CASE REPORT

Rare insights into SPAX5: integrating genetic evidence and whole-exome sequencing with progressive clinical features

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ABSTRACT

Background: Spastic ataxia type 5 (SPAX5) is a rare autosomal recessive neurodegenerative disorder that is characterized by a progressive combination of spasticity, cerebellar ataxia, and difficulties with fine motor coordination. This report aims to highlight the clinical profile, diagnostic findings, and genetic aspects of SPAX5, emphasizing the value of Whole-exome sequencing in diagnosing rare hereditary disorders.

Case Presentation: In this report, we present the clinical progression, findings, and genetic classification of a 47-year-old male diagnosed with spastic ataxia type 5, who, over the past decade, has experienced worsening balance instability, weakness, and increasing walking disturbances. Upon follow-up, he presented with gaze palsy and a noticeable decline in cognitive function. Family history noted a cousin aged 60 with similar symptoms, consistent with the autosomal recessive inheritance pattern characteristic of SCA5.

Genetic analysis: Whole exome sequencing (WES) revealed a homozygous likely pathogenic variant in the AFG3L2 gene, confirming the diagnosis of SPAX5. This discovery emphasizes the genetic etiology of the disease and underscores the role of familial inheritance in its pathogenesis and progression.

Conclusion: This case stresses the value of genetic testing, particularly WES, in diagnosing disorders like SPAX5, which often present with nonspecific clinical manifestations and overlap with other neurodegenerative disorders. It also further illustrates the importance of community-based genetic studies to better understand the inheritance patterns of rare hereditary disorders and to enhance management strategies.

Keywords: Spastic Ataxia Type 5, autosomal recessive inheritance, AFG3L2 gene, neurodegenerative disorder, whole exome sequencing, case report.

Introduction

Hereditary spastic ataxias are a distinct subgroup of cerebellar ataxias, characterized by a predominant combination of ataxia and spasticity. These conditions typically present with early-onset symptoms that progressively worsen, ultimately leading to significant impairments in locomotion and cognitive function (1). Given their clinical overlap with other neurological disorders, accurately identifying the specific spastic ataxia phenotype is crucial for achieving diagnostic precision. However, the individual rarity and genetic heterogeneity of these pathologies complicate the genetic diagnosis, rendering it both challenging and time consuming.

Spastic ataxia type 5 is a rare autosomal recessive neurodegenerative disorder primarily affecting the cerebellum (1). It is characterized by a combination of progressive cerebellar ataxia, abnormal eye movements, and dysarthria, alongside additional hallmark features. The disease typically manifests in early adulthood with symptoms such as instability, impaired balance, muscle stiffness, and coordination difficulties, which gradually worsen over time. As the disorder progresses, patients

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may also develop lower limb spastic paraparesis, motor degeneration, peripheral neuropathy, dysmetria, dysdiadochokinesia, and, in some cases, cognitive changes.

SPAX5 is caused by variations in the *AFG3L2* gene, located on chromosome 18p11, which encodes a protein that forms part of the m-AAA protease complex (2). This complex plays a critical role in maintaining mitochondrial protein quality control by degrading misfolded or damaged proteins. Variants in the *AFG3L2* gene impair the m-AAA protease's function, resulting in the accumulation and aggregation of damaged proteins. These aggregates disrupt key mitochondrial processes, such as ATP production, and induce oxidative stress, leading to mitochondrial dysfunction, particularly in neurons in the cerebellum and corticospinal tracts, contributing to the clinical manifestations of the disease (3,4).

The rarity of SPAX5, its clinical overlap with other conditions such as SCA28,(2) combined with its inherent clinical complexity, presents difficulties in its diagnosis and management, underscoring the need for a multidisciplinary approach. Despite these obstacles, advances in genetic testing modalities, particularly Whole Exome Sequencing (WES), have been instrumental in enabling the early detection and precise subtype classification of SPAX5, thereby supporting the development of targeted therapeutic strategies.

In this context, we present the clinical progression and diagnosis of SPAX5, emphasizing the role of genetic testing techniques, such as WES, not only in diagnosing the primary condition but also in detecting variants that could influence other aspects of the patient's health. Additionally, this case highlights the genetic etiology of SPAX5 and illustrates the importance of understanding familial inheritance in diagnosing rare genetic disorders. Finally, it reinforces the need for community-based genetic studies and widespread genetic screening to establish a broader understanding of the disease, refine diagnostic criteria, and develop more effective management strategies.

Case Presentation

Patient is a 47-year-old male with a 10-year history of progressive loss of balance, weakness, and walking disturbances. His medical history was unremarkable with no prior surgery, seizures, or other chronic illnesses. Neurological examination demonstrated dysmetria, dysdiadochokinesia, fasciculations in the tongue and dysarthria, and impaired facial muscle control with visible tension and discoordination illustrated in Figure 1. The patient's clinical manifestations and follow-up findings are summarized in Table 1. Despite other motor disturbances, he had normal muscle strength. Upon follow up, additional symptoms were noted, including upward gaze palsy and cognitive impairment as difficulty recalling recent events (Figure 2). The complete set of clinical features is outlined in Tables 1 and 2. Family history revealed that his parents were first-degree cousins from Dumlupinar, and a 60-year-old cousin who exhibited similar symptoms. Based on phenotype–genotype correlation and database consultation (OMIM), sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO) were considered in the differential diagnosis before confirmation by whole-exome sequencing (WES).

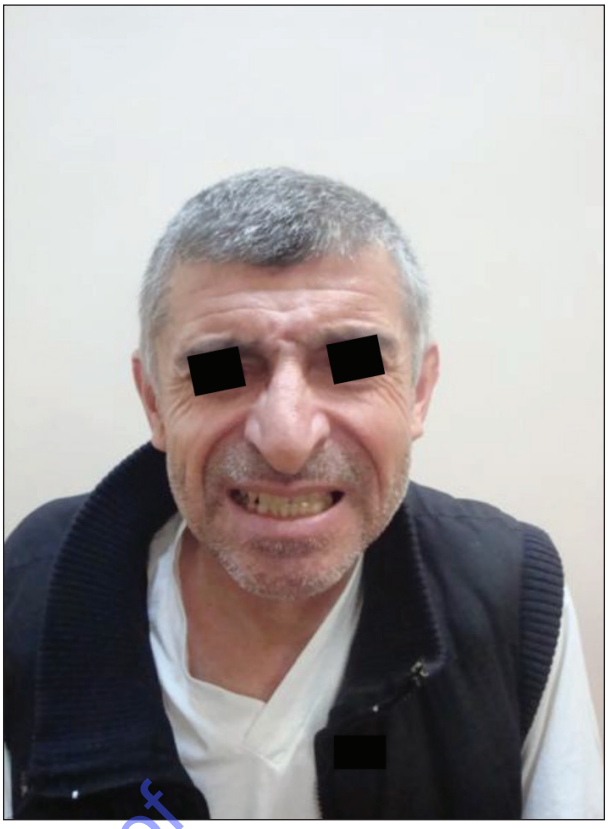

Figure 1. *Facial expression demonstrating muscle tension and discoordination, indicative of impaired facial muscle control.*

Genetic findings

Whole-exome sequencing identified a primary, phenotype-related variant in the AFG3L2 gene (*NM_006796.2*), described as c.2044G>T (p.Asp682Tyr) and classified as a Class 3 variant. The identified genetic variants and their clinical significance are summarized in Table 2. This variant is associated with Spastic Ataxia Type 5 (SPAX5) and is considered relevant to the patient's clinical presentation.

Additionally, secondary findings were detected in the HFE gene (*NM_000410.4*), including c.845G>A (p.Cys282Tyr)and c.187C>G (p.His63Asp). These variants are related to phenotypes not directly investigated in this study but may have clinical importance for genetic counseling and preventive health management. Both are classified as Class 1 variants, indicating benign or likely benign significance with respect to the current phenotype.

All variants were annotated and reported according to Human Genome Variation Society (HGVS) recommendations, using the following reference sequences: *AFG3L2*—NG_008058.1 (genomic), NM_006796.2 (mRNA); and *HFE*—NG_008720.2 (genomic), NM_000410.4 (mRNA). No incidental findings were detected in this patient.

Table 1. Clinical features of the patient with SPAX5 (OMIM #614487).

Category	Feature	Finding/Description
Initial symptoms	Loss of balance	Present, gradual onset
	Weakness	Present, progressive; frequent falls
	Walking disturbances	Present, progressive
Neurological exam	Dysmetria	Present
	Dysdiadochokinesia	Present
	Fasciculations in tongue	Present
	Dysarthria	Present, slurred speech
	Muscle strength	Normal
Follow-up findings	Gaze palsy	Present, impaired upward gaze
	Cognitive impairment	Present, difficulty recalling recent events
	Sensory ataxic neuropathy & ophthalmoparesis (SANDO)	Considered in differential diagnosis

Figure 2. *Patient exhibits facial asymmetry, ptosis, and a dysarthric expression, reflecting motor disturbances, gaze palsy, and speech difficulties consistent with spastic ataxia type 5.*

WES results confirmed the diagnosis of spastic ataxia type 5 (SPAX5) caused by a homozygous variant in the *AFG3L2* gene (c.2044G>T / p.Asp682Tyr, Class 3).

Discussion

This case report underscores the critical role of WES in the diagnosis of Spastic Ataxia Type 5 (SPAX5), a condition marked by its clinical overlap with other neurodegenerative disorders. The patient's progression from initial balance and coordination difficulties to severe neurological manifestations, including gaze palsy and cognitive decline, illustrates the progressive and debilitating nature of SPAX5. Notably, the identification of a homozygous likely pathogenic variant in the *AFG3L2* gene not only solidifies the diagnosis but also enhances our understanding of the genetic basis of the disease. This finding is pivotal as variants in *AFG3L2* have been associated with a spectrum of mitochondrial dysfunctions, leading to varied clinical manifestations across different patients.

In addition to the primary finding in *AFG3L2*, our patient was also found to carry a variant in the *HFE* gene. Pathogenic and likely pathogenic variants in *HFE*, particularly p.Cys282Tyr (C282Y) and p.His63Asp (H63D), are known to predispose to hereditary hemochromatosis, an autosomal recessive iron overload disorder (OMIM #235200). Although penetrance is variable, individuals with these variants may be at increased risk of developing hepatic dysfunction, diabetes mellitus, cardiomyopathy, and other complications of iron overload. The clinical significance of the *HFE* variant in our patient should therefore not be overlooked. From a management perspective, periodic monitoring of serum ferritin and transferrin saturation is recommended to detect early evidence of iron accumulation. If biochemical evidence of iron overload emerges, referral to hematology and initiation of therapeutic phlebotomy would be appropriate. Even in the absence of clinical disease, identification of *HFE* variants has implications for genetic counseling and cascade testing of at-risk family members.

Our study significantly contributes to the burgeoning understanding of Spastic Ataxia Type 5 (SPAX5) by presenting a case characterized by a homozygous likely pathogenic variant in the *AFG3L2* gene, thereby corroborating its critical role in the disease's molecular pathogenesis. This aligns with findings by Dosi et al. (2), who emphasized the genetic and phenotypic heterogeneity inherent to SPAX5. SPAX5 is known to be clinically heterogeneous, with patients often presenting in childhood or adolescence with progressive spasticity, cerebellar ataxia, and oculomotor abnormalities. Our patient fits within this spectrum by demonstrating

Table 2. *Genetic findings of the patient with SPAX5 (OMIM #614487) detected by whole-exome sequencing, described according to HGVS guidelines.*

Finding	Gene	Transcript	Nucleotide change	Protein change	Clinical significance
Primary	AFG3L2	NM_006796.2	c.2044G>T	p.Asp682Tyr	Phenotype-related Associated with SPAX5 (Spastic Ataxia Type 5), Class 3
Secondary	HFE	NM_000410.4	c.845G>A	p.Cys282Tyr	Variant related to another phenotype not investigated, Class 1 variant
Secondary	HFE	NM_000410.4	c.187C>G	p.His63Asp	Variant related to another phenotype not investigated, Class 1 variant

Variants described according to HGVS guidelines using *AFG3L2* reference sequence NG_008058.1 (genomic), NM_006796.2 (mRNA), and *HFE* reference sequence NG_008720.2 (genomic), NM_000410.4 (mRNA).

spasticity and progressive gait instability but diverges by exhibiting cognitive impairment and gaze palsy features that have been less frequently reported and not comprehensively characterized in earlier studies. This highlights the variability of SPAX5 and broadens its recognized clinical phenotype, underscoring the importance of considering this diagnosis even in atypical or late-onset presentations.

These findings expand the recognized clinical spectrum of SPAX5, highlighting the necessity of comprehensive phenotypic documentation to enhance diagnostic accuracy (5,6). Furthermore, the identification of HFE gene variants, uncovered via WES, underscores the indispensable utility of genomic testing not only in pinpointing the primary likely pathogenic variant but also in identifying ancillary genetic factors with potential implications for patient management.

Our findings also resonate with recent literature by Ghosh Dastidar et al. (7), who explored the multifaceted roles of *AFG3L2* in mitochondrial homeostasis and its association with diverse neurodegenerative phenotypes. Their work elucidates how variants in *AFG3L2* disrupt mitochondrial proteostasis, driving neurodegenerative processes, particularly in cerebellar and corticospinal regions. This aligns seamlessly with our observations, where *AFG3L2* dysfunction likely contributed to the neurodegenerative trajectory observed in our patient. By integrating these molecular insights with clinical findings, our report emphasizes the pivotal role of *AFG3L2* in maintaining neuronal integrity and underscores the deleterious impact of its dysfunction. This synthesis of molecular and clinical perspectives reinforces the necessity of integrating advanced genomic diagnostics into routine clinical practice for rare neurodegenerative conditions like SPAX5.

Conclusion

The case of a 47-year-old male diagnosed with SPAX5 via WES exemplifies the indispensable role of advanced genetic testing in the field of neurology. By confirming the specific genetic etiology of the patient's condition, WES not only facilitated a precise diagnosis but also informed potential familial implications due to the autosomal recessive inheritance pattern. This report reaffirms the necessity of integrating genetic testing into the diagnostic process of rare neurodegenerative disorders, which often present with non-specific symptoms and may mimic other conditions. Future community-based genetic studies should aim to expand our understanding of SPAX5, potentially leading to the development of targeted therapies and management strategies that could significantly improve patient outcomes.

Furthermore, this case promotes the broader application of WES in clinical practice, advocating for its use as a first-line diagnostic tool in similar cases of ambiguous neurodegenerative diseases, thereby enabling more accurate diagnoses and better patient care.

This case presents several novel aspects that expand the current understanding of Spastic Ataxia Type 5 (SPAX5). Our patient's late onset of symptoms contrasts with the predominantly early-onset cases previously described, thereby broadening the recognized age spectrum of disease presentation. Furthermore, the presence of cognitive decline and upward gaze palsy represents a distinct clinical profile, as such features are rarely documented in SPAX5 and suggest more widespread neurodegeneration involving frontal–subcortical circuits and brainstem pathways. In addition, the patient exhibited bulbar features, including tongue fasciculations, facial asymmetry, and dysarthria, indicating possible lower motor neuron involvement and adding to the phenotypic diversity observed in AFG3L2-related ataxias. Finally, this represents the first genetically confirmed case of SPAX5 from the Dumlupinar region, underscoring the importance of regional genetic documentation in consanguineous populations. Collectively, these findings highlight the phenotypic and genotypic heterogeneity of SPAX5 and emphasize the value of WES in identifying atypical or late-onset presentations of rare neurodegenerative disorders.

Author contributions

Galia Baalbaki: Concepts, literature search, clinical studies, data acquisition, manuscript preparation, and manuscript editing.

Hajira Karim: Concepts, literature search, clinical studies, data acquisition, manuscript preparation, and manuscript editing.

Lima Oria: Concepts, literature search, clinical studies, data acquisition, manuscript preparation, and manuscript editing. Muhsin Elmas: Supervision, definition of intellectual content, data interpretation, manuscript review, final approval of the version to be published, and guarantor of the work.

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Conflict of interest

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Consent for participate

Informed consent was obtained from the patients.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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