Ataxia and Diplopia
A New SCN8A-Related Phenotype

Alexandra Laliberté, MSc, RD, and Kenneth A. Myers, MD, PhD, FRCPC

Neurol Genet 2023;9:e200085. doi:10.1212/NXG.0000000000200085

Abstract
Objectives
The objective of this study was to describe the first patient with recurrent ataxia and diplopia in association with a pathogenic variant in SCN8A.

Methods
We identified a girl with a heterozygous SCN8A pathogenic variant and performed thorough phenotyping.

Results
A 10-year-old girl was previously well with normal intelligence. She had recurrent diplopia, dysmetria, and unsteady gait, which occurred only in the context of febrile illnesses. EEG during her initial acute episode showed multifocal epileptiform discharges, with similar findings seen on a follow-up study 3 months later when she was well. Brain MRI finding was normal. A gene panel identified a de novo SCN8A variant, p.Arg847Gln, classified as likely pathogenic. One year after her initial presentation, the girl is well and developmentally normal and has never had an event concerning for seizure.

Discussion
This case presentation demonstrates that SCN8A pathogenic variants should be considered in children with transient ataxia, dysmetria, and diplopia in the context of viral febrile illnesses, even if there is no history of seizures. While there are clinical and molecular data suggesting that SCN8A dysfunction can cause temperature-sensitive phenotypes, further research is necessary to determine how the functional changes caused by our patient’s SCN8A variant result in her unique phenotype.
SCN8A (OMIM 600702) encodes the sodium channel voltage-gated alpha-8 subunit (Na_v1.6) and is widely expressed in the brain. Pathogenic variants in SCN8A are a recognized cause of moderate-to-severe infantile-onset developmental and epileptic encephalopathy, often associated with other neurologic signs, including movement disorders, hypotonia, and ataxia. Other phenotypes have also been reported in association with SCN8A, including self-limited infantile seizures, as well as intellectual disability with movement disorders or ataxia, but no history of seizures. In this study, we describe a girl with a de novo heterozygous SCN8A pathogenic variant, who presented with recurrent ataxia and diplopia in the context of viral febrile illnesses. This report further expands the phenotypic spectrum that may be associated with SCN8A pathogenic variants.

**Patient Description**

A 10-year-old girl initially presented with a 3-day history of fever, sore throat, fatigue, diplopia, dysmetria, and unsteady gait and was found to be influenza A positive. The severity of symptoms fluctuated, directly correlating with fever. Her medical history was unremarkable. She had a history of mild language delay, but was in a normal class at school and considered an average student. Her mother was originally from Cambodia and father was of Vietnamese descent; there was no known consanguinity and no known family history of seizures, ataxia, or other neurologic disorders.

On examination, she had normal growth parameters and was nondysmorphic. On extraocular muscle testing, she had limited abduction of the right eye. Her gait was wide-based and unsteady, and she had bilateral dysmetria. Head CT and MRI findings were both normal. EEG showed frequent-to-abundant focal epileptiform discharges, mostly from the left frontal region in addition to the right frontal and left occipital regions (Figure). The patient’s ataxia and diplopia resolved spontaneously over several days, and she was discharged home.

Two months later, she had fever in association with COVID-19 infection and again developed ataxia, fatigue, and diplopia. These symptoms again worsened with higher fever and improved after antipyretic medication, resolving after 2–3 days, in concert with the illness. EEG was repeated 3 months after her initial presentation, while asymptomatic, and showed occasional-to-abundant focal spikes, most commonly over the left occipital region but also over the right occipital region. Her development remained as per baseline, and the ataxia and other symptoms again resolved after the viral illness.

Comparative genomic hybridization microarray was normal, as were plasma amino acids, acylcarnitine profile, and urine organic acids. An autism/intellectual disability gene panel including more than 2,300 genes (GeneDx, Gaithersburg, MD) identified a de novo heterozygous variant in SCN8A (NM014191.3, c.2540G>A, p.Arg847Gln), classified as likely pathogenic by American College of Medical Genetics & Genomics criteria. In silico testing predicts deleterious effects on protein structure and function, and the variant is not present in the Genome Aggregation Database. The patient’s family provided written consent for this publication.

**Discussion**

This case presentation expands the phenotypic spectrum that may be associated with SCN8A pathogenic variants to include transient ataxia, dysmetria, and diplopia in the context of viral febrile illnesses. EEG showed frequent-to-abundant focal epileptiform discharges, mostly from the left frontal region in addition to the right frontal and left occipital regions (Figure). The patient’s ataxia and diplopia resolved spontaneously over several days, and she was discharged home.

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**Figure** EEG at Initial Presentation

On longitudinal bipolar montage in drowsiness, a burst of spike-wave discharges at approximately 3.5 Hz is seen, maximal over the left anterior region, but having broad bilateral field (arrows). Background activity is normal.
febrile illnesses. Notably, the girl has normal intelligence and developmental history. She has no history of seizures, though her EEG showed multifocal interictal epileptiform discharges, and we cannot rule out the possibility that her symptoms reflected postictal phenomena after subtle, unrecognized focal seizures.

Ataxia has been previously described in at least 5 patients with SCN8A pathogenic variants, 4 with de novo heterozygous missense variants,\(^1,3,7\) and 1 with a maternally inherited deletion (Table);\(^5\) however, this case presentation is markedly different. All the previously described patients had significant intellectual disability and developmental impairment, and ataxia was usually stable or progressive, when compared with intermittent with febrile illness in our patient. Three of the previously described patients had cerebellar atrophy on brain MRI.

The pattern of presentation in this patient also suggests that sodium channel dysfunction due to SCN8A pathogenic variants can be temperature sensitive, exacerbated by hyperthermia. This is interesting because, while febrile seizures have been reported in association with SCN8A, such presentations are rare.\(^9\) Studies using mouse models have shown that the Na\(_V\)1.6 subtype is relatively less susceptible to hyperthermia than Na\(_V\)1.2.\(^10\) Functional evaluation of our patient’s SCN8A variant would be helpful in determining how and why it results in a temperature-sensitive, apparently fully reversible, phenotype.

Of interest, the variant in our patient has a known pathogenic paralog in another sodium channel subunit gene. The SCN2A variant, p.Arg853Gln, is one of the most frequent recurrent pathogenic variants identified in SCN2A-related disease. This variant results in decreased neuronal excitability, with clinical phenotype of a later-onset developmental and epileptic encephalopathy with epileptic spasms and moderate-to-severe developmental impairment.\(^11\) Choreoathetosis and/or dysarthria are also frequently reported.\(^11\) The clinical significance of the patient is unclear, but the observation supports the pathogenicity of the SCN8A variant identified in our patient.

### Study Funding
The authors report no targeted funding.

### Disclosure
The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

### Publication History
Received by Neurology: Genetics April 10, 2023. Accepted in final form June 9, 2023. Submitted and externally peer reviewed. The handling editor was Associate Editor Alexandra Durr, MD, PhD.

### Table
Previously Published Patients With Ataxia and SCN8A Pathogenic Variants

<table>
<thead>
<tr>
<th>Ref</th>
<th>Sex</th>
<th>Age</th>
<th>SCN8A variant</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>33 y</td>
<td>c.4351G&gt;A, p.Gly1451Ser</td>
<td>From age 18 mo, generalized seizures. Moderate-to-severe developmental impairment, nystagmus, cerebellar atrophy, and ataxia. At age 29 y, decline in motor function</td>
</tr>
<tr>
<td>Trudeau et al.(^8)</td>
<td>M</td>
<td>9 y</td>
<td>p.Pro1719ArgfsX6</td>
<td>Marked cognitive and motor impairment, cerebellar atrophy, and ataxia</td>
</tr>
<tr>
<td>Wagnon et al.(^3)</td>
<td>M</td>
<td>10 y</td>
<td>c.3652G&gt;A, p.Glu1218Lys</td>
<td>Marked speech and motor impairment, ID, ataxic gait (resolved)</td>
</tr>
<tr>
<td>Veeramah et al.(^1)</td>
<td>F</td>
<td>15 y</td>
<td>c.5302A&gt;G p.Asn1768Asp</td>
<td>From 6 mo, generalized seizures. At age 4 y, epileptic spasms with regression. Hypotonia, ataxia, developmental delay, and ID. SUDEP at age 15 y</td>
</tr>
</tbody>
</table>

Abbreviations: ID = intellectual disability; SUDEP = sudden unexpected death in epilepsy.

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