Autosomal Dominant Hypocalcemia Type 1: A Systematic Review of the Genotypic and Phenotypic Spectrum, and Effects of Treatment

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Introduction

- Autosomal dominant hypocalcemia type 1 (ADH1) is a rare form of hypoparathyroidism due to activating mutations of the calcium-sensing receptor (CaSR) gene (*CASR*) causing low parathyroid hormone (PTH) levels, hypocalcemia, hyperphosphatemia, and relative hypercalciuria.
- Conventional therapy includes calcium and active vitamin D; however, this treatment can worsen hypercalciuria and lead to renal complications.

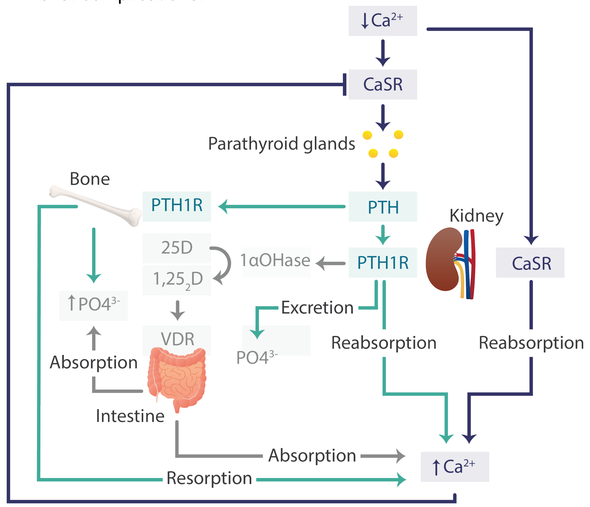

Figure 1: Regulation of systemic mineral metabolism. In the parathyroid, low levels of extracellular Ca^{2+} diminish signaling through the CaSR which leads to increased synthesis and secretion of PTH. PTH stimulates bone resorption to release Ca^{2+} and phosphate into the blood. It also acts in the kidney to increase the synthesis of 1,25-dihydroxyvitamin D_3, which then increases the absorption of dietary calcium and phosphate in the small intestine. PTH decreases phosphate and increases Ca^{2+} reabsorption in the kidney. CaSRs in the kidney regulate Ca^{2+} and phosphate reabsorption and possibly 1,25-dihydroxyvitamin D synthesis, opposing the actions of PTH.

Systematic Review Methodology

- **Search Criteria:** autosomal dominant hypocalcemia; familial hypoparathyroidism; genetic/congenital hypoparathyroidism; hypercalciuric hypocalcemia; activating *CASR* variants
- **Extracted Data:** age at clinical presentation, mode of diagnosis, *CASR* variant, presenting symptoms, pre-treatment biochemical profile, on-treatment blood calcium, urine calcium, and complications
- **Final Analysis Set:** 339 ADH1 cases across 76 published reports spanning 1994-2021.

Cohort Identification

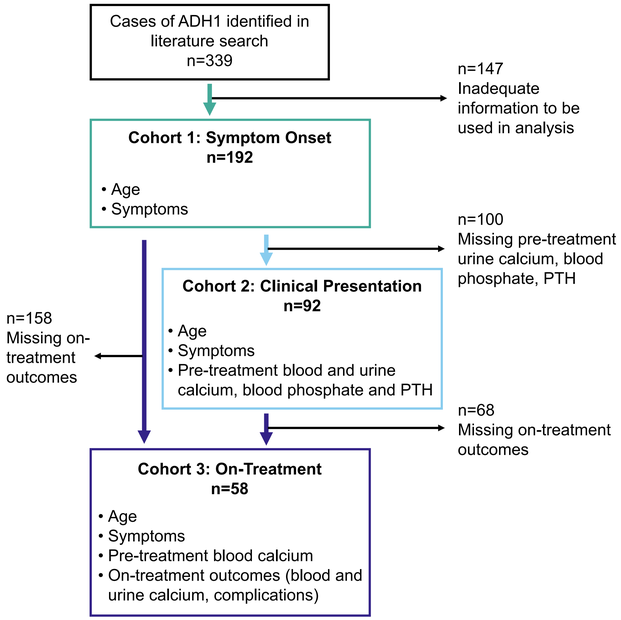

Figure 2: Flowchart for ADH1 case cohort inclusion and exclusion criteria

Symptom Onset (Cohort 1)

Table 1: Characteristics of individuals with ADH1 (Cohort 1)

	Reported Cases
Age at dx of a hypocalcemia- related disorder, median (range)	5 (0-66)
Age of dx of ADH1, median (range)	25 (0-77)
Primary driver of dx (%)	
Symptom Driven	71%
Family Screen	23%
Incidental	6%
Symptom burden at presentation (%)	
Asymptomatic	27%
Moderate	32%
Severe	41%

Primary driver of dx refers to the main factor contributing to a diagnosis of a hypocalcemia-related disorder. Asymptomatic symptom burden refers to the absence of hypocalcemia-related symptoms. Moderate symptom burden includes muscle cramps/spasms, bone/joint pain, tetany, paresthesia, brain fog, and/or fatigue. Severe symptom burden includes seizures, loss of consciousness, and/or laryngospasm.

Clinical Presentation (Cohort 2)

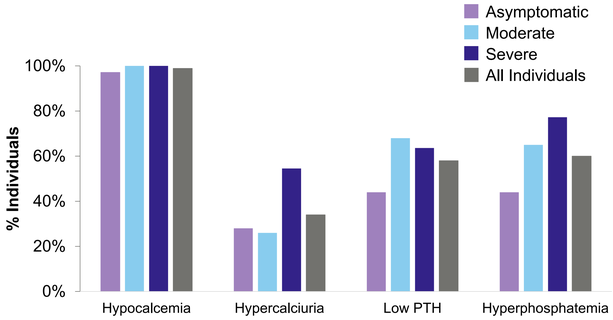

Figure 4: Biochemical features at the time of presentation. Observation of hypocalcemia, hypercalciuria, low PTH, and hyperphosphatemia for asymptomatic, moderate, severe, and all individuals in Cohort 2. Sample size: n=36 asymptomatic; n=34 mild/moderate symptomatic; n=22 severe symptomatic (total n=92).

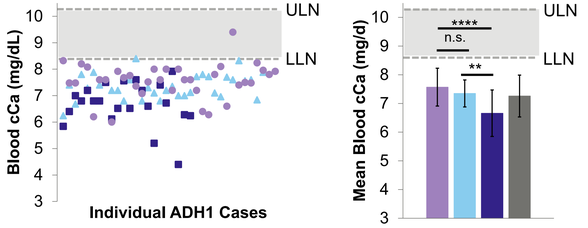

Figure 5: Blood calcium levels at time of presentation. Blood calcium levels for all individuals in Cohort 2 (left). Average blood calcium for asymptomatic, moderate, severe, and all individuals in Cohort 2 (right). Data presented as mean ± SD **P <0.01, and ****P < 0.0001. Gray shading reflects normal range.

Genotype-Phenotype Relationship

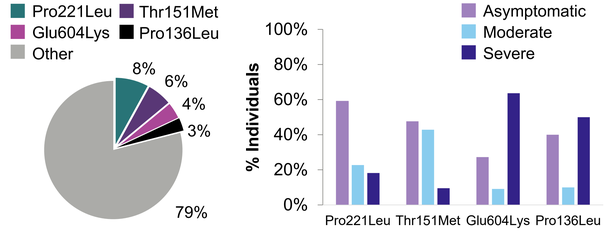

Figure 6: *CASR* variants. Four most common variants with reported symptoms as a proportion of all the variants identified the literature (n=339), regardless of kindred (left). Symptom severity for each common variant was analyzed (right). Overall, there was no direct correlation between *CASR* genotype and clinical phenotype. Unique variants (n=114) were present throughout the CaSR but most (55%) were in the extracellular domain, 33% were within the transmembrane domain, and 12% in the intracellular domain.

On-Treatment (Cohort 3)

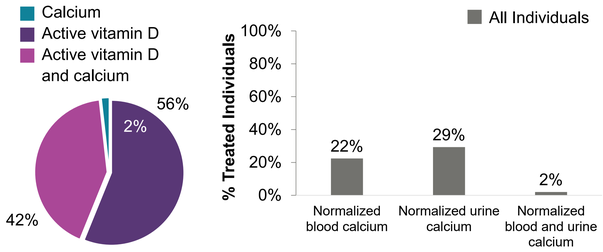

Figure 7: ADH1 medical intervention. Treatment regimens for individuals in Cohort 3 (left). Percentage of individuals in Cohort 3 with normalized blood calcium, normalized urine calcium and both normalized blood and urine calcium (right, n=58).

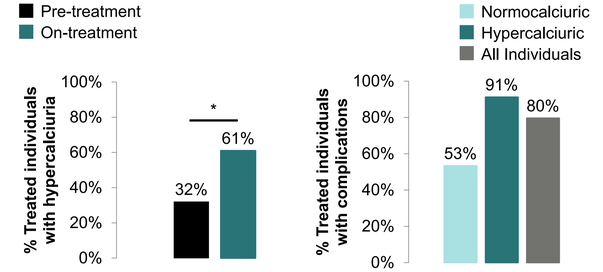

Figure 8: Treatment-emergent complications. In a subset of individuals in Cohort 3 (n=28), the incidence of hypercalciuria increased 91% while on treatment compared to pre-treatment (p<0.05) (left). Treatment-emergent complications were associated with hypercalciuria and were observed in 80% of individuals in Cohort 3 (OR=8.1; 95% CI=2.2-30.6; p<0.01) (right). Complications assessed include nephrocalcinosis, nephrolithiasis, renal impairment, and basal ganglia calcifications.

Conclusion

- This is the largest systemic literature review of ADH1 cases which analyzed 339 cases and uncovered >100 unique *CASR* variants
- There was a wide range of clinical heterogeneity and a general lack of genotype/phenotype correlation in ADH1 individuals
- Lower blood calcium levels were associated with more severe symptoms
- Conventional treatment was associated with an increase in hypercalciuria, and the available data suggest an inability to simultaneously normalize blood and urine calcium
- These findings underscore the limitations of the current standard of care for ADH1 patients

References

1. Roszko KL, et al. Front Physiol. 2016; 7:458.
2. Gorvin, CM, et al. J Mol Endocrinol. 2019; 63:2.