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Ataxia and Parkinsonism in a Woman With a VCP Variant and Long-Normal Repeats in the SCA2 Allele

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We present the case of a 46-year-old woman with gradually progressive ataxia, parkinsonism, and neuropathy. Symptoms started at age 29 years with speech impairment and difficulty walking. At presentation, she had mild midline ataxia and dysarthria. Left hand rest tremor began at age 33 years. Over the next decade, she developed parkinsonism and lower extremity weakness, which was more prominent than ataxia (Videos 1 and 2). Her parkinsonism was responsive to levodopa, and over time, she developed motor fluctuations. She also developed urinary retention and constipation. Medical history was otherwise notable for lumbar radiculopathy, ankylosing spondylitis, elevated anti-nuclear antibodies, migraine, and depression. Current examination reveals appendicular and gait ataxia, dysarthria, parkinsonism (left predominant), bilateral hip flexor weakness and foot drop, length-dependent decrease in pinprick sensation, and hyperreflexia (bilateral Babinski and jaw jerk reflexes). She is adopted and has 2 healthy teenaged sons. She is apparently of European descent but does not know her family history.

On initial workup, very long chain fatty acids and vitamin E were normal, and human T-lymphotropic virus type I and II testing was negative. Electromyogram/nerve conduction study showed sensorimotor demyelinating neuropathy. MRI of the brain (Figure) showed no cerebellar atrophy or white matter abnormalities. I-123 ioflupane SPECT imaging showed decreased reuptake in the basal ganglia bilaterally. A spinocerebellar ataxia (SCA) trinucleotide repeat panel showed long-normal repeats (31 and 32) in the *ATXN2* gene encoding ataxin-2. An ataxia exome panel was unremarkable; later testing showed a heterozygous intronic AAGGG repeat expansion (115 repeats) of the *RFC-1* gene encoding replication factor C subunit 1. Whole-exome sequencing identified a known pathogenic variant in the *VCP* gene encoding valosin-containing protein (heterozygous p.R159C c.475C>T). There was no evidence of myopathy or Paget disease of bone (PDB).

Valosin-containing protein (VCP) is a ubiquitous enzyme that catalyzes the decomposition of adenosine triphosphate (ATP) into adenosine diphosphate, that is involved in multiple cellular processes including protein degradation. The R159C variant is associated with autosomal dominant inheritance but variable neurodegenerative phenotypes within and between kindreds; the most common being a combination of inclusion body myopathy and frontotemporal dementia (FTD) with onset around 50–60 years,[1] but Parkinson disease,[2] spastic paraplegia, and PDB have also been reported. Of interest, 1 individual in an R159C kindred (genotype unknown) was initially diagnosed with spinocerebellar degeneration,[3] but we are not aware of other reports of ataxia. Classically, pathogenic variants in *VCP* have been associated with a combination of myopathy, PDB, and FTD, but these phenotypes have been reported individually as well as in combination with amyotrophic lateral sclerosis (ALS), Parkinson, and Charcot-Marie-Tooth.[1,2] Penetrance is not well defined because of variability in age at onset.

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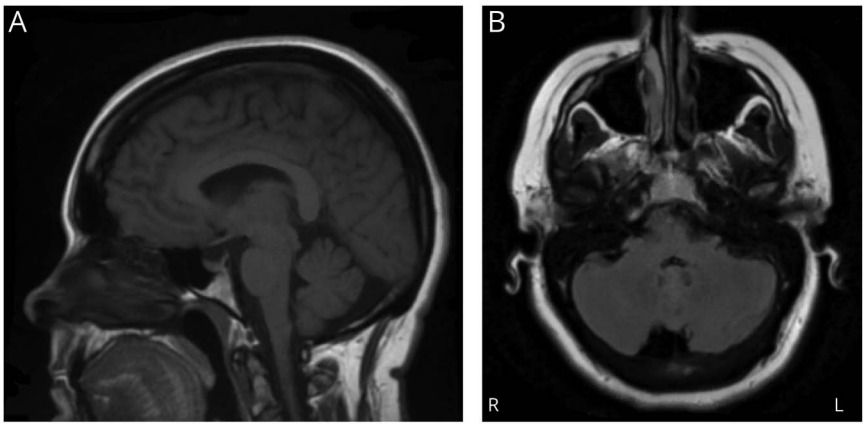
Figure MRI of the Brain Without Contrast 11 Years After Symptom Onset



(A) Sagittal and (B) axial T2 fluid attenuated inversion recovery sequence. An incidental arachnoid cyst is present (right of midline). There is minimal cerebellar atrophy.

Pathogenic expansions of CAG repeats in the *ATXN2* gene are associated with a variety of neurodegenerative phenotypes that segregate with trinucleotide repeat size.[4] Repeats ≥33 cause autosomal dominant SCA type 2 (SCA2) with a range of neurodegenerative phenotypes including progressive cerebellar dysfunction, slowed saccades, pyramidal dysfunction, neuronopathy and peripheral neuropathy, as well as levodopa-responsive parkinsonism. Long-normal CAG repeats (30–33 repeats) have been associated with an increased risk of ALS,[5] as well as progressive supranuclear palsy (30–32 repeats)[6] and multiple system atrophy (29–31 repeats).[7] Autosomal recessive pattern of inheritance has been reported in a Japanese woman with two 31-repeat alleles who developed SCA2 at age 80 years.[8]

Cerebellar ataxia with neuropathy and vestibular areflexia syndrome causes late-onset disease and was recently shown to be associated with biallelic intronic repeat expansions in *RFC-1*. Heterozygous expansions are overrepresented in patients with undiagnosed ataxia compared with control populations.[9]

In summary, our patient's phenotype of parkinsonism, cerebellar ataxia, and neuropathy is most similar to that seen in SCA2. Furthermore, a SCA2 phenotype has been reported in association with long-normal CAG expansions in *ATXN2*[8] but at a much later age at onset. Parkinsonism is well described in *VCP* variants; however, the *VCP* R159C variant alone does not explain her ataxic symptoms.[1] Our patient's heterozygous intronic AAGGG repeat expansion in *RFC-1* does not explain her age at onset or parkinsonism.[9] We speculate that the phenotype of her long-normal *ATXN2* expansions has been modified by her pathogenic *VCP* variant and heterozygous expansion in *RFC-1*. Although no direct interactions between any of these proteins have been reported,[10] VCP and ataxin-2 protein mutations are strongly associated with pathologic accumulation of TDP-43.[1-3,5-7] It is important to counsel our patient that she could still develop typical symptoms of her *VCP* variant (myopathy, PDB, and FTD) as the disease progresses. This combination of a *VCP* variant, long-normal biallelic CAG repeats in *ATXN2*, and heterozygous intronic AAGGG repeat expansion in *RFC-1* has not been reported previously. This case illustrates the potential for interactions between genes associated with neurodegeneration and their role in the pathogenesis of new phenotypes.

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Alana E. Kirby, MD, PhD	Rush University Medical Center, Chicago, IL	Interpreted the data and drafted the manuscript for intellectual content
Virginia Kimonis, MD	University of California at Irvine	Interpreted the data and revised the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Contribution
Katie Kompoliti, MD	Rush University Medical Center, Chicago, IL	Interpreted the data and revised the manuscript for intellectual content

References

1. Al-Obeidi E, Al-Tahan S, Surampalli A, et al. Genotype-phenotype study in patients with valosin-containing protein mutations associated with multisystem proteinopathy. *Clin Genet.* 2018;93(1):119-125.
2. Chan N, Le C, Shieh P, et al. Valosin-containing protein mutation and Parkinson's disease. *Parkinsonism Relat Disord.* 2012;18(1):107-109.
3. Spina S, Van Laar AD, Murrell JR, et al. Phenotypic variability in three families with valosin-containing protein mutation. *Eur J Neurol.* 2013;20(2):251-258.
4. Pulst SM. The complex structure of *ATXN2* genetic variation. *Neurol Genet.* 2018; 4(6):e299.
5. Neuenschwander AG, Thai KK, Figueroa KP, Pulst SM. Amyotrophic lateral sclerosis risk for spinocerebellar ataxia type 2 ATXN2 CAG repeat alleles: a meta-analysis. *JAMA Neurol.* 2014;71(12):1529-1534.
6. Ross OA, Rutherford NJ, Baker M, et al. Ataxin-2 repeat-length variation and neurodegeneration. *Hum Mol Genet.* 2011;20(16):3207-3212.
7. Zhou X, Wang C, Ding D, et al. Analysis of (CAG)n expansion in ATXN1, ATXN2 and ATXN3 in Chinese patients with multiple system atrophy. *Sci Rep.* 2018;8(1): 3889.
8. Tojima M, Murakami G, Hikawa R, et al. Homozygous 31 trinucleotide repeats in the SCA2 allele are pathogenic for cerebellar ataxia. *Neurol Genet.* 2018;4(6): e283.
9. Syriani DA, Wong D, Andani S, et al. Prevalence of *RFC-1*-mediated spinocerebellar ataxia in a North American ataxia cohort. *Neurol Genet.* 2020;6(3); e440.
10. Chung CG, Lee H, Lee SB. Mechanisms of protein toxicity in neurodegenerative diseases. *Cell Mol Life Sci.* 2018;75:3159-3180.