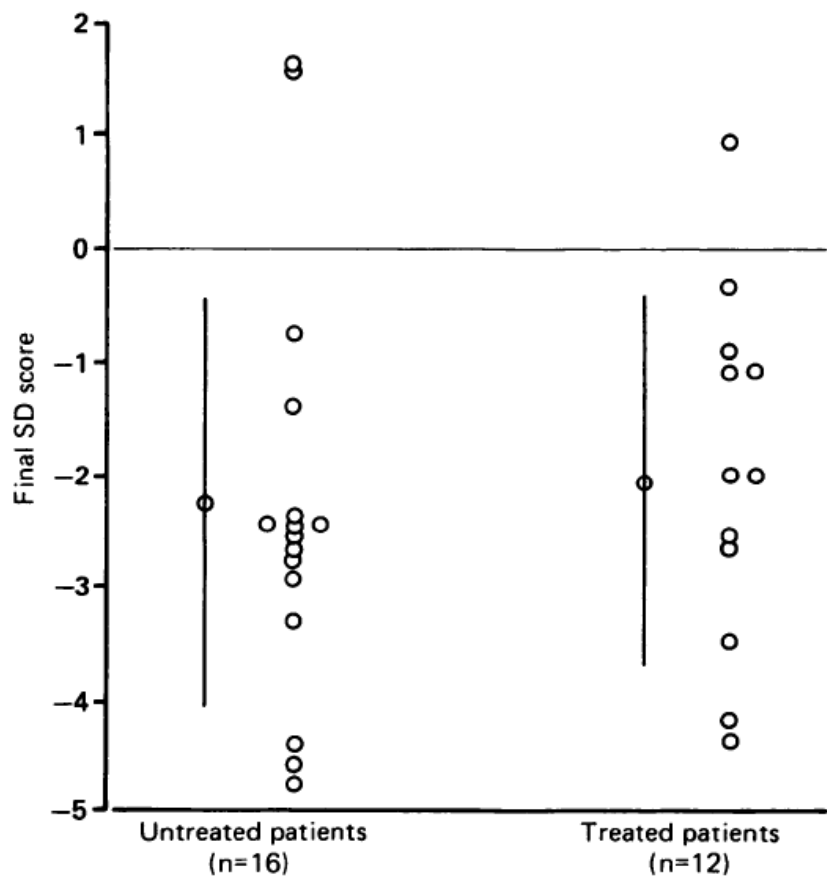
# Conventional treatment

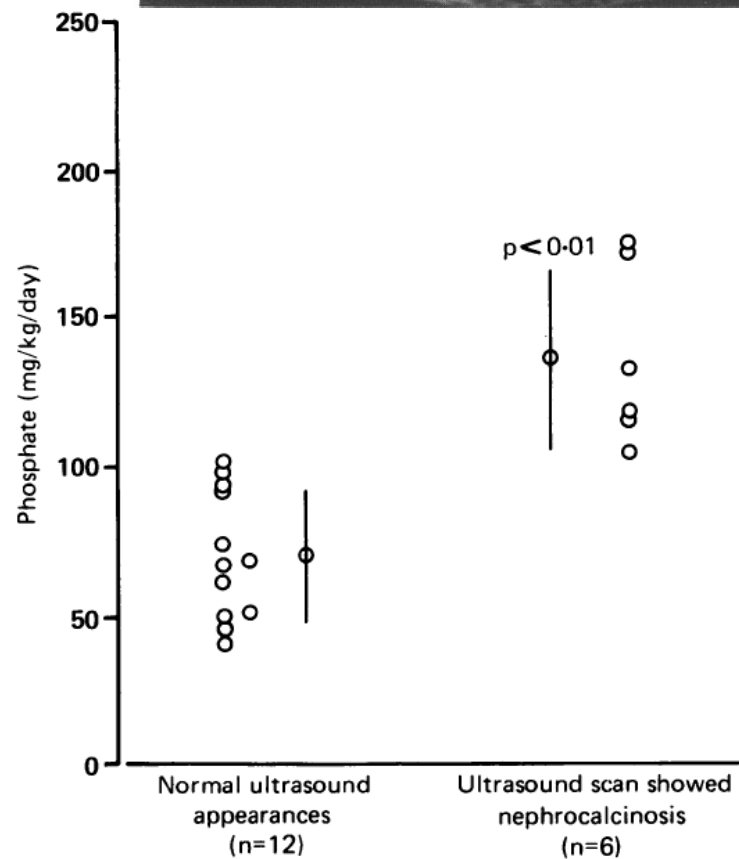
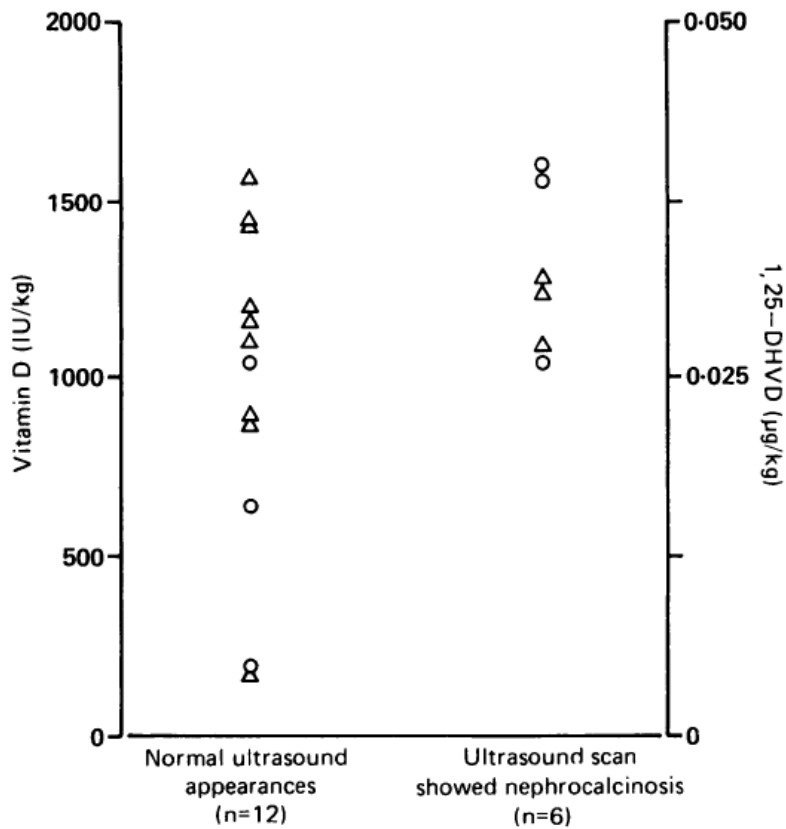
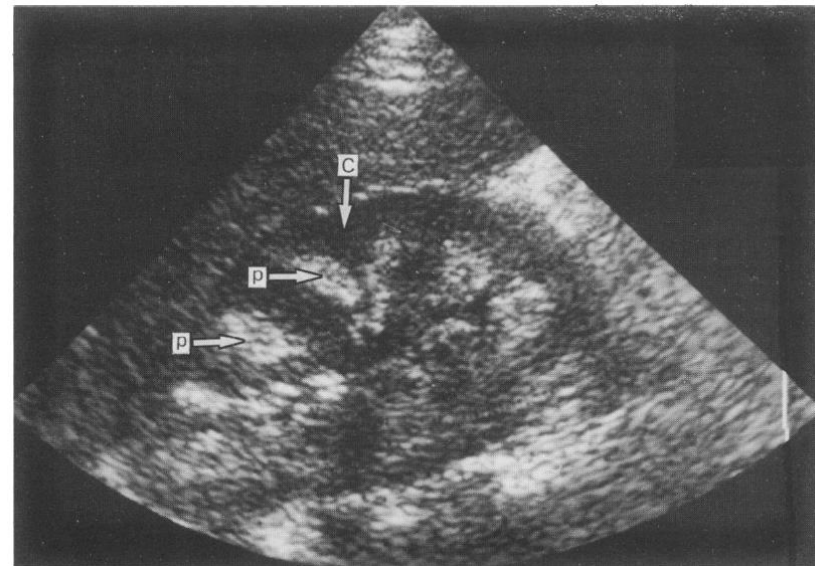
- Vitamin D(30-40.000IU)
- Calcitriol
- P solution
- Surgical interventions (neurosurgery, orthopedics)
- Dental care
- Multi-disciplinary team (psychical and physical rehabilitation)

# X linked hypophosphataemia: treatment, height gain, and nephrocalcinosis

*Archives of Disease in Childhood* 1990; 65: 1125–1128

G S Reusz, P F Hoyer, M Lucas, H P Krohn, J H H Ehrich, J Brodehl

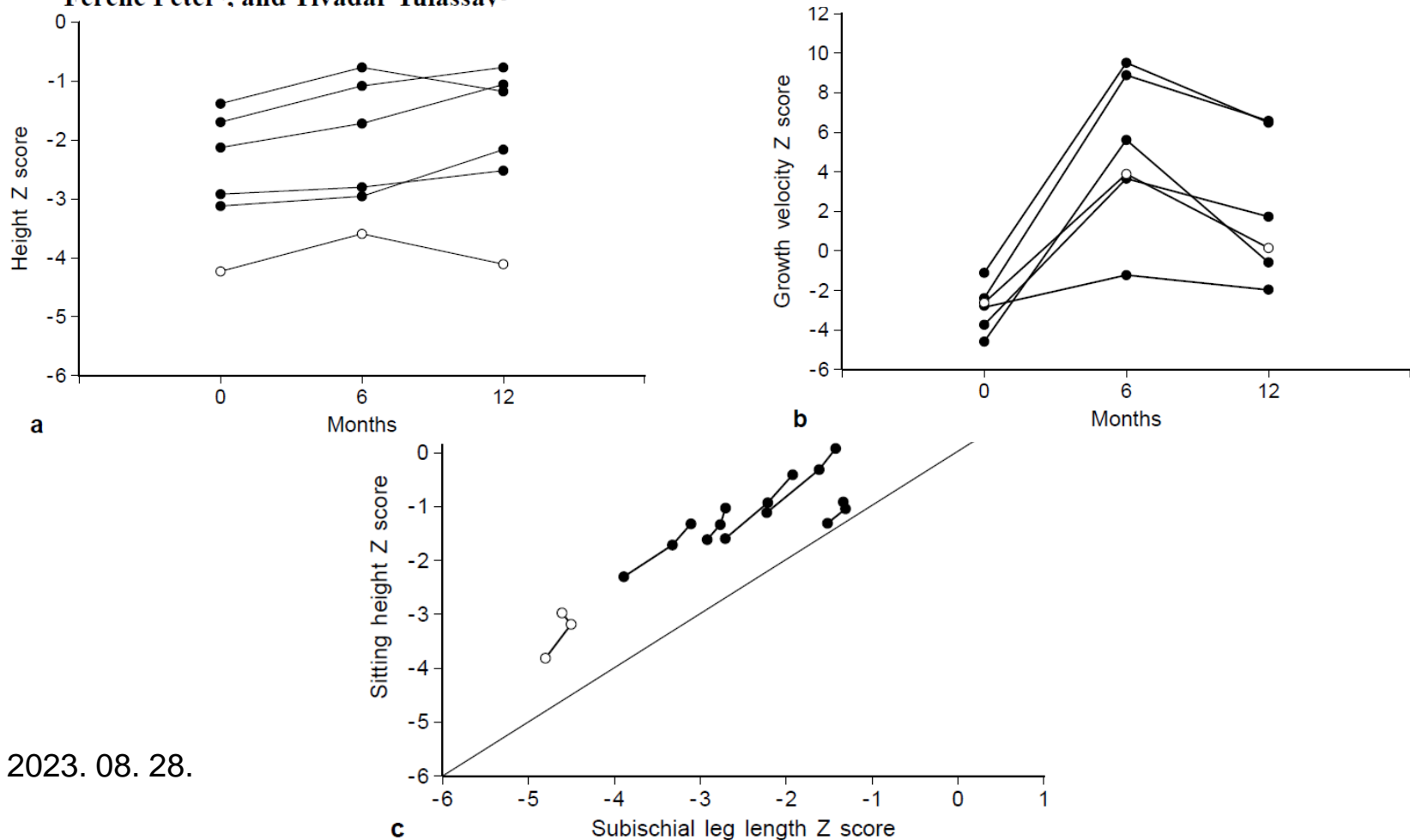


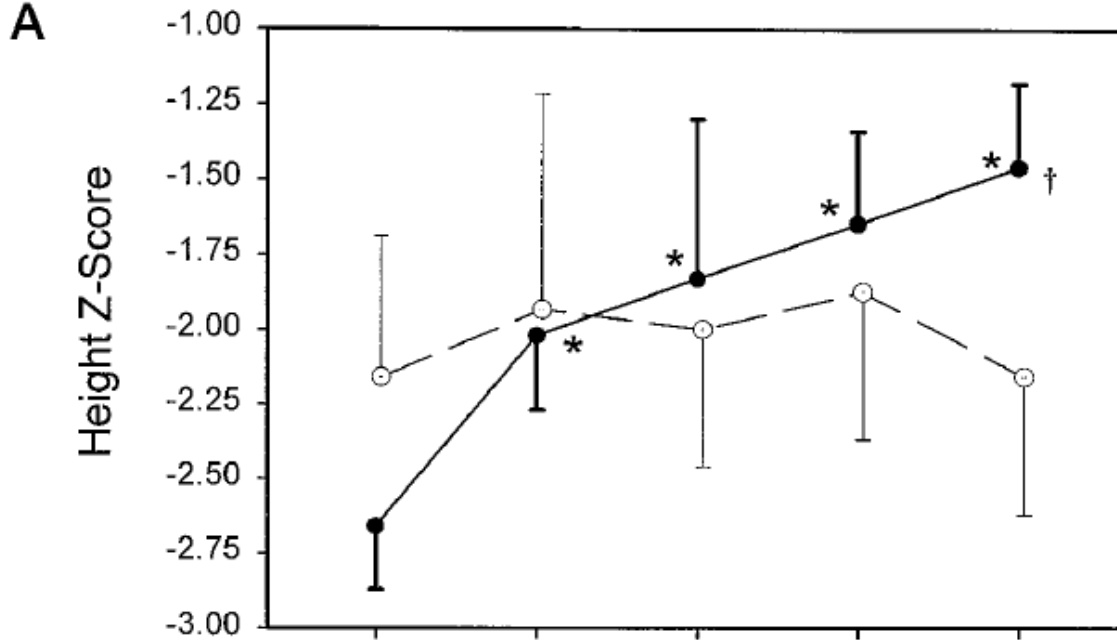


## Original article

# X-linked hypophosphatemia: effects of treatment with recombinant human growth hormone

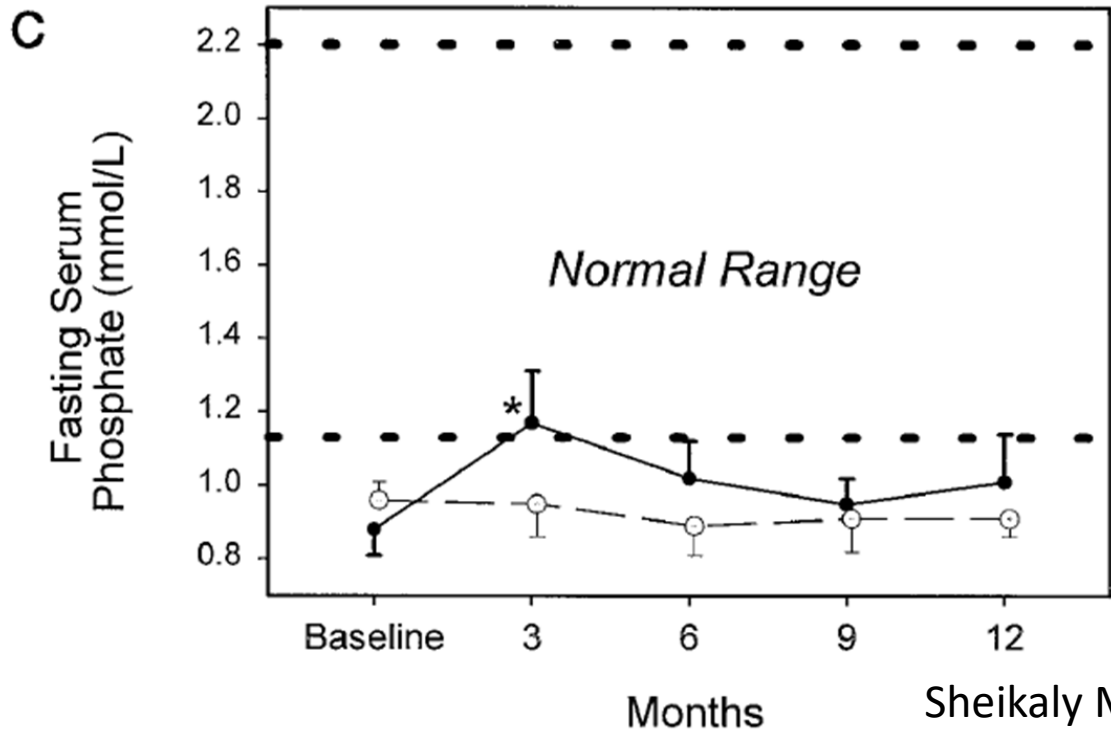
György S. Reusz<sup>1</sup>, Gabriel Miltényi<sup>1</sup>, Gusztáv Stubnya<sup>1</sup>, András Szabó<sup>1</sup>, Csaba Horváth<sup>2</sup>, Dennis J. Byrd<sup>3</sup>, Ferenc Péter<sup>4</sup>, and Tivadar Tulassay<sup>1</sup>





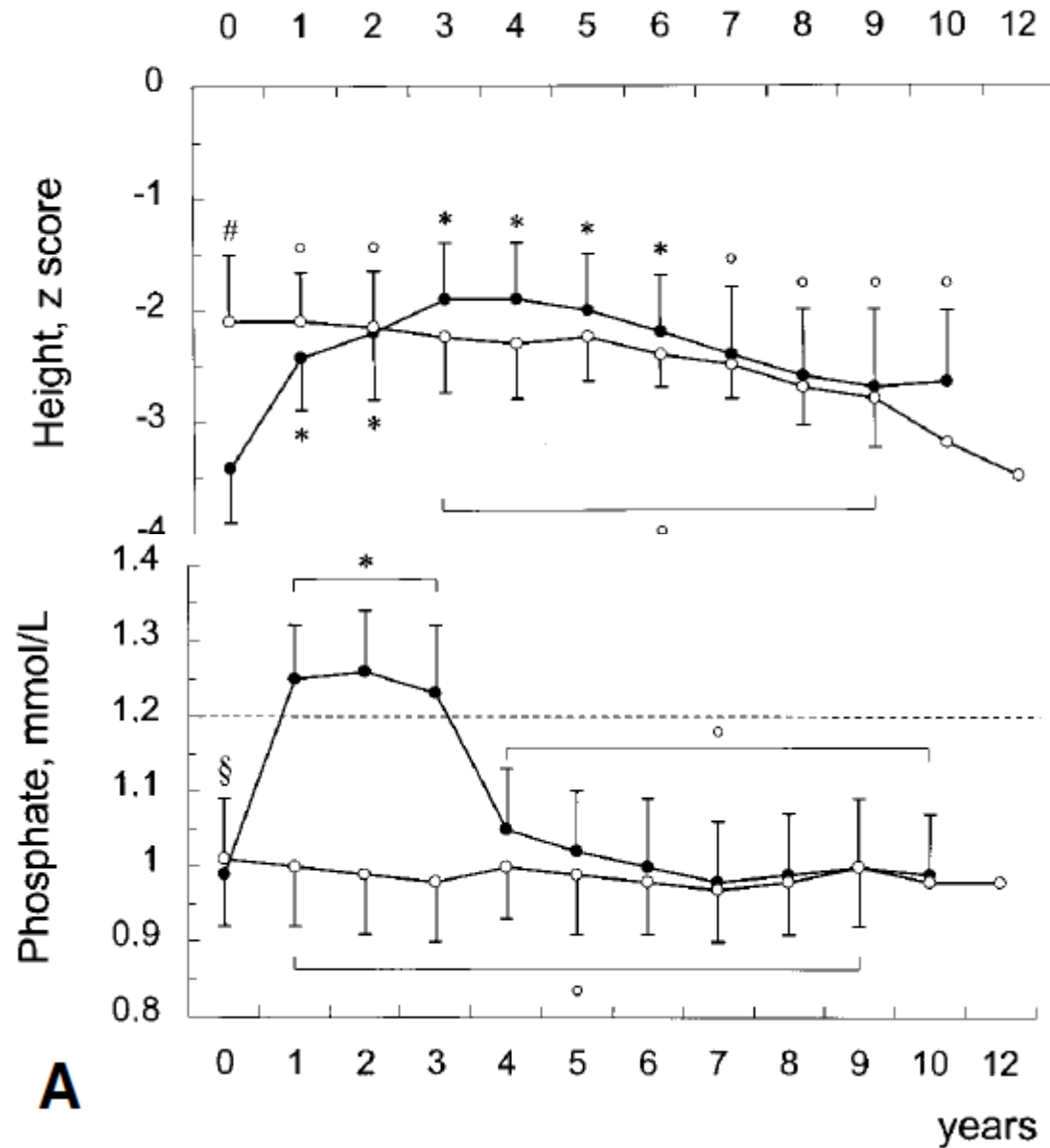
**HGH in XLH**

linear growth



**P metabolism**

# rHGH and XLH years



**A**

# Recombinant growth hormone therapy for X-linked hypophosphatemia in children.

Smith S, Remington T. Cochrane Database Syst Rev.  
2021 Oct 7;10(10):CD004447.  
doi: 10.1002/14651858.CD004447.pub3.



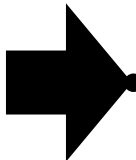
**THE COCHRANE  
COLLABORATION®**

We do not have enough high-certainty evidence to recommend the use of recombinant human growth hormone therapy in children with X-linked hypophosphatemia.

# Outline

- Classical concept of phosphate metabolism
- XLH
  - The clinical spectrum
- Conventional therapy
- **Additional data**
- XLH, ADHR, OOM, TC
- Unifying concept
- PHEX, FGF23 and hereditary hypophosphatemia
- A new therapy on the horizon

# Additional data - XLH

- Kidney Tx (HYP mouse)
    - Hyp kidney → wild type m → wild type m
    - Wild type kidney → Hyp m → Hyp m
  - Human case report
    - Healthy sister → brother (XLH and CKD5)  
XLH dominates (Morgan, Arch Intern. Med. 1974)
  - Parabiosis between wild and HYP mouse
    - HYP dominates (!)
-  **ENDOCRINE EFFECT**

# Outline

- Classical concept of phosphate metabolism
- XLH
  - The clinical spectrum
- Conventional therapy
- Additional data
- XLH, ADHR, OOM, TC
- **Unifying concept**
- PHEX, FGF23 and hereditary hypophosphatemia
- A new therapy on the horizon

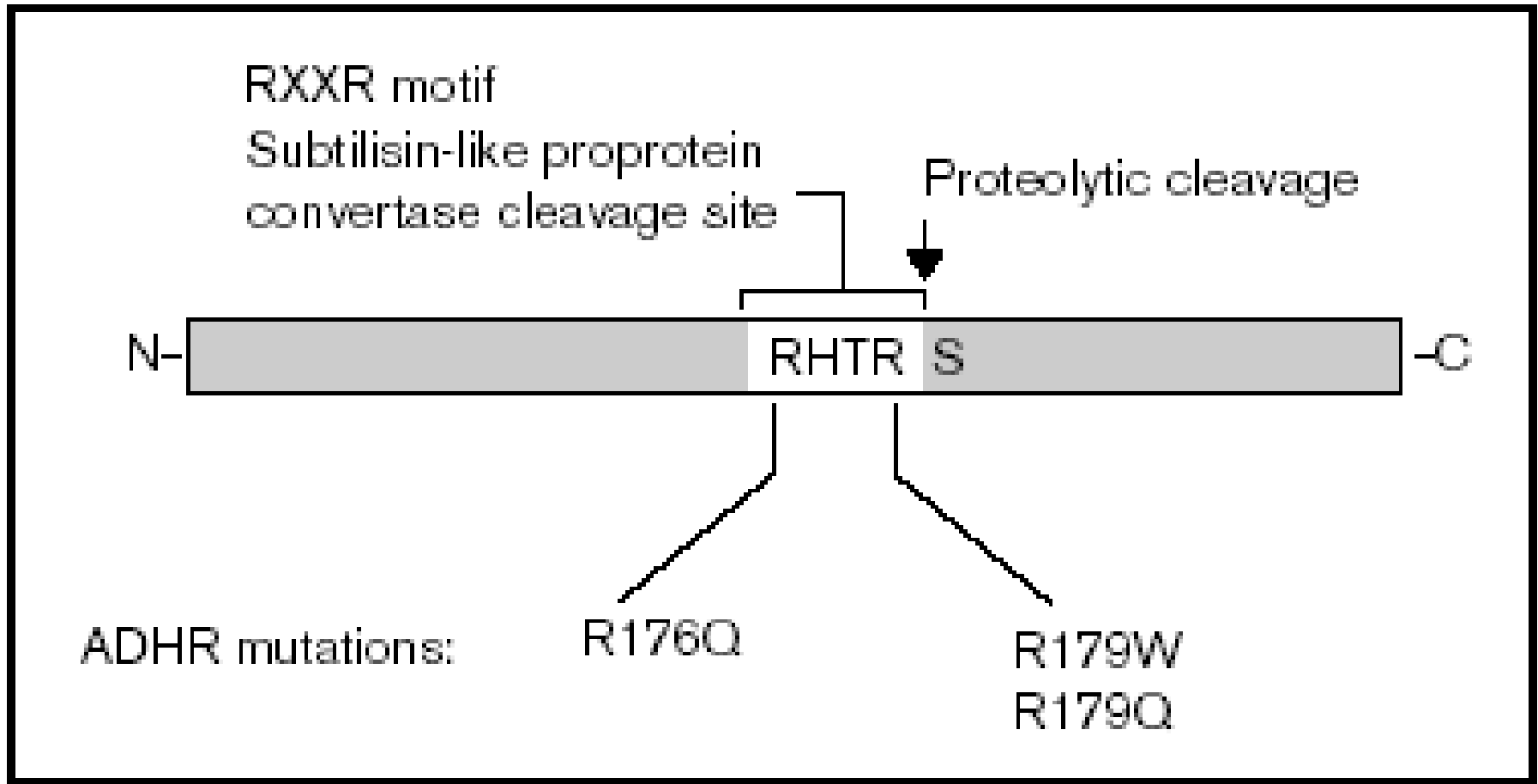
# **XLH: PHEX gene and FGF23**

= ***P***hosphateregulating gene with ***H***omology to ***E***ndopeptidases on the ***X*** chromosome

= ***F***ibroblast ***G***rowth ***F***actor 23

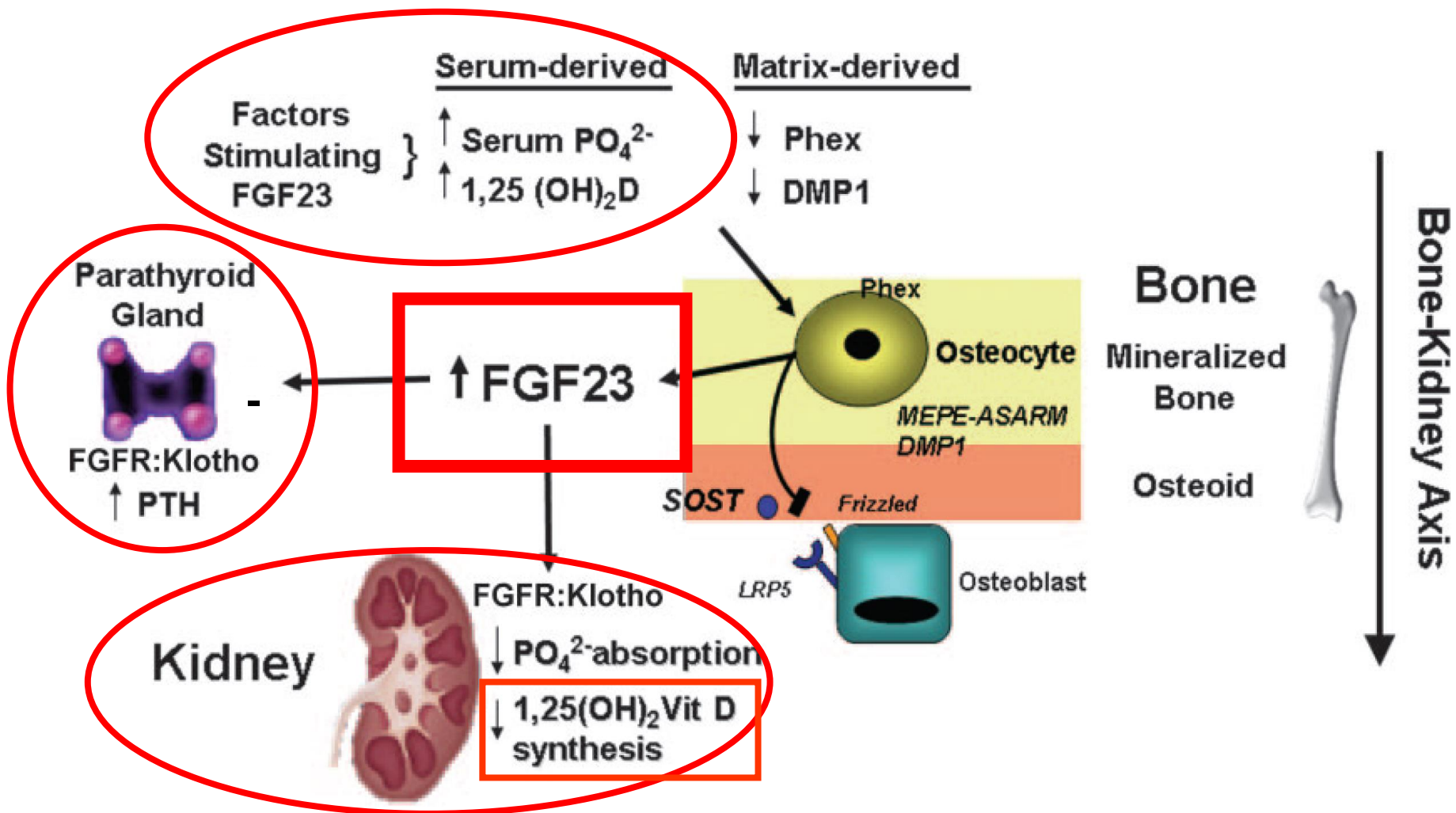
# Structure of FGF23

Schiavia SC Moe OW: Phosphatonins: a new class of phosphate-regulating proteins  
Current Opinion in Nephrology and Hypertension 2002, 11:423±430



ADHR, autosomal dominant hypophosphatemic rickets.

# Regulation of FGF23

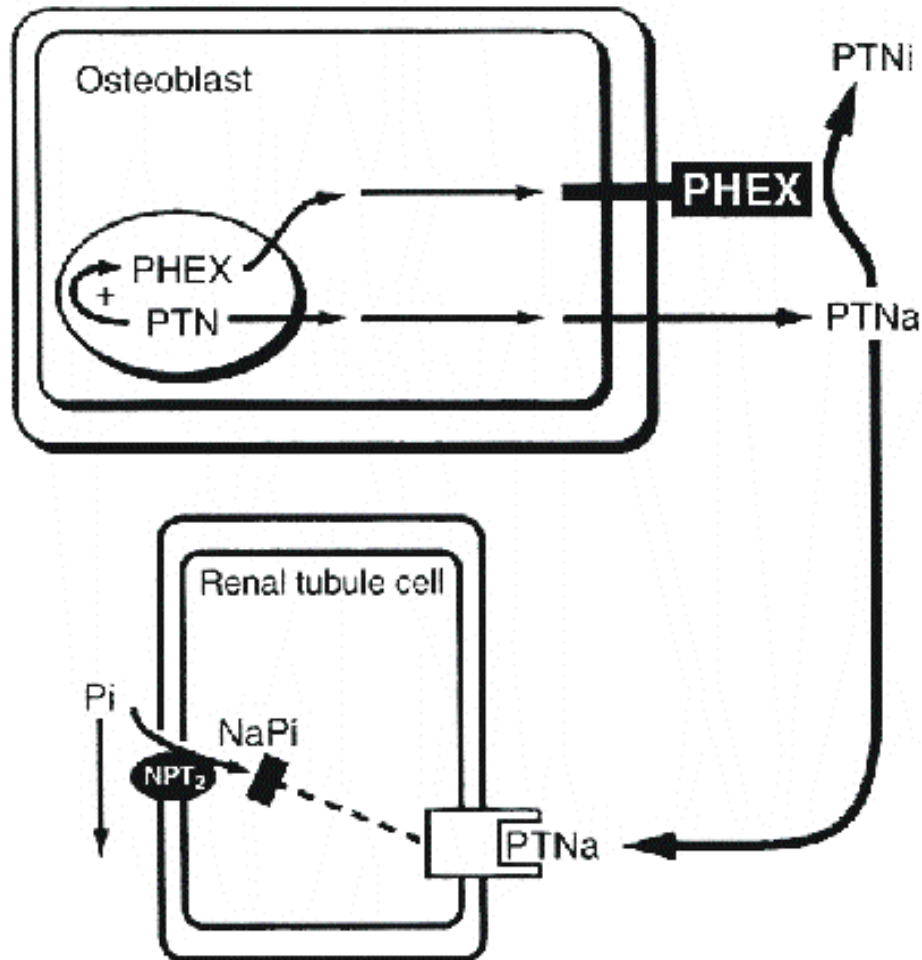


Shiguang Liu and L. Darryl Quarles

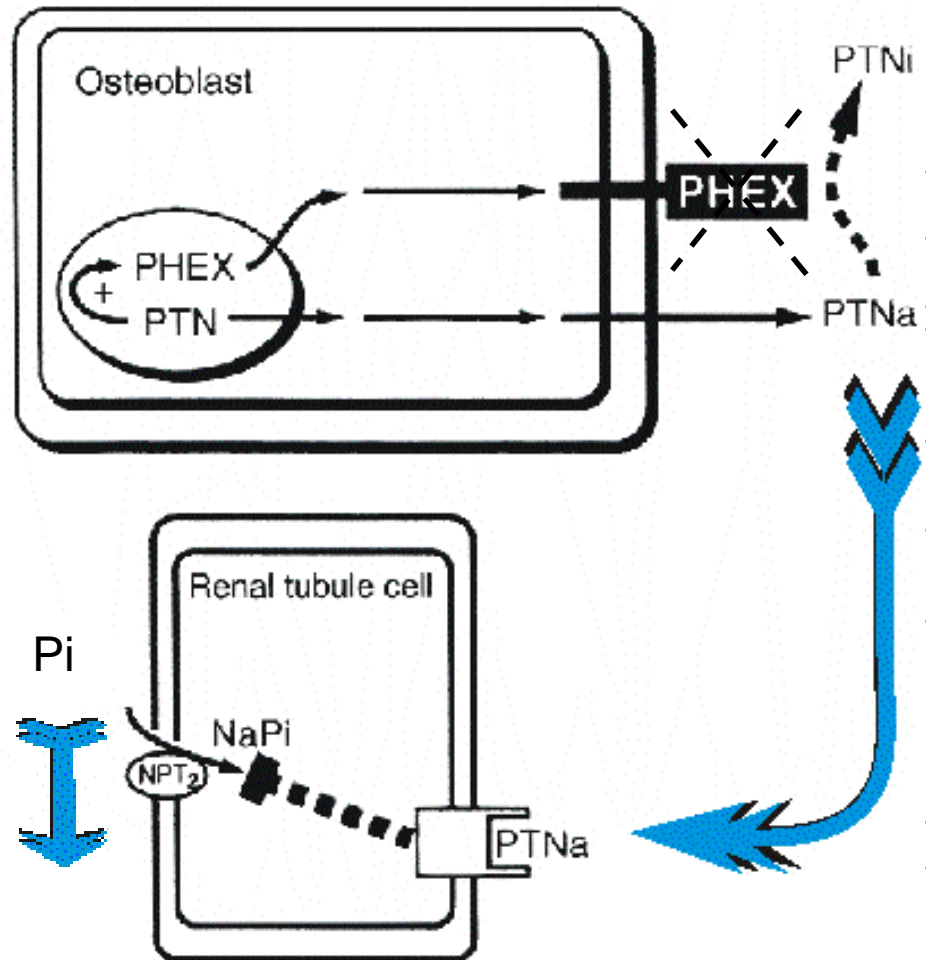
*J Am Soc Nephrol* 18: 1637–1647, 2007. doi: 10.1681/ASN.2007010068

# PHEX and XLH

Normal



XLH

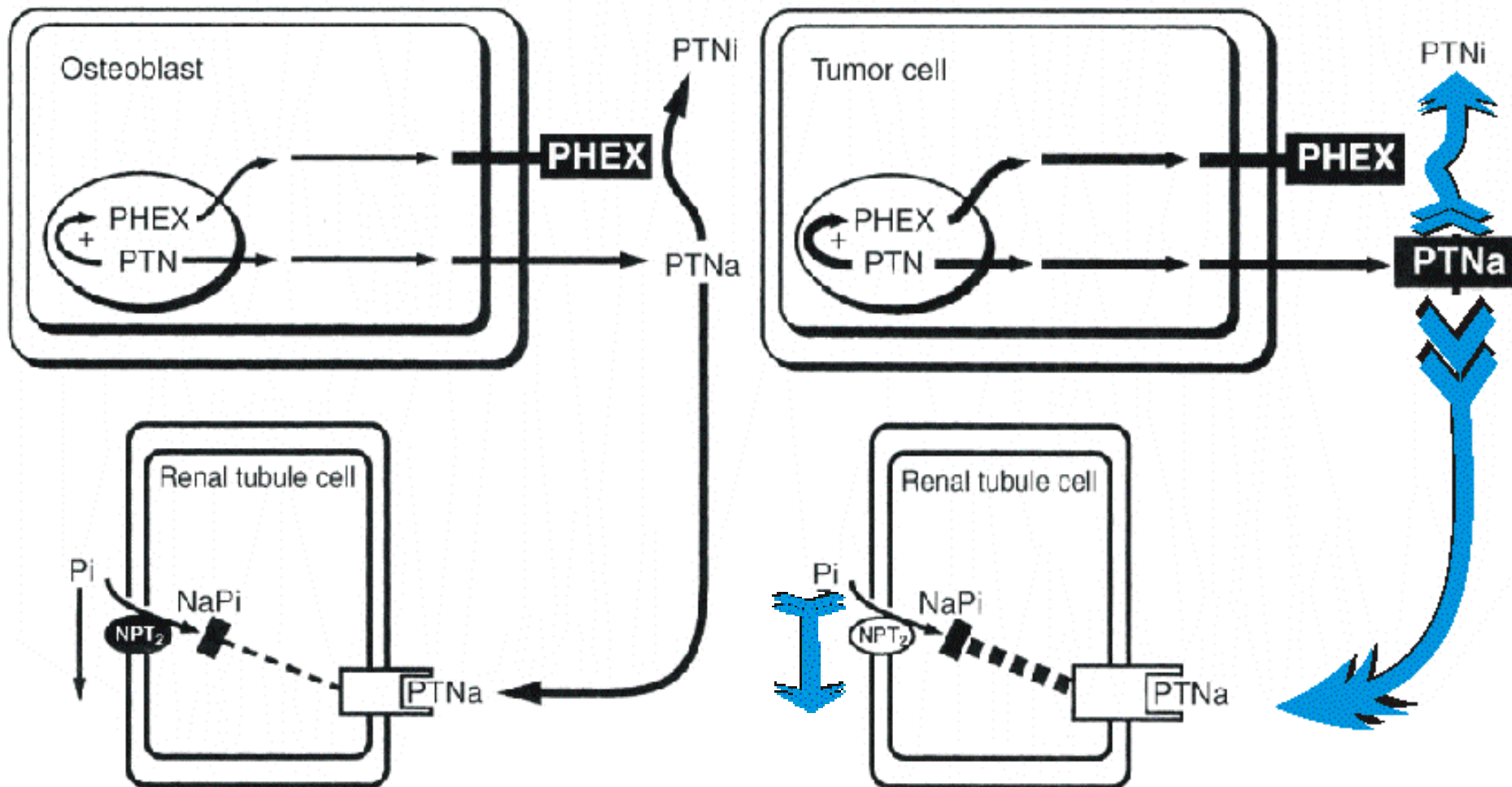


# PHEX and Tumor Induced Osteomalata (TIO)

[Drezner MK, KI 2000; 57, 9-18](#)

Normal

TIO

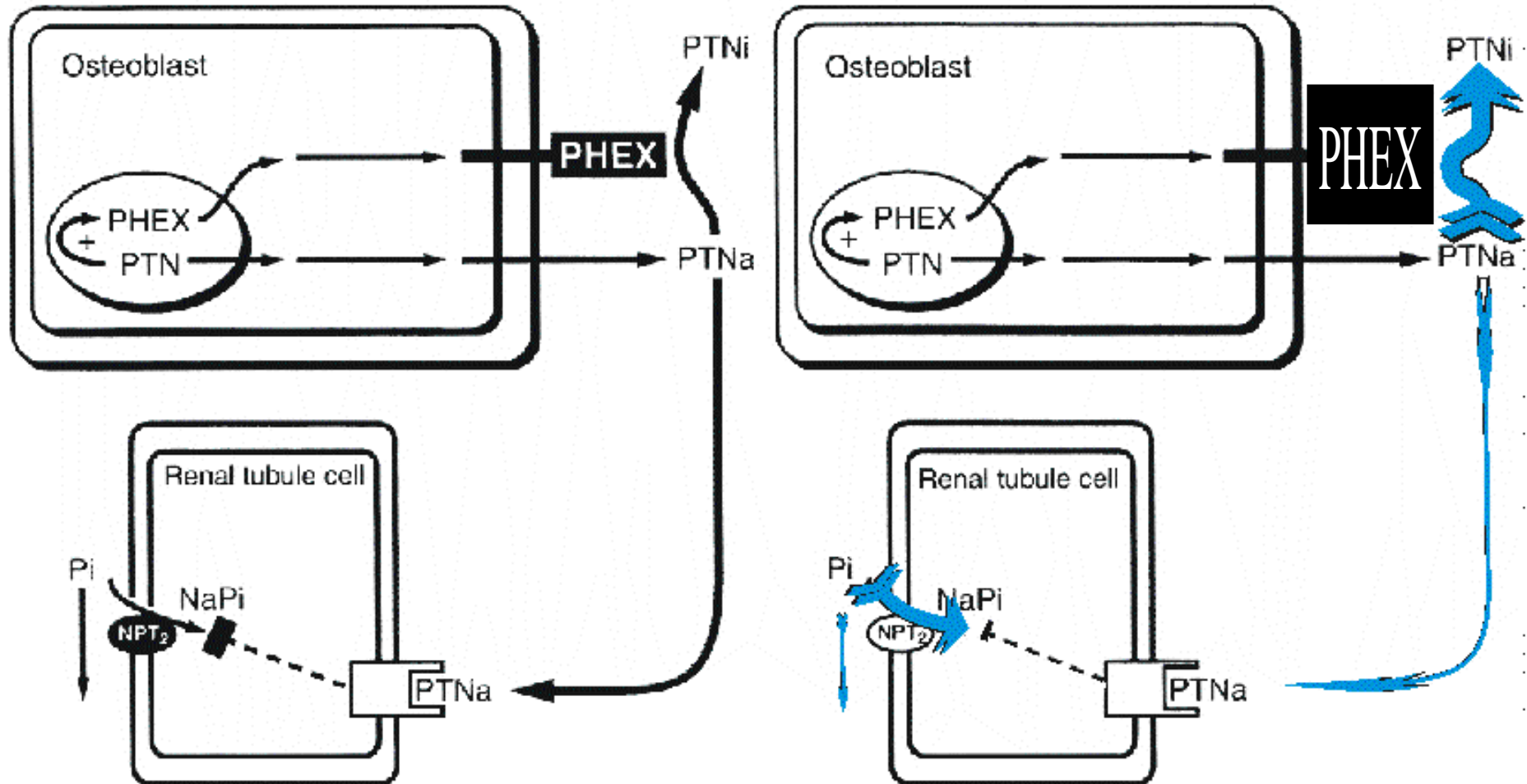


# PHEX and “tumoral calcinosis (TC)”

[Drezner MK, KI 2000; 57, 9–18](#)

Normal

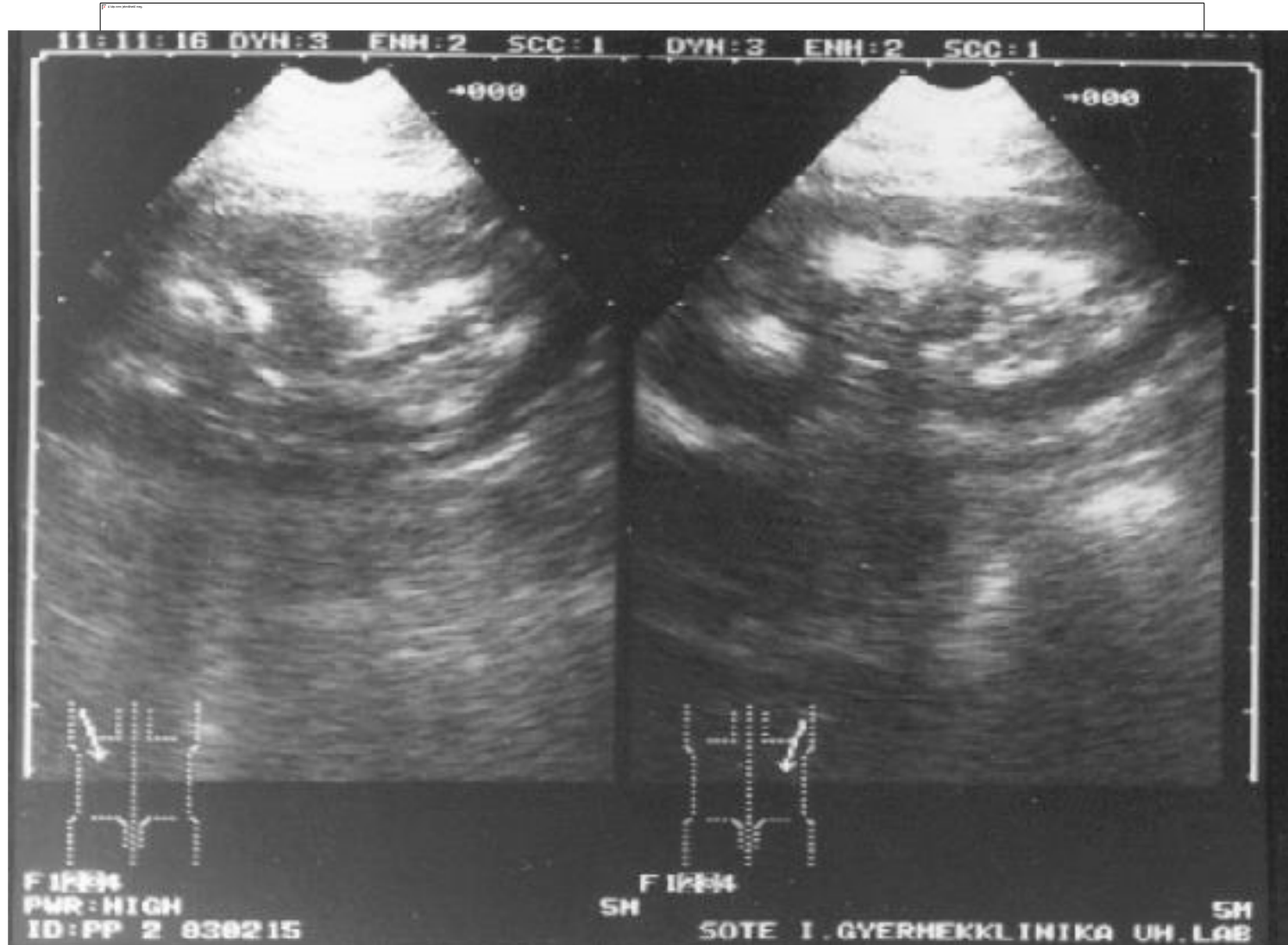
TC



# Rickets



# Nephrocalcinosis



# Calcification in a patient with tumoral calcinosis before and after treatment

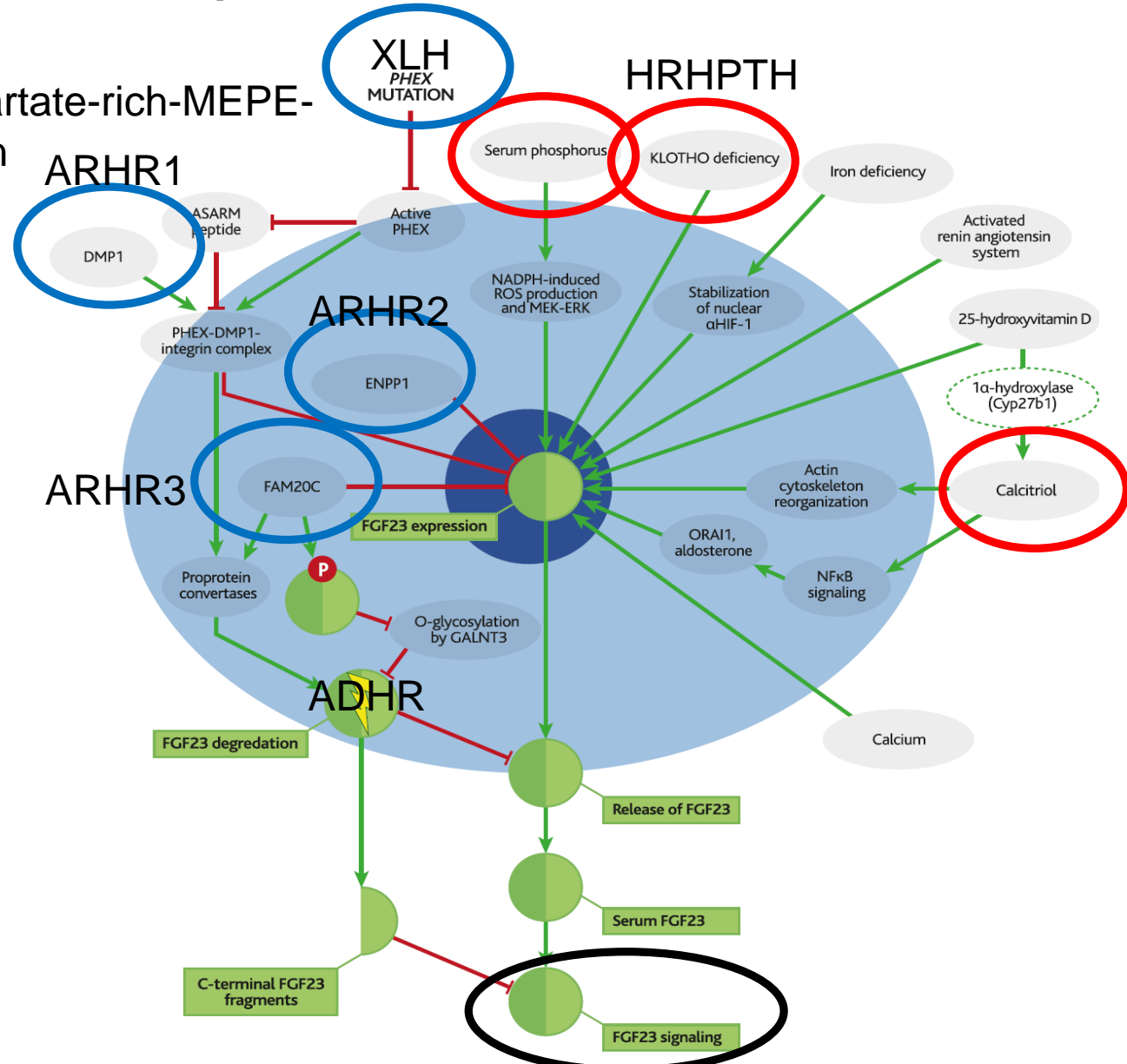


# Outline

- Classical concept of phosphate metabolism
- XLH
  - The clinical spectrum
- Conventional therapy
- Additional data
- XLH, ADHR, OOM, TC
- Unifying concept
- **PHEX, FGF23 and hereditary hypophosphatemia**
- A new therapy on the horizon

# Az FGF23 expression and excretion in XLH

acidic serine aspartate-rich-MEPE-associated protein (ASARM)



# Outline

- Classical concept of phosphate metabolism
- XLH
  - The clinical spectrum
- Conventional therapy
- Additional data
- XLH, ADHR, OOM, TC
- Unifying concept
- PHEX, FGF23 and hereditary hypophosphatemia
- **A new therapy at the horizon**

# Conventional vs biological (causal) treatment therapy

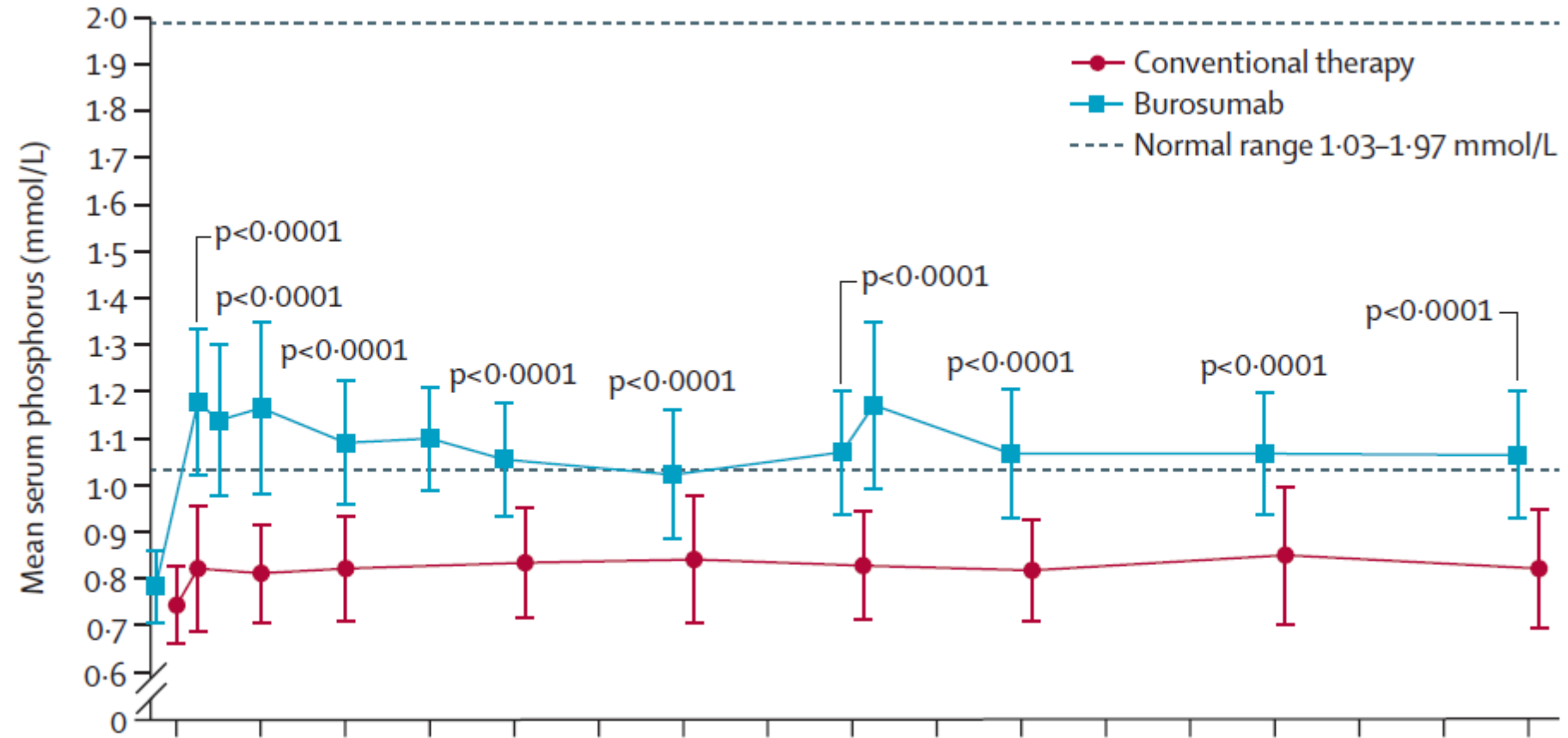
- Conventional treatment
- Vitamin D
- Calcitriol
- P solution
- Surgical interventions
- Complex care

Biological treatment  
Anti-FGF23 antibody

- ((Surgical interventions
- Complex care))

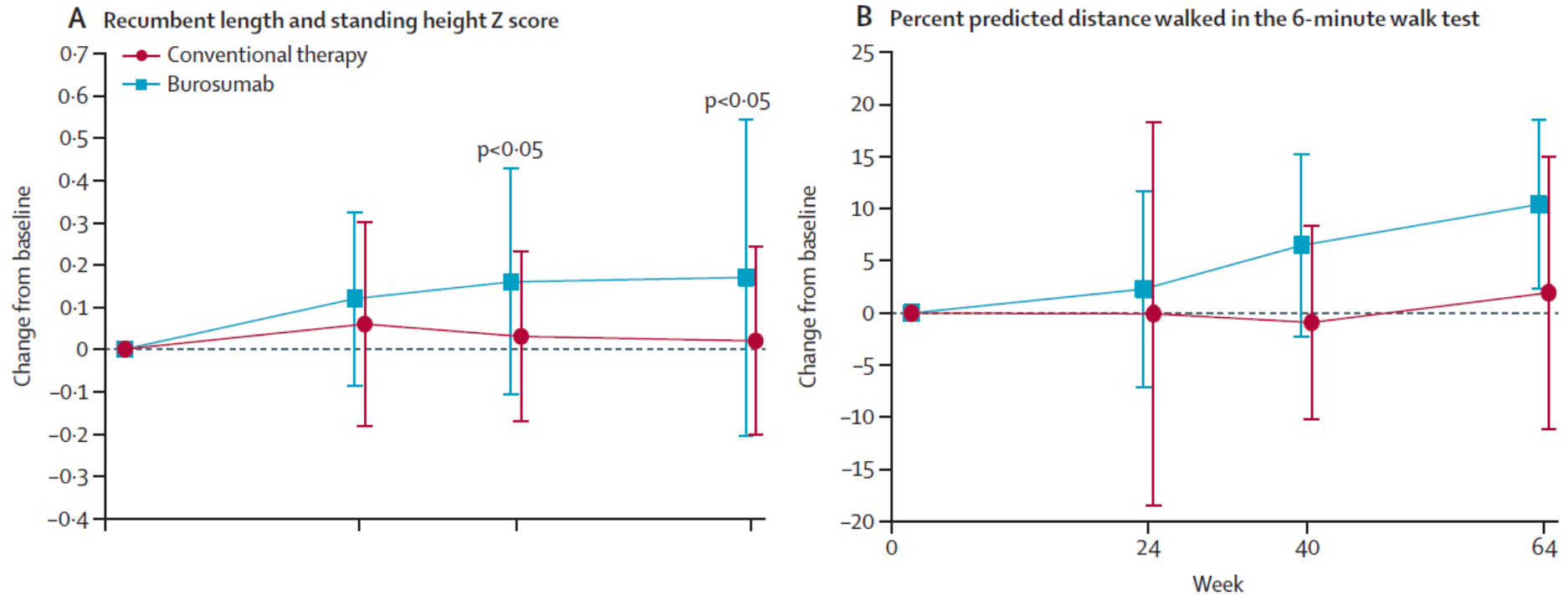
# Biological therapy: Anti-FGF23 antibody

A Serum phosphorus



# Biological therapy: Anti-FGF23 antibody

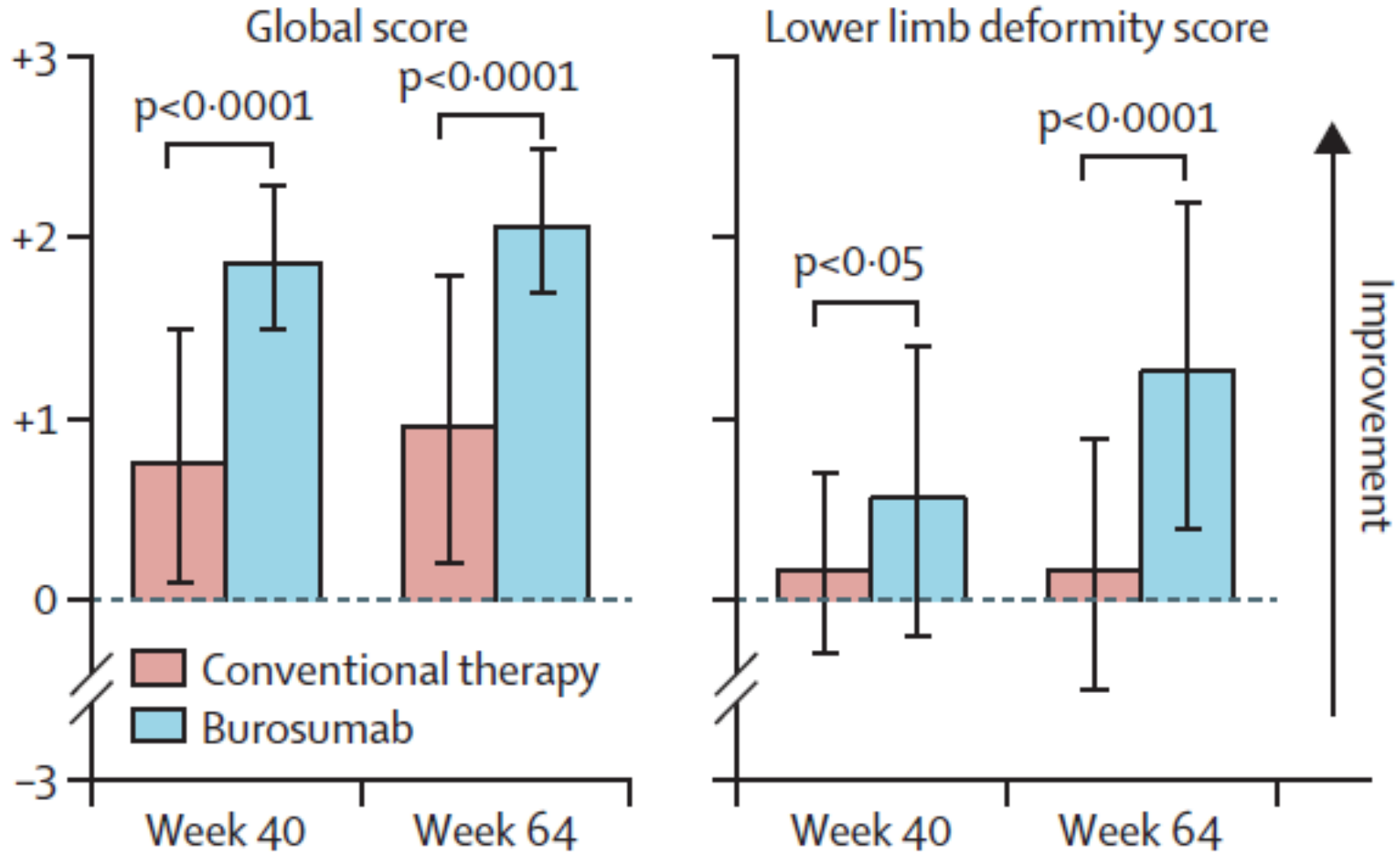
## Growth and physical activity



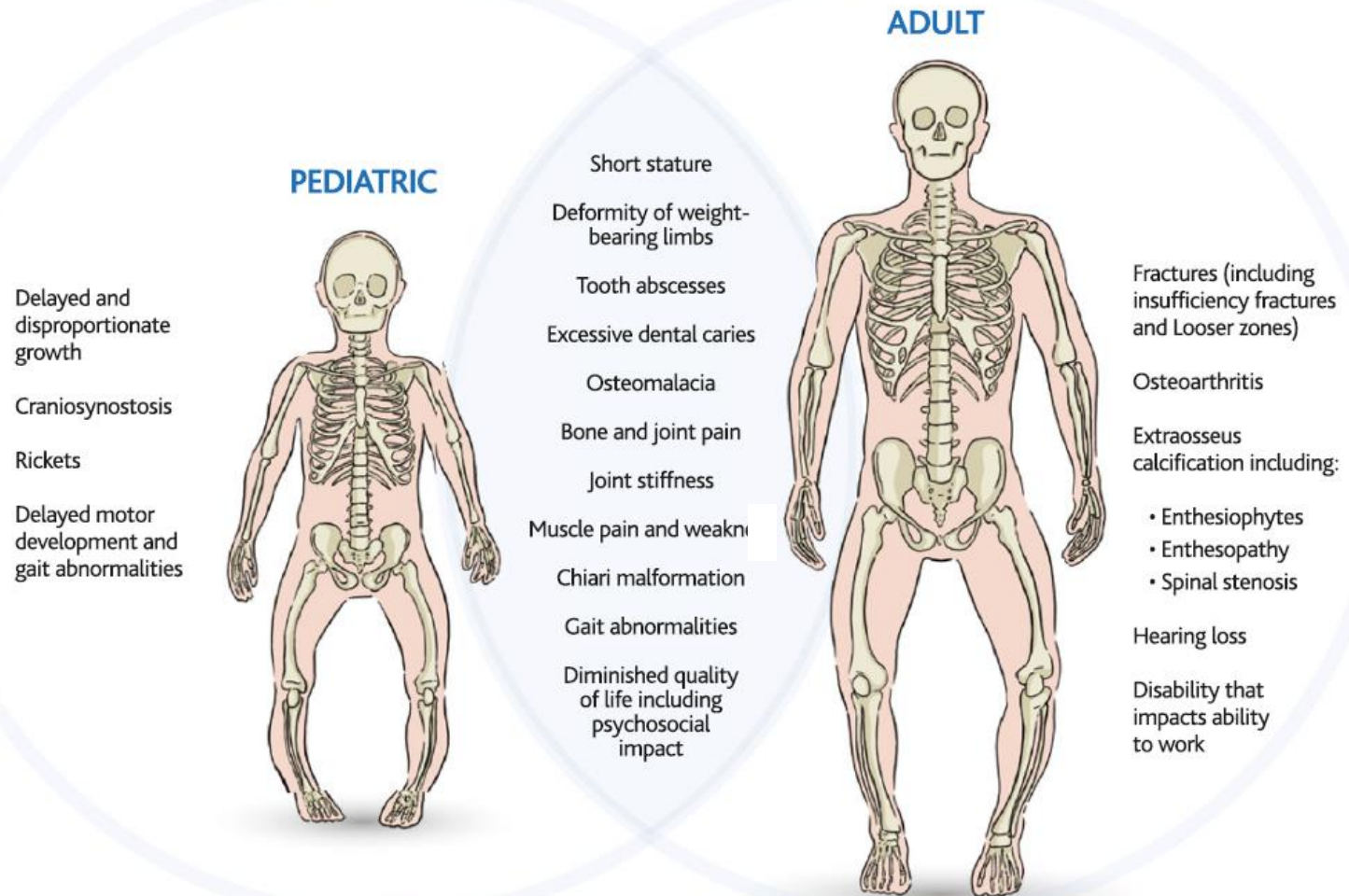
# Biological therapy: Anti-FGF23 antibody

## Radiological and orthopedic improvement

### A Radiographic Global Impression of Change



# XLH – Complex care



OPEN

EVIDENCE-BASED GUIDELINE

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

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

ÖSSZEFOGLALÓ KÖZLEMÉNY

## Újdonságok az X-hez kötött hypophosphataemia diagnózisában és kezelésében

REUSZ György Sándor, MIKES Bálint, CSIZEK Zsófia, HORVÁTH Orsolya  
Semmelweis Egyetem, I. Sz. Gyermekgyógyászati Klinika

DOI: <https://doi.org/10.55006/1111.20.009>

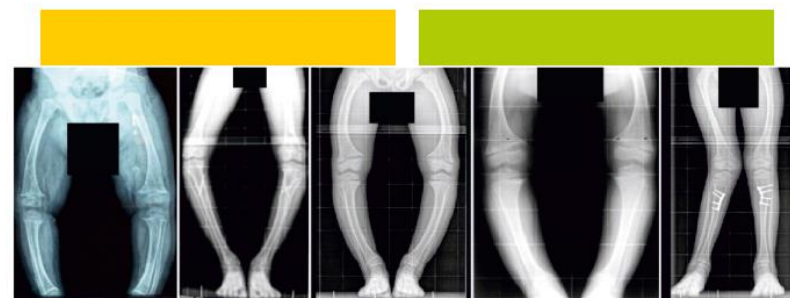
Hypertonia és Nephrologia  
2022;26(2):77-85.

2023. 08. 28.

# Gyermekgyógyászat

tudományos és továbbképzési szaklap

A MAGYAR GYERMEKORVOSOK TÁRSASÁGÁNAK ORSZÁGOS FOLYÓIRATA



8  
kreditpont

KONSZENZUS NYILATKOZAT

BIZONYÍTÉKON ALAPULÓ IRÁNYELVEK

Klinikai gyakorlati ajánlások az X-kromoszómához kötött hypophosphataemia diagnosztizálására és kezelésére

# XLH – complex care

- EARLY RECOGNITION
- XLH "specialist"
- Nephrologist
- Endocrinologist
- Bone specialist
- Neurosurgeon
- Orthopedic surgeon
- Dentist/orthodontist
- Rheumatologist
- Physical therapist
- Psychologist
- =Team work
- = The matter of transition



This project is extremely important, but there is no money for it, no help, and it must be finished by tomorrow morning. But at least here is the great opportunity to amaze everyone