Abstract

The CYP24A1 gene encodes 1,25-hydroxyvitamin-D₃-24-hydroxylase, a key enzyme responsible for the catabolism of active vitamin D (1,25-dihydroxyvitamin D₃). Loss-of-function mutations in CYP24A1 lead to increased levels of active vitamin D metabolites. Clinically, two distinct phenotypes have been recognised from this: infants with CYP24A1 mutations present with infantile idiopathic hypercalcaemia, often precipitated by prophylactic vitamin D supplementation. A separate phenotype of nephrolithiasis, hypercalciuria and nephrocalcinosis often presents in adulthood. CYP24A1 mutations should be suspected when a classical biochemical profile of high active vitamin D metabolites, high or normal serum calcium, high urine calcium and low parathyroid hormone is detected. Successful treatment with fluconazole, a P450 enzyme inhibitor, has been shown to be effective in individuals with CYP24A1 mutations. Although CYP24A1 mutations are rare, early recognition can prompt definitive diagnosis and ensure treatment is commenced.

Keywords: CYP24A1, vitamin D, hypercalcaemia, idiopathic infantile hypercalcaemia, nephrolithiasis

1. Introduction

The supplementation of formula milk with vitamin D₃ (cholecalciferol) prompted a rise in infants presenting with symptomatic hypercalcaemia in the United Kingdom during the 1950s [1]. While this public health initiative was proving highly successful in preventing rickets, for the small cohort of infants presenting with failure to thrive, dehydration and nephrocalcinosis, the consequences of their hypercalcaemia were at times fatal. A diagnosis of idiopathic infantile hypercalcaemia was given to many in this cohort. The apparent
increased susceptibility of this minority group to vitamin D toxicity prompted research into a genetic predisposition. Fifty-nine years later, CYP24A1 mutations were identified demonstrating loss-of-function mutations encoding 1,25-hydroxyvitamin D₃ 24-hydroxylase, an enzyme with a key role in vitamin D metabolism [2].

More recently, CYP24A1 mutations have been recognised in an adult population of patients presenting with calcium-containing renal stones. On investigation, these patients typically displayed hypercalciuria, nephrocalcinosis and occasionally chronic kidney impairment. Vitamin D supplementation was not a feature in all cases [3], demonstrating a clinically significant phenotype manifesting from normal dietary vitamin D intake. Importantly, some patients had been symptomatic for many years, undergoing extensive investigations before a diagnosis was made. A continuing focus on preventative medicine, including oral vitamin D supplementation for maintenance of bone health and during pregnancy, is likely to continue to risk triggering manifestations of vitamin D toxicity in individuals carrying biallelic mutations in CYP24A1. As diagnostic tests and successful treatments are starting to emerge, it is important to recognise clinical presentations which should prompt screening for CYP24A1 deficiency [4–6].

2. **CYP24A1 and the vitamin D pathway**

The crucial role of vitamin D in calcium and phosphate homeostasis means excessive levels of its active form can precipitate symptomatic hypercalcaemia. The activation of vitamin D takes place in two stages. The first stage takes place in the liver: vitamin D₃ is converted to 25-hydroxyvitamin D₃, a reaction catalysed by 25-hydroxylase (CYP2R1). The second stage occurs in the kidney, when 25-hydroxyvitamin D₃ is hydroxylated to 1,25-dihydroxyvitamin D₃, the active form. This stage is catalysed by 1α-hydroxylase, an enzyme encoded by the CYP27B1 [2].

![Figure 1. Vitamin D metabolism pathway. Activation of Vitamin D: 1. Stage 1 occurs in the liver. Vitamin D₃ is converted to 25-hydroxyvitamin D₃ by the enzyme 25-hydroxylase. The CYP2R1 gene encodes 25-hydroxylase. 2. Stage 2 occurs in the kidney. 25-hydroxyvitamin D₃ is converted to 1,25-dihydroxyvitamin D₃ by the enzyme 1α-hydroxylase. The CYP27B1 gene encodes 1α-hydroxylase. 1,25-dihydroxyvitamin D₃ is the physiologically most active form of vitamin D₃ which binds to the vitamin D receptor. Inactivation of Vitamin D: Several hydroxylation steps occur in the catabolism of 1,25-dihydroxyvitamin D₃ to calctroic acid. The first of these steps is catalysed by the enzyme 1,25-hydroxyvitamin-D₃-24-hydroxylase, which is encoded by the CYP24A1 gene.](image-url)
The inactivation of vitamin D metabolites relies upon two pathways which both include steps catalysed by 1,25-hydroxyvitamin-D₃-24-hydroxylase; CYP24A1 encodes this mitochondrial enzyme which is part of the cytochrome P450 system [6]. The enzyme is present in vitamin D target cells, predominantly located in the intestine and kidneys (Figure 1) [5].

2.1. Phenotypes

2.1.1. Idiopathic infantile hypercalcaemia

The first recognised phenotype of CYP24A1 mutations was in infants diagnosed with idiopathic infantile hypercalcaemia. These individuals presented with vomiting, dehydration, fevers and failure to thrive. On investigation, a typical biochemical profile of high serum calcium and suppressed parathyroid hormone levels emerged. Renal ultrasound often demonstrated nephrocalcinosis, deposition of calcium salts within the kidney. It was not initially known whether the underlying pathophysiology of idiopathic infantile hypercalcaemia (IIH) was due to excess production of vitamin D metabolites, or an inability to inactivate vitamin D. A candidate gene approach was used to investigate families with typical presentations of idiopathic infantile hypercalcaemia. This research revealed a recessive loss-of-function mutation, in which patients with CYP24A1 mutations were unable to inactivate vitamin D as they were deficient in the enzyme catalysing this pathway (1,25-hydroxyvitamin-D₃-24-hydroxylase). Affected children presented either after sustained low-dose vitamin D prophylaxis or directly following bolus doses of vitamin D. One sibling in which vitamin D prophylaxis was avoided was proven to carry the same mutation but had remained clinically silent. This supported evidence directly linking exogenous vitamin D supplementation with precipitation of symptomatic hypercalcaemia [2].

2.1.2. Adult nephrolithiasis

Hypercalciuria is the most common cause of calcium-containing kidney stones. The recognition that 40–45% of patients with idiopathic hypercalciuria have at least one relative with nephrolithiasis implicates a genetic predisposition in many cases [4]. CYP24A1 mutations have now been proven in a cohort of adults presenting with nephrolithiasis, hypercalciuria, nephrocalcinosis and intermittent hypercalcaemia [4]. These patients had undergone extensive investigations before the cause of their nephrolithiasis was known, and multiple stone episodes and nephrocalcinosis may lead to progressive chronic kidney disease (CKD) [7]. This is important in highlighting the potential clinical spectrum of the phenotype, which may manifest without the trigger of vitamin D exposure. A typical biochemistry profile was found within this phenotype group, with normal/high serum calcium levels, suppressed parathyroid hormone, high levels of active vitamin D metabolites (25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃) and low levels of inactivated vitamin D (24,25-dihydroxyvitamin D₃). A recent study screening patients with known calcium nephrolithiasis for CYP24A1 mutations did not identify any biallelic variants in a cohort of 166 patients, suggesting CYP24A1 mutations are a rare cause of idiopathic nephrolithiasis [8]. However, given our increased understanding of this phenotype, it is imperative that recognition of the
typical biochemical pattern (suppressed PTH, hypercalcaemia, hypercalciuria) in any patients with nephrolithiasis prompts investigation for \textit{CYP24A1} mutations \cite{4, 6, 8}. Establishing a molecular diagnosis in this small cohort of patients can facilitate correct treatment and lifestyle modification (\textit{Table 1}) \cite{9}.

| Clinical features                        | Biochemical profile                                      |
|------------------------------------------|----------------------------------------------------------|
| Idiopathic infantile hypercalcaemia:    | • ↑ 25-hydroxyvitamin D$_3$                              |
| • Vomiting                               | • ↑ 1,25-dihydroxyvitamin D$_3$                          |
| • Dehydration                            | • ↑ 24,25-dihydroxyvitamin D$_3$                         |
| • Failure to thrive                      | • ↓ or high normal serum calcium                         |
| • Fever                                  | • ↑ urine calcium                                        |
| • Adult presentation:                    | • ↑ urine calcium                                        |
| • Nephrolithiasis                        | • ↓ parathyroid hormone                                 |
| • Nephrocalcinosis                       |                                                          |

\textit{Table 1.} Key features of \textit{CYP24A1} mutation phenotypes.

\textit{2.1.3. Investigation}

In patients with \textit{CYP24A1} mutations, an elevation in total vitamin D levels is typically seen. In particular, 1,25-dihydroxyvitamin D$_3$ levels are increased, but this assay is not routinely performed in many laboratories. Conversely, serum 24,24-dihydroxyvitamin-D$_3$ levels are sometimes low or undetectable in patients with \textit{CYP24A1} mutations. A blood test that calculates the ratio between vitamin D metabolites could be utilised in future clinical practice as a screening tool for \textit{CYP24A1} mutations in those patients presenting with a typical biochemical profile. In the first study of this, Molin et al. used liquid chromatography–tandem mass spectrometry to calculate the ratio of active to inactive vitamin D metabolites: Molar ratio (R) of 25-hydroxyvitamin-D$_3$: 24,25-dihydroxyvitamin D$_3$. A large increase in the ratio of active to inactive vitamin D metabolites, usually R > 80, was demonstrated in subjects who had biallelic mutations resulting in loss of function of \textit{CYP24A1}. Importantly, through use of a ratio calculation, this test can avoid misleading results in patients who might have low 24,24-dihydroxyvitamin-D$_3$ levels due to vitamin D deficiency \cite{6}.

\textit{2.2. \textit{CYP24A1} variants}

Several different loss-of-function mutations have now been identified within the \textit{CYP24A1} gene. The mutations are reported to be inherited in an autosomal recessive pattern, although it is not yet clear whether partial penetrance or environmental factors may alter manifestation of a recognised phenotype. One study showed individuals with biallelic mutations presented with the clinically recognised phenotype and that heterozygous carriers were not
sufficient to manifest clinical disease. However, it was hypothesised that infants with haploinsufficiency/heterozygous variants may be more sensitive to hypercalcaemia during childhood while the kidney is still developing, and this could become relevant in considering additional vitamin D supplementation which might overwhelm the 1,25-hydroxyvitamin-D₃-24-hydroxylase enzyme pathway in this cohort (Table 2) [4, 6].

| Year mutation reported | Age at presentation | Phenotype          | CYP24A1 mutation                  | Reference                          |
|------------------------|---------------------|--------------------|-----------------------------------|------------------------------------|
| 2011                   | 6 months            | IIH                | A475fsX490 homozygote             | Schlingmann et al. [2]             |
| 2011                   | 6 months            | IIH                | delE143 and E151X                 | Schlingmann et al. [2]             |
| 2011                   | Asymptomatic        | Identified on family screening | delE143 and E151X            | Schlingmann et al. [2]             |
| 2011                   | 8 months            | IIH                | L409S and R396W                   | Schlingmann et al. [2]             |
| 2011                   | Asymptomatic        | Identified on family screening | L409S and R396W            | Schlingmann et al. [2]             |
| 2011                   | 11 months           | IIH                | delE143 and R159Q                 | Schlingmann et al. [2]             |
| 2011                   | 7 months            | IIH                | E322K and R396W                   | Schlingmann et al. [2]             |
| 2011                   | 3.5 months          | IIH                | E322K and R396W                   | Schlingmann et al. [2]             |
| 2011                   | 7 weeks             | IIH                | R396W homozygote                  | Schlingmann et al. [2]             |
| 2011                   | 5 weeks             | IIH                | Complex deletion                  | Schlingmann et al. [2]             |
| 2012                   | 10 months           | IIH                | Homozygous delE143                | Dauber et al. [10]                 |
| 2012                   | 44 years            | Intermittent       | 2 canonical intron-exon splice junction mutations (IVS5 +1G>A and IVS6 -2A>G) | Tebben et al. [11] |
| 2013                   | 4 months            | IIH                | Homozygous R396W                  | Fencl et al. [12]                  |
| 2013                   | 9 years             | Nephrocalcinosis, nephrolithiasis | Homozygous delE143            | Dinour et al. [4]                  |
| 2013                   | 19 years            | Nephrolithiasis, nephrocalcinosis, bladder calcification | Compound heterozygous L409S and W268X | Dinour et al. [4]                  |
| 2013                   | 13 years            | Nephrolithiasis, nephrocalcinosis, hypercalcaemia, hypercalciuria | Compound heterozygous L409S and W268X | Dinour et al. [4]                  |
| 2013                   | 9 years             | Nephrocalcinosis, hypercalciuria | Compound heterozygous             | Nesterova et al. [5]               |
| 2013                   | 25 years            | Nephrolithiasis, hypercalcaemia, hypercalciuria | Compound heterozygous             | Nesterova et al. [5]               |
| 2013                   | 4.5 months          | IIH                | Homozygous R396W                  | Skalova et al. [13]                |
| Year mutation reported | Age at presentation | Phenotype | CYP24A1 mutation | Reference |
|------------------------|---------------------|-----------|------------------|-----------|
| 2013                   | 3 months            | IIH followed by adult presentation with nephrocalcinosis, CKD, hypercalcaemia and hypercalciuria | Homozygous W210R | Meusburger et al. [14] |
| 2014                   | ~20 years           | Nephrolithiasis, hypercalcaemia, hypercalciuria | Homozygous delE143 | Jacobs et al. [15] |
| 2015                   | 10 years            | Nephrolithiasis, hypercalcaemia, hypercalciuria | Homozygous delE143 | Sayers et al. [7] |
| 2015                   | 45 years            | Nephrocalcinosis, hypercalcaemia, hypercalciuria | Compound heterozygous G469Afs*22 and P21R | Figueres et al. [19] |
| 2015                   | 32 years            | Nephrolithiasis, nephrocalcinosis, hypercalcaemia, hypercalciuria | Compound heterozygous L409S and R157W | Figueres et al. [19] |
| 2015                   | 28 days             | IIH | Compound heterozygous R157W and M374T | Figueres et al. [19] |
| 2015                   | 2 months            | IIH | Compound heterozygous L409S and R396W | Figueres et al. [19] |
| 2015                   | 6 months            | IIH | Homozygous L409S | Figueres et al. [19] |
| 2015                   | 2 months            | IIH | Compound heterozygous R396W and R396G | Figueres et al. [19] |
| 2015                   | 6 months            | IIH | Compound heterozygous delE143 and L409S | Figueres et al. [19] |
| 2015                   | 1 day               | Hypercalcaemia, apnoea | Heterozygous M374T | Molin et al. [6] |
| 2015                   | 3 days              | Infection, hypercalcaemia, suppressed PTH | Heterozygous M374T | Molin et al. [6] |
| 2015                   | 11 days             | Prematurity, hypercalcaemia, suppressed PTH | Heterozygous G322A | Molin et al. [6] |
| 2015                   | 4 days              | Prematurity, hypercalcaemia, suppressed PTH | Heterozygous R439C | Molin et al. [6] |
| 2015                   | 13 days             | Small for gestational age, hypercalcaemia, suppressed PTH | Heterozygous M374T | Molin et al. [6] |
### Table 2. Identified mutations in CYP24A1.

| Year mutation reported | Age at presentation | Phenotype | CYP24A1 mutation | Reference |
|------------------------|---------------------|-----------|------------------|-----------|
| 2015                   | 24 years            | Hypercalcaemia, suppressed PTH, nephrocalcinosis, CKD | Homozygous delE143 | Jobst-Schwan et al. [3] |
| 2015                   | Asymptomatic        | Identified on family screening | Homozygous delE143 | Jobst-Schwan et al. [3] |
| 2015                   | 26 years            | Nephrocalcinosis, hypercalcaemia, hypercalciuria | Homozygous delE143 | Tray et al. [16] |
| 2015                   | 21 years            | Nephrocalcinosis, nephrolithiasis, hypercalcaemia | Heterozygous delE143 and R396W | Tray et al. [16] |
| 2015                   | 5 months            | IIH       | Compound heterozygous R396W and W134G | Dinour et al. [17] |
| 2015                   | 9 months            | IIH       | Compound heterozygous G315X and W134G | Dinour et al. [17] |
| 2015                   | 5 months            | IIH       | Homozygous delE143 | Dinour et al. [17] |
| 2015                   | 35 years            | Nephrolithiasis, nephrocalcinosis and hypercalcaemia during pregnancy | Homozygous delE143 | Dinour et al. [17] |

CKD, chronic kidney disease; IIH, idiopathic infantile hypercalcaemia; PTH, parathyroid hormone.

#### 2.3. Treatment

CYP24A1 mutations lead to calcium stone formation, and conventional treatments for calcium stones are recommended. These would include maintaining a high fluid intake and avoiding excess dietary sodium. Specific measures would include avoiding dietary vitamin D supplements (in foods and drinks) and avoidance of excessive sunlight exposure [7]. Ketoconazole was first demonstrated as an effective treatment for reducing the effects of vitamin D toxicity in patients with CYP24A1 mutations. As a non-specific P450 enzyme inhibitor ketoconazole inhibits the enzyme catalysing production of 1,25-dihydroxyvitamin D₃ (1α-hydroxylase), thereby decreasing levels of active vitamin D₃. However, CYP24A1-deficient individuals require lifelong treatment as they will always lack the enzyme to inactivate vitamin D, and the side-effect profile of ketoconazole, which includes hepatotoxicity, hypogonadism and adrenal insufficiency, makes it unsuitable for this purpose [4]. More recently, low-dose fluconazole, also acting as a P450 enzyme inhibitor, has been shown to reduce serum calcium levels and
urinary calcium excretion in a patient with CYP24A1 mutation. It is likely that this drug, alongside lifestyle modifications such as avoiding excess sun exposure and following a low calcium and oxalate diet, will become the main treatment offered to patients diagnosed with CYP24A1 mutations (Figure 2) [7, 18, 19].

Figure 2. Chemical structures of ketoconazole, an imidazole antifungal agent, and fluconazole, a triazole antifungal agent. Azole agents are cytochrome inhibitors primarily used as antifungal agents. They are heterocyclic ring compounds and are generally classified as either imidazoles (e.g. ketoconazole) or triazoles (e.g. fluconazole), containing two or three nitrogen atoms, respectively, in the azole ring. They exhibit their antifungal action through inhibition of lanosterol 14-α demethylase, a cytochrome P450 enzyme important for the synthesis of a fungal plasma membrane constituent.

2.4. Evidence for genetic heterogeneity of idiopathic infantile hypercalcaemia

Since the discovery of CYP24A1 mutations underlying idiopathic infantile hypercalcaemia (IIH) in 2011, a cohort of IIH patients has been identified without CYP24A1 mutations. In 2015, a new loss-of-function mutation in SLC34A1, which encodes the renal sodium–phosphate cotransporter 2A (NaPi-IIa), was recognised in this group [20]. These patients presented with a classical IIH phenotype, with symptoms of hypercalcaemia. Importantly, however, their symptoms did not resolve with removal of vitamin D supplementation. Instead, their hypercalcaemia corrected rapidly after commencing phosphate replacement, highlighting the different mechanism driving the hypercalcaemia. In patients with SLC34A1 mutations, renal phosphate wasting leads of inappropriately high levels of 1,25-dihydroxyvitamin-D$_3$, which in turn causes hypercalcaemia. It is crucial to distinguish between patients carrying mutations in CYP24A1 versus SLC43A1, as different intervention is required to successfully treat their hypercalcaemia [20]. As SLC34A1 mutations have also been identified as a cause of nephrolithiasis, there is overlap between SLC34A1 and CYP24A1 mutation phenotypes in both paediatric and adult presentations [21].
3. Conclusions

Overall, CYP24A1 mutations are rare and account for a small proportion of symptomatic hypercalcaemia or nephrolithiasis cases. However, a greater awareness of their phenotypes will increase clinical suspicion in patients presenting with a typical biochemical profile. Testing for mutations in CYP24A1 can establish a definitive diagnosis, avoiding protracted further investigations and allowing treatment to commence. Alongside dietary and lifestyle advice, aimed at minimising vitamin D intake, fluconazole is proving a promising lifelong treatment to prevent effects of vitamin D toxicity.

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References

[1] British Paediatric Association. Hypercalcemia in infants and vitamin D. British Medical Journal 1956; 2: 149.

[2] Schlingmann KP, Kaufmann M, Weber S, Irwin A, Goos C, John U et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. The New England Journal of Medicine 2011; 365(5): 410–421.

[3] Jobst-Schwan T, Pannes A, Schlingmann KP, Eckardt K-U, Beck BB, Wiesener MS. Discordant clinical course of vitamin-D-hydroxylase (CYP24A1) associated hypercalcaemia in two adult brothers with nephrocalcinosis. Kidney and Blood Pressure Research 2015; 40: 443–451.
[4] Dinour D, Beckerman P, Ganon L, Tordjman K, Eisenstein Z, Holtzman EJ. Loss-of-function mutations of CYP24A1, the vitamin D 24-hydroxylase gene, cause long-standing hypercalciuric nephrolithiasis and nephrocalcinosis. The Journal of Urology 2013; 190: 552–557.

[5] Nesterova G, Malicdan MC, Yasuda K, Sakaki T, Vilboux T, Ciccone C. 1,25-(OH)2D-24 hydroxylase (CYP24A1) deficiency as a cause of nephrolithiasis. Clinical Journal of the American Society of Nephrology 2013; 8: 649–657.

[6] Molin A, Baudoin R, Kaufmann M, Soubrierelle JC, Ryckewaert A, Vantyghem MC. CYP24A1 mutations in a cohort of hypercalcemic patients: evidence for a recessive trait. Journal of Clinical Endocrinology and Metabolism 2015; 100(10): E1343–E1352.

[7] Sayers J, Hynes AM, Srivastava S, Down F, Quinton R, Datta HK, Sayer JA. Successful treatment of hypercalcaemia associated with a CYP24A1 mutation with fluconazole. Clinical Kidney Journal 2015; 8(4): 453–455.

[8] Sayers J, Hynes AM, Rice SJ, Hogg P, Sayer JA. Searching for CYP24A1 mutations in cohorts of patients with calcium nephrolithiasis. OA Nephrology 2013; 1(1): 1–6.

[9] Sayer JA. Re: Loss-of-function mutations of CYP24A1, the vitamin D 24-hydroxylase gene, cause long-standing hypercalciuric nephrolithiasis and nephrocalcinosis. The Journal of Urology 2015; 68: 164–165.

[10] Dauber A, Nguyen TT, Sochett E, Cole DEC, Horst R, Abrams SA et al. Genetic defect in CYP24A1, the vitamin D 24-hydroxylase gene, in a patient with severe infantile hypercalcaemia. The Journal of Clinical Endocrinology and Metabolism 2012; 97(2): E268–E274.

[11] Tebben PJ, Milliner DS, Horst RL, Harris PC, Singh RJ, Wu Y et al. Hypercalcaemia, hypercalciuria, and elevated calcitriol concentrations with autosomal dominant transmission due to CYP24A1 mutations: effects of ketoconazole therapy. The Journal of Clinical Endocrinology and Metabolism 2012; 97(3): E423–E427.

[12] Fencl F, Bláhová K, Schlingmann KP, Konrad M, Seeman T. Severe hypercalcemic crisis in an infant with idiopathic infantile hypercalcaemia caused by mutation in CYP24A1 gene. European Journal of Pediatrics 2013; 172: 45–49.

[13] Skalova S, Cerna L, Bayer M, Kutilek S, Konrad M, Schlingmann KP. Intravenous pamidronate in the treatment of severe idiopathic infantile hypercalcaemia. Iranian Journal of Kidney Diseases 2013; 7(2): 160–164.

[14] Meusburger E, Mündlein A, Zitt E, Obermayer-Pietsch B, Kotzot D, Lhotta K. Medullary nephrocalcinosis in an adult patient with idiopathic infantile hypercalcaemia and a novel CYP24A1 mutation. Clinical Kidney Journal 2013; 6: 211–215.

[15] Jacobs TP, Kaufman M, Jones G, Kumar R, Schlingmann KP, Shapses S. A lifetime of hypercalcaemia and hypercalciuria, finally explained. The Journal of Clinical Endocrinology and Metabolism 2014; 99(3): 708–712.
[16] Tray KA, Laut J, Saidi A. Idiopathic infantile hypercalcaemia, presenting in adulthood-no longer idiopathic nor infantile: two case reports and review. Connecticut Medicine 2015; 79(10): 593–597

[17] Dinour D, Davidovits M, Aviner S, Ganon L, Michael L, Modan-Moses D et al. Maternal and infantile hypercalcaemia caused by vitamin-D-hydroxylase mutations and vitamin D intake. Pediatric Nephrology 2015; 30: 145–152.

[18] Dusso AS, Gomez-Alonso C, Cannata-Andia JB. The hypercalcaemia of CYP24A1 inactivation: new ways to improve diagnosis and treatment. Clinical Kidney Journal 2015; 8(4): 456–458.

[19] Figueres M-L, Linglart A, Bienaime F, Allain-Launay E, Roussey-Kessler G, Ryckewaert A. Kidney function and influence of sunlight exposure in patients with impaired 24-hydroxylation of vitamin D due to CYP24A1 mutations. American Journal of Kidney Disease 2015; 65(1): 122–126.

[20] Schlingmann KP, Ruminska J, Kaufmann M, Dursun I, Patti M, Kranz B et al. Autosomal-recessive mutations in SLC34A1 encoding sodium-phosphate cotransporter 2a cause idiopathic infantile hypercalcemia. Journal of American Society of Nephrology 2015; 27: 604–614.

[21] Oddsson A, Sulem P, Helgason H, Edvardsson VO, Thorleifsson G, Sveinbjörnsson G et al. Common and rare variants associated with kidney stones and biochemical traits. Nature Communications 2015; 6(7975): 1–9
