

HYPOPARATHYROIDISM

The Critical Role of GENETICS in Your Differential Diagnosis



RAPID RECAP

ADH1 Is a Cause of Hypoparathyroidism^{1,2}

- **ADH1 (Autosomal Dominant Hypocalcemia Type 1)** is an underrecognized genetic cause of nonsurgical hypoparathyroidism (hypoPT)
 - Conventional therapy for hypoPT (calcium and calcitriol) can worsen renal complications
 - Untreated or missed diagnosis can lead to renal complications
- **Clinical clues suggesting ADH1:**
 - Persistent hypocalcemia with low or inappropriately normal parathyroid hormone (PTH)
 - Hypercalciuria or renal calcifications disproportionate to therapy
 - Family history of hypocalcemia, seizures, or kidney stones
- **ADH1 results from gain-of-function variants in the *CASR* gene**, causing ↓ PTH secretion, ↓ serum calcium, and ↑ urinary calcium (distinguishing feature)

Diagnostic Strategies¹⁻⁶

Initial Evaluation Before Testing

- Confirm persistent hypocalcemia
- Assess history (surgery, autoimmune disease, and medications)
- Obtain 3-generation family history
- Measure: PTH, calcium, phosphate, magnesium, vitamin D, renal function, and urine calcium

Genetic Testing

- All patients with nonsurgical or idiopathic hypoPT, especially with positive family history or syndromic features of hypoPT
- Use targeted hypoparathyroidism panel
- Positive test (pathogenic *CASR* variant) supports ADH1 diagnosis, negative does not exclude genetic disease if suspicion remains, and variant of uncertain significance (VUS) requires phenotype and family correlation

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Explain the Role of Genetic Testing to Patients^{2,4,6}

Use clear, patient-centered language

Key points to explain to patients:

- Clarifies diagnosis and cause of hypocalcemia
- May explain kidney findings (hypercalciuria)
- Guides family screening (autosomal dominant inheritance)
- May inform future or targeted therapies
- Implications for first-degree relatives after confirming pathogenic variant
- Role of genetic counseling

Key Takeaways

- Reassess patients with idiopathic or nonsurgical HypoPT
- Suspect ADH1 when low calcium and low PTH coexist with hypercalciuria, renal calcifications, early-life symptoms, or positive family history
- Incorporate genetic testing into routine evaluation for unexplained nonsurgical hypoPT
- Consider the impact of an ADH1 diagnosis on monitoring, treatment strategy, and family counseling
- Explain to patients that a genetic diagnosis provides mechanistic clarity and guides long-term care

Genetic Testing and Counseling Resources

- Prevention Genetics. [DetectHypoPara Sponsored Testing Program](#). Includes 26 genes.
 - Free genetic testing and counseling for patients with diagnosed nonsurgical or idiopathic HypoPT
 - Free variant-specific testing and counseling for first degree relatives
- Invitae Panel. [Hypoparathyroidism gene panel](#). Includes 18 genes. Fee based service.

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References

1. Chang JB, et al. [*Am J Hum Genet.* 2025;112\(8\):1818-1832.](#)
2. Roszko KL, et al. [*J Bone Miner Res.* 2022;37\(10\):1926-1935.](#)
3. Khan AA, et al. [*Metabolism.* 2025;171:156335.](#)
4. De Coster T, et al. [*J Endocrinol Invest.* 2025;48\(4\):831-844.](#)
5. Gafni RI, et al. [*N Engl J Med.* 2019;380\(18\):1738-1747.](#)
6. Orloff LA, et al. [*Thyroid.* 2018;28\(7\):830-841.](#)