INTERNAL MEDICINE JOURNAL



# Novel inactivating mutation of the calcium-sensing receptor in a young woman with mild hypercalcaemia

D. D. W. Kim,[1] L. Que,[2] A. M. Raizis[3] and C. M. Florkowski[4]

[1]Department of Endocrinology and Diabetes, Waitemata District Health Board and [2]Radiology/Nuclear Medicine, Auckland District Health Board, Auckland, and [3]Molecular Pathology and [4]Clinical Biochemistry Units, Canterbury Health Laboratories, Christchurch, New Zealand

**Key words**
hypercalcaemia, hyperparathyroidism, calcium sensing receptor, familial hypocalciuric hypercalcaemia.

**Correspondence**
David D. W. Kim, North Shore Hospital, Waitemata District Health Board, Private Bag 93-503, Takapuna, Auckland 0740, New Zealand.
Email: David.Kim@waitematadhb.govt.nz

Received 6 August 2013; accepted 24 November 2013.

doi:10.1111/imj.12383

## Abstract

A young woman with mild hypercalcaemia and an inappropriately normal serum parathyroid hormone had parathyroid scintigraphy suggestive of an active ectopic parathyroid tissue in the superior mediastinum. Urinary calcium to creatinine clearance ratio was low, and a subsequent genetic analysis confirmed a novel mutation (Q164K) in the calcium sensing receptor gene, consistent with familial hypocalciuric hypercalcaemia. We propose that this mutation accounts for her clinical and investigational findings, although a double pathology of Q164K and an ectopic parathyroid adenoma is also conceivable.

Familial hypocalciuric hypercalcaemia (FHH), an infrequent cause of hypercalcaemia, results from an autosomal dominant inactivating mutation of the calcium-sensing receptor (CaSR).[1,2] FHH is usually a benign condition, generally causing mild hypercalcaemia without overt symptoms.[3,4] Unlike primary hyperparathyroidism, the commonest cause of hypercalcaemia with normal or raised parathyroid hormone (PTH), FHH does not warrant aggressive intervention such as surgery.[4,5] Distinguishing FHH from primary hyperparathyroidism is, therefore, important. Low urinary calcium to creatinine clearance ratio (UCa : Cr) is a helpful indicator of FHH, but observed ranges overlap that of primary hyperparathyroidism.[6] Primary hyperparathyroidism is mostly caused by a single hyperfunctioning parathyroid adenoma, but approximately 6% of lesions were seen to be due to parathyroid hyperplasia.[7] About 15–20% of the culprit lesions in hyperparathyroidism are thought to arise from ectopic sites, mostly in the superior mediastinum.[8,9]

A 24-year-old Caucasian woman presented with a 2-year history of generalised arthralgia and malaise. Primary rheumatological conditions were excluded, but mild hypercalcaemia was noted on laboratory evaluation. Albumin-adjusted serum calcium (SCa) was 2.65 mmol/L (2.1–2.6) with a normal serum creatinine of 33 μmol/L (45–90). PTH was in mid normal range at 3.4 pmol/L (1.5–7.0). She was referred to endocrinology services for further evaluation. Aside from generalised aches, fatigue and intermittent constipation, she denied specific hypercalcaemic symptoms. She has not had nephrolithiasis or fragility fractures; however, she has had depression and anxiety in the past. Family history was negative for a known hypercalcaemic disorder. Maternal grandmother had Paget disease and osteoporosis with thoracic compression fractures, and paternal grandfather had renal stones. Both parents and a brother are well without significant medical illnesses, as is her 3-year-old daughter. Further laboratory investigations showed persistence of mildly raised SCa of 2.60 mmol/L with a mildly raised PTH of 7.9 pmol/L, low normal serum phosphate of 0.88 mmol/L (0.7–1.5), magnesium 0.85 mmol/L (0.7–1.0) and a 25 hydroxyvitamin D mildly insufficient at 46 nmol/L (50–250). A spot urinary calcium concentration was 2.0 mmol/L, urinary creatinine of 5.1 mmol/L, with a low calculated UCa : Cr of 0.0049 (>0.01). It was noted that a similar degree of mild hypercalcaemia was seen 2 years prior. PTH then was again normal at 5.2 pmol/L, with a low calculated UCa : Cr of 0.0025 on a

Funding: None.
Conflict of interest: None.

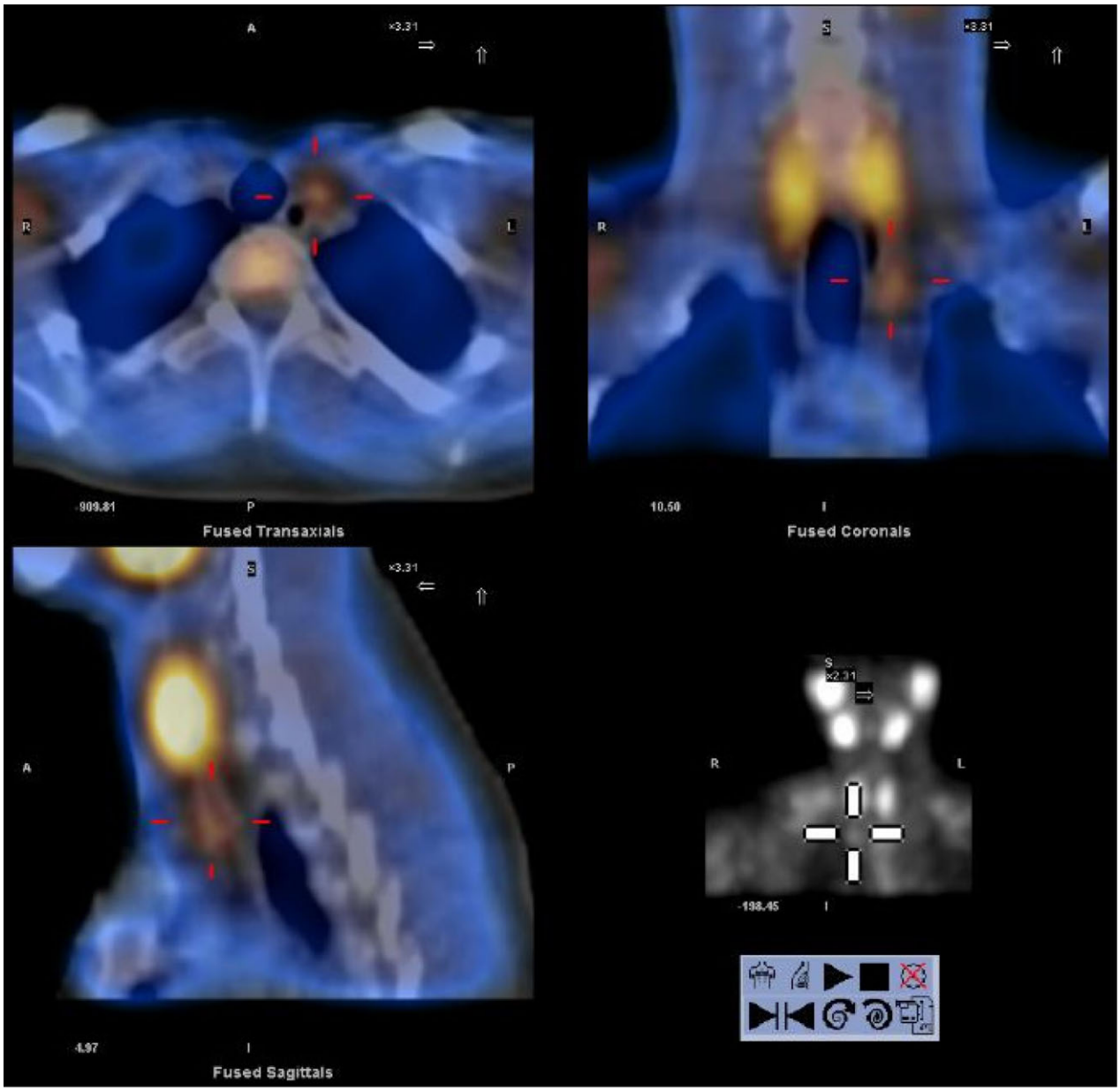


**Figure 1** Tc99m-sestamibi scintiscan with single-photon emission computed tomography showing a focus of increased tracer uptake in the left superior mediastinum.

spot urine. Further endocrine evaluation had not been sought at the time.

Tc99m-sestamibi parathyroid scintiscan with single-photon emission computed tomography (SPECT) was performed and revealed a focus of increased tracer uptake in the left superior aspect of the mediastinum (Fig. 1). Subsequent ultrasound scan showed a 6 × 5 × 3 mm hypoechoic ovoid lesion lying inferior to and separate from the left thyroid lobe, corresponding to anomaly seen on scintigraphy. Interim diagnosis of primary hyperparathyroidism secondary to an ectopic (mediastinal) parathyroid adenoma was made. Granulomatous conditions, such as sarcoidosis, were considered especially with her history of general malaise. Plain chest X-ray was normal, as were C-reactive protein (<3 mg/L) and $1,25(OH)_2D$ (130 pmol/L, normal range 65–135). Possibility of FHH was considered in light of compatible UCa : Cr. CaSR gene mutation analysis was performed.

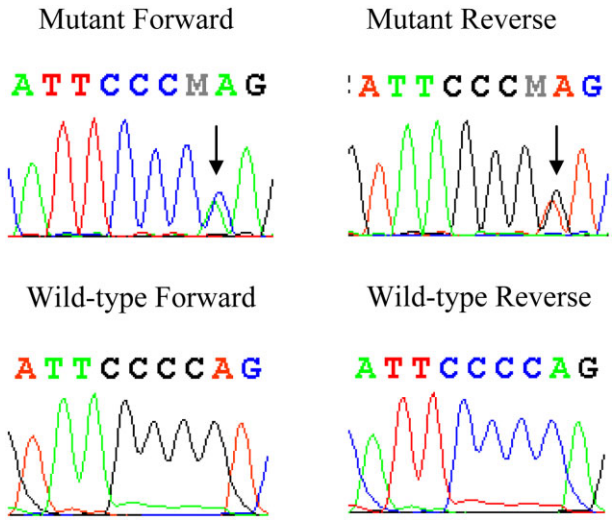


**Figure 2** Automated fluorescent DNA sequencing analysis of the calcium-sensing receptor gene (exon 3) showing the missense mutation. NM_000388.2(CASR):c.490C>A (p.Gln164Lys) (arrowed) identified in the proband.

Coding regions and flanking intronic sequences of the CaSR gene were amplified by polymerase chain reaction and analysed by automated fluorescent sequencing. DNA sequence was compared with the GenBank reference sequence (GenBank NC_000003.10; Range 123385220–123488032). Sequence nomenclature was based on the mRNA coding reference sequence for the CaSR gene (GenBank NM_000388.2).

She was found to be heterozygous for the mutation NM_000382.2(CaSR):c.490C> A (Q164K) (Fig. 2) and for the known non-pathogenic single nucleotide polymorphism M_000382.2(CaSR):c.2968A> G (R990G).

This mutation, although not previously described, was considered to support the diagnosis of familial hypocalciuric/hypercalcaemia in this patient. The c.490C>A mutation is novel and *in silico* analysis with the Polyphen algorithm suggests that the mutation is probably damaging with a score of 0.982.

As further corroborative evidence, the genotype was found to segregate with the phenotype within the family. Her father was also found to be mildly hypercalcaemic (SCa of 2.62 mmol/L) and carrying the same Q164K mutation, whereas other family members who were normocalcaemic did not.

She has been referred for genetic counselling. Surgery to remove mediastinal gland was felt to be inappropriate given the likelihood of FHH as well as the modest degree of hypercalcaemia.

Our patient with mild hypercalcaemia was found to have a novel mutation, Q164K in the CaSR gene, consistent with FHH. We propose that her laboratory and imaging findings are attributable to the mutation. Biochemical findings of mild hypercalcaemia, inappropriately normal/mildly raised PTH and low UCa : Cr are entirely consistent with FHH. Presence of the Q164K mutation in her hypercalcaemic father reinforces our proposition. Parathyroid hyperplasias in patients with FHH have been well described in the literature,[10–12] and it is plausible that our patient has an ectopic (superior mediastinal) parathyroid gland with hyperplasia associated with her CaSR mutation.

However, it is onceivable that she has a dual pathology of FHH and a hyperfunctioning ectopic parathyroid adenoma. Such cases of coexistence of FHH and parathyroid adenoma have also been described in the literature.[13–15] Parathyroid adenomas were more likely to be detectable on both scintiscan/SPECT and ultrasound scan, as did in our patient, than hyperplasias.[16] Although concordance in both imaging techniques is associated with high accuracy of localising hyperfunctioning parathyroid lesion,[17,18] neither can reliably distinguish between parathyroid adenoma and hyperplasia.

In summary, we report a novel inactivating mutation of CaSR (Q164K) in a young woman. We propose that this mutation causing FHH is the unifying diagnosis. However, concurrent hyperfunctioning ectopic parathyroid adenoma remains plausible.

## References


1 Pollak MR, Brown EM, Chou YH, Hebert SC, Marx SJ, Steinmann B *et al.* Mutations in the human Ca(2+)-sensing receptor gene cause familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. *Cell* 1993; **75**: 1297–303.

2 Brown EM, Pollak M, Seidman CE, Seidman JG, Chou YW, Riccardi D *et al.* Calcium-ion-sensing cell-surface receptors. *N Engl J Med* 1995; **333**: 234–40.

3 Marx SJ, Attie MF, Levine MA, Spiegel AM, Downs RW Jr, Lasker RD. The hypocalciuric or benign variant of familial hypercalcemia: clinical and biochemical features in fifteen kindreds. *Medicine (Baltimore)* 1981; **60**: 397–412.

4 Law WM Jr, Heath H 3rd. Familial benign hypercalcemia (hypocalciuric hypercalcemia): clinical and pathogenetic studies in 21 families. *Ann Intern Med* 1985; **102**: 511–19.

5 Heath H 3rd. Familial benign (hypocalciuric) hypercalcemia. A troublesome mimic of mild primary hyperparathyroidism. *Endocrinol Metab Clin North Am* 1989; **18**: 723–40.

6 Stuckey BG, Kent GN, Gutteridge DH, Pullan PT, Price RI, Bhagat C. Fasting calcium excretion and parathyroid hormone together distinguish familial hypocalciuric hypercalcaemia from

primary hyperparathyroidism. *Clin Endocrinol (Oxf)* 1987; **27**: 525–33.
7 Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg* 2005; **132**: 359–72.
8 Lumachi F, Zucchetta P, Varotto S, Polistina F, Favia G, D'Amico D. Noninvasive localization procedures in ectopic hyperfunctioning parathyroid tumors. *Endocr Relat Cancer* 1999; **6**: 123–5.
9 Noussios G, Anagnostis P, Natsis K. Ectopic parathyroid glands and their anatomical, clinical and surgical implications. *Exp Clin Endocrinol Diabetes* 2012; **120**: 604–10.
10 Fukumoto S, Chikatsu N, Okazaki R, Takeuchi Y, Tamura Y, Murakami T *et al*. Inactivating mutations of calcium-sensing receptor results in parathyroid lipohyperplasia. *Diagn Mol Pathol* 2001; **10**: 242–7.
11 Thorgeirsson U, Costa J, Marx SJ. The parathyroid glands in familial hypocalciuric hypercalcemia. *Hum Pathol* 1981; **12**: 229–37.
12 Szabo E, Hellman P, Lundgren E, Carling T, Rastad J. Parathyroidectomy in familial hypercalcemia with clinical characteristics of primary hyperparathyroidism and familial hypocalciuric hypercalcemia. *Surgery* 2002; **131**: 257–63.
13 Burski K, Torjussen B, Paulsen AQ, Boman H, Bollerslev J. Parathyroid adenoma in a subject with familial hypocalciuric hypercalcemia: coincidence or causality? *J Clin Endocrinol Metab* 2002; **87**: 1015–16.
14 Brachet C, Boros E, Tenoutasse S, Lissens W, Andry G, Martin P *et al*. Association of parathyroid adenoma and familial hypocalciuric hypercalcaemia in a teenager. *Eur J Endocrinol* 2009; **161**: 207–10.
15 Egan AM, Ryan J, Aziz MA, O'Dwyer TP, Byrne MM. Primary hyperparathyroidism in a patient with familial hypocalciuric hypercalcaemia due to a novel mutation in the calcium-sensing receptor gene. *J Bone Miner Metab* 2013; **31**: 477–80.
16 Whitson BA, Broadie TA. Preoperative ultrasound and nuclear medicine studies improve the accuracy in localisation of adenoma in hyperparathyroidism. *Surg Today* 2008; **68**: 222–6.
17 Akbaba G, Berker D, Isik S, Aydin Y, Ciliz D, Peksoy I *et al*. A comparative study of pre-operative imaging methods in patients with primary hyperparathyroidism: ultrasonography, 99mTc sestamibi, single photon emission computed tomography, and magnetic resonance imaging. *J Endocrinol Invest* 2012; **35**: 359–64.
18 De Feo ML, Colagrande S, Biagini C, Tonarelli A, Bisi G, Vaggelli L *et al*. Parathyroid glands: combination of 99mTc MIBI scintigraphy and US for demonstration of parathyroid glands and nodules. *Radiology* 2000; **214**: 393–402.