Hereditary hypophosphatasia (HPP) is a rare autosomal recessive disorder, characterized by disrupted mineralization of bones and teeth. It is often caused by loss-of-function (LOF) mutations in the ALPL gene that encodes the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP).

Accumulation TNSALP substrates
Inorganic pyrophosphate (PPI): inhibitor of bone mineralization
Phosphoethanolamine (PEA)
Vitamin B6/Pyridoxal 5-Phosphate
Infantile (severe), childhood, adult (mild)
Symptoms can vary, even with the same mutation
Defective mineralization of bone and teeth, leading to bone deformities, rickets, fractures, bone pain, loss of teeth, poor dentition, ↑ serum Ca2+
Multiple systemic effects such as respiratory compromise, seizures, myopathy, and renal complications
Diagnosis: Low ALP → genetic testing
Elevated PEA and Vitamin B6
Adult onset HPP can be missed, given the uncommon and complex nature of disease.
Few reports of HPP presenting in adulthood mistaken for osteoporosis.

30-year-old female, PMH of endometriosis and leg pain
Presented to her family medicine physician with long history of chronic, progressive bone pain
As a child and adolescent, her bone pain was classified as growing pain.
Her alkaline phosphatase level at the time of the visit was 31 U/L (35-147 U/L).
She previously had decreased alkaline phosphatase levels intermixed with levels on the low side of the normal range.
Her physician noted bone pain, short stature, and decreased alkaline phosphatase levels and discussed possible genetic causes.

Genetic testing identified an ALPL gene .571G>A (p.Glu191Lys) mutation, indicating HPP.
Since diagnosis:
Renal ultrasound negative for stones
Normal DEXA scans
Normal tibial x-rays
Treatments:
Pain management
Tapentadol 200 mg, gabapentin 300 mg, buprenorphine 10 mcg/hour weekly transdermal patch
Enzyme Replacement
Asfotase alfa (Strensiq)—recombinant glycoprotein active site of TNSALP, started January 2021, required extensive testing for insurance approval
Other treatment options: alkaline phosphatase replacement therapy, Teriparatide—modified parathyroid hormone that promotes bone growth

Figure 1: Results of a normal bone density DEXA scan

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Result</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>urinal PEA</td>
<td>30–200</td>
<td>10–80</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>67.1 mg/dL</td>
<td>20–125</td>
</tr>
<tr>
<td>Pyridoxal 5-Phosphate</td>
<td>13 mcg/L</td>
<td>5–50</td>
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</tbody>
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HPP is important to consider in patients with chronic bone pain
Low to low-normal alkaline phosphatase levels
Distinguish bone pain compared to pain of muscular origin, as seen with fibromyalgia.
Consider HPP in patients thought to have early-onset osteoporosis
Fragility fractures → ALP levels
Diagnosis of HPP may provide more treatment options with asfotase alfa, teriparatide, and alkaline phosphatase replacement.
Pain management has not been enough for this patient
Insurance coverage is a barrier
Results of asfotase alfa (Strensiq) is unknown for this patient, as treatment started recently, but provides hope

REFERENCES