Loss of function CYP24A1 mutations in patients with hypercalcemia and low PTH level: an autosomal dominant or recessive trait

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Abstract

Homozygous or compound heterozygous mutations of the gene CYP24A1 coding vitamin D 24-hydroxylase have recently been reported to cause Infantile Hypocalcemia (IIH) due to increased intestinal absorption of calcium [1]. However, an autosomal dominant transmission with partial penetrance of the trait was also suggested [2]. So far, only case-reports have been published. Frequency of CYP24A1 mutations in hypercalcemic patients remains unknown.

Here we describe a cohort of patients presenting with hypercalcemia and low PTH rate, to better define the phenotype of patients who should benefit of CYP24A1 genetic screening and to evaluate the frequency of the disease.

In addition, we also show that simultaneous measurement of vitamin D metabolites by liquid chromatography-tandem mass spectrometry (LC-MS/MS) is a valuable screening tool for these patients.

Methods

Patients
We studied 72 index cases presenting with hypercalcemia (>2.6 mmol/L) and low PTH levels (<20pg/mL) and 22 heterozygous relatives.

Biochemical parameters
Data on clinical symptoms, renal ultrasound examination and biological explorations were collected at the time of the diagnosis, or retrospectively using records from hospitals or primary care physicians.

Simultaneously assay of vitamin D metabolites
LC-MS/MS analysis was performed at the time of molecular diagnosis as previously described [3] including 25-OH D$_3$ and 24,25-(OH)$_2$D$_3$ using 100μl of serum; results are expressed as a ratio of 25-OH D$_3$:24,25-(OH)$_2$D$_3$. Values under 25 indicated no defect in 24-hydroxylase activity and were considered as normal.

Molecular analysis
11 coding exons of CYP24A1 and their intron-exon junctions were sequenced as previously described (Castanet et al 2013). New variations of sequence interpreted according to pathogenicity prediction programs (PolyPhen-2, Align-GVGD, MutationTaster, SIFT).

Results 1

We identified 25 patients (35%) harboring mutations in coding sequence of CYP24A1: 20 patients (28%) with bi-allelic mutations (10 homozygous, and 10 compound heterozygous) and 5 children with heterozygous mutation (7%). All were neonates, under 2 weeks (range 1 to 13 days). In these patients, hypercalcemia was found during routine exams performed for another pathology: prematurity, growth retardation, infection or apnea. None presented with renal pathology.

Conclusions

We identified mutation in CYP24A1 as a major cause of hypercalcemia associated to low PTH level.

We confirm the accuracy and effectiveness of a novel blood test estimating the ratio between relevant vitamin D metabolites 25-OH D$_3$ and 24,25-(OH)$_2$D$_3$. This test constitutes a useful screening tool.

We suggest that in patients with CYP24A1 haplo-insufficiency, vitamin D supplementation associated with a low renal function could trigger hypercalcemia and hypercalciuria.

References

2-Tebben P et al. 2011, J Clin Endocrinol Metab 97:E423-E7

Positions of observed mutations in the human CYP24A1 gene.

A : no mutation        C : heterozygous index
B : bi-allelic mutation  D : heterozygous relatives

In patients heterozygous for CYP24A1 mutations, probands (group C) as well as relatives (group D), simultaneous assay of both 25-OH D$_3$ and 24,25-(OH)$_2$D$_3$ provides evidence for the presence of normal CYP24A1 activity with a 25-OH D$_3$:24,25-(OH)$_2$D$_3$ ratio within the normal range (R= 13.7 [9.3-18]).