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Hypophosphatasia

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HYPOPHOSPHATASIA

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ABSTRACT

We review here clinical, pathophysiological, diagnostic, genetic and molecular aspects of Hypophosphatasia (HPP), a rare inherited metabolic disorder. The clinical presentation is a continuum ranging from a prenatal lethal form with no skeletal mineralization to a mild form with late adult onset presenting with nonpathognomonic symptoms. The prevalence of severe forms is low, whereas less severe forms are more frequently observed. The disease is caused by loss-of-function mutations in the *ALPL* gene encoding the Tissue Nonspecific Alkaline Phosphatase (TNSALP), a central regulator of mineralization. Severe forms are recessively inherited, whereas moderate forms are either recessively or dominantly inherited, and the more severe the disease is, the more often it is subject to recessive inheritance. The diagnosis is based on a constantly low alkaline phosphatase (AP) activity in serum and genetic testing that identifies *ALPL* mutations. More than 340 mutations have been identified and are responsible for the extraordinary clinical heterogeneity. A clear but imperfect genotype-phenotype correlation has been observed, suggesting that other genetic or environmental factors modulate the phenotype. Enzyme replacement therapy is now available for HPP, and other approaches, such as gene therapy, are currently being investigated.

HIGHLIGHTS

- The overall prevalence of severe HPP range from 1/100 000 to 1/300 000
- Mild forms of HPP are more frequent than severe forms
- There is a clear but imperfect genotype phenotype correlation
- Carriers of ALPL mutations may have unspecific signs not due to their heterozygosity

KEYWORDS

Hypophosphatasia, TNSALP, ALPL mutation, genotype-phenotype correlation, prevalence, dominant mutation

ABBREVIATIONS

5' UTR	5' untranslated region
3' UTR	3' untranslated region

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