

# Adult hypophosphatasia with a single heterozygous c.572A > G p.Glu191Gly mutation in the *ALPL* gene: Case report

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## ABSTRACT

Adult-onset hypophosphatasia manifests after age 18, and is characterised by reduced tissue-nonspecific alkaline phosphatase activity. This can lead to fractures, pseudo-fractures, osteomalacia, decreased bone density (bone loss), muscle weakness, myalgia, arthralgia, headache, dental symptoms (loss of permanent teeth, periodontal disease), and pseudogout. Over 480 distinct genetic mutations have been identified to date, with eight cases reported for the c.572A > G (p.Glu191Gly) mutation. However, all reported cases involved compound heterozygous mutations, and there have been no previous reports of cases of a single heterozygous mutation. We report the case of a 40-year-old woman with persistent hypophosphatasia, elevated urinary phosphoethanolamine levels suggesting adult-onset hypophosphatasia, and a heterozygous missense mutation (c.572A > G p.Glu191Gly) in the *ALPL* gene according to genetic testing. Treatment with subcutaneous injections of aspartate phosphatase alpha was initiated, which was followed by significant improvement of the pain, enhanced range of motion in both upper limbs, and improved gait. This patient's case differed from previously reported cases in that it involved a heterozygous c.572A > G (p.Glu191Gly) mutation alone in adult-onset hypophosphatasia. Adult-onset hypophosphatasia is an extremely rare disorder. However, its symptoms resemble those of systemic rheumatic diseases such as polymyalgia rheumatica and fibromyalgia, and rheumatologists may encounter this condition in routine clinical practice. Importantly, it can be detected based on low serum ALP levels.

**KEYWORDS** Hypophosphatasia; ALP; tissue-nonspecific alkaline phosphatase

## Introduction

Hypophosphatasia is a hereditary disorder caused by loss-of-function mutations in the *ALPL* gene, which encodes tissue-nonspecific alkaline phosphatase (ALP), resulting in reduced ALP activity [1]. Even with the same gene mutation, there is wide variation in the phenotype, ranging from cases presenting systemic symptoms to asymptomatic carriers and cases that are entirely limited to dental manifestations. Over 480 *ALPL* gene mutations have been reported to date, among which the c.572A > G p.Glu191Gly mutation has been reported in eight cases as part of a compound heterozygote [2]. To the best of our knowledge, there are no reported cases involving this mutation alone. We report a case of adult-onset hypophosphatasia with the c.572A > G p.Glu191Gly single mutation. The patient demonstrated rapid clinical improvement following initiation of initial treatment with aspartate aminotransferase alpha (Strensiq®). She exhibited previously unreported genetic characteristics and demonstrated favourable responsiveness to initial treatment.

## Case presentation

Case: A 40-year-old woman (X-2) first noticed numbness in her right arm. Approximately three months later, she

developed a fever of 39°C and severe pain in her lower back, right lower limb, and both shoulders and scapular regions. The fever subsided after about two days, but the pain persisted. CT and MRI scans revealed no abnormalities. Mirtazapine besylate tablets were prescribed to address her symptoms, but no improvement was observed. Subsequently, the pain, specifically that in both shoulders, continued. Loxoprofen sodium hydrate tablets were prescribed at the hospital, but there was still no improvement. Approximately five months after that, upon exiting a car, the patient had severe pain in the lower back and right lower limb that caused difficulty walking. Later that month, during a visit to another physician, blood tests revealed a low serum ALP level of 28 U/l (38–113 U/l). Two months after that, the patient was referred to our department for further evaluation. Neither the patient's parents nor her children had a history of frequent fractures, and there was no family history of bone disorders. In addition, there was no excessive physical strain, and their nutritional status was not thought to be unbalanced. Blood tests showed decreased ALP at 21 U/l (IFCC method) and elevated urinary phosphoethanolamine (PEA) at 137.8 µmol/gCr (7–70 µmol/gCr) (Table 1). Genetic testing was performed at the Genetic Testing Laboratory of the Kazusa DNA Research Institute (Kazusa Genetic Testing Laboratory, Kisarazu, Chiba, Japan). This test analysed the protein-coding exons

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**Table 1.** Blood and urine tests at the first visit.

| Test                             | Result                              |
|----------------------------------|-------------------------------------|
| <b>Haematology</b>               |                                     |
| WBC                              | 6850/ $\mu$ l                       |
| RBC                              | 4,650,000/ $\mu$ l                  |
| Hb                               | 14.1 g/dl                           |
| Ht                               | 42.2%                               |
| Platelet                         | 337,000/ $\mu$ l                    |
| <b>Biochemistry</b>              |                                     |
| Total Protein                    | 7.4 g/dl                            |
| Alb                              | 4.4 g/dl                            |
| Globulin                         | 3.0 g/dl                            |
| CK                               | 67 U/l                              |
| AST                              | 17 U/l                              |
| ALT                              | 10 U/l                              |
| LDH                              | 150 U/l                             |
| ALP (IFCC)                       | 21 U/l                              |
| $\gamma$ -GTP                    | 16 U/l                              |
| ChE                              | 303 U/l                             |
| Cre                              | 0.66 mg/dl                          |
| Uric Acid                        | 6.0 mg/dl                           |
| BUN                              | 11.4 mg/dl                          |
| Glucose                          | 84 mg/dl                            |
| Triglycerides                    | 168 mg/dl                           |
| LDL-cholesterol                  | 128 mg/dl                           |
| Sodium                           | 137 mmol/l                          |
| Potassium                        | 4.1 mmol/l                          |
| Chloride                         | 105 mmol/l                          |
| Calcium                          | 9.4 mg/dl                           |
| Inorganic phosphate              | 4.0 mg/dl                           |
| Total bilirubin                  | 0.5 mg/dl                           |
| Erythrocyte sedimentation rate   | 6 mm/h                              |
| CRP                              | 0.18 mg/dl                          |
| <b>Autoantibodies</b>            |                                     |
| Antinuclear antibody (FA method) | $\times 40$ (Speckled, Homogeneous) |
| Anti-CCP antibody                | $<0.5$ U/ml                         |
| Rheumatoid factor                | 6.8 U/ml                            |
| Anti-SS-A antibody               | Negative                            |
| Anti-SS-B antibody               | Negative                            |
| <b>Urinalysis</b>                |                                     |
| PEA                              | 137.8 $\mu$ mol/gCr                 |

of the *ALPL* gene (gene number 1) and the splice site regions at both ends using the NextSeq 2000 next-generation sequencer. Based on a comparison with the internationally-used human genome reference sequence, we received a report on rare variants with a detected allele frequency of  $\leq 1\%$ . The average depth was 418. Genetic testing confirmed a missense mutation c.572A > G p.Glu191Gly, where adenine at position 572 in the coding DNA was substituted with guanine, resulting in a substitution of glutamine acid at amino acid position 191 with glycine. No other genetic mutations were detected. This established a definitive diagnosis of adult-onset hypophosphatasia. Two months later, the patient was admitted as an inpatient. Concurrently with treatment, the patient, her husband, and their three children (18-year-old son, 14-year-old daughter, 11-year-old son) received thorough explanations regarding hypophosphatasia and genetic testing. Genetic testing was performed on all three children, but the mutation was not detected in any of them.

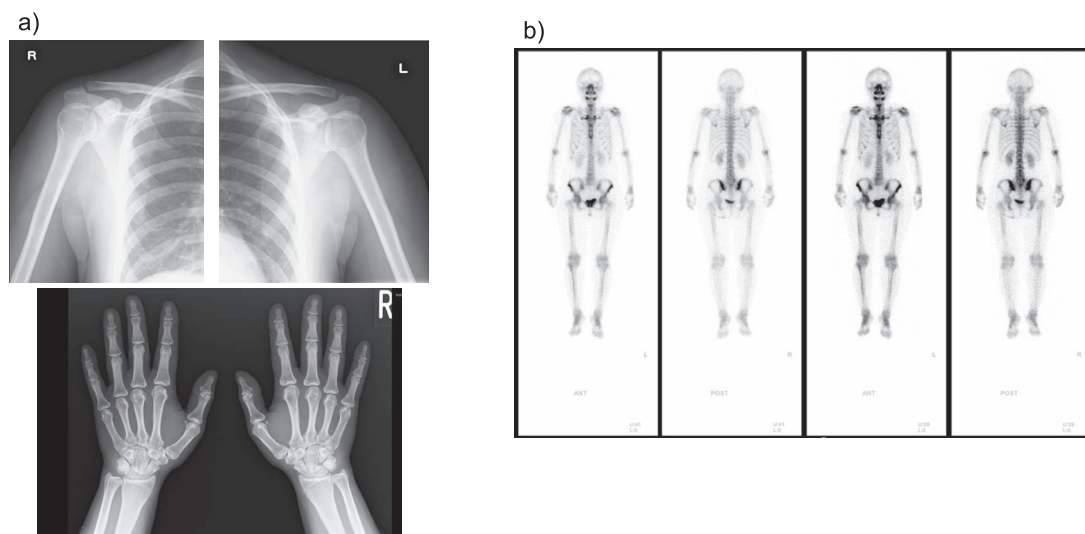
At admission, the patient's vital signs were: height 159 cm, weight 58.7 kg, body mass index 23.22, temperature 37.0°C, blood pressure 147/96 mmHg, heart rate 73 beats per minute, and SpO<sub>2</sub> 99%. Mild elevation in temperature and blood

pressure was noted. The pain visual analogue scale score was 100 mm, and no tender or swollen joints were noted. The patient walked with a cane. Manual muscle testing revealed mild weakness in both distal and proximal muscles of the upper and lower limbs. Joint range of motion findings showed limitation with active movement predominating: both shoulders had 130° of abduction (active) and 150° (passive). No other abnormalities were noted. The 6-min walk test showed a reduced distance of 295 m due to the pain she had while walking with a cane. Plain radiographs showed no obvious fractures or hypocalcification, and we observed no deformities of long bones or rickets-like epiphyseal irregularities. Bone scintigraphy revealed no significant abnormal uptake (Figure 1). Bone mineral density was 116% at the lumbar spine and 112% at the left femur compared with young adult reference values, showing no decrease. Treatment with aspartase alfa (Strensiq®) for adult-onset hypophosphatasia was initiated seven weeks after entry as an inpatient. Initial loading was performed with 6 mg/kg/week administered subcutaneously three times weekly. Significant improvement in pain was observed 10 min after the start of administration, along with increased range of motion in both upper limbs. Prior to treatment, the patient required a cane for walking (Supplementary Video S1), but within 1 h of administration, it became possible to walk without it (Supplementary Video S2). Grip strength improved from 5.4 to 25.9 kg in the right hand and from 19.8 to 27.5 kg in the left hand before and after the first treatment, respectively. The 20 m walking time decreased from 26 s to 17 s, indicating an increase in walking speed. Enzyme replacement therapy with asfotase alpha was continued thereafter. Although there was initial improvement of pain and muscle weakness, a gradual worsening was subsequently observed. However, serum ALP showed a sustained increase, while urinary PEA showed a sustained decrease (Figure 2). To investigate the cause of residual pain, neutralising antibodies against asfotase alpha were measured but were negative. Other conditions were considered, such as polymyalgia rheumatica or pseudogout, but blood tests showed no elevated CRP, and radiographs revealed no abnormalities. Some pain was therefore determined to have persisted due to hypophosphatasia, and treatment was continued. Adverse events observed after the initiation of treatment in this case included injection site reactions (CTCAE Grade 1) and appendicitis (CTCAE Grade 3). The patient has provided informed consent to the publication of the details of her case. Ethical approval was not required for this case study.

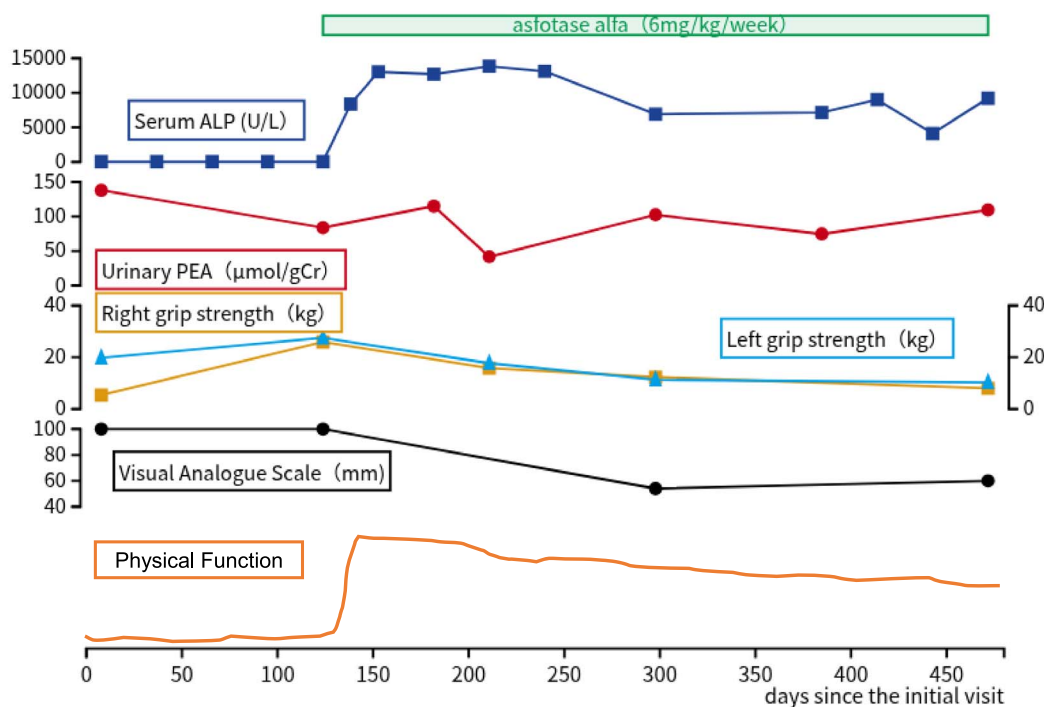
All genetic testing in this case was conducted in accordance with the *Guidelines on Genetic Testing and Diagnosis in Clinical Settings* issued by the Japan Medical Association. Furthermore, the genetic testing was performed after following the appropriate procedures at our hospital's genetic clinic.

## Discussion

We report a case of adult-onset hypophosphatasia caused by a single heterozygous c.572A > G p.Glu191Gly mutation. Hypophosphatasia is a disorder caused by mutations in the *ALPL* gene, leading to reduced ALP activity and the accumulation of pyridoxal 5'-phosphate (PLP), inorganic pyrophosphate (PPi), and PEA. Accumulation of PLP is thought to cause neurological symptoms, while accumulation of PPi is



**Figure 1.** a) Bone X-ray: no remarkable findings were observed. b) Bone scintigraphy: no abnormal radiotracer uptake was observed.



**Figure 2.** Course of treatment: After treatment initiation, ALP levels increased, whereas urinary PEA levels decreased. These trends persisted at 12 months. Handgrip strength markedly improved immediately after treatment initiation but subsequently showed a gradual decline. Physical function also showed improvement after treatment began – for example, the patient became able to walk – but the level of physical function has not been maintained at the same level as seen in the early stages of treatment.

associated with skeletal, respiratory, muscular/articular, and renal disorders [3]. Symptoms of PEA accumulation are not yet fully understood at this time. The loss-of-function mutation in the *ALPL* gene was considered to be the primary cause of disease onset in this case. As for acquired factors, previous reports have cited ageing, mechanical stress [4], and extreme excess or deficiency of phosphorus and calcium [5]. In this case, there was no excessive exercise load, and the patient did not have an unbalanced nutritional status. The c.572A > G p.Glu191Gly mutation means that the 572nd base in the coding DNA was substituted from adenine to guanine, resulting in a missense mutation where the 191st

amino acid changed from glutamine acid to glycine. The *ALPL* gene mutation database reports eight previous cases of this mutation, all as compound heterozygotes [2]. This case represents the first isolated heterozygous mutation (Table 2). Furthermore, all previously reported cases were perinatal, paediatric, or dentition-limited types, and this case is the first reported adult-onset type. In compound heterozygous cases of this mutation, residual ALP activity has been confirmed to decrease to approximately 35%, which reflects reduced activity due to the absence of a wild-type allele following mutation in both alleles [6]. Conversely, a known mechanism for hypophosphatasia onset in single-mutation cases involves

**Table 2.** Past cases with c.572A > G mutation and current case.

| No.              | Genotypes                | Variant types                           | Phenotypes      |
|------------------|--------------------------|-----------------------------------------|-----------------|
| 1 <sup>6)</sup>  | c.[572A > G];[119C > T]  | Compound heterozygous variant mutations | Childhood       |
| 2 <sup>13)</sup> | c.[572A > G];[119C > T]  | Compound heterozygous variant mutations | Prenatal Benign |
| 3 <sup>14)</sup> | c.[572A > G];[1276G > A] | Compound heterozygous variant mutations | Childhood       |
| 4 <sup>6)</sup>  | c.[572A > G];[1348C > T] | Compound heterozygous variant mutations | Odonto          |
| 5 <sup>15)</sup> | c.[572A > G];[1559del]   | Compound heterozygous variant mutations | Childhood       |
| 6 <sup>16)</sup> | c.[572A > G];[1559del]   | Compound heterozygous variant mutations | Childhood       |
| 7 <sup>6)</sup>  | c.[572A > G];[1559del]   | Compound heterozygous variant mutations | Odonto          |
| 8 <sup>6)</sup>  | c.[572A > G];[1559del]   | Compound heterozygous variant mutations | Perinatal       |
| Current case     | c.[572A > G];[=]         | Single heterozygous variant mutation    | Adult           |

a dominant-negative effect, where the protein produced by the mutant allele impairs the function of the protein produced by the wild-type allele. Regarding specific mechanisms of dominant-negative effects, the p.Asp361Val (D361V) mutation reportedly forms dimers with the wild-type protein [7], while the p.Gly232Val (G232V) mutation causes the wild-type protein to be sequestered with the mutant protein within the Golgi apparatus, preventing it from reaching the membrane [8]. Although the detailed pathogenesis in this case is unclear, considering that the disease was caused by a heterozygous mutation, there is a strong suggestion of a dominant-negative effect. This case involved the onset of adult-onset hypophosphatasia due to a single heterozygous mutation. However, there are reports of adult-onset hypophosphatasia caused by heterozygous mutations, cases of the dental form [9] and of the paediatric form [10], which suggests that even heterozygous mutations may present with clinical manifestations other than adult-onset disease.

In this case, the patient demonstrated worsening subjective symptoms, including muscle weakness and increased pain, beginning 3 months after treatment initiation. Conversely, compared with pre-treatment levels, elevated serum ALP activity and decreased urinary PEA were observed, indicating a discrepancy between subjective symptoms and serum markers. Neutralising antibody production against asfotase alfa was considered to be a potential cause of treatment resistance and was measured, but the result was negative. Generally, asfotase alfa demonstrates high efficacy in patients with adult hypophosphatasia. Even after five years of follow-up, sustained normalisation of PLP and PPi, along with improvements in muscle strength and six-minute walk distance, have been observed. However, regarding pain, a residual score of 4 on the Brief Pain Inventory Short Form remained, even after five years [11]. Furthermore, there are cases in adult hypophosphatasia patients, similar to this case, in which aspartate aminotransferase alpha treatment resulted in elevated serum ALP but chronic pain persisted [12]. This suggests that there might be cases where therapeutic effects for pain have not been adequately achieved. The mechanism of pain in patients with hypophosphatasia remains unclear, and the reason for persistent pain in this case is currently unknown. In paediatric and perinatal forms, saving the patient's life is the top priority, and it may not be possible to perform an objectively accurate pain assessment with children. In contrast, in the adult form, the treatment goal is improving quality of life, and pain is particularly common and there are currently no clear effective pain relief strategies. Improvements in treatment efficacy are anticipated with future elucidation of the underlying pathology.

Adult-onset hypophosphatasia is rare, but the carrier frequency of the c.1559delT mutation, which is considered to be relatively common in Japan, is reported to be one in 480 individuals [17]. In a literature review summarising the symptoms of patients with adult-onset hypophosphatasia, the most common symptom was pain (64.5%), followed by dental symptoms (42.6%), skeletal disorders (37.6%), and rheumatic symptoms (20.6%) [18]. We therefore suggest that rheumatologists treating patients presenting with musculoskeletal pain as the primary complaint may encounter this disease in daily practice, and that its recognition is important. Differential diagnoses include rheumatic polymyalgia and fibromyalgia, but low serum ALP levels are specific to adult-onset hypophosphatasia.

As a limitation, the genetic test used in this case reports somatic mosaicism only when it is detected by VariantCaller, so variants not detected by VariantCaller are not reported. It is possible that additional undetected variants were present in somatic cells.

## Conclusion

We reported the case of a patient with adult hypophosphatasia with a single heterozygous mutation c.572A > G p.Glu191Gly. This is the first report of the c.572A > G variant outside of compound heterozygosity. The onset was thought to be due to a dominant-negative effect. Some pain persisted and the treatment outcome did not match that of the initial therapy, and approaches for cases with residual chronic pain remain a challenge. Adult-onset hypophosphatasia is rare, and presents musculoskeletal pain symptoms similar to rheumatic diseases such as polymyalgia rheumatica and fibromyalgia. Importantly, however, it can be detected based on low serum ALP levels.

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## Conflict of interest

All authors declare no conflict of interest.

## Supplementary data

Supplementary data is available at *Modern Rheumatology Case Reports* online.

## Patient consent

Written informed consent for the publication of this report was obtained from the patient by the corresponding author.

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## Ethical approval

Not applicable.

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