

## Spinocerebellar Ataxia Type 2 with Focal Epilepsy – An Unusual Association

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### Abstract

**Introduction:** The spinocerebellar ataxias are a rare group of inherited neurodegenerative disorders. Epilepsy has not previously been associated with spinocerebellar ataxia type 2 (SCA2). **Clinical Picture:** We describe a family with 3 affected members who had typical phenotypic and MRI features of SCA2. Two had focal epilepsy with complex partial seizures and epileptiform discharges on electroencephalography. Trinucleotide expansions in the pathological range were found in the SCA2 gene, confirming SCA2. Sequencing of the expanded SCA2 gene did not reveal any new mutations that could account for epilepsy. **Treatment and Outcome:** The focal epilepsy was well-controlled with carbamazepine. **Conclusion:** We hypothesise that the new feature of focal epilepsy is due to co-existence of a separate unlinked epilepsy susceptibility gene with the expanded SCA2 gene. Under this oligogenic model, both genes must be present, and co-inheritance of this susceptibility gene with the expanded SCA2 gene causes a complex interaction which triggers epilepsy.

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**Key words:** Ion channelopathy, Oligogenic model of epilepsy, Polymerase chain reaction, Susceptibility gene, Trinucleotide repeat

### Introduction

The spinocerebellar ataxias (SCAs) are a rare group of neurodegenerative disorders that are clinically and genetically heterogeneous. Almost all SCAs are due to trinucleotide repeat expansions and 16 types of SCAs have been described.<sup>1,2</sup> Cerebellar dysfunction is the universal clinical feature; other associated neurological features include dementia, extrapyramidal signs, peripheral neuropathy, optic atrophy, ophthalmoplegia and slow eye saccades. Epilepsy is not a feature of the SCAs, with the exception of SCA10.<sup>3</sup> We describe a family with genetically proven spinocerebellar ataxia type 2 (SCA2) with the previously undescribed feature of epilepsy.

### Case Report

A 52-year-old Malay man presented with a 3-month history

of complex partial seizures. The seizures consisted of blank stares, lasting for 2 to 3 minutes, during which he was unresponsive. These were sometimes associated with oral automatisms. The seizures became secondarily generalised on one occasion.

He also complained of slow progressive gait unsteadiness for 5 years. His deceased mother, his brother and son also had a history of similar gait difficulties (Fig. 1). His mother and brother had noticed gait difficulties in the fifth decade of life, while his son developed symptoms much earlier at age 13.

The affected son was also noticed to have episodes of blank stares, sometimes associated with blinking, lasting several minutes during which he was unresponsive to calling. These were likely to represent complex partial seizures. No automatisms or secondary generalisation was seen in the affected son.

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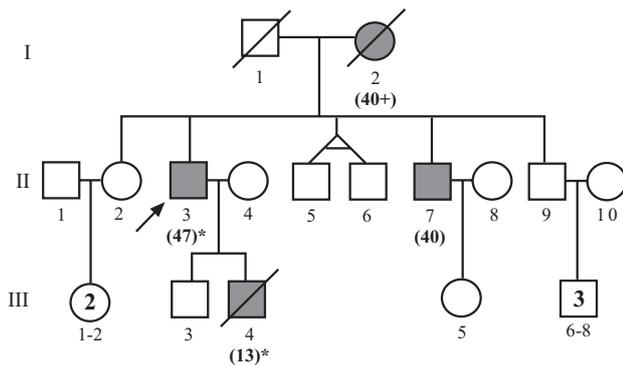


Fig. 1. Pedigree of the family with SCA2, using standard nomenclature.<sup>4</sup> Squares represent males; circles represent females. Roman numerals identify generations, Arabic numerals identify each individual within a generation. Shaded symbols represent affected individuals; symbols with slashes represent deceased individuals. The number within the symbol represents the number of unaffected individuals. The index patient is indicated by an arrow. The age of onset is shown in brackets in a larger boldface font; presence of focal epilepsy indicated by an asterisk. Genomic DNA was obtained from II-2, II-3, II-4, and III-4 for sequencing analysis of their SCA2 gene exons and flanking intronic sequences.

The onset of epilepsy was 4½ years after the onset of ataxia for father and son. There was no other family history of epilepsy. Neither father nor son had prior significant head injury, neurosurgical intervention nor a previous history of febrile convulsions.

On examination, the index patient was found to have marked limb and truncal ataxia and dysarthria. Ocular saccades were distinctly slow. Deep tendon reflexes were absent. There were no dementia, extrapyramidal signs, nor retinal abnormalities. His affected brother showed similar signs. His son was clinically more severely affected; he was dysarthric to the point of anarthria, wheelchair-bound and dependent in his activities of daily living, requiring nasogastric tube feeding.

Thyroid function tests, vitamin E levels and ceruloplasmin were normal. Nerve conduction studies showed an axonal sensorimotor peripheral neuropathy. An electroencephalogram (EEG) of the index patient showed right temporal slowing and right fronto-temporal epileptiform activity (Fig. 2). Genetic studies confirmed the diagnosis of SCA2 with 39 CAG repeats (normal range, 13 to 34) in the SCA2 gene. The brother and the son of the index patient were found to have 37 and 52 repeats respectively, confirming SCA2. An EEG of the affected son showed background slowing, bilateral independent temporal slowing and left temporal epileptiform activity (Fig. 3). The presence of an abnormal background, and absence of centro-temporal, occipital or frontal sharp waves in the EEG made the differential diagnosis of idiopathic partial epilepsy of childhood less likely in the son.

The magnetic resonance imaging (MRI) of the brain of the father (Fig. 4) and son both showed cerebellar and brainstem atrophy. No structural abnormalities were found in either that

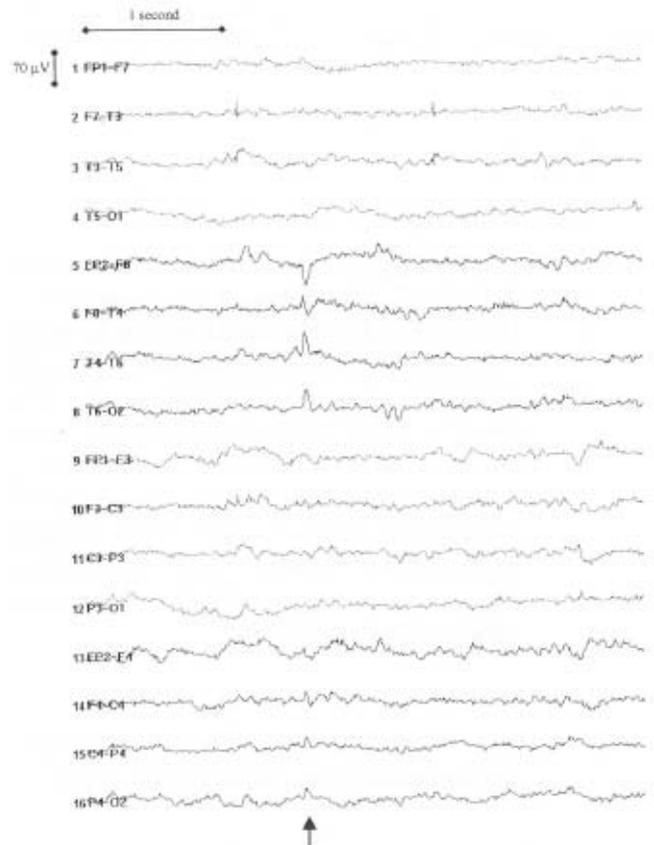


Fig. 2. Electroencephalogram (AP bipolar montage) of the index patient showing right fronto-temporal epileptiform discharges (solid arrow).

could cause epilepsy or the epileptiform EEG findings; in particular, the hippocampi and the temporal lobes were normal on fine coronal sections.

We analysed the SCA2 gene on chromosome 12q24 in the affected index patient, his affected son (partial sequencing), his unaffected wife and his unaffected sister. All 25 exons and flanking genomic DNA sequences were amplified by the polymerase chain reaction (PCR) in 22 separate fragments and sequenced. We identified a total of 11 single nucleotide differences among the 4 samples studied, of which 3 involved an amino acid change. However, none of the differences were observed only in the affected or the unaffected individuals, to account for the new feature of focal epilepsy in the index patient and his similarly-affected son.

The index patient was started on amantidine for ataxia. There was mild functional improvement, but it was stopped when he developed hallucinations and psychosis. He achieved good seizure control with slow-release carbamazepine. Both the index patient and his brother are still alive 2 years after the diagnosis, while the son has passed away from infected bedsores.

## Discussion

The SCAs are trinucleotide repeat disorders, with the exception of SCA10 where a pentanucleotide is involved.<sup>3</sup>

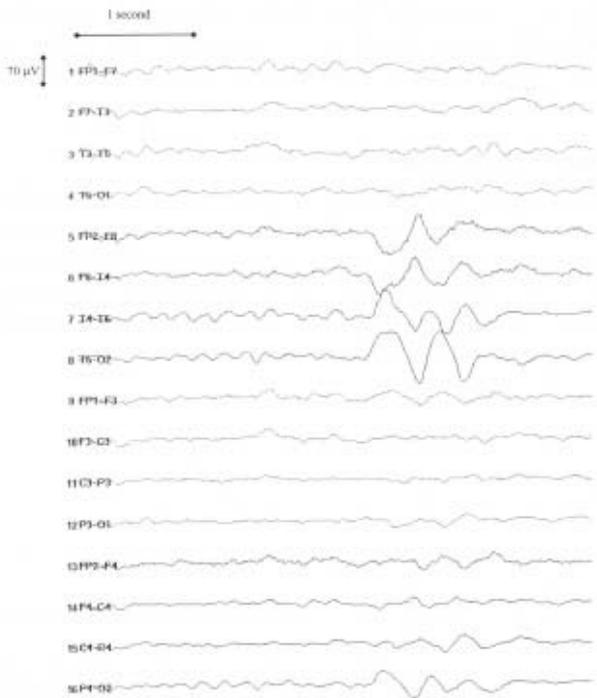


Fig. 3. Electroencephalogram (AP bipolar montage) of the index patient's son showing background slowing and right temporal slowing

Antenatal diagnosis is possible. Our SCA2 family showed phenotypic features consistent with SCA2.<sup>5</sup> They had ataxia, markedly slowed eye saccades and peripheral neuropathy.

The SCAs also exhibit genetic anticipation, where the disease begins earlier with each succeeding generation. Anticipation is due to increasing size of trinucleotide expansions with each generation; all the SCAs, except SCA5, show more dramatic anticipation with paternal transmission.<sup>2</sup> Our family demonstrates this feature clearly – paternal transmission from the index patient to his son resulted in a dramatic increase in repeat size from 39 to 52, resulting in the son becoming symptomatic before even his father or uncle. Maternal transmission from the index patient's mother did not show such marked anticipation. The expanded SCA genes produce ataxins, proteins of unknown function which aggregate in neurons of affected patients to form neuronal intranuclear inclusions (NII). The probability of NII formation increases with the number of repeats.<sup>6</sup> This could account for the phenomenon of anticipation. The exact pathophysiological mechanism by which NIIs cause cellular dysfunction is uncertain, but binding and inactivation of transcription factors by the abnormal proteins has been postulated.<sup>6</sup>

Ataxia and anticipation are core features of the SCAs. Epilepsy, however, is not a feature of the SCA family, except

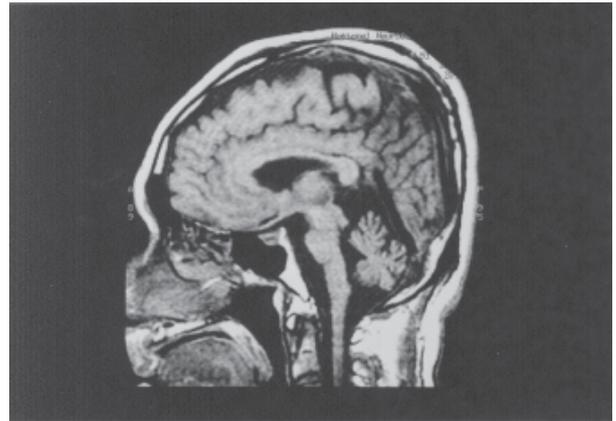


Fig. 4. T1-weighted sagittal MRI brain of the index patient showing marked atrophy of the cerebellum and brainstem.

in SCA10 and a related disorder, dentatorubral-pallidoluysian atrophy (DRPLA).

SCA10, described predominantly in patients of Mexican descent,<sup>7</sup> is distinct from the other SCAs phenotypically because of epilepsy. It is also unusual in that an ATTCT pentanucleotide repeat expansion, and not a trinucleotide repeat, is the genetic culprit.<sup>3</sup> Our family with ataxia and epilepsy however had SCA2, not SCA10.

DRPLA is another trinucleotide repeat neurodegenerative disorder<sup>2</sup> that was considered as a differential diagnosis in this family. It also presents with ataxia and epilepsy. However, choreoathetosis, dementia and myoclonus are also features of DRPLA that were absent in our family. Genetic analysis of the DRPLA locus at chromosome 12p in our family excluded DRPLA.

We had initially hypothesised that a new mutation within the SCA2 gene, besides the known trinucleotide expansion, accounted for the new phenotypic feature of focal epilepsy. Complete sequencing of the SCA2 gene did not yield any consistent differences, besides the trinucleotide expansion, between affected and unaffected members that could explain the epilepsy. It is unlikely that the expanded SCA2 gene alone could account for the epilepsy, as no previously described families with SCA2 have had epilepsy, even at advanced stages of the disease.

Several mutations causing focal epilepsy have been described in the past decade; all except one are ion channel disorders.<sup>8,9</sup> Could one of these known mutations causing epilepsy be linked with the SCA2 gene? We feel this is unlikely; all existing identified genes causing non-progressive epilepsy syndromes are located on other chromosomes and none are on 12q24.

The combination of epilepsy and ataxia could also suggest a channelopathy and mouse models have been described.<sup>10</sup> Rare families and individuals with mutations in the postassium<sup>11</sup> and calcium channels<sup>12</sup> causing epilepsy and ataxia have also been described. However, neither these 2 mutations, nor any of

the other described channelopathies causing neurological dysfunction in humans<sup>13</sup> are close to the SCA2 gene. We therefore feel that a linked channelopathy is less likely in our family.

We postulate, therefore, that there may be a separate unlinked susceptibility gene for focal epilepsy in this family. The susceptibility gene by itself is insufficient to manifest epilepsy and may be a mild non-manifesting mutation in one of the existing ion channels. However, co-inheritance with the expanded SCA2 gene causes a complex interaction which triggers epilepsy. Both genes need to be present to manifest the epilepsy.

Such an oligogenic (as opposed to monogenic) model of epilepsy has recently been proposed as a potential genetic model for generalised epilepsy.<sup>14</sup> Under this hypothesis, the focal epilepsy in the affected son of the index is ascribed to co-inheritance of both the SCA2 gene and the epilepsy-susceptibility gene from his affected father. Likewise, the absence of epilepsy in the SCA2-affected brother of the index is attributed to absence of the epilepsy-susceptibility gene in him. The hypothesis of an epilepsy-susceptibility gene requiring the presence of the expanded SCA2 gene for manifestation is also consistent with the absence of epileptic findings in the other family members without SCA2.

SCA10 is the only other SCA with epilepsy. In 1 study of 2 large families with SCA10, half of the affected patients overall had epilepsy.<sup>3</sup> However, the inter-family frequency of epilepsy in affected individuals was significantly different (80% vs. 25%,  $P = 0.01$ ) between these 2 families. No patients without SCA10 had epilepsy. There was no correlation between the pentanucleotide repeat size and epilepsy, and the mechanism by which the SCA10 mutation leads to epilepsy has yet to be elucidated. The authors concluded that other genetic influences in different families with SCA10 may modify the phenotypic expression of the SCA10 mutation.

This lends support to our hypothesis that a co-inherited epilepsy susceptibility gene, together with an expanded SCA2 gene, can account for the finding of focal epilepsy in only some affected patients with SCA2 in our family. Both genes must be present to cause epilepsy. This susceptibility gene could be a mild non-manifesting mutation in one of the existing ion channels known to cause focal epilepsy, or it could be present in a as-yet undescribed location. Assuming an oligogenic model, locating and identifying this epilepsy susceptibility gene in our family by linkage analysis will be a daunting challenge. Given the small size of our SCA2 family and the small number of affected individuals, as well as the lack of other families with similar findings, it would also be very difficult to validate our hypothesis using existing disease-association strategies.

In conclusion, we describe a family with confirmed SCA2 with the previously undescribed phenotypic feature of focal epilepsy, a feature which had previously been exclusive to SCA10 among all the SCAs. We believe this new feature

reflects the influence of a co-existing epilepsy susceptibility gene on the expanded SCA2 gene. Future clinicians, when confronted with a patient with a spinocerebellar ataxia and focal epilepsy, should consider both SCA10 and SCA2 as possible diagnoses.

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