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# Intractable Generalized Epilepsy and Autosomal Dominant Hypocalcemia: A Case Report

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**Abstract**

Calcium-sensing receptor gain-of-function mutations are known to cause autosomal dominant hypocalcemia and independently an epilepsy syndrome. We report the unique case of a child with both intractable generalized epilepsy and a chronic abnormality in calcium homeostasis due to a calcium-sensing receptor gene mutation. She is a 16-year-old female who began having staring events around 3 years of age. After her first generalized convulsion at age 5 years, investigations revealed hypocalcemia, hypercalciuria, and central nervous system calcifications. Her electroencephalogram demonstrated generalized epileptiform discharges, a hyperventilation-induced electroclinical seizure, and a photoconvulsive response. She has since been diagnosed with intellectual impairment, behavior disorder, and intractable childhood-onset seizures, the latter of which include eyelid myoclonia with absences. We conclude that calcium-sensing receptor gain-of-function mutations may precipitate an intractable generalized epilepsy syndrome with a comorbid endocrinopathy and that further investigations should be pursued in children with seizures presumed to be provoked by hypocalcemia.

**Keywords**

epilepsy, epileptic encephalopathy, seizures, pediatric, genetics

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Epilepsy is a heterogeneous disease of the brain. Abnormalities in brain function arise from genetic predispositions, metabolic derangements, structural anomalies, immune-mediated and infectious-mediated insults, and otherwise unknown causes.[1] When recurrent seizures are accompanied by a pattern of clinical features, then an epilepsy syndrome is suspected. Several epilepsy syndromes have an identified genetic link, but many more have yet to be discovered. We describe a patient with intractable generalized epilepsy and a comorbid endocrinopathy associated with a calcium-sensing receptor gene mutation.

An activating calcium-sensing receptor gene mutation was first suggested to be associated with an autosomal dominant form of hypocalcemia by Pollak et al in 1994.[2] Shortly thereafter, Janicic et al[3] used fluorescence in situ hybridization to definitively map the calcium-sensing receptor gene to 3q13.3-q21.1. The gene encodes for a plasma membrane G-protein-coupled receptor that is activated by small changes in extracellular calcium levels and is involved in calcium homeostasis.[4] This receptor is found predominantly in parathyroid glandular tissue, the renal tubule, and in both central nervous system gray and white matter.[4] In patients with activating calcium-sensing receptor gene mutations and seizures, their seizures were previously thought to be symptomatic to hypocalcemia, hypomagnesemia, or febrile illnesses in early childhood. However, many affected patients experience recurrent, unprovoked seizures despite correction of serum electrolyte abnormalities and others despite a lack of electrolyte disturbance altogether—clues to an underlying susceptibility for epilepsy.

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**Table 1.** Summary of Reported Epilepsy Patients With CaSR Mutations.

| CaSR Mutation | Phenotype | Seizure Semiology | Electrophysiological Data | Country of Origin | Authors |
|---|---|---|---|---|---|
| Phe788Cys in a single patient | Seizures, ADH, intellectual disability, impulse control disorder | Generalized tonic–clonic, eyelid myoclonia with absences | Generalized and bioccipital epileptiform discharges with photoconvulsive and hyperventilation-induced seizures | United States | Rossi G, Patterson A, McGregor A, Wheless J[a] |
| Arg898Gln in a single family; Glu354Ala, Ile686Val, Ala988Val, and Ala988Gly in 5 of 96 unrelated JME patients | Seizures, normal serum calcium, one affected member with undefined abnormal intellectual development | Febrile convulsions, myoclonic, absence, generalized tonic–clonic, focal to bilateral tonic–clonic | Generalized bursts of spikes with polyspikes | India | Kapoor et al.[6] |

Abbreviations: ADH, autosomal dominant hypocalcemia; CaSR, calcium-sensing receptor; JME, Juvenile myoclonic epilepsy.
[a]This publication, provided for comparison.

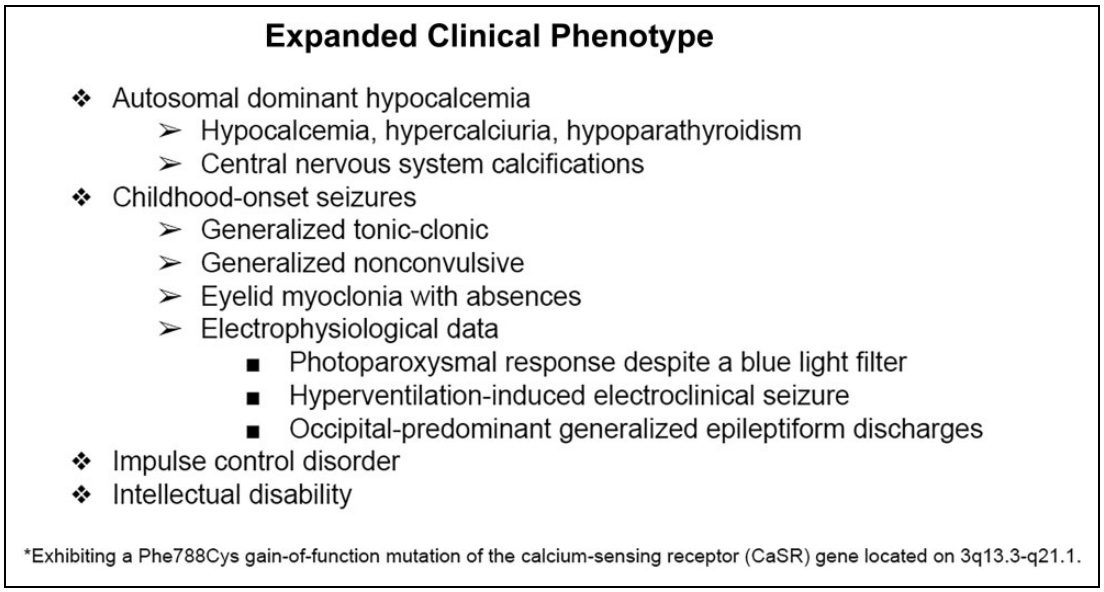


**Figure 1.** Summary of the clinical characteristics of our patient.*

It is important to differentiate the type of calcium-sensing receptor gene mutation. Heterozygous inactivating calcium-sensing receptor gene mutations result in benign familial hypocalciuric hypercalcemia, and homozygous inactivating mutations lead to neonatal severe hyperparathyroidism.[5] Alternatively, activating mutations in the calcium-sensing receptor gene lead to autosomal dominant hypocalcemia and a potential for generalized epilepsy, which is the focus of this report.[2,5,6] In the case of calcium-sensing receptor activating mutations, patients may present with bouts of abdominal pain, nephrolithiasis, and seizures with evaluations leading to the discovery of hypocalcemia, nephrocalcinosis, and central nervous system calcifications.[7]

We review the clinical presentation, diagnostic testing including electroencephalogram (EEG), neuroimaging, genetic testing, neuropsychological testing, and ensuing clinical course over several years of a child with intractable generalized epilepsy characterized by generalized convulsive and nonconvulsive seizures including eyelid myoclonia, an endocrinopathy characterized by autosomal dominant hypocalcemia, and an encephalopathy characterized by intellectual disability and impulse control disorder. We summarize the published cases to date as searched through PubMed (Table 1) as well as the characteristics of our patient with a Phe788Cys gain-of-function mutation on the calcium-sensing receptor gene (Figure 1).

## Case Presentation

Our patient is now a 16-year-old right-handed female. She was first diagnosed with absence seizures when she was 4 years old, and at that time, she had been having staring events for about a

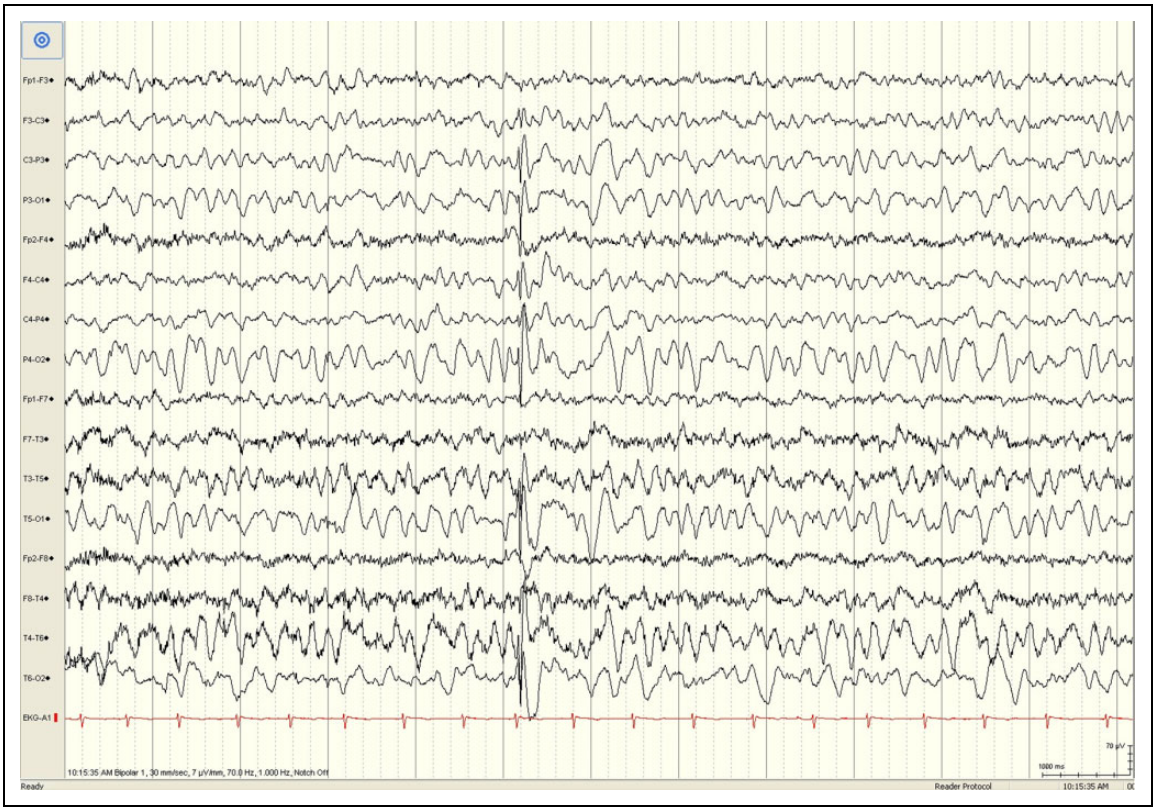


**Figure 2.** Electroencephalogram in bipolar montage of our patient showing an occipital-predominant generalized epileptiform discharge (recorded sensitivity 7 μV/mm, time base 30 mm/s, low-frequency filter 1 Hz, high-frequency filter 70 Hz, notch filter off).

year. Her EEG revealed generalized epileptiform discharges (Figure 2), a hyperventilation-induced electroclinical seizure, and a photoconvulsive response. The seizures involved her looking up with rhythmic eyelid blinking. She was initially treated with valproic acid by an outside neurology group. She was not trialed on ethosuximide. When she was 5 years old, she had her first generalized tonic–clonic seizure, which occurred in the setting of diarrhea and fever and was associated with hypocalcemia (Ca 4.7 mg/dL [our laboratory reference low normal is 8.8 mg/dL], ionized Ca 0.65 mmol/L [reference low normal 1.0 mmol/L], hypomagnesemia (Mg 1.3 mg/dL [reference low normal 1.6 mg/dL], and missed medication doses [valproic acid level undetectable]). She was restarted on valproic acid. Computed tomography (CT) of her head at the time demonstrated basal ganglia calcifications.

The patient was evaluated by endocrinology and treated for hypoparathyroidism. She had a normal fluorescence in situ hybridization study for DiGeorge syndromes I and II. A chromosomal microarray (CombiSNP Array by CombiMatrix) showed no diagnostic copy number changes. A calcium-sensing receptor full gene analysis was ordered by her endocrinologist and showed a heterozygous sequence change detected at exon 7, DNA change c.2363T>G, and amino acid change p.Phe788Cys (p.F788C). This particular variant has been previously reported in a family with suspected autosomal dominant hypocalcemia, the variant was shown to cosegregate with disease, and functional studies have indicated that this missense variant confers a gain-of-function effect on the calcium-sensing receptor.[8,9] All in all, this result was reported consistent with a diagnosis of autosomal dominant hypocalcemia. Family history was pertinent for a paternal aunt with seizures—the type and etiology were not known. Our patient remains on calcium and magnesium supplementation and is followed by endocrinology.

She continued to have daily nonconvulsive seizures consisting of eye-rolling and eyelid fluttering. She was followed for several years by outside neurology group, and over the years, she was treated with lamotrigine, levetiracetam, and clorazepate. When she was 10 years old, she was monitored in our epilepsy monitoring unit, and had multiple eyelid fluttering episodes that were not associated with EEG changes; however, she continued to have interictal generalized epileptiform discharges not associated with clinical change. She was continued on medication.

When she was 13 years old, she had a 48-hour ambulatory EEG, which was normal. She had multiple events that were associated with muscle artifact but no epileptiform discharges.

She returned to our facility a few months later, at which time she was taking valproic acid, levetiracetam, and clorazepate. She continued to have multiple eyelid fluttering episodes daily. She was again evaluated in the epilepsy monitoring unit. At that time, she had multiple push-button events for eyelid fluttering with a normal EEG. She was weaned off of valproic acid during that hospitalization and

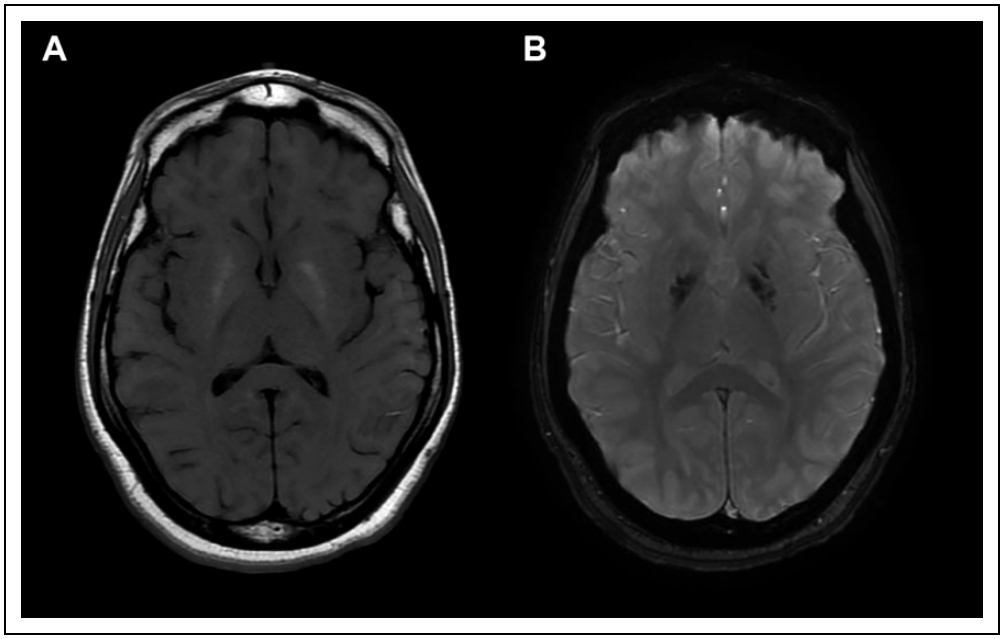


**Figure 3.** Magnetic resonance imaging of our patient's brain showing symmetric T1-hyperintense signal (A) and corresponding decreased susceptibility signal (B) within the globi pallidi bilaterally.

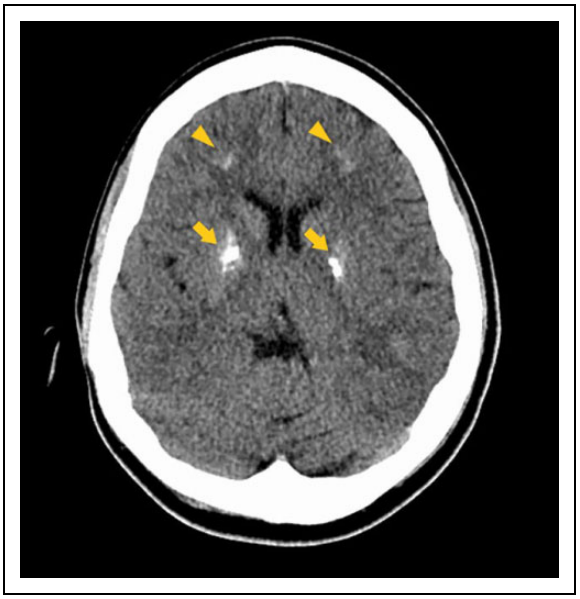

**Figure 4.** Computed tomography of our patient's brain showing dense calcification in the bilateral globi pallidi (arrows) and subtle calcification (arrowheads) in the bilateral frontal white matter.

has remained off of this medication. She had a brain magnetic resonance imaging during that hospitalization that showed T1-hyperintense signal and decreased susceptibility signal within the globi pallidi bilaterally in a symmetric pattern and a head CT that showed moderate progression of calcifications in the bilateral globi pallidi and the subcortical white matter of both frontal lobes when compared with the prior CT done at age 5 years (Figures 3 and 4). Neuropsychological testing supported a diagnosis of intellectual disability with a full-scale intelligence quotient of 45 as well as impaired adaptive functioning. Within the context of her intellectual disability, her expressive and receptive language skills were also impaired. Additionally, she was diagnosed with an impulse control disorder and started following with psychiatry.

Two months after her hospitalization, she was reevaluated in clinic and was weaned off of clorazepate. Three months later, she had a 24-hour ambulatory EEG, which was normal, and she was weaned off of levetiracetam. She had a repeat EEG 4 months after coming off of all medications, which showed generalized epileptiform discharges; a photoparoxysmal response which did not change even after using a blue filter; and 2 episodes of eyelid flutter associated with generalized epileptiform discharges suspicious for generalized nonconvulsive seizures. She was restarted on levetiracetam and remains on this medication. Most recently, an EEG was repeated after reinitiating levetiracetam and continues to show generalized epileptiform discharges, some of which were induced by eye closure and a generalized photoparoxysmal response.

## Discussion

A genetic epilepsy syndrome associated with mutations in the extracellular calcium-sensing receptor gene has been previously described in a single family from South India, but these individuals lacked the serum electrolyte abnormalities seen in our patient and seemed to have a less severe phenotype.[6] Genetic linkage analysis in this previously reported family revealed a preserved calcium-sensing receptor missense mutation leading to a single amino acid substitution: Arg898Gln.[6] Since the above publication, we now know that the Arg898 residue is part of an

arginine-rich region in the proximal carboxyl terminus of the calcium-sensing receptor gene, and disruption of this region results in increased release of the receptor from the endoplasmic reticulum for allocation to the cellular surface.[10] Gain-of-function mutations such as this are associated with autosomal dominant hypocalcemia. Similarly, the gene mutation found in our patient (Phe788Cys) was previously shown to cosegregate with disease, and functional studies have indicated that this missense variant confers a gain-of-function effect on calcium-sensing receptor.[8,9] Therefore, our patient could be considered the archetypal child with both autosomal dominant hypocalcemia and epilepsy as a result of her pathogenic mutation in calcium-sensing receptor.

Case reports of various mutations in the calcium-sensing receptor gene leading to endocrinopathy and more recently this type of genetic epilepsy have spurred further interest in the study of the receptor. Investigators have isolated calcium-sensing receptor protein in normal human brain cortices and hippocampi as well as in central nervous system tumors.[6,11,12] Although formal localization of calcium-sensing receptor by immunohistochemistry in human neuronal synapses is lacking, animal studies have identified the receptor at nerve terminals and have yielded pathophysiologic evidence for its role in neurotransmission, synaptic plasticity, neuronal migration and cell growth, glial function, and response to nervous tissue injury.[2,13] Thus, the susceptibility for epilepsy in this previously well-known endocrinopathy builds on a framework of our emerging understanding of the altered cell surface signaling mechanisms involving calcium-sensing receptor in the central nervous system.

The occurrence of clinical seizures appears independent of the serum calcium level.[9,10,13–16] For instance, a similar previously reported gain-of-function calcium-sensing receptor mutation (Phe788Cys) was found in a Japanese family diagnosed with autosomal dominant hypocalcemia in which multiple family members experienced seizures.[9] Certain members with the genetic defect and evidence of severe hypocalcemia were not reported to have seizures. However, electrophysiological data were lacking and may reveal nonconvulsive seizures and abnormalities with activation procedures as noted in our patient. Furthermore, the dissociation between the severity or frequency of clinical seizures and calcium homeostasis in patients with autosomal dominant hypocalcemia may be nuanced by several factors: the regional physiologic changes in the brain that lead to calcium–phosphorus complex formation, the temporal accumulation of these calcifications, and the likelihood of other genetic and metabolic contributors to epileptogenesis. Likewise, others have purported that the effect of calcium-sensing receptor for epilepsy phenotypes is tissue-specific.[6] The precise neuronal pathways involved are yet to be determined, but they are likely complex and widespread given the clinical seizure semiology and the ubiquitous distribution of calcium-sensing receptor in the central nervous system.

Patients with autosomal dominant hypocalcemia from a calcium-sensing receptor gain-of-function mutation classically exhibit the biochemical profile of hypocalcemia, hypercalciuria, and hypoparathyroidism which may be difficult to distinguish from parathyroid hormone–deficient hypoparathyroidism. As endocrinologists may indicate, the electrolyte abnormalities seen in autosomal dominant hypocalcemia patients may respond minimally to oral calcium and vitamin D3 supplementation, and in some cases, clinical symptoms magnify in the pursuit of normalizing hypocalcemia with these supplements.[7] Therefore, judicious use of calcium and vitamin D3 supplementation has been suggested, and involving an endocrinologist in the care of these patients is essential.[7] It has yet to be determined whether mineral or vitamin supplementation, dietary modification, diuretics, calcium channel blockers, or parathyroid hormone replacement will modulate seizure burden. Future study into the mechanism of this disease process and associated epileptogenesis may guide targeted therapy.

## Author Contributions

GCR and ALP drafted the manuscript. All authors contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

## Declaration of Conflicting Interests

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## Ethical Approval

This case report and review of the related literature follows the recommendations set forth by the University of Tennessee Health Science Center for the conduct, reporting, editing, and publication of scholarly work in medical journals. Written consent from the Institutional Review Board was deferred per our institution's guidelines.

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