Calcium-Sensing Receptor (CaSR), a GPCR, Signalling Pathway Disorders: New Insights Enable Repurposing of Drugs for Treatment

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May Professor of Medicine
University of Oxford, U.K.

49th Annual Meeting of the Israel Endocrine Society
Tel Aviv, Israel
Plenary 1, 29-30th April 2018
Parathyroids secrete PTH in response to hypocalcaemia.

PTH regulates ECF calcium (Ca^{2+}), directly or indirectly via vitamin D, bone resorption, kidney reabsorption and gut absorption.
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PTH regulates ECF calcium (Ca$^{2+}$), directly or indirectly via vitamin D, bone resorption, kidney reabsorption and gut absorption.

How is the ECF Ca$^{2+}$ sensed?

ECF Ca$^{2+}$ is detected by a Calcium-Sensing Receptor (CaSR), a GPCR: CaSR mutations lead to Hyper- and Hypo-calcemic Disorders.

Cloning and characterization of an extracellular Ca$^{2+}$-sensing receptor from bovine parathyroid

Edward M. Brown*, Gerardo Gamba††, Daniele Riccardi†, Michael Lombardi†, Robert Butters†, Olga Kifor†, Adam Sun†, Matthias A. Hediger†, Jonathan Lytton† & Steven C. Hebert†

Nature 1993

Calcium-sensing Receptor Mutations in Familial Benign Hypercalcemia and Neonatal Hyperparathyroidism


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Mutations in the Human Ca$^{2+}$-Sensing Receptor Gene Cause Familial Hypocalciuric Hypercalcemia and Neonatal Severe Hyperparathyroidism

Martin R. Pollak*, Edward M. Brown†, Yih-Huei Wu Chou, Steven C. Hebert*, Stephen J. Marks, Beat Stevenson, Tatiana Low, Christine E. Balderson, and J. G. Balderson

Cell 1993

A FAMILIAL SYNDROME OF HYPOCALCEMIA WITH HYPERCALCIURIA DUE TO MUTATIONS IN THE CALCIUM-SENSING RECEPTOR


Hum Mol Genet 2012
Calcium-Sensing Receptor (CaSR) – a GPCR

- GPCR with 3 domains: ECD (VFTD), 7 TDMs, and an ICD; forms dimers
- Ligands are cations e.g. Ca$^{2+}$
- Signals via G$\alpha$-proteins G11/q, G12/13, Gi/o and Gs, and different pathways e.g. IP$_3$ pathway to increase Ca$_{i}$$^{2+}$ and decrease PTH expression and secretion
- Pivotal role Ca homeostasis
- Widely expressed, including parathyroids and kidneys
- Calcitropic and non-calcitropic roles (kidney, CNS, eye, lung, & cancers - breast, prostate and colon)

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Calcium sensing receptor (CaSR) and its Seven Calcitropic Disorders

<table>
<thead>
<tr>
<th>Clinical Phenotype</th>
<th>Serum Ca(^{2+})</th>
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<tr>
<td>1  Familial benign hypocalciuric hypercalcaemia (FBHH) (^{\wedge})</td>
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<td>↑</td>
<td>↑↑</td>
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<td>4  Autosomal dominant hypercalciuric hypocalcaemia (ADHH) (^{\wedge})</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>5  Bartter syndrome Type V (^{\wedge})</td>
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<td>↑</td>
</tr>
<tr>
<td>6  Autoimmune hypocalciuric hypercalcaemia (AHH)</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>7  Autoimmune hypoparathyroidism (AH)</td>
<td>↓</td>
<td>?</td>
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CaSR Mutations: \(^{\wedge}\) = +/- ; \(^{*}\) = -/-

Thakker Cell Calcium 2004
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*Thakker Cell Calcium 2004*
Familial Benign Hypocalciuric Hypercalcaemia (FBHH)

• Raised serum calcium, reduced urinary calcium excretion (Ca Cl: Cr Cl <0.01)
• Autosomal dominant inheritance
• Due to loss of function CaSR heterozygous mutations; and over 250 reported mutations
• Results in an altered set-point of CaSR with a right-ward shift in dose-response curve.
• Some FBHH patients may not have a family history, and CaSR mutations may arise de novo.
• Patients may develop pancreatitis and/or chondrocalcinosis

Hannan et al Hum Mol Genet (2012)
Calcium-Sensing Receptor (CaSR) Mutations cause Hypercalcaemic and Hypocalcaemic Disorders

- **Loss-of-function** CaSR mutations cause Familial Hypocalciuric Hypercalcaemia (FHH) and Neonatal Hyperparathyroidism (NHPT), a life threatening hypercalcaemic disorder, with bone demineralisation, fractures, hypotonia and respiratory distress.

  *NHPT, 3 weeks old, Pre PTX*  
  *NHPT, 4.5 months old, Post PTX*

- **Gain-of-function** CaSR mutations cause Autosomal Dominant Hypocalcaemia (ADH) with Hypercalciuria

Autosomal dominant hypercalciuric hypocalcaemia (ADHH) – Due to CaSR Gain of Function Mutations

• “Hypoparathyroidism” diagnosed in patients, on basis of low serum calcium and serum PTH in the “normal” range, a combination consistent with CaR set-point abnormality.

• Due to gain of function CaSR heterozygous mutations.

• Results in an altered set-point of CaSR with a left-ward shift in dose-response curve.

• ADHH needs to be distinguished from hypoparathyroidism, as ADHH patients may have a more benign hypocalcaemia that does not require treatment with vitamin D, which may cause with polyuria, polydipsia, nephrocalcinosis and renal failure.

• ADDH patients with severe CaSR activating mutations may develop hypokalaemic metabolic alkalosis, salt wasting and secondary hyperaldosteronism - Bartter syndrome type V

*Pearce et al NEJM 1996; Hannan et al HMG, 2012*
Mutations of same CaSR residues can cause FHH and ADH, due to loss- or gain- of function (right- and left- ward shifts): Switch Residues of VFTD - roles of salt bridges at dimer interface.

Functional analysis of FHH and ADH mutations of Leu173 and Pro221

L173 and P221 are near R172-D215 salt bridges, which mediate agonist-induced changes at the dimer interface.

Drugs - CaSR allosteric modulators

• CaSR allosteric modulators bind to the extracellular aspect of the transmembrane domain
• 2 Classes:

Positive - Calcimimetics e.g. Cinacalcet
  • Decrease PTH and plasma calcium
  • Therapy for secondary hyperparathyroidism and parathyroid carcinoma

Negative - Calcilytics e.g. NPS2143
  • Increase PTH and plasma calcium
  • Potential therapy for hypocalcaemia of ADH(H)

**Nuf mouse is a model for autosomal dominant hypocalcaemia with hypercalciuria**

<table>
<thead>
<tr>
<th>Features</th>
<th>ADHH</th>
<th>Nuf mouse model</th>
</tr>
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<tbody>
<tr>
<td>Hypocalcaemia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hyperphosphataemia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Low/normal PTH</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ectopic calcification</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Raised BMD</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Cataracts</td>
<td>?</td>
<td>✓</td>
</tr>
<tr>
<td>Activating CaSR mutation</td>
<td>✓, various</td>
<td>✓, Leu723Gln</td>
</tr>
</tbody>
</table>

In vitro studies: NPS 2143 corrects gain of function due to Leu723Gln CaSR mutation, occurring in Mouse Model, Nuf, for ADH
**NPS2143 increases plasma PTH and calcium without causing hypercalciuria in *Nuf* mice with an activating CaSR mutation**

Single dose of calcilytic drug (NPS2143) given to *Nuf* mice by intraperitoneal injection

### PTH

![Bar chart showing PTH levels](chart)

- **Untreated heterozygous-affected *Nuf* (*Nuf/+*) mice**
- *Nuf/+* mice given drug-vehicle only
- *Nuf/+* mice given 30 mg/kg of NPS2143
- n = 4-14 mice per study group

**p<0.01, ***p<0.001**

### Plasma calcium

![Bar chart showing plasma calcium levels](chart)

**p<0.01, ***p<0.001**

### 24-hr urine Ca:Cr ratio

![Bar chart showing urine Ca:Cr ratio](chart)

**p<0.01, ***p<0.001**

CaSR Mutations found in ≅65% of Familial Hypocalciuric Hypercalcemia (FHH) Patients—Genetic Heterogeneity

FHH is genetically heterogeneous with 3 defined types - FHH1, FHH2 and FHH3 - with chromosomal locations of 3q21.1, 19p and 19q13.3, respectively.

- FHH1 is caused by loss-of-function mutations of the calcium-sensing receptor (CaSR) GPCR.
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Mutations Affecting G-Protein Subunit \( \alpha_{11} \)

in Hypercalcemia and Hypocalcemia

M. Andrew Nesbit, Ph.D., Fadil M. Hannan, D.Phil., F.R.C.Path.,
Sarah A. Howles, B.M., B.Ch., Valerie N. Babinsky, M.Sc., Rosie A. Head, M.A.,
Treena Cranston, B.Sc., Dip.R.C.Path., Nigel Rust, M.Phil., Maurine R. Hobbs, Ph.D.,
Hunter Heath III, M.D., and Rajesh V. Thakker, M.D.

Mutations in AP2S1 cause familial hypocalciuric hypercalcemia type 3

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Familial Hypocalciuric Hypercalcemia Type 2 (FHH2)

- FHH2 reported in 1 kindred from USA
- Affected members of FHH2 have non-progressive mild hypercalcemia not associated with the classical manifestations of primary hyperparathyroidism such as hyperparathyroid bone disease or renal calculi

Prioritised candidate gene analysis undertaken to identify the causative gene for FHH2

*Heath et al., AJHG, 1993*
Hypothesis-Driven: $G\alpha_{11}$ mutations cause FHH2

Mutations of the guanine nucleotide-binding protein, $G\alpha_{11}$, may cause FHH2 for the following reasons:

1. *GNA11*, encoding $G\alpha_{11}$, is located on chromosome 19p13.3 – the location of FHH2

2. CaSR signals through $G\alpha_q$ and $G\alpha_{11}$ to PLC

2. Mice harbouring parathyroid-specific deletions of $G\alpha_{11}$ and $G\alpha_q$, develop hypercalcaemia

FHH patients without CaSR mutations investigated for $G\alpha_{11}$ mutations.

*Nesbit et al. New Engl J Med 2013*
GNA11 Ile200del mutation identified in the FHH2 kindred

Predicted effects, based on 3-D Structural Analysis, of GNA11 Mutation

**Ile199/200** - conserved in all vertebrate Gα11 subunit orthologues
- located within a 13 amino acid region whose length is conserved amongst Gα11 orthologues and human paralogues

- Sits in a loop linking the β2 and β3 strands that forms part of the interface at which Gα subunits interact with GPCRs
- Has a role in GPCR-mediated GDP release and G-protein activation.

*Nesbit et al. New Engl J Med 2013*
**GNA11 loss- and gain-of-function mutations lead to FHH2 and ADH2, respectively (Nesbit et al. New Engl J Med 2013)**

**FHH2-associated GNA11 mutations**
- **Ile200del**
- **Leu135Gln**

**ADH2-associated GNA11 mutations**
- **Arg181Gln**
- **Phe341Leu**

**GNA11 mutations may cause loss- or gain of CaSR signal transduction**

<table>
<thead>
<tr>
<th></th>
<th>EC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type (WT)</td>
<td>2.35</td>
<td>2.31-2.39</td>
<td>-</td>
</tr>
<tr>
<td>Arg181Gln (mutant)</td>
<td>1.68</td>
<td>1.59-1.78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leu135Gln (mutant)</td>
<td>3.12</td>
<td>3.05-3.19</td>
<td>&lt;0.0001</td>
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</table>

**GNA11 mutations also reported In 2 families with hypoparathyroidism (Mannstadt et al NEJM 2013)**
In Vitro: Cinacalcet (a calcimimetic) and NPS-2143 (a calcilytic) rectify Ca^{2+}_i responses of FHH2- and ADH2- causing Gα_{11} mutant proteins, respectively.

**Effect cinacalcet on the EC_{50} values of FHH2 Gα_{11} mutants**

![Graph showing EC_{50} values for FHH2 Gα_{11} mutants](image)

**Effect NPS-2143 on the EC_{50} values of ADH2 Gα_{11} mutants**

![Graph showing EC_{50} values for ADH2 Gα_{11} mutants](image)

*In vivo*: Cinacalcet and NPS-2143 rectify the Hypercalcaemia and Hypocalcaemia of FHH2 - and ADH2 - mouse models, respectively.

FHH2- Het (+/195G) mice

Plasma albumin-adjusted calcium:

\[ *p<0.05, **p<0.01 \]

ADH2- Het (+/62V) mice

Plasma PTH:

\[ *p<0.05, **p<0.01 \]

**Gorvin et al JCI Insight, 2017;**

**Howles et al JCI Insight, 2017**
In FHH2 patient with Phe220Ser Gα₁₁ mutation: Cinacalcet (Cin) Rectifies Hypercalcaemia

**In vitro** effects of Cin on Ca²⁺ EC₅₀ values of Ser220 Gα₁₁ mutant

**In vivo** effects of Cin on serum ionised calcium in FHH2 patient

\[ EC_{50} \text{ (mM)} \]

<table>
<thead>
<tr>
<th>Cin (nM)</th>
<th>WT</th>
<th>Ser220 (FHH2 mutant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.0</td>
</tr>
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**p<0.01** compared to WT

\[ \text{Cin 30mg} \]
\[ \text{Cin 60mg} \]
\[ \text{Cin stopped} \]

\[ \text{Ionised calcium (mmol/L)} \]

\[ \text{Time (months)} \]

**Gorvin et al, JBMR, 2017**
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Hypothesis Driven

**ORIGINAL ARTICLE**

**Mutations Affecting G-Protein Subunit $\alpha_{11}$ in Hypercalcemia and Hypocalcemia**


Hypothesis Generating

**LETTERS**

**Mutations in AP2S1 cause familial hypocalciuric hypercalcemia type 3**

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Familial Hypocalciuric Hypercalcemia Type 3 (FHH3) – Hypothesis Generating Approach Used

- FHH3 is located on chromosome 19q13.3

Causative gene \( AP2S1 \) for FHH3 identified by whole exome sequencing – a method that enables exons to be captured and enriched from genomic DNA, thereby facilitating high-throughput DNA sequence analysis.

C to T transition in \( AP2S1 \), resulting in missense mutation of highly conserved Arg15 residue to Cys15 in AP2\( \sigma \)

*McMurtry et al 1992; Lloyd et al 1999; Nesbit et al, 2013*
Co-Segregation of AP2S1 Mutation, Arg15Cys, due to C to T transition in FHH3 Kindred

DNA sequence analysis of AP2S1 in 50 additional unrelated FHH patients without CaSR mutations revealed occurrence of 11 missense heterozygous mutations all involving Arg15 residue (x4Arg15Cys; x3 Arg15His; x4 Arg15Leu)
Hypothesis for the role of AP2σ2 in CaSR signalling.

Adaptor Protein 2 (AP2) – a heterotetrameric protein complex of α, β, μ, and σ subunits.

AP2 has a pivotal role in clathrin-mediated endocytosis.

σ subunit (Arg15) binds to -dileucine motifs in cargo proteins.

*Nesbit, Hannan, Howles et al. Nat. Gen. 2013*
FHH3: Exome Sequencing Reveals Adaptor Protein 2 Sigma (σ) Subunit Mutations

- AP2, a heterotetrameric protein complex of α, β, μ, and σ subunits has pivotal role in clathrin-mediated endocytosis
- Mutations AP2σ2 mutations (R15C, R15H and R15L) alter sensitivity of CaSR expressing cells, and disrupt CaSR internalisation

**AP2σ2 mutations** (R15C, R15H and R15L) found in FHH3 patients result in loss of key polar contact with dileucine motif on CaSR

*Nesbit et al. Nature Genetics 2013*
Genotype-phenotype correlation at the R15 residue – Serum calcium

FHH3 probands harbouring R15L AP2σ2 mutation have the highest serum calcium concentrations

* p<0.05, ** p<0.01

Cinacalcet improves CaSR signal transduction in HEK-CaSR cells expressing all three FHH3-causing AP2σ mutations

10 nM of Cinacalcet normalises EC\textsubscript{50} values of cells expressing R15C, R15H or R15L AP2σ mutants

*Howles et al. NEJM, 2016*
Cinacalcet lowers serum calcium concentrations in FHH3 patients

Serum calcium

Serum phosphate

Serum PTH

Howles et al. NEJM, 2016
Mechanisms of CaSR Signalling and Trafficking: Role of FHH3 - associated AP2σ Mutants (R15C, R15H and R15L)

• **Paradox:** AP2σ mutants ➖ CaSR endocytosis and trafficking, thereby ➕ CaSR at plasma membrane (PM), yet ➖ signalling

• **Hypothesis:** CaSR signals through canonical (PM) and non-canonical (via endosomes (EE)) pathways

• **Signalling:**
  - Normal = PM + EE
  - Mutant AP2σs = PM only

*Gorvin et al 2018*  
*Cell Reports*
Summary – CaSR Pathway Disorders

• FHH and ADH are genetically heterogeneous disorders
• Manipulations by calcimimetic and calcilytic drugs can rectify the abnormalities for patient benefit

Signalling

FHH1 & ADH1
• Loss- and gain-of-function mutations of the CaSR gene on 3q21.1

FHH2 & ADH2
• Loss- and gain-of-function mutations of the G protein alpha 11 gene (GNA11) on 19p

Trafficking

FHH3
• Loss-of-function mutations of the adaptor protein 2 sigma subunit (AP2S1) gene on 19q13.3

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Mie Kronborg Olesen Morten Frost
Vicky Stokes     Mark Stevenson Anna Gluck
Acknowledgements

UK
Liz Bentley
Steve Brown
Roger Cox
Treena Cranston
Bill Fraser
Andrew Freidin
Aylin Hanyaloglu
Benoit Hastoy
Tertius Hough
Alison Hugill
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