

Maternal hypercalcaemia due to CYP24A1 loss of function mutations

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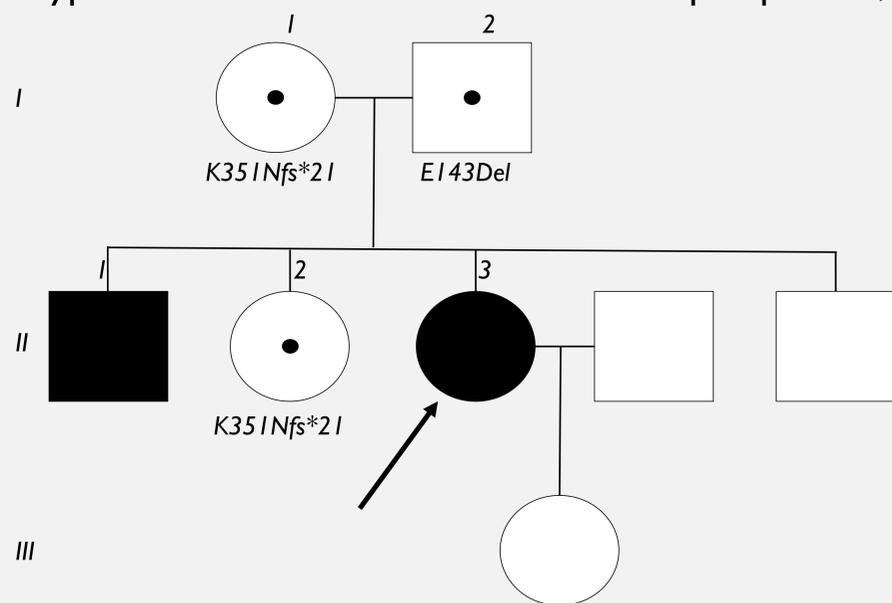
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Introduction

- Changes in calcium homeostasis occur during normal pregnancy to meet the needs of the growing fetus
- These include marked rise in 1,25-dihydroxyvitamin D (1,25-(OH)₂D₃) and suppression of parathyroid hormone (PTH)
- However, maternal hypercalcaemia is very uncommon and should prompt further investigation

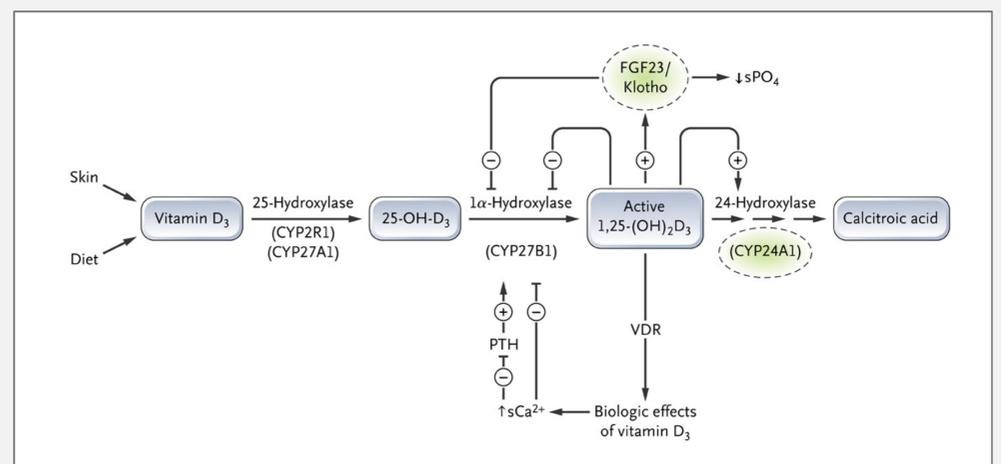
Case history

- A 24-year-old primigravida was diagnosed with hypercalcaemia from 6/40 gestation
- The pregnancy was otherwise uncomplicated and she delivered a healthy male infant at 38/40
- Hypercalcaemia resolved within 4 weeks postpartum, although hypercalciuria persisted



CYP24A1 mutations identified in the family

The asymptomatic younger brother of the index case (II-1) was identified during genetic screening



A model of vitamin D metabolism

- 1,25-(OH)₂D₃ (calcitriol) is metabolised by CYP24A1 encoded 24-hydroxylase to the inactive calcitroic acid (24,25-(OH)₂D₃)
- Mutations in CYP24A1 impair 24-hydroxylase activity resulting in reduced vitamin D metabolism, rises in 1,25-(OH)₂D₃, and increased susceptibility to hypercalcaemia

Figure reproduced from Schlingmann et al. NEJM 2011

	Calcium (2.2-2.6 mmol/L)	PTH (1.6-7.0 pmol/L)	Urine Ca:Cr ratio (0.06-0.45)	25-OH-D ₃ (50-150 nmol/L)	1,25-(OH) ₂ D ₃ (65-175 pmol/L)	24,25-(OH) ₂ D ₃ (nmol/L)	25-OH-D ₃ :24,25-(OH) ₂ D ₃ ratio
Index (II-3)							
I3/40	2.9	0.7	2.09	116	380		
Post-partum	2.5	1.8	0.76	65	149	0.6	107
I-1	2.4	3.0	0.37	82		5.0	16
I-2	2.5	3.4	0.26	52		2.7	19
II-1	2.7	0.9	1.23	88	ULN	0.6	157
II-2	2.4	3.9	0.14	46		1.9	24

Learning points

- The differential diagnosis of hypercalcaemia in pregnancy should include disordered 1,25-(OH)₂D₃ metabolism caused by mutations in CYP24A1
- Other clinical manifestations include hypercalciuria, which may persist even when calcium is within the normal range
- Ratio of 25-OH-D₃:24,25-(OH)₂D₃ is significantly elevated in affected cases, predicting mutation status
- Vitamin D metabolite analysis is therefore a useful adjunct to genetic testing in suspected cases

References

- Schlingmann et al. (2011). Mutations in CYP24A1 and idiopathic infantile hypercalcemia. *New Engl. J. Med.* <http://doi.org/10.1056/NEJMoal103864>
- Kaufmann et al. (2014). Clinical utility of simultaneous quantitation of 25-hydroxyvitamin D and 24,25-dihydroxyvitamin D by LC-MS/MS involving derivatization with DMEQ-TAD. *J. Clin. Endocrinol. Metab.* 99(7), 2567–2574. <http://doi.org/10.1210/jc.2013-4388>

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