Prenatal/Infant Diagnostic Pathway

Common presenting signs/symptoms

Fetal ultrasound findings

- Pericardial effusion
- Cardiomyopathy (cardiac hypertrophy)
- Non-immune hydrops
- Polyhydramnios

Neonatal/infant

- Cardiomyopathy (cardiac hypertrophy)
- Pulmonary hypertension
- Diminished pulses
- Hypertension
- Respiratory distress
- Heart failure

Other complications may include seizure, stroke, encephalopathy, pleural effusion, ascites, and gastrointestinal complications.

Indications to test

Abnormal brightness
of arteries or heart valves (ultrasound, ECHO, CT, MRI)

OR

Vascular stenosis
(CTA, MRA, ECHO)

OR

Family history
of fetal/neonatal death or hypophosphatemic rickets

Genetic testing for ***ENPP1*** and ***ABCC6***

ABCC6, adenosine triphosphate binding cassette subfamily C member 6; CT, computed tomography; CTA, computed tomography angiography; ECHO, echocardiogram; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

References: 1. Mulcahy CH, et al. *J Congenit Cardiol.* 2019;3(1). doi:10.1186/s40949-018-0022-1 **2.** Nasrallah FK, et al. *Ultrasound Obstet Gynecol.* 2009;34(5):601-604. **3.** Rutsch F, et al. *Circ Cardiovasc Genet.* 2008;1(2):133-140. **4.** Ferreira CR, et al. In: Adam MP, et al, eds. *GeneReviews® [Internet].* University of Washington, Seattle; 1993-2020. **5.** Ferreira CR, et al. *J Bone Miner Res.* 2021;36(11):2193-2202. **6.** Ferreira CR, et al. *Genet Med.* 2021;23(2):396-407. **7.** Chong CR, Hutchins GM. *Pediatr Dev Pathol.* 2008;11(5):405-415. **8.** Ramirez-Suarez KI, et al. *Pediatr Radiol.* Published online April 19, 2022. doi:10.1007/s00247-022-05364-0

Pediatric/Adult Diagnostic Pathway

Common presenting signs/symptoms

Pediatric
- Rickets
- Widened/frayed growth plates
- Delayed shedding of teeth
- Hearing loss

Adult
- Osteomalacia
- Osteoporosis
- Recurrent fractures
- Enthesopathy

- Bowed legs (genu varum or valgum)
- Short stature
- Gait abnormalities
- Bone and joint pain/stiffness
- Fused cervical vertebrae

Potential differential diagnoses include PHEX-negative X-linked hypophosphatemia, tumor-induced osteomalacia (TIO) without tumor ossification of posterior longitudinal ligament (OPLL), and diffuse idiopathic skeletal hyperostosis (DISH).

Indications to test

Hypophosphatemic rickets/osteomalacia
(X-ray, biochemistry[a])

OR

History of calcification
of joints, ligaments, arteries, or organs (X-ray, ECHO)

OR

Family history
of fetal/neonatal death or hypophosphatemic rickets

Genetic testing for *ENPP1*

Ca, calcium; ECHO, echocardiogram; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23, fibroblast growth factor 23; PO_4, phosphate; PPi, inorganic pyrophosphate. [a]Ca and PO_4^{3-} homeostasis test panel and plasma PPi . Ca and PO_4^{3-} homeostasis test panels include testing for Ca, FGF23, alkaline phosphatase (ALP), parathyroid hormone (PTH), tubular maximum reabsorption of phosphate/glomerular filtration rate (TmP/GFR), 25-hydroxyvitamin D3, 1,25-dihydroxyvitamin D3, and serum and urine phosphate.

References: 1. Levy-Litan V, et al. *Am J Hum Genet.* 2010;86(2):273-278. **2.** Haffner D, et al. *Nat Rev Nephrol.* 2019;15(7):435-455. **3.** Ferreira CR, et al. *J Bone Miner Res.* 2021;36(11):2193-2202. **4.** Höppner J, et al. *Bone.* 2021;153:116111. **5.** Lorenz-Depiereux B, et al. *Am J Hum Genet.* 2010;86(2):267-272. **6.** Kotwal A, et al. *J Bone Miner Res.* 2020;35(4):662-670. **7.** Ferreira CR, et al. *J Bone Miner Res.* 2022;37(3):494-504. **8.** Thumbigere-Math V, et al. *J Dent Res.* 2018;97(4):432-441. **9.** Kato H, et al. *J Bone Miner Res.* Published online March 26, 2022. doi:10.1002/jbmr.4550