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# Autosomal dominant hypocalcemia with a novel *CASR* mutation: a case study and literature review

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## Abstract

Autosomal dominant hypocalcemia type 1 (ADH1) is a rare inherited disorder characterized by hypocalcemia with low parathyroid hormone (PTH) levels and high urinary calcium. Its clinical presentation varies from mild asymptomatic to severe hypocalcemia. It is caused by gain-of-function mutations in the calcium-sensing receptor gene (*CASR*) which affect PTH secretion from the parathyroid gland and calcium resorption in the kidney. Here, we describe a case who presented with symptoms of recurrent seizure caused by hypocalcemia with a novel *CASR* variant. We comprehensively analyzed the phenotypic features of this presentation and reviewed the current literature to better understand clinical manifestations and the genetic spectrum.

## Keywords

Autosomal dominant hypocalcemia type 1, hypoparathyroidism, seizure, calcification, CASR, hyperphospheremia

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## Introduction

Autosomal dominant hypocalcemia type 1 (ADH1) is a rare inherited disorder characterized by hypocalcemia with low parathyroid hormone (PTH) levels and high urinary calcium.[1] It was first described in 1994, with patients mainly presenting with asymptomatic hypocalcemia.[2] ADH1 is more common than ADH2, accounting for 70% of cases. [3,4]

ADH1 is caused by mutations in the calcium-sensing receptor gene (*CASR*) which maps to chromosome 3q13.3-21 and is composed of six exons. CASR is a plasma membrane G protein-coupled receptor containing a large extracellular domain of 612 amino acids, seven transmembrane domains, and one intracellular domain.[5,6] It plays an important role in maintaining systemic calcium homeostasis, and is mainly expressed in the parathyroid gland, kidney, bone and gut.[7]

Herein, we describe a patient with a *de novo CASR* mutation and performed a detailed literature review of ADH1 to summarize clinical manifestations and biochemical characterizations, and to widen our knowledge of the genetic spectrum.

## Case presentation

A 24-year-old man (Figure 1a) was admitted to our hospital with recurrent tonic-clonic seizures. He was born at term with a normal weight, length, and head circumference, following an uneventful pregnancy. He had his first tonic-clonic seizure with no obvious cause at the age of 9 months. At this time, he was admitted to hospital where biochemical analyses revealed low serum calcium and high serum phosphate levels. Blood glucose levels, and abdominal and parathyroid ultrasound were normal, so other causes of hypocalcemia were ruled out. Although he was prescribed phenobarbital, the epileptic seizures were not well controlled.

At the age of 1 year, he experienced recurrent seizures, which were more frequent when he had a fever. Computed tomography of the brain revealed multiple intracranial calcifications, and electroencephalography showed extensive epileptic discharges. Since then, he has been repeatedly hospitalized with recurrent seizures, and intracranial calcification was shown to be progressively aggravating. He was diagnosed with congenital cataracts at the age of 14 years.

Physical examination on admission at our hospital showed no obvious abnormalities. After written informed consent was obtained from the patient to participate in this study, clinical evaluation including laboratory testing and brain imaging were performed. Laboratory data on admission and 1 week after admission are shown in Table 1. Hypocalcemia, hyperphosphheremia, and hypoparathyroidism were clearly evident, and brain computed tomography showed multiple intracranial calcifications (Figure 1b). The patient had no further seizures during his hospitalization while being administered calcium and antiepileptic drugs.

Genomic DNA was extracted from the patient's peripheral blood using the Gentra Puregene Blood kit (QIAGEN, Hilden, Germany). Whole-exome sequencing was performed using SureSelectXT reagents (Agilent, Santa Clara, CA, USA) for capturing exons and the Illumina platform for sequencing (Illumina, San Diego, CA, USA). This revealed a novel, heterozygous missense *CASR* variant, c.416 T>C (p.Ile139Thr), which was found to be absent from the following reference databases: 1000 Genomes Project, the dbSNP database, the Exome Aggregation Consortium, and the Human Gene Mutation Database. Variant pathogenicity was interpreted and classified following the

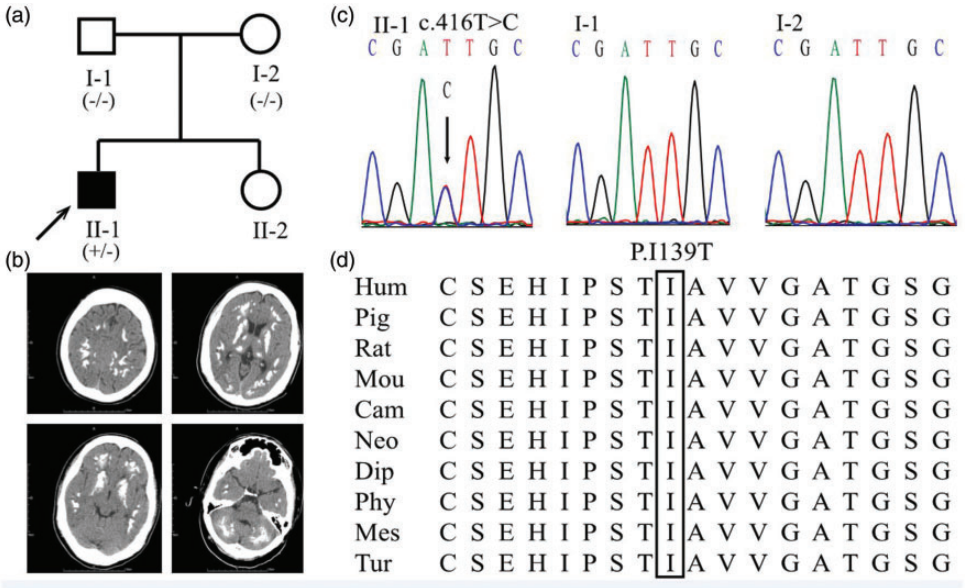


**Figure 1.** (a) Family pedigree. (b) Brain CT showing multiple calcifications in the bilateral frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia, and cerebellum. (c) Sanger sequencing showing a *CASR* heterozygous mutation (c.416T > C) in the proband, and wild-type sequence in his parents and (d) Conservation of the 139th amino acid among different species.

**Table 1.** Laboratory findings of the patient on admission and 1 week after admission.

| Serum variables | On admission | One week after admission | Normal range |
|---|---|---|---|
| Calcium (mmol/L) | 1.73 | 1.76 | 2.00–2.75 |
| Phosphate (mmol/L) | 1.81 | 2.19 | 0.80–1.60 |
| Magnesium (mmol/L) | 0.67 | 0.70 | 0.74–1.03 |
| PTH (pg/mL) | – | 9.40 | 15–68.30 |
| Sodium valproate (mmol/L) | 45 | 61.30 | 50–100 |

PTH = parathyroid hormone.

American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines.[8] MutationTaster and PolyPhen-2 algorithms predicted the variant to be pathogenic, and Sorting Intolerant From Tolerant predicted it to be a benign variant. Sanger sequencing and segregation analysis showed that the mutation was *de novo* (Figure 1c). It was evaluated as 'likely pathogenic (PS1 + PM1 + PP1)' according to ACMG guidelines. The amino acid sequence at position 139 of the extracellular domain was shown to be highly conserved among different species (Figure 1d).

The reporting of this study conforms to CARE guidelines.[9]

## Discussion

Here, we report a novel heterozygous *CASR* variant in a patient with severe hypocalcemia and hypoparathyroidism. ADH1 can manifest at any age, but most

commonly starts in childhood. Clinical manifestations vary from asymptomatic hypocalcemia to mild neuromuscular symptoms such as muscle cramps, tetany, cataracts, and baldness.[10] Severe cases may present with epileptic seizures. Studies have found that approximately 50% of patients with ADH1 have symptomatic hypocalcemia and >30% have renal and/or intracerebral calcifications.[11,] Seizures are less common, and our review of the current literature found that 19.8% (50/253) of patients experienced them.

Our patient had both intracranial calcification and seizures, which is a relatively rare phenotype. Indeed, our literature review found that this was seen in only 8.7% (22/253) of patients (Table 2). The cause of epilepsy in patients with ADH1 is unclear. A previous study found that the severity of hypocalcemia was related to the severity of neurological symptoms,[12] while other studies showed the occurrence of epilepsy to be independent of serum calcium levels.[13,14] Of note, epileptic seizures appear to be a prominent feature of ADH1, suggesting that levels of electrolytes, especially serum calcium, should be measured to rule out ADH1 in patients with epilepsy.

CASR is a plasma membrane G protein-coupled receptor that is widely expressed in the peripheral tissue, including the parathyroid gland, pancreas, duodenum, kidney, bone, stomach and respiratory system. Its primary function is to maintain systemic calcium homeostasis.[5] More than 400 *CASR* mutations have been reported to date according to the Human Gene Mutation Database. Loss- or gain-of-function *CASR* mutations lead to opposing clinical manifestations. For instance, heterozygous and homozygous loss-of-function mutations and inactivating variants cause familial hypocalciuric hypercalcemia (FHH) and neonatal severe hyperparathyroidism, respectively.[15] Conversely, gain-of-function mutations and activating variants are a major cause of type-5 Bartter syndrome and ADH1. Type-5 Bartter syndrome and ADH1 have similar clinical features, although the former leads to electrolyte imbalances from hypokalemia.[16] Their clinical manifestations differ from those of FHH.

Abnormal CASR function has previously been implicated in central nervous system disorders such as epilepsy[11,17] where an undefined association between genotype and phenotype was observed. Clinical presentations also vary widely among members of the same family with identical *CASR* genotypes, indicating the possibility of interactions among genetic, epigenetic, and environmental factors.[14] Studies revealed that approximately 95% of ADH1 cases are caused by missense substitutions, whereas 5% result from in-frame or frameshift insertion/deletion mutations.[11,18] Our literature review found that 7.5% (19/253) of ADH1 cases were caused by *de novo* *CASR* mutations. Missense *CASR* mutation hotspots cluster in exons 3, 4, and 7.[19] The *de novo* heterozygous p.Ile139Thr variant identified in the present case is located in exon 3, within the extracellular domain. Amino acids 116 to 136 of CASR were shown to be ligand binding sites that are more sensitive to calcium levels than other amino acids.[3] The variant identified in our patient is close to these ligand binding sites, suggesting it is likely to be more pathogenic than mutations in transmembrane and intracellular domains.

Once a diagnosis of ADH1 has been confirmed, the need for therapeutic correction of hypocalcemia is controversial.[19] Recent studies reported that correction treatment should be avoided for asymptomatic patients. Indeed, it is thought necessary to begin treatment with the lowest amount of calcium and activated vitamin D when symptoms occur frequently because the therapeutic aim is to alleviate symptoms rather than restoring normal levels of

**Table 2.** Literature review summary of patients with ADH1 with both epilepsy and intracranial calcification.

| Sex | Age of disease onset | Biomarker | Epilepsy seizure | Site of calcification | *CASR* variant | Exon | Het/ Hom | Author |
|---|---|---|---|---|---|---|---|---|
| F | 18y | Hypocalcemia<br>Hyperphosphatemia<br>Hypocalciuria<br>Low PTH | + | Basal ganglia | 1631G > A;<br>p.Arg544Gln | 6 | Hom | Cavaco et al. (2018)[25] |
| F | 23y | Hypocalcemia<br>Hypocalciuria<br>Normal PTH | + | Basal ganglia | 2269G > A;<br>p.Glu757Lys | 7 | Het | Kwan et al. (2018)[1] |
| – | 25y | Hypocalcemia<br>Hyperphosphatemia<br>Hypomagnesemia<br>Normal PTH | + | Basal ganglia | 354C > A;<br>p.Asn118Lys | 3 | Het | Pearce et al. (1996)[26] |
| F | 44y | Hypocalcemia<br>Hypomagnesemia<br>Normal phosphorus | + | Basal ganglia | 382T > C;<br>p.Phe128Leu | 3 | Het | |
| M | 8y | Normal calcium<br>Hypophosphatemia<br>Normal magnesium<br>Hypercalciuria | + | Frontal lobe | p.Ala784Val | 7 | Het | Winer et al. (2018)[23] |
| F | 1y | Normal calcium<br>Hyperphosphatemia<br>Hypomagnesemiav<br>Hypercalciuria | + | Basal ganglia;<br>Thalamus | p.Glu127Lys | 3 | Het | |
| M | 2y | Normal calcium<br>Hyperphosphatemia<br>Hypercalciuria | + | Basal ganglia | p.Phe128Cys | 3 | Het | |
| F | 25y | Hypocalcemia<br>Hyperphosphatemia<br>Normal magnesium<br>Low PTH<br>Hypocalciuria | + | Basal ganglia | 2086C > G<br>p.Leu696Val | 7 | Het | Gomes et al. (2020)[27] |
| F | 42y | Hypocalcemia<br>Low PTH | + | Bilateral basal ganglia | 372C > A<br>p.Asn124Lys | 2 | Het | Hu et al. (2002)[28] |
| F | 25y | Hypocalcemia<br>Normal phosphorus<br>Normal PTH | + | Basal ganglia | 372C > A<br>p.Asn124Lys | 2 | Het | |
| F | 25y | Hypocalcemia<br>Normal phosphorus<br>Normal magnesium<br>Hypocalciuria<br>Normal PTH | + | CNS calcification | 386G > A<br>p.Cys129Tyr | 3 | Het | Burren et al. (2005)[29] |
| M | 4w | Hypocalcemia<br>Hyperphosphatemia<br>Normal magnesium<br>Normal PTH | + | CNS calcification | 386G > A<br>p.Cys129Tyr | 3 | Het | |

(continued)

**Table 2.** Continued.

| Sex | Age of disease onset | Biomarker | Epilepsy seizure | Site of calcification | *CASR* variant | Exon | Het/ Hom | Author |
|---|---|---|---|---|---|---|---|---|
| F | 3d | Hypocalcemia<br>Hyperphosphatemia<br>Low PTH | + | Basal ganglia | 2530G > C<br>p.Ala844Pro | 7 | Het | Nakajima et al. (2009)[30] |
| M | 54y | Hypocalcemia<br>Normal phosphorus<br>Low PTH<br>Normal calciuria | + | Basal ganglia; Frontal lobe | 1666G > A<br>p.Glu556Lys | 6 | Het | Livadariu et al. (2011)[31] |
| F | 5y | Hypocalcemia<br>Hyperphosphatemia<br>Normal magnesium<br>Low PTH<br>Normal calciuria | + | Basal ganglia | 734A > G<br>p.Gln245Arg | 4 | Het | Raue et al. (2011)[32] |
| M | 8y | Hypocalcemia<br>Hyperphosphatemia<br>Hypomagnesemia<br>Normal calciuria<br>Low PTH | + | Basal ganglia | 452C > G<br>p.Thr151Arg | 3 | Het | |
| M | 38y | – | + | Basal ganglia | 662C > T<br>p.Phe221Leu | 4 | Het | |
| F | 7m | Hypocalcemia<br>Hyperphosphatemia<br>Normal PTH<br>Hypercalciuria | + | Basal ganglia | 354C > A<br>p.Asn118Lys | 2 | Het | De Luca et al. (1997)[33] |
| M | 7d | Hypocalcemia<br>Normal PTH | + | Basal ganglia | 2363T > G<br>p.Phe788Cys | 7 | Het | Watanabe et al. (1998)[34] |
| F | 6d | Hypocalcemia<br>Hyperphosphatemia | + | Basal ganglia | 2363T > G<br>p.Phe788Cys | 7 | Het | |
| F | 12d | Hypocalcemia<br>Hypomagnesemia<br>Low PTH | + | Basal ganglia; Bilateral sub-frontal cortex | 2486A > G<br>p.Tyr829Cys | 7 | Het | Choi et al. (2015)[5] |
| F | 6y | Hypocalcemia<br>Hyperphosphatemia<br>Hypomagnesemia<br>Low PTH | + | Basal ganglia | 2204A > C<br>p.Gln735Pro | 7 | Het | Wong et al. (2011)[35] |

Het = heterozygous, Hom = Homozygous, F = female, M = male, y = years, m = months, w = weeks, d = days, PTH = parathyroid hormone, CNS = central nervous system.

calcium,[20] which could increase the risk of nephrocalcinosis and/or intracranial calcification. However, some reports suggest that twice- or thrice-daily subcutaneous PTH 1–34 injection is safe and effective. [21] Human recombinant PTH 1-84 has also been used to treat patients with ADH1,[22] and to avoid nephrocalcinosis and slow the progress of intracranial calcification.[23] Although there is currently no standard therapeutic approach for ADH1, some reports suggest that slightly increasing

serum calcium levels prevent hypercalciuria. Additionally, calcilytics are under development for the treatment of ADH1, while thiazide-like diuretics have been used to treat hypercalciuria.[24] Our patient continued to receive calcium supplements and antiepileptic drugs to avoid the recurrence of epilepsy.

## Conclusion

ADH1 is a rare genetic disease characterized by hypocalcemia. Genetic exploration of *CASR* should be considered during the initial work-up of hypocalcemia to aid earlier recognition, and the implementation of targeted preventive and therapeutic strategies. By reviewing ADH1 cases, we comprehensively analyzed the phenotypic and genetic features to better understand the genotype and phenotype spectra.

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The authors declare that there is no conflict of interest.

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### Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (approval no: 2021-219). Written informed consent was obtained from the patient for participation in the study and the publication of any potentially identifiable images or data included in this article.

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