Mild Hypophosphatasia in a Family with a Novel Mutation in the *ALPL* gene

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Introduction: **Hypophosphatasia (OMIM 146300, 241500, 241510) is a rare autosomal recessive/dominant genetic disorder characterized by the abnormal development of bones and teeth and deficiency of tissue non-specific alkaline phosphatase activity. These abnormalities occur due to defective mineralization, the process by which bones and teeth take up minerals such as calcium and phosphorus. The specific symptoms can vary greatly from one person to another, sometimes even among members of the same family. The transmission of severe forms is autosomal recessive while milder forms may be transmitted as dominant or recessive autosomal traits.**

Case: **A 6 year old boy visited the clinic because of short stature, intermittent bone pain and mild developmental delay. He was born at 36 weeks via vaginal delivery, weighed 3.02 kg, and had hypoglycemia history after birth. The patient was the 1st child of non-consanguineous parents with above average height. He was 105.6 cm (<3th percentile) in height, 17.4 kg (3rd percentile) in weight. He had high arched palate and low set, large ears. Blood chemistry findings were as follows: total calcium 10.3 mg/dL (Reference range, RR, 8.3–10.0); phosphorous 5.3 mg/dL (RR, 2.5–4.5); alkaline phosphatase (ALP) 341 IU/L (RR, 104–338 in adult). Serum electrolytes, glucose, blood gases, hepatic and renal function tests, as well as routine urinalysis were normal. The growth hormone stimulation test showed normal response. Next-generation sequencing (NGS) was carried out, we identified heterozygous variant, including a truncating variant (p.Leu276Ter) in the *ALPL* gene. According to 2015 ACMG/AMP guidelines and absence in Population DB – GnomAD, it was judged by "likely pathogenic". The mother of the patient were confirmed to have same variant. We could not find bone hypomineralization and flared metaphysis in skeletal X-ray, like childhood type of hypophosphatasia.**

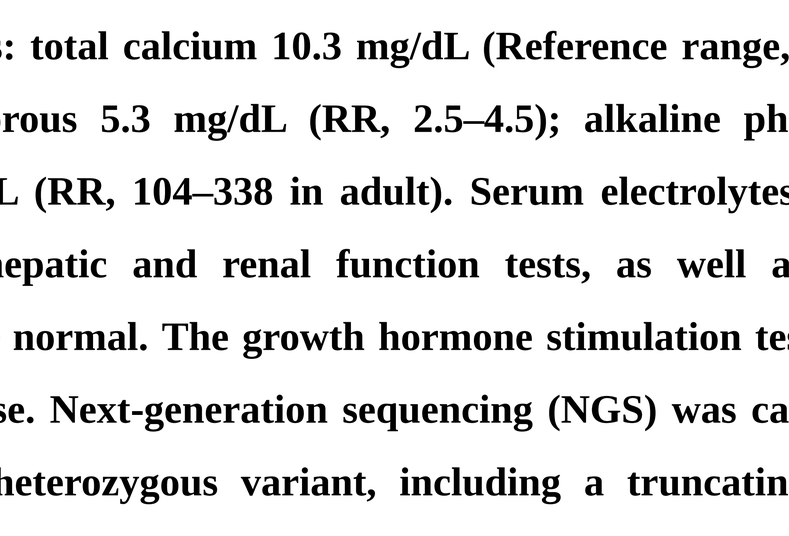

Figure 1. Radiologic findings of the patient showed no hypomineralization

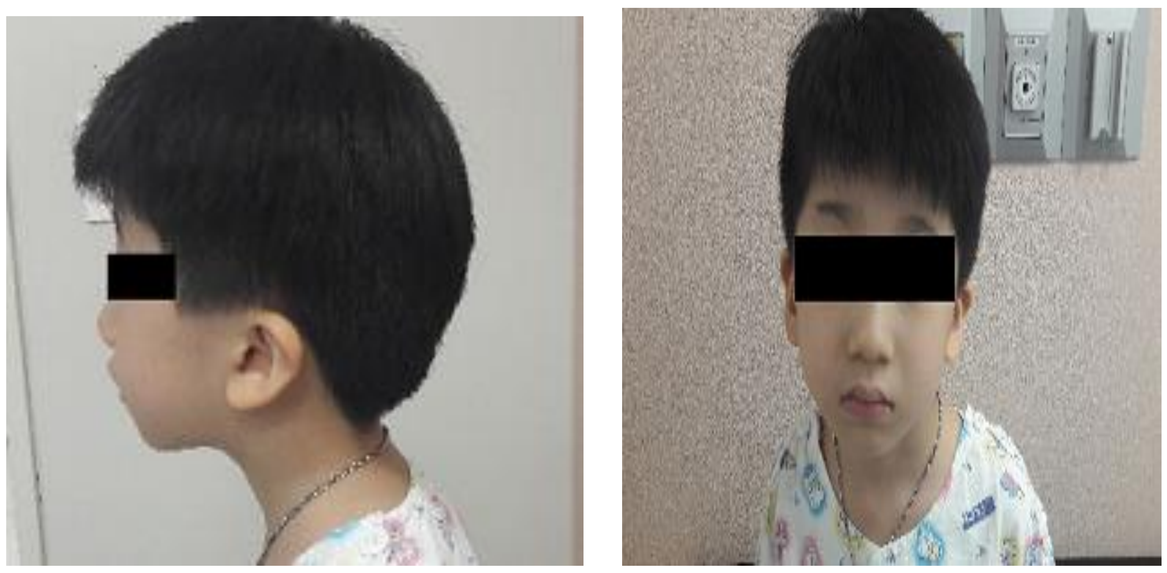

Figure 2. Morphology of the patient showed low wet, large ears

	Perinatal lethal (21)	Perinatal benign (14)	Infantile (5)	Childhood (9)
Shortening or deformity of the extremities	15	13	0	4
Bone fracture	3	4	1	0
Respiratory failure	21	0	1	0
Convulsion	9	0	1	2
Enlargement of the anterior fontanelle	4	2	4	0
Renal calcification	3	0	0	0
Short stature	5	8	2	6
Failure to thrive	9	4	5	1
Premature loss of deciduous teeth	3	4	0	3
Mental retardation	5	2	1	3
Premature synostosis of skull	2	0	2	0
Deafness	5	0	0	0

Table 1. Clinical characteristics of hypophosphatasia (Adopted from Taketani T, Onigata K, Kobayashi H, et al. Arch Dis Child 2014;99:211–215)

Discussion & Conclusion: **According to the Taketani, et al, the main symptom were short extremities, deformed limbs and bone fractures, short stature, failure to thrive, mental retardation and constipation in childhood type hypophosphatasia. We report a novel mutation of *ALPL* presenting with short stature in a Korean family. We should consider mild hypophosphatasia in a patient with short stature and relatively low ALP level.**

References : **1. Taketani T, et al. Clinical and genetic aspects of hypophosphatasia in Japanese patients. Arch Dis Child 2014;99:211–215**