A Rare Genetic Variant of type 1 Familial Hypocalciuric Hypercalcaemia (FHH)

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CASE HISTORY

A 60 year old Caucasian woman was referred to endocrine clinic with persistent hypercalcaemia between 2.8-2.9mmol/L (2.2-2.6), with inappropriately normal PTH at 7pmol/L (1.48-7.63).
Her hypercalcaemia was noted first in 2008.

She had no signs or symptoms associated with hypercalcemia.

There was no history of pancreatitis.

Family History:
She has a strong family history of hypercalcaemia, where her mother required Cinacalcet to control her hypercalcaemia despite two previous parathyroid resections.

She has 3 children in their 30's who had not had calcium screening before. However, one of the son had a renal stone.

INVESTIGATIONS

She received replacement for her 25OH vitamin D deficiency.
Under the context of strong family history of hypercalcaemia with normohormonal hyperparathyroidism, further investigations were intended to explore the possibility of hereditary conditions, i.e. Multiple Endocrine Neoplasia (MEN) or Familial Hypocalciuric Hypercalcaemia (FHH).

Inconsistent with MEN, her anterior pituitary axes and plasma normetanephrine/metanephrine were normal.

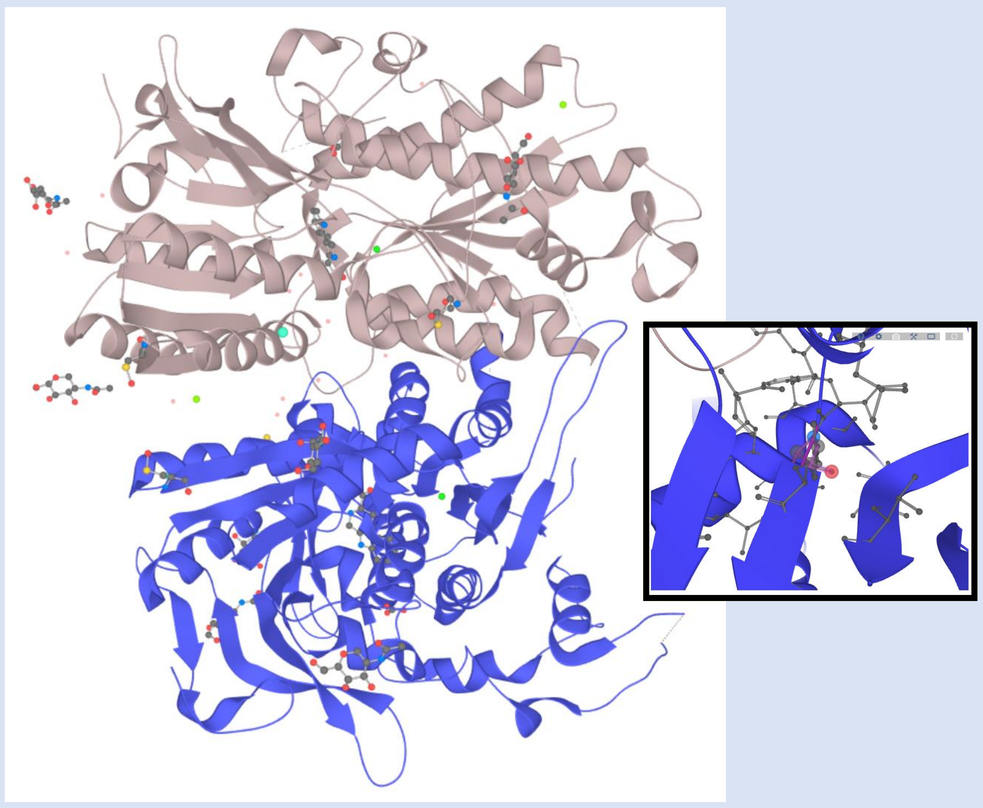
Her urine calcium: creatinine clearance ratio was **<0.01** with urine volume of 965ml/day leading to suspicion for FHH. FHH was then confirmed on genetic screening.

Investigations	Value	Reference range
Adjusted calcium	**2.82 mmol/L**	2.20 - 2.60
Phosphate	0.97 mmol/L	0.80 – 1.50
PTH	**7 pmol/L**	1.48 – 7.63
Vitamin D	20.8 nmol/L	<30 - deficient
Creatinine	105 mmol/L	45 -84
eGFR	47 units	
Prolactin	134 mU/L	59 - 619
9 am cortisol	379 nmol/L	
FT4	10.9 pmol/L	10.0 – 19.8
FT3	4.6 pmol/L	3.5-6.5
TSH	1.45 mU/L	0.35 – 5.50
IGF-1	12.1 nmol/L	12.9 -33.0
Plasma normetanephrine	928 pmol/L	<1000
Plasma metanephrine	270 pmol/L	<600
Urine Calcium:Creatinine Ratio (urine Volume 965ml/day)	**<0.01**	

REFERENCE

1. Vargas-Poussou R, Mansour-Hendili L, Baron S, Bertocchio J-P, Travers C, Simian C, et al. Familial Hypocalciuric Hypercalcemia Types 1 and 3 and Primary Hyperparathyroidism: Similarities and Differences. J Clin Endocrinol Metab. 2016 May 1;101(5):2185–95.
2. Murugaian EE, Ram Kumar RM, Radhakrishnan L, Vallath B. Novel mutations in the calcium sensing receptor gene in tropical chronic pancreatitis in India. Scand J Gastroenterol. 2008;43(1):117–21.

DIAGNOSIS: CASR: c.488C>G, p.(Pro163Arg),



- FHH types 1, 2, and 3 are due to loss-of-function mutations of the *CASR*, *GNA11*, or *AP2S1* genes, respectively (1). The detected CASR mutation confirmed the diagnosis of FHH type 1.
- A genetic screening revealed a heterogenous pathogenic variant in **CASR: c.488C>G, p.(Pro163Arg)**, which is an extremely rare variant ***not listed in population frequency databases*** (Genome Aggregation Database, Exome Variant Server, 1000 Genome).
- The CASR gene is predicted to be intolerant to missense variation and missense variants are reported as a common mechanism of disease in Human Gene Mutation Database (www.hgmd.cf.ac.uk).
- The nucleotide and amino acid are highly conserved across species. This variant lies within several protein domains.
- ***Computational analysis programmes predict a disease causing impact*** of this variant on the protein (PhD-SNP, PolyPhen, SIFT, and MutationTaster).
- This particular variant has previously been reported in patient with Tropical Chronic Pancreatitis (2). The postulated mechanism leading to pancreatitis involves high intracellular levels of calcium activating trypsinogen within the acinar cells, although this reported cases had normal serum calcium. Our index case did not manifest the phenotype with pancreatitis.
- Segregation studies in three families performed by the Oxford Genetics laboratory has shown the variant to segregate with hypercalcaemia in two affected first-degree relatives in each family. This is consistent with the clinical presentation in this patient. Therefore, we seek to offer her first-degree relatives genetic counselling and screening.

CONCLUSION LEARNING POINTS

The treatment for FHH is mainly conservative as it is not known to lead to complications. Hence, making the appropriate diagnosis may avoid unnecessary parathyroid surgery.

With the presence of strong family history, this case emphasises the importance of investigating the calcium: creatinine clearance ratio and subsequent genetic testing for CASR mutations, (FHH panel and isolated familial hyperparathyroidism panel).

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