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Hypophosphatemic Nephrolithiasis/Osteoporosis Type 1 Phenotype —A Novel Npt2a-Encoding SLC34A1 Mutation: A Case Report

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Abstract

We report the case of a 15-year-old female patient presenting with bone deformity characterized by genu varum in the lower extremities since the age of five, with a clinical diagnosis of X-linked hypophosphatemic rickets (XLHR). Laboratory tests revealed hypophosphatemia and a tubular reabsorption of phosphate (TRP) rate of 46 %. The patient was treated with 250 mg of oral potassium phosphate (Kphos)® and 0.25 μg of calcitriol twice daily. Genetic testing to confirm the XLHR diagnosis identified a heterozygous mutation (c.1315_1316delAG) in the SLC34A1 gene, causing arginine substitution at codon 439 with glycine and a frameshift, leading to a premature stop (p. Arg439Glyfs*165). This rare, previously unreported variant is consistent with a hypophosphatemic nephrolithiasis/osteoporosis type 1 (NPHLOP1) phenotype-associated autosomal dominant inheritance pattern. The girl's progress is favorable; she continues treatment with phosphorus supplements and has also received orthopedic treatment, and she has not developed nephrolithiasis to date.

Keywords

Hypophosphatemic Rickets Type 1, Genu Varum, NPT2A

1. Introduction

Phosphorus, present as phosphate, is a crucial molecule in biological systems, most (85 %) being distributed in bones and teeth and contributing to bone mineralization, while the rest is in other tissues. In these tissues, phosphate is vital for cellular structure and metabolism through adenosine triphosphate (ATP) generation, and intracellular signaling regulation [1].

The kidneys are primarily responsible for phosphate homeostasis through filtration and tubular reabsorption mechanisms, with no demonstrably active secretion [2]. Approximately 80 % of the phosphate is reabsorbed in the proximal convoluted tubule via Solute Carrier Family 34 Member 1 and 3 (SLC34A1- and SLC34A3)-encoded a protein sodium-phosphate cotransporter 2A (NPT2A), located in the proximal tubular cell brush border, being the most significant [3].

Mutations in the SLC34A1 gene, which encodes the sodium-phosphate cotransporter 2A (NPT2A) protein, can lead to diverse and specific clinical phenotypes depending on the type of mutation [4].

Autosomal recessive mutations are associated with hypercalcemia, hypercalciuria, nephrocalcinosis, or a renal tubular syndrome resembling Fanconi syndrome. In contrast, heterozygous autosomal dominant mutations are linked to a rare Mendelian clinical phenotype known as hypophosphatemic nephrolithiasis/osteoporosis type 1 (NPHLOP1), characterized by variable hyperphosphaturia, hypophosphatemia, renal calculi, and rapid osteoporosis onset [5].

2. Objective

To report on NPT2A an SLC34A1 mutation-carrying patient. This case is noteworthy as it represents a rare mutation and the first reported case in Peru.

3. Materials and Methods

A 15-year-old girl, born to non-consanguineous parents, presented with a history of bone deformity in the form of Genu varum in her lower extremities since the age of five. She had been previously diagnosed at another medical center with X-linked hypophosphatemic rickets (XLHR). Laboratory tests revealed serum and urinary phosphorus of 2.4 and 140 mg/dL, respectively, alkaline phosphatase of 55 U/L, calcium/creatinine ratio of 0.16, parathyroid hormone level of 41 pg/mL, and 1,25-dihydroxyvitamin D level of 41 pg/mL (reference range: 20 - 54 pg/mL). The tubular reabsorption of phosphate (TRP) rate was 46 %. Consequently, she received 250 mg of potassium phosphate (Kphos®) (65 mg/kg/day) and 0.25 µg of calcitriol orally, twice daily.

Genetic testing to confirm the XLHR diagnosis was conducted courtesy of Ultragenyx and Lab Mendelics Análise Genómica (Brazil). The analysis was performed by sequencing the exonic and flanking intronic regions of a panel of 13 genes related to Hypophosphatemic Rickets (ALPL, CLCN5, CYP27B1, CYP2R1, DMP1, ENPP1, FAH, FGF23, KL, PHEX, SLC34A1, SLC34A3, and VDR). The target region was captured using probes, followed by next-generation sequencing with Illumina technology. Variant alignment and identification were performed using bioinformatics protocols, with the GRCh37 version of the human genome as a reference.

Genetic analysis identified a heterozygous frameshift variant in exon 10 of the SLC34A1 gene (NM_003052.5: 1315_1316delAG). The deletion is predicted to alter the reading frame from codon 439, leading to the predicted protein change p.(Arg439Glyfs*165) and generating a premature termination codon 165 amino

acids downstream. This variant is extremely rare with no previously reported case in the scientific literature. Premature protein translation termination predictably produces an aberrant protein, deemed definitively pathogenic. This condition follows an autosomal dominant inheritance pattern (OMIM*182309).

Bioinformatics analysis was performed to assess the pathogenicity of the mutation, including sequence alignment (Clustal, OMEGA) and hydrophobicity profile analysis (ProtScale, EXPASY) of the wild-type versus mutant protein. These analyses aimed to predict the transmembrane domain loss resulting from the mutation-induced frameshift.

The patient is now progressing favorably; she is receiving phosphorus and calcitriol supplements as well as orthopedic treatment, which has improved her quality of life, and she has not developed kidney stones to date (**Figure 1**, **Figure 2**).

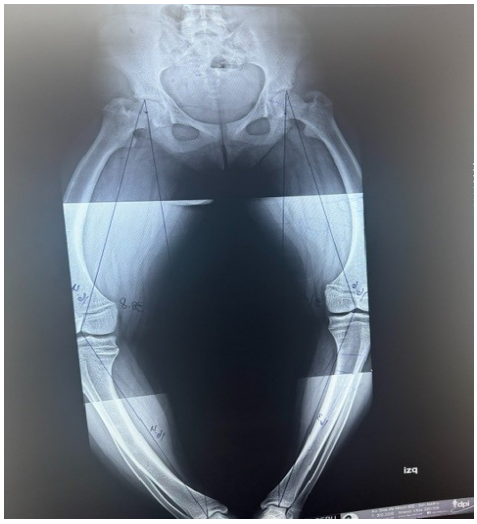

Figure 1. Bone deformity in the form of Genu varum in her lower extremities.

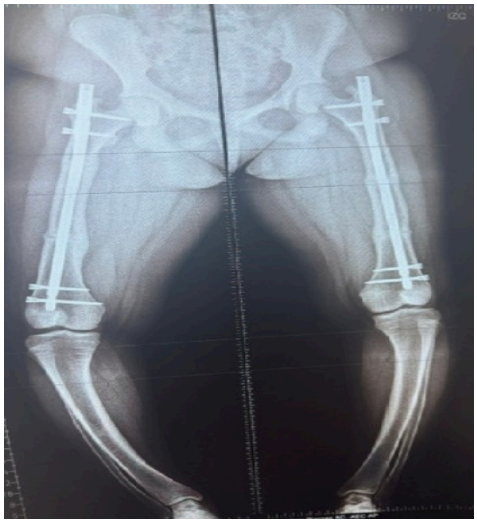

Figure 2. Orthopedic treatment with external and internal fixation.

4. Discussion

The NPT2A protein consists of 639 amino acids and is crucial for phosphorus homeostasis. It includes eight transmembrane domains located at amino acid positions 10-12, 14-16, 165-185, 348-370, 413-436, 467-487, 514-534, and 540-561 [5] (**Figure 3**). Finally, Giusti et al. described a patient with the NPHLOP1 phenotype who carried a novel heterozygous mutation, p. Gly543Cys, though classified as a rare variant of uncertain significance based on an algorithm predicting a probable functional alteration in the NPT2A protein due to this mutation [5]-[7].

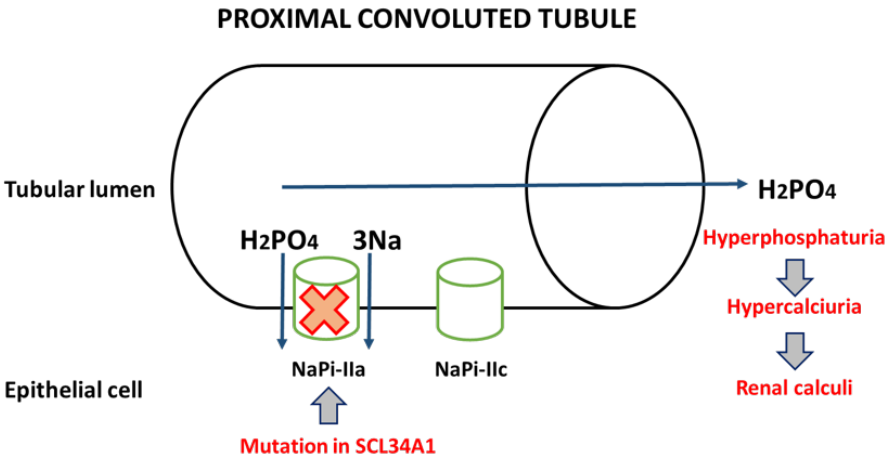

Figure 3. SLC34A1 Gene-Encoded NPT2A Protein Localization in the Proximal Convoluted Tubule.

The amino acid affected by the hereby identified heterozygous dominant mutation (p. Arg439Glyfs*165) is situated near the fifth transmembrane domain, while the following sixth, seventh, and eighth domains are lost, resulting in a notable conformational change in the mutant protein.

A previous study already documents the first report linking heterozygous mutations in the SLC34A1 gene to the hypophosphatemic nephrolithiasis/osteoporosis type 1 (NPHLOP1) phenotype [6], describing two patients identified with the following genotypes: one with phenylalanine substitution for alanine at position 48 (p. Ala48Phe) and another with methionine substitution for valine at position 147 (p. Val147Met). The first mutation affected the amino-terminal end of the NPT2A protein, while the second affected the second transmembrane domain. Functional testing of these mutations in the NPT2A protein, using a Xenopus laevis oocyte model, revealed reduced phosphate affinity as well as decreased sodium- and inorganic phosphate-induced current-voltage responses [6].

Subsequently, Braun *et al.* described five patients showing the nephrolithiasis/nephrocalcinosis phenotype with heterozygous genetic mutations in the SLC34A1 gene as follows: p. Gly153Val, p. Ala133Val, p. Pro146Leu, p. Ile456Asn, and p. Gly450Ser (7). However, the functional impact of these mutations was not assessed, nor were their spatial locations determined. Other patients with mixed clinical phenotypes were described by Fearn *et al.*, including one with the p.

Ile456Asn mutation and another with biallelic mutations p. Arg512Cys and p. Val91_Ala97del [4]. Functional evaluation demonstrated a significant reduction in phosphate uptake and deficient NPT2A receptor-related cell traffic.

Finally, Giusti et al. described a patient with the NPHLOP1 phenotype who carried a novel heterozygous mutation, p. Gly543Cys, though classified as a rare variant of uncertain significance based on an algorithm predicting a probable functional alteration in the NPT2A protein due to this mutation [5]-[7].

The mutation identified in our case has not been previously reported, suggesting that it represents a novel NPHLOP1 phenotype-associated mutation. We lack functional studies or predictive models to determine how this mutant protein behaves concerning its sodium-phosphate cotransport capacity. However, it is the sole phosphate-regulating protein-linked mutation, and such a mutation occurs at a low frequency, which warrants future research.

Based on the above-described considerations, we can assert that when a patient presents with an association of deformities and renal calculi, mutations in the SLC34 gene family should be investigated due to the high likelihood of a genetic cause underlying the clinical phenotype.

Consent

The written consent of the patient was obtained for the publication of this clinical case and the use of the attached images.

Data Availability Statement

Further information and requests for data should be directed to and will be fulfilled by the corresponding author Reyner Loza (reyner.loza@upch.pe).

Author Contributions

RL, LV, FA, VY, wrote and edited the manuscript. SS collected all the images and their respective descriptions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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