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Adult-Onset Ataxia With Neuropathy and White Matter Abnormalities Due to a Novel *SAMD9L* Variant

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Variants in tumor suppressor genes and in genes encoding DNA repairing proteins are associated with syndromes conferring neurologic features and increased risk for malignancy. The best example for these conditions is ataxia-telangiectasia (AT). A more rare and recent disease is an ataxia-pancytopenia syndrome (ATXPC) associated with heterozygous gain-of-function variants in the tumor suppressor gene *SAMD9L* (MIM 159550). Here, we describe a patient with a complex cerebellar syndrome associated with a novel *SAMD9L* pathogenic variant.

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Video

Case Presentation

A 54-year-old Swedish man presented with progressive gait difficulties, impaired coordination, dizziness, falls, slurred speech, and urinary urgency. Age at onset was 42 years. Later, recurrent episodes with profuse sweating and crawling in both calves started to occur. There was no family history of movement disorders or other neurologic diseases. His mother died of glioblastoma at age 65 years and his father of cardiac disease. His medical history was unremarkable. Examination revealed dysmetria, inability to perform tandem gait, reduced arm swing, dysarthria, positive Romberg test, conjunctival telangiectasias, nystagmus, and *pes cavus* (Video 1). Reflexes were brisk, with mild spasticity in the legs. Muscle tone in the arms, sensation to pinprick, strength, and proprioception were normal, and the Babinski sign was absent, but vibration was reduced in both malleoli. At age 50 years, his Scale for the Assessment and Rating of Ataxia score was 10 p, and 3 years later, it was 11.5 p (range 0–40 points).[1] There were no signs of orthostatism, and the patient denied gastrointestinal symptoms. ENeG and quantitative sensory testing demonstrated a demyelinating sensorimotor neuropathy and elevated thresholds for heat and cold. EMG revealed chronic mild neurogenic abnormalities in the distal leg and arm muscles with no signs of active denervation, whereas motor evoked potential yielded normal findings. A mild symmetric sensorineural hearing loss was found, but the patient does not require hearing aids. Ophthalmologic evaluation, which included optical coherence tomography and eye-bottom examination, demonstrated presbyopia but no evidence of retinal pathology.

Brain MRI with contrast demonstrated marked cerebellar atrophy and confluent periventricular hyperintensities. Additional hyperintensities were found in deep white matter regions that included the corpus callosum's left trunk. There were multiple cysts ranging in size between 1.5 and 3 mm within the hyperintensities and increased T2-weighted signal in the putamen, caudate, and dentate nuclei (Figure). A CT scan ruled out calcifications in the brain. A large

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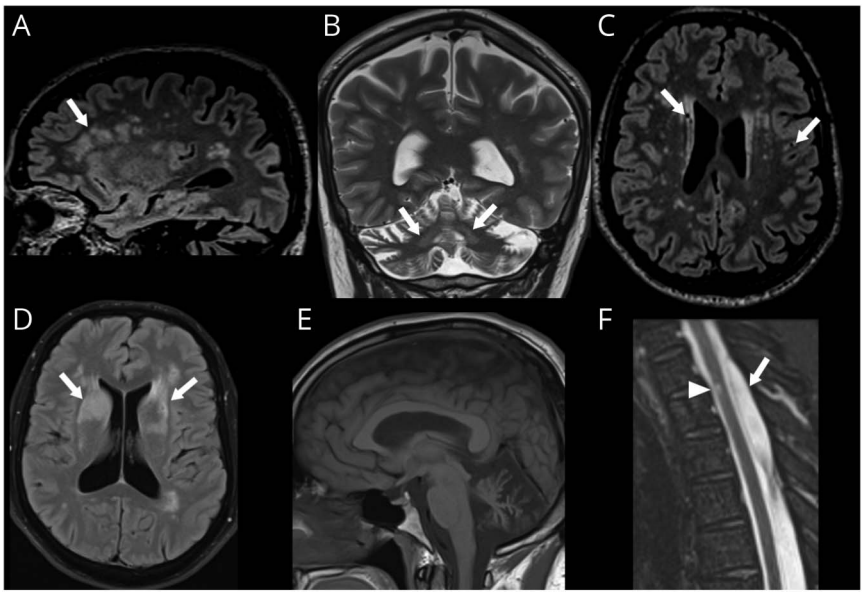
Figure Neuroimaging Findings



(A) 3D T2 weighted FLAIR sections demonstrate partially confluent periventricular hyperintensities. Hyperintensities are also seen in other white matter locations with frontal predominance in a parasagittal section (arrow). (B) Bilateral hyperintensities are shown in the dentate nuclei in a coronal section (arrows). (C) The axial section demonstrates multiple cysts within the periventricular hyperintensities (arrows). Axial T2 turbo spin echo FLAIR section displays an increased signal in the putamen and caudate nucleus bilaterally (D, arrows). Severe cerebellar atrophy is shown on this parasagittal T1 turbo spin echo section (E). T2 turbo inversion recovery magnitude section demonstrates a large posterior arachnoidal cyst with dural ectasia extending from Th1 to L2 levels (F, arrow) and an anterior lesion with possible slight loss of volume at the Th1 level (Arrow head). FLAIR = fluid-attenuated inversion recovery.

posterior arachnoidal cyst with dural ectasia was found extending from Th1 to L2 levels which prevented a lumbar puncture. A more subtle dural ectasia was found at C1-C2 and sacral levels but no evidence of spinal cord atrophy. The neuroimaging abnormalities remain unchanged 3 years later. Cobalamin was mildly reduced, but extensive laboratory tests were normal (eTable 1, links.lww.com/NXG/A481). Pathologic nucleotide expansions were ruled out. Blood-derived DNA was investigated by whole genome sequencing (WGS). WGS analysis revealed a heterozygous variant in *SAMD9L* (NM_152703, c.2915T>C p.Ile972Thr), encoding the sterile alpha motif domain containing 9-like protein, present in 19 of 38 sequencing reads. A second variant in *SAMDL9L*, c.3229C>T p.Arg1077*, was present in 6 out of 32 reads. Both variants were absent in the gnomAD database. Somatic reversion in hematopoietic cells, by uniparental disomy or *cis* loss-of-function mutations, can resolve the cytopenias otherwise associated with ATXPC[2,e1]). The patient had a normal complete blood count. Bone marrow aspiration demonstrated normal cellularity, no dysplastic features, and no evidence of acquired mutations indicative of a myelodysplastic syndrome (targeted sequencing by the TruSight panel). Furthermore, the karyotype was normal, and fluorescence in situ hybridization analysis showed no evidence for monosomy 7 or del(7q). Deep sequencing of *SAMD9L* in blood, bone-marrow, as well as fibroblast-derived DNA from a skin biopsy confirmed the germline origin of the *SAMD9L* c.2915T>C variant, whereas the *SAMD9L* c.3229C>T variant as well as another c.3456_3458del (p.Leu1153del) were detected exclusively in blood and bone-marrow from the patient (eTable 2, links.lww.com/NXG/A482). Segregation studies for the germline variant were not possible because both parents were deceased. Stable HEK-293T cell transfectants with inducible expression of *SAMD9L* variants were generated. *SAMD9L* wild-type and patient-derived variants were readily expressed on induction with doxycycline (eFigure 1A, links.lww.com/NXG/A480). Cellular assays demonstrated that expression of the novel germline *SAMD9L* c.2915T>Cp.Ile972Thr variant diminished cell proliferation to similar levels as the previously reported *SAMD9L* p.His880Gln gain-of-function variant (eFigure 1, B and C). Although several truncating *SAMD9L* gain-of-function variants around amino acids 876–889 have been described,[e2] the *SAMD9L* c.3229C>T p.Arg1077* truncation did not inhibit cell proliferation (eFigure 1C). In other patients, revertant truncations have been positioned at the N-terminus of disease-causing variants. Notably, a construct containing both the disease-causing *SAMD9L* c.2915T>C p.Ile972Thr and somatic c.3229C>T p.Arg1077* variants did not inhibit cell proliferation, revealing that the revertant mutation alleviated in *cis* the pathogenic variant.

Discussion

The presence of revertant mosaicism at high variant allele frequency explains the lack of hematologic phenotype in the patient, indicating that the C-terminus is required for the pathology of the *SAMD9L* c.2915T>C p.Ile972Thr germline variant. In the original publications delineating ATXPC, most patients displayed cerebellar features.[3,4] However, in subsequent articles, only few patients, most diagnosed as children, with hematologic abnormalities displayed ataxia or neuropathy (~14%).[5,6,e1,e3,e4,e5,e6] The absence of family history in this case might be due to the germline *SAMD9L* variant c.2915T>C being de novo or to reduced penetrance and variable expressivity of neurologic and hematologic signs.[e1, e7]

The growing spectrum of ATXPC includes white matter abnormalities.[2-8] Cysts or enlarged perivascular spaces have been reported in ATXPC,[6,7] while dural ectasia along with spinal cord atrophy has been reported only once.[7] Age at onset, the presence and types of neuropathy, and pyramidal signs[4,7,8] are variable. In a few instances, telangiectasias retinal thinning and alveolar proteinosis occur in patients with *SAMD9L* variants.[2,8,e8] Age at onset, phenotype, and slow rate of progression in our case are striking similar to what is seen in variant ataxia-telangiectasia (vA-T). However, the absence of systemic features (immunodeficiency, pulmonary symptoms, endocrinological abnormalities, and intellectual disability) and the type of underlying polyneuropathy differentiate ATXPC from vA-T. Prognosis in ATXPC relies on monitoring for and treating the hematologic abnormalities; thus, a regular follow-up with a hematologist is warranted.

The *SAMD9L* gene product is an interferon-regulated tumor suppressor, with an important role in the regulation of protein synthesis.[e9-e11] When *SAMD9L* variants are identified in blood, genetic studies in other tissues are needed to distinguish germline from revertant variants. Our case illustrates the importance of C-terminal truncations for disrupting/reversing pathogenic *SAMD9L* variants. The mechanism of neurologic dysfunction in ATXPC remains to be understood. In addition, the unknown is whether revertant mosaicism takes place in the brain and might explain variable expressivity.

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Eva Hellström-Lindberg, MD, PhD	Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden	Patient care, hematologic workup, study concept and planning, and editing of the article
Yenan T. Bryceson, PhD	Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden University of Bergen, Norway	Study concept and planning for experimental evaluation of genetic variants, supervision, and major editing of the article
Per Svenningsson, MD, PhD	Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden	Supervision, analysis and interpretation of clinical data, and editing of the article

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