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Case Report

Familial Nephrocalcinosis Associated With Heterozygous SLC34A1 and TRPV5 Variants Presenting With Elevated 1,25-Dihydroxyvitamin D

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Abstract
Nephrocalcinosis is frequently associated with inherited disturbances of calcium-phosphate metabolism and renal tubular transport. Variants affecting renal phosphate reabsorption or distal tubular calcium handling may result in hypercalciuria, nephrolithiasis, and progressive renal calcification. The SLC34A1 gene encodes the sodium-phosphate cotransporter NaPi-IIa in the proximal tubule, and loss-of-function variants can cause renal phosphate wasting with inappropriate activation of 1α-hydroxylase, leading to elevated 1,25-dihydroxyvitamin D. The TRPV5 gene encodes a calcium-selective channel in the distal nephron and is essential for transcellular calcium reabsorption. We report a familial nephrocalcinosis phenotype in a 30-year-old woman and her 2-year-old daughter. The mother presented with bilateral flank pain, dysuria, palpitations, and fatigue. Laboratory evaluation demonstrated suppressed parathyroid hormone (PTH 9.6 pg/mL), serum calcium at the upper limit of normal (9.7 mg/dL), normal phosphate (3.1 mg/dL), chronically low 25-hydroxyvitamin D (24 ng/mL), and elevated 1,25-dihydroxyvitamin D, suggesting PTH-independent calcitriol excess. Nephrocalcinosis had previously been detected in the child. Targeted next-generation sequencing revealed a heterozygous splice-region variant in SLC34A1 (NM_003052.5:c.644+5G>C) and a heterozygous missense variant in TRPV5 (NM_019841.7:c.1849G>A; p.Gly617Arg) in both individuals. This case is presented as a hypothesis-generating report. Although both variants are classified as variants of uncertain significance, the shared genotype and characteristic biochemical profile suggest a potential disturbance of renal phosphate and calcium handling that may contribute to familial nephrocalcinosis and PTH-independent elevation of active vitamin D. However, definitive causal inferences cannot be established without additional evidence including segregation analysis in extended family members, functional studies, and comprehensive biochemical characterization.

Keywords: Nephrocalcinosis, Hypercalciuria, Vitamin D, Sodium-Phosphate Cotransporter Proteins (SLC34A1)

INTRODUCTION

Nephrocalcinosis refers to the deposition of calcium salts within the renal parenchyma and is associated with disorders affecting renal calcium and phosphate handling. In pediatric and familial cases, monogenic defects affecting tubular transport or vitamin D metabolism represent an important etiologic group (1-3). Genetic causes include abnormalities in renal phosphate transporters, epithelial calcium channels, and enzymes involved in vitamin D metabolism.

SLC34A1 encodes the sodium-dependent phosphate cotransporter NaPi-IIa located in the proximal renal tubule. This transporter mediates a major fraction of renal phosphate reabsorption (1). Loss-of-function variants in SLC34A1 reduce tubular phosphate reabsorption, resulting in renal phosphate wasting. Reduced phosphate availability stimulates renal 1α-hydroxylase activity and increases production of 1,25-dihydroxyvitamin D (1,2). Increased calcitriol enhances intestinal calcium absorption and contributes to hypercalciuria (2,3). This mechanism has been described in idiopathic infantile hypercalcemia type 2 and related phenotypes characterized by nephrolithiasis and nephrocalcinosis (2,3).

TRPV5 encodes a calcium-selective epithelial channel expressed in the distal convoluted tubule and connecting tubule. This channel mediates the apical calcium entry step of distal tubular transcellular calcium reabsorption and is therefore a biologically plausible determinant of urinary calcium excretion and calcium stone risk (4).

Variants in SLC34A1 are recognized causes of disorders

of renal phosphate handling. The clinical significance of combined variants involving SLC34A1 and TRPV5 in familial nephrocalcinosis has not been well defined. The present report describes a mother-child pair with nephrocalcinosis and a biochemical pattern characterized by suppressed parathyroid hormone and increased 1,25-dihydroxyvitamin D in whom heterozygous variants in SLC34A1 and TRPV5 were detected.

CASE

A 30-year-old woman was evaluated in a nephrology outpatient clinic because of bilateral flank pain, dysuria, palpitations, and fatigue. She had no previous diagnosis of nephrolithiasis, endocrine disease, chronic kidney disease, or granulomatous disease. She reported no use of vitamin D supplementation or calcium preparations.

Laboratory evaluation demonstrated suppressed parathyroid hormone (PTH 9.6 pg/mL). Serum calcium was 9.7 mg/dL, corresponding to the upper limit of the reference range. Serum phosphate was 3.1 mg/dL. The concentration of 25-hydroxyvitamin D was 24 ng/mL, whereas the active metabolite 1,25-dihydroxyvitamin D was elevated. This biochemical profile was compatible with PTH-independent calcitriol excess. Other routine biochemical parameters, including serum creatinine and electrolytes, were within reference ranges. The coexistence of suppressed PTH and increased 1,25-dihydroxyvitamin D prompted evaluation for disorders associated with extrarenal calcitriol production. Granulomatous diseases such as sarcoidosis were initially considered. During the clinical evaluation, it was noted that the patient's 2-year-old daughter had previously been diagnosed with nephrocalcinosis during pediatric assessment. The presence of nephrocalcinosis in a first-degree relative, as seen the case, suggested a possible hereditary disorder affecting mineral metabolism (**Figure 1A and Figure 1B**).

Genetic analysis was performed using next-generation sequencing with a targeted hypercalcemia gene panel that included 85 genes associated with calcium and phosphate metabolism. Genomic DNA extracted from peripheral blood samples of both the mother and the child was analyzed for variants in coding regions and exon-intron boundaries. The analysis detected a heterozygous splice-region variant in SLC34A1 (NM_003052.5:c.644+5G>C; rs1420848876) in both individuals. According to American College of Medical Genetics and Genomics criteria, this variant was classified as a variant of uncertain significance. In addition, both individuals carried a heterozygous missense variant in TRPV5 (NM_019841.7:c.1849G>A; p.Gly617Arg).

The presence of the same variants in both affected individuals suggested a possible association with the clinical phenotype. The biochemical profile was consistent with a disturbance of renal calcium-phosphate metabolism characterized by increased renal 1α-hydroxylase activity, elevated 1,25-dihydroxyvitamin D, suppressed parathyroid hormone levels, and episodic hypercalcemia.

Vitamin D supplementation was avoided because of the risk of aggravating hypercalciuria. The patient was advised to maintain adequate hydration and to avoid excessive dietary calcium intake. Neutral phosphate

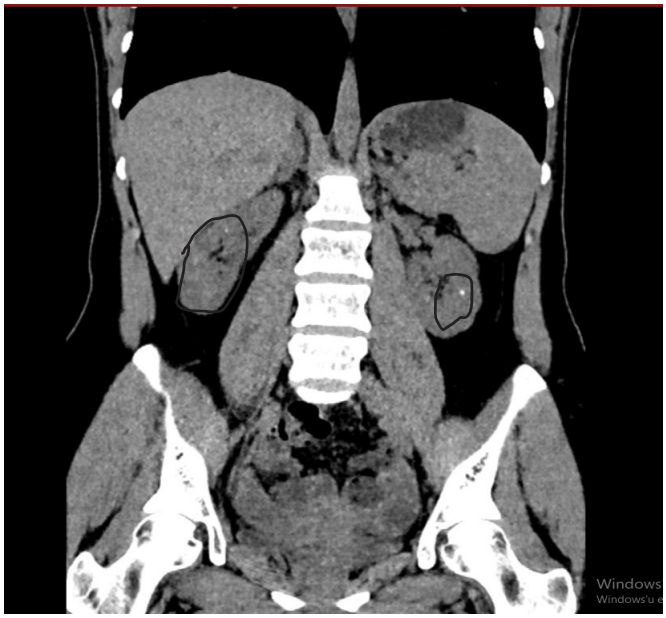

Figure 1A. Both kidneys demonstrate multiple corticomedullary calcifications.

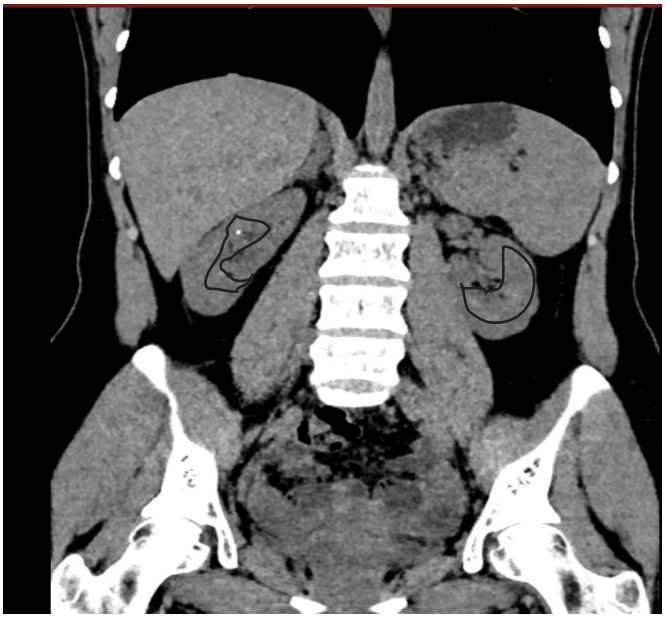

Figure 1B. Both kidneys demonstrate multiple corticomedullary calcifications.

therapy was initiated using a compounded phosphate solution consisting of $NaH_2PO_4 \cdot H_2O$ (18.2 g) and $Na_2HPO_4 \cdot 7H_2O$ (145 g) dissolved in 1000 mL of distilled water. The prescribed dose was 15 mL 3 times daily.

Follow-up evaluation was planned to monitor serum calcium, phosphate, parathyroid hormone, vitamin D metabolites, urinary calcium excretion, and renal imaging findings. Genetic counseling was recommended for the family. Additional segregation analysis involving other family members was considered to further evaluate the potential clinical significance of the identified variants.

While genetic analysis revealed identical variants in both the mother and child, segregation analysis involving additional family members was not performed. Furthermore, key biochemical parameters, including urinary calcium excretion and phosphate transport indices (TmP/GFR), were not assessed. These limitations restrict our ability to fully characterize renal calcium and phosphate handling and to establish a robust genotype–phenotype correlation. A detailed pedigree encompassing both affected and unaffected family members would be essential to determine the inheritance pattern and penetrance. These limitations are acknowledged and discussed in detail below.

DISCUSSION

Nephrocalcinosis is a radiologic and pathologic finding characterized by calcium salt deposition within the renal parenchyma and is commonly associated with disorders of calcium-phosphate metabolism, renal tubular transport defects, or dysregulation of vitamin D metabolism. In pediatric or familial presentations, monogenic causes should be actively considered (1-3).

Variants affecting renal phosphate transport represent an established cause of nephrocalcinosis and hypercalciuria. Among these, pathogenic alterations in SLC34A1, which encodes the sodium-dependent phosphate cotransporter NaPi-IIa located in the proximal tubule, have been associated with idiopathic infantile hypercalcemia type 2 (1-3). Reduced function of this transporter results in renal phosphate wasting and decreased tubular phosphate reabsorption capacity, which in turn stimulates renal 1α-hydroxylase activity and increases synthesis of 1,25-dihydroxyvitamin D (1,2). Elevated calcitriol increases intestinal calcium absorption and promotes hypercalciuria, which contributes to nephrocalcinosis and nephrolithiasis (2,3).

SLC34A1-related disease most commonly presents during infancy with hypercalcemia, suppressed parathyroid hormone, hypercalciuria, and nephrocalcinosis (2). However, phenotypic variability has been increasingly recognized, and milder or later-onset phenotypes, including cases with monoallelic variants or partial loss of transporter function, have been reported (3,5). These patients may present with isolated hypercalciuria, nephrolithiasis, or nephrocalcinosis without severe hypercalcemia (3,5).

The biochemical profile observed in the present case (suppressed PTH, elevated 1,25-dihydroxyvitamin D, and relatively normal serum calcium) supports a mechanism involving increased renal calcitriol synthesis rather than primary hyperparathyroidism or vitamin D intoxication. Similar biochemical patterns have been reported in mild idiopathic infantile hypercalcemia and related phosphate-wasting phenotypes (3).

Another established genetic cause of nephrocalcinosis associated with increased calcitriol levels is CYP24A1 deficiency. CYP24A1 encodes vitamin D 24-hydroxylase, the enzyme responsible for inactivation of active vitamin D metabolites. Loss-of-function mutations lead to accumulation of calcitriol and symptomatic hypercalcemia with nephrocalcinosis, and vitamin D exposure may accentuate the phenotype (6). However, CYP24A1 variants were not detected in the present patient using a targeted hypercalcemia gene panel, making this mechanism unlikely.

In the present report, both the mother and the child carried the same heterozygous splice-region variant in SLC34A1 (c.644+5G>C). According to ACMG criteria, this variant is currently classified as a variant of uncertain significance. Nevertheless, several observations support its possible clinical relevance. First, the variant segregated with the phenotype in two affected family members. Second, the biochemical profile was compatible with a disturbance in phosphate-dependent regulation of calcitriol synthesis. Third, the clinical presentation was consistent with previously reported mild SLC34A1-related phenotypes. Heterozygous SLC34A1-associated presentations with renal calcification and relatively subtle biochemical abnormalities have been documented in recent cohorts (3,5).

In addition to the SLC34A1 variant, both individuals also carried a heterozygous missense variant in TRPV5. TRPV5 encodes a calcium-selective epithelial channel located in the distal convoluted tubule and connecting tubule and represents the rate-limiting apical entry step in distal tubular calcium reabsorption (4). Recent human genetic evidence indicates that loss of TRPV5 function can cause renal calcium-wasting hypercalciuria, thereby supporting TRPV5 as a biologically plausible contributor to hypercalciuric kidney disease (7).

However, because the strongest current human evidence for TRPV5-related disease involves biallelic loss-of-

function, the contribution of a single heterozygous TRPV5 variant in the present family remains uncertain (7). The detected variant should therefore be interpreted cautiously, and a modifier effect rather than a definitively causal role is more appropriate at present.

The heterozygous TRPV5 missense variant (c.1849G>A; p.Gly617Arg) detected in this family warrants particularly cautious interpretation. The strongest and most robust human genetic evidence for TRPV5-related disease involves biallelic loss-of-function mutations, which cause autosomal recessive renal calcium-wasting hypercalciuria. In contrast, heterozygous TRPV5 variants have not been well-characterized in the literature, and their contribution to disease phenotypes remains uncertain. The present heterozygous missense variant may act as a phenotypic modifier that exacerbates the effects of the SLC34A1 variant, rather than serving as a primary causal determinant. Alternatively, this variant may be a benign polymorphism with no functional consequence. Functional studies such as patch-clamp electrophysiology to assess calcium permeability or cellular transport assays to measure TRPV5-mediated calcium uptake would be essential to determine whether this variant impairs channel function. Without such evidence, the role of the TRPV5 variant in the present case must be considered speculative.

Although the TRPV5 variant detected in our case was heterozygous, the coexistence of rare variants affecting proximal tubular phosphate transport (SLC34A1) and distal tubular calcium handling (TRPV5) offers a mechanistically coherent explanation for the observed phenotype. A proximal tubular defect may increase calcitriol production and intestinal calcium absorption, while a distal tubular defect may impair calcium reabsorption and increase urinary calcium loss. The combined effect of these mechanisms could enhance hypercalciuria and promote renal calcification. Similar additive effects of rare variants in more than one renal phosphate transport gene have been described in digenic disease (8).

The coexistence of heterozygous variants in both SLC34A1 and TRPV5 raises the possibility of digenic or oligogenic inheritance, wherein variants in two or more genes contribute additively or synergistically to the phenotype. A proximal tubular defect affecting phosphate reabsorption could increase calcitriol production and intestinal calcium absorption, while a concurrent distal tubular defect affecting calcium reabsorption could increase urinary calcium loss, thereby amplifying hypercalciuria and promoting renal calcification. This model is mechanistically plausible and is supported by precedent in the literature, as similar additive effects of rare variants in multiple renal phosphate transport genes have been described in digenic disease. However, this model remains speculative in the present case. To test this hypothesis, the following evidence would be necessary: (1) functional demonstration that both variants impair their respective protein functions; (2) segregation analysis showing that the phenotype correlates with the presence of both variants rather than either variant alone; (3) measurement of key biochemical parameters (urinary calcium, TmP/GFR) to confirm the proposed mechanism; and (4) evaluation of additional family members to establish inheritance pattern and penetrance. Without such evidence, the combined contribution of these variants cannot be confirmed.

Another feature supporting a genetic mechanism in the present case is the familial occurrence of nephrocalcinosis. The presence of the same variants in both the mother and the child suggests segregation of a genetic predisposition.

While the presence of identical variants in both the mother and child suggests familial segregation of a genetic predisposition, this observation alone is insufficient to establish causality or to determine the inheritance pattern. To properly evaluate familial segregation, a comprehensive pedigree including both affected and unaffected family members would be essential. Such a pedigree would allow assessment of: (1) whether the phenotype segregates with the genotype across multiple generations; (2) the inheritance pattern (autosomal dominant, autosomal recessive, X-linked, or complex); (3) penetrance and expressivity; and (4) whether other family members carry the variants but remain unaffected (incomplete penetrance) or whether unaffected family members lack the variants (supporting segregation). In the present case, segregation analysis involving extended family members was not performed, which represents a meaningful limitation. Therefore, while the familial occurrence of nephrocalcinosis in a mother-child pair is suggestive of a genetic mechanism, it does not constitute definitive proof of causality without broader segregation analysis.

From a clinical perspective, recognition of this mechanism has implications for management. In disorders characterized by calcitriol excess, vitamin D supplementation may aggravate hypercalcemia or hypercalciuria (6). In SLC34A1/SLC34A3-related disease, phosphate supplementation has been used, but recent cohort data suggest that biochemical improvement may be incomplete and that treatment should be individualized with careful longitudinal monitoring (5).

The present report has several limitations that should be considered. First, the detected variants are currently

classified as variants of uncertain significance, and functional studies were not performed to confirm pathogenicity. Second, segregation analysis involving additional family members was not available at the time of writing. Third, urinary calcium measurements and phosphate transport indices such as TmP/GFR (tubular maximum reabsorption of phosphate to glomerular filtration rate) were not reported in this case.

The central mechanistic hypothesis of this case (that the SLC34A1 variant causes renal phosphate wasting leading to increased calcitriol synthesis) is not directly supported by biochemical measurements. Specifically, urinary calcium excretion and phosphate transport indices such as TmP/GFR (tubular maximum reabsorption of phosphate to glomerular filtration rate) were not measured. These parameters are essential for characterizing the renal handling of calcium and phosphate and for confirming the proposed mechanism. Without urinary calcium measurements, we cannot quantify the degree of hypercalciuria or assess whether it is truly elevated relative to the degree of serum calcium elevation. Without TmP/GFR, we cannot directly assess the efficiency of tubular phosphate reabsorption or confirm that phosphate wasting is occurring. The absence of these measurements represents not merely a minor limitation but a meaningful restriction on the ability to establish a robust mechanistic link between the identified variants and the clinical phenotype. Future follow-up of this patient should include comprehensive biochemical characterization including 24-hour urinary calcium excretion, serum and urinary phosphate, and calculation of TmP/GFR to better define the renal handling defects

Despite these limitations, several findings support a mechanistic link between the identified variants and the clinical phenotype. These include familial occurrence, biochemical evidence of calcitriol excess with suppressed PTH, and genetic alterations affecting both proximal phosphate transport and distal calcium handling.

CONCLUSION

This report describes a familial nephrocalcinosis phenotype in a mother and her child associated with heterozygous variants in SLC34A1 and TRPV5 and accompanied by suppressed parathyroid hormone and elevated 1,25-dihydroxyvitamin D levels. The biochemical pattern suggests dysregulation of renal phosphate handling and calcium transport leading to increased calcitriol activity and hypercalciuria. Although the detected variants are currently classified as variants of uncertain significance, their segregation in affected family members and the compatible biochemical phenotype support a potential contribution to the observed disorder of mineral metabolism. This case highlights the importance of considering inherited tubular transport disorders in patients with unexplained nephrocalcinosis and atypical vitamin D metabolism. Recognition of such mechanisms has clinical implications for diagnostic evaluation, avoidance of inappropriate vitamin D supplementation, and implementation of genetic counseling and long-term renal monitoring.

DECLARATIONS

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Data Availability: All data supporting the findings of this study are included in the article. Additional information may be available from the corresponding author upon reasonable request.

Author Contributions: O.J. and F.G. conceived the study, supervised the clinical evaluation, and contributed to manuscript preparation. E.Ç. contributed to the clinical interpretation, literature review, and drafting of the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethics Statement: This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent for publication of clinical information was obtained from the patient and the patient's legal guardian for the child. Institutional ethical approval was not required for this single case report according to local regulations.

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