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CASE REPORT

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Odontohypophosphatasia caused by a novel combination of two heterozygous variants: a case report

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Abstract

Hypophosphatasia (HPP) is a rare genetic disorder mainly characterized by skeletal dysplasia that results from a deficiency in tissue-nonspecific alkaline phosphatase (TNSALP), which is encoded by the alkaline phosphatase (*ALPL*) gene. Odontohypophosphatasia (odonto-HPP) is a mild form of HPP characterized by oral symptoms, such as premature loss of primary teeth. This study was to describe a 4-year-old boy with premature loss of primary teeth who was diagnosed with odonto-HPP. X-ray radiography and laboratory examinations were performed for the diagnosis. Genetic etiology was revealed by whole-exome sequencing. A novel combination of two variants in the *ALPL* gene was identified in this case; this combination resulted in the odonto-HPP phenotype. c.346G>A (p.Ala116Thr) was inherited from the proband's father, whereas c.1563C>G (p.Ser521Arg) was inherited from the proband's mother. The proband's 8-year-old sister was a heterozygous carrier of c.346G>A (p.Ala116Thr) in the *ALPL* gene. Thus far, the proband's sister has been asymptomatic. Our findings indicate that c.346G>A is a pathogenic genetic alteration; c.1563C>G might cause a predisposition to the dental phenotype in combination with c.346G>A. It is important for pediatric dentists to consider a diagnosis of odonto-HPP in children with premature loss of primary teeth.

Keywords

Premature loss of primary teeth; Odontohypophosphatasia; *ALPL*; Heterozygous missense variants

1. Introduction

Deficient tissue-nonspecific alkaline phosphatase (TNSALP) enzyme activity is caused by a loss-of-function variant within the alkaline phosphatase (*ALPL)* gene and has been recognized as the underlying etiology of hypophosphatasia (HPP), a rare inborn-error-of-metabolism disease [1]. The resultant extracellular accumulation of TNSALP substrates, including inorganic pyrophosphate (a mineralization inhibitor) can impair the mineralization of teeth and bones. Clinical manifestations of HPP are extremely variable, ranging from perinatal death to adult dental problems and osteomalacia [2].

Six major classes of clinical manifestations of HPP have been reported, including lethal perinatal, prenatal (or perinatal) benign, infantile, childhood, adult, and odontohypophosphatasia (odonto-HPP) (Table 1). In lethal perinatal and infantile forms, variants usually affect both alleles of the *ALPL* gene. In milder subtypes (*e.g.*, benign perinatal, childhood, adult, and odonto-HPP), the inheritance patterns may be autosomal dominant or autosomal recessive [3, 4]. Odonto-HPP is characterized by premature loss of primary teeth without skeletal abnormalities [5]. In most pediatric patients, at least one primary tooth (before the age of 5 years) is lost before resorption occurs because cementum hypoplasia impairs the connection between the tooth and the periodontal ligament. Typically, primary incisors are the first teeth affected, and the lower incisors are lost before the upper incisors [6]. To our knowledge, the genotype-phenotype relationship of odonto-HPP, a mild form of HPP, has not been described in the literature. Here, we describe a 4-year-old boy with odonto-HPP who carried two compound heterozygous missense variants in the *ALPL* gene.

2. Case report

A 4-year-old boy was referred to our hospital because he had experienced premature loss of primary teeth. He had no other clinical manifestations (*e.g.*, involving other organs), and his body weight and height were normal. The proband had lost primary tooth 71 at the age of 18 months. Two years later, he lost teeth 72, 81, and 82. Subsequently, teeth 51 and 61 exhibited mobility, root exposure, and fan-shaped displacement. Three months later, these teeth were lost. Clinical examination of teeth 52 and 62 revealed grade II mobility,

TABLE 1. Forms of hypophosphatasia (HPP) and their clinical manifestations.

Type	Clinical manifestations
Lethal perinatal	Perinatal death, hypercalcemia, respiratory complications, long bone bowing
Prenatal benign	Limb shortening and bowing (may progressively improve during the third trimester of pregnancy and after birth)
Infantile	Craniosynostosis, rachitic ribs, hypercalcemia and nephrocalcinosis, short stature
Childhood	Skeletal deformities and fractures, premature loss of primary teeth, short stature
Adult	Stress fractures, thigh pain, chondrocalcinosis, osteoarthropathy, early loss of adult teeth
Odonto-HPP	Premature loss of primary teeth (most commonly the incisors)

TABLE 2. Biochemical analyses of the proband and his family.

		Proband		Father		Mother		Sister	
Test	Unit	Results	Reference range	Results	Reference range	Results	Reference range	Results	Reference range
Alkaline phosphatase	U/L	49	142–335	31	40–130	60	40–130	83	142–335
Phosphorus	mmol/L	2.52	1.05–1.80	1.56	0.81–1.45	1.36	0.81–1.45	2.26	1.00–1.80
25-hydroxyvitamin D	ng/mL	26.2	20.1–100.0	24.0	30.1–100.0	23.1	30.1–100.0	25.3	20.1–100.0
Calcium	mg/L	66.9	46.0–84.0	52.6	46.0–84.0	59.3	46.0–84.0	61.9	46.0–84.0

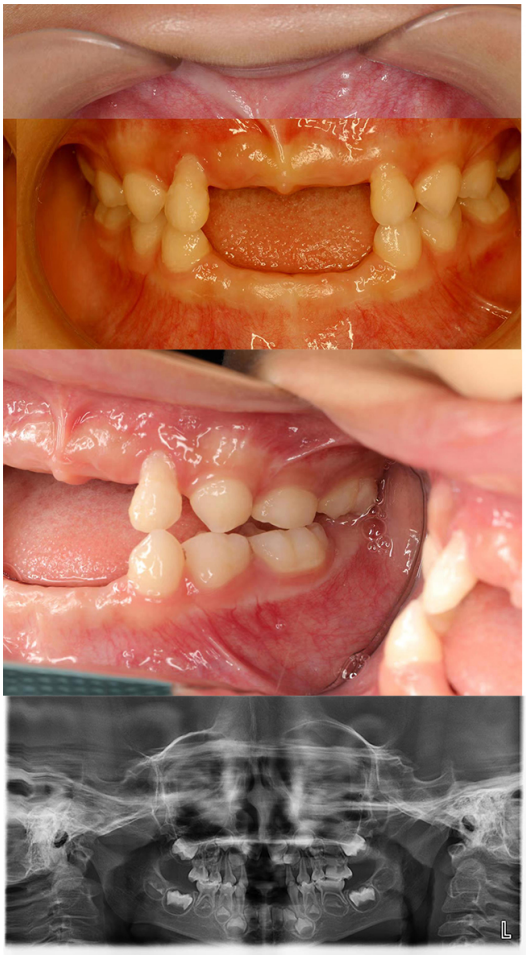

FIGURE 1. Clinical presentation of anterior dentition, gingival recession, and generalized horizontal bone loss.

as well as gingival recession. Periodontal probing analysis showed that teeth 55 and 85 both had a probing depth of 5 mm; teeth 54, 65, 75, and 74 all had a probing depth of 4 mm. X-ray radiography revealed generalized horizontal alveolar bone loss comprising one-third of the bone in affected teeth (Fig. 1). The proband exhibited lower values of serum alkaline phosphatase (Table 2). Based on the clinical and biochemical findings, the proband was diagnosed with odonto-HPP.

The proband's 8-year-old sister was asymptomatic. The proband's mother exhibited periodontal disease and had lost four teeth between the ages of 36 and 38 years. As a child, the proband's father had experienced intermittent spasms in the lower limbs while walking; these spasms had disappeared in adulthood. Moreover, the proband's father had lost two teeth between the ages of 38 and 39 years. Biochemical tests showed that the proband's mother had a serum alkaline phosphatase level within the normal range, whereas the proband's father and sister both had low serum alkaline phosphatase levels. Furthermore, the proband's mother had a serum phosphorus level within the normal range, but the serum phosphorus levels were elevated in the proband, proband's father, and proband's sister. The proband's father and mother both had low levels of 25-hydroxyvitamin D, whereas the proband and his sister had normal levels of 25-hydroxyvitamin D. The calcium levels were normal in all family members. Pyridoxal 5'-phosphate/vitamin B6 levels were not analyzed. To explore the genetic etiology, peripheral blood samples from the family members were subjected to whole-exome sequencing and Sanger sequencing. Genetic analysis of the proband's *ALPL* gene revealed two compound heterozygous missense variants: c.346G>A (p.Ala116Thr) and c.1563C>G (p.Ser521Arg). Each of these two variants was derived from one of his parents. The proband's mother was a heterozygous carrier of c.1563C>G (p.Ser521Arg), whereas his father and

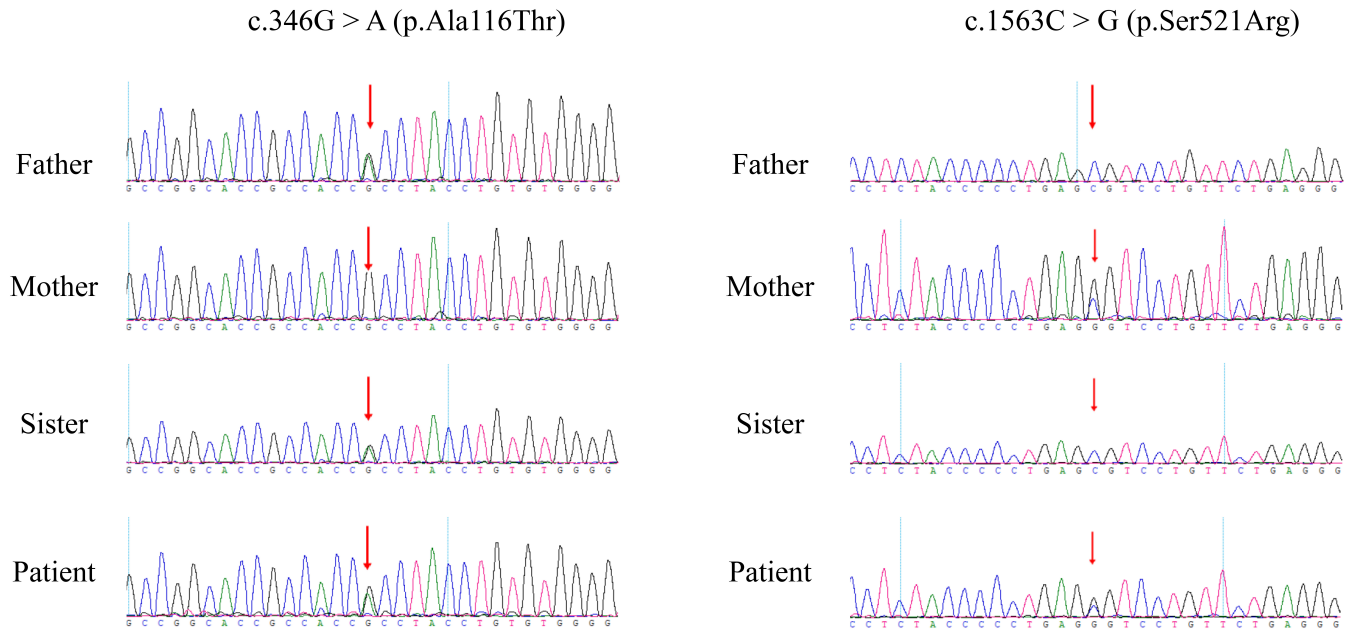

FIGURE 2. Sequencing analysis of the *ALPL* gene in the proband and his family members.

sister were heterozygous carriers of c.346G>A (p.Ala116Thr) (Fig. 2).

To characterize the relationship between genotype and phenotype, three-dimensional protein structure analysis was performed using UCSF Chimera software version 1.14 (Resource for Biocomputing, Visualization, and Informatics, San Francisco, CA, USA). c.346G>A (p.Ala116Thr) resulted in a change from alanine to threonine at amino acid 116 in the TNSALP protein. The hydrogen bond interactions between threonine-116 and threonine-113 were increased (purple dashed lines), compared with the hydrogen bond interactions between alanine-116 and threonine-113 in the wild-type protein. In the three-dimensional structure, amino acid 116 is located in the core region and is a buried residue. c.346G>A (p.Ala116Thr) causes side chain enlargement and hydrophilicity enhancement, leading to the disruption of structural stability (blue dashed lines). c.1563C>G (p.Ser521Arg) resulted in a change from serine to arginine at amino acid 521. The polarity (blue dashed lines) and hydrogen bond interactions (purple dashed lines) were not affected by the variant. The amino acid side chains were enlarged and the hydrophobicity was increased (dark blue dashed lines) in exposed residues at the C-terminus of the protein (Fig. 3). According to the American College of Medical Genetics guidelines [7], c.346G>A (p.Ala116Thr) was classified as "pathogenic", whereas c.1563C>G (p.Ser521Arg) was classified as "unclear significance".

3. Discussion

Variants in *ALPL* diminish expression of the gene, compromise its mRNA stability, and inactivate the enzyme by altering its various domains. Thus far, >400 (usually missense) *ALPL*-related genetic defects have been recorded. Our patient exhibited a novel combination of two compound heterozygous missense variants in the *ALPL* gene, c.346G>A (p.Ala116Thr) and c.1563C>G (p.Ser521Arg), which resulted in the odonto-HPP phenotype.

Genetic analyses by SIFT, Condel, and SpliceAI predicted that c.346G>A was deleterious; PhyloP Vertebrates, PhyloP Placental Mammals, and GERP++ predicted that the variant was evolutionary conserved. A previous study revealed heterozygous expression of c.346G>A in patients with odonto-HPP and childhood HPP [8], but the clinical significance of c.1563C>G was not previously described. The allele frequencies of c.1563C>G in humans were reported to be 0.000021, 0.000026, and 0.000297 in the Exome Aggregation Consortium database, Genome Aggregation Database, and GnomAD-EAS database, respectively. An *in vitro* study showed that the c.1563C>G variant impairs enzymatic alkaline phosphatase activity [9]. Our present findings indicate that c.346G>A is a pathogenic genetic alteration, whereas c.1563C>G might contribute to the dental phenotype when combined with c.346G>A.

Thus, genetic diagnosis might be considered when early tooth loss occurs in a patient with a positive family history. Pediatric dentists providing primary care should consider a diagnosis of odonto-HPP in children with premature loss of primary teeth; they should also ensure rapid referral for patients who require specialized medical management based on their inheritance patterns. Odonto-HPP is a progressive disease; thus, parents should be informed that the affected patient might manifest bone symptoms with maturity because of inorganic pyrophosphate accumulation. Alkaline phosphatase enzyme replacement therapy has been reported to improve bone hypomineralization in patients with HPP [10]. Although there are minimal published data concerning the management of oral health in patients with HPP, dental therapeutic options (*e.g.*, promoting awareness of rigorous dental hygiene prevention, periodontal cleaning to control local determinants of alveolysis, early clinical management of caries caused by bacterial biofilm, orthodontic management, and functional re-

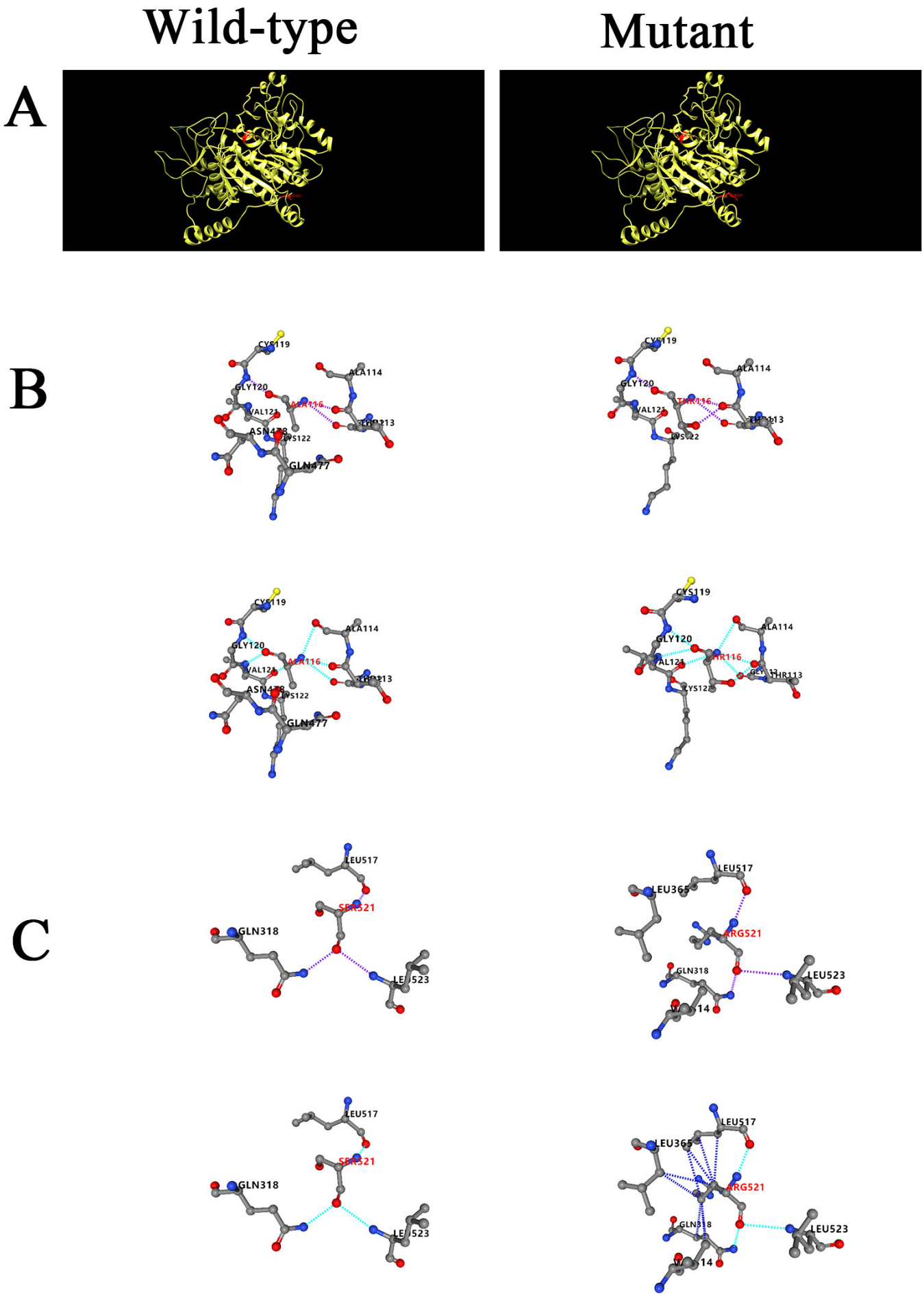

FIGURE 3. Three-dimensional modeling structures of *ALPL* variants. (A) Ribbon presentation of wild-type and mutant *ALPL* monomers. (B) Structural representation of amino acid 116 in wild-type and mutant proteins. (C) Structural representation of amino acid 521 in wild-type and mutant proteins.

habilitation) might delay disease progression in the oral cavity [11]. Therefore, pediatricians and pediatric dentists should collaborate to prepare appropriate therapeutic plans.

ABBREVIATIONS

HPP: hypophosphatasia; TNSALP: tissue-nonspecific alkaline phosphatase; ALPL: alkaline phosphatase; odonto-HPP: odontohypophosphatasia.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

JX and JJ—conceived the ideas and wrote the manuscript. HWL, JJ and HYK—performed the clinical treatment. LSG and XHZ—conducted the data analysis and revised the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Research study protocols were approved by the Ethics Committee of Shenzhen Longgang E.N.T. Hospital. Reference number of approval of the Ethics Committee was ZSSOM2022-0001. The parents gave their written consent for their child's personal or clinical details to be published in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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