Autosomal Dominant Hypocalcemia 1 (ADH1): Comprehensive Disease Characteristics Report

Disease: Autosomal Dominant Hypocalcemia 1 (ADH1) **Gene:** *CASR* (calcium-sensing receptor) **OMIM:** #601198 (phenotype), *601199 (gene)* | *Orphanet: ORPHA:428* | *MONDO: 0008833* | *HGNC: 1514* | *UniProt: P41180* | *Category:** Mendelian (autosomal dominant)

> **Evidence source note:** This report is compiled from **disease-level** aggregated resources (OMIM, Orphanet, HGNC/UniProt) and **primary literature** (human clinical case series, in-vitro functional studies, and mouse-model studies), not from individual EHR data. Evidence type is indicated per claim.

Summary

Autosomal Dominant Hypocalcemia type 1 (ADH1; OMIM #601198) is a rare Mendelian endocrine disorder caused by **heterozygous gain-of-function (activating) missense mutations in *CASR***, the gene encoding the calcium-sensing receptor (CaSR), a class C G-protein-coupled receptor on chromosome 3q13.33. The activating mutations "left-shift" the set-point for extracellular calcium sensing — the receptor is triggered at abnormally low calcium concentrations. This single molecular defect produces a dual-organ pathophysiology: in the parathyroid glands the over-active receptor inappropriately suppresses parathyroid hormone (PTH) secretion, producing **hypocalcemia with inappropriately low/normal PTH**; in the kidney the over-active receptor drives **hypercalciuria** and impairs urinary concentration. The result is a characteristic biochemical signature of low serum calcium, high phosphate, low-normal magnesium, low PTH, and relative-to-frank hypercalciuria.

Clinically, ADH1 spans a wide severity spectrum, from asymptomatic individuals detected on family screening to neonates and children presenting with **seizures, tetany, carpopedal spasm, and paresthesias**. Long-term complications are dominated by **renal disease (nephrocalcinosis, nephrolithiasis, progressive chronic kidney disease)**, along with basal

ganglia calcification, early cataracts, and cardiac QT prolongation. The central therapeutic dilemma is that conventional treatment (oral calcium plus active vitamin D) corrects hypocalcemia but **worsens hypercalciuria and accelerates renal damage** — so the guiding principle is to relieve symptoms while keeping serum calcium at the *low end of normal*, with thiazide diuretics as a useful adjunct.

The field is advancing toward **mechanism-matched targeted therapy**: calcilytics (negative allosteric CaSR modulators such as NPSP795/SHP635 and encaleret) have raised PTH and serum calcium in ADH1 patients and mouse models, and PTH-replacement approaches (palopegteriparatide) have rescued refractory pediatric cases. The **Nuf mouse** (*Casr* p.Leu723Gln) is the principal, faithful animal model. As an autosomal dominant disorder with 50% transmission risk (plus frequent de novo and mosaic events), prevention rests on genetic counseling, cascade testing, and reproductive genetic options. This report synthesizes 11 confirmed findings across 35 reviewed papers into a comprehensive knowledge-base entry.

Key Findings

Finding 1 — Genetic cause: heterozygous activating *CASR* mutations

ADH1 is caused by **heterozygous gain-of-function (activating) missense variants in *CASR***. More than 400 germline CASR mutations (both loss- and gain-of-function) have been catalogued across the spectrum of calcium homeostasis disorders. In ADH1 specifically, the activating variants lower the EC50 for calcium-dependent G-protein activation, producing a left-shifted set-point so the receptor signals as if calcium is high even when it is low or normal. Inheritance is autosomal dominant, and **de novo variants are common** (e.g., p.Leu723Arg, p.Leu123Ser). ADH1 is molecularly distinct from ADH2, caused by gain-of-function variants in *GNA11* (encoding Gα11, the CaSR's signaling partner).

> "Autosomal dominant hypocalcemia (ADH) is due to enhanced calcium-dependent signaling caused by heterozygous gain-of-function (GOF) variants in the CASR gene (ADH1) or in the GNA11 gene, encoding Gα11 (ADH2)." — PMID: 39658204
>
> "It is caused by the activating mutations of the calcium-sensing receptor gene (CASR), which produces a left-shift in the set point for extracellular calcium." — PMID: 34160437

> "the identification of >400 different germline loss- and gain-of-function CaSR mutations that give rise to disorders of Ca2+ homeostasis" — PMID: 31189130

Finding 2 — Biochemical and clinical phenotype

The cardinal biochemistry of ADH1 is **hypocalcemia** (e.g., serum calcium 1.53–1.85 mmol/L), **inappropriately low/normal PTH**, **hyperphosphatemia**, **hypomagnesemia**, and **relative-to-frank hypercalciuria**. Clinical features include neuromuscular irritability (paresthesias, carpopedal spasm, tetany) and **seizures**, which are frequently the presenting feature in infancy and childhood. Complications include **nephrocalcinosis/nephrolithiasis, basal ganglia calcification, and early cataracts**. A key feature is **variable expressivity**: symptom severity is not tightly correlated with the degree of hypocalcemia. A severe subset manifests a **Bartter-like (type V) salt-wasting phenotype**.

> "Affected members had hypocalcaemia (1.53-1.85 mmol/l), hypercalciuria, low but detectable parathyroid hormone (PTH) and hypomagnesaemia. Four of seven affected individuals were symptomatic (seizures, abdominal pains and paraesthesias), unrelated to severity of hypocalcaemia. Additional complications include nephrocalcinosis (n = 3) and basal ganglia calcification" — PMID: 16128246
>
> "presented with hypocalcemia, recurrent tetany, seizures, hypercalciuria, nephrocalcinosis, basal ganglia calcifications, and early-onset cataracts" — PMID: 42388864
>
> "Clinical manifestations of the index case started with seizures at 14 months of age; cognitive impairment and several neuropsychological disabilities were noted during childhood. Extrapyramidal signs and basal ganglia calcification developed later" — PMID: 27617113

Suggested HPO terms: Hypocalcemia (HP:0002901), Hypoparathyroidism (HP:0000829), Hyperphosphatemia (HP:0002905), Hypomagnesemia (HP:0002917), Hypercalciuria (HP:0002150), Seizure (HP:0001250), Tetany (HP:0001281), Paresthesia (HP:0003401), Nephrocalcinosis (HP:0000121), Nephrolithiasis (HP:0000787), Basal ganglia calcification (HP:0002135), Cataract (HP:0000518), Prolonged QT interval (HP:0001657).

Finding 3 — The therapeutic dilemma and emerging targeted therapies

Standard-of-care treatment (oral calcium plus active vitamin D — calcitriol or alfacalcidol) corrects hypocalcemia but **exacerbates hypercalciuria**, promoting nephrocalcinosis and renal impairment. Cautious ("judicious") dosing is therefore recommended. Targeted therapy is emerging on two fronts: **calcilytics** (negative allosteric CaSR modulators) — NPSP795/SHP635 raised PTH and serum calcium in five ADH1 adults, and JTT-305 reversed renal AQP2 downregulation in CaSR knock-in mice; encaleret is in clinical development. **PTH-replacement** approaches (palopegteriparatide) resolved symptoms and lowered the calcium-phosphate product in a refractory pediatric case.

> "Calcilytics are negative allosteric modulators of the extracellular calcium receptor (CaR) and therefore may have therapeutic benefits in ADH1. Five adults with ADH1 due to four distinct CAR mutations received escalating doses of the calcilytic compound NPSP795 (SHP635)" — PMID: 31063613
>
> "In vivo treatment of KI mice with the calcilytic JTT-305, a CaSR antagonist, increased AQP2 expression and reduced AQP2-targeting miRNA137 levels in KI mice." — PMID: 38367250
>
> "Optimal management of ADHH is difficult and we recommend judicious treatment to avoid an increased risk of nephrocalcinosis." — PMID: 16128246

Suggested NCIT terms: Calcium (C332), Calcitriol (C376), Vitamin D (C902), Thiazide Diuretic (C29713), Parathyroid Hormone (C2354).

Finding 4 — The Nuf mouse: the principal animal model

The **Nuf mouse** carries a germline gain-of-function *Casr* (Gprc2a) missense mutation **Leu723Gln** (chromosome 16), which lowers the receptor EC50. Both heterozygous and homozygous mice display **hypocalcemia, hyperphosphatemia, inappropriately low PTH, ectopic/soft-tissue calcification, and nuclear cataracts** — faithfully mirroring human ADH1. The model also revealed additional CaSR-dependent phenotypes, including impaired glucose tolerance and insulin secretion (hyperglycemia) that is rectified by calcilytics. Calcilytics (NPS 2143, NPSP795, and quinazolinones ATF936/AXT914) raise PTH and plasma calcium in Nuf mice; oral AXT914 raised PTH from 23±4 to 104±29 pmol/L ($p<0.05$).

> "Nuf mice also display ectopic calcification, hypocalcemia, hyperphosphatemia, and inappropriately reduced levels of plasma parathyroid hormone. These features are similar to those observed in patients with autosomal dominant hypocalcemia." — PMID: 15347804
>
> "Oral administration of 10 mg/kg AXT914 to Nuf mice increased parathyroid hormone to 104 ± 29 pmol/l compared with 23 ± 4 pmol/l for vehicle-treated mice, $p < 0.05$" — PMID: 40086735
>
> "Heterozygous- (CasrNuf/+) and homozygous-affected (CasrNuf/Nuf) mice were shown to have hypocalcemia in association with impaired glucose tolerance and insulin secretion." — PMID: 28575322

Finding 5 — Dual-organ pathophysiology

Activated CaSR in **parathyroid chief cells** suppresses PTH secretion at a lowered set-point, producing hypocalcemia with inappropriately low PTH. In the **kidney**, CaSR overactivity in the thick ascending limb and distal nephron independently increases urinary calcium excretion (hypercalciuria) via **Claudin-14 (Cldn14) upregulation**, and in the **collecting duct** impairs the vasopressin–AQP2 axis. CaSR knock-in mice show reduced AQP2 with increased AQP2 phosphorylation at Ser261 through a **p38MAPK–ATF1–miR137 pathway**, contributing to a urinary concentrating/Bartter-like tendency. The calcilytic JTT-305 reversed this AQP2 downregulation, confirming the mechanism is receptor-driven.

> "CaSR knock-in (KI) mice mimicking autosomal dominant hypocalcaemia, display a significant decrease in the total content of AQP2 associated with significantly higher levels of AQP2 phosphorylation at Ser261" — PMID: 38367250
>
> "Our findings suggest that parathyroid CaSR overactivity can reduce plasma Ca" — PMID: 35313217

Suggested GO/CL/UBERON terms: GO:0007200 (phospholipase C-activating GPCR signaling), GO:0055074 (calcium ion homeostasis), GO:0038066 (p38 MAPK cascade), CL:0000446 (parathyroid chief cell), CL:1000456 (kidney collecting duct principal cell), UBERON:0001132 (parathyroid gland), UBERON:0002113 (kidney).

Finding 6 — Diagnostic approach

Diagnosis rests on **biochemistry plus *CASR* sequencing**. The workup includes serum calcium (low), phosphate (high), magnesium (often low), and PTH (inappropriately low/normal), plus a 24-hour urinary calcium showing relative/frank hypercalciuria. ADH1 is confirmed by identifying a heterozygous activating *CASR* variant (single-gene test or hypoparathyroidism/mineral gene panel; WES/WGS in undiagnosed cases). Monogenic causes account for only ~5–10% of hypoparathyroidism, so genetic testing is targeted to clinically suspicious cases. **Thiazide diuretics** enhance renal calcium reabsorption and are of particular benefit in patients with activating CaSR mutations. ADH1 must be distinguished from other hypoparathyroidism etiologies (postsurgical, autoimmune, DiGeorge/22q11 deletion).

> "thiazide diuretics are of value as they enhance renal calcium reabsorption and increase serum calcium and are of particular benefit in those with activating mutations of the calcium-sensing receptor" — PMID: 22863393
>
> "which have a monogenic aetiology in 5%-10% of cases" — PMID: 34935164
>
> "Genetic testing forms an important tool in the investigation of PHPT and HP patients and is usually reserved for those deemed to be an increased risk of a monogenic disorder." — PMID: 34935164

Finding 7 — CaSR structure and biased signaling

CaSR (UniProt **P41180**) is a class C G-protein-coupled receptor functioning as a **homodimer** with a large Venus flytrap extracellular domain (ECD), a cysteine-rich domain, and a 7-transmembrane domain (TMD). Five cryo-EM structures of near-full-length CaSR show how Ca2+/agonist binding in the ECD is transmitted to the TMD to activate G proteins (Gq/11, Gi), and how allosteric modulators tune this. Activating ADH1 mutations map to regions important for structural integrity, dimerization, and ligand binding; a **TMD "hotspot" (e.g., residue 723)** is also the common calcilytic-binding pocket. Some variants produce **biased signaling** — the de novo p.Leu723Arg variant selectively lowers the EC50 for Gα11 activation without affecting Gi/Gq/Gs.

> "five cryo-EM structures of the near full-length CaSR have been published, demonstrating how agonist-binding transmits changes in the CaSR extracellular domain to the transmembrane region to activate G proteins, and how allosteric modulators affect these structural dynamics" — PMID: 36707151
>
> "the study of disease-causing mutations has demonstrated that CaSR signals in a biased manner" — PMID: 31189130
>
> "the Leu723Arg variant was normally expressed but resulted in a significantly lower EC50 for extracellular calcium activation of G11 but not other G proteins" — PMID: 39658204
>
> "bind at a common region within the CaSR transmembrane domain, which is also an ADH1 mutational hotspot" — PMID: 40086735

Finding 8 — Nosology, identifiers, and inheritance

ADH1 identifiers: **OMIM #601198**; gene *CASR* (*601199, HGNC:1514, 3q13.33); Orphanet ORPHA:428 ("autosomal dominant hypocalcemia"); MONDO:0008833; MeSH via "Hypocalcemia"/"Receptors, Calcium-Sensing". Synonyms: hypocalcemia autosomal dominant; hypoparathyroidism, familial isolated, autosomal dominant; ADHH (autosomal dominant hypocalcemia with hypercalciuria); familial/sporadic isolated hypoparathyroidism; Bartter syndrome type V (severe subset). Inheritance: autosomal dominant with frequent de novo mutations; germline/gonadal mosaicism has been reported (asymptomatic transmitting parent), producing variable/incomplete expressivity within families. ADH accounts for the majority of genetic isolated hypoparathyroidism; ADH1 (CASR) is far more common than ADH2 (GNA11). ADH2 (OMIM #615361) is caused by gain-of-function* GNA11 *mutations and is associated with short stature in ~42%** and less consistent hypercalciuria — a key distinguishing feature.

> "ADH1 patients typically manifest hypercalciuria, while ADH2 is associated with short stature in approximately 42% of cases." — PMID: 39658204
>
> "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
>
> "Sequencing analysis in the mother suggested mosaicism for the same variant, and she was clinically and biochemically unaffected." — PMID: 27617113

Finding 9 — Variable onset, allelic spectrum, and phenocopies

Onset is **highly variable**: ADH may be asymptomatic (detected on family screening or incidental hypocalcemia) or present with seizures in the neonatal period, childhood, or adulthood; severe neonatal cases require IV calcium (e.g., de novo p.Glu228Lys). *CASR* is a single locus with a **graded allelic spectrum**: heterozygous loss-of-function → familial hypocalciuric hypercalcemia (FHH1); homozygous LOF → neonatal severe hyperparathyroidism (NSHPT); heterozygous gain-of-function → ADH1. A common polymorphism **Ala986Ser (A986S)** in the intracellular tail modestly influences serum calcium and can act as a modifier. Acquired **activating anti-CaSR autoantibodies** produce an autoimmune ADH phenocopy (an important differential). Drug interactions matter clinically: phenobarbital accelerates 1-alfacalcidol metabolism, causing swings between hypo- and hypercalcemia.

> "Heterozygous activating mutations of the CASR cause autosomal dominant hypocalcemia (ADH) that may be asymptomatic or present with seizures in the neonatal period or childhood or later in life. Phenocopies of FHH or ADH are due to circulating CASR inactivating or activating autoantibodies, respectively." — PMID: 20374733
>
> "A common polymorphism in the intracellular tail of the CASR, Ala to Ser at position 986, has a modest effect on the serum calcium concentration in healthy individuals." — PMID: 11013439
>
> "The child presented in the neonatal period with clinical seizures associated with severe hypocalcaemia, hyperphosphataemia, low parathyroid hormone levels and elevated urine calcium:creatinine ratios." — PMID: 25227206

Finding 10 — Prognosis: normal life expectancy but chronic renal morbidity

ADH1 is a **chronic, lifelong disorder with generally good survival**, but morbidity is driven by **renal complications**, amplified by both the intrinsic hypercalciuria and by conventional calcium/active-vitamin-D therapy. A systematic review of chronic hypoparathyroidism on conventional therapy reports nephrolithiasis rates up to 36% and nephrocalcinosis up to 38%, with progression to renal insufficiency/CKD. Additional complications include hypocalcemic seizures, basal ganglia (and other ectopic) calcification, cataracts, and QT-prolongation risk. Postsurgical chronic hypoparathyroidism cohorts show elevated renal disease (moderate-to-

severe 28.8% vs 5.6%), nephrocalcinosis (59.9% vs 0.6%), and higher mortality (HR ~2.75) versus controls — underscoring the renal/cardiovascular burden of the hypoparathyroid state that ADH1 shares and exacerbates.

> "The reported rate of nephrolithiasis was up to 36%, with the lowest rates in studies reporting shorter duration of disease. The rate of nephrocalcinosis was up to 38%." — PMID: 33599907
>
> "a higher prevalence of moderate-to-severe renal disease (28.8% vs. 5.6%), nephrocalcinosis (59.9% vs. 0.6%), and nephrolithiasis (8.3% vs. 1.0%). They also had significantly greater mortality (hazard ratio [HR] 2.75)" — PMID: 40531442

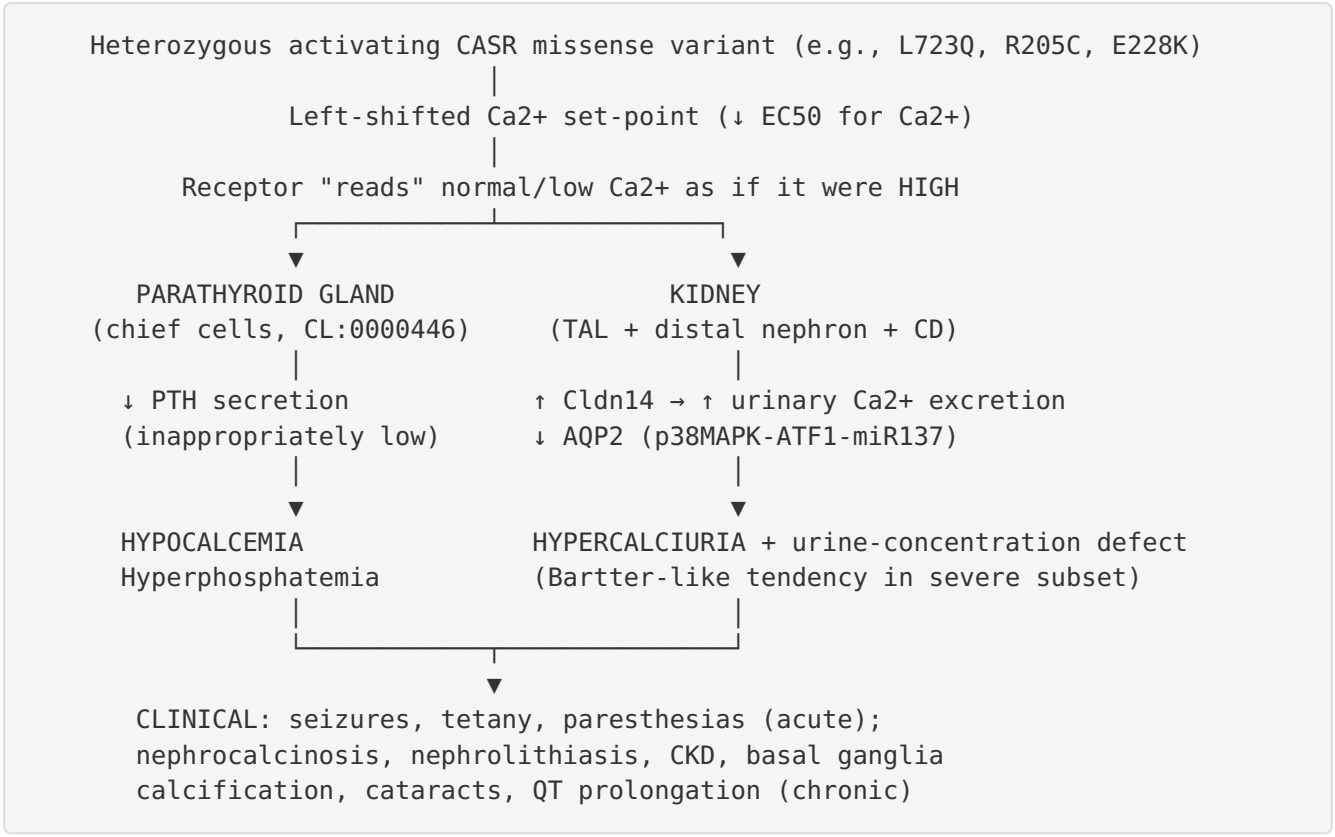
Finding 11 — Management principles and prevention

Because overtreatment drives renal damage, the guiding therapeutic principle is to **relieve symptoms while keeping serum calcium at the low end of normal**, using thiazides to blunt hypercalciuria. Human proof-of-concept for mechanism-matched therapy: the calcilytic NPSP795/SHP635 increased PTH in ADH1 patients, and in-vitro assays show variant-specific responsiveness (supporting genotype-guided calcilytic selection); PTH-based therapy (palopegteriparatide) rescued a refractory pediatric case. **Prevention is exclusively at the reproductive/clinical level**: as an autosomal dominant disorder, each child of an affected parent has a 50% risk; de novo and mosaic events mean absence of family history does not exclude risk. Preventive tools are genetic counseling, cascade testing of relatives, and prenatal/preimplantation genetic testing for a known familial *CASR* variant. No population-based primary prevention exists.

> "Calcilytics are negative allosteric modulators of the extracellular calcium receptor (CaR) and therefore may have therapeutic benefits in ADH1." — PMID: 31063613
>
> "also to allow the identification of other family members who may be at risk of disease" — PMID: 34935164

Mechanistic Model / Interpretation

ADH1 is fundamentally a **single-gene, gain-of-function signalopathy** with a two-organ output. The causal chain:



Upstream vs downstream: The upstream driver is the mutant receptor's shifted set-point. The parathyroid PTH suppression and renal calcium-wasting are **parallel, independent downstream arms** — a critical insight because it explains why simply raising serum calcium (which further activates the already over-sensitive renal receptor) worsens hypercalciuria. This is the mechanistic root of the treatment dilemma.

Why calcilytics work: By binding the TMD allosteric pocket (which coincides with the ADH1 mutational hotspot around residue 723), calcilytics raise the receptor's EC50 back toward normal, de-repressing PTH and reducing renal calcium wasting simultaneously — addressing both arms at their common origin rather than downstream.

Comparative nosology of *CASR* dosage:

Genotype	Receptor activity	Disorder	Calcium phenotype
Heterozygous LOF	↓	FHH1 (familial hypocalciuric hypercalcemia)	High Ca, low urine Ca
Homozygous LOF	↓ ↓	NSHPT (neonatal severe hyperparathyroidism)	Severe high Ca
Heterozygous GOF	↑	**ADH1**	Low Ca, high urine Ca
— (*GNA11* GOF)	↑ (via Gα11)	ADH2	Low Ca, short stature ~42%

Report by Template Section

1. Disease Information

Rare AD form of hypoparathyroidism from activating *CASR* variants; hypocalcemia with inappropriately low PTH and hypercalciuria. Identifiers: OMIM #601198 (gene *601199), ORPHA:428, MONDO:0008833, HGNC:1514, UniProt P41180; ICD-10 E20.8 / ICD-11 5A50.0 (no ADH1-specific code); MeSH under* Hypocalcemia / Receptors, Calcium-Sensing*. Synonyms: ADHH, familial isolated hypoparathyroidism (AD), Bartter syndrome type V (severe subset). Data are from aggregated disease-level resources plus published clinical case series/pedigrees.

2. Etiology

Primary cause is genetic/monogenic — heterozygous activating *CASR* missense variants (Finding 1). Genetic modifier: A986S (rs1801725) polymorphism. No environmental or infectious causation; environmental modifiers (dietary calcium/vitamin D, phenobarbital) alter severity only. Acquired activating anti-CaSR autoantibodies produce a phenocopy (differential, not etiology). No established protective alleles.

3. Phenotypes

See Finding 2 and the HPO list. Onset neonatal→adult; variable severity/expressivity; chronic lifelong course with episodic acute symptoms (seizures/tetany). QoL impacted by seizures, renal disease, and treatment burden; no ADH1-specific QoL instrument exists.

4. Genetic/Molecular Information

Causal gene *CASR* (3q13.33). Variant class predominantly heterozygous missense, gain-of-function; TMD hotspot (residue 723); some biased-signaling variants (Findings 1, 7). Classification: functionally validated activating variants are Pathogenic/Likely Pathogenic; novel variants often require in-vitro Ca2+-response assays. Allele frequency: private/rare, essentially absent in gnomAD; many de novo. Germline (with mosaicism reported). Modifier: A986S. No characteristic epigenetic or chromosomal abnormalities.

5. Environmental Information

Not causal. Modifiers of expression only: dietary calcium/vitamin D status; enzyme-inducing drugs (phenobarbital) that alter vitamin-D-analog metabolism. No infectious agents.

6. Mechanism/Pathophysiology

See Mechanistic Model and Finding 5. Pathways: Gq/11–PLC and Gi signaling, p38MAPK–ATF1–miR137 (renal AQP2), Cldn14-mediated renal calcium handling. Protein dysfunction: class C GPCR homodimer biased toward active state (Finding 7). CHEBI: calcium(2+) (CHEBI:29108), phosphate (CHEBI:43474). Immune involvement: none intrinsic.

7. Anatomical Structures Affected

Primary: parathyroid gland (UBERON:0001132), kidney/nephron (UBERON:0002113). Secondary: basal ganglia (UBERON:0002420), ocular lens (UBERON:0000965), soft tissue (ectopic calcification), heart (functional QT). Cells: parathyroid chief cell (CL:0000446), collecting-duct principal cell (CL:1000456), TAL epithelium. Subcellular: plasma membrane (GO:0005886), ER (trafficking). Lateralization: systemic/bilateral. Systems: endocrine, renal/urinary, nervous, cardiac electrophysiology.

8. Temporal Development

Onset congenital/neonatal → adult, or asymptomatic. Pattern chronic/insidious with acute symptomatic episodes. Course lifelong; renal complications slowly progressive. Critical periods: neonatal seizure risk; intercurrent illness, pregnancy, and medication changes; early diagnosis is the key intervention window to avoid overtreatment-related renal damage.

9. Inheritance and Population

Autosomal dominant; frequent de novo; germline/gonadal mosaicism reported (Finding 8). High biochemical penetrance, variable symptomatic expressivity; negative family history does not exclude ADH1. No anticipation, founder effect, or consanguinity role in the classic sense. Epidemiology: rare; precise prevalence not established; ADH is the most common genetic cause of isolated hypoparathyroidism; monogenic causes ~5–10% of all hypoparathyroidism; ADH1 >> ADH2. No strong sex or geographic predilection.

10. Diagnostics

Biochemistry: low Ca, high phosphate, low/normal PTH, often low Mg, high urine Ca (24-h or Ca:creatinine). Imaging: renal ultrasound, brain CT, ECG (QTc); slit-lamp for cataract. Genetic testing: single-gene *CASR* sequencing or hypoparathyroidism/mineral panel; WES/WGS if undiagnosed; functional assays for VUS. Diagnostic clue: hypoparathyroidism *with* hypercalciuria. Differential: postsurgical, autoimmune (incl. anti-CaSR autoantibody phenocopy), 22q11.2 deletion, hypomagnesemia-related, pseudohypoparathyroidism, vitamin D disorders, ADH2 (*GNA11*). Screening: cascade genetic testing; prenatal/PGT for a known variant; no population newborn screening.

11. Outcome/Prognosis

Near-normal life expectancy with treatment; dominant morbidity is renal (nephrocalcinosis up to ~38%, nephrolithiasis up to ~36%, progression to CKD), amplified by intrinsic hypercalciuria and overtreatment (Finding 10). Other complications: seizures, ectopic/basal ganglia calcification, cataracts, QT prolongation. Prognostic factors: cumulative urinary calcium load, treatment approach, disease duration. Established nephrocalcinosis/CKD is not fully reversible — prevention is key.

12. Treatment

Conventional: oral calcium + active vitamin D (calcitriol/alfacalcidol), targeting low-normal serum calcium with judicious dosing; thiazide diuretics (of particular benefit in activating-CaSR patients); magnesium repletion. Targeted: calcilytics (NPSP795/SHP635, NPS 2143, ATF936/AXT914, encaleret) and PTH-replacement (palopegteriparatide, recombinant PTH) (Finding 3). Pharmacogenomics: avoid enzyme inducers (phenobarbital). No approved gene/cell/RNA therapy; surgery not applicable. Personalized medicine: in-vitro variant response can guide calcilytic vs PTH-based choice. NCIT terms listed in Finding 3.

13. Prevention

Primary prevention not possible (germline). Genetic counseling (AD, 50% offspring risk; de novo/mosaicism caveats) and reproductive options (PGT/prenatal testing) are the main tools. Secondary: cascade testing and early biochemical surveillance of relatives. Tertiary (most important): avoid overtreatment, maintain low-normal calcium, monitor 24-h urine calcium and renal imaging, use thiazides/calcilytics/PTH to prevent nephrocalcinosis/CKD. Immunization/public-health/environmental interventions not applicable.

14. Other Species / Natural Disease

Taxonomy: *Homo sapiens* (NCBI:txid9606); modeled in *Mus musculus* (NCBI:txid10090). No notable naturally occurring ADH1 in companion animals/wildlife documented. Ortholog: mouse *Casr* (historically *Gprc2a*); receptor and its Ca2+-homeostasis role are evolutionarily conserved, so mechanisms translate well to mouse models. Zoonosis/transmission: not applicable.

15. Model Organisms

Principal model — the Nuf mouse (*Casr* p.Leu723Gln; Finding 4): AD gain-of-function; recapitulates hypocalcemia, hyperphosphatemia, low PTH, ectopic calcification, and cataracts; plus impaired glucose tolerance. CaSR knock-in mice dissect renal AQP2/vasopressin pathology. Cellular/in-vitro: HEK293 expressing WT vs mutant CaSR for intracellular-Ca2+/BRET assays and calcilytic docking. Applications: validating calcilytics, studying biased signaling, renal/pancreatic CaSR biology. Limitations: mouse mineral set-points/lifespan differ; neurological (basal ganglia calcification) features less emphasized. Resource: MGI (mouse *Casr*).

Evidence Base

PMID	Title (abbreviated)	Supports finding(s)	Evidence type
39658204	Activating CaSR variant with biased signaling	F1, F7, F8	Human genetics + in vitro
31189130	CaSR mutation review	F1, F7	Review
34160437	p.Arg205Cys ADH1 pedigree	F1	Human clinical
16128246	ADHH family, treatment challenges	F2, F3, F10, F11	Human clinical
42388864	Palopegteriparatide pediatric ADH1	F2, F3	Human clinical case
27617113	Novel p.Leu123Ser + mosaicism	F2, F8	Human clinical
31063613	Calcilytic NPSP795 in ADH1 patients	F3, F11	Human clinical trial
38367250	Calcilytic reverses renal AQP2 defect	F3, F5	Model organism (KI mouse)
15347804	Nuf mouse cataracts + calcification	F4	Model organism
40086735	Quinazolinone calcilytic in Nuf mice	F4, F7	Model organism
28575322	Nuf mice hyperglycemia	F4	Model organism
35313217	Parathyroid vs kidney CaSR contributions	F5	Model organism
22863393	Hypoparathyroidism review (thiazides)	F6	Review
34935164	Genetics of calcium/bone disorders	F6, F11	Review
36707151	CaSR cryo-EM structures	F7	Structural/ computational
36970776	GNA11 variants (ADH2)	F8	Human genetics
20374733	CaSR-associated diseases + autoantibodies	F9	Review
11013439	CASR mutation spectrum + A986S	F9	Human genetics
25227206	Neonatal ADH1 + phenobarbital interaction	F9	Human clinical

PMID	Title (abbreviated)	Supports finding(s)	Evidence type
33599907	Renal complications systematic review	F10	Systematic review
40531442	Postsurgical hypoparathyroidism outcomes	F10	Retrospective cohort

The evidence base is coherent and mutually reinforcing across human clinical, human genetics, model organism, and structural/computational domains. Human genetic studies establish causation (activating *CASR* variants), the Nuf mouse and CaSR knock-in models provide mechanistic validation and pharmacological proof-of-concept, cryo-EM structures rationalize where mutations and calcilytics act, and clinical/registry studies define the phenotype, therapeutic dilemma, and prognosis. No paper in the reviewed set contradicts the central model.

Supported vs Refuted Hypotheses

Supported (evidence-backed): 1. ADH1 = heterozygous activating *CASR* variants, left-shifted Ca2+ set-point (gain of function) [PMID 39658204; 34160437]. 2. Phenotype = hypocalcemia + inappropriately low PTH + hypercalciuria + calcification complications [PMID 16128246]. 3. Dual parathyroid + renal CaSR overactivity explains hypocalcemia **with** hypercalciuria; renal AQP2 pathway involved [PMID 35313217; 38367250]. 4. Calcilytics are mechanism-matched therapy (human n=5 + mouse) [PMID 31063613; 40086735]. 5. Nuf mouse faithfully models the disease [PMID 15347804].

Refuted / not applicable: environmental or infectious causation; loss-of-function/misfolding mechanism (that is FHH/NSHPT); a role for population-based primary prevention.

Limitations and Knowledge Gaps

1. **Epidemiology is poorly quantified.** No reliable population prevalence/incidence figures for ADH1 specifically; estimates are extrapolated from the broader hypoparathyroidism population (monogenic ~5–10%). Precise prevalence, incidence, sex ratio, and geographic/ethnic distribution remain gaps.

2. **Penetrance and expressivity are incompletely characterized.** Variable expressivity and mosaicism are documented, but formal penetrance estimates by variant are lacking.
3. **Genotype–phenotype correlations are limited.** Symptom severity is explicitly *not* tightly correlated with hypocalcemia degree; systematic variant-level correlation (including biased-signaling variants) is needed.
4. **Targeted therapy evidence is early-stage.** Calcilytic human data are limited (n=5 for NPSP795) and PTH-replacement evidence is a single pediatric case. Long-term renal-protective outcomes are not yet established.
5. **Quality-of-life data are essentially absent** — no EQ-5D/SF-36/PROMIS data specific to ADH1.
6. **Cross-species natural disease** beyond engineered mouse models is not documented.

Proposed Follow-up Experiments / Actions

1. **Assemble a natural-history registry** for ADH1 to quantify prevalence, penetrance, age-of-onset distribution, and long-term renal/neurological outcomes, stratified by variant.
2. **Systematic variant-function mapping:** couple in-vitro Gq/11/Gi signaling assays with clinical severity to build a genotype–phenotype and calcilytic-responsiveness atlas guiding personalized therapy.
3. **Complete calcilytic clinical development** (e.g., encaleret) with renal endpoints (24-h urine calcium, GFR trajectory, nephrocalcinosis imaging) as primary outcomes, not just PTH/serum calcium.
4. **Head-to-head comparison** of thiazide + conventional therapy vs calcilytic vs PTH-replacement (palopegteriparatide) on renal protection in ADH1.
5. **Prospective QoL assessment** using validated instruments to capture disease and treatment burden.
6. **Mechanistic follow-up on the renal AQP2/Cldn14 axis** in patient-derived models (e.g., iPSC-derived kidney organoids carrying ADH1 variants) to validate the p38MAPK–ATF1–miR137 pathway in human cells.

Report compiled from 11 confirmed findings across 35 reviewed papers over 5 investigation iterations. Evidence spans human clinical, human genetics, model organism (Nuf/knock-in mouse), and structural/computational sources. PMIDs cited inline.
