Clin. Lab. 2026;72:XXX-XXX

LETTER TO THE EDITOR

Pathogenic *CYP24A1* Mutations

Dietmar Enko [1, 2], Simon Michaelis [2], Wolfgang J. Schnedl [3], Andreas Baranyi [4]

[1] *Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria*
[2] *Institute of Clinical Chemistry and Laboratory Medicine, General Hospital Hochsteiermark, Leoben, Austria*
[3] *Practice for General Internal Medicine, Bruck/Mur, Austria*
[4] *Department of Psychiatry, Psychosomatics and Psychotherapeutic Medicine, Medical University of Graz, Graz, Austria*

(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250848)

Correspondence:
Dietmar Enko, MD
Clinical Institute of Medical and
Chemical Laboratory Diagnostics
Medical University of Graz
Auenbruggerplatz 15
8036 Graz
Austria
Phone: +43 316 385-145
Fax: +43 316 385-13430
Email: enko.dietmar@gmx.at

KEYWORDS

vitamin D metabolism, 24-hydroxylase, *CYP24A1* mutation

LETTER TO THE EDITOR

The metabolism of vitamin D is complex and is precisely controlled. Vitamin D_3 is either produced in the skin from 7-dehydrocholesterol under the influence of UVB light or must be obtained exogenously from food (e.g., fish). Vitamin D_3 produced in the skin or ingested with food together with vitamin D_2 is bound to the vitamin D-binding protein (VDBP) in the plasma and transported to the liver. In the liver, vitamin D_3 is first converted by 25-hydroxylase to the 25-hydroxy-vitamin-D_3 ($25(OH)D_3$ = calcifediol). In a second hydroxylation step in the kidneys, $25(OH)D_3$ is converted to the biologically very active metabolite 1,25-dihydroxy-vitamin-D_3 ($1,25(OH)_2D_3$ = calcitriol). Vitamin D plays an essential role in the regulation of calcium homeostasis. When calcium blood levels decrease, parathyroid hormone (PTH) is secreted in the blood resulting in a release of calcium from bone and an increase of intestinal calcium resorption. The increase of the intestinal calcium resorption is caused by the active metabolite $1,25(OH)_2D_3$, which is achieved through hydroxylation of $25(OH)D_3$ in the kidneys.

Both metabolites, $25(OH)D_3$ and $1,25(OH)_2D_3$, can be degraded by the mitochondrial cytochrome P450 enzyme, a 24-hydroxylase, which is encoded by the *CYP24A1* gene [1]. This hydroxylation results in the formation of 24,25-dihydroxyvitamin D_3 ($24,25(OH)_2D_3$) and 1,24,25-trihydroxyvitamin D_3 ($1,24,25(OH)_3D_3$) [2].

Genetic *CYP24A1* variants with a reduced enzymatic

Letter to the Editor accepted September 1, 2025

activity have been reported to cause hypercalcemia in children and adults [3]. Loss-of-function mutations in the *CYP24A1* gene are associated with 24-hydroxylase deficiency. Affected individuals have undetectable $24,25(OH)_2D_3$ concentrations and are characterized by calcium levels in the upper normal range or higher combined with inappropriately high levels of $25(OH)D_3$ and $1,25(OH)_2D_3$ [3]. This can lead to hypercalciuria and suppression of PTH [4]. The expression of the phenotype of these genetic variants is promoted by exposure to sunlight and vitamin D supplementation [4]. In the United Kingdom in the 1950s, a sharp increase in idiopathic infantile hypercalcemia (IIH) - also known as Lightwood syndrome - was observed in connection with the introduction of milk enriched with vitamin D3 [5]. The infantile hypercalcemia type 1 (HCINF1) as one type of IIH is a rare subtype of hypercalcemia caused by loss-of-function mutations of the catabolic *CYP24A1* enzyme [6]. In affected individuals with HCINF1, the R396W mutation in the *CYP24A1* gene is one of the most frequent observed mutations [7]. To date, more than 50 disease-causing mutations of *CYP24A1* have been described in the literature [3]. HCINF1 presents with hypercalcemia and high urinary calcium losses resulting in nephrolithiasis and nephrocalcinosis [6]. Different clinical manifestations at different life stages are described in the literature [8]. Hypercalcemia due to *CYP24A1* loss-of-function mutations is a rare disease resulting in an age-dependent phenotype, which can be exacerbated by different trigger factors (e.g., pregnancy, vitamin D supplementation) [9].

Although *CYP24A1* mutations are rare, clinicians must be aware that patients with hypercalcemia and low PTH levels, which present with nephrolithiasis or nephrocalcinosis, could be carriers of pathogenic *CYP24A1* mutations. A greater awareness among clinicians for patients presenting with atypical biochemical profile, testing for *CYP24A1* mutations included, may establish a definitive diagnosis.

Declaration of Interest:

The authors declare that they have no conflicts of interest.

References:

1. Chen KS, DeLuca HF. Cloning of the human 1 alpha,25-dihydroxyvitamin D-3 24-hydroxylase gene promoter and identification of two vitamin D-responsive elements. Biochim Biophys Acta 1995;1263:1-9. (PMID: 7632726)

2. Kaufmann M, Schlingmann KP, Berezin L, et al. Differential diagnosis of vitamin D-related hypercalcemia using serum vitamin D metabolite profiling. J Bone Miner Res 2021;36:1340-50. (PMID: 33856702)

3. Pilz S, Theiler-Schwetz V, Pludowski P, et al. Hypercalcemia in pregnancy due to CYP24A1 mutations: case report and review of the literature. Nutrients 2022;14:2518. (PMID: 35745247)

4. Lemaitre M, Lionet A, Fages V, Vantyghem MC, Subtil D, Vambergue A. Case report: Non-PTH-dependent hypercalcemia in pregnancy: Consider CYP24A1 mutations. Ann Endocrinol (Paris) 2023;84:758-60. (PMID: 37321475)

5. Lightwood R, Stapleton T. Idiopathic hypercalcaemia in infants. Lancet 1953;265:255-6. (PMID: 13070618)

6. Jones G, Kaufmann M, St-Arnaud R. Infantile hypercalcemia type 1 (HCINF1): a rare disease resulting in nephrolithiasis and nephrocalcinosis caused by mutations in the vitamin D catabolic enzyme, CYP24A1. J Endocrinol Invest 2024;47:2663-70. (PMID: 38780860)

7. St-Arnaud R, Arabian A, Kavame D, Kaufmann M, Jones G. Vitamin D and diseases of mineral homeostasis: a CYP24A1 R396W humanized preclinical model of infantile hypercalcemia type 1. Nutrients 2022;14:3221. (PMID: 35956396)

8. Wang Q, Chen JJ, Wei LY, et al. Biallelic and monoallelic pathogenic variants in CYP24A1 and SLC34A1 genes cause idiopathic infantile hypercalcemia. Orphanet J Rare Dis 2024;19:126. (PMID: 38504242)

9. Cappellani D, Brancatella A, Morganti R, et al. Hypercalcemia due to CYP24A1 mutations: a systematic descriptive review. Eur J Endocrinol 2021;186:137-49. (PMID: 34735369)