

Case Report:

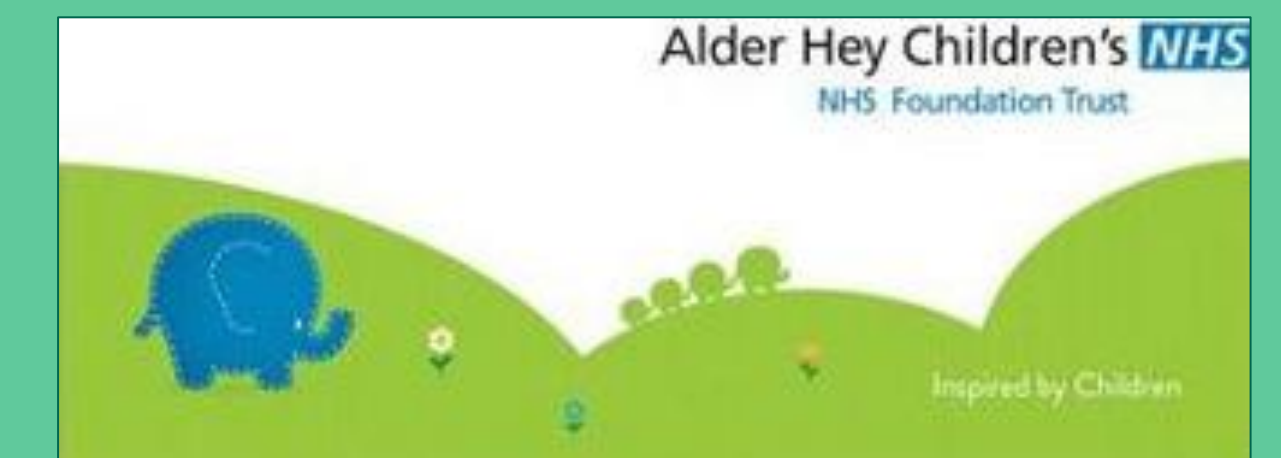
A novel mutation in the calcium sensing receptor in a Welsh family with hypercalcaemia

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Authors declare no conflict of interest



Objective

We report a novel mutation in the calcium-sensing receptor (CaSR) in a family with 3 generations affected with hypercalcaemia

Background

- Familial Hypocalciuric Hypercalcaemia (FHH) is an autosomal dominant disorder due to inactivating mutations in the calcium sensing receptor (CaSR)¹.
- FHH is generally benign with asymptomatic hypercalcaemia, low urinary calcium excretion and normal or mildly elevated parathyroid hormone (PTH)¹.
- The CaSR is a parathyroid and renally expressed G-protein-coupled receptor that maintains circulating ionised calcium concentrations by regulation of PTH secretion and urinary calcium excretion. The human *CASR* gene, located on chromosome 3q21.1, encodes a 1078 amino acid protein (Fig.1). More than 230 different disease-causing CaSR mutations have been reported^{1,2}.

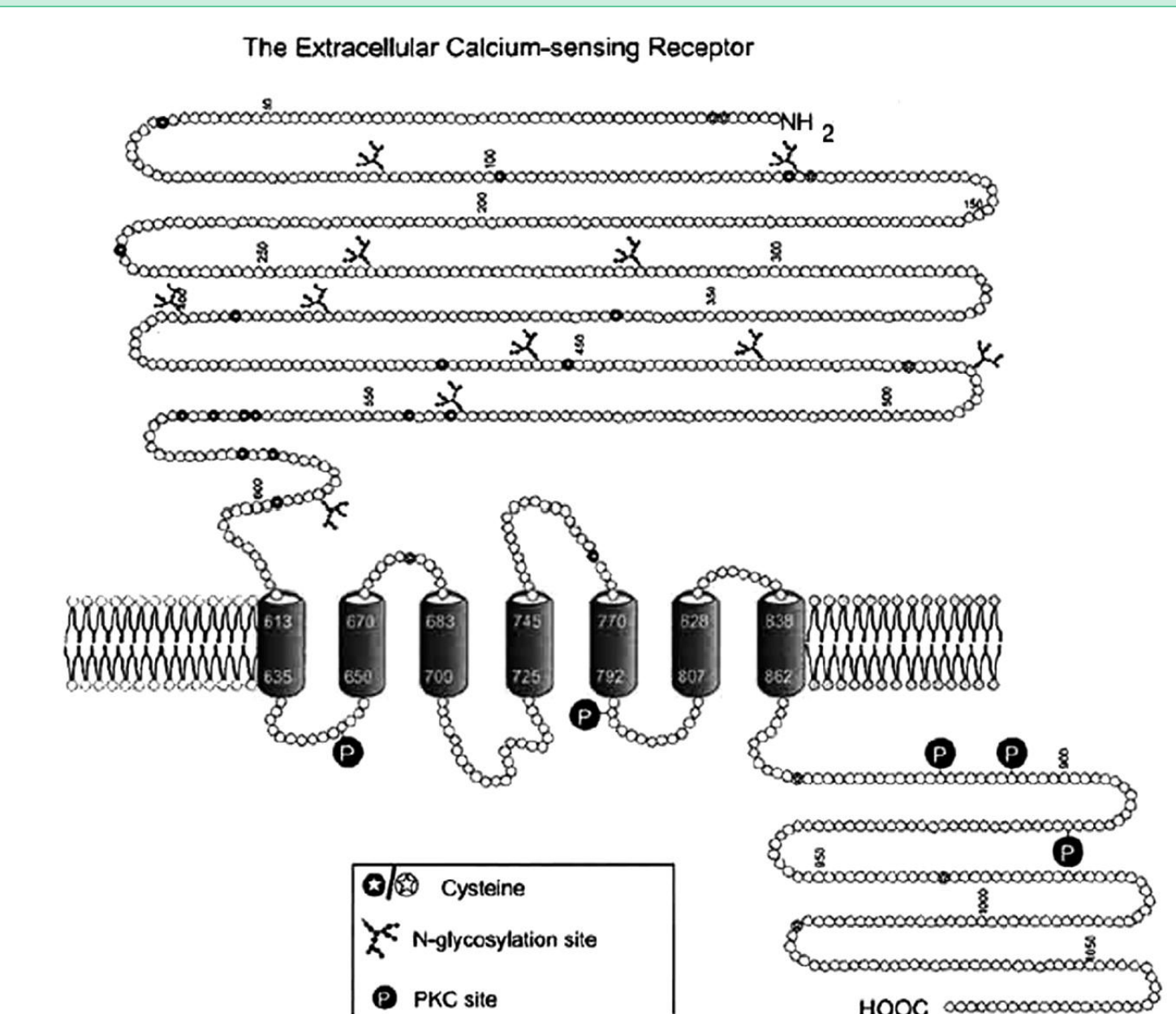


Fig 1. CASR Protein showing its extracellular, transmembrane and intracellular domains.

Smajilovic S, Tfelt-Hansen J. Calcium acts as a first messenger through the calcium-sensing receptor in the cardiovascular system. Cardiovascular Research 2007;75:457-67.

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- A 15 month old boy was found to have asymptomatic hypercalcaemia when admitted for elective tonsillectomy. Further investigations revealed normal phosphate, PTH, and vitamin D levels. Urine calcium/creatinine (Ca/Cr) clearance ratio was low.
- A younger brother born a few months later also had asymptomatic hypercalcaemia and hypocalciuria. Investigation of family members showed raised calcium in the index case's mother and maternal grandfather, but not in his father or older brother (Fig. 2). To confirm a diagnosis of FHH, *CASR* mutational analysis was undertaken.

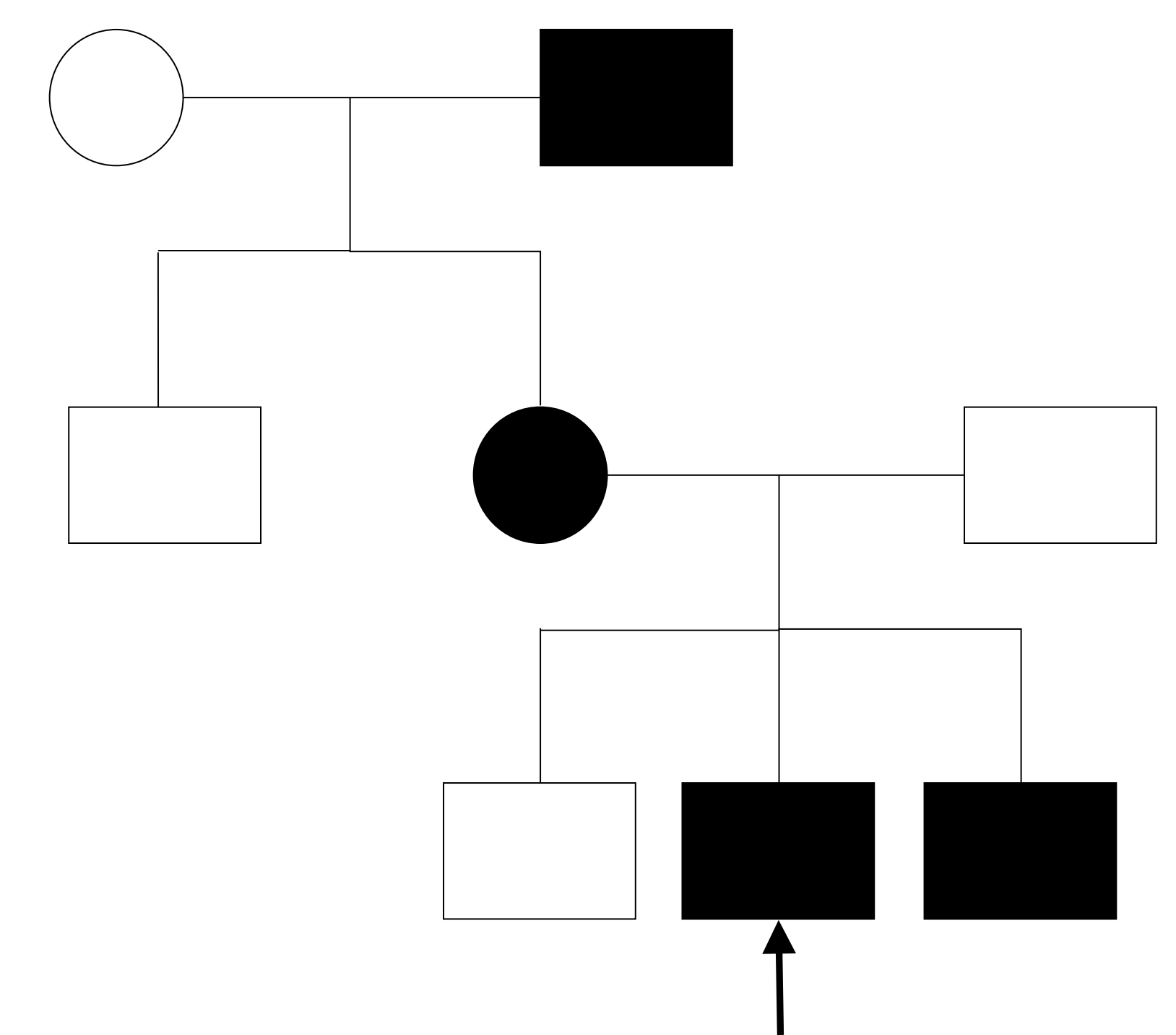


Fig 2. Pedigree of the family.

	Adj. S. Calcium (2.2-2.79 mmol/l)	PTH (1.1- 6.9mmol/l)	S. Phosphate (1.36-2.26 mmol/l)	Ca/Cr Clearance Ratio	Vitamin D (nmol/l)
Index Case	3.22	2.1	1.44	0.003	47
Mother	2.91	2.6	1.06	0.004	32
Younger Brother	3.05	5.1	1.57	0.01	77
Grandfather	2.69	9.7	0.84		
Father	2.46	4.8			

CaSR Mutational Analysis

- *CASR* sequencing revealed a previously undescribed heterozygous T to C nucleotide substitution in exon 4 (c.1342T>C (p.Ser448Pro)) (Fig. 3) in the index case, younger brother, mother and grandfather.
- This variant fulfills the criteria for being a pathogenic mutation as it leads to the substitution of a highly conserved polar serine residue for a non-polar proline residue that is predicted to disrupt the CaSR protein, and it co-segregates with the hypercalcaemic phenotype in this family.

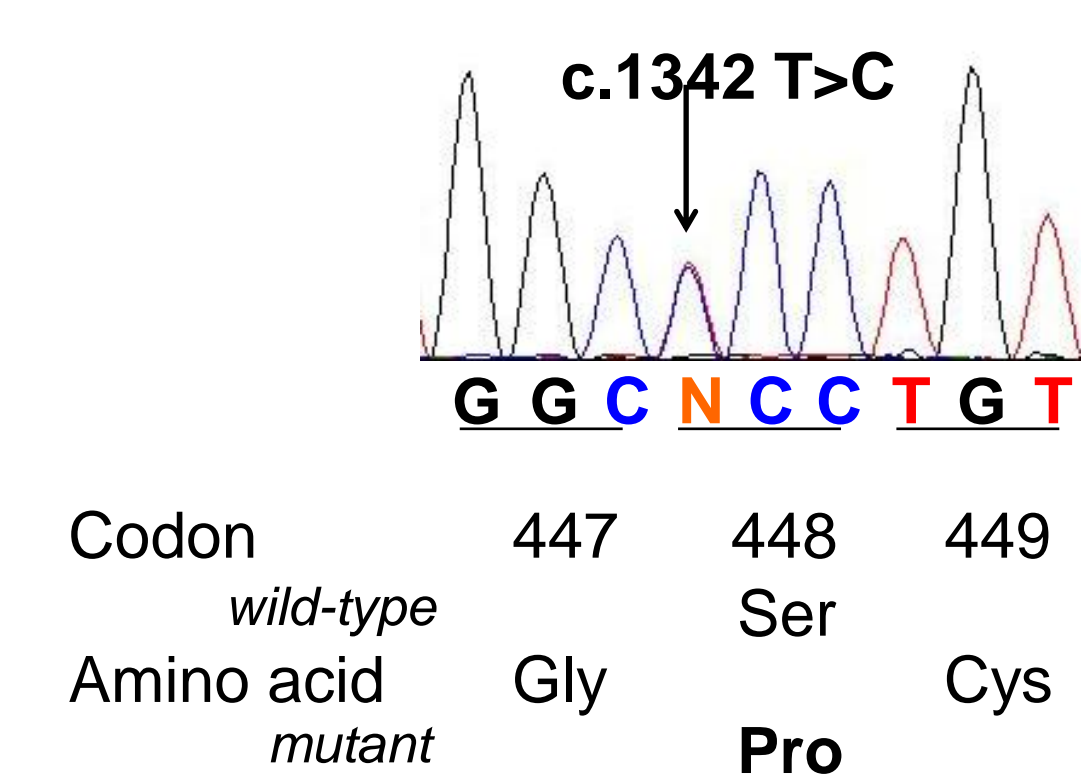


Fig 3. S448P mutation description

Conclusion

We describe a novel mutation in the *CASR* gene in 3 generations of the same family with a biochemical diagnosis of FHH.

Learning Points

The learning points from this case are as follows:

- Consider FHH in a patient with asymptomatic hypercalcaemia and serum PTH within the reference range.
- Diagnosis of FHH requires measurement of urine calcium creatinine clearance ratio and screening of family members for hypercalcaemia.
- CaSR gene analysis is helpful to confirm FHH. However, any novel variant that is identified requires further analysis such as family co-segregation studies to establish its pathogenicity.

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References

1. Hannan FM, Nesbit MA, Zhang C, et al. Identification of 70 calcium-sensing receptor mutations in hyper- and hypo-calcaemic patients: evidence for clustering of extracellular domain mutations at calcium-binding sites. Human Molecular Genetics 2012
2. Hannan FM, Thakker RV. Calcium-sensing receptor (CaSR) mutations and disorders of calcium, electrolyte and water metabolism. Best Pract Res Clin Endocrinol Metab. 2013 Jun;27(3):359-71.