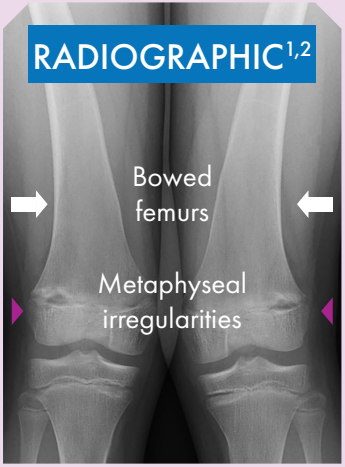
Hypophosphatemic Rickets?

If you see the following features:



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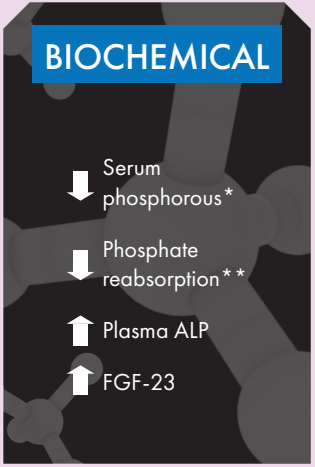

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It could be...

Autosomal
Recessive
Hypophosphatemic
Rickets
2 Type 2

ARHR2, **also known as ENPP1 Deficiency**, is a rare mineralization disorder caused by mutations in the *ENPP1* gene. Similar to patients with X-linked hypophosphatemic rickets (XLH), patients with ARHR2 typically present with bone deformities, short stature, bone and joint pain and stiffness, radiographic evidence of rickets/osteomalacia, and hypophosphatemia with urinary phosphate wasting[1–13]

*Fasting serum phosphorous below age-adjusted reference range. **TmP/GFR, tubular maximum reabsorption of phosphate/glomerular filtration rate. ALP, alkaline phosphatase; FGF-23, fibroblast growth factor 23; XLH, X-linked hypophosphatemic rickets.
X-ray: Reused from Boyce AM, et al. *Curr Osteoporos Rep.* 2020;18(3):232–241. This image is derived from a US Government work in the public domain.

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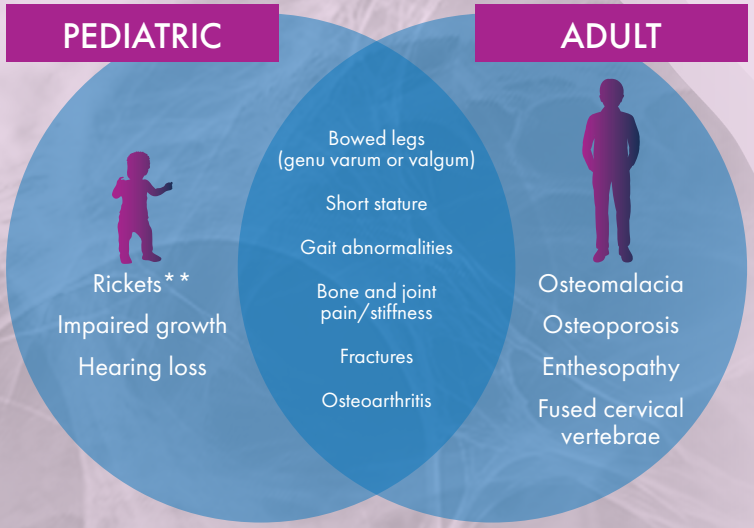
ARHR2 Diagnostic Pathway

Common presenting signs/symptoms[1–13]



Potential differential diagnoses include PHEX-negative X-linked hypophosphatemia, or tumor-induced osteomalacia (TIO) without tumor

Indications to test[1–13]

Hypophosphatemia
With FGF-23-mediated phosphate wasting*

OR

Ectopic calcification
of arteries, heart, joints, or ligaments

OR

Patient or family history
of infantile cardiovascular disease

Genetic testing for *ENPP1*

*Fasting serum phosphorous below age-adjusted reference range, with high urinary phosphate or low TmP/GFR, and inappropriately elevated FGF-23.
**Characterized by growth plate abnormalities, including metaphyseal fraying, splaying, and cupping.
FGF-23, fibroblast growth factor 23; TmP/GFR, tubular maximum reabsorption of phosphate/glomerular filtration rate.

References: 1. Boyce AM, et al. *Curr Osteoporos Rep.* 2020;18(3):232–241. **2.** Choe Y, et al. *Front Endocrinol (Lausanne).* 2022;29:911672. **3.** Levy-Litan V, et al. *Am J Hum Genet.* 2010;86(2):273–278. **4.** Haffner D, et al. *Nat Rev Nephrol.* 2019;15(7):435–455. **5.** Ferreira CR, et al. *J Bone Miner Res.* 2021;36(11):2193–2202. **6.** Höppner J, et al. *Bone.* 2021;153:116111. **7.** Lorenz-Depiereux B, et al. *Am J Hum Genet.* 2010;86(2):267–272. **8.** Kotwal A, et al. *J Bone Miner Res.* 2020;35(4):662–670. **9.** Ferreira CR, et al. *J Bone Miner Res.* 2022;37(3):494–504. **10.** Thumbigere-Math V, et al. *J Dent Res.* 2018;97(4):432–441. **11.** Kato H, et al. *J Bone Miner Res.* 2022;37(6):1125–1135. **12.** Edouard T, Linglart A. *Arch Pediatr.* 2024;4S1:4S27–4S32. **13.** Ferreira CR, et al. *JBMR Plus.* 2025;9(5):ziaf019.

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