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Importance of Recurrent Falls: Adult-Onset Cerebellar Ataxia and an IRF2BPL Variant of Uncertain Significance

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Abstract

Neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures (NEDAMSS) is a rare condition caused by heterozygous pathogenic variants in the interferon regulatory factor 2 binding protein-like (*IRF2BPL*) gene. It usually arises *de novo* and presents in childhood, although milder, later-onset phenotypes dominated by cerebellar ataxia have also been described.

We report the case of a 45-year-old woman who first presented to primary care at 40 years of age with a two-month history of imbalance and falls. She had no history of cognitive regression, seizures, or loss of speech, although learning difficulties had been reported in childhood without formal assessment. Generalized tremor developed two years later. Her mother and four of her mother's five siblings had progressive late-onset ataxia and speech disturbance, and the presence of affected individuals of both sexes in two consecutive generations, together with documented parent-to-child transmission, raised the clinical suspicion of a hereditary ataxia with autosomal dominant inheritance.

Neurological examination showed mild gait instability, lumbar spine CT revealed degenerative changes without nerve root compression, and lower limb electromyography was normal. She was referred to neurology, where thoracolumbar MRI excluded radicular and spinal cord involvement. She was subsequently discharged from follow-up and referred to rheumatology for suspected fibromyalgia. The patient continued to experience falls. Brain CT showed moderate accentuation of the cortical sulci with pericentral predominance, prompting a second neurology referral, and brain MRI demonstrated predominantly vermian cerebellar atrophy together with frontoparietal cortical atrophy. After an etiological workup that included a normal serum vitamin E status and normal *ATXN3* repeat sizing, a hereditary ataxia next-generation sequencing panel identified the heterozygous frameshift variant NM_024496.4(*IRF2BPL*):c.626del, p.(Pro209Glnfs*3), classified as a variant of uncertain significance. A co-segregation study has been requested but has not yet been performed, so the contribution of this variant to the patient's phenotype remains unconfirmed.

This case highlights that recurrent falls in a young adult with a positive family history deserve longitudinal follow-up, which, together with a detailed family history, can lead primary care to recognize a hereditary ataxia even when initial assessments are inconclusive. In this patient, this approach led to the identification of an *IRF2BPL* variant of uncertain significance, whose role will be clarified by segregation analysis and the exclusion of repeat expansion ataxias.

Categories: Family/General Practice, Neurology, Genetics
Keywords: ataxia, family medicine, generalized tremor, genetic disorder, irf2bpl, nedamss, neurodevelopmental disorder, neuroimaging, neurological disorder, primary care

Introduction

Adult-onset cerebellar ataxia is a diagnostic challenge because its early manifestations, such as imbalance and occasional falls, are nonspecific and may coexist with a nearly normal neurological examination, so the first investigations are reasonably directed at commoner causes. When a similar disorder affects several relatives, a hereditary ataxia becomes likely, but its genetic causes are numerous and include both repeat expansion disorders, such as the dominantly inherited spinocerebellar ataxias, and sequence variants in a growing number of genes, which require different testing strategies [1,2]. A carefully documented family history is therefore central to recognizing these disorders, and it is often in primary care that it is first obtained.

One of the genes more recently associated with hereditary neurological disease is interferon regulatory factor 2 binding protein-like(*IRF2BPL) gene*, an intronless gene on chromosome 14q24.3 whose heterozygous pathogenic variants were first described in children with neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures (NEDAMSS) [3-6]. Most of these variants arise *de novo*, but the clinical spectrum now extends to adolescent- and adult-onset presentations dominated by ataxia,

dystonia, and dysarthria, sometimes preceded by mild intellectual disability, and autosomal dominant transmission has been documented, including in a large family with late-onset cerebellar ataxia [4,5,7-9]. Brain imaging typically shows cerebral and cerebellar atrophy with vermian predominance, and management remains supportive, since no disease-modifying therapy is available [3,4,7].

The diagnosis of *IRF2BPL*-related disease is confirmed by the identification of a heterozygous pathogenic or likely pathogenic variant in the gene [4]. A variant of uncertain significance, by contrast, neither establishes nor excludes the diagnosis, and its interpretation depends on further evidence, such as the segregation of the variant with the disease in affected relatives [4,10].

Familial adult-onset presentations of *IRF2BPL*-related disease remain few, and the diagnostic pathway through which such families come to clinical attention is rarely described. We report a woman with adult-onset cerebellar ataxia and an unusual concentration of affected relatives on the maternal line, in whom a probable hereditary ataxia was first suspected in primary care and a heterozygous *IRF2BPL* frameshift variant of uncertain significance was later identified. We discuss the clinical recognition of hereditary ataxia in primary care and the challenges of interpreting an uncertain genetic finding while the molecular diagnosis remains unconfirmed.

Case Presentation

A 45-year-old woman with six years of formal education was followed in primary care. She had previously worked as a care assistant in a nursing home until she was granted medical retirement because of the functional limitations imposed by her medical condition. Her medical history included learning difficulties in childhood, without formal assessment or diagnosis, and major depressive disorder with generalized anxiety disorder, treated with duloxetine (120 mg daily) and clonazepam (2 mg daily). Both drugs were started in 2022, after the onset of imbalance, and had no apparent effect on her complaints. Cognition was not formally assessed in adulthood. She denied smoking, alcohol consumption, or illicit drug use.

The patient's mother, like the patient herself, was evaluated by both authors, whereas information on the four other affected relatives, all of whom had died, was obtained from family report, and these data are summarized in Table *1*. Her mother, now aged 67 years, began to experience imbalance with recurrent falls at 56 years of age, followed by lower limb weakness at 58 years and by a worsening of these complaints with speech disturbance at 60 years. She lost independent ambulation at 61 years, when she began to use a wheelchair. At approximately 66 years of age, she developed dysphagia and became bedridden. Four of her mother's five siblings (three brothers and one sister, all now deceased) had been similarly affected, with symptom onset between 58 and 67 years of age and imbalance or gait ataxia and speech disturbance in all of them. Generalized tremor was also present in one brother and in the sister, in whom it preceded the gait disturbance by five years and was followed by progressive muscle weakness, so that she had become fully dependent by 70 years of age. The four siblings died between 64 and 75 years of age. The remaining brother was unaffected at 72 years of age. Both maternal grandparents had died, and their clinical status was unknown, whereas the patient's brother, aged 48 years, and her two children, aged 19 and 23 years, were unaffected. A four-generation genogram was constructed to support the diagnostic evaluation and to assess the possibility of autosomal dominant inheritance (Figure *1*).

Relative	Sex	Age at onset (years)	First manifestation	Speech disturbance (age, years)	Age at death (years)
II-1	M	64	Imbalance, gait ataxia	Yes (NA)	65
II-2	M	67	Imbalance with falls	Yes (70)	75
II-3	F	58	Generalized tremor	Yes (NA)	73
II-5	M	59	Imbalance	Yes (61)	64
II-6	F	56	Imbalance with falls	Yes (60)	Alive
III-3	F	40	Imbalance with falls	No	Alive

TABLE 1: Clinical features of the patient and her affected maternal relatives

Data for deceased relatives (II-1, II-2, II-3, II-5) were obtained from family reports.

M: male; F: female; NA: not available

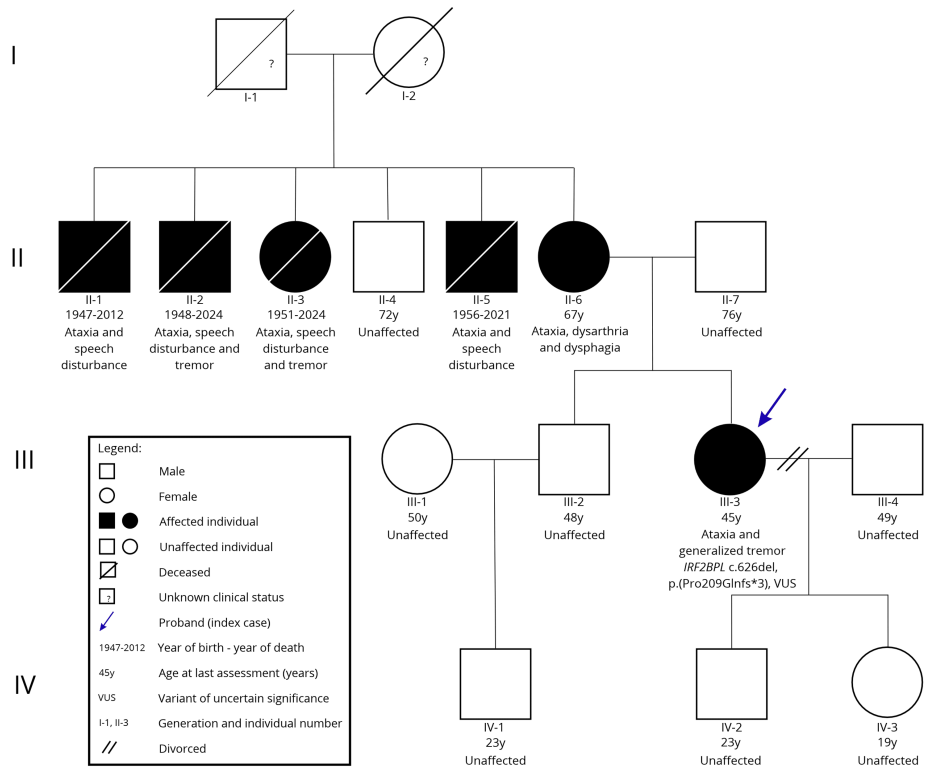


FIGURE 1: Four-generation genogram

VUS: variant of uncertain significance; y: years

In April 2021, at 40 years of age, the patient presented to primary care after two falls from standing height, preceded by a two-month history of imbalance and of subjective weakness and sensory disturbance in the lower limbs. She expressed considerable concern, as her mother, three maternal uncles, and one maternal aunt had experienced similar episodes, none with an established diagnosis. Neurological examination was unremarkable apart from mild gait instability. Lumbar spine CT showed only degenerative changes, with no evidence of nerve root compression, and lower limb electromyography was normal, but given the family history, she was referred to neurology.

At the first neurology consultation, in September 2021, the only finding was a mildly limping gait. A thoracolumbar MRI was performed and showed no significant radicular or spinal cord involvement, so in October 2022 she was discharged from neurology and referred to rheumatology for suspected fibromyalgia. In December 2022, she returned to primary care after a further fall with head and knee trauma, and skull and knee radiographs showed no acute injury.

In June 2023 she presented again to primary care after a fall preceded by generalized tremor, and given the progressive course and the family history, a head CT was requested, which showed moderate accentuation of the cortical sulci over the high convexity with pericentral predominance, consistent with atrophy, prompting a second neurology referral.

At the neurology consultation in January 2024, examination showed mild symmetric ataxia on finger-to-nose and heel-to-knee testing, dysdiadochokinesia, a wide-based gait with markedly unstable tandem walking, and a positive Romberg sign. Spinocerebellar ataxia type 3 was considered the leading hypothesis, and brain and cervical MRI, an etiological laboratory workup, and targeted *ATXN3* analysis were requested.

The laboratory workup performed in January 2024, which included serum copper, ceruloplasmin, folic acid, total cholesterol, alpha-tocopherol and its ratio to total cholesterol, total immunoglobulin A, anti-gliadin IgA and IgG antibodies, and anti-tissue transglutaminase antibodies, was unremarkable. By May 2024, brain MRI had shown accentuation of the cortical sulci of the cerebellar convexity, most marked over the vermis and consistent with cerebellar atrophy, together with roughly symmetric accentuation of the cortical sulci over the high frontoparietal convexity that exceeded what would be expected for age, in keeping with the changes previously identified on CT, with no brainstem atrophy (Figure *2*). Cervical spine MRI showed no spinal cord atrophy and only an incidental C5-C6 disc protrusion. Targeted testing showed two normal *ATXN3* alleles (22 and 27 CAG repeats), excluding spinocerebellar ataxia type 3. Neuro-otological evaluation demonstrated saccadic pursuit, hypometric saccades, and gaze-evoked nystagmus, a nonspecific pattern

consistent with degenerative cerebellar ataxia and not suggestive of any particular ataxia subtype.

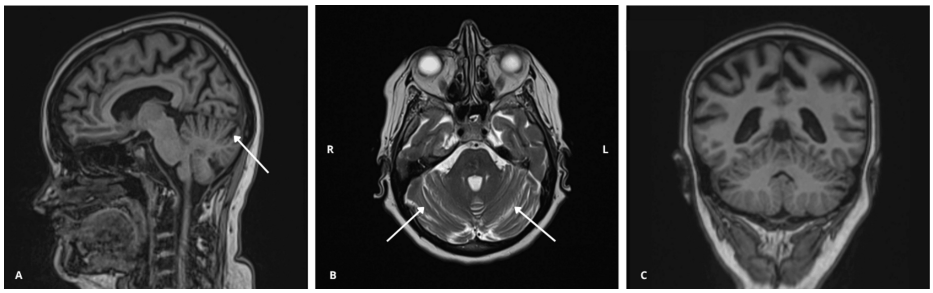


FIGURE 2: Brain MRI performed in 2024

A: midsagittal T1-weighted image showing atrophy of the cerebellar vermis, with widened vermian fissures (arrow) and preservation of the brainstem, as well as prominence of the cerebral cortical sulci; B: axial T2-weighted image at the level of the posterior fossa showing widening of the cerebellar fissures in both hemispheres (arrows) and in the vermis; C: coronal T1-weighted image showing atrophy of the cerebellar hemispheres and vermis, together with widening of the parietal cortical sulci.

A next-generation sequencing panel of genes associated with hereditary ataxia, requested in June 2024 and reported in January 2025, identified the heterozygous frameshift variant NM_024496.4(*IRF2BPL*):c.626del, p.(Pro209Glnfs*3) (NC_000014.9:g.77027171del, GRCh38, rs1469620543), which is predicted to introduce a premature termination codon at residue 211. The variant had been observed in a single heterozygous individual in the Genome Aggregation Database (gnomAD v4.1, allele count 1 of 1,612,974, allele frequency approximately 6×10^{-7}) and had not been reported in the published literature, and it was classified by the testing laboratory as a variant of uncertain significance under the American College of Medical Genetics and Genomics and Association for Molecular Pathology framework, although the individual criteria applied were not specified in the report [10,11]. The same variant had previously been submitted to ClinVar by a different clinical laboratory, also as of uncertain significance, in another individual reported as affected but without phenotypic details (Variation ID 3343272) [12]. The panel did not include repeat expansion analysis, and repeat expansion testing was limited to *ATXN3*, which showed two normal alleles (22 and 27 CAG repeats), excluding spinocerebellar ataxia type 3. Repeat expansion testing for other spinocerebellar ataxias (types 1, 2, 6, 7, and 17), dentatorubral-pallidoluysian atrophy, spinocerebellar ataxia 27B, and Friedreich ataxia was not performed. Only the proband has undergone genetic testing, and she was referred for genetic counseling.

In October 2025, in support of her application for medical retirement, a neurology report described a cerebellar ataxia of probable genetic origin and progressive course, expected to cause increasing limitation of speech, swallowing, coordination, and balance, and she was consequently unable to continue working as a care assistant.

At genetic counseling in March 2026, the possible association between the identified variant and the clinical spectrum of *IRF2BPL*-related disease was discussed with the patient, together with the uncertainty implied by its classification. A co-segregation study was requested but has not yet been carried out, as the patient's mother, the only affected relative still alive, has since become bedridden. Three years and nine months elapsed between her first presentation to primary care in April 2021 and the identification of the variant in January 2025.

At the time of writing, the patient remains able to walk independently, although her ataxia and gait instability have continued to progress. She is followed in primary care, neurology, and genetic counseling, and further investigation is planned to establish the molecular cause of her ataxia. In summary, the workup excluded structural causes, peripheral nerve involvement, vitamin E and folate deficiency, disorders of copper metabolism, and gluten-related ataxia, documented progressive cerebellar and cortical atrophy, and excluded spinocerebellar ataxia type 3, which had been the leading hypothesis given the family history, before the gene panel was requested. The clinical course and diagnostic workup are summarized in Table *2*.

Date	Setting	Clinical events	Investigations and outcome
Childhood	—	Learning difficulties, not formally assessed	—
April 2021 (age 40)	Primary care	Two falls from standing height after two months of imbalance and lower limb symptoms	Mild gait instability on examination. Lumbar spine CT showed degenerative changes. EMG was normal. Referred to neurology
September 2021	Neurology	Mildly limping gait	Thoracolumbar MRI without radicular or spinal cord involvement
October 2022	Neurology	—	Discharged from neurology and referred to rheumatology for suspected fibromyalgia
December 2022	Primary care	Fall with head and knee trauma	Radiographs without acute injury
June-July 2023	Primary care	Fall preceded by generalized tremor	Head CT showed cortical atrophy with pericentral predominance. Second neurology referral
January 2024	Neurology	Limb and gait ataxia, dysdiadochokinesia, unstable tandem gait, positive Romberg sign	Laboratory workup unremarkable, including vitamin E. MRI and *ATXN3* testing requested
March 2024	Neurology	—	Normal *ATXN3* alleles (22 and 27 CAG repeats)
April 2024	Neurology	—	Neuro-otological signs of cerebellar dysfunction
May 2024	Neurology	—	Brain MRI showed cerebellar atrophy, predominantly vermian, and frontoparietal cortical atrophy. Cervical MRI showed no cord atrophy
June 2024	Neurology	—	Hereditary ataxia gene panel requested
January 2025	Neurology	—	*IRF2BPL* c.626del, p.(Pro209Glnfs*3), variant of uncertain significance
October 2025	Neurology	Progressive ataxia limiting work	Neurology report supporting medical retirement
March 2026	Genetic counseling	—	Segregation study requested, pending
Present (age 45)	Primary care, neurology, genetic counseling	Walks independently, ataxia progressing	Follow-up ongoing

TABLE 2: Timeline of the patient's clinical course and diagnostic workup

CT: computed tomography; EMG: electromyography; MRI: magnetic resonance imaging; CAG: cytosine-adenine-guanine

Discussion

NEDAMSS was first described as a childhood-onset disorder characterized by developmental regression, abnormal movements, loss of speech, and seizures, usually caused by *de novo* variants in the *IRF2BPL* gene [3,4]. Subsequent studies have widened this picture into a spectrum extending from severe infantile regression to movement disorders beginning in adult life, with onset reported between the first year of life and the sixth decade, and both adult-onset ataxia and familial transmission have already been described [4,5,8,9,13,14].

Clinically, this patient has an adult-onset, slowly progressive cerebellar ataxia that is very probably hereditary, supported by the cerebellar signs and predominantly vermian atrophy, by the exclusion of acquired and treatable causes, and above all by a family history in which the patient's mother and four of her mother's five siblings developed progressive gait and speech disturbance. Duloxetine may cause tremor and clonazepam may impair balance, but both drugs were started in 2022, after the onset of imbalance, without any change in the patient's complaints, and neither accounts for the progressive cerebellar signs and the

cerebellar atrophy documented on MRI, although a contribution of duloxetine to the generalized tremor that appeared in 2023 cannot be excluded. The genogram is consistent with autosomal dominant inheritance, with affected individuals of both sexes in two consecutive generations, but it does not establish that pattern, because the clinical status of the maternal grandparents is unknown, male-to-male transmission was not observed, and all affected relatives belong to the maternal line. Whether the *IRF2BPL* variant accounts for this hereditary disorder remains to be established, since only the proband has so far undergone genetic testing.

The variant should therefore be regarded as a candidate explanation rather than an established cause. Several findings support it. It predicts a truncated protein lacking about three-quarters of its length, and it is extremely rare, with a single observation among approximately 800,000 individuals in gnomAD [3,11]. It lies in the N-terminal third of the protein, where other truncating variants have been classified as pathogenic, within the first PEST sequence and close to variants reported in adult-onset cases [9,12,14]. The same variant has also been submitted to ClinVar in another affected individual, although without clinical details [12].

Other findings limit its classification. Because *IRF2BPL* is intronless, truncated transcripts escape nonsense-mediated decay, and truncating variants appear to act through a toxic or dominant-negative effect rather than simple loss of function [3,6]. The usual weight given to predicted loss-of-function variants therefore cannot be fully applied [15]. In addition, the variant was not shown to be *de novo*, no functional or segregation data are available, and the phenotype is not specific to *IRF2BPL*. Its presence in gnomAD is compatible with an adult-onset disorder with asymptomatic carriers, but the variant cannot be regarded as absent from controls [8]. A variant of uncertain significance neither establishes nor excludes the diagnosis, so a molecular diagnosis of *IRF2BPL*-related disorder cannot yet be established in this patient [4,10].

Segregation analysis in the patient's mother, the only affected relative still alive, would provide only limited support if positive, because a single informative transmission carries little weight, but would argue strongly against causality if negative, whereas testing unaffected relatives would be less informative, given that asymptomatic carriers have been reported [8,10].

Normal *ATXN3* repeat sizing excludes spinocerebellar ataxia type 3 but not the other CAG repeat expansion ataxias, such as types 1, 2, 6, 7, and 17 and dentatorubral-pallidoluysian atrophy, nor non-coding expansions such as the *FGF14* GAA expansion that causes spinocerebellar ataxia 27B, now recognized as a frequent cause of late-onset cerebellar ataxia [1,2]. Symptoms began at 40 years of age in the patient, compared with 56 to 67 years in the preceding generation, an earlier onset that may reflect anticipation, a characteristic feature of repeat expansion disorders, although closer surveillance prompted by the family history may also have led to earlier recognition in the patient [2]. Sequencing panels do not reliably detect expanded repeats, and the panel used here did not include repeat expansion analysis, so a repeat expansion disorder cannot be excluded as the cause of the ataxia in this family, and targeted repeat expansion testing is the appropriate next step alongside segregation analysis.

Neuroimaging in *IRF2BPL*-related disease typically shows cerebral and cerebellar atrophy with particular involvement of the vermis [4,7]. The findings in this patient followed that description, since brain CT performed two years after symptom onset already showed cortical sulcal prominence over the high convexity with a pericentral predominance, and MRI subsequently confirmed a roughly symmetric frontoparietal cortical atrophy beyond what would be expected for age, accompanied by a more pronounced cerebellar atrophy that was most marked over the vermis, with preservation of the brainstem. Combined cerebral cortical and vermian cerebellar involvement in a patient in her early forties is consistent with the imaging spectrum reported for the disorder, although this pattern is shared with other late-onset degenerative ataxias and cannot by itself implicate a particular gene.

Because adult-onset ataxia and familial transmission have already been reported, the contribution of this report lies in the longitudinal documentation of a family with six affected members and a candidate variant in a region associated with adult-onset disease, and in the diagnostic pathway itself. Three years and nine months elapsed between the first consultation for imbalance and the identification of the variant, an interval that included discharge from neurology and a referral for suspected fibromyalgia, and what redirected the investigation was a four-generation genogram constructed in primary care, read against a record of accumulating falls held only by the family physician, which made progression visible when isolated assessments could not.

Because variants of uncertain significance should not be used for predictive testing, such testing is not currently appropriate for the patient's two children, aged 19 and 23 years, and genetic counseling can at present rest only on the clinical evidence of a probably autosomal dominant ataxia, to be revisited if the variant is reclassified or another cause is identified [4,10]. Management remains supportive with anticipatory attention to falls, speech, and swallowing as part of follow-up in primary care [3,4,7].

This report has limitations. The molecular basis of the ataxia in this family has not been established, since the variant remains of uncertain significance and neither segregation analysis nor repeat expansion testing

has been performed. The clinical data on the deceased relatives were obtained from family reports. No standardized ataxia rating scale was applied, so progression could be described only in functional terms. Finally, neither the tremor nor cognition was formally characterized.

Despite these limitations, this case demonstrates the value of a carefully constructed genogram in primary care and the role of the family physician in suspecting a hereditary disorder when a slowly progressive neurological syndrome recurs across generations. It also shows that recurrent falls in a young adult with a positive family history deserve longitudinal follow-up, since their accumulation over time may be the first evidence of a progressive neurological disease.

Conclusions

Adult-onset cerebellar ataxia with a striking family history warrants genetic investigation even when the first neurological assessments are inconclusive, and in primary care the recognition of a progressive hereditary ataxia may depend less on any single examination than on the family history and on the longitudinal observation of recurrent falls. In this family, the clinical evidence points to a hereditary, probably autosomal dominant cerebellar ataxia, but its molecular cause remains unresolved. The *IRF2BPL* frameshift variant identified in the patient, currently classified as of uncertain significance, raises the possibility of an *IRF2BPL*-related disorder, but its role in this family remains to be confirmed. Segregation analysis and testing for repeat expansion ataxias are the next steps towards a molecular diagnosis, and until then, predictive testing of unaffected relatives should not be offered.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Melanie Lopes

Acquisition, analysis, or interpretation of data: Melanie Lopes, Osvaldo Parreira

Drafting of the manuscript: Melanie Lopes

Critical review of the manuscript for important intellectual content: Melanie Lopes, Osvaldo Parreira

Supervision: Melanie Lopes, Osvaldo Parreira

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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