CASE REPORT

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Novel Variant of *SLC34A3* in a Compound Heterozygous Brazilian Girl with Hereditary Hypophosphatemic Rickets with Hypercalciuria

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What is already known on this topic?

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is caused by loss-of-function variants of the sodium-phosphate co-transporter NPT2c and is an fibroblast growth factor-23-independent disorder that causes rickets. Phosphate supplementation alone is the standard of care. As $1,25(OH)_2D$ is already elevated, active vitamin D analogs are not indicated. The best approach for managing hypercalciuria has not yet been established.

What this study adds?

We report a novel variant of the *SLC34A3* gene that was present in compound heterozygosity in a Brazilian girl with HHRH. We discuss treatment strategies and observed that thiazide diuretics may be useful as adjunctive therapy to lower urinary calcium excretion.

Abstract

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a rare fibroblast growth factor-23-independent disorder caused by biallelic variants in the *SLC34A3* gene. The disease severity varies, and patients have an increased risk of developing renal complications. Phosphate supplementation is the standard of care and active vitamin D analogs are not indicated as they could worsen the hypercalciuria. We report a Brazilian girl with HHRH who presented with knee pain and progressive genu valgum deformity that became apparent from the age of eight years onwards. Nephrocalcinosis was also identified at age 13 years. Targeted next-generation sequencing for hereditary forms of rickets detected compound heterozygous pathogenic variants in *SLC34A3*, including a novel missense variant c.1217G>T (p.Gly406Val). Compliance to oral phosphorus therapy was suboptimal and adjunctive chlorthalidone therapy improved hypercalciuria. This report highlights the phenotypic variability and also expands the list of *SLC34A3* variants associated with HHRH. An accurate diagnosis is key for optimal treatment. Of note, thiazide diuretics may be useful as adjunctive therapy for controlling hypercalciuria.
Keywords: Hereditary hypophosphatemic rickets with hypercalciuria, *SCL34A3* pathogenic variants, hypercalciuria

Introduction

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a rare disorder caused by biallelic mutations in *SLC34A3*, the gene encoding the sodium-phosphate co-transporter type 2c (NPT2c) (1). NPT2c is expressed in the renal proximal tubule cells and mediates renal phosphate resorption. HHRH is a fibroblast growth factor-23 (FGF-23)-independent disorder, and pathogenic variants of *SLC34A3* lead to hypophosphatemia due to excessive urinary phosphate wasting. Circulating levels of 1,25

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di-hydroxyvitamin D [1,25$(OH)_2$D] are appropriately elevated, leading to increased intestinal calcium resorption, hypercalciuria, and parathyroid hormone (PTH) suppression (1,2).

The clinical spectrum of skeletal disease varies, while renal complications including nephrolithiasis and nephrocalcinosis, may occur in approximately half of the affected subjects (2). Correct diagnosis is important as patients should receive only oral phosphate treatment. Active vitamin D analogs should not be used, as they may exacerbate hypercalciuria and increase the risk of renal complications (2).

We describe a Brazilian girl with HHRH who presented with progressive genu valgum deformity that became apparent after the age of eight years. Genetic analysis detected compound heterozygous pathogenic variants in *SLC34A3*, including a novel pathogenic variant. Here, we discuss the clinical spectrum of the disease and its treatment strategies.

This study was approved by the Ethics Committee of the SARAH Network of Rehabilitation Hospitals (Certificate of Presentation for Ethical Appreciation number: 36961620.9.0000.0022) and performed in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from the patient and her parents.

Case Report

A 16-year-old Brazilian girl was initially admitted for orthopedic evaluation at the age of 10 years because of knee pain and genu valgum deformity that became apparent after she reached the age of eight years.

She was born healthy to non-consanguineous parents. No dental or hearing problems or other signs of rickets, such as muscle weakness, widening of knees or wrists, rachitic rosary or cranial abnormalities (dolichocephaly, craniosynostosis), were observed. Pubertal development was normal, and menarche occurred at 12 years of age. At age 16 years, Tanner stage was 4 for both breast development and pubic hair. However, her height (144.5 cm; standard deviation score -2.8) was below her parental target height (father was 170 cm, and mother was 159 cm tall) and near the final height prediction (145.4 ± 0.8). She had no family history of bone disease but her father reported a history of nephrolithiasis.

Laboratory data at the first orthopedic evaluation at age 10 years showed elevated alkaline phosphatase (ALP), low-normal serum PTH, normal calcium and phosphorous levels, a 25-hydroxyvitamin D value of 29.54 ng/mL, and elevated urinary calcium excretion (calcium/creatinine ratio of spot urine: 407 mg/g) (Table 1). Blood gas analysis did not indicate acidosis, and the urinalysis results were negative

Table 1. Laboratory data of the patient and her parents

Biochemical parameters	10-year-old (age at presentation)	13-year-old	16-year-old	Mother	Father	Reference range
Serum						
Calcium (mg/dL)	9.22	9.15	8.68	8.99	8.86	8.5-10.1
Phosphorous (mg/dL)	3.41 (3.2-5.7)	2.61 (2.9-5.1)	2.53 (2.7-4.9)	3.01 (2.5-5.1)	2.87 (2.5-5.1)	[a]
25(OH)D (ng/mL)	29.54	27.0	21.84	24.51	19.3	> 20
PTH (pg/mL)	16.1	12.92	20.1	52.62	49.35	15-65
ALP (U/L)	486 (51-332)	249 (50-162)	157 (47-119)	56 (42-98)	64 (53-128)	[a]
CTX (ng/mL)	-	2.61 (0.144 1.202)	1.07 (0.048-0.579)	0.429 (0.025-0.573)	0.868 (0.016-0.584)	[a]
Creatinine (mg/dL)	0.76	0.62	0.68	0.71	0.96	0.46-0.81 > 18 y: 0.70-1.30
eGFR	120	136	129	122	104	> 90
Urine						
Calcium/creatinine (mg/mg)	0.407	0.333	-	0.108	0.102	< 0.200
Urine calcium excretion	-	8.2 mg/kg/d	3.4 mg/kg/d	115 mg/d	118 mg/d	Child < 4 mg/kg/d Adult Female < 250 mg/d Male < 300 mg/d
TRP (%)	-	84	82	-	-	> 85
TmP/GFR (mg/dL)	-	2.19 (2.9-6.5)	2.07 (2.9-6.5)	-	-	[a]

Laboratory data were obtained after fasting overnight.

[a]Reference ranges according to age and sex; Urinary calcium/creatinine: analyzed in spot urine.

TRP: Tubular resorption of phosphate, TmP/GFR: ratio of the maximal renal phosphate reabsorption to glomerular filtration rate, 25(OH)D: 25 hydroxyvitamin D, PTH: parathyroid hormone, ALP: alkaline phosphatase, CTX: C-telopeptide of type 1 collagen, eGFR: estimation of glomerular filtration rate according to the CKD-EPI equation, Dashes: data not available, y: year

for aminoaciduria and glycosuria. Skeletal radiographs showed marked genu valgum deformity (Figure 1), and she underwent bilateral distal femoral epiphysiodesis at age 11 years.

Biochemical analysis when she was 13 years revealed an elevated ALP and C-telopeptide of type 1 collagen, hypophosphatemia with a reduced maximum rate of renal tubular reabsorption of phosphate per glomerular filtration rate (TmP/GFR) indicating urinary phosphate wasting, and elevated 24-h urinary calcium excretion of up to 8 mg/kg/day, with normal serum calcium and low PTH levels, raising suspicion of HHRH (Table 1). Renal ultrasonography revealed discrete bilateral increases in the renal medullary echogenicity, suggesting nephrocalcinosis. Bone mineral density (BMD) obtained by dual-energy X-ray absorptiometry showed decreased BMD in the lumbar spine (Z-score -2.7) and total body (Z-score total body less head -3.3).

A targeted next-generation sequencing (NGS) panel for 13 genes associated with inherited forms of rickets (*ALPL*, *CLCN5*, *CYP27B1*, *CYP2R1*, *DMP1*, *ENPP1*, *FAH*, *FGF23*, *KL*, *PHEX*, *SLC34A1*, *SLC34A3*, and *VDR*) was performed using genomic DNA extracted from oral mucosa. A compound heterozygous mutation in *SLC34A3* was detected (Refseq NM_080877.3). The novel missense variant c.1217G>T (p.Gly406Val) was identified in the paternal allele, and classified as a variant of uncertain significance. Glycine at position 406 of the protein is highly conserved among different species (Figure 2), and this variant was predicted to be deleterious or disease-causing by *in silico* analysis (PolyPhen and Mutation Taster). The second variant c.1058G>T (p.Arg353Leu), inherited from the mother, was previously described in patients with HHRH and classified as likely pathogenic (1).

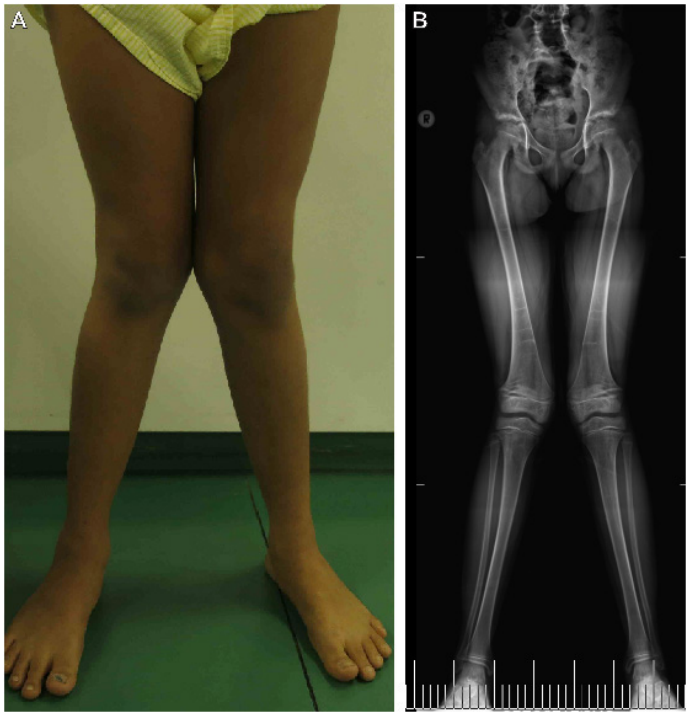

Figure 1. (A) Clinical photographs of lower limbs at age 10 years showing marked genu valgum. B) Panoramic radiograph of lower limbs showing diffuse bone demineralization, marked valgus deviation of the knees, coxa valga, and sclerotic and irregular contour of the acetabulum.

Phosphate therapy (20 mg/kg of elemental phosphorous per day) was initiated after genetic diagnosis, with poor tolerance due to gastrointestinal symptoms and suboptimal compliance. A thiazide diuretic (chlorthalidone 25 mg/day) was initiated as an adjunctive treatment for hypercalciuria when she was 15 years of age. Bone turnover markers decreased, and urinary calcium excretion improved following treatment (Table 1). No adverse effects of thiazide diuretic, such as hypercalcemia or electrolytic abnormalities, were reported during the follow-up period. She required right femoral osteotomy at age 15 years and left femoral osteotomy at age 16 years to correct lower limb deformities.

Serum calcium, phosphorous, ALP, and PTH levels of her parents were normal. The 24-h urinary calcium excretion of the father was normal, but he exhibited concurrent vitamin D deficiency (Table 1).

Discussion

This report describes the clinical and biochemical features of a Brazilian girl with HHRH caused by compound heterozygous variants in *SLC34A3*, one of which was novel.

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HUMAN LGWLGGYLAVLAGAGLTFALQSSSVFTAAVVPLMGVGVISLDRAYP
RAT FGWLSGYLAILVGAGLTFLLQSSSVFTAAIVPLMGVGVINLERAYP
MOUSE FGWLSGYLAILVGAGLTFLLQSSSVFTAAIVPLMGVGVIDLERAYP
CATTLE FGWLSGYLAMLVGAGLTFALQSSSVFTAATVPLIGVGVISLERAYP
DOG FSWLSGYLAILVGAGLTFVLQSSSVFTAAIVPLMGVGVISLERAYP
RHESUS MONKEY LGWLGGYLALLAGAGLTFALQSSSVFTAAIVPLMGVGVISLDRAYP
CHIMPANZEE LGWLGGYLAVLAGAGLTFALQSSSVFTAAVVPLMGVGVISLDRAYP
:.**.****:*.****** ********** ***:*****.*:****
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Figure 2. Multiple amino acid alignment of human NPTC2 protein (sodium-dependent phosphate transport protein 2C) with other mammalian *SLC34A3* proteins. p.406G is shown in red and is highly conserved among different species. Sequence alignment was performed with BLAST/UniProt (www.uniprot.org). Human (*Homo sapiens*, Q8N130|). Rat (*Rattus norvegicus*, G3V7E1); Mouse (*Mus musculus,* Q80SU6|); Cattle *(Bos taurus*, G3MXY5), Dog (*Canis lupus familiaris*, A0A8I3PKB4), Rhesus monkey (*Macaca mulatta,* A0A5F8AJ48), Chimpanzee (*Pan troglodytes*, A0A2J8N9J5). Alignment data (*) identical and conserved; (:) strongly similar; (.) weakly similar

This expands the knowledge of the phenotype and genetic variants associated with HHRH, a rare metabolic disorder.

HHRH has an estimated prevalence of 1:250.000, which is approximately 10-fold less frequent than X-linked hypophosphatemia (XLH), the most common form of inherited hypophosphatemic rickets (2). Pathogenic variants in *SLC34A3* result in hypophosphatemia due to urinary phosphate wasting from NPT2c dysfunction. FGF-23 is downregulated in response to hypophosphatemia, leading to the compensatory up-regulation of renal 1-alfa hydroxylase. Thus, patients present with hypophosphatemic rickets/osteomalacia, increased $1,25(OH)_2D$ levels, and hypercalciuria (2,3). These biochemical findings differentiate HHRH from FGF-23-mediated disorders (4).

Skeletal abnormalities typically occur in childhood, but some patients may exhibit late-onset clinical features, such as early-onset osteoporosis, recurrent fractures, and renal stones (5,6,7). The patient described herein presented with knee pain and progressive lower-limb deformity that only became apparent after eight years of age. This contrasts with the XLH phenotype, in which bone involvement is usually present in the first years of life.

In the present case, the laboratory findings were not entirely consistent with hypophosphatemic rickets at first evaluation, with normal phosphorus levels. Subsequent biochemical evaluation revealed hypophosphatemia with a low TmP/GFR, indicating renal phosphate wasting. Although serum $1,25(OH)_2D$ and FGF-23 levels could not be measured, concurrent findings of hypercalciuria and low serum PTH are not expected in FGF-23-mediated disorders, raising the suspicion of HHRH. Kremke et al. (8) also reported a case in which hypophosphatemia was absent at the first evaluation, suggesting that serum phosphorous levels may fluctuate in this condition, and repeated biochemical evaluation may be necessary to establish the diagnosis.

Individuals with HHRH carry homozygous or compound heterozygous pathogenic variants in *SCLA34A3* (1,2). A single heterozygous pathogenic variant has been associated with isolated hypercalciuria, which increases the risk of nephrocalcinosis and nephrolithiasis without apparent bone disease (2,3). However, skeletal abnormalities, including osteomalacia, predominant cortical loss, and osteoporosis, have been observed in subjects with monoallelic *SCLA34A3* variants (9).

Rickets is more prevalent in homozygous patients than in those with compound heterozygous pathogenic variants in *SCLA34A3* (10). The milder phenotypes of subjects carrying heterozygous variants are probably related to a lower degree of urine phosphate loss, possibly because of increased residual NPT2c activity and higher serum phosphate levels (11). The variability in the age of onset may be related to the incomplete penetrance of variants and complex interactions with environmental and nutritional factors.

Accurate diagnosis of HHRH is important for correct treatment, as a presumptive diagnosis of XLH or another FGF-23-mediated disorder may lead to inappropriate therapy with calcitriol, which would worsen the hypercalciuria and increase the risk of renal complications (2,4). Target genetic panels directed to inherited forms of rickets are relevant for accurate diagnosis and facilitate correct treatment.

In the presented patient, a targeted NGS panel identified a previously reported pathogenic heterozygous variant in the maternal allele of *SLC34A3* (p.Arg353Leu) and a novel heterozygous mutation in the paternal allele (p.Gly406Vl). Although we did not perform *in vitro* functional tests, the glycine at position 406 of the protein is highly conserved among different species and the p.Gly406Val variant was predicted to be deleterious or disease-causing by *in silico* analysis. A rare variant at the same codon (c.1217G > A, p.G406E, rs139408872*)* is described in dbSNP and, like the p.G406V, is predicted to be pathogenic (12). In addition, the heterozygous father reported a history of nephrolithiasis, which reinforced the probable pathogenicity of this *SLC34A3* variant. Although hypercalciuria was not detected in the father, the increased level of urinary calcium excretion may have been concealed by his vitamin D deficiency (8).

The standard treatment of HHRH consists of monotherapy with oral inorganic phosphate (Pi), which improves skeletal bone disease and hypercalciuria, presumably by reducing $1,25(OH)_2D$ (2,4,11). However, Pi therapy can cause several adverse events, including gastrointestinal symptoms and, with chronic treatment, secondary or tertiary hyperparathyroidism, and nephrocalcinosis (13). Long-term patient compliance to oral Pi can be challenging. In addition, data regarding the long-term safety of Pi therapy for renal calcification are unknown, and the best approach for managing hypercalciuria has not been established.

It is also unclear whether a biochemical parameter or genetic factor (variant type) could be associated with an increased risk of renal complications in HHRH. Dasgupta et al. (14) found that serum $1,25(OH)_2D$, low serum phosphate and decreased tubular resorption of phosphate (TRP) may be positive predictors of renal calcifications. Recently, Stürznickel et al. (9) reported that urinary calcium excretion and $1,25(OH)_2D$ levels, but not TRP levels, were associated with nephrocalcinosis, and urinary calcium excretion was suggested as a therapeutic target.

In patients with idiopathic hypercalciuria, thiazide is used

to decrease urinary calcium excretion and may prevent or delay the progression of renal complications (15). Thiazide diuretics can be used to reduce calciuria in patients with familial hypomagnesemia with hypercalciuria and nephrocalcinosis, a rare disorder characterized by renal magnesium wasting, hypercalciuria, nephrocalcinosis and kidney failure (16). Hydrochlorothiazide also decreases calciuria and may prevent the sonographic progression of nephrocalcinosis in patients with XLH (17). Therefore, it is plausible that thiazide diuretics may be useful in other metabolic disorders with hypercalciuria, such as HHRH.

In the presented patient, compliance with Pi therapy was suboptimal, and so it was not possible to evaluate if higher doses of Pi alone would have led to resolution of her hypercalciuria. However, considering the risk of nephrocalcinosis progression and deterioration of renal function with persistent hypercalciuria, adjunctive thiazide diuretic was initiated. We observed that oral Pi therapy with a thiazide diuretic led to improved serum markers of rickets and adequate control of hypercalciuria. Longitudinal follow-up and additional studies are required to evaluate whether this treatment strategy protects against or slows the progression of nephrocalcinosis (9).

Conclusion

In summary, we described a Brazilian girl with HHRH whose skeletal abnormalities only became apparent later in childhood. Genetic analysis revealed compound heterozygous variants in *SLC34A3*, including a novel variant. Accurate diagnosis of HHRH is crucial for proper treatment as calcitriol is contraindicated in this condition. Furthermore, thiazide diuretics may be useful as adjunctive therapy for controlling hypercalciuria but more data is required.

Ethics

Informed Consent: Informed consent was obtained from the patient and her parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Luciana Pinto Valadares, Daniel Rocha de Carvalho, Concept: Luciana Pinto Valadares, Daniel Rocha de Carvalho, Design: Luciana Pinto Valadares, Daniel Rocha de Carvalho, Data Collection or Processing: Luciana Pinto Valadares, Analysis or Interpretation: Luciana Pinto Valadares, Daniel Rocha de Carvalho, Literature Search: Luciana Pinto Valadares, Daniel Rocha de Carvalho, Writing: Luciana Pinto Valadares, Daniel Rocha de Carvalho.

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