Hypophosphatasia

Genetics

-Gene: ALPL (Alkaline phosphatase, tissue-nonspecific isozyme; 1p36.12)

-AR; milder forms, i.e. odontohypophosphatasia, may be AR or AD

Clinical findings/Dysmorphic features

-Defective mineralization of bone/teeth due to low activity of bone alkaline phosphatase

-Continuum: stillbirth w/o mineralized bone - pathologic fractures of extremities in adulthood

-Six clinical forms: 1) Perinatal (severe): respiratory insufficiency and hypercalcemia; 2) Perinatal (benign): prenatal skeletal manifestations resolve into milder form; 3) Infantile: onset between birth and age 3mths of rickets without elevated serum alkaline phosphatase activity; 4) Childhood (juvenile): ranges from low bone mineral density for age with unexplained fractures to rickets and premature loss of primary teeth with intact roots; 5) Adult: stress fractures/pseudofractures of lower extremities in middle age; 6) Odontohypophosphatasia: premature exfoliation of primary teeth and/or severe caries without skeletal manifestations

Etiology

-Prevalence of severe forms has been estimated at 1:300,000 in Europe

Pathogenesis

-Alkaline phosphatase, tissue-nonspecific isozyme (TNSALP): isozyme present in liver, kidney, bone --> acts as a (lipid) membrane-bound ectophosphatase with PPi, PLP, and PEA as natural substrates; pathogenic variants are LoF

Genetic testing/diagnosis

-All forms with reduced activity of unfractionated serum alkaline phosphatase (ALP)

-Presence of one or two pathogenic variants in ALPL; ALPL-Seq: 95%; In/Del unknown

Others

-Biphosphonates contraindicated --> phosphate motifs in bisphosphonates have similar conformation to inorganic pyrophosphate (PPi), the natural substrate of TNSALP --> treatment with bisphosphonates is thought to be analogous to "adding fuel to the fire”

-Excess vitamin D can exacerbate hypercalcemia/hypercalciuria

-Craniosynostosis is often found in the perinatal or infantile form