Amyotrophic Lateral Sclerosis and Spinocerebellar Ataxia Type 2 in a Family With Full CAG Repeat Expansions of ATXN2

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IMPORTANCE A family with coexistence of spinocerebellar ataxia type 2 and amyotrophic lateral sclerosis (ALS) is described.

OBSERVATIONS Intermediate or full CAG repeat expansions of ATXN2 are associated with ALS. However, no coexistence of spinocerebellar ataxia type 2 and ALS in a family has been reported in the literature. We describe a 47-year-old woman with an 11-year history of ataxia and her paternal uncle with ALS who were evaluated at Columbia University Medical Center since July 2006. Both our patient with ataxia and her uncle with ALS have full pathological CAG repeat expansions of ATXN2.

CONCLUSIONS AND RELEVANCE The diverse clinical phenotypes of ATXN2 CAG expansions and their coexistence in a single family are highlighted. A clinician should consider the diagnosis of spinocerebellar ataxia type 2 when encountering a patient with ataxia and a family history of ALS.

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Full expansion of the CAG repeat (≥34) in ATXN2 is a known cause of spinocerebellar ataxia type 2 (SCA2).1 More recently, an intermediate expansion of the CAG repeat (between 27 and 33) has been associated with amyotrophic lateral sclerosis (ALS).2-9 Full CAG repeat expansions in ATXN2 can also occur in rare cases of ALS.3-7 To our knowledge, the coexistence of SCA2 and ALS with full CAG repeat expansions in ATXN2 within a family has not been reported. We describe a family with SCA2 and ALS and provide a detailed phenotypic description of the affected individuals.

Report of a Case

A 47-year-old woman developed gait difficulty at age 36 years, slurred speech at age 37 years, and loss of hand dexterity at age 41 years. She did not have swallowing difficulty. Neurological examination revealed clinical signs typical for SCA2 including slow saccadic eye movements, truncal titubation, and hyporeflexia (Video). She was able to walk without a walker with a wide-based gait and marked staggering (3 points on the Scale for the Assessment and Rating of Ataxia [SARA]). She was able to stand only with intermittent support (4 points on SARA). She had a slight sway while sitting (1 point on SARA). She had scanning speech and occasionally was difficult to understand (3 points on SARA). She had mild dysmetria on finger chase (1 point on SARA bilaterally), moderate intention tremor on nose-finger test (2 points on SARA bilaterally), and abnormal findings on the heel-shin slide test (2 points on SARA bilaterally). She had normal fast alternating movements (0 points on SARA). Her total SARA score was 16 (Video). She also had jaw-opening dystonia, facial myokymia, and shoulder muscle fasciculations but did not have spasticity, muscle weakness, bradykinesia, rest tremor, or rigidity. Magnetic resonance imaging showed marked cerebellar atrophy. Electromyography showed fasciculations and myokymia in the mentalis muscle without denervation. Genetic testing showed an expanded CAG repeat of 40/22 in ATXN2. She had no expanded hexanucleotide repeats in C9orf72 (2/5).

She had a paternal uncle who developed difficulty walking at age 62 years (Figure). Within 9 months of his symptom onset, he had lost dexterity in his hands, worse on the left side. He did not have imbalance. His neurological examination showed muscle atrophy and fasciculation in all 4 extremities. His muscle strength using the Medical Research Council grading scale was 4+/5 in the neck flexor and right upper extremity muscles, 4−/5 in the left upper extremity muscles, and 4-5/5 in both lower extremities. He also had increased tone in all limbs, hyperreflexia, and a spastic gait. Sensory examination findings were normal. He also had a mild postural tremor, but there were no other clinical signs of cerebellar dysfunction. He had normal sac-
Tube placement 18 months after the initial symptom, and patients with ALS. We describe 2 members in 1 family diagnosed with ALS and SCA2, with full CAG repeat expansions in ATXN2. The patient with SCA2 has both maternal and paternal ATXN2 involvement, similar to our reported case. Interestingly, our patient with SCA2 had fasciculations but no weakness or spasticity, whereas her paternal uncle with ALS had postural tremor without other signs of cerebellar dysfunction, indicating a wide range of phenotypic variability in CAG repeat expansions in ATXN2. The patient with SCA2 has both maternal and paternal family history of ALS, but she inherited the expanded ATXN2 allele from the paternal side of the family given the history of her paternal grandmother having ataxia and paternal uncle having ALS and full CAG repeat expansions in ATXN2. The fact that the maternal great aunt had ALS seems to be coincidental.

In pathologic studies, TAR DNA binding protein 43 (TDP-43) is abnormally localized in SCA2 and ATXN2 is abnormally localized in spinal cord neurons in ALS, suggesting a relationship between these two disorders. In animal and cellular models, ATXN2 is a modifier for TDP-43 toxicity. Furthermore, TDP-43 directly interacts with ATXN2, and intermediate expanded CAG repeat expansions in ATXN2 can increase the pathologic form of TDP-43 by enhancing C-terminal cleavage and phosphorylated TDP-43.

This article provides insights into the variability of neurologic presentation of CAG repeat expansions in ATXN2, which include Parkinson disease, SCA2, and ALS. Members in the same family carrying a mutation in ATXN2 can have different phenotypes. Genetic testing for CAG repeat expansions in ATXN2 should be considered when encountering a patient with ataxia and a family history of ALS.

Discussion

Intermediate CAG repeat expansion in ATXN2 is associated with an increased risk for ALS. Full expansions of CAG repeats in ATXN2 (repeat range 34-39) have been reported in 10 patients with ALS. We describe 2 members in 1 family diagnosed as having ALS and SCA2, with full CAG repeat expansions in both individuals. To our knowledge, this is the first description of coexisting ALS and SCA2 in a single family. Patients with ALS who have CAG repeat expansions in ATXN2 have a younger age at onset and early spinal motor neuron involvement, similar to our reported case. Interestingly, our patient with SCA2 had fasciculations but no weakness or spasticity, whereas her paternal uncle with ALS had postural tremor without other signs of cerebellar dysfunction, indicating a wide range of phenotypic variability in CAG repeat expansions in ATXN2. The patient with SCA2 has both maternal and paternal family history of ALS, but she inherited the expanded ATXN2 allele from the paternal side of the family given the history of her paternal grandmother having ataxia and paternal uncle having ALS and full CAG repeat expansions in ATXN2.

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REFERENCES


Figure. Family Pedigree

ALS indicates amyotrophic lateral sclerosis; DM, diabetes mellitus; MI, myocardial infarction; SCA2, spinocerebellar ataxia type 2.

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