Two Children with Early-Onset Strokes and Intractable Epilepsy, Both with CACNA1A Mutations

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Abstract
Background: Mutations in the CACNA1A gene have been associated phenotypically with Familial Hemiplegic Migraine Type 1, Episodic Ataxia Type 2, Idiopathic Generalized Epilepsy, and Developmental and Epileptic Encephalopathy 42. Only six cases have linked ischemic strokes to mutations in the CACNA1A gene. Summary of Cases: We describe two unrelated patients who were found to have different mutations of the CACNA1A gene, one being a novel mutation, as shown by whole exome sequencing. One presented with seizures at birth and the other with seizures at 17 months old, both eventually exhibiting intractable epilepsy, ischemic stroke, and developmental delays. Results: Whole exome sequencing demonstrated de novo pathogenic mutations in the CACNA1A gene, which both caused similar phenotypes in unrelated patients. Conclusion: Pediatric patients who present with ischemic stroke and a history of seizures should be evaluated for CACNA1A mutations, as prompt recognition can help providers facilitate appropriate medical management.

Keywords
epilepsy, genetics, mutation, refractory, seizures, status epilepticus, stroke, magnetic resonance imaging

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Introduction
The CACNA1A gene (OMIM #601011) found on chromosome 19p13.13 encodes the a1 pore-forming subunit of the Cav2.1 (P/Q-type) voltage-gated calcium channel.¹,² Calcium channels play an important role in neurotransmission, muscle contraction, and gene expression, among other things. Prior research has demonstrated that the CACNA1A gene plays a critical role in neonatal survival and that mRNA expression of the CACNA1A gene is transcribed maximally from birth to age 20, then continually declines in production until age 50 when the levels plateau.³ Mutations in the CACNA1A gene can lead to multiple phenotypic presentations, some of which have yet to be fully elucidated. Perhaps best characterized is episodic ataxia type 2 (EA2, OMIM #108500), which involves recurring episodes of ataxia, vertigo, and nystagmus caused by loss-of-function mutations in the CACNA1A gene.²,⁴ Gain-of-function mutations in the CACNA1A gene are associated with Familial Hemiplegic Migraine Type 1 (FHM1, OMIM #141500), a migraine disorder associated with ictal hemiparesis.⁵,⁶ Other associated phenotypes include Developmental and Epileptic Encephalopathy 42 (DEE42, OMIM #617106), a condition characterized by multiple seizure types in the neonatal period with subsequent global developmental delay and severe intellectual disability, as well as idiopathic generalized epilepsy (IGE).⁷ To date, only six cases of a pathogenic CACNA1A variant associated with strokes in pediatric populations have been described in the literature.⁸⁻¹¹ We report the cases of two young girls with pathogenic CACNA1A gene variants that have not been previously associated with strokes in literature. The first patient we

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describe presented with seizures in the setting of an acute cerebral infarction. The second patient we describe presented with seizure and was found to have periventricular leukomalacia secondary to ischemic insult, with subsequent development of hydrocephalus ex vacuo and white matter volume loss. These cases are presented with the intention of further expanding the phenotypic associations of CACNA1A, specifically as it pertains to ischemic injury, as well as providing further evidence for the utility of verapamil in the treatment of the cerebrovascular complications involved with this gene mutation.

Case Presentations

Patient 1

Our first patient is a now 13-year-old female born to non-consanguineous parents with a family history of migraines in her mother. She was born at 38 weeks, 4 days, and experienced neonatal myoclonus immediately after birth. She was admitted to the Neonatal Intensive Care Unit (NICU), where she was loaded with 20mg/kg of phenobarbital and the seizures ceased. She stayed in the NICU for 1 week and then continued on levetiracetam for 4 months. She was clinically seizure free and did not require further anti-epileptic medications until 2 years of age, when she presented to the Emergency Department (ED) in status epilepticus (SE). This seizure was characterized by whole-body weakness, eye deviation superiorly and to the left with blank staring, and unresponsiveness. She was given midazolam and lorazepam with minimal response. Eventually she was given IV phenobarbital and the seizures were controlled. At this time, her electroencephalogram (EEG) demonstrated background slowing. From ages 2 to 5 years old, she continued to have refractory seizures, many of which required PICU admission and intubation for SE. Over these 3 years her seizures became polymorphic and included focal to secondarily generalized seizures, generalized tonic-clonic seizures, and tonic seizures. Multiple EEGs were performed, all after clinical seizures were observed and treated, and all demonstrated excessive beta activity consistent with pharmacologic interventions. Although most of the patient’s seizures during this time seemed to be unprovoked, one seizure at age 27 months was thought to be triggered by a fever, while two others at ages 3 and 4 years old were associated with minor head traumas. During this period between ages 2 and 5 years old, she also developed cognitive and developmental delays and ataxia, all of which were absent in her prior medical records. At the age of 5 years old, she had yet another episode of SE with residual right-sided weakness. An EEG at this time demonstrated slowing in the left hemisphere with sharp and frequent left parieto-occipital epileptiform activity. Magnetic Resonance Imaging (MRI) of the brain at that time demonstrated an acute ischemic cerebrovascular accident involving the left occipital lobe, without much underlying cytotoxic edema as expected for a stroke or seizure. Brain MRA of the Circle of Willis and the carotid arteries at this time was normal. At the age of 7 years, the patient had another seizure and brain MRI showed subtle restricted diffusion involving the right occipital cortex, indicative of an acute ischemic cerebrovascular accident (Figure 1). EEG at this time demonstrated generalized slowing and excessive beta activity, consistent with pharmacologic intervention. Brain MRA at that time showed unremarkable intracranial arterial anatomy at this time as well. Most recently, at the age of 11 years, the patient presented to the ED with sudden-onset right sided weakness after a seizure, and brain MRI demonstrated acute ischemic cerebrovascular accident (Figure 2). EEG at this time demonstrated moderate to severe background slowing, slowing of the left hemisphere more prominently in the temporal and occipital areas, and multiple subclinical focal seizures in the left temporo-occipital area with rare extension to the frontal electrodes. The patient remained in the hospital and eventually returned to her baseline strength prior to discharge, despite the significant ischemia shown on MRI. A follow up brain MRI was completed one month later demonstrated mild residual T2 FLAIR hyperintensities consistent with a late subacute cortical infarct (Figure 3). To prevent ischemic infarcts with

![Figure 1. Cerebral MRI images of Patient 1 at age 7 years old. DWI (Figure 1A), ADC (Figure 1B), and T2 FLAIR (Figure 1C) images demonstrate subtle restricted diffusion involving the right occipital cortex and the immediately subjacent subcortical white matter, consistent with an acute ischemic cerebrovascular accident.](image-url)
future episodes of SE, the patient was started on Verapamil 0.2–0.3mg/kg/day divided into three doses daily and has not had a recurrence of cerebrovascular accidents to date.

**Patient 2**

Our second patient is a now 10-year-old female born to non-consanguineous parents with a non-contributory family history. She was born at 33 weeks due to precipitous labor complicated by chorioamnionitis and required a 1-month NICU stay, although she did not have intraventricular hemorrhage or retinopathy at that time. Per the patient’s records, she developed neurotypically for her first 17 months of life when age-adjusted. The patient first presented to the ED at 17 months old in SE for 90 minutes. This seizure began with the patient going limp, then the eyes deviated to the left, the jaw clenched, and the entire body became stiff. At that time, the patient’s Head Computed Tomography (CT) was normal, but brain MRI showed periventricular leukoencephalopathy and EEG showed excessive beta artifact and background slowing. The following day, she developed right sided twitching and left sided hemiplegia and facial droop, and another brain MRI was performed that showed possible new subtle parietal lobe restriction diffusion that was thought to reflect acute ischemia, with stable periventricular leukomalacia. The brain MRA done at that time was unremarkable. A follow-up EEG at this time demonstrated right hemispheric slowing. For 5 days after the onset of these symptoms, our patient experienced left sided hemiplegia, although it improved daily with steroids. She had a third brain MRI performed during this hospitalization which remained stable, and a follow up EEG demonstrated a symmetric background that had improved from the prior EEG studies. Five months after the aforementioned hospitalization, at 23 months old, she was hospitalized for seizures in the setting of fever and required intubation. An EEG at that time demonstrated asymmetry with moderately high voltage, left hemispheric slowing compared to the right without any epileptiform discharges seen. From then on, she continued to have refractory seizures that often required an endotracheal tube to stabilize the airway. One of these seizures was captured on EEG at 25 months old, which demonstrated recurrent left frontal epileptiform discharges and an electrographic seizure originating from the left hemisphere. Of note, these seizures did not respond to

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**Figure 2.** Cerebral MRI images of Patient 1 at age 11 years old. DWI (Figures 2A, 2B), ADC (Figures 2C, 2D), and T2 FLAIR (Figure 2E) images demonstrate signal abnormalities in the left temporal, parietal, frontal, and lateral occipital lobes, consistent with acute or subacute ischemia.
midazolam, lorazepam, fosphenytoin, or levetiracetam. She also began to experience developmental regression and progressive neurologic decline. At the age of 4 years old, she had a follow up brain MRI performed which was stable from prior imaging and continued to show evidence of periventricular leukomalacia (Figure 4). She then transferred care for the following 2 years and not all records were able to be obtained. From the records that were received, at age 5 years she experienced an 18-hour episode of SE with a subsequent brain MRI performed at that time demonstrating T2/Flair white matter hyperintensity with diffuse bilateral diffusion restriction. After this event she developed choreiform movements and oculogyric crisis. One month later a follow up brain MRI demonstrated volume loss and encephalomalacia in addition to the diffusion restriction and white matter hyperintensities. Yet another month later, two months after the 18-hour episode of SE, she returned to our practice and had another brain MRI performed which confirmed she had marked supratentorial white matter volume loss, encephalomalacia, and associated ex vacuo dilatation of the ventricular system, particularly posteriorly (Figure 5). At that time her EEG showed left-sided slowing. The following year, at age 6 years old, the patient had an EEG performed to evaluate new-onset myoclonic jerks. This EEG demonstrated generalized slowing of the background, 1 sharp-slow complex that was not associated with a clinical event, and a higher voltage sharp-slow complex centered in the bifrontal region and associated with a myoclonic jerk. At age 7 years, she had another EEG done which demonstrated frequent bursts of interictal, generalized, anterior predominant or right hemisphere spike- and polyspike-and-wave discharges which occurred singly or in clusters. At 8 years old, following another episode of SE where the patient was found unresponsive, the patient underwent another brain MRI which showed T2 hyperintensities in patchy areas of cortex (Figure 6). EEG at this time demonstrated high

**Figure 3.** Cerebral T2 FLAIR MRI of Patient 1 at age 11 years old, 1 month after the CVA identified in Figure 2. Findings are consistent with late subacute cortical infarcts in the left temporo-occipital and parietal lobes and correspond to areas of diffusion restriction seen in Figure 2.

**Figure 4.** Cerebral T2 FLAIR MRI of Patient 2 at the age of 4 years old demonstrates biparietal periventricular white matter T2 hyperintensity consistent with leukencephalopathy from prior ischemic/hypoxic insult.

**Figure 5.** Cerebral T2 FLAIR MRI of Patient 2 at age 5 years old demonstrates marked supratentorial white matter volume loss, encephalomalacia, and associated ex vacuo dilatation of the ventricular system, particularly posteriorly.
amplitude generalized delta waves with multifocal spikes, as well as excessive beta activity. At age 9 years, the patient presented to the ED with sudden onset right sided weakness and a right sided facial droop. Brain MRI demonstrated continued, chronic hydrocephalus without acute cerebrovascular injury (Figure 7). At this time, the patient was started on Verapamil 0.2–0.3mg/kg/day divided into three doses daily and like Patient 1, has not had another episode of cerebrovascular ischemia to date.

Diagnostic Work-Up and Genetics

Patient 1

Diagnostic work-Up. Extensive diagnostic workup was pursued throughout the patient’s course of treatment. These tests included serum acylcarnitine, ceruloplasmin, CRP, pyruvic acid, and vitamin D levels; cerebrospinal fluid lactic acid, cysticercosis antibodies, and amino acids; and genetic anomalies including mitochondrial disorders, Factor V Leiden genetic mutation, prothrombin time gene mutations, an epilepsy gene panel, a female febrile epilepsy panel, an SCN1A large deletion/duplication test, and chromosomal microarray, all of which were negative. A cardiac workup was also performed and was negative. It was determined that our patient has two polymorphisms on the SCN1A and SCN1B gene, specifically 3199 A > G and 629 T > C respectively. These polymorphisms have been observed in healthy individuals and have not been associated with disease. The other atypical finding in our patient is that she is compound heterozygous for the polymorphism C677T and A1298C in the MTHFR gene. These polymorphisms have been associated with hyperhomocysteinemia, although our patient’s homocysteine levels were within normal limits.

Genetic findings. To find a definitive etiology for this patient’s seizures and abnormalities on brain MRI, a trio whole exome sequencing (XomeDxPlus test with GeneDX) was performed. Her exome sequencing identified a heterozygous de novo variant, c.2137 G > A (p.A713T) in exon 17 in the CACNA1A gene (NM_001127221.1).

Patient 2

Diagnostic work-Up. Similar to patient 1, an extensive diagnostic workup was pursued throughout the patient’s course of treatment with no definitive answers. This included serum acylcarnitine, carnitine, lactate, pyruvate, and coccidioides titers;
cerebrospinal fluid lactate, anti-NMDA antibodies, anti-VGKC receptor antibodies, and amino acids; urine amino acids; and chromosomal microarray. Additionally, a cardiac workup was performed and was negative.

**Genetic findings.** After the 18-hour SE episode, a trio whole exome sequencing was ordered for the patient. Her exome sequence identified a *de novo* pathogenic gene variant, c.4015 T>C (p.C1369R) in the *CACNA1A* gene (NM_001127221.1).

**Discussion**

We describe two young girls who each have a pathogenic mutation in the *CACNA1A* gene. The first had a heterozygous, *de novo* variant, c.2137 G>A (p.A713T) which presented phenotypically as developmental delays, recurring status epilepticus, and cerebral infarctions related to seizure episodes. The second had a heterozygous, *de novo*, pathogenic variant, c.4015 T>C (p.C1369R) in the *CACNA1A* gene which manifested as developmental delays, recurrent refractory seizures, and recurring episodes of hemiplegia related to encephalomalacia and worsening hydrocephalus *ex vacuo*.

As genetic testing continues to rapidly evolve and as it becomes more widely available to patients, our understanding of the genetic basis of diseases has also rapidly expanded. Mutations in the *CACNA1A* gene can result in numerous different pathologies as described earlier, and there are countless different point mutations that have been implicated. In fact, of all genes in the human genome, the *CACNA1A* gene is within the top 2% of the most intolerant genes. The specific variant seen in Patient 1 (c.2137 G>A (p.A713T)) is a recurrent, gain-of-function variant that affects the transmembrane S6 segment of Domain II. Whole cell recording studies indicate that this mutation in the pore-forming subunit of the Ca_{2.1} channel results in facilitated current activation, slowed current inactivation, and a hyperpolarized shift. Clinically, this variant presents with severe intellectual disability and status epilepticus, with a vast spectrum of other possible clinical findings. For example, this mutation was described by Le Roux et al in 4 separate patients, all of whom experienced severe global developmental delays, intellectual disability, status epilepticus, episodes of sudden-onset hemiplegia, pyramidal signs, and paroxysmal ataxia. However, there were differences among the patients as well. Two were diagnosed with Lennox-Gastaut Syndrome, two were diagnosed with Autism Spectrum Disorder, and two developed progressive cerebellar and cerebral atrophy; one experienced nystagmus, one experienced paroxysmal tonic up-gaze, and one experienced a gaze-evoked nystagmus. This mutation was also described in 2 patients by Zhang et al, both of whom experienced early infantile epileptic encephalopathy (EIIE). In a study done by the Epi4K consortium, two patients were found to have this mutation and both experienced convulsive status epilepticus, severe intellectual disability, and early onset epileptic encephalopathy (EOEE). Lastly, in a study by Jiang et al, another patient was found to have this mutation and presented with Lennox-Gastaut syndrome, severe intellectual disability, hyperreflexia, ataxia, and tremors.

The specific mutation seen in Patient 2 (c.4015 T>C (p.C1369R)) is novel to our knowledge. However, in 2007 Thomsen et al described four family members in Denmark who experienced Familial Hemiplegic Migraine, three of whom were found to have a C1369Y mutation. Interestingly, the fourth affected family member was not found to have this mutation. Of note, this is a different variant of the same residue as our second patient. Additionally, Geerlings et al reported a patient with the same variant as the Danish patients (C1369Y, also named C1370Y due to differences in nomenclature) who presented clinically with a tremor of the head and hands, primary generalized epilepsy, cerebellar atrophy, and migraine without aura. Our patient’s particular variant is predicted to damage the protein structure and function based on *in silico* analysis, but more studies need to be performed to further characterize the functional alterations of this mutation.

Other variants of *CACNA1A* gene mutations have been associated with childhood strokes, but this is the first report of strokes associated with either the A713T mutation or the C1369R mutation. Knierim et al first described a 6-year-old female with a heterozygous, spontaneous, dominant variant, c.4046G>A (p.R1349Q) in the *CACNA1A* gene. She presented with significant ischemic injury after a head trauma at the age of 3.5 years. This same variant was later seen in children with strokes as reported by Ho et al and Le Roux et al. The next patient described in literature was a 4-year-old girl who was found to have a heterozygous, *de novo* variant, c.5075T>A (p.L1692Q) in the *CACNA1A* gene. She presented with ischemic injury secondary to fever as young as 6 weeks old. More recently, Le Roux et al reported 3 unrelated children who had recurrent ischemic strokes, one with a *de novo* variant c.5083G>C, one with a paternal inherited variant c.2815_2816del, and one with the aforementioned *de novo* variant c.4046G>A.

Treatment of ischemic and hypoperfusion episodes related to mutations in the *CACNA1A* gene appear to be on the horizon. Verapamil is a non-dihydropyridine calcium channel blocker that works by inhibiting the influx of calcium ions via voltage-sensitive calcium channels in the vascular smooth muscle and myocardium. It is primarily used in the pediatric population for the treatment of supraventricular tachycardia, but in adult populations it is primarily used as an anti-hypertensive agent, and as a class, calcium channel blockers have been shown to reduce the risk of stroke in hypertensive populations. Verapamil can also be used off-label for prevention of migraines, cluster headaches, and hemiplegic migraines, and is often used by neuro-interventionalists for the treatment of cerebral vasospasm. Verapamil was successfully used in an episode of stroke after head trauma and seizures in the patient described by Knierim et al. In fact, many of the reported cases of ischemic injury associated with this gene mutation have been treated with verapamil with either unchanged or improved clinical outcomes (including our own, whom were treated with 0.2-0.3mg/kg/day divided into three doses daily). Looking at the functional aberration of the Ca_{2.1} channel in Patient 1 specifically, it logically
follows that treating a hyperpolarized channel that exhibits facilitated current activation with an agent that attenuates calcium influx would improve clinical response. Additional studies are needed to further characterize the effects of Verapamil in these patients’ clinical courses.

To properly treat this condition and prevent or minimize adverse long-term outcomes, diagnostic testing must first confirm the genetic mutation. Clinical incorporation of whole exome sequencing (WES) is still a relatively new practice. As such, many patients never receive WES despite puzzling clinical presentations. Correctly diagnosing CACNA1A gene mutations can help guide clinical decision making when treating patients with many of the various phenotypes, including hemiplegic migraine and ischemic strokes alike. In children with stroke-like events and a history of intractable seizures, we posit that genetic testing, specifically WES, is a rational test to consider aiding in diagnosis, especially as we find treatments to manage complications specific to this mutation.

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Ethical Approval

We obtained written consent from the parents of the children, including informed consent to report the individual cases and to publish the MRI images. As a retrospective case study, we did not need an IRB protocol at our institution.

Declaration of Conflicting Interests

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Not applicable, because this article does not contain any clinical trials.

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