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Chapter 4

Clinical and Biochemical Features of Patients with *CYP24A1* Mutations

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Abstract

The *CYP24A1* gene encodes 1,25-hydroxyvitamin-D_3-24-hydroxylase, a key enzyme responsible for the catabolism of active vitamin D (1,25-dihydroxyvitamin D_3). 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 D_3 (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 D_3 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 D_3 is converted to 25-hydroxyvitamin D_3, a reaction catalysed by 25-hydroxylase (*CYP2R1*). The second stage occurs in the kidney, when 25-hydroxyvitamin D_3 is hydroxylated to 1,25-dihydroxyvitamin D_3, the active form. This stage is catalysed by 1α-hydroxylase, an enzyme encoded by the *CYP27B1* [2].

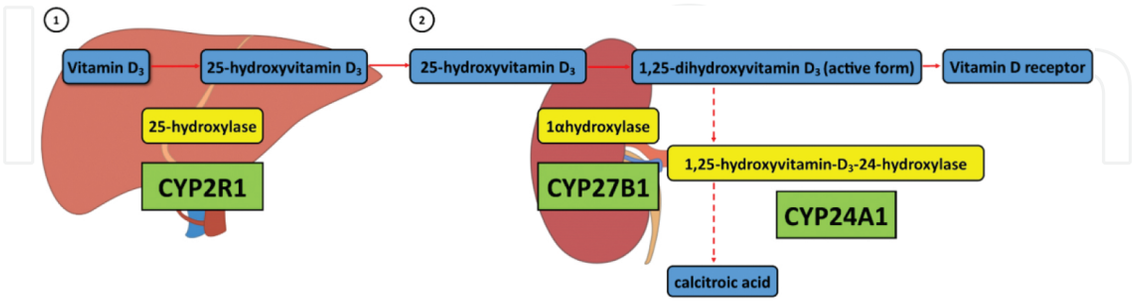

Figure 1. Vitamin D metabolism pathway. Activation of Vitamin D: 1. Stage 1 occurs in the liver. Vitamin D_3 is converted to 25-hydroxyvitamin D_3 by the enzyme 25-hydroxylase. The *CYP2R1* gene encodes 25-hydroxylase. 2. Stage 2 occurs in the kidney. 25-hydroxyvitamin D_3 is converted to 1,25-dihydroxyvitamin D_3 by the enzyme 1α-hydroxylase. The *CYP27B1* gene encodes 1α-hydroxylase. 1,25-dihydroxyvitamin D_3 is the physiologically most active form of vitamin D_3 which binds to the vitamin D receptor. Inactivation of Vitamin D: Several hydroxylation steps occur in the catabolism of 1,25-dihydroxyvitamin D_3 to calcitroic acid. The first of these steps is catalysed by the enzyme 1,25-hydroxyvitamin-D_3-24-hydroxylase, which is encoded by the *CYP24A1* gene.

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The inactivation of vitamin D metabolites relies upon two pathways which both include steps catalysed by 1,25-hydroxyvitamin-D_3-24-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-D_3-24-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 D_3 and 1,25-dihydroxyvitamin D_3) and low levels of inactivated vitamin D (24,25-dihydroxyvitamin D_3). 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 *CYP24A1* mutations [4, 6, 8]. Establishing a molecular diagnosis in this small cohort of patients can facilitate correct treatment and lifestyle modification (**Table 1**) [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:	• ↓ parathyroid hormone
• Nephrolithiasis	
• Nephrocalcinosis	

Table 1. Key features of *CYP24A1* mutation phenotypes.

2.1.3. Investigation

In patients with *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 *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 *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 *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 [6].

2.2. *CYP24A1* variants

Several different loss-of-function mutations have now been identified within the *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

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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-D_3-24-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 hypercalcaemia, hypercalciuria, nephrolithiasis	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 delE143 and L148P	Nesterova et al. [5]
2013	25 years	Nephrolithiasis, hypercalcaemia, hypercalciuria	Compound heterozygous delE143 and L409S	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]

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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.

Table 2. Identified mutations in *CYP24A1*.

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 D_3, (1α-hydroxylase), thereby decreasing levels of active vitamin D_3. 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].

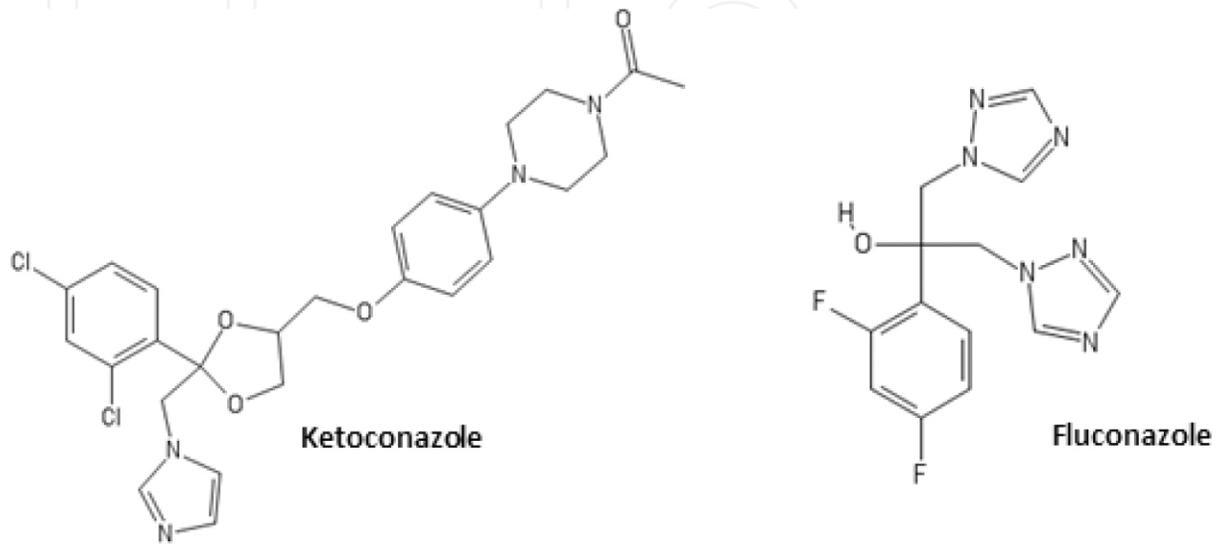

Figure 2. Chemical structures of ketoconazole, an imidazole antifungal agent, and fluconazole, a triazole antifungal agent. Azole agents are cytochrome inhibitors primarily used as antifungal agents. They are heterocyclic ring compounds and are generally classified as either imidazoles (e.g. ketoconazole) 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].

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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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