A novel mutation in *CYP24A1* gene in an infant with severe hypercalcemia and unique neurological presentation

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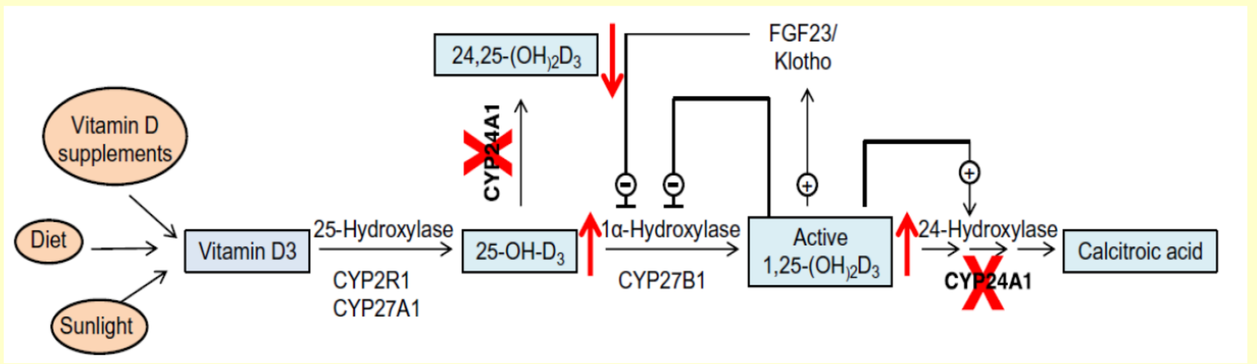
Introduction:

- Loss of function mutations of *CYP24A1*, encoding vitamin D-24-hydroxylase, have been identified in idiopathic infantile hypercalcemia (IIH), a rare entity which may lead to severe complications.
- We describe a unique neurological presentation in an infant with IHH due to a novel *CYP24A1* mutation.

Figure 1. Vitamin D Metabolism



Case presentation:

- The patient was born at term after normal pregnancy to healthy non-consanguineous parents.
- He presented at age 7 months with weakness, failure to gain weight, and developmental arrest in the preceding 2 months.

Physical examination: pale, thin, apathetic infant with severe hypotonia and tonic upward gaze.

Laboratory investigation:

Ca-20.3 mg/dl (nl 7.2-10), ionized calcium-2.7 mmol/l (nl 1.0-1.2), Phos-3.8 mg/dl (nl 4.7-8.0), PTH<3 pg/ml (nl 16-87).
25-hydroxy-vitamin D-53 ng/ml (normal 30-100), 1,25dihydroxy-vitamin D-92 pg/ml (normal 20-100).
Urine calcium/creatinine ratio=2.3 (normal for age <0.8). Renal ultrasonography demonstrated normal-sized kidneys without nephrocalcinosis.

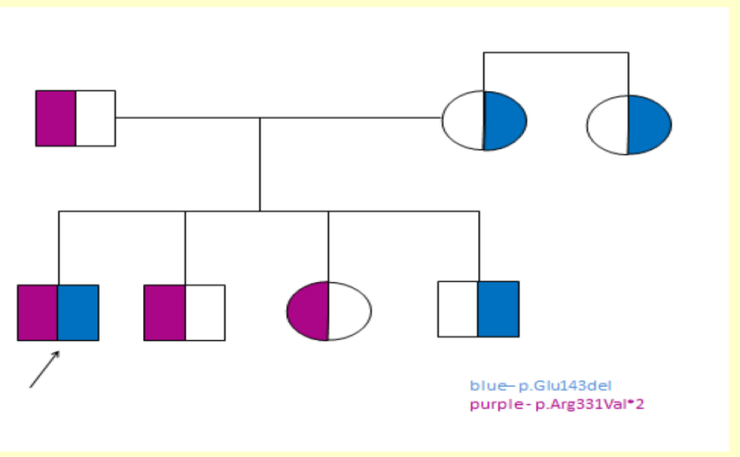
Management:

- After acute management with fluids, diuretics, pamidronate and calcitonin, calcium level decreased to 9.6 mg/dl, and the patient was discharged on low-calcium formula with no supplemental vitamin D.
- A month later, calcium level increased to 12.9 mg/dl and he received a second dose of pamidronate.

Genetic analysis:

- DNA was extracted from whole blood and full sequencing of the coding regions of the *CYP24A1* gene was performed.
- The patient is a compound heterozygote of two mutations: **delE143** in exon 2 (a mutation that has been previously reported) and a novel truncating mutation in exon 8 (**p.Arg331Val*2**).
- Each parent carried one of the mutations.

Figure 2. Family Pedigree



Follow up:

- Currently, the patient is 19 months old, with normal calcium level with no additional treatment; however, the neurological symptoms did not resolve.
- Developmental delay
- Brain MRI – increased signal intensity in the tegmental tracts of the brainstem
- The result of whole exome sequencing is pending.

Conclusions:

This patient presents a case of severe hypercalcemia due to a novel *CYP24A1* mutation associated with neurologic deterioration and tonic upward gaze that have not been previously reported in IHH.

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