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Ghahremani Nezhad, H., Franklin, J.P., Alix, J.J.P. [orcid.org/0000-0001-8391-9749](https://orcid.org/0000-0001-8391-9749) et al. (10 more authors) (2020) Simultaneous ALS and SCA2 associated with an intermediate-length ATXN2 CAG-repeat expansion. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*. ISSN 2167-8421

<https://doi.org/10.1080/21678421.2020.1853172>

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# Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: <https://www.tandfonline.com/loi/iafd20>

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To cite this article: Helia Ghahremani Nezhad , John P. Franklin , James J. P. Alix , Tobias Moll , Michael Patrick , Johnathan Cooper-Knock , Priya Shanmugarajah , Nick J. Beauchamp , Marios Hadjivissiliou , David Paling , Christopher Mcdermott , Pamela J. Shaw & Thomas M. Jenkins (2020): Simultaneous ALS and SCA2 associated with an intermediate-length *ATXN2* CAG-repeat expansion, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: [10.1080/21678421.2020.1853172](https://doi.org/10.1080/21678421.2020.1853172)

To link to this article: <https://doi.org/10.1080/21678421.2020.1853172>



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Published online: 07 Dec 2020.



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## SHORT REPORT

## Simultaneous ALS and SCA2 associated with an intermediate-length *ATXN2* CAG-repeat expansion

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### Abstract

Spinocerebellar ataxia type 2 (SCA2) and amyotrophic lateral sclerosis (ALS) share a common molecular basis: both are associated with CAG-repeat expansion of *ATXN2* and TDP-43-positive neuronal cytoplasmic inclusions. To date, the two disorders are viewed as clinically distinct with ALS resulting from 30–33 CAG-repeats and SCA2 from >34 CAG-repeats. We describe a 67-year old with a 32 CAG-repeat expansion of *ATXN2* who presented with simultaneous symptoms of ALS and SCA2. Our case demonstrates that the clinical dichotomy between SCA2 and *ATXN2*-ALS is false. We suggest instead that CAG-repeat expansion length determines the timing of SCA2 clinical symptoms relative to onset of ALS; consistent with this age of onset of SCA2 but not *ATXN2*-ALS, is dependent upon expansion length. Review of the literature and our local cohort provides evidence for occurrence of ALS in late stage SCA2, which may be under-recognised by clinicians who think of the two diseases as distinct.

**Keywords:** Risk, neurophysiology, genetics

### Introduction

Spinocerebellar ataxia type 2 (SCA2), is a neurodegenerative disease primarily of the cerebellum, brainstem and spinal cord, caused by >34 CAG-repeat expansion within *ATXN2*; clinical onset is between childhood and mid-adulthood (1). Amyotrophic lateral sclerosis (ALS) features selective degeneration of motor neurons and typically manifests in late adulthood (2). The genetic basis of ALS is more diverse than SCA2, however ALS is associated with 30–33 CAG-repeat expansions within *ATXN2* (3) although penetrance is incomplete (4) which is consistent with additional genetic and/or environmental modifiers. Age of onset in SCA2 is inversely proportional to expansion length (5) but in ALS it is unrelated (4).

Currently, ALS and SCA2 are considered clinically distinct.

There is evidence that ALS and SCA2 share a common molecular pathway to neuronal toxicity. The pathological hallmark of ALS, including *ATXN2*-ALS (6,7), is TDP-43-positive neuronal cytoplasmic inclusions within motor neurons. Post mortem study of SCA2 reveals identical TDP-43-positive neuronal cytoplasmic inclusions but not within lower motor neurons (8). If the molecular basis for the two diseases is similar, then the strict dichotomy in the clinical presentation between SCA2 and ALS is puzzling because it requires that longer *ATXN2*-expansions should be associated with both amelioration, and increased severity of the same process, in distinct neuronal populations.

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(Received 1 September 2020; revised 26 October 2020; Accepted 15 November 2020)

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DOI: 10.1080/21678421.2020.1853172

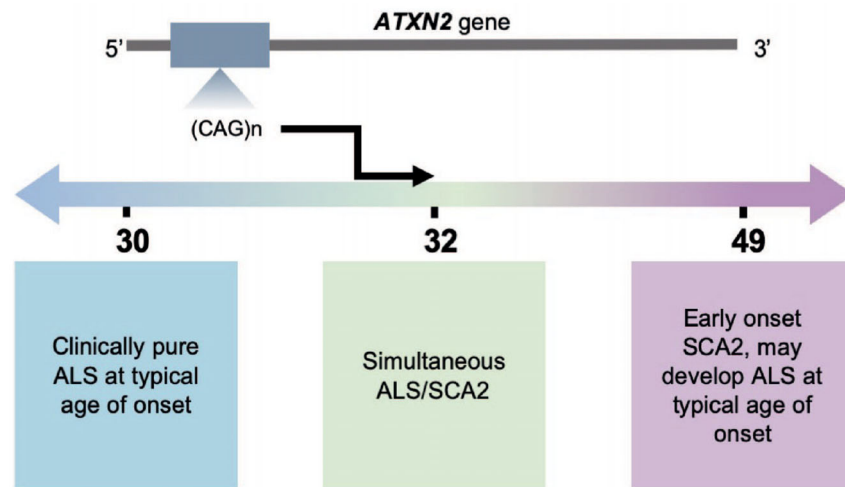


Figure 1. Variability in timing of ALS-symptoms relative to SCA2-symptoms depends on ATXN2-expansion length.

We propose that the true effect of increased expansion length is not on toxicity but in timing (Figure 1).

### Clinical case

We present a previously well, 67-year old Caucasian female, with no family history of neurological disease. She presented with a two month history of difficulty walking; examination revealed evidence of cerebellar dysfunction including limb ataxia and horizontal nystagmus on lateral gaze; accompanied by evidence of motor neuron degeneration including weakness of right hip flexion and right-sided brisk reflexes. Six months after symptom onset she had developed bilateral wasting of the dorsal interossei, globally reduced power with increased muscle tone and brisk reflexes, and dysarthria with tongue fasciculations. MRI with single-photon emission computed tomography revealed bilateral atrophy of the cerebellar vermis and hemispheres. EMG confirmed active and chronic denervation in three segments, fulfilling Awaji-Shima electrodiagnostic criteria for ALS. Genetic testing revealed a heterozygous *ATXN2* expansion: she carried an uninterrupted 32 CAG-repeat expansion and a normal length allele containing 22 repeats with one interruption of CAA at position 9. No significant mutation was identified in any other ALS gene contained within our clinical genetic panel (<https://www.sheffieldchildrens.nhs.uk/download/321/ngs/9291/next-generation-sequencing-v7.pdf>). Eighteen months after symptom onset she required noninvasive ventilation for respiratory failure.

### Discussion

To our knowledge, presentation of SCA2 and ALS symptoms *together* in the context of an *ATXN2* expansion is previously unreported. Based on our

case, we propose that a dichotomy between *ATXN2*-ALS and SCA2 is false. We suggest that expansion length determines the timing of cerebellar degeneration whereas the timing of motor neuron degeneration is similar to ALS more broadly and independent of expansion length. Patients with shorter expansions develop motor neuron degeneration before late onset cerebellar involvement and are labeled as ALS. Patients with longer expansions develop cerebellar degeneration at an early age and are labeled as SCA2; if they survive until the typical age of onset for ALS they may develop superimposed motor neuron degeneration, as previously reported (9). The expansion length in our patient is at the border between the reported ranges for ALS and SCA2; we propose that she developed both disorders simultaneously because the age of onset for her cerebellar degeneration determined by her expansion length, happened to coincide with the typical age of onset for ALS.

It has been suggested that *ATXN2*-ALS is exclusively associated with interrupted CAG-repeat expansions within *ATXN2* versus pure CAG-repeats in SCA2 (10). In contrast, our case carried an uninterrupted CAG-repeat expansion but presented with ALS. Interrupted CAG-repeat expansions may be more stable than pure repeats through cell division leading to reduced somatic mosaicism (11). In our framing of the relationship between expansion length and phenotype this could explain an overrepresentation of interrupted CAG-repeats in blood samples from patients presenting initially with ALS: patients carrying uninterrupted unstable alleles would be more likely to develop longer expansion lengths in the CNS, which would in turn be associated with early presentation of SCA2 prior to any motor neuron degeneration.

Review of SCA2 neurophysiology literature supports our hypothesis. Typical SCA2 patients with longer *ATXN2* expansions and young age of onset do develop muscle denervation consistent

Table 1. Patients with CAG-repeat expansions of ATXN2 identified at our center over a 10-year period.

Diagnosis	Gender	ATXN2 Expansion length	Age of Onset (years)	Family History	Age at Neurophysiology (years)	Neurophysiology
ALS	F	30	76	None	77	Active and chronic denervation
ALS	F	30	47	None	47	Active and chronic denervation
<b>SCA2/ALS*</b>	<b>F</b>	<b>32</b>	<b>65</b>	None	66	Active and chronic denervation
<b>SCA2</b>	<b>F</b>	<b>33</b>	<b>56</b>	<b>ALS</b>	<b>60</b>	<b>Normal</b>
SCA2	M	37	50	<b>SCA2</b>	<b>50</b>	<b>Sensory ganglionopathy</b>
SCA2	M	37	40	SCA2	44	Early motor neuropathy
SCA2	M	37	NA	NA	71	Sensory ganglionopathy and active denervation
SCA2	F	38	45	SCA2	NA	NA
SCA2	M	40	36	SCA2	56	Sensory ganglionopathy
SCA2	F	43	30	None	35	Sensory ganglionopathy
SCA2	F	44	27	NA	NA	NA
SCA2	M	49	14	SCA2	NA	NA

Cases with expansion lengths borderline between typical ALS/SCA2 lengths are highlighted in bold. \*Index case.

with motor neuron loss but this occurs >10 years after ataxia onset (12). We conclude that the typical SCA2 patient does develop ALS but this may be masked by ongoing severe ataxia.

We performed a retrospective review of ATXN2-positive cases diagnosed at our center (Table 1). The expansion length of our index case divides patients with longer expansions, who presented clinically with SCA2 at an earlier age, from patients with shorter expansions who presented with pure ALS. The exception is a 62-year old female with family history of ALS who presented with ataxia and a 33 CAG-repeat expansion. We propose that she is at risk of developing ALS; consistent with this she has upper motor neuron signs.

If ATXN2-ALS and SCA2 share a common molecular pathogenesis then study of differential toxicity between neuronal populations may lead to new therapeutic targets. Furthermore clinicians responsible for SCA2 patients should be aware that they may develop an ALS-phenotype at the typical age of onset for ALS.

### Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

### Funding

Funding from a Kingsland Fellowship (TM), 'My Name's Doddie Foundation (JF), a NIHR Senior Investigator award (PJS), the Wellcome Trust (JCK, 216596/Z/19/Z), and the NIHR Sheffield Biomedical Research Centre.

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