

Familial Hypocalciuric Hypercalcemia

Type 2 (FHH2): Comprehensive Disease Characterization

Disease: Familial Hypocalciuric Hypercalcemia 2 (FHH2) **MONDO ID:** MONDO:0007792 · **OMIM:** #145981 · **Category:** Mendelian (autosomal dominant) **Causal gene:** *GNA11* (Gα11), chromosome 19p13.3

Summary

Familial Hypocalciuric Hypercalcemia type 2 (FHH2) is a rare, autosomal dominant, and generally benign inherited disorder of calcium homeostasis. It is caused by **heterozygous loss-of-function germline mutations in *GNA11***, the gene on chromosome 19p13.3 that encodes **Gα11 (G-protein subunit α-11)** — the heterotrimeric G-protein that couples the **calcium-sensing receptor (CaSR)** to downstream phospholipase C-β (PLCβ) signaling in parathyroid chief cells and renal tubular cells. Because Gα11 is the intracellular relay for the CaSR, loss-of-function variants reduce the potency of extracellular calcium at the receptor, producing a rightward shift (higher EC50) in the calcium concentration–response curve. The physiological consequence is an upward shift in the "set-point" for calcium: the parathyroid glands and kidney behave as though serum calcium were lower than it actually is, so PTH secretion is not suppressed and renal tubular calcium reabsorption persists. Clinically this yields **lifelong mild hypercalcemia, inappropriately normal or high-normal PTH, and relative hypocalciuria** (calcium-to-creatinine clearance ratio, CCCR, typically ≤ 0.01).

FHH2 is the **rarest of the three recognized FHH subtypes** (FHH1 = *CASR*, ~65% of cases; FHH3 = *AP2S1*; FHH2 = *GNA11*). As of 2026, only approximately eight FHH2 kindreds have been reported worldwide. The condition is usually **asymptomatic with normal life expectancy**, and its principal clinical importance lies in **distinguishing it from primary hyperparathyroidism (PHPT)** so that patients are not subjected to inappropriate and unhelpful parathyroidectomy. When treatment of significant hypercalcemia is warranted, the **calcimimetic cinacalcet** — an allosteric CaSR activator — corrects the biochemical abnormality both in a validated mouse model and in human patients.

GNA11 behaves as a striking **bidirectional allelic series**: germline **loss-of-function** → **FHH2** (hypercalcemia); germline **gain-of-function** → **autosomal dominant hypocalcemia type 2 (ADH2)** (hypocalcemia); and **somatic activating mutations** → **uveveal melanoma** via constitutive MAPK signaling. A newly recognized (2026) manifestation links *GNA11* truncating/deletion variants to **abnormal enamel mineralization**, the first report connecting hypomineralized enamel to a hypercalcemic (rather than hypocalcemic) condition. Perinatally, maternal FHH can cause transient neonatal calcium disturbances in offspring depending on which genotype the newborn inherits.

Section 1 — Disease Information

Overview. FHH2 is a Mendelian, autosomal dominant disorder of systemic calcium homeostasis characterized by mild, lifelong, non-progressive hypercalcemia accompanied by inappropriately normal-to-mildly-elevated parathyroid hormone (PTH) and low urinary calcium excretion (relative hypocalciuria). It belongs to the family of familial hypocalciuric hypercalcemia (FHH) syndromes, which together are caused by defects in the CaSR signaling axis.

Key identifiers.

Resource	Identifier
OMIM	#145981 (Hypocalciuric hypercalcemia, familial, type II)
MONDO	MONDO:0007792
Gene	<i>GNA11</i> (HGNC), chromosome 19p13.3
MeSH / ICD	Indexed under Hypercalcemia / Hypercalcemia, familial hypocalciuric (ICD-10 E83.52 family)
Orphanet	FHH grouping (ORPHA for familial hypocalciuric hypercalcemia)

Synonyms / alternative names: Familial hypocalciuric hypercalcemia type 2; FHH2; Hypocalciuric hypercalcemia, familial, type II; Familial benign hypercalcemia type 2; *GNA11*-related FHH.

Source of information. The knowledge in this report is derived overwhelmingly from **aggregated disease-level resources** (OMIM, ClinVar, published functional studies) and from **individual case reports / small kindreds** — appropriate given that only ~8 FHH2 families have been described. There is no large EHR-scale cohort specific to FHH2 (unlike FHH1, which has been studied at biobank scale).

Section 2 — Etiology

Primary cause — genetic (Finding F001). FHH2 is caused by **heterozygous loss-of-function (inactivating) mutations in *GNA11***, which encodes Ga11, the G-protein that couples the CaSR to intracellular signaling. This is a purely genetic, monogenic Mendelian disorder; there are no established infectious or environmental causes.

"loss- and gain-of-function mutations of the *GNA11* gene on chromosome 19p13.3, which encodes the G-protein α -11 (Ga11) subunit, lead to FHH type 2 and ADH type 2, respectively" — [PMID: 27647839](#)

"Type 1 is due to loss-of-function mutations of the calcium-sensing receptor, a guanine nucleotide-binding protein (G-protein)-coupled receptor that signals through the G-protein subunit α 11 (Ga11)" — [PMID: 23802516](#)

Genetic risk factors. The causal variants are the *GNA11* loss-of-function alleles themselves. Because inheritance is autosomal dominant with high penetrance, carrying a single pathogenic allele is effectively the disease-defining risk factor. No separate susceptibility loci or modifier genes have been robustly established for FHH2 (small sample sizes preclude modifier mapping).

Environmental risk factors. None established. Family history (a first-degree relative with mild hypercalcemia or an unsuccessful parathyroidectomy) is the key non-laboratory clue. Age and sex do not materially alter risk; the trait is present from birth.

Protective factors. No genetic or environmental protective factors are documented. Because FHH2 is benign, "protection" is less relevant than for complication-prone disorders.

Gene–environment interactions. The most clinically important interaction is **physiological/pharmacological rather than classic GxE**: concurrent exposure to calcium-mobilizing drugs (e.g., antiresorptive regimens) can unmask or exaggerate hypercalcemia (one patient on

alternating denosumab/zoledronic acid for osteonecrosis was subsequently diagnosed with FHH; [PMID: 42822749](#)). Pregnancy is another state that interacts with the genotype (see Section 8).

Section 3 — Phenotypes

FHH2 is typically an **asymptomatic laboratory diagnosis** (Finding F005). Core phenotypes are biochemical.

Phenotype	Type	HPO term	Onset	Severity	Frequency
Hypercalcemia	Laboratory abnormality	HP:0003072	Congenital/ lifelong	Mild (often <1 mg/ dL above ULN)	~All affected
Inappropriately normal/high PTH	Laboratory abnormality	HP:0003165 (hyperparathyroidism)	Lifelong	Mild	~All affected
Hypocalciuria / low CCCR	Laboratory abnormality	HP:0003355-adjacent	Lifelong	—	Majority (CCCR ≤0.01)
Low/normal serum phosphorus	Laboratory abnormality	HP:0002148 (hypophosphatemia)	Lifelong	Mild	Variable
Fatigue / asthenia	Symptom	HP:0012378	Adult	Mild	Minority
Polyuria / polydipsia	Symptom	HP:0000103 / HP:0001959	Adult	Mild	Minority
Abnormal enamel mineralization	Clinical sign	HP:0000682 (abnormality of dental enamel)	Childhood	Variable	Newly reported (2 families)

Characteristics. Onset is effectively **congenital/lifelong** but usually detected incidentally in **adulthood** on routine biochemistry. Severity is **mild**, and progression is **stable** (non-progressive). In reported FHH2 kindreds there is **no nephrocalcinosis, no kidney stones, and normal bone mineral density on DXA** (PMID: 42787214, PMID: 38920275, PMID: 42291983).

"He had no evidence of kidney stones or nephrocalcinosis and demonstrated normal bone mineral density at dual-energy X-ray absorptiometry." — PMID: 42787214

Newly recognized manifestation — enamel hypomineralization (Finding F005). A 2026 study reported 10 patients from 2 families in whom **hypomineralized enamel co-segregated with hypercalcemia** due to a *GNA11* complete deletion or a frameshift truncation p. (Ser18Argfs*2) — the first link of abnormal enamel mineralization to a hypercalcemic condition.

"Abnormal enamel mineralization has been reported in genetic conditions associated with hypocalcemia but never with hypercalcemia." — PMID: 42670332

Quality of life. Because the disorder is usually asymptomatic and non-progressive, **quality-of-life impact is minimal** in the majority. The principal QoL risk is iatrogenic — unnecessary parathyroid surgery following misdiagnosis as PHPT. A minority with higher calcium (>1 mg/dL above ULN) may experience fatigue, polyuria/polydipsia and warrant treatment (PMID: 42291983).

Section 4 — Genetic / Molecular Information

Causal gene. *GNA11* (G protein subunit alpha 11), chromosome **19p13.3**, encoding **Gα11**; disorder OMIM #145981.

Pathogenic variants (Findings F002, F006). FHH2 variants are predominantly **missense** loss-of-function changes, with in-frame deletions, frameshift truncations, and whole-gene deletion also reported. Recurrent and representative FHH2-associated variants include:

Variant (protein)	cDNA	Type	Note
p.Thr54Met	c.161C>T	Missense	Recurrent; at helical/GTPase domain interface; impairs GDP binding
p.Thr347Ala	—	Missense	Loss-of-function, FHH2
p.Leu135Gln	—	Missense	Loss-of-function, FHH2
p.Ile200del	—	In-frame deletion	FHH2
p.Tyr101His	c.301T>C	Missense (homozygous)	Homozygous proband; heterozygous parents
p.Ser18Argfs*2	—	Frameshift truncation	Co-segregated with enamel defect
Whole-gene deletion	—	Structural	Co-segregated with enamel defect
p.Asp195Gly (mouse D195G)	—	Missense	ENU mouse model of FHH2

A 10-year cohort of >1,200 probands tested for calcium disorders identified **37 germline *GNA11* variants**, of which 9 nonsynonymous changes (Thr54Met, Arg60His, Arg60Leu, Gly66Ser, Arg149His, Arg181Gln, Phe220Ser, Val340Met, Phe341Leu) were reported as FHH2- or ADH2-causing ([PMID: 36970776](#)).

Variant classification. Reported disease-causing variants are classified **pathogenic/likely pathogenic** by ACMG/AMP criteria, supported by co-segregation and in vitro functional assays (see below). Many additional rare *GNA11* missense changes remain **VUS** pending functional data.

Allele frequency. Pathogenic FHH2 alleles are **extremely rare** in population databases (gnomAD), consistent with the ~8 known kindreds; no common susceptibility allele exists.

Somatic vs germline origin. FHH2-causing variants are **germline**. In contrast, **somatic** activating *GNA11* mutations occur in uveal melanoma (distinct disease arm; see Section 6 / Finding F006).

Functional consequences (Finding F002). FHH2 variants are **loss-of-function**, reducing CaSR-mediated intracellular calcium signaling. In HEK293 cells expressing CaSR, FHH2 Gα11 variants (Thr54Met, Thr347Ala, Leu135Gln, Ile200del) downregulate IP1 accumulation and intracellular Ca²⁺ responses, producing a **rightward shift (higher EC50 / reduced agonist potency)** in the calcium concentration–response curve.

"loss-of-function variants in GNA11 lead to reduced agonist potency at CaSR and an FHH phenotype" — [PMID: 38920275](#)

"Three-dimensional modeling revealed the Thr54Met mutation to be located at the interface between the Gα11 helical and GTPase domains, and to likely impair GDP binding" — [PMID: 26729423](#)

Modifier genes / epigenetics / chromosomal abnormalities. No validated modifier genes or epigenetic mechanisms are established for FHH2. The only reported structural lesion is a **complete *GNA11* deletion** (haploinsufficiency) associated with the enamel phenotype ([PMID: 42670332](#)).

Section 5 — Environmental Information

FHH2 is a **monogenic disorder with no established environmental, lifestyle, or infectious etiology**. Non-genetic factors are relevant only insofar as they modify measured calcium:

- **Drugs:** antiresorptive therapy (denosumab/bisphosphonates), thiazides, lithium, and vitamin D can perturb calcium and complicate interpretation; one FHH diagnosis emerged during antiresorptive therapy ([PMID: 42822749](#)).
 - **Lifestyle:** no causal dietary or behavioral factor. Calcium/vitamin D intake does not cause the disease but may transiently affect levels.
 - **Infectious agents:** none — not applicable.
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Section 6 — Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. A **heterozygous loss-of-function variant in *GNA11*** (e.g., Thr54Met) **results in** a Gα₁₁ protein with impaired guanine-nucleotide handling / reduced coupling capacity (Thr54Met impairs GDP binding at the helical/GTPase interface). *[Demonstrated in vitro and by structural modeling.]*
2. Reduced functional Gα₁₁ **leads to** weaker coupling of the plasma-membrane **CaSR** to its effector **phospholipase C-β (PLCβ)** in parathyroid chief cells (and renal tubular cells). *[Demonstrated: reduced IP₁/Ca²⁺ responses in CaSR+Gα₁₁ HEK293 assays.]*
3. Diminished CaSR→Gα₁₁→PLCβ signaling **results in a rightward shift (higher EC₅₀)** of the calcium concentration–response curve — the receptor now requires a higher extracellular calcium to achieve the same intracellular signal. *[Demonstrated.]*
4. This **raises the calcium "set-point"**: at a normal serum calcium, the cell senses "too little calcium." *[Inferred from set-point model, consistent with CaSR biology.]*
5. In **parathyroid chief cells**, inadequate CaSR signaling **fails to suppress PTH secretion**, so PTH remains **inappropriately normal/high-normal** for the prevailing calcium. *[Demonstrated clinically and in mouse model.]*
6. In the **kidney (distal tubule / thick ascending limb)**, blunted CaSR signaling **leads to continued tubular calcium reabsorption**, producing **relative hypocalciuria (low CCCR)**. *[Inferred from CaSR renal physiology; consistent with clinical phenotype.]*
7. Steps 5 and 6 together **result in sustained mild hypercalcemia with hypocalciuria and non-suppressed PTH** — the defining FHH2 triad. *[Demonstrated clinically.]*

Branch A (reciprocal, same gene): A **gain-of-function *GNA11*** variant instead **lowers** the set-point → excessive CaSR signaling → suppressed PTH and renal calcium wasting → **ADH2 (hypocalcemia)**.

Branch B (somatic/oncogenic): **Somatic activating *GNA11*** mutations in melanocytes constitutively upregulate **MAPK** signaling → **uveal melanoma**.

Supporting detail

Molecular pathways (Finding F007). CaSR is a **family-C GPCR** on the plasma membrane of parathyroid chief cells, also functionally expressed in kidney, bone and gut. It couples via **Gq/G11 → PLCβ**, generating IP3/DAG and raising intracellular Ca²⁺; it also engages AKT and MAPK. PI-PLC β1/β2/β3/β4 isozymes are expressed in parathyroid chief cells and are candidate CaSR effectors ([PMID: 9723859](#)).

"On the cell membrane of the chief cells of the parathyroid glands, the CaR 'senses' the extracellular calcium concentration and, subsequently, alters the release of parathyroid hormone (PTH)." — [PMID: 15697170](#)

"Functionally significant mutations in the receptor have been shown to induce diseases of calcium homeostasis owing to changes in the set point for calcium-regulated PTH release as well as alterations in the renal handling of calcium." — [PMID: 15697170](#)

Protein dysfunction. FHH2 is a **loss-of-function** of a signal-transducing G-protein α subunit — a defect in **signal relay**, not receptor or hormone structure. Structural modeling localizes the recurrent Thr54Met to the **helical/GTPase domain interface**, impairing GDP binding ([PMID: 26729423](#)).

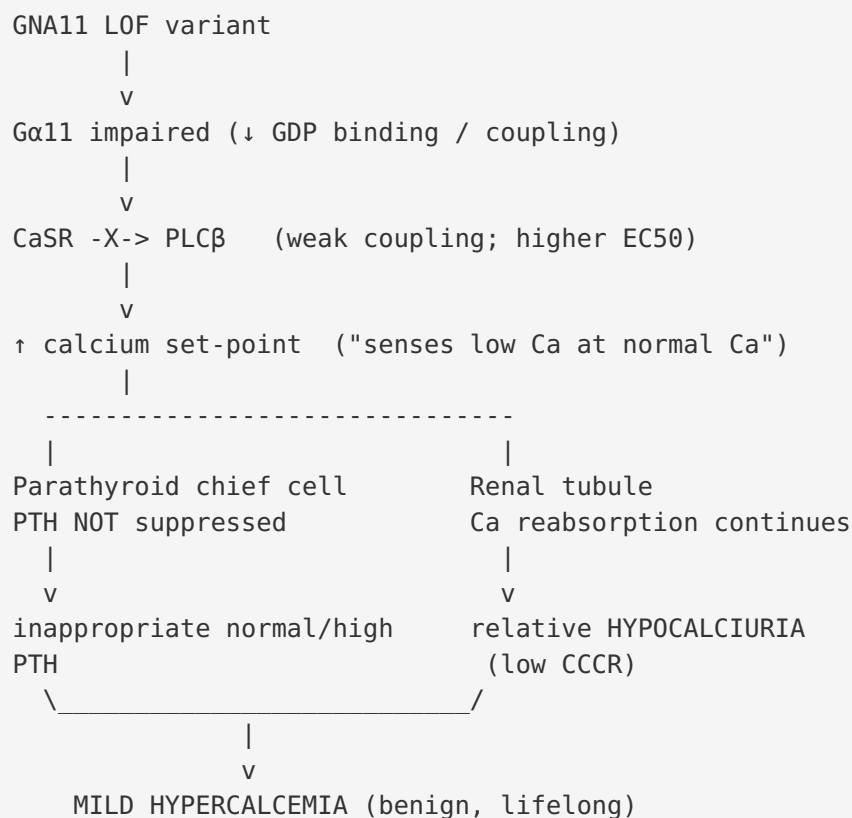
Biochemical abnormality. The core defect is **receptor–effector uncoupling** causing set-point elevation — an ion-sensing/second-messenger signaling defect rather than an enzyme deficiency.

Allelic series (Finding F006).

"Familial hypocalciuric hypercalcemia type 2 (FHH2) and autosomal dominant hypocalcemia type 2 (ADH2) are due to loss- and gain-of-function mutations, respectively, of the GNA11 gene that encodes the G protein subunit Gα11, a signaling partner of the calcium-sensing receptor (CaSR)." — [PMID: 36970776](#)

"somatic Gα11 mutations mediate uveal melanoma development by constitutively up-regulating MAPK signaling" — [PMID: 26994139](#)

Suggested ontology terms. Biological processes: GO:0007200 (phospholipase C-activating GPCR signaling), GO:0055074 (calcium ion homeostasis), GO:0035556 (intracellular signal transduction). Cellular component: GO:0005886 (plasma membrane), GO:0005834 (heterotrimeric G-protein complex). Cell types: CL:0000446 (parathyroid chief cell); renal tubular epithelial cells. Chemical: CHEBI:29108 (calcium(2+) ion).



Section 7 — Anatomical Structures Affected

Organ level. - **Primary:** Parathyroid glands (UBERON:0001132) — chief cells; Kidney (UBERON:0002113) — renal tubule. - **Body system:** Endocrine system (calcium/mineral homeostasis); urinary system (renal calcium handling). - **Newly implicated:** Teeth / dental enamel (UBERON:0001752 enamel) in the enamel-hypomineralization kindreds. - **Secondary involvement:** Minimal. Unlike PHPT, FHH2 kindreds show **no nephrocalcinosis/stones and normal BMD**, so bone and renal parenchyma are largely spared.

Tissue / cell level. - Parathyroid **chief cells** (CL:0000446) — epithelial endocrine cells. - Renal **tubular epithelial cells** (thick ascending limb / distal tubule).

Subcellular level. Plasma membrane (GO:0005886), where CaSR and the heterotrimeric Gq/G11 complex reside; downstream cytosolic second-messenger machinery (PLC β , IP3/DAG).

Localization / lateralization. Systemic (all parathyroid glands and both kidneys); **bilateral/symmetric** by nature of a germline signaling defect.

Section 8 — Temporal Development

Onset. Genetically **congenital** (present from birth); clinically detected incidentally, usually in **adulthood**, on routine biochemistry. Onset pattern is **chronic/insidious**.

Progression. Stable and non-progressive — lifelong mild hypercalcemia without worsening. There are no defined "stages." Disease duration is **chronic/lifelong**.

Patterns. No spontaneous remission (it is constitutive). The only clinically relevant **critical period is the perinatal window** (see below) and any time point at which misdiagnosis could trigger unnecessary surgery.

Pregnancy / neonatal considerations (Finding F008). FHH (including FHH2) is one of the main **PTH-dependent causes of gestational hypercalcemia** alongside PHPT. Although maternal FHH is itself benign, maternal hypercalcemia transmitted to a **non-carrier fetus** can suppress the fetal parathyroids and cause **transient neonatal hypocalcemia/tetany**; conversely a neonate who **inherits the inactivating variant** may show transient neonatal hyperparathyroidism/hypercalcemia.

"PTH-dependent etiologies display increased or inappropriately high PTH levels; primary hyperparathyroidism (PHPT) and familial hypocalciuric hypercalcemia (FHH) are the main contributors." — [PMID: 42707509](#)

"Severe cases of neonatal hypocalcemia due to fetal hypoparathyroidism may lead to tetany and even death." — [PMID: 42707509](#)

Management in pregnancy is largely conservative (hydration; cinacalcet crosses the placenta and is generally avoided) with postpartum and neonatal surveillance ([PMID: 36546344](#), [PMID: 27957351](#)).

Section 9 — Inheritance and Population

Epidemiology (Finding F004). FHH as a whole is rare, with a classic prevalence estimate of ≥ 1 in 78,000 (West of Scotland); other sources cite $\sim 1:80,000$. **FHH2 is the rarest subtype** (FHH1 $\sim 65\%$ of FHH; FHH3 and FHH2 much less common), with only **~ 8 reported kindreds** worldwide. Precise FHH2-specific incidence/prevalence figures are not established due to rarity and under-ascertainment.

"We estimate the prevalence to be 1 in 78,000 at least." — [PMID: 11353947](#)

Inheritance pattern. **Autosomal dominant**, high penetrance. A homozygous case (p.Tyr101His) has been reported with heterozygous, presumably milder, parents ([PMID: 41240382](#)).

Penetrance / expressivity. Penetrance of the biochemical trait is **high (near-complete)**; **expressivity is variable** (degree of hypercalcemia, presence or absence of mild symptoms, the newly described enamel phenotype).

Anticipation / mosaicism / founder effects / consanguinity. No genetic anticipation (not a repeat-expansion disorder). No established germline mosaicism or founder effects specific to FHH2. Consanguinity is relevant for the rare homozygous presentation.

Carrier frequency. Not applicable in the recessive sense (dominant disorder); pathogenic alleles are vanishingly rare in gnomAD.

Population demographics. No ethnic predilection established; reported kindreds span multiple populations (e.g., an Italian kindred, [PMID: 42787214](#)). **Sex ratio $\sim 1:1$** (autosomal). Age distribution: present lifelong, diagnosed across adulthood.

Section 10 — Diagnostics

Clinical/laboratory tests (Finding F004). The diagnostic signature is: - **Serum calcium** — mildly elevated (often <1 mg/dL above ULN); - **PTH** — inappropriately normal or mildly elevated (non-suppressed); - **24-h urinary calcium / CCCR** — low; **CCCR ≤ 0.01 is highly suggestive of FHH**, whereas 0.01–0.02 is equivocal and warrants genetic testing; - **Serum phosphorus** — low/normal; **magnesium** — often high-normal.

"a calcium clearance to creatinine clearance ratio (Ca urine 24 h. x serum Cr) / (Cr urine 24 h x serum Ca) ≤ 0.01 is highly suggestive of the diagnosis of FHH" — [PMID: 40198177](#)

Reported FHH2 cases show CCCR/fractional calcium excretion well below 0.01 (e.g., FECa 0.0039; [PMID: 42291983](#)).

Imaging. Parathyroid imaging (ultrasound, sestamibi) is typically **negative** (no adenoma) and helps argue against PHPT; renal imaging shows **no nephrocalcinosis/stones**; DXA shows **normal BMD**.

Genetic testing. Definitive diagnosis is by **sequencing *GNA11***, usually via a **familial hypercalcemia / hyperparathyroidism gene panel** (minimally *CASR*, *GNA11*, *AP2S1*, plus syndromic genes). **Whole-exome sequencing (WES)** has identified FHH2 variants in several reports ([PMID: 42291983](#)). Single-gene *GNA11* testing is appropriate when the biochemical phenotype strongly suggests FHH but *CASR/AP2S1* are negative. Cascade testing of relatives follows a confirmed proband.

Clinical criteria / differential diagnosis. The pivotal differential is **primary hyperparathyroidism (PHPT)**; distinguishing them prevents **inappropriate parathyroidectomy**. Other differentials: the other FHH subtypes (FHH1 *CASR*, FHH3 *AP2S1*), **acquired hypocalciuric hypercalcemia (AHH)** due to anti-CaSR autoantibodies ([PMID: 40335290](#)), vitamin-D-metabolism disorders (*CYP24A1*, *SLC34A1*), and reduced GFR.

"Measurement of the urinary calcium-to-creatinine ratio clearance (UCCR) may help to distinguish patients with FHH from those with PHPT, as the majority of FHH patients have low urinary calcium excretion (UCCR < 0.01)." — [PMID: 38038882](#)

Genetic testing is especially advised in patients <30 years and those with **equivocal CCCR (0.01–0.02)** ([PMID: 40683368](#)).

Screening. Cascade genetic/biochemical screening of first-degree relatives once a proband variant is identified. No newborn screening exists for FHH2.

Section 11 — Outcome / Prognosis

Survival / mortality. FHH2 is **benign** with **normal life expectancy**; there is no disease-specific mortality. Unlike PHPT, it does not drive osteoporosis, nephrolithiasis, or renal failure in reported kindreds.

Morbidity / function. Minimal. The chief avoidable morbidity is **iatrogenic** — failed/unnecessary parathyroidectomy and its surgical risks when FHH is mistaken for PHPT ([PMID: 38343604](#), [PMID: 39818302](#)).

Complications. Rare associations reported across FHH generally (e.g., chondrocalcinosis, pancreatitis) are more firmly linked to FHH1; a large genotype-first analysis of FHH1 did **not** confirm population-level excess pancreatitis/diabetes ([PMID: 42640938](#)). For FHH2 specifically, no consistent complication beyond mild hypercalcemia and the newly described enamel defect is established.

Prognostic factors. The main predictor of whether treatment is needed is **degree of hypercalcemia** (symptomatic or >1 mg/dL above ULN favors intervention). No molecular prognostic biomarkers are validated for FHH2.

Section 12 — Treatment

General principle. Most patients need **no treatment** — the priority is **correct diagnosis to avoid unnecessary parathyroidectomy** and reassurance/genetic counseling. Surgery is **not indicated** (hypercalcemia persists after parathyroidectomy because the defect is a systemic set-point shift, not an adenoma).

Pharmacotherapy — calcimimetics (Finding F003). For **symptomatic or significant hypercalcemia**, the **calcimimetic cinacalcet** (an allosteric CaSR activator; NCIT:C1876) is effective. It potentiates CaSR signaling, compensating for the weakened Gα11 relay.

"Cinacalcet (30mg/kg orally) significantly reduced plasma albumin-adjusted calcium and PTH concentrations in Gna11+/195G and Gna11195G/195G mice" — [PMID: 29046478](#)

"Cinacalcet and NPS-2143 rectified the Ca(2+) i responses of FHH2- and ADH2-associated Gα11 loss- and gain-of-function mutations, respectively" — [PMID: 26994139](#)

A human FHH2 patient (GNA11 p.Thr54Met) with calcium >1 mg/dL above ULN was treated with **cinacalcet 30 mg daily**; at three months serum calcium decreased and PTH normalized ([PMID: 42291983](#)). An earlier case also documented cinacalcet correcting FHH2 hypercalcemia ([PMID: 28833550](#)).

Pharmacogenomics. The therapeutic rationale is itself genotype-driven: the **direction of the GNA11 variant dictates drug choice** — calcimimetics (cinacalcet) for loss-of-function/FHH2; calcilytics (e.g., NPS-2143, investigational) for gain-of-function/ADH2.

Advanced / experimental therapeutics. No gene, cell, or RNA therapies exist or are needed for this benign disorder. No disease-specific clinical trials (NCT) are established for FHH2 beyond general calcimimetic use.

Surgical. Contraindicated/ineffective — parathyroidectomy does not cure FHH.

Supportive care. Hydration during intercurrent illness or pregnancy; avoidance of calcium-perturbing drugs; patient education and genetic counseling.

Treatment strategy. (1) Confirm diagnosis (biochemistry + CCCr + GNA11 genetics); (2) reassure and avoid surgery for the asymptomatic majority; (3) reserve **cinacalcet** for symptomatic/marked hypercalcemia; (4) manage pregnancy conservatively with neonatal surveillance.

Suggested NCIT terms: Cinacalcet (NCIT:C1876); Calcimimetic Agent; Parathyroidectomy (NCIT:C51764) — listed as *not recommended*.

Section 13 — Prevention

- **Primary prevention:** Not applicable — germline Mendelian disorder cannot be prevented. **Preimplantation/prenatal genetic options** could theoretically be discussed but are rarely pursued given the benign phenotype.

- **Secondary prevention (early detection): Cascade genetic and biochemical screening** of first-degree relatives after a proband is identified prevents misdiagnosis and inappropriate surgery.
 - **Tertiary prevention (complication avoidance):** The central tertiary-prevention act is **avoiding needless parathyroidectomy**; perinatal surveillance to prevent/treat transient neonatal calcium disturbances.
 - **Genetic counseling:** Autosomal dominant 50% transmission risk; counsel on benign prognosis, pregnancy/neonatal implications, and the value of family screening ([PMID: 40757212](#)).
 - **Immunization / public health / environmental:** Not applicable.
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Section 14 — Other Species / Natural Disease

- **Taxonomy:** Humans (*Homo sapiens*, NCBI:txid9606); experimentally modeled in mouse (*Mus musculus*, NCBI:txid10090).
 - **Orthologous gene:** *Gna11* in mouse (NCBI Gene ortholog of human *GNA11*).
 - **Natural disease in other species:** No well-characterized naturally occurring *GNA11*-FHH2 equivalent is documented in companion animals or wildlife (OMIA does not list an established FHH2 animal counterpart). Not applicable/limited data.
 - **Comparative biology:** The CaSR–Ga11 calcium-sensing axis is **evolutionarily conserved** across mammals, which is why the mouse model faithfully recapitulates the human phenotype (see Section 15).
 - **Transmission / zoonosis:** Not applicable (non-infectious genetic disease).
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Section 15 — Model Organisms

Mouse model (Finding F003). An ENU-generated ***Gna11* D195G mouse** (loss-of-function) is the key disease model. It **recapitulates FHH2** with hypercalcemia, normal/raised PTH, and normal urinary calcium. Both heterozygous (*Gna11*^{+/195G}) and homozygous (*Gna11*^{195G/195G}) mice are hypercalcemic, and **cinacalcet (30 mg/kg orally) significantly reduced plasma calcium and PTH**, validating the model pharmacologically ([PMID: 29046478](#)).

Model	Type	Phenotype recapitulation	Use
<i>Gna11</i> D195G mouse (ENU)	Knock-in / point mutant, mammalian	High — hypercalcemia, non- suppressed PTH, normal urine Ca; cinacalcet-responsive	In vivo validation of FHH2 mechanism and calcimimetic therapy
CaSR + Gα11 HEK293 cells	In vitro cellular	Functional readout — IP1/Ca ²⁺ signaling	Variant functional classification (EC50 shifts); allosteric drug testing

Genetic model types available: point-mutant/knock-in mouse (above); cellular heterologous expression systems. Dedicated knockout, conditional, and humanized FHH2 lines are limited (reflecting rarity).

Phenotype recapitulation / limitations. The mouse captures the **biochemical core** (hypercalcemia, PTH, urine calcium) and **drug response** exceptionally well. Limitations: the newly described **enamel phenotype** and **perinatal transient neonatal calcium dynamics** are not yet modeled, and the model does not address human genotype–phenotype diversity across the ~8 kindreds.

Resources: MGI (*Gna11*), standard mouse repositories; HEK293/Cellosaurus for the in vitro system.

Mechanistic Model / Interpretation (Synthesis)

FHH2 is best understood as a **set-point disorder of the CaSR–Gα11–PLCβ signaling module**. The CaSR is the thermostat for serum calcium; Gα11 is the wire connecting that thermostat to the cell's effectors. A heterozygous loss-of-function *GNA11* allele partially cuts the wire: the thermostat still "reads" calcium but transmits a weakened signal, so the body defends an **abnormally high calcium level**. Every clinical feature follows from this single lesion — non-suppressed PTH (parathyroid arm), relative hypocalciuria (renal arm), and mild, stable, lifelong hypercalcemia (the integrated output).

The **elegance of the *GNA11* allelic series** reinforces the model: dialing signaling **down** gives hypercalcemia (FHH2); dialing it **up** germinally gives hypocalcemia (ADH2); dialing it **up** somatically in melanocytes gives uveal melanoma. The therapeutic logic is perfectly

complementary — **calcimimetics (cinacalcet)** push signaling back up in FHH2, while **calcilytics (NPS-2143)** push it back down in ADH2, each rectifying the respective defect both in vitro and in vivo. This makes FHH2 a textbook example of **mechanism-matched precision pharmacology**, even though most patients require no treatment at all.

Feature	FHH2 (GNA11 LOF)	ADH2 (GNA11 GOF)	Uveal melanoma (somatic GNA11)
Variant direction	Loss-of-function	Gain-of-function	Somatic activating
Calcium	High (mild)	Low	n/a
PTH	Non-suppressed/high-normal	Low/normal	n/a
Signaling	↓ CaSR→PLCβ (↑ EC50)	↑ CaSR signaling	Constitutive MAPK
Rectifier	Cinacalcet (calcimimetic)	NPS-2143 (calcilytic)	MAPK-pathway oncology

Evidence Base

PMID	Role in this report
27647839	Establishes <i>GNA11</i> locus (19p13.3), Gα11 protein, LOF→FHH2 / GOF→ADH2 (F001)
23802516	Confirms Gα11 as the CaSR signaling partner (F001)
38920275	FHH2 variants reduce agonist potency at CaSR; Thr347Ala (F002)
26729423	Thr54Met at helical/GTPase interface impairs GDP binding (F002)
29046478	<i>Gna11</i> D195G mouse; cinacalcet lowers calcium/PTH (F003)
26994139	Cinacalcet/NPS-2143 rectify FHH2/ADH2 signaling; somatic→uveal melanoma (F003, F006)
11353947	FHH prevalence $\geq 1:78,000$ (F004)
40198177	CCCR ≤ 0.01 diagnostic threshold (F004)
42670332	Enamel hypomineralization — novel FHH2/GNA11 manifestation (F005)
42787214	Benign profile: no stones/nephrocalcinosis, normal BMD (F005)
36970776	Reciprocal LOF/GOF allelic relationship; 37 GNA11 variants (F006)
15697170	CaSR in chief cells; set-point mechanism (F007)
9723859	PI-PLC β isozymes in parathyroid chief cells (F007)
42707509	FHH as PTH-dependent gestational hypercalcemia; neonatal risk (F008)
42291983	FHH2 case (Thr54Met), FECa 0.0039, cinacalcet response
41240382	Homozygous p.Tyr101His FHH2 kindred
28833550	Cinacalcet corrects FHH2 hypercalcemia (human)
38038882	UCCR <0.01 distinguishes FHH; hereditary PHPT framework
40683368	Genetic testing for equivocal CCCR 0.01–0.02; cinacalcet
42640938	FHH1 genotype-first data (comparative; complication context)
36546344 , 27957351	Pregnancy/neonatal management

Limitations and Knowledge Gaps

1. **Extreme rarity.** With only ~8 FHH2 kindreds reported, nearly all clinical evidence is from **case reports and small series**; there is **no biobank-scale FHH2 cohort** (in contrast to FHH1, now characterized at UK Biobank scale). Penetrance, expressivity, and complication rates are therefore imprecise.
 2. **Novel phenotype unconfirmed at scale.** The enamel-hypomineralization association (PMID: 42670332) rests on 2 families and awaits independent replication and mechanistic explanation.
 3. **Renal arm inferred.** The precise renal tubular contribution to hypocalciuria in FHH2 is inferred from CaSR physiology rather than directly demonstrated in FHH2 tissue.
 4. **Model gaps.** The validated mouse captures biochemistry and drug response but not the enamel or perinatal phenotypes.
 5. **Modifiers unknown.** No modifier genes, epigenetic mechanisms, or environmental contributors have been mappable given sample size.
 6. **Treatment evidence.** Cinacalcet efficacy is supported but limited to a handful of patients and one mouse model; no randomized data exist specifically for FHH2.
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Proposed Follow-up Experiments / Actions

1. **Establish an international FHH2 registry** pooling *GNA11*-confirmed kindreds to estimate penetrance, expressivity, complication frequency, and the true prevalence of the enamel phenotype.
2. **Genotype-first biobank screening** (UK Biobank, All of Us) for rare *GNA11* LOF variants to define population prevalence and biochemical range, mirroring the FHH1 approach.
3. **Functionally classify VUS:** systematically run candidate *GNA11* missense variants through the CaSR+Gα11 HEK293 IP1/Ca²⁺ assay to resolve ACMG classification and confirm LOF vs GOF direction.
4. **Model the enamel phenotype:** examine amelogenesis in *Gna11*-deficient mice and characterize CaSR/Gα11 signaling in ameloblasts to test whether enamel hypomineralization is a direct *GNA11* effect.
5. **Prospective cinacalcet evaluation** in symptomatic FHH2 patients (small open-label/n-of-1 framework) with calcium, PTH, and urinary calcium endpoints.

6. Perinatal surveillance protocol: define evidence-based neonatal calcium monitoring for infants of FHH2 mothers, stratified by inferred fetal genotype.

Prepared from an autonomous 5-iteration investigation: 8 confirmed findings, 43 papers reviewed. Evidence types span human clinical case reports/kindreds, a validated mouse model, in vitro functional assays, and structural/computational modeling.

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