SPG7 P.A510V HETEROZYGOSITY AS A CAUSE OF ADULT-ONSET CEREBELLAR ATAXIA WITHOUT SPASTICITY: LONGITUDINAL EVIDENCE FROM A SPORADIC CASE

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Objectives

Mutations in the SPG7 gene are typically associated with autosomal recessive hereditary spastic paraplegia (HSP). However, growing evidence supports a pathogenic role for the heterozygous SPG7 p.A510V variant in patients with adult-onset cerebellar ataxia without spasticity. This study aims to provide longitudinal clinical and instrumental data supporting this association.

Materials and methods

We report a 72-year-old woman with no family history of neurological disease who presented with a slowly progressive cerebellar syndrome. A comprehensive clinical, neurophysiological, neuroradiological, and genetic work-up was performed, with follow-up over two years. Neurological examinations were combined with brain and spine MRI, nerve conduction studies, electromyography, cerebrospinal fluid analysis, and vestibular and oculomotor assessments. Genetic analysis included next-generation sequencing (NGS) with a cerebellar ataxia gene panel, multiplex ligation-dependent probe amplification (MLPA) for SPG7, screening for trinucleotide repeat expansions associated with spinocerebellar ataxias (SCAs), including SCA27B.

Results

The patient showed gaze-evoked nystagmus, dysarthria, limb dysmetria, impaired tandem gait, and distal sensory deficits (Video 1). Brain MRI revealed predominant cerebellar vermis atrophy (Figure 1). Neurophysiology confirmed a length-dependent sensory axonal neuropathy with normal motor conduction. Genetic analysis identified a heterozygous SPG7 c.1529C>T (p.A510V) mutation (Table 1). No second pathogenic SPG7 variant was found, and MLPA excluded large-scale deletions. All repeat expansion tests for SCAs were negative. At two-year follow-up, the patient's condition remained stable without spasticity, extrapyramidal signs, or cognitive decline.

Discussion

This case broadens the phenotypic spectrum linked to heterozygous SPG7 p.A510V mutations, supporting its pathogenic role even in the absence of a second allele. The presentation as a pure cerebellar ataxia with sensory neuropathy, and no upper motor neuron involvement, contrasts with typical recessive SPG7-related HSP. The clinical stability over two years and exclusion of common genetic ataxias reinforce this interpretation. These findings suggest a possible dominant-negative or haploinsufficiency effect of the p.A510V variant and advocate for its inclusion in the diagnostic workflow for late-onset ataxias of unclear etiology.

Conclusion

This longitudinal case study highlights the relevance of the heterozygous SPG7 p.A510V mutation in non-spastic cerebellar ataxia. Comprehensive genetic screening is essential for accurate diagnosis and management, especially when common repeat expansion disorders are excluded.

Scan Me

Video 1. Scan to watch the full video

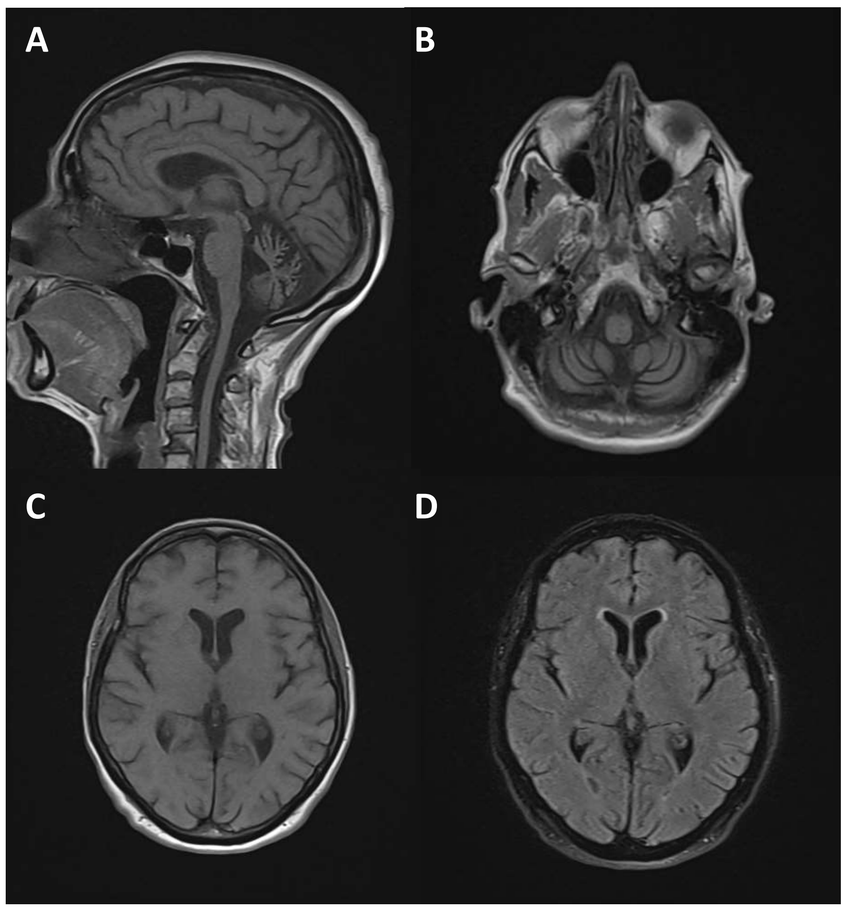

Figure 1. MRI findings. Sagittal (A) and axial (B) MRI sequences revealed subtentorial cerebellar atrophy, more prominent in the vermis, without associated brainstem involvement. Axial MRI sequences of the supratentorial region at T1 (C) and FLAIR (D) did not show frontal horn abnormalities, consistent with absence of the "*ears of the lynx*" sign

Cerebellar ataxia trinucleotide repeat expansions: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, DRPLA, SCA27B
Cerebellar ataxia NGS Gene Panel: ABCB7, AFG3L2, AHI1, ARL13B, ATM, ATP1A3, ATXN10, CACNA1A, CC2D2A, CLN5, COQ8A, FGF14, FXN, GFAP, GSS, ITPR1, KCNC3, KIF7, LMNB1, NDUFS4, NDUFS7, NDUFS8, NDUFV1, NPHP1, OFD1, PDYN, PEX7, PHYH, PNPLA6, POLG, PRKCG, RPGRIP1L, SCN2A, SETX, SLC2A1, SPG7, SPTBN2, SYNE1, TBP, TCTN1, TCTN2, TDP1, TMEM216, TMEM67, TPP1, TTBK, TTPA, ZFYVE26
Genetic Finding: SPG7, c.1529C>T [p.(Ala510Val)], Heterozygosis, potentially pathogenic variant

Table 1. Genetic analysis

Major references

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