



**HAL**  
open science

# The impact of functional characterization of variants in calcium sensing receptor gene (CASR) on the clinical diagnosis

Andreea Apetrei, Nicolas Richard, Stéphane Allouche, A. Groso, Paul Fontaine, Antoine Resbeut, Nicolas Gruchy, Arnaud Molin

## ► To cite this version:

Andreea Apetrei, Nicolas Richard, Stéphane Allouche, A. Groso, Paul Fontaine, et al.. The impact of functional characterization of variants in calcium sensing receptor gene (CASR) on the clinical diagnosis. European Human Genetics Conference (ESHG ) 2022, Jun 2022, Vienne, Austria. hal-03705417

**HAL Id: hal-03705417**

**<https://hal.science/hal-03705417v1>**

Submitted on 27 Jun 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# The impact of functional characterization of variants in calcium sensing receptor gene (*CASR*) on the clinical diagnosis

Apetrei A<sup>1,2</sup>, Richard N<sup>1,2</sup>, Allouche S<sup>3</sup>, Groso A<sup>2</sup>, Fontaine P<sup>1</sup>, Resbette A<sup>1</sup>, Nicolas G<sup>1,2</sup>, Molin A<sup>1,2</sup>

<sup>1</sup> Department of Genetics, Caen University Hospital; <sup>2</sup> Normandy University, EA7450 BioTARGen, Caen, France; <sup>3</sup> Department of Biochemistry, Caen University Hospital, France

\*The authors declare no conflict of interest. This research received a grant from Normandy region (RIN Normandy Genomic Medicine).

## Introduction

The human calcium-sensing receptor (CaSR) is a G-protein-coupled receptor that signals *via* intracellular calcium mobilization and MAPK pathway to regulate extracellular calcium homeostasis. Loss- or gain-of-function heterozygous *CASR* variants lead to familial hypocalcemic hypercalcemia type 1 (FHH1) or autosomal-dominant hypocalcemia (ADH), respectively.

## Material and methods

We analysed the *CASR* gene in eleven unrelated families presenting abnormalities of the calcium and phosphate metabolism. The missense variants of unknown significance were induced by site-directed mutagenesis into a wild-type (WT) CaSR-expressing plasmidic vector. HEK293 cells were transfected with either the WT, the variant or cotransfected with both CaSR-containing vectors. We conducted two luciferase reporter gene assays using NFAT and SRE response elements to measure the function of CaSR on the two major CaSR-associated pathways.

## Results

Eleven heterozygous *CASR* genetic variants were identified in eight different FHH1 families, one ADH family and one patient presenting nephrolithiasis and hypercalciuria. In families I and J we identified two different variants *in cis* (complex allele) and *in trans* (compound heterozygote), respectively (Table 1). The variant didn't cosegregate with the phenotype for the H family.

The functional assays on MAPK pathway allowed to classify the eleven variants as :

- gain of function (1/11)
- loss of function (6/11 + 1 complex allele with 2 variants)
- without impact (2/11) (Figure 1)

The Ca<sup>2+</sup><sub>i</sub> pathway were concordant with these results. Co-transfections : absence of negative dominant effect.

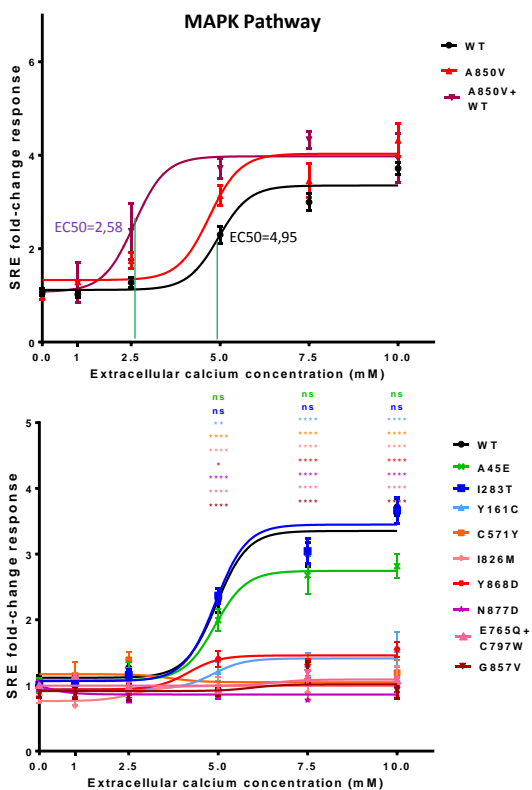


Table 1. Clinical and genetic data for 11 families.

ADH = autosomal dominant hypocalcemia;  
FHH = familial hypocalcemic hypercalcemia type 1;  
HTZ = heterozygous.

## Discussion and conclusion

- ✓ Study of 11 families with clinical and genetic heterogeneity.
- ✓ The protocol is effective to detect the gain of function, loss of function and polymorphic variants.
- ✓ The co-transfection variant/WT is important to reproduce the HTZ state *in vitro*, especially for gain of function variants or complex.
- ✓ The fonctionnal studies are important for the clinical interpretation, especially in complex situations.
- ✓ Clinical impact : choice of medical management, genetic counselling in the affected families.