Outline

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Review

CYP24A1 loss of function: Clinical phenotype of monoallelic and biallelic mutations

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Highlights

- Loss-of-function mutations in *CYP24A1* disrupt calcium homeostasis.
- Clinical consequences include hypercalcemia, hypercalciuria, and kidney stones.
- Biallelic mutations are typical, although heterozygotes may have a mild phenotype.
- Such mutations are an important cause of “idiopathic” hypercalcemia.

Abstract

CYP24A1, encoding the vitamin D-24-hydroxylase, is of major clinical and physiologic importance, serving to regulate the catabolism of 1,25-$(OH)_2$D, the physiologically active vitamin D metabolite. In addition to facilitating catabolism of 1,25-$(OH)_2$D, *CYP24A1* also enhances the turnover and elimination of 25-OHD, the abundant precursor metabolite and storage form of the vitamin. *CYP24A1* can be stimulated hormonally by 1,25-$(OH)_2$D and by FGF23, whereas *CYP27B1,* encoding the vitamin D-1α–hydroxylase, is stimulated hormonally by parathyroid hormone (PTH) and downregulated by FGF23. Thus *CYP24A1* and *CYP27B1,* together, provide for alternate and regulated fates of 25-OHD, and control the availability of the active metabolite, 1,25-$(OH)_2$D, depending upon physiologic needs. These two enzymes, are therefore central to the homeostatic control of vitamin D metabolism, and as a result affect calcium metabolism in critical ways. Disruption of *CYP24A1* in mice results in elevated circulating 1,25-$(OH)_2$D, substantiating the importance of the enzyme in the maintenance of vitamin D metabolism. The consequential skeletal phenotype in these mice further demonstrates the biologic sequelae of the disruption of the vitamin D pathway, and illustrates a specific developmental pathology mediated largely by oversupply of 1,25-$(OH)_2$D. More recent evidence has identified loss of function mutations in *CYP24A1* in association with hypercalcemia, hypercalciuria and nephrolithiasis in humans. Initial reports described certain variant mutations in *CYP24A1* as an unrecognized cause of “Idiopathic Infantile Hypercalcemia,“ and more recently older children and adults have been identified with a similar phenotype. Over 25 likely disease-causing variants are described. Homozygous and compound heterozygote mutations account for the overwhelming majority of cases, however the heterozygous loss-of-function mutations of *CYP24A1* do not appear to consistently result in symptomatic hypercalcemia. Considerations ripe for exploration include the potential role for such mutations in the tolerance to challenges to the calcium homeostatic system, such as changes in dietary calcium intake, vitamin D supplementation, sunlight exposure or pregnancy.

Abbreviations

FGF23, fibroblastic growth factor 23; PTH, parathyroid hormone; WS, Williams syndrome; 1,25-$(OH)_2$D, 1,25-dihydroxyvitamin D; 24,25-$(OH)_2$D, 24,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D

Keywords

24-hydroxylase; hypercalcemia; hypercalciuria; vitamin D; Williams syndrome

1. Idiopathic infantile hypercalcemia

Disorders of hypercalcemia occur across the entire age span and with considerable heterogeneity of severity. Traditional approaches to the evaluation of patients with hypercalcemia are generally directed to ascertaining the mechanism of hypercalcemia, and thus measurements of parathyroid hormone and vitamin D metabolites are employed to identify hyperparathyroidism and vitamin D intoxication. In the absence of securing such a mechanistic diagnosis, hypercalcemia has often been termed “idiopathic.” As parathyroid disease occurs infrequently in infants, pediatric specialists are likely to entertain the diagnosis of “idiopathic infantile hypercalcemia” with some frequency. Indeed in the 1950s, several series of cases of infantile hypercalcemia were published and carefully characterized clinically [1,2]. Features consistent with a diagnosis of Williams syndrome (WS) were noted in some of these children. WS, associated with deletions at the elastin gene locus, is manifest by a characteristic facial appearance, specific associated cardiac anomalies (often supravalvular aortic stenosis), short stature, and hypercalcemia during infancy [3,4]. The term “idiopathic infantile hypercalcemia” has eventually come to be used in reference to children without WS, although early literature on IIH is often inclusive of those children carrying the diagnosis of WS.

In a number of these reports, limited investigation into the mechanism of hypercalcemia was not definitive, but with the development of immunoassays for the measurement of circulating levels of parathyroid hormone (PTH), it became clear that this calciotropic hormone was not the usual mediator of hypercalcemia in the vast majority of these cases. Such findings led to the speculation that increased sensitivity to vitamin D may play a role in the hypercalcemia seen in many cases of IIH [5]. Prior to the availability of methods to directly measure circulating vitamin D metabolites in clinical samples, an in vivo bioassay was developed to assess “anti-rachitic” activity in patient samples. The anti-rachitic activity was determined by the relative quantity of sera required to correct the rickets in the animal. One classic paper identified markedly increased amounts of anti-rachitic material in the serum of IIH patients, providing evidence, albeit crude by contemporary standards, of an etiology related to the speculated “increased sensitivity” to vitamin D [5].

2. *CYP24A1*: identifying a mechanism for regulated vitamin D catabolism

With the eventual discovery of a multitude of vitamin D metabolites and development of reliable methodology for quantification of them in biological samples, details of vitamin D metabolism and its regulation have become evident (see Ref. [6] for review). The importance of the 24-hydroxylase enzyme has become particularly evident. This cytochrome P-450 complex provides for an energy-favorable conversion of 25-dihydroxyvitamin D [25-OHD] to 24,25-$(OH)_2D$ as an alternative to the synthesis of 1,25-dihydroxyvitamin D [1,25-$(OH)_2D$], the systemically active vitamin D metabolite. Promoting the metabolism of 25-OHD to 24,25-$(OH)_2D$ thereby serves to reduce stores of 25-OHD leading to accelerated clearance of the most abundant circulating vitamin D metabolite. Numerous factors up-regulate the catalytic unit of the cytochrome P-450 1-hydroxylase, with simultaneous down-regulation of the 24-hydroxylase, and vice versa. Thus, when conditions demand enhanced vitamin D activity, regulation of the enzymes favor increased 1,25-$(OH)_2D$ and limited 24,25-$(OH)_2D$ production; in the setting of vitamin D excess, synthesis of 24,25-$(OH)_2D$ increases and further 1,25-$(OH)_2D$ production is curtailed.

Of note, 1,25-$(OH)_2D$ itself is the preferred substrate for the 24-hydroxylase, allowing for conversion to 1,24,25-trihydroxyvitamin D as an initial step in catabolism of the active metabolite [7], thus the enzyme serves to enhance clearance of the active metabolite, as well as to provide a means to reduce stores of 25-OHD.

The physiological activity of 24,25-$(OH)_2D$ is controversial. A significant body of evidence suggests that 24,25-$(OH)_2D$ has distinct physiological actions itself, including inhibition of PTH secretion [8,9], enhancement of fracture healing [10], and various functions of growth plate cartilage [11]. Much recent work related to a role in fracture healing is discussed elsewhere in this issue [12].

3. The *CYP24A1* null mouse

Clues to a potential phenotype in humans with loss-of-function mutations of the 24-hydroxylase are evident from study of the *Cyp24a1* knockout mouse [13]. These mice are characterized by complete loss of function of the 24-hydroxylase. Interestingly initial characterization of this animal model demonstrated normal circulating levels of 1,25-$(OH)_2D$ levels at early sampling, but impaired clearance of administered 1,25-$(OH)_2D$. Furthermore, 1,25-$(OH)_2D$ levels increase excessively with addition of a vitamin D-supplemented diet. The early survival of these mice is limited and appears to depend upon the capacity to down-regulate 1,25-$(OH)_2D$ production. Cortical bone is reduced in the *Cyp24a1* null mouse as a consequence of 1,25-$(OH)_2D$-induced bone resorption. The observed skeletal pathology seems to primarily be related to limited clearance of 1,25-$(OH)_2D$ rather than the inability to generate 24,25-$(OH)_2D$. The 24-hydroxlyase null mouse has been shown to have impaired fracture healing, suggesting that increased *CYP24A1* expression and the resultant increased 24,25-$(OH)_2D$ production in forming callus (see Refs. [13–15] for review) may have clinically relevant consequences.

4. *CYP24A1* loss-of-function mutations in humans

In a series of children with IIH, 24-hydroxylase activity was assayed in cultured fibroblasts from an affected subject and several controls [16]. Baseline 24-hydroxlase activity in fibroblasts obtained from the affected subject was comparable to controls, but the marked stimulation observed in control fibroblasts after incubation with 1,25-$(OH)_2$D was absent in the patient's fibroblasts, providing physiologic evidence suggesting that altered 24-hydroxlase activity may explain some cases of idiopathic hypercalcemia of infancy.

Subsequently, mutational analysis of a large German cohort of children with idiopathic hypercalcemia (or an exaggerated response to vitamin D prophylaxis) identified 10 children with complete loss of function mutations in *CYP24A1*[17]. All but one child (who was asymptomatic and detected only upon family screening) were hypercalcemic. The normocalcemic infant, also detected during family screening had nephrocalcinosis detected by renal ultrasonography. The cohort had a mean serum calcium level of 15.6 mg/dl and a mean 1,25-$(OH)_2$D level of 75 pg/ml. All but one patient had biallelic (homozygous or compound heterozygous) mutations in *CYP24A1*. The remaining patient was found to have a complex heterozygous deletion in the gene. Functional assays indicated a complete loss of enzyme activity in most of the mutations.

A second report by Dauber et al. [18] documented severe hypercalcemia, and undetectable circulating 24,25-$(OH)_2$D levels in an individual with a homozygous mutation of *CYP24A1* (an identical mutation to that reported by Schlingmann contributing to compound heterozygosity in 2 cases). Elevated fractional absorption of calcium (90%) was documented using stable calcium isotope methodology, providing further data of a vitamin D-dependent physiologic mechanism (enhanced intestinal calcium absorption) for the hypercalcemia. Interestingly, the circulating 1,25-$(OH)_2$D level was not elevated (33 pg/ml), suggesting the possibility that local vitamin D metabolism may be a factor in intestinal calcium absorption. The heterozygous mother of the patient raised the consideration that mono-allelic mutations in *CYP24A1* may have a milder phenotype, with evidence of chronic hypercalciuria rather than overt IIH.

A 44-year old man with biallelic canonical splice site mutations in *CYP24A1* was reported by Tebben et al. [19]. Careful investigation of the family revealed that individuals carrying heterozygous loss-of-function mutations may have a biochemical phenotype. Several older children and adults were included in this report, raising the consideration that loss of function in *CYP24A1* may have implications beyond infantile hypercalcemia, and in particular that the mutation may account for, or contribute to, more common disorders such as idiopathic hypercalcuria and nephrolithiasis. Furthermore, the occurrence of a phenotype in the more common heterozygous state suggests a more widespread impact of this gene than in the less frequent association of biallelic mutations with IIH.

A number of related reports have now emerged [20–34], and there is a general consistency of phenotype amongst individuals carrying biallelic mutations, either homozygotes or compound heterozygotes. The biochemical phenotype of the reported cases represents the expected physiological consequences of excess vitamin D activity: i.e., hypercalcemia, hypercalciuria, low or low-normal PTH levels, and the absence of hypophosphatemia or toxic levels of 25-OHD. Nephrocalcinosis appears as a function of chronic hypercalcemia/hypercalciuria. Renal stones may be present. Dedicated analysis of vitamin D metabolites has revealed that, the circulating 24,25-$(OH)_2$D level is low, and the molar ratio of circulating 25-OHD to 24,25-$(OH)_2$D has been found to be a good marker of 24-hydroxylase function [35]. Interestingly, although 1,25-$(OH)_2$D levels are often elevated, there is some inconsistency in this regard, and several patients with biallelic mutations are reported to have normal 1,25-$(OH)_2$D levels, as was observed in the *Cyp24a1* null mice [13]. In some cases disease was exacerbated in adults with sunlight exposure [29] or during pregnancy [30,33].

5. Is the heterozygous state of clinical significance?

The clinical significance of the heterozygous state has been specifically explored further in two studies [36,37]. Molin et al. recruited 72 patients with hypercalcemia (or history thereof) in concert and suppressed PTH levels [36]. Of this cohort, 47 patients (58%) no mutation in *CYP24A1* was identified, 20 (35%) had biallelic mutations, and 5 (7%) were heterozygous for *CYP24A1* mutations. The 5 patients with heterozygous mutations did not have the characteristic biochemical profile described above, and their presentation was limited to hypercalcemia and hypercalciuria. To further examine the question, a study of asymptomatic adult relatives of those with biallelic mutations was carried out. No striking phenotype in the heterozygotes was found, however, the group did have slightly elevated circulating 1,25-$(OH)_2$D levels and one individual had renal stones. Another individual in this screen was found to be homozygous for a *CYP24A1* mutation and had renal stones, but had not presented with IIH. These authors concluded that the biochemical abnormalities indicative of 24-hydroxylase loss-of-function are not associated with the heterozygous state, and propose nephrolithiasis and hypercalcemia were due to other factors.

Similarly, Cools et al. [37] studied 8 relatives of a patient with a known homozygous mutation, identifying 6 heterozygous carriers. Three of these 6 heterozygotes had either previous documentation of renal stones or suggestive history for nephrolithiasis, but no current renal abnormalities were detected and biochemical investigations were normal. In contrast to Molin et al., these authors suggest that heterozygosity for *CYP24A1* mutations may predispose the carrier to nephrolithiasis, despite the lack of overt biochemical abnormalities. These authors suggest that the molar ratio of circulating 25-OHD to 24,25-$(OH)_2$D may serve as a marker for the clinical findings in the heterozygous state. Our review of the 53 recorded heterozygotes from all the studies referenced above indicates a clinical phenotype in 19 (36%), and no significant clinical phenotype is described in the remaining 34 (64%). The phenotype is usually

mild, with nephrolithiasis or nephrocalcinosis as typical features. In two reported heterozygous cases severe phenotypes were identified [17,25], although the possibility that unidentified deletions or intronic mutations occur on the allele in which no coding region mutation was found cannot be excluded.

6. Clinical implications of the current body of knowledge

- Biallelic (homozygous or compound heterozygous) loss of function mutations in *CYP24A1* are a distinct cause of IIH, and appear to most commonly result in a severe hypercalcemic phenotype. However the spectrum of disease is broad, and a small minority of patients has been identified in later childhood or adulthood with hypercalciuria, nephrolithiasis or nephrocalcinosis.

- Heterozygote carriers may have a clinically significant phenotype, usually milder and less overt than those with biallelic mutations. Rarely, a severe phenotype has been described in presumed heterozygous individuals. Biochemical findings, and particularly, the molar ratio of circulating 25-OHD to 24,25-$(OH)_2D$, may be a useful screen for clinical significance in obligate carriers. Clinical effects are renal in nature and primarily relate to the propensity for stone formation.

- Several factors may serve as important modifiers of the phenotype, including:

- Vitamin D supplementation and dietary calcium; it remains to be determined whether certain heterozygous individuals may be more prone to the development of nephrolithiasis/nephrocalcinosis with generous vitamin D supplementation or dietary calcium intake.

- Adults vs. children: Adults tend to have a broad spectrum of clinical severity at presentation, whereas children are more likely to present with acute severe hypercalcemia.

- The mutation may exaggerate the physiologic hypercalcemia of pregnancy [30,33].

- Sunlight exposure has been associated with exacerbation of clinical symptoms [29].

- Other genetic modifiers may well account for other differences in presentation.

- Recent considerations of a role of 24,25-$(OH)_2D$ in promoting fracture healing raises the possibility that delayed fracture healing may occur; future studies in this regard are indicated.

- Treatment of infants usually consists of the application of a low-calcium, vitamin D-restricted diet, with avoidance of supplements. If refractory to this measure, other

measures, mostly in older children or adults, have included intravenous bisphosphonates, glucocorticoids, ketoconazole, and fluconazole meeting with reasonable success.

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