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Novel *SPAST* Deletion Mutation in an American Family With Hereditary Spastic Paraplegia: A Case Report

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Abstract

The diverse group of neurodegenerative disorders known as hereditary spastic paraplegia (HSP) is characterized by spasticity and weakness of the bilateral lower extremity due to degeneration of the corticospinal tract. The pathogenesis of HSP is broad, with autosomal dominant, autosomal recessive, X-linked recessive, mitochondrial inheritance, and de novo mutations reported, along with remarkable heterogeneity of mutations and clinical presentation. Of these, the most common subtype of HSP is HSP type 4 (HSP-*SPG4*), a result of mutations in the *SPAST* gene (chromosome 2p22.3) that leads to impaired activity of the microtubule-severing protein spastin. Typically presenting as an uncomplicated, autosomal dominant form of the disease, HSP-*SPG4* has been documented worldwide with vast genomic variance across the *SPAST* gene. Despite common features in clinical phenotypes, a clear link between *SPAST* gene variants and disease presentation remains vague. Here, we report a novel 26.1 kb deletion in the *SPAST* gene (del exons 4-7) in a US family with previously undiagnosed HSP-*SPG4*.

Keywords

case report, hereditary spastic paraplegia, *SPAST* gene, genetic neurological disorders, neurodegeneration

Introduction

Hereditary spastic paraplegia (HSP) encompasses a heterogeneous group of inherited neurodegenerative disorders that primarily affect the corticospinal tract, presenting with spasticity and weakness of the lower limbs.[1] Affecting 2 to 5 individuals in every 100 000 worldwide, HSP can either be inherited in autosomal dominant, autosomal recessive, X-linked recessive, and mitochondrial patterns or be the result of a *de novo* mutation.[2,3]

By far the most common etiology of HSP involves a range of mutations in the *SPAST* gene (chromosome 2p22.3), impairing the synthesis of the microtubule-severing enzyme spastin.[4] Patients with implicated mutations in *SPAST* (HSP-*SPG4*) primarily present with autosomal-dominant HSP and comprise approximately one third of all cases.[4,5] This protein, responsible for the binding and ATP-dependent cleavage of tubulin from the microtubule lattice, belongs to the ATPase associated with various cellular activities (AAA) superfamily, which are largely necessary for a diverse range of cellular functions.[5-7] Here, we report a novel ~26.1 kb deletion in *SPAST* in exons 4 to 7 across 2 generations of an American family presenting with previously undiagnosed HSP-*SPG4*.

Case Presentation

A 66-year-old Caucasian male with a prior diagnosis of ankylosing spondylitis (AS) was referred to the neurology clinic due to jerking movements in both legs. The patient described difficulties with walking and coordination since childhood, resulting in him being wheelchair-bound 20 years ago. The patient also reported significant back pain and difficulty urinating, along with bilateral foot drop. His recent presentation for jerking movements in his legs occurred when attempting to transfer himself from bed to chair or extending his legs. He denied any related symptoms in his upper extremities.

With further interview, the patient described similar lower extremity weakness and walking difficulties in his father

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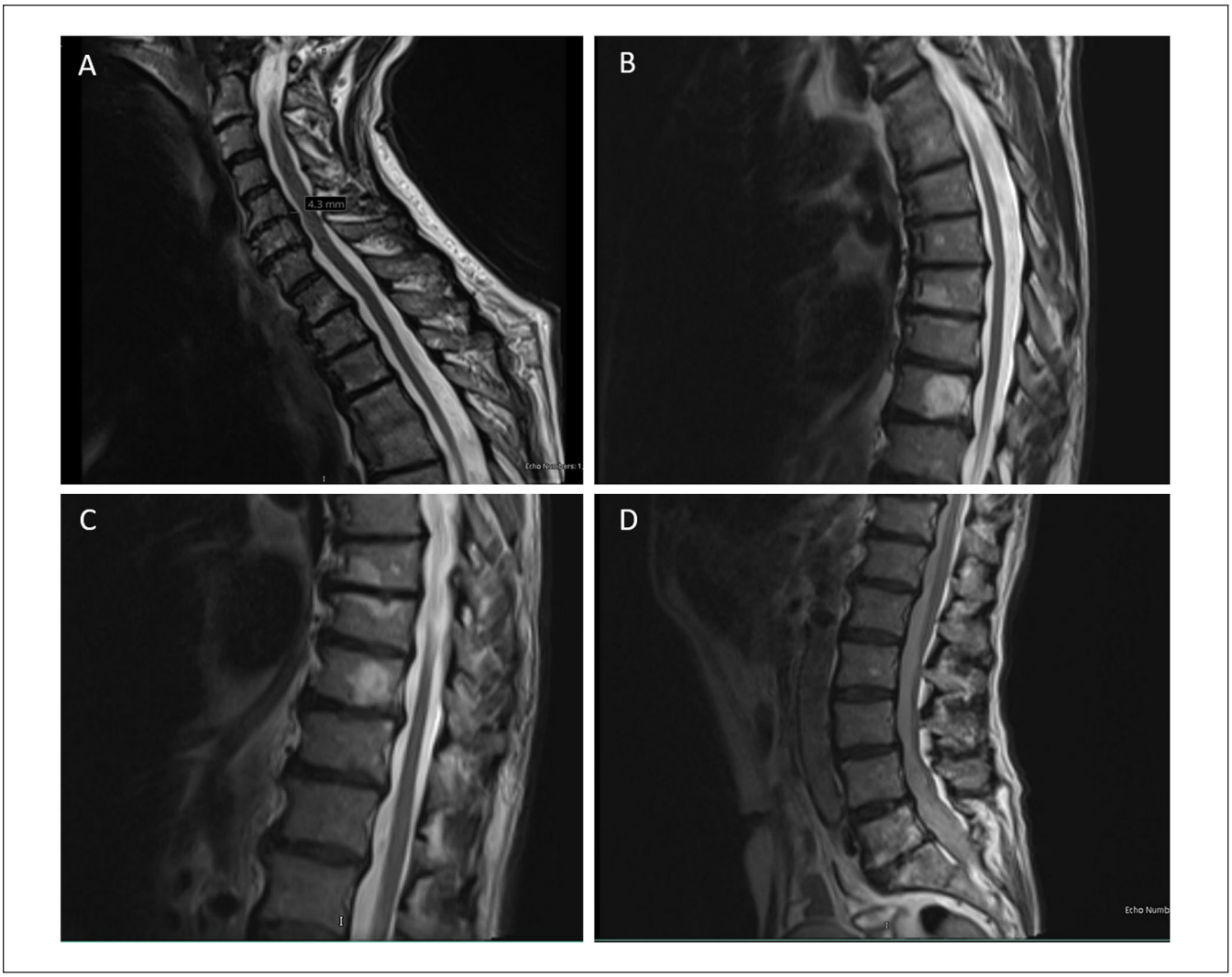

Figure 1. Cervical (panel A), thoracic (panels B and C), and lumbar (panel D) spine MRI imaging reported advanced multilevel degenerative disk and facet changes, C5-6 and C6-7 spinal canal stenosis, T4 and T5 vertebral body fusion, and posterior disk osteophyte complex at T7-8. There was no abnormal signal change in the spinal cord.

(deceased), son, and daughter. Both affected children are also wheelchair-bound after similarly presenting in childhood with weakness and walking on their tiptoes. Despite the strong indication of a genetic element, no formal diagnosis had been made.

Upon neurological examination, the patient was awake, alert, and oriented to person, place, and time with normal speech. Cranial nerves were intact. Motor examination revealed muscle strengths were 5/5 in bilateral upper extremities and 3/5 in bilateral lower extremities. Muscle tone was normal in bilateral upper extremities, but severe spasticity was noted in bilateral lower extremities. Deep tendon reflexes were 2+ in bilateral upper extremities. Patellar reflex was 4+ bilaterally, and ankle reflex was 2+ bilaterally. There was persistent bilateral ankle clonus. Babinski signs were positive bilaterally. Finger-to-nose was intact bilaterally, but heel-to-shin was unable to be evaluated due to lower extremity weakness. Sensory examination was grossly normal. When he was assisted to stand up, myoclonic jerking movement was noted in bilateral lower extremities. Gait was not able to be assessed due to lower extremity weakness and spasticity.

The above history and examination findings were consistent with spastic paraparesis. Magnetic resonance imaging (MRI) of the brain reported nonspecific white matter microvascular disease. Cervical/thoracic spine MRI revealed no spinal cord signal abnormalities; however, there were multilevel degenerative disk and facet changes, C5-6 and C6-7 spinal canal stenosis, T4 and T5 vertebral body fusion, and posterior disk osteophyte complex at T7-8 level (Figure 1). These imaging findings were believed to be not significant enough to explain the patient's spastic paresis. Other serum markers for myelopathy work-up included normal copper

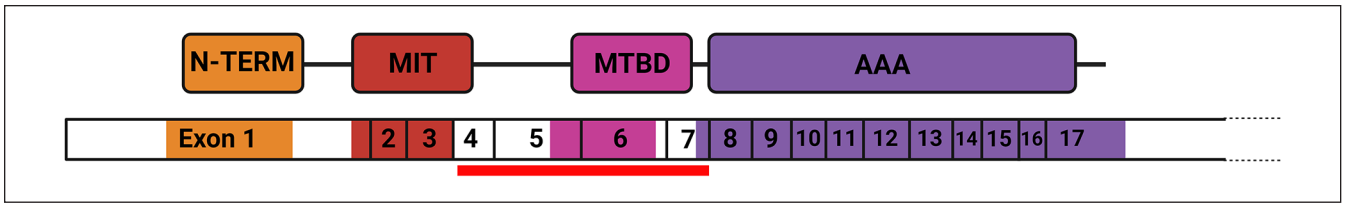

Figure 2. Domain structure of spastin and *SPAST*. Spastin is composed of the N-terminal domain, microtubule interacting and trafficking domain (MIT), the microtubule-binding domain (MTBD), and the AAA ATPase cassette (AAA). The corresponding exons on the mRNA coding for these regions are depicted above, with the deleted exons indicated with a red line. Figure adapted from Solowska et al.[8]

(102 [70-175] µg/dL) and vitamin B12 (415 [232-1245] pg/mL) levels. Although our patient carries a diagnosis of AS, serum HLA-B27, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), and rheumatoid factor (RF) all reported normal or negative. Given the significant family history of similar presentations, clinical diagnosis of HSP was suspected.

A HSP comprehensive genetic panel via array CGH (PreventionGenetics) revealed the patient was heterozygous for a novel 26.1 kb deletion (chr2:32, 323, 537-32, 349, 640 [GRCh37/hg19]) within the *SPAST* (NM 014046.3) gene, including exons 4-7, with breakpoints in introns 3 and 7 (Figure 2).[8] To confirm pathogenicity of this deletion mutation, further genetic testing of a family member (the patient's symptomatic daughter) was sought. By the time the genetic test was obtained, she was 48 years old with a history of bilateral lower extremity weakness and difficulty walking since her late thirties. Her neurological examination revealed lower extremity spasticity and bilateral positive Babinski signs. Genetic testing in this patient revealed the same 26.1 kb pathogenic deletion in *SPAST*. After the patient and his daughter were confirmed by the above genetic test, the patient's granddaughter from his affected daughter also presented to our clinic and asked to be tested. She reported symptoms of back pain and difficulty walking, but her neurological examination did not show any evidence of spasticity. She was not believed to be symptomatic from a phenotype standpoint. Her *SPAST* genetic test did not report the 26.1 kb deletion or any other abnormalities (Figure 3). Her work-up later on with spine MRIs did reveal lumbar spinal canal stenosis, which likely explained her symptoms.

Discussion

The clinical phenotypes of HSP can be further classified by the extent of central nervous system involvement into pure and complex forms. Pure, uncomplicated HSP is characterized by symptoms largely restricted to lower limb spasticity and gait impairment, sometimes extending to urinary urgency with minimal dorsal column involvement.[1,2,5] Complex cases of HSP are accompanied by other neurological deficits, such as dementia, cerebellar ataxia, cognitive or intellectual disabilities, seizures, peripheral neuropathy, and brain atrophy.[9-11] The median age of HSP onset and clinical progression vary significantly, even within mutations of the same subtype.[5,10,11]

An array of mutations exists across the 4 domains of spastin, consisting of the hydrophobic N-terminal domain (residues 1-87), the microtubule interacting and trafficking domain (MIT) (residues 116-194), the microtubule-binding domain (MTBD) (residues 270-328), and the AAA ATPase cassette (residues 342-616).[4,5,12] Since its characterization, many variants of HSP-*SPG4* have been identified, with mutations including missense, nonsense, insertion-deletions, and in splice sites.[5,13] Of these, at least 150 exon deletion mutations have been reported in all 17 exons of the *SPAST* gene, aside from the alternatively spliced exon 4.[14] The resultant destabilization in spastin causes improper microtubule severance, leading to impaired axonal transport and damage to the corticospinal tract.[1,2,4,5] Such mutations prevent adequate axonal transport and preferentially damage the axons of the corticospinal tract, although this mechanism has yet to be fully elucidated.[5,9,15]

Despite the vast documentation of exon deletions, not much progress has been made in correlating the loss of particular exons to the impact on the spastin protein. Even among *SPAST* variants that cause deletion of the same exon—including those that cause deletion of all 17 exons—age of onset and phenotype vary significantly among genotypes, although patients with exon deletions often have a significantly younger age of onset.[5,10,11]

In addition, reports indicate that approximately 18% to 20% of HSP cases harbor large deletions in *SPAST*, ranging from 1.3 to 1283.9 kb (mean 73.1 kb) and 40 to 50 combinations of exon deletions, with a myriad of pathogenic variations.[5,16] One explanation for the prevalence and diversity of such deletions is the *Alu*-rich architecture of the *SPAST* gene, increasing the vulnerability of the gene to *Alu*-mediated rearrangements.[16,17] Such deletions have been shown to destabilize spastin, with some affecting neighboring genes, and indicate haploinsufficiency as a cause of HSP.[5,14,16-18]

Here, we have documented a novel 26.1 kb deletion in *SPAST* including exons 4 to 7 in a US family, with clinical

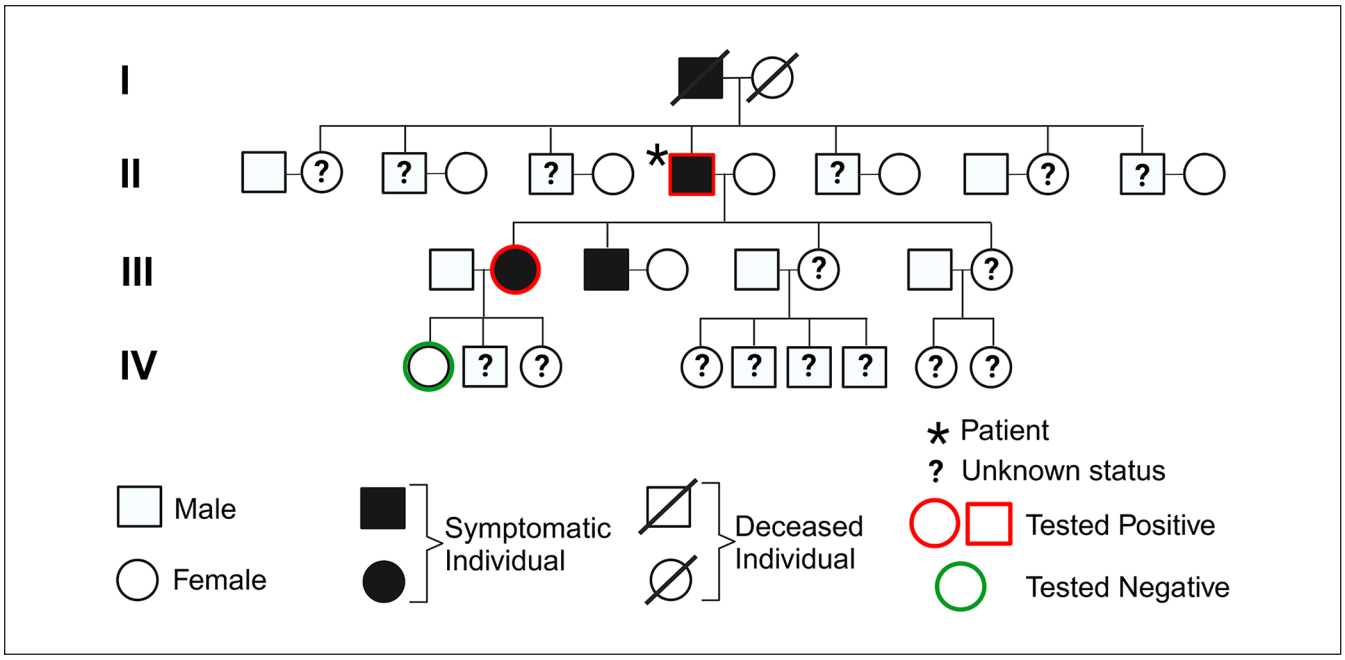

Figure 3. Family tree.

findings characteristic of HSP-*SPG4*. The novelty of the chr2:32, 323, 537-32, 349, 640 (GRCh37/hg19) deletion in *SPAST* (NM 014046.3) discovered in our clinic was established via search of genetic databases such as ClinVar and UniProt.[19,20] In our case, the precise consequences of the deletion on downstream processing of the gene are unclear and will need further analysis. However, based on previous reports of exon deletions in *SPAST*, we posit that, in our case as well, the transcript generated will be unstable, leading to haploinsufficiency of functional spastin protein.[14,18,21]

Here, the proband and his daughter demonstrated bilateral lower extremity weakness and spasticity of varying severity, which highlights the known heterogeneity of this disease, even among identical genotypes. It can be noted that this patient exhibited a much earlier age of onset than the average (25.4 years) reported by one large-scale case study on *SPAST* deletions, yet this clinical feature cannot currently be correlated to the location or size of the deletion alone.[14] This lack of clarity in the HSP genotype-phenotype relationship further highlights the need to report novel mutations in the *SPAST* gene alongside detailed history and physical examination findings.

In discussion of this case, it is important to note the late diagnosis of this patient and his daughter, despite a clear hereditary pattern of symptoms and significant debilitation of the disease in both affected members since childhood. Such a delay can likely be attributed to both lack of patient access to health care and the lack of awareness of rare hereditary diseases like HSP in general health care providers. As a matter of fact, our case carries a historical diagnosis of AS, and for many years, he and his family believed the AS was the cause of his lower extremity weakness and difficulty walking. Although we do not have any records from his previous physicians to verify the diagnosis retrospectively, we think that this could be a misdiagnosis, as his most recent pan-spine MRI did not report any typical findings suggesting AS, and his serum HLA-B27 reported negative.

As a result of the late presentation and diagnosis of this family, we are unable to clearly document progression of symptoms from first onset in childhood. Much work is needed to be done in educating health care providers, particularly those practicing in underserved communities, on rare genetic diseases and the large impact that going undiagnosed can have on patients and their families.

Conclusions

We have reported here a novel pathogenic variant of *SPAST* across at least 2 generations in a southeastern US family, although we suspect this mutation may be present in other, untested family members. Genomic testing, along with a thorough search of online genetic databases, confirmed the novelty and pathogenicity of the mutation. However, despite the significant documentation of *SPAST* mutations in the literature, along with that which was discussed here, there is still much to be learned about such variants and their implications on clinical presentation and treatment. Such a gap in knowledge is further exacerbated by barriers to health care and subsequent diagnosis, as mentioned in the case of this family. Future studies should aim to mend the gap in understanding how *SPAST* mutation variants correlate to clinical phenotypes.

Author Contributions

J.H.: Patient diagnosis and treatment.
S.B.B., J.H.: Writing and editing the manuscript.
S.B.B.: Preparing the figures.

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Our institution does not require ethical approval for reporting individual cases.

Informed Consent

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