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Case Report

Effects of enzyme replacement therapy in sibling cases of hypophosphatasia of varying severities

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Highlights

- Siblings with HPP of varying disease severities had the same *ALPL* variants.
- ERT should be considered for perinatal benign HPP if bone symptoms worsen.
- Patients with odonto-HPP should be examined for bone and extraosseous symptoms.

Abstract. Hypophosphatasia (HPP) is a hereditary disorder characterized by impaired bone mineralization caused by decreased tissue-nonspecific alkaline phosphatase (TNSALP) activity. Specifically, HPP is caused by a loss-of-function variant in the *ALPL* gene encoding TNSALP. Although genotype-phenotype correlations have been described, phenotypic differences have been reported in patients with the same variants, even within families. The proband, a girl, was suspected to have in utero fractures of the long bones, suggestive of osteogenesis imperfecta. No respiratory impairment was observed after birth; however, the patient's serum alkaline phosphatase level was low. In addition, the patient's perinatal findings were consistent with those of perinatal benign HPP, although the bone symptoms subsequently worsened. The patient's brother, initially suspected to have odonto-HPP due to the premature loss of primary teeth, later developed compression fractures and extraosseous symptoms. Both patients had the same *ALPL* variants, c. 572A>G(;)1559del, p. Glu191Gly(;)Leu520ArgfsTer86; however, the severity of their conditions differed. Patients with HPP with identical genotypes in the same family may have varying severity levels of HPP. In this case report, both patients received enzyme replacement therapy (ERT), which improved the clinical symptoms. Therefore, for perinatal benign HPP, ERT should be considered if bone symptoms worsen. In addition, odonto-HPP should be closely monitored, and ERT should be considered if bone and extraosseous symptoms arise.

Key words: hypophosphatasia, TNSALP, enzyme replacement therapy, recombinant alkaline phosphatase

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Introduction

Hypophosphatasia (HPP) is a hereditary disorder characterized by diminished bone mineralization caused by impaired tissue-nonspecific alkaline phosphatase (TNSALP) activity (1, 2). TNSALP is an alkaline phosphatase (ALP) isoform predominantly expressed in the bone, liver, and kidney, and it is important for bone mineralization (3). Other TNSALP substrates include pyridoxal-5-phosphate (PLP) (vitamin B6) and phosphoethanolamine (PEA) (4). Reduced TNSALP activity in HPP inhibits PLP dephosphorylation to pyridoxal, elevates circulating PLP levels, and decreases intracellular PLP and seizures (5, 6). High urinary PEA levels have been reported in patients with HPP, suggesting its potential as a diagnostic marker (4). HPP is caused by loss-of-function pathogenic variants in the *ALPL* gene encoding TNSALP (1, 2), and it is inherited as an autosomal recessive or dominant trait (1, 2).

The first known case of an infant with HPP was characterized by low ALP levels, severe rickets, and epilepsy (7, 8). The clinical symptoms of HPP vary with age and severity, and the disease is generally classified into perinatal severe, perinatal benign, infantile, childhood, adult, and odonto forms (6, 9). Perinatal severe HPP presents with fatal bone symptoms during the fetal and neonatal periods, whereas perinatal benign HPP shows spontaneous improvements in bone symptoms (6, 9). Conversely, odonto-HPP is characterized solely by tooth involvement without bone symptoms (6, 9). In Japan, perinatal or infantile HPP is predominantly inherited as an autosomal recessive trait (1, 9–11). The pathogenic variant of *ALPL*, c.1559del, p.Leu520ArgfsTer86, is highly prevalent in the general Japanese population, occurring in approximately one in 480 individuals (10). In addition, this variant presents with an almost complete loss of TNSALP activity (9–11). Patients with the homozygous autosomal recessive p.Leu520ArgfsTer86 variant exhibit the perinatal severe form of the disease (9–11). Genotype-phenotype correlations have been described in patients with HPP, particularly in patients with the perinatal severe form; however, phenotypic differences have been reported in patients within the same family with identical variants (9, 12–14).

However, the reasons for phenotypic differences among identical genotypes in HPP remain unclear. Patients with severe HPP, including perinatal severe and infantile forms, often experience fatal outcomes during the perinatal or infant period due to respiratory failure, multiple fractures, and pyridoxine-dependent seizures (1, 15, 16). Enzyme replacement therapy (ERT) using bone-targeted recombinant ALP (asfotase alfa [AA]) has been developed to improve patient prognosis (17–19). ERT has demonstrated safety and efficacy in the treatment of patients with HPP in several clinical trials and significantly improved survival rates (17–19).

The present study describes the clinical course of two siblings with HPP having identical genotypes but differing disease severities. We evaluated the therapeutic efficacy of ERT with AA in both patients and discussed the significance of treating less severe or nonperinatal HPP cases.

Case Report

Patient 1

The patient, a girl, is the third child of nonconsanguineous Japanese parents. Prenatal ultrasound at 28 wk and 6 d of gestation revealed a fetus with short and bowed limbs. Subsequent computed tomography at 30 wk and 5 d revealed suspected in utero fracture of the long bones, suggesting osteogenesis imperfecta. The mother was referred to our hospital at 34 wk and 3 d of gestation. The patient was delivered via cesarean section at 38 wk and 1 d, with Apgar scores of 8 and 9 at 1 and 5 min, respectively. No respiratory problems were observed after birth. The patient exhibited a significantly shorter stature and had very low ALP levels (**Table 1**). In addition, the patient's bone radiographs revealed hypomineralization, irregular and widened metaphyses, and bowing of the long bones; however, there were no thoracic hypoplasia or cranial abnormalities (**Fig. 1a**). Perinatal findings were consistent with those of perinatal benign HPP. The patient was discharged at 6 d of age without any respiratory complications. Follow-up bone radiographs obtained during an outpatient visit at 27 d of age revealed worsening bowing and hypomineralization of the long bones (**Fig. 1b**). Mild hypercalcemia and irritability were also observed. Based on the clinical symptoms and worsening bone conditions, the patient was ultimately diagnosed with an infantile HPP. Genetic sequence analysis identified two variants of *ALPL* (**Table 1**). Mild hypercalcemia improved after the regular use of low-Ca milk formula. The patient's parents consented to the patient's participation in the clinical trial for HPP. ERT with AA was initiated at 5 mo. At the start of AA treatment, the short stature of the patient was prominent (**Table 1**). Following the initiation of AA, the patient's ALP levels increased, with improvements in the bowing and mineralization of the long bones (**Fig. 1c**). However, craniosynostosis, first detected on bone radiographs at 1 yr and 10 mo, did not improve despite ongoing AA treatment (**Figs. 1d, e**). This condition was observed in the sagittal and frontal sutures; however, as it was mild, asymptomatic, and did not progress, no neurosurgical intervention was required. The child's early motor development was slightly delayed, with the child being able to turn over at 8 mo and sit up at 9 mo. However, the patient caught up in motor development, with the ability to pull up on things at 11 mo and walk independently at 1 yr and 2 mo. The patient's psychological development was normal. The AA dose was increased according to weight gain until 4 yr, after which the dose was not increased. Subsequently, the patient's overall health remained good, even with a dose of < 2 mg/kg administered three times per wk.

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Table 1. Clinical features of the two cases

	Patient 1	Patient 2	Reference range
Sex	Female	Male	
ALPL variants	p. Glu191Gly p. Leu520ArgfsTer86	p. Glu191Gly p. Leu520ArgfsTer86	
Type of hypophosphatasia At the time of initial diagnosis (age) At the time of final diagnosis (age) *ALP level at the time of diagnosis (age)	 perinatal benign (0 d) infantile (1 mo) 55 IU/mL (1 d)	 odonto (7 yr 11 mo) childhood (10 yr 1 mo) 136 IU/mL (7 yr 11 mo)	 525–1,590 454–1,250
Length or height (SD, age) At the time of birth At the time of diagnosis At the time of ERT initiation At last observation	 42 cm (−3.08, 0 mo) 42 cm (−3.08, 0 mo) 57 cm (−3.40, 5 mo) 123.7 cm (−1.97, 9 yr 11 mo)	 46 cm (−1.38, 7 yr 11 mo) 119.2 cm (−1.07, 7 yr 11 mo) 131.3 cm (−0.92, 10 yr) 159 cm (−1.82, 16 yr 2 mo)	
Age at the time of ERT initiation	5 mo	10 y 1 mo	
Dosage of ERT mg/kg/time (mg/kg/wk) At the time of ERT initiation At last observation	 2 (6) 1.24 (3.72)	 1.89 (5.67) 1.31 (3.93)	
Main clinical manifestations	bone deformity hypomineralization premature craniosynostosis mild hypercalcemia (13 mg/dL)	early loss of deciduous teeth ankle pain exercise difficulty	

ERT, enzyme replacement therapy. * Japan Society of Clinical Chemistry method.

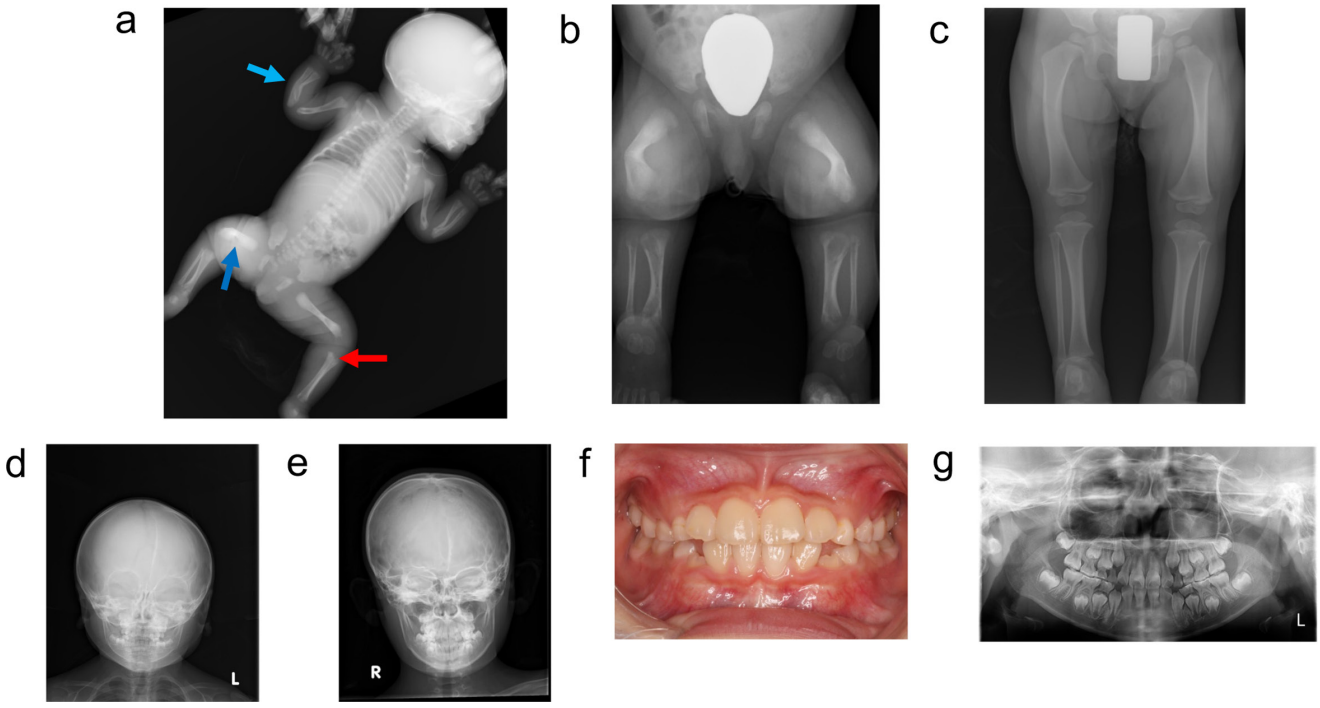

Fig. 1. Bone radiographs and intraoral photographs of Patient 1. (a) At birth, the patient exhibited hypomineralization, irregular and widened metaphyses (red arrows), and bowing of long bones (blue arrows) but had no thoracic hypoplasia or cranial abnormalities. (b) At 27 d, the bowing and hypomineralization of the long bones worsened. (c) Lower limbs at 1 yr and 10 mo. (d) Head radiograph at 1 yr and 10 mo. Premature fusion in the sagittal and frontal sutures are obserbed. (e) At 9 yr and 11 mo. Craniosynostosis did not improve with continued asfotase alfa (AA) treatment. (f) Intraoral photographs of Patient 1 at 8 yr and 9 mo. The patient had no loose teeth. No problems with permanent tooth eruption were encountered. (g) Panoramic radiograph of Patient 1 at 8 yr and 9 mo. No major abnormalities.

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The patient was 9 yr and 11 mo old at the time of study. The patient attends a regular elementary school and demonstrates good academic and athletic performance. Regular dental examinations revealed no major dental problems (**Figs. 1f, g**).

Patient 2

Patient 2, a boy, is the older brother of Patient 1. The patient was born at 40 wk of gestation. The patient's motor development during infancy was normal. However, the patient's incisor had fallen out before 1 yr of age, followed by six deciduous teeth by the age of 4. The permanent teeth erupted at age 6 without subsequent loss. The patient could not run fast and exhibited difficulties with motor activities. Given that the patient's younger sister had been diagnosed with HPP diagnosis and the patient's history of premature deciduous tooth loss, a characteristic of HPP, HPP was suspected. Although the patient did not exhibit bone symptoms, early loss of primary teeth occurred. Neither the patient's parents nor older sister displayed dental symptoms or fractures. The father's ALP levels were not assessed; however, the mother's ALP level was 160 IU/L, which fell within the reference range of 106–322 U/L. The patient visited our hospital at the age of 7 yr and 11 mo. The measured serum ALP levels were lower but less severe at presentation compared to the sister (**Table 1**).

The patient's brother was initially diagnosed with odonto-HPP; however, subsequent bone radiographs revealed mild lumbar spine compression (**Fig. 2a**). Furthermore, the patient did not have the craniosynostosis observed in Patient 1. These findings were consistent with those of childhood HPP. The patient could not run fast, had difficulty exercising, could only leap over three vaulting boxes, and reported occasional ankle pain. Although the patient's symptoms were less severe than those of Patient 1, genetic analysis confirmed that they had two identical *ALPL* variants. Consequently, ERT was initiated at age 10. Subsequently, the ankle pain resolved. The incisor tooth movement gradually improved from approximately 12 yr and 8 mo of age. In addition, radiographic findings revealed an improvement in lumbar spine compression (**Fig. 2b**). The patient's overall health remained stable despite receiving ERT at < 2 mg/kg three times per wk (6 mg/kg/wk). The patient was 16 yr and 2 mo old at the time of this study. In addition, the patient attends high school, is doing well academically and athletically, and is a badminton club member. The patient's dental findings before treatment showed that the mobility of the mandibular anterior teeth was slightly greater than physiological tooth mobility. Maxillary incisor eruption was delayed for 1 yr (**Figs. 2c, d**). The patient underwent regular dental checkups, which revealed no major dental problems (**Fig. 2e**). Our patients were included in two previous nationwide surveys (9, 20).

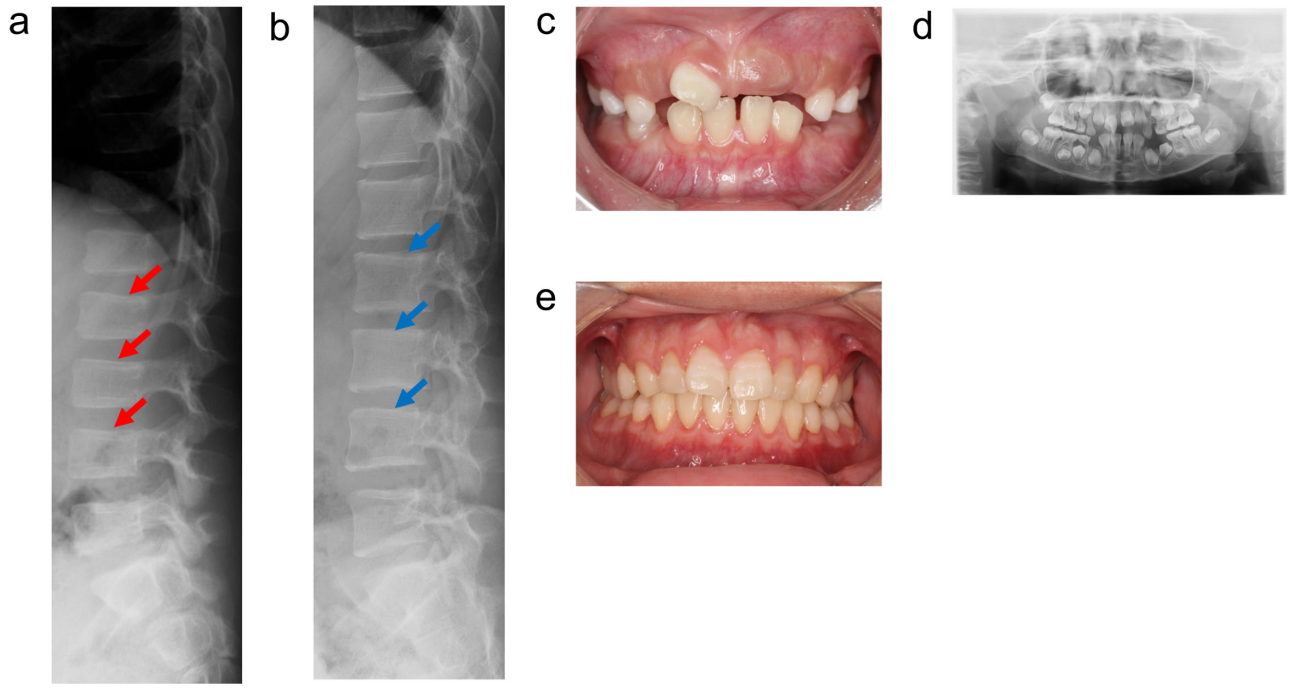

Fig. 2. Bone radiographs and intraoral photographs of Patient 2. (a) At 7 yr and 11 mo. The patient's bones showed mild lumbar spine compression (red arrows). (b) At 14 yr old, radiographic findings exhibited improvements in lumbar spine compression (blue arrows). (c) Intraoral photographs of Patient 2 at 8 yr and 0 mo. The mobility of the mandibular anterior tooth was slightly greater than the mobility of the physiological tooth. (d) Panoramic radiograph of Patient 2 at 8 yr and 0 mo. The root formation of permanent teeth was delayed, and some alveolar bones had been absorbed. (e) Intraoral photographs of Patient 2 at 16 yr and 10 mo. No significant abnormalities are observed.

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Genetic analysis

The Institutional Review Board of Osaka Women's and Children's Hospital approved the genetic analysis protocol. Genomic DNA was extracted from peripheral blood leukocytes, followed by polymerase chain reaction (PCR) amplification of all coding exons and exon/intron boundaries using previously reported primers (9, 21). The PCR products were gel-purified and sequenced using Sanger sequencing (9, 21). Genetic sequencing revealed that the two patients shared two identical variants of *ALPL* (NM_000478.5), c. 572A>G(;)1559del, p. Glu191Gly(;)Leu520ArgfsTer86. These variants are present in the Clin Var and *ALPL* mutation database (https://alplmutationdatabase.jku.at). Furthermore, these variants were scored according to the American College of Medical Genetics and Genomics standards and guidelines for the interpretation of sequence variants as follows: the former was scored as "likely pathogenic" (PS3, PM3 and PM5) and the latter as "pathogenic" (PVS1, PS3 and PS4), respectively (9, 11, 22). The patients' parents opted not to undergo subsequent genetic analyses. Written informed consent was obtained from the parents after ensuring patient anonymity and confidentiality. This study was approved by the Ethics Committee of Tohoku University School of Medicine.

Discussion

The two siblings in this case report shared the same two pathological *ALPL* variants, c.572A>G(;)1559del, p. Glu191Gly(;)Leu520ArgfsTer86, which were assumed to be biallelic. Only two cases of these compound heterozygous variants have been described (23, 24). In a study by Goseki *et al*., a Japanese female patient presented with isolated symptoms of premature deciduous tooth loss, without clinical or radiographic evidence of bone symptoms. The patient was diagnosed with odonto-HPP (23). In contrast, Sugiyama et al. reported a patient with mild childhood HPP. Of the two variants found in our patients, c.1559del, p.Leu520ArgfsTer86 is the more common pathogenic *ALPL* variant in the Japanese population, resulting in a nearly absent TNSALP activity (9–11). Patients with a homozygous variant typically have perinatal severe HPP, whereas individuals with a monoallelic variant may display a range of HPP forms (9–11). The second variant found in our patients, c.572A>G, p.Glu191Gly, shows residual activity similar to the p.Phe327Leu variant, which is a well-known variant with high residual activity and is associated with HPP only when it occurs in a compound heterozygous form, supporting the compound heterozygosity in our two siblings (9, 20, 23, 24).

One of the siblings was initially diagnosed with perinatal benign HPP but later developed symptoms consistent with the infantile form. The other sibling, diagnosed with odonto-HPP during infancy, was later confirmed to have the childhood form after further evaluation. The factors underlying the phenotypic variability among individuals with identical HPP genotypes are poorly understood. Michigami *et al*. demonstrated that the *ALPL* genotype may predict the clinical course of HPP to a degree in Japanese patients with HPP; however, symptom severity may differ among patients with identical genotypes, suggesting the influence of modifying factors (9). In adults with heterozygous *ALPL* variants, *COL1A2* has been reported as a potential modifier of HPP (25).

In our case report, Patient 1 had a fetal bony deformity but presented with mild symptoms immediately after birth, with no respiratory disturbance, and was initially diagnosed with perinatal benign HPP. Subsequently, the patient exhibited an infantile-form-like course, with worsening bone symptoms and hypercalcemia. However, early ERT improved the patient's symptoms. Furthermore, the patient had a markedly short stature and delayed motor development in infancy, which improved after ERT administration. Patient 2, Patient 1's older brother, was diagnosed with odonto-HPP during infancy and was later confirmed to have the childhood form after further evaluation. The patient experienced ankle pain and difficulty exercising; however, the symptoms improved after ERT induction. HPP exhibits considerable variability over the course of disease (6). Consequently, close monitoring of disease progression in patients initially diagnosed with odonto-HPP or perinatal benign HPP and timely ERT initiation are crucial.

Craniosynostosis is a well-known complication of HPP. The first study on AA in severe cases reported improvement in two of 11 patients within the first 6 mo of treatment (17). Patient 1 exhibited craniosynostosis, as observed in bone radiographs at 1 yr and 10 mo (**Fig. 1g**), which persisted despite continued AA therapy (**Fig. 1h**). However, the effect of ERT on craniosynostosis in patients with HPP remains unclear (6).

The indication for ERT for Patient 2 was based on two considerations: dental symptoms and extraosseous problems in less severe HPP. Only few cases of ERT for the treatment of odonto-HPP have been reported (26, 27). A recent study of ERT for odonto-HPP did not report any new mobile tooth after ERT initiation (26). The premature loss of deciduous teeth causes alveolar bone loss, dental misalignment, and premature permanent tooth loss (28). In odonto-HPP, an average of 4.2 deciduous teeth are lost prematurely, which correlates with HPP severity (29). Patient 1 had undergone ERT since infancy and did not experience premature loss of deciduous teeth, unlike Patient 2. To date, none of the patients has experienced complications affecting their permanent teeth (**Fig.1f**, **Fig. 2e**). Regarding the assessment of the effect of ERT on dental symptoms in patients with HPP, further investigation is necessary because of the limited number of cases involving odonto-HPP treatment. In addition, Patient 2 experienced improvements in mobility and relief from ankle pain with the treatment. Besides, HPP guidelines recommend ERT even for patients with disease forms with a relatively favorable prognosis.

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This is because HPP-related symptoms, including bone symptoms and muscle weakness, improve significantly after ERT administration (6). In addition, the guidelines recommend ERT for improving motor function (6). This is consistent with the findings of a study on the effects of 5-yr ERT in pediatric patients, which reported improved motor function, similar to our cases (18). Thus, ERT should be considered for bone and extraosseous symptoms, even in mild forms of HPP.

Few stuides exist on AA treatment for mild HPP (26, 30, 31). A recent Japanese case report a patient with HPP with relatively mild symptoms revealed the efficacy of lower AA doses in improving bone symptoms (31). In both cases, ERT with AA was initiated at a dose of 2 mg/kg three times weekly. Despite this lower dose, no worsening of bone findings or clinical symptoms was observed, even at AA doses below the usual 6 mg/kg per wk. More cases are needed to validate the dose for patients with mild HPP after treatment initiation.

Conclusion

Siblings with HPP exhibited varying disease severities despite sharing the same *ALPL* variants. If bone symptoms worsen, ERT should be considered for perinatal benign HPP, and odonto-HPP should be carefully monitored for bone and extraosseous symptoms.

Conflict of interests: Toshimi Michigami received consulting and lecture fees from Alexion Pharmaceuticals, Inc. and Kyowa Kirin Co., Ltd. The other authors have no conflicts of interest to declare.

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