FAMILIAL HYPOCALCIURIC HYPERCALCEMIA – CASE REPORT

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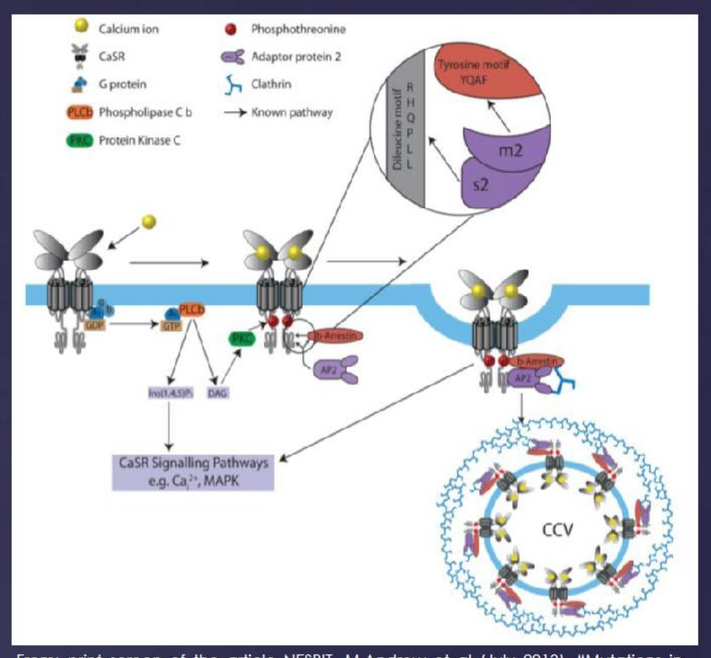
INTRODUCTION

Familial Hypocalciuric Hypercalcemia (FHH) is a rare genetically heterogeneous disorder with 3 known variants, all present with autosomal dominant inheritance.

An inactivacting mutation of calcium sensor receptor (CaSR) is the cause of subtype 1, which results in general hyposensitivity to calcium and represents 65% of FHH cases. Subtype 2 is due to an inactivating mutation in a11 subunit of G protein that is involved in the signaling cascade of CaSR. It was identified in > 10% of patients with FHH in whom sutype 1 and 3 had been excluded. Type 3 FHH, or Oklahoma variant, results from a mutation in the sigma subunit of AP2 (Adaptor protein), a protein with an important role in the endocytosis process of CaSR. It occurs in > 20% of FHH patients without mutation in CaSR.

FHH is characterized by hypercalcemia and relative hypocalciuria, with inappropriately normal or elevated PTH. It is generally asymptomatic and no treatment is needed.

The differential diagnosis with Primary Hyperparathyroidism (PHPT) is essential and it is based on the calculation of Calcium-Creatinine Clearance Ratio (CCCR), which, when under 0.02 points to the diagnosis of FHH. Genetic test is necessary for confirmation.



From: *print screen* of the article NESBIT, M.Andrew et al (July 2013), "Mutations in AP2S1 cause familial hypocalciuric hypocalcemia type 3", *Europe PMC Funders Author Manuscripts*, Nat Genet; 45 (1): 93-97.

CASE REPORT

S.V.C. ♀, caucasian, 16 years-old (yo)

Referred to **ENDOCRINOLOGY** for:

Hypercalcemia found in routine analysis

Ca 11,5mg/dl (rv 8,8-10,4)

Previous Medical History:
Unremarkable

Family History:
- Mother died at 39 yo from hepatocellular carcinoma
- Maternal aunt died at 13 yo from sarcoma
- Maternal cousin died at 18 yo from ovarian carcinoma

EVALUATION:

Clinical:
asymptomatic

Physical Examination:
Normal

Thyroid/Parathyroid Ultrasound (US) → • Thyroid gland with normal size, rough echoestructure, without nodules. No alterations in parathyroid.

Tc-Sestamibi Parathyroid Scan: → • Normal

NO ALTERATIONS:

Renal/Abdominal US

Thorax X-ray

Routine Analysis
CBC, SV, kidney and hepatic function, proteinogram - normal

LABORATORIAL	28/2/05	12/9/05
Calcium mg/dl (8,4-10,2)	**11,3**	**11,5**
Phosphorus mg/dl (2,5-4,5)	2,7	3,1
Ca (U) mg/24h	130	92
PTH pg/ml	34,5	32

CCCR: 0,007 → **FAMILAL HYPOCALCIURIC HYPERCALCEMIA** → *HETEROZIGOTY*

GENETIC TEST:
Germinal mutation in exon 7 of CASR gene (c.1945delG)

HETEROZIGOTY

RELATIVES EVALUATION

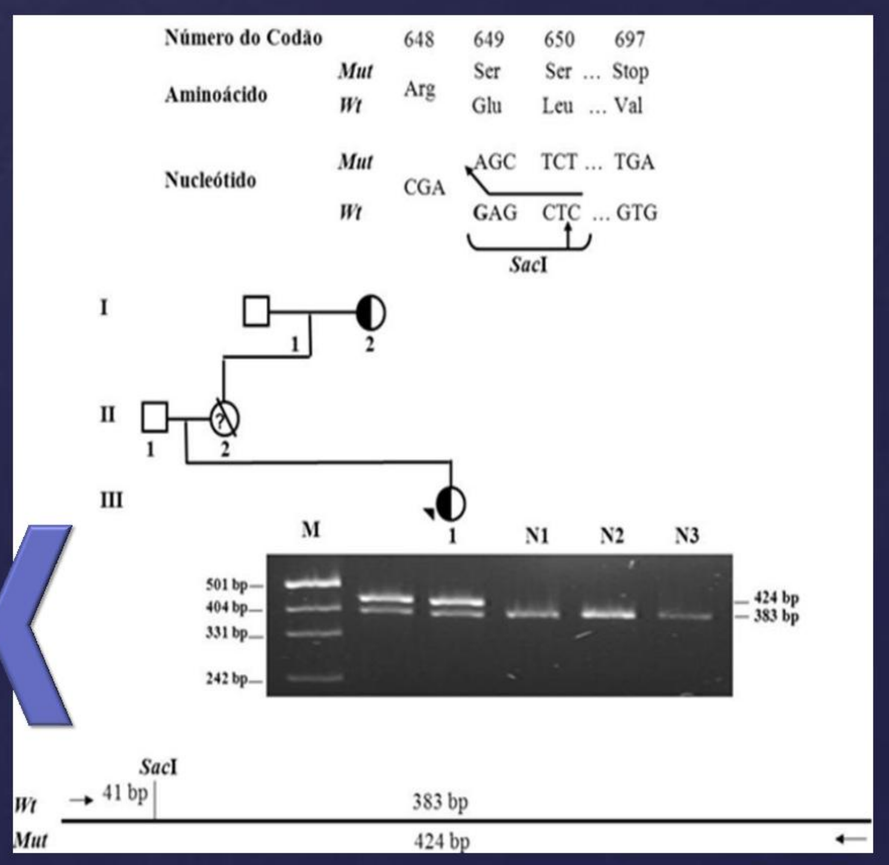
❖ Serum Ca and PTH in S.V.C.'s father and paternal half-brother were normal.

H.M.V.H., ♀, caucasian, 64 yo, S.V.C. maternal grandmother
Referred to **ENDOCRINOLOGY** for:

Multinodular Goiter

Clinical:
euthyroidism

LABORATORIAL	19/03/08	01/12/10
Calcium mg/dl	**11,9**	**11,1**
Phosphorus mg/dl	3,1	2,8
PTH pg/ml (10-70)		93
Ca(U) mg/24h		86
25OHD3 ng/ml (30–100)		21,8



➢ DNA sequencing of CaSR gene revealed a novel frameshift mutation in heterozigoty in III.1 and I.2:

Delection of G residue in codon 649 of exon 7 produces a premature stop in codon 697

✓ This mutation is predicted to result in a truncated form of CaSR receptor and is the probable cause of FHH.

✓ The receptor encoded by the mutant allele is not expected to be expressed at the cell surface and therefore, it will not interact, in a dominant negative manner, with the wild-type CASR present on the cell membrane, thus explaining the modest effect on plasma calcium values, and the typical asymptomatic FHH observed in the heterozygotes.

CONCLUSIONS

FHH is a rare benign condition, that must be considered in the differential diagnosis of hypercalcemia with normal or elevated PTH. CCCR is recognized as adequate to distinguish FHH from PHPT. However, there is a range of values from which the test is not safe and the definite diagnosis of FHH requires genetic confirmation, saving this patients from unnecessary surgeries. In this case report, we outstand the identification of a mutation in CaSR not previously described in the literature.

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Clinical Cases - thyroid/others
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