Reviewer's report

Title: Familial hypocalciuric hypercalcemia: A novel Mutation in the Calcium Sensing Receptor gene in an Irish Pedigree

Version: 1 Date: 17 January 2010

Reviewer: AYSIN UCKUN-KITAPCI

Which of the following best describes what type of case report this is?: Other

If other, please specify:

A new molecular finding of CASR (coinciding clinical picture needs to be clarified and any relationship with this molecular finding needs to be presented and explained)

Has the case been reported coherently?: No

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: No

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: No

Will the case report make a difference to clinical practice?: No

Is the anonymity of the patient protected?: Yes

Comments to authors:

General comments:

The general information included in the “discussion” should be moved to “introduction”. The repeated parts should be deleted. The anonymity of the patient protected in the case report. However, I would rather say “two years without symptoms....” or “two years before this hospital course....” etc. instead of
giving particular dates in the patient's history. Then in the "discussion", the authors should discuss how their findings relate with the literature.

Revisions necessary for publication:

This case report may make a difference to clinical practice if it is completed and well presented.

The authors clearly identified a new sequence variation of the CASR. However, nothing can be concluded about the relationship of this molecular finding with the clinical picture here. Because of some problems, this finding provides no insight into the function of the CASR or the clinical management issues in this subject.

A) The work-up of the patient is relatively poor or insufficiently presented in the text here. Therefore, nothing can be concluded about the patient's diagnosis. The clinical findings should be described well after completing the lacking information about laboratory studies. The differential diagnosis of a patient with "hypercalcemia and hypocalciuria" should be discussed before reaching the conclusion of clinical diagnosis of “familial hypocalciuric hypercalcemia (FHH)”.

B) Conducted biochemical studies are lacking. Nothing can be concluded about whether this new “sequence variation” is a new "benign polymorphism" or a new "mutation". If the authors have no opportunity to perform the lacking biochemical studies, this paper would be more convincing if a good discussion could be done about the role of this new sequence in the known CASR structure.

WHAT NEEDS TO BE DONE ?

A)
Determinations of urinary calcium, creatinine and phosphorus excretions should be performed using 24-h urine collections in family members and proband. If it is already done, it should be noted in the text.

There are several questions about the clinical diagnosis of this patient. Again, if the relevant laboratory testing is already done, this missing information should be included in the text. This patient may even have more than one condition leading to hypercalcemia. The authors should include lacking test results and discuss those conditions before concluding their clinical diagnosis here.

1) This is a hypertensive postmenopausal woman with chronic hypercalcaemia. Those features may be more suggestive of kidney disease or primary hyperparathyroidism. There is no mention of the patient's kidney function tests and urinalysis, which is very important to know in this case.

2) It is also important to know this patient's simultaneous 25OH vitamin D level for differential diagnosis. Urinary calcium excretion may be <0.01 in some patients with primary hyperparathyroidism, particularly those with vitamin D deficiency. Being a 76-year-old lady puts her at risk for having vitamin D deficiency that is a common condition for elderly females. In a recent community based study, half of the patients were found to have low vitamin D [Am J Clin Nutr 2010]
3) The patient may also have chronic kidney disease (she does have hypertension) and tertiary hyperparathyroidism. Has she hypoalbuminemia?

4) Calcium values above 3.25 mmol/L are more commonly due to malignancy. How did the authors rule out a possibility of malignancy? Does she have any abdominal imaging studies?

5) Some diuretics (she may be receiving for her hypertension) and antiepileptic medications (she does have epilepsy) affect calcium balance. Is she receiving any medications?

B)

Expression of the A213E mutant may be a simple coincidence. In discussion, the authors should discuss whether this is a benign polymorphism or a mutation? Was that mutation (A213E) absent in DNA from a large group of control subjects? Or did the authors do a functional analysis of mutated CASR? If not, alternatively, perhaps the changes in the three-dimensional configuration of the mutated CASR could be compared to those conferred by confirmed mutations with the same phenotype. In other words, how does this particular amino acid change lead to decreased Ca2+ sensitivity of the CASR? The authors may want to comment about the intra-molecular site of this particular mutation and its relationship to the structural model of the CaSR.

**Quality of written English:** Acceptable

**Declaration of competing interests:**

'I declare that I have no competing interests'