Table 1 Subtypes of hypophosphatasia and features

Subtypes	*Onset*	*Features*
Perinatal lethal	Fetus, neonate	Respiratory failure, severe mineralization defect, convulsion
Perinatal non-lethal	Fetus, neonate	Bone deformity
Infantile	Infant	Failure to thrive, hypercalcemia
Childhood	Child, especially toddlers	Premature loss of teeth, rickets-like changes
Adult	Adulthood	Fragile bone
Odonto	Not indicated	Teeth involvement only

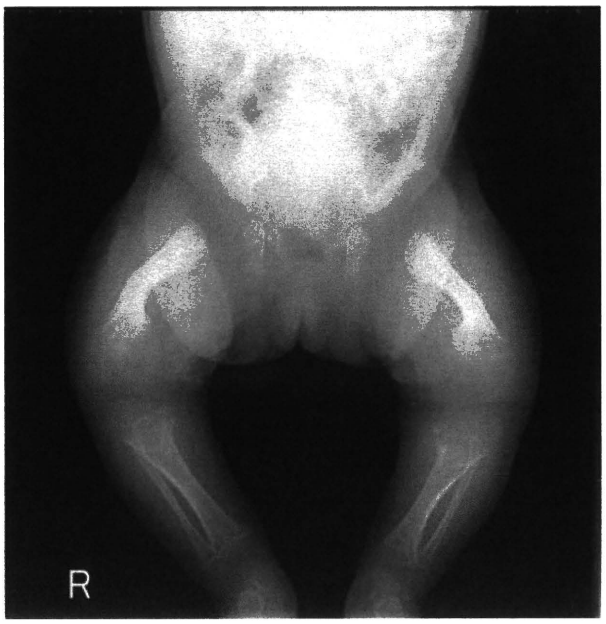

Figure 1 X-ray of legs of a neonate of hypophosphatasia. Severe rachitic changes of metaphysis of long bones are characteristic to hypophosphatasia. Bone deformity is also recognized.

the genotype–phenotype relationship, consistent with the enzymatic activity of the mutant ALP proteins; c.1559delT caused a complete loss of activity, whereas p.F327 L retains some residual activities. Therefore, genotyping patients with hypophosphatasia may help to predict their prognosis. In Europe, the E174K (renamed to p.E191K) mutation is reported to be frequent with a frequency of 31% in patients with mild hypophosphatasia.[7] As the E174K is associated with the same rare haplotype, the E174K mutation is surmised to be an ancestral mutation. However, the allele frequency of the E174K mutation is not investigated in normal population. In this issue of the journal, Watanabe *et al.*[8] reported prevelance of c. 1559delT in *ALPL*, a common mutation resulting in the perinatal (lethal) form of hypophosphatasias in Japanese. According to the article, the frequency is one per 480 (1/480), resulting in 1/920 000 homozygotes, because *de novo* mutation seems extremely rare. The frequency indicates more than one patient with this homozygous mutation is born per year in Japan, which has ~1 100 000 newborns per year. In our experience of examination of mutation in the *ALPL* gene in 42 patients with hypophosphatasia, homozygous mutation of c.1559delT was found in 17% patients. Thus, around seven patients with hypophosphatasia per year may be born in Japan based on the small number of examination. The carrier frequency for the mutant allele is estimated to be 1/25 in the Manitoba Mennonite community in Canada, which has the highest incidence rate for severe form of hypophosphatasia.[9]

There is no established medical treatment to cure hypophosphatasia, but there are some specific treatments for complications of hypophosphatasia.[1] In severe form of hypophosphasia, patients often suffer from intractable convulsions. This complication was also reported in $akp2^{-/-}$ mice.[10] The convulsion can be controlled by administration of vitamin B6 because abnormal metabolism of vitamin B6 leading to the deficient γ-aminobutyric acid in brain is observed in $akp2^{-/-}$ mice. In an infantile form of hypophosphatasia, patients tend to have hypercalcemia because of low bone formation. Low calcium-containing milk is recommended for hypercalcemia. Recently, treatment with parathyroid hormone 1–34, teriparatide, has been reported to improve bone formation, although its effect is still controversial.[11,12] Bone marrow transplantation has been reported to treat several patients with hypophosphatasia.[13] However, a method must be developed that improves the survival of donor mesenchymal cells in patients. Likewise, other congenital enzyme defect disorders, such as Hurler or Hunter disease, recombinant enzyme replacement therapy is being attempted in hypophosphatasia. Recombinant bone-targeted ALP therapy is effective in terms of mineralization and life-span in $akp2^{-/-}$ mice.[14] The therapy is now on clinical trial and expected to be available in near future.

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