Odonto-hypophosphatasia with Tooth Agenesis: a Case Report

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Odonto-hypophosphatasia (odonto-HPP) is a mild form of hypophosphatasia (HPP) characterised by premature exfoliation of primary and/or permanent teeth accompanied by low serum alkaline phosphatase (ALP) activity levels, without abnormalities of the skeletal system. Tooth agenesis (TA) is a common developmental anomaly characterised by the absence of one or more teeth due to the failure of tooth formation. In this study, the present authors report on a family simultaneously affected by odonto-HPP and TA for the first time. Comprehensive genetic analysis identified two novel missense variants (c.103G>A and c.247G>A) in the ALPL gene associated with odonto-HPP and no pathogenic variants in the reported TA genes, which may expand the genetic spectrum of odonto-HPP and imply an unforeseen additional dental abnormality associated with HPP.

Keywords: *ALPL, odonto-hypophosphatasia, premature loss of primary teeth, tooth agenesis, variant*

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Hypophosphatasia (HPP) is a rare inherited disorder characterised by reduced serum alkaline phosphatase (ALP) activity, which is usually caused by loss-of-function mutations in the liver-bone-kidney alkaline phosphatase (*ALPL*) gene and mainly affects bone and teeth mineralisation.[1] The incidence of HPP shows disparities among various regions and demographic groups, with rates spanning from 1/300,000 to 1/6,370.[2,3] The clinical phenotype of HPP is extremely variable, ranging from mild dental abnormalities to severe skeletal issues and potentially life-threatening complications. Currently, according to the age of diagnosis and the presence or absence of skeletal symptoms, HPP is divided into six types: perinatal, prenatal benign, infantile, childhood, adult and odonto-HPP.[1] Odonto-HPP is one of the mildest and likely most prevalent forms of HPP. Premature loss of primary teeth is the common phenotype of patients with childhood, adult and odonto-HPP,[4] and is also likely to be the earliest clinical manifestation.[5] Premature loss of primary teeth may be attributed to low serum ALP activity levels, which lead to defects in the development of acellular cementum and affect the development of tooth root and periodontal ligament attachment.[1,6-8]

Tooth agenesis (TA) is one of the common tooth development abnormalities and refers to a reduction in the number of teeth due to tooth germ development disorder. The reported prevalence is around 2.2% to 10.1% (excluding the third molars).[9] TA can occur in isolation or as an accompanying symptom of certain systemic diseases, with over 150 known syndromes having been linked to this dental anomaly.

Thus far, there are no clinical reports connecting odonto-HPP and TA. In this study, the present authors report on a family affected by odonto-HPP and TA at the

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same time and analyse their relationship from a clinical and genetic viewpoint.

Case presentation

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the School of Stomatology, Fourth Military Medical University (IRB-YJ-2022040). Informed consent was obtained from all subjects involved in the study. Written consent was specifically acquired from the patients for the publication of this paper.

A 4.5-year-old boy attended the Clinic of Oral Rare Diseases and Genetic Diseases of the Fourth Military Medical University with his parents and complained of premature loss of his primary anterior teeth. He had normal growth and development, no significant medical history of abnormal birth weight, rickets or osteomalacia, bone fracture, late closure of fontanels or delayed walking with a characteristic "waddling" gait. The oral examination revealed several dental caries and the absence of teeth 72 and 82 (Fig 1a to c). Panoramic radiographs revealed that the tooth germ for teeth 15, 17, 25, 27, 35, 37, 42, 45 and 47 was not visible, and there was reduced alveolar bone, enlarged pulp chambers and root canals in the proband (Fig 1d). The authors provided comprehensive treatment for the proband's dental caries and removed the non-salvageable teeth (Fig 1e to g). After the 3-month postoperative review, it was found that teeth 73, 75 and 81 had fallen out (Fig 1h to j). Notably, the root structure of the prematurely lost mandibular right primary central incisor was mainly preserved (Fig 1k). Subsequently, a removable functional space maintainer was inserted to maintain the missing tooth space in the primary dentition and restore chewing function (Fig 1l to n). The patient's serum ALP level (58U/L) was lower than the reference value (143-406 U/L). There were no abnormalities in serum calcium, serum phosphorus, parathyroid hormone and 25-hydroxyvitamin D.

The proband's father also reported a history of premature loss of primary teeth (details unavailable) and mandibular anterior teeth (32 and 41) with a low serum ALP level of 22 U/L (reference range 40 to 150 U/L). Panoramic radiographs showed that teeth 35 and 45 were congenitally missing and that there was alveolar bone I to II resorption (Fig 1o). The proband's mother did not have a history of premature loss of primary teeth and presented a normal serum ALP level. They did not report any other significant bone abnormalities and did not have a history of epilepsy or other systemic diseases.

In summary, considering the clinical presentation along with the results from laboratory tests and radiological assessments, the proband and his father were identified as having concurrent odonto-HPP and TA.

Genomic DNA was extracted from the peripheral blood of the family members and analysed using whole-exome sequencing (WES) and Sanger sequencing. Exons were captured using the Agilent SureSelect Human All Exon V6, and sequencing was performed on the BGISEQ-500 platform (BGI, Shenzhen, China). The mean sequencing depth of target region was higher than 100, and 20× coverage for more than 98% targeted bases was achieved for each sample. The secondary analysis was performed using the Genome Analysis Toolkit (GATK) (v4.4.0.0) software suite (Broad Institute, Cambridge, MA, USA) for sequencing data analysis. Sequencing fragments were compared with the human reference genome hg38 reference genome using the Burrows-Wheeler-Alignment (BWA) Tool and screened based on ClinVar, OMIM, HGMD, 1000G, SnpEff and gnomAD databases. A panel of the silico pathogenicity prediction tools (including SIFT, PolyPhen-2 HVAR, PolyPhen-2 HDIV, FATHMM, PROVEAN, MutationAssesor, MutationTaster and CADD) was employed to evaluate the variants.

Two novel missense variants (c.103G>A/p.Glu35Lys and c.247G>A/p.Glu83Lys) in the *ALPL* gene were found in the proband and his father (Fig 2a). According to the American College of Medical Genetics classification standards, the variants c.247G>A (PM1, PM2, PP2, PP3, PP4) and c.103G>A (PM1, PM2, PP2, PP4) were classified as variants of likely pathogenic (LP). To verify the variants in *ALPL*, regular polymerase chain reaction (PCR) was performed, the PCR products were analysed by Sanger sequencing and sequence data were analysed using Sequencher software 5.4.5 (Gene Codes, Ann Arbor, MI, USA) (Fig 2b). The sequence conservation analysis indicated that p.Glu83 has a high degree of sequence conservation in 10 distinct species, followed by p.Glu35 (Fig 2c). Structural prediction of ALPL variants indicated that the Glu83Lys substitution (Fig 2d and e) eliminates two hydrogen bonds between this residue and Arg391/Gly392, which reduces intermolecular interactions. By contrast, the Glu35Lys variant (Fig 2f and g) gains a novel hydrogen bond with Gln32 but loses the native hydrogen bond linked to Lys38. Such rearrangement of hydrogen-bonding networks disturbs intermolecular forces and ultimately impairs the structural stability and physicochemical characteristics of the target protein.Furthermore, multiple in silico pathogenicity prediction tools indicated that the c.247G>A variant is predicted to be deleterious,

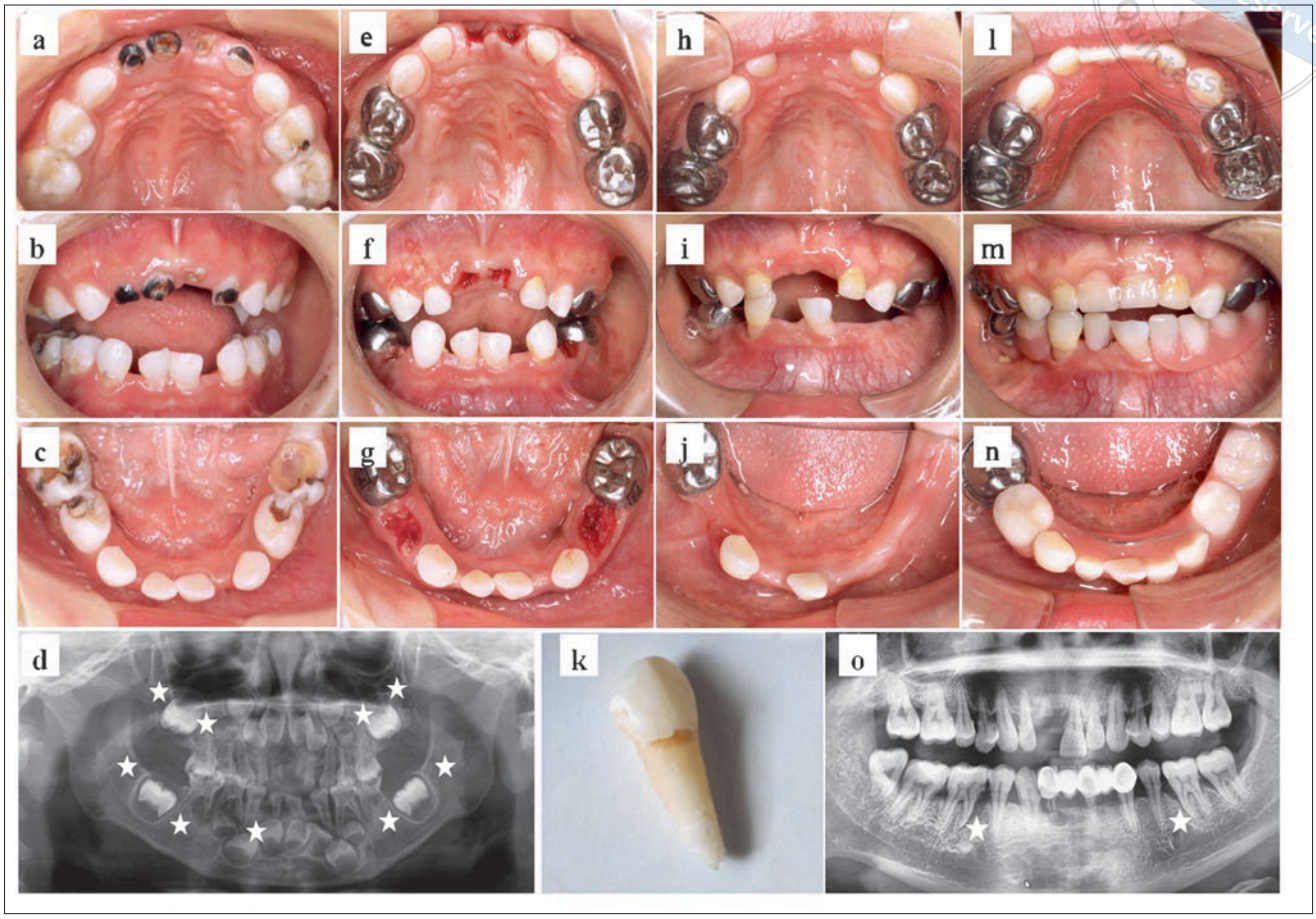

Fig 1a to o Intraoral images of the proband taken at the initial visit **(a to c)**. Panoramic radiograph of the proband **(d)**. Intraoral images of the proband taken after initial treatment **(e to g)**. Intraoral images of the proband taken 3 months postoperatively **(h to j)**. The proband's exfoliated tooth 81 **(k)**. Intraoral images of the proband taken after wearing a removable functional space maintainer **(l to n)**. Panoramic radiograph of the proband's father **(o)**. The star symbol represents a congenitally missing permanent tooth.

whereas the c.103G>A variant is predicted to be benign or well-tolerated.

Next, given the presence of TA in both the proband and his father, the present authors screened the WES data against known pathogenic genes associated with this condition. However, following an autosomal dominant inheritance pattern, no causative variant was identified, and it was not possible to explain why the proband presented with a more severe congenital phenotype than his father.

Discussion

Odonto-HPP is an inherited disorder characterised by a decline in serum ALP activity, which is in turn characterised by premature exfoliation of primary and/or permanent teeth, without abnormalities of the skeletal system. Thus far, the *ALPL* gene remains the sole identified gene associated with HPP, and there have been reports of over 400 *ALPL*-related mutations (usually missense). The *ALPL* gene, situated on chromosome 1p, encompasses 12 exons and encodes for 524 amino acids. There are five domains identified in *ALPL*: the active site, the homodimer interface, the crown domain, the N-terminal α-helix and the metal-binding site. The N-terminal α-helix region plays a critical role in guiding the correct folding of tissue-nonspecific alkaline phosphatase (TNAP) and supports the assembly of other functional domains, with its stability dependent on an integrated "hydrogen bond network and local charge balance" system.

In this study, the present authors identified two new missense variants responsible for the odonto-HPP phenotype in the proband and his father. Both p.Glu35Lys and p.Glu83Lys localised within the core segment of α-helix domain. These dual-site perturbations synergistically amplify local charge repulsion, inducing complete destabilisation of the N-terminal

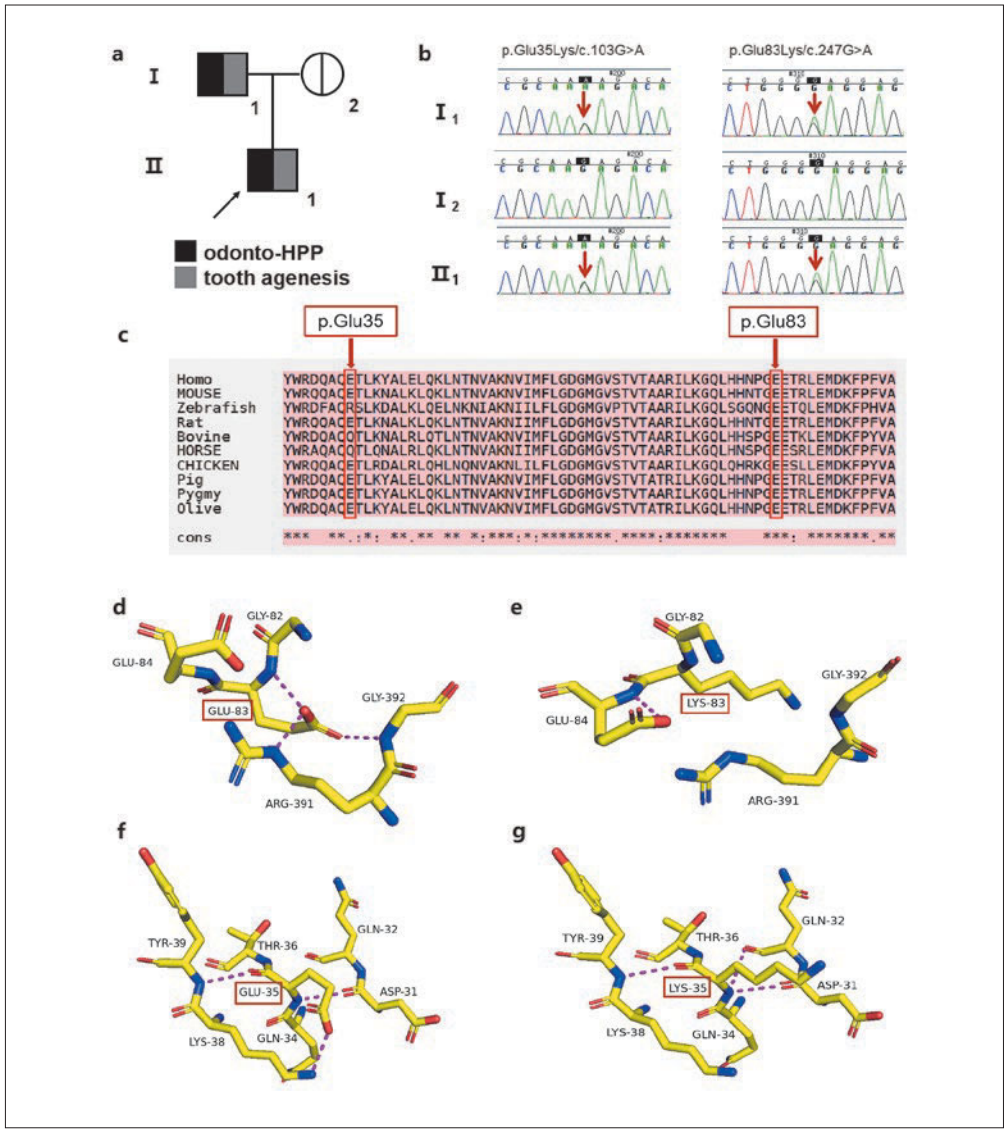

Fig 2a to g Pedigree map (black arrows represent the proband) **(a)**. Sanger sequencing chromatograms (red arrows represent the position of mutated bases) **(b)**. Protein sequence alignment comparing the partial amino acid sequences of *ALPL* between humans and a number of other species (red arrows indicate the amino acids that were altered in *ALPL*) **(c)**. Structural representation of amino acid 83 in wild-type and mutant proteins. Glu83 formed three hydrogen bonds to Gly82, Arg391 and Gly392, while Lys83 formed only one hydrogen bond to Glu84 **(d and e)**. Structural representation of amino acid 35 in wild-type and mutant proteins. Glu35 formed three hydrogen bonds to Asp31, Try39 and Lys38, while Lys35 formed three hydrogen bonds to Asp31, Gln32 and Try39 (pink dotted lines denote hydrogen bonds) **(f and g)**.

α-helix, an effect far more severe than that of either single variant alone, which results in the loss of its core function as the backbone for protein folding. Theoretically, the two missense variants are expected to synergistically disrupt TNAP structure, causing severe functional defects. Paradoxically, the carriers (the proband and his father) exhibited only mild clinical symptoms. This discrepancy highlights the complexity of genotype-phenotype correlations, likely mitigated by in vivo compensatory mechanisms.

A number of mechanisms may explain the milder phenotypes. First, partial functional retention might be the key. Theoretically, the dual variants are expected to induce structural collapse of TNAP, reducing its activity below 20% of normal, the threshold for HPP. However, the unique structural characteristics of the N-terminal α-helix domain mean its disruption may cause only partial misfolding rather than complete destabilisation. Consequently, a fraction of functionally competent TNAP can still localise to mineralisation sites, meeting

basic physiological demands.[10] This possibility is supported by the recently revealed octameric architecture of TNAP.[11]

Second, a weak dominant-negative effect further explains the phenotypic heterogeneity in HPP. In the present case, both variants were located in the N-terminal α-helix domain. Although they caused misfolding, their interference with wild-type TNAP dimerisation and function was limited, resulting in a weak dominant-negative effect. Crucially, the impact differs drastically if a variant affects the dimer interface itself, where it can block dimerisation and exert a strong dominant-negative effect, leading to severe disease. This spectrum is illustrated by functional data: p.Glu191Lys (mild, 68% activity, no dominant-negative effect) versus p.Gly334Asp (severe, 1.2% activity, strong dominant-negative effect).[12]

Third, the buffering effect of modifying factors serves as a key mechanism that encompasses two dimensions: genetic and environmental modification. HPP exhibits pronounced phenotypic heterogeneity. Even with the same combination of variants, modifying factors can significantly attenuate disease severity. In terms of genetic modification, since the mechanism of mineralisation has been greatly deciphered, a series of genes involved in the inorganic phosphate and the inorganic phosphate metabolism has been suggested as possible modifiers of the HPP phenotype.[13] Regarding environmental modification, the early nutritional status, living environment and health conditions of patients can substantially influence phenotypic severity.[1]

Fourth, the dissociation between early onset and mild features can be explained by the developmental stage–specific function of the N-terminal α-helix. This domain is critical for the early membrane localisation and folding of TNAP during primary tooth development and initial bone mineralisation.[10] The structural defects caused by our variants are therefore most consequential at this early, high-demand stage, leading to identifiable yet mild manifestations. With aging, the activation of compensatory pathways may mitigate further functional decline, preventing the progressive features typical of moderate-to-severe HPP.[14]

The "structural damage potential" of the dual variants is counteracted by in vivo compensatory mechanisms, including the enzyme activity remaining above the clinical threshold, the weak dominant negative effects and the buffering role of modifying factors. Ultimately, the final clinical phenotype is characterised by "early onset yet mild manifestations". Thus, it is essential to recognise that even if dual variants are theoretically predicted to cause "severe structural disruption", they may still result in mild HPP. Clinical diagnosis should integrate serum ALP activity measurement with comprehensive clinical symptom assessment for accurate evaluation.

Previous studies have indicated that many patients with odonto-HPP exhibit other dental abnormalities. The present authors summarised the dental abnormalities of 26 odonto-HPP cases from the PubMed and CNKI databases from January 2000 to June 2024 (Table S1, available on request), which mainly include premature loss of primary teeth, alveolar bone resorption, abnormal tooth morphology, short root anomaly, enamel hypoplasia, enlarged pulp chambers and root canals, abnormal tooth eruption and dental caries; however, there are no reports of TA. Therefore, this represents the first documented case report of concurrent odonto-HPP and TA. Since no pathogenic genes for tooth agenesis were identified in this pedigree, the present authors prefer to hypothesise that tooth agenesis and odonto-HPP coexist incidentally, which may represent an unforeseen additional dental anomaly associated with odonto-HPP. However, due to limitations of sequencing technologies and potential biases in variant screening strategies, the possibility that this pedigree harbours novel pathogenic genes for tooth agenesis cannot be completely ruled out.

Notably, previous studies have indicated that many patients with HPP exhibit dental abnormalities and/or other symptoms during childhood, but the final diagnosis often occurs significantly later than the onset of these symptoms.[15,16] In this case, the proband lost his first primary anterior tooth at the age of 3 years and 6 months, and the confirmation of odonto-HPP was delayed by 12 months. Immediate evaluation for HPP is recommended for patients who experience early loss of primary teeth without a known cause to minimise diagnostic delays.

When dental symptoms appear early in life in the absence of skeletal disease, a diagnosis of odonto-HPP may seem appropriate at the time, but a subset of affected patients may later develop signs of childhood/adult HPP. Berkseth et al retrospectively reviewed the medical records of 22 adult patients with HPP. Most of these individuals presented with childhood dental abnormalities including premature exfoliation, retention, or agenesis of primary teeth, followed by the subsequent onset of chronic myalgia, arthralgia and recurrent pathological fractures. Some patients diagnosed with odonto-HPP in childhood may later present abnormalities other than teeth and develop signs of adult or childhood forms of HPP.[15] Consequently, patients presenting with apparently isolated dental symptoms should be monitored for the emergence of

bone or systemic symptoms during the remainder of childhood and throughout adulthood.

Conclusion

The present study reported on a family simultaneously affected by odonto-HPP and TA for the first time. Comprehensive genetic analysis identified two novel missense variants (c.103G>A and c.247G>A) in the *ALPL* gene associated with odonto-HPP and no pathogenic variants in the reported TA genes, which may expand the genetic spectrum of odonto-HPP and imply an unforeseen additional dental abnormality associated with HPP.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

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Author contribution

Dr Tao Yun XU contributed to clinical data collection, bioinformatics analysis and the manuscript draft; Dr Xin Yue GUO contributed to the critical review and revision of the manuscript; Dr Bai Ze ZHANG contributed to clinical data collection and patient follow-up; Dr Xiao Hong DUAN contributed to the study design and supervision and critical revision of the manuscript. All authors have read and agreed to the final version of the manuscript.

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References

1. Whyte MP. Hypophosphatasia - Aetiology, nosology, pathogenesis, diagnosis and treatment. Nat Rev Endocrinol 2016;12:233–246.
2. Watanabe A, Karasugi T, Sawai H, et al. Prevalence of c.1559delT in ALPL, a common mutation resulting in the perinatal (lethal) form of hypophosphatasia in Japanese and effects of the mutation on heterozygous carriers. J Hum Genet 2011;56:166–168.
3. Mornet E, Taillandier A, Domingues C, et al. Hypophosphatasia: A genetic-based nosology and new insights in genotype-phenotype correlation. Eur J Hum Genet 2021;29:289–299.
4. Bloch-Zupan A. Hypophosphatasia: Diagnosis and clinical signs - A dental surgeon perspective. Int J Paediatr Dent 2016;26:426–438.
5. Hughes SL, Parkes RC, Drage N, Collard M. Tooth loss in children: A warning sign of childhood hypophosphatasia. Dent Update 2017;44:317–318, 320–321.
6. Bloch-Zupan A, Vaysse F. Hypophosphatasia: Oral cavity and dental disorders. Arch Pediatr 2017;24:5S80-5S84.
7. Whyte MP, Zhang F, Wenkert D, et al. Hypophosphatasia: Validation and expansion of the clinical nosology for children from 25 years experience with 173 pediatric patients. Bone 2015;75:229–239.
8. Foster BL, Nagatomo KJ, Nociti FH Jr, et al. Central role of pyrophosphate in acellular cementum formation. Plos One 2012;7:e38393.
9. Polder BJ, Van't Hof MA, Van der Linden FP, Kuijpers-Jagtman AM. A meta-analysis of the prevalence of dental agenesis of permanent teeth. Community Dent Oral Epidemiol 2004;32:217–226.
10. Hoylaerts MF, Ding L, Narisawa S, Van Kerckhoven S, Millan JL. Mammalian alkaline phosphatase catalysis requires active site structure stabilization via the N-terminal amino acid microenvironment. Biochemistry 2006;45:9756–9766.
11. Yu Y, Rong K, Yao D, et al. The structural pathology for hypophosphatasia caused by malfunctional tissue non-specific alkaline phosphatase. Nat Commun 2023;14:4048.
12. Hofmann C, Girschick H, Mornet E, Schneider D, Jakob F, Mentrup B. Unexpected high intrafamilial phenotypic variability observed in hypophosphatasia. Eur J Hum Genet 2014;22:1160–1164.
13. Mornet E. Molecular genetics of hypophosphatasia and phenotype-genotype correlations. Subcell Biochem 2015;76:25–43.
14. Millán JL. The role of phosphatases in the initiation of skeletal mineralization. Calcif Tissue Int 2013;93:299–306.
15. Mori M, DeArmey SL, Weber TJ, Kishnani PS. Case series: Odontohypophosphatasia or missed diagnosis of childhood/adult-onset hypophosphatasia? – Call for a long-term follow-up of premature loss of primary teeth. Bone Rep 2016;5:228–232.
16. Seefried L, Dahir K, Petryk A, et al. Burden of illness in adults with hypophosphatasia: Data from the global hypophosphatasia patient registry. J Bone Miner Res 2020;35:2171–2178.