Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Two Cases of *SPEN* Haploinsufficiency Presenting with Dystonia: Expanding the Genotype and Phenotype

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1p36 deletion syndrome (1p36DS, MIM 619343) is a terminal deletion syndrome that affects approximately 1 in 5000 live births.[1] It involves a heterozygous deletion on the short arm of chromosome 1 that leads to various clinical features such as developmental delay (DD), hypotonia, seizures, congenital heart defects (CHD), facial dysmorphism (FD), visual and hearing impairment.[2,3] Diagnosis can be challenging due to the different deletion sizes and breakpoints that affect the symptom severity.[4] Recent research has shown that haploinsufficiency of the split ends homologue gene (*SPEN*, OMIM: 613484), located in the 1p36 region, contributes significantly to the phenotypic presentation of the neurodevelopmental disorder that overlaps with 1p36DS.[2] We hereby describe a mother and a daughter with a novel *SPEN* variant leading to haploinsufficiency presenting with cervical dystonia and dystonic head and upper limb tremor.

Case Report

Mother (Proband)

A 37-year-old female was referred to the neurologist because of a neck dystonia. She had a history of DD, anxiety with panic attacks and delusions. Family history revealed tremor and/or dystonia in her daughter, mother and sister; her brother committed suicide at a young age. No consanguinity was reported (Fig. 1). Cognitive screening revealed MMSE score 25/30 and MoCA score 16 + 1/30. The physical examination revealed leftward torticollis with mixed no-no/yes-yes dystonic head tremor, as well as fine, irregular postural and kinetic dystonic tremor in the upper extremities. No bradykinesia or rigidity were present (Video 1). The diagnostic investigations, including laboratory tests and brain MRI (Fig. 2A–C), were unremarkable. First, exome sequencing of the dystonia and related movement disorders genes, together with bioinformatic copy-number variant analysis, was performed, which did not reveal any clinically relevant findings. This was followed by a gene-agnostic analysis focusing on rare coding variants compatible with the suspected autosomal dominant inheritance pattern. This approach identified a heterozygous likely pathogenic stop-gain variant in SPEN (NM_015001.3: c.2170C>T, p.Arg724*). No other clinically relevant variants were detected. No additional cytogenetic or molecular genetic methods were performed. Her mother and sister were not available for genetic counseling. She was summoned for a neuropsychological examination but refused to attend. Treatment included clonazepam and botulinum toxin injections for the dystonia and escitalopram for the psychiatric symptoms, with some reduction of the symptoms at follow-up.

Daughter

The proband's 18-year-old daughter showed similar behavioral and neurological symptoms. The birth and pregnancy were uneventful. However, she showed delayed developmental milestones—shortly after birth she received a hip brace and at the age of 1.5 she began to walk and talk. Hand tremor was

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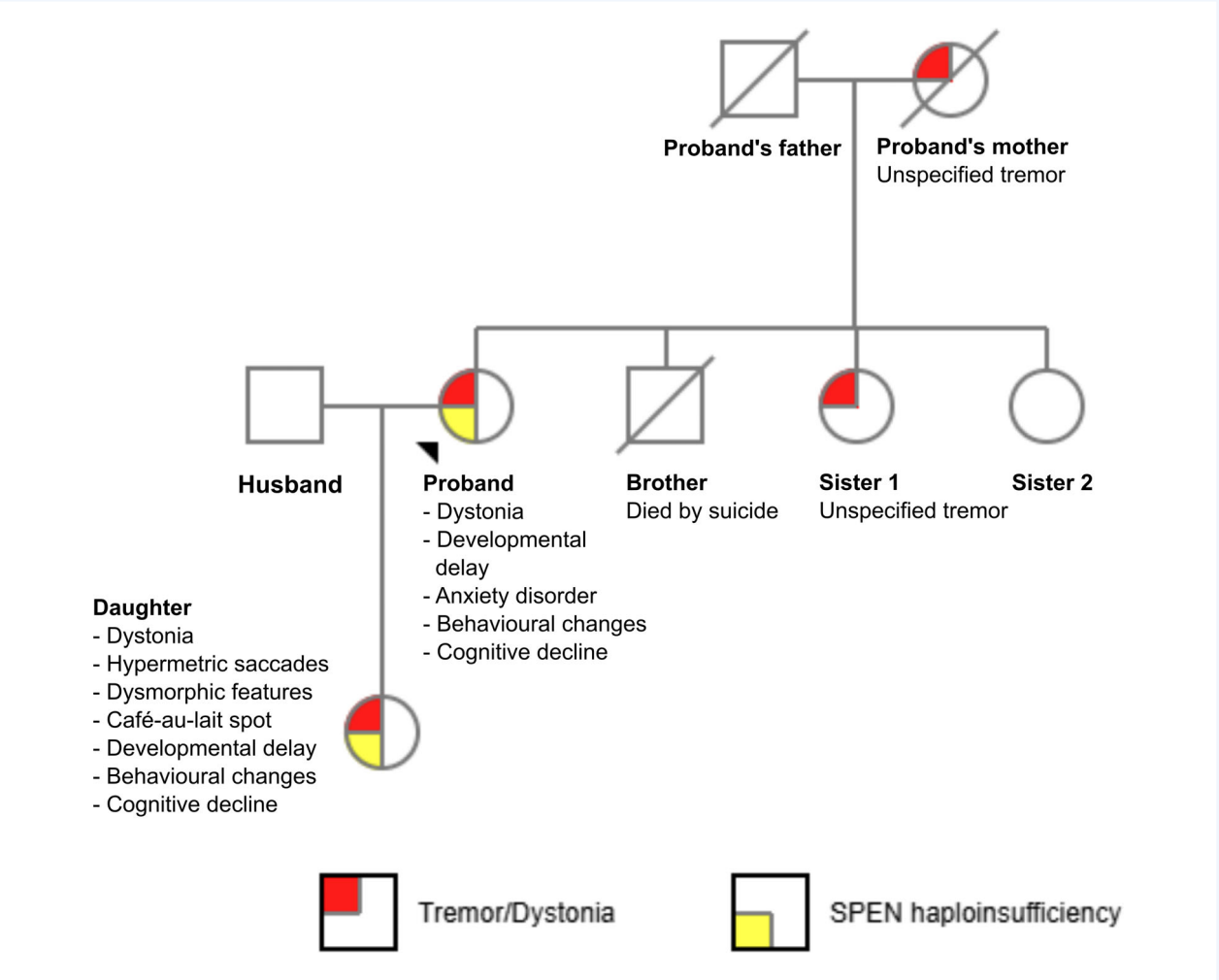


Figure 1. Pedigree chart showing the clinical findings and genetically confirmed SPEN haploinsufficiency in the probands family. Note that the probands sister and mother both experienced tremor/dystonia, but no genetic testing was performed in them due to their unavailability.

noticed at primary school. At the age of 15, she was examined by a pediatric neurologist who described exostoses on the knees, a contracture of the third left finger, hyperactivity, neck tremor, upper limb postural tremor and poor coordination. Current cognitive screening revealed an MMSE score of 23/30 and a MoCA score of 19 + 1/30. Physical examination revealed a bulbous nose, contracture of the third left finger, a shortened third to fifth right toe and fifth left toe, and a café-au-lait spot on the left thigh. Oculomotor examination revealed saccadic dysmetria. Occasional head tremor and postural and kinetic tremor in all limbs were observed, but no bradykinesia or rigidity were present. Fine motor skills were slightly impaired (Video 2). MRI of the brain was normal (Fig. 2D–F). Sanger sequencing confirmed the presence of the likely pathogenic *SPEN* variant previously revealed in her mother. Neuropsychological examination and an echocardiogram were scheduled for a later appointment, but she did not attend.

Discussion

SPEN gene, located on chromosome 1p36.21p36.13, encodes a transcriptional repressor likely involved in neural development. A recent seminal study linked truncating variants in *SPEN* to Radio-Tartaglia syndrome (RTS, MIM 619312), which is characterized by DD, anxiety, aggression, attention deficit disorder, FD, CHD and CNS abnormalities.[2] In our report the patients exhibited clinical features consistent with the phenotypic spectrum of RTS, including DD, behavioral abnormalities and FD. However, neither patient showed structural brain abnormalities or symptoms suggestive of CHD, although no proper cardiological assessment was performed.

In both patients, dystonia affecting the upper limbs was the most characteristic finding. Additionally, in the mother, cervical dystonia was the most prominent feature, whereas in the daughter, the symptoms were very mild. While dystonia can be

Video 1. Showing the mother, presenting with cervical and upper limbs dystonia along with associated postural and kinetic upper limbs tremor. The remaining components of the neurological examination are unremarkable.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70531

idiopathic or associated with other neurological disorders, it has never been reported in patients with *SPEN* haploinsufficiency and RTS.[5] Interestingly, in 2001 Valente et al[6] identified a region on chromosome 1p36.13p36.32 associated with primary cervical dystonia, which overlaps with *SPEN* genetic locus. The phenotypical features of dystonia in our cases mimic those presented by Valente et al,[6] which suggest *SPEN* may be a candidate gene for dystonia. Moreover, we observed hypermetric saccades in the daughter. While saccadic dysmetria has been previously reported in dystonic disorders, we are not aware of any prior descriptions in RTS.[7]

To the best of our knowledge, this is the first report of the *SPEN* genetic variant c.2170C>T, p.Arg724* in the literature. The variant results in premature stop codon, likely leading to loss of normal protein function, which is a known cause of RTS.[2] Furthermore, the variant is absent in the gnomAD database. According to ACMG/ACGS guidelines we classified it as likely pathogenic (PVS1, PM2).[8] The genetic variant represents the likely cause of our patients' clinical features, including dystonia.

In conclusion, we described a mother and her daughter with a novel likely pathogenic *SPEN* variant, presenting as cervical dystonia and neck tremor. This report expands the current phenotypical and genotypical background of the *SPEN* haploinsufficiency, RTS and 1p36DS and emphasizes the importance of comprehensive neurological assessments and genetic testing for accurate diagnosis and management of this condition.

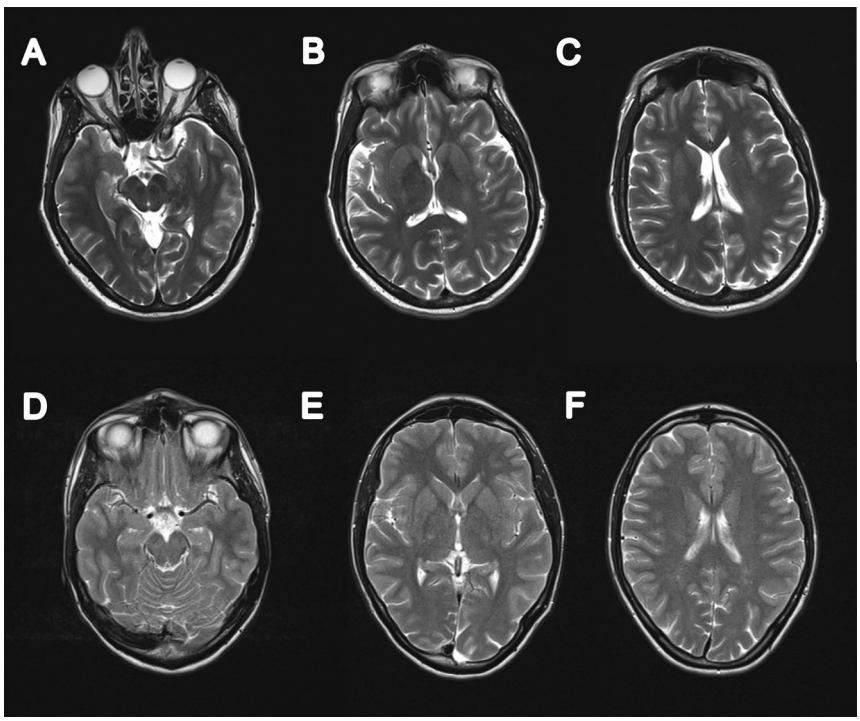
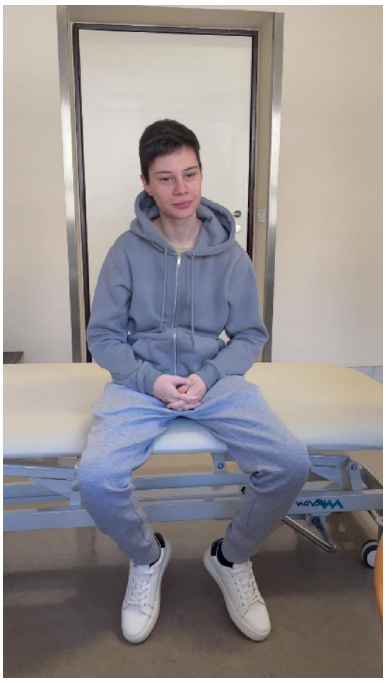


Figure 2. T2-weighted brain MRI for mother (A-C) and daughter (D-F), showing no relevant structural abnormalities.



Video 2. Showing the proband's daughter. On inspection dysmorphic features, including a prominent bulbous nose tip and finger abnormalities, can be seen. Clear overshoot is demonstrated during eye movement examination. Simultaneously, occasional discrete head tremor can be noted. Moreover, upper limb dystonia, particularly affecting the fingers, is present with associated mild postural and kinetic tremor in all four extremities. During finger tapping and rapid alternating movements the patient shows mild difficulties with executing fine finger movements, but without apparent bradykinesia. The patient's gait and pull-test are unremarkable. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70531

Author Roles

(1) Case Report: A Conception, B. Data Collection, C. Analysis, D. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Editing.

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M.L.: 1A, 1B, 1C, 1D, 2A, 2B.

V.S.: 1A, 2B.

B.P.: 2B.

G.B.:1A, 2B.

D.G.: 1A, 1B, 1C, 2B.

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this publication. Written informed consent for video recording, use and publication of the patients' videos was obtained. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

References

1. Shapira SK, McCaskill C, Northrup H, et al. Chromosome 1p36 deletions: the clinical phenotype and molecular characterization of a common newly delineated syndrome. *Am J Hum Genet* 1997;61(3):642–650. https://doi.org/10.1086/515520.
2. Radio FC, Pang K, Ciolfi A, et al. *SPEN* haploinsufficiency causes a neurodevelopmental disorder overlapping proximal 1p36 deletion syndrome with an episignature of X chromosomes in females. *Am J Hum Genet* 2021;108(3):502–516. https://doi.org/10.1016/j.ajhg.2021.01.015.
3. Jacquin C, Landais E, Poirsier C, et al. 1p36 deletion syndrome: review and mapping with further characterization of the phenotype, a new cohort of 86 patients. *Am J Med Genet A* 2023;191(2):445–458. https://doi.org/10.1002/ajmg.a.63041.
4. Jordan VK, Zaveri HP, Scott DA. 1p36 deletion syndrome: an update. *Appl Clin Genet* 2015;8:189–200. https://doi.org/10.2147/TACG.S65698.
5. Albanese A, Bhatia KP, Fung VSC, et al. Definition and classification of dystonia. *Mov Disord* 2025;40(7):1248–1259. https://doi.org/10.1002/mds.30220.
6. Valente EM, Bentivoglio AR, Cassetta E, et al. DYT13, a novel primary torsion dystonia locus, maps to chromosome 1p36.13--36.32 in an Italian family with cranial-cervical or upper limb onset. *Ann Neurol* 2001;49(3):362–366.
7. Pollini L, Pettenuzzo I, Tijssen MAJ, Koens LH, de Koning TJ, Leuzzi V, Eggink H. Eye movement disorders in genetic dystonia syndromes: a literature overview. *Parkinsonism Relat Disord* 2025;133:107325. https://doi.org/10.1016/j.parkreldis.2025.107325.
8. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17(5):405–424. https://doi.org/10.1038/gim.2015.30.