Rare Diseases of Bone Development

Disease	Overview	Signs and Symptoms	Gene Defect	Underlying Impairment	Diagnostics	Treatment
Hypophosphatasia (HPP)	Metabolic disorder causing impaired bone mineralization	• Soft, fragile bones that fracture easily and heal slowly • Bowed legs/ other skeletal deformities • Premature loss of primary teeth	Mutations in ALPL (also called TNSALP) gene	Inability to manufacture alkaline phosphatase (ALP) enzyme needed for bone development	• Bone x-rays • Lab tests for serum ALP (low) • Lab tests for vitamin B-6 (high) • Gene testing	Enzyme-replacement therapy called asfotase alfa (Strensiq™)
Osteogenesis imperfecta (OI)	Connective-tissue disorders resulting in fragile, brittle bones that can fracture upon minimal trauma	• Frequent broken bones in infancy, puberty, and late adulthood • Bone deformity • Short stature	Mutations in COL1A1 or COL1A2 genes	Impairment of quality or quantity of type 1 collagen, a protein needed for healthy bone, cartilage, tendons	• Gene tests • Bone x-rays • DXA scan • Prenatal ultrasound for severe forms	• Lifestyle to minimize fractures • Surgery • Physical therapy • Off-label use of bisphosphonates, growth hormone • Investigational drugs
Familial Hypophosphatemia (XLH)	Metabolic disorder that affects bone mineralization through an impairment that leads to low levels of phosphate and vitamin-D	• Bowed legs (congenital rickets) • Concave chest • Short stature • Progressive bone-softening • Long head shape • Tooth abscesses • Late teeth	Mutations of the PHEX gene, located on the X chromosome, in most cases; inherited as a dominant gene and thus can affect both sexes	Impaired phosphate transport to cells; impaired vitamin D metabolism in kidneys	• Lab tests for serum phosphate, magnesium, calcium, and potassium • 24-hour urine phosphate excretion • Bone x-rays • Genetic tests	• Nutritional supplements • Supportive measures for pain and mobility • Tooth sealants • Surgery
Hereditary Hyperphosphatasia	Very rare bone disorder that causes progressive skeletal malformations, mostly in long bones of arms and legs.	• Widened/bowed arm/leg bones • Thickened long bones • Difficulty walking • Short stature • Thickened upper skull	Mutations of the TNFRSF11B gene, in about 2/3 of cases.	Rapid bone turnover resulting from deficiency of the osteoprotegerin protein.	• Bone X-rays • Lab test for serum alkaline phosphatase • Urine tests for markers of bone turnover	• Supportive, symptomatic • Off-label bisphosphonates • Investigational drugs