

# Case report of novel *CACNA1A* gene mutation causing episodic ataxia type 2

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## Abstract

**Background:** Episodic ataxia type 2 (OMIM 108500) is an autosomal dominant channelopathy characterized by paroxysms of ataxia, vertigo, nausea, and other neurologic symptoms. More than 50 mutations of the *CACNA1A* gene have been discovered in families with episodic ataxia type 2, although 30%–50% of all patients with typical episodic ataxia type 2 phenotype have no detectable mutation of the *CACNA1A* gene.

**Case:** A 46-year-old Caucasian man, with a long history of bouts of imbalance, vertigo, and nausea, presented to our hospital with 2 weeks of ataxia and headache. Subsequent evaluation revealed a novel mutation in the *CACNA1A* gene: c.1364 G > A Arg455Gln. Acetazolamide was initiated with symptomatic improvement.

**Conclusion:** This case report expands the list of known *CACNA1A* mutations associated with episodic ataxia type 2.

## Keywords

neurology, episodic ataxia, *CACNA1A*

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## Introduction

Episodic ataxia type 2 (EA2) is an autosomal dominant channelopathy characterized by paroxysms of ataxia, vertigo, nausea, and occasionally diplopia, tinnitus, dystonia, hemiplegia, and migraine.<sup>1,2</sup> The typical onset is in childhood and adolescence.<sup>1</sup> Attacks persist for minutes (usually more than 10 min)<sup>3</sup> or days and can be precipitated by stress, exertion, caffeine, and alcohol.<sup>1</sup>

Of the seven subtypes of episodic ataxia so far described, EA2 is the most prevalent.<sup>4</sup> EA2 is allelic with spinocerebellar ataxia 6 (SCA6) and familial hemiplegic migraine, all involving mutations of the *CACNA1A* gene on chromosome 19p13, which encodes Cav2.1, the pore-forming alpha-1 subunit of the P/Q-type voltage-gated calcium channel.<sup>1,5</sup> More than 50 mutations have been discovered in families with EA2, the majority involving a truncation mutation, although missense mutations have also been reported.<sup>5–7</sup> We report a patient with a novel missense mutation in *CACNA1A* presenting with a phenotype consistent with episodic ataxia.

## Case study

A 46-year-old Caucasian man with no medical history developed worsening headache, diplopia, and difficulty with ambulation over 2 weeks. The headache was holocephalic

but with left frontal predominance and was associated with mild photophobia but no phonophobia or nausea.

The patient was evaluated by an ophthalmologist, who detected no intra-ocular pathology, and a neurologist, who noted “extraocular movement abnormalities,” as well as significant truncal and appendicular ataxia. Brain magnetic resonance imaging (MRI) was reportedly normal, and he was given a 3-day course of prednisone. While on prednisone, the headache, horizontal diplopia, and incoordination all improved; however, within days of completion, his neurologic syndrome reemerged with the addition of tinnitus and bradyphrenia. No infectious symptoms occurred during or prior to presentation. His medications were fish oil and omeprazole.

Two weeks after symptom-onset, the patient presented to our institution. Examination demonstrated bilaterally impaired upgaze with intact downgaze, limitation of left eye adduction, mild ataxic dysarthria, and significant axial and appendicular ataxia involving all limbs. Unremarkable laboratory testing

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included complete metabolic profile, complete blood count, C-reactive protein, erythrocyte sedimentation rate, thyroid function studies, Vitamin B12, folic acid, HIV (human immunodeficiency virus), and serum aquaporin-4 antibody. Due to concern for an inflammatory process, a lumbar puncture was performed, revealing normal cell counts and glucose, mildly elevated protein (71 mg/dL), absent oligoclonal bands, normal IgG index (0.66), negative HSV (herpes simplex virus) and VZV (varicella zoster virus) polymerase chain reactions (PCRs), negative Gram stain and culture, normal angiotensin converting enzyme level (12 U/L), negative aquaporin-4 antibody, and flow cytometry with no abnormal cell populations. MRI of brain, orbits, and cervical spine without and with contrast was normal. He was given 3 days of methylprednisolone with improvement in his headache and diplopia.

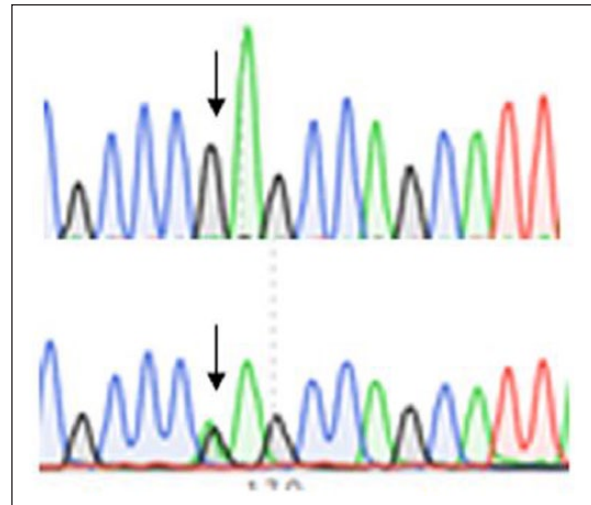
At 1-month follow-up, the patient reported that upon discontinuation of steroids, he suffered several bouts of imbalance, each lasting a few days. Examination demonstrated bilaterally impaired upgaze and minimal gaze-evoked nystagmus but was otherwise normal. Of critical significance, at that time he recalled that, since his teenage years, he had experienced episodes of rapid-onset ataxia with associated vertigo and nausea. The episodes would last a few days to a week and occurred 2–3 times per year. No maternal family members manifested similar symptoms; his paternal family history was unknown. The patient's two children have no neurologic symptoms.

Given this additional history, analysis of the following genes was ordered from Athena diagnostics: *CACNA1A*, *CACNB4*, *KCNA1*, and *SLC1A3*. A novel heterozygous mutation in the *CACNA1A* gene was identified: c.1364 G > A Arg455Gln. The patient's genetic mutation was confirmed at our laboratory with bidirectional Sanger sequencing (Figure 1). This variant was previously identified in the 1000 Genomes Project Phase 3 as rs561858384, with a very low frequency (minor allele frequency (MAF) < 0.01).<sup>8</sup> Such variants identified in population-wide genetic studies often represent incidental findings, with no clear pathological significance. However, in silico analysis using PolyPhen-2 software showed that this missense mutation is probably damaging, with a score of 1.00 (highest possible score);<sup>9</sup> analysis conducted with SIFT software also indicated that the mutation was likely deleterious.<sup>10</sup> We analyzed the patient's mother's DNA; she was not found to have the mutation. His father was unavailable for testing.

Acetazolamide 250 mg twice daily was initiated, with marked reduction in the severity of ataxic episodes, although they still occurred 2–3 times per year and lasted 1 day on average. At his 9-month follow-up appointment, his extraocular movements had normalized, with no pursuit or saccade abnormalities.

## Discussion

As mentioned in the "Introduction" section, more than 50 mutations in *CACNA1A* have been discovered in families



**Figure 1.** Sanger sequence of control and patient DNA: upper panel shows a wild-type (normal) sequence and lower panel shows a heterozygous c.1364 G > A mutation (arrow).

with EA2,<sup>5–7</sup> with pathologic effects primarily attributed to haploinsufficiency.<sup>4</sup> The loss-of-function results in diminished calcium-channel density and reduced calcium currents, causing excessive release of neurotransmitter, predominant symptoms being mainly attributable to overabundant GABA (gamma-aminobutyric acid) in cerebellar Purkinje and granule cells, and acetylcholine at the neuromuscular junction.<sup>6,7</sup> Approximately 30%–50% of all patients with typical EA2 phenotype have no detectable mutation of the *CACNA1A* gene, indicating genotypic heterogeneity.<sup>6</sup> Intra- and inter-familial clinical heterogeneity highlight the lack of genotype-phenotype correlation.<sup>2,6</sup> In the case presented above, our data support that the detected mutation c.1364 G > A Arg455Gln is a disease-causing mutation. The most likely explanation for its prior detection as a rare variant of unknown significance is reduced penetrance of the mutation.

This case report demonstrates several typical, as well as a few atypical, features of EA2 in a patient with a novel *CACNA1A* mutation. While most attacks of EA2 persist only for minutes or days, longer duration episodes, such as our patient experienced on presentation, have previously been reported in genetically confirmed cases (see Patient 7 in Mantuano et al.<sup>7</sup>). It is notable that our patient's prior attacks, though less severe, lasted several days to 1 week; he consistently experienced paroxysms of greater duration than typical for EA2. Attacks can be associated with headache, as in our patient, and at least 50% of patients with EA2 suffer from migraines.<sup>1</sup>

Interictal nystagmus and ataxia are often but not universally present in EA2.<sup>1,2</sup> Additional neuro-ophthalmologic signs include impaired visual tracking, optokinetic nystagmus, and suppression of the vestibulo-ocular reflex, as well as saccadic dysmetria and reduced saccade velocity.<sup>11</sup> Our patient demonstrated impaired upgaze at his follow-up visits, in the absence of ataxia or other neurologic symptoms; interestingly, his eye movements were normal at his 9-month

follow-up, though interictal symptoms often do not respond to acetazolamide. Many patients with EA2 develop progressive interictal ataxia,<sup>3,12</sup> emphasizing the phenotypic overlap with its allelic disorder, SCA6.

Both acetazolamide and 4-aminopyridine reduce the frequency of attacks,<sup>1</sup> and our patient has noted significant improvement on low-dose acetazolamide. It is difficult to interpret our patient's symptomatic improvement following initiation of steroids and decline upon steroid withdrawal. We were unable to find any reports in the literature describing steroid administration as a treatment for EA2.

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### Declaration of conflicting interests

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### Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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### Informed consent

Written informed consent was obtained from the patient for his anonymized information to be published in this article.

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