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RESEARCH ARTICLE

Expanding the Genotypic and Phenotypic Spectrum of *AP5Z1*-Related Spastic Paraplegia: A Novel Variant and Comprehensive Literature Review

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ABSTRACT

Background: Hereditary spastic paraplegias are a diverse group of neurodegenerative diseases, clinically divided into pure and complex types. Spastic paraplegia 48 is caused by pathogenic biallelic variants in the *AP5Z1* gene. Our study aims to expand the phenotypic and genotypic spectrum in this very rare syndrome.

Materials and Methods: Case files, detailed anamnesis, radiological imaging, physical examination findings, ophthalmological examination and genetic results were evaluated as part of the clinical assessment. Whole-exome sequencing was performed for the proband. Sanger sequencing and next-generation sequencing were performed for confirmation of the variants and segregation analysis.

Results: We identified two disease-causing variants in the *AP5Z1* (NM_014855.3) gene, including a pathogenic nonsense variant (c.1322G > A, p.(Trp441Ter)) and a pathogenic frameshift variant (c.857_866del, p.(Leu286ProfsTer25)). Segregation analysis showed compound heterozygosity of the variants.

Conclusion: In this report, we present a patient from Turkey with spasticity, who has compound heterozygous variants in the *AP5Z1* gene, representing the 17th case described in the literature. This report expands the phenotypic spectrum of the *AP5Z1*-related spastic paraplegia type 48, which has only rarely been reported in the literature. It underscores the importance of comprehensive genetic testing and variant interpretation in achieving an accurate diagnosis and providing genetic counselling for affected families with spastic paraplegia.

1 | Introduction

Hereditary spastic paraplegias (HSPs) are a heterogeneous group of neurodegenerative disorders, clinically classified in pure and complex forms. Genetically, more than 70 different forms of HSP have been characterized (Schule and Schols 2011; Finsterer et al. 2012; Fink 2013; Novarino et al. 2014). Pure HSPs present progressive spasticity and weakness of the lower limbs, often associated with mild sensory abnormalities and urinary dysfunctions. Complicated forms encompass the previous clinical features associated with a large variety of additional neurological and non-neurological manifestations, including cerebellar signs, amyotrophy, peripheral neuropathy, optic atrophy, cognitive decline, deafness, retinopathy or cataracts (Finsterer et al. 2012; Fink 2013; Harding 1983). Disease-causing variants exhibit closely overlapping clinical features, which include thin

corpus callosum, retinal abnormalities, sensory and motor neuropathy, mild ataxia, cognitive impairment and parkinsonism (Pensato et al. 2014).

Spastic paraplegia 48 (SPG48) is a rare autosomal recessive neurodegenerative disorder caused by pathogenic variants in the *AP5Z1* gene (OMIM #613653), which encodes the zeta-1 subunit of the adaptor-related protein complex 5 (Hirst et al. 2015). Clinically, SPG48 is characterized by a broad spectrum of neurologic and systemic manifestations. Central nervous system involvement includes lower limb spasticity and weakness, spastic and wide-based gait, ataxia, dysmetria and parkinsonism (Pensato et al. 2014; Hirst et al. 2016; Slabicki et al. 2010). Cognitive decline of adult onset has been reported, along with thin corpus callosum and periventricular white matter abnormalities on neuroimaging. Peripheral neuropathy has also been described. Adult cases usually exhibit more complex clinical features, including urinary dysfunction, cognitive decline, cerebellar signs and parkinsonism, reflecting a more advanced neurodegenerative process. In contrast, childhood-onset SPG48 may initially present with mild neurodevelopmental manifestations, such as global developmental delay, before motor symptoms become apparent (Papoff et al. 2024). Systemic features also include urinary incontinence. Additionally, ocular manifestations such as retinopathy, cataracts, glaucoma and nystagmus have been reported in individuals with SPG48 (Hirst et al. 2016; Slabicki et al. 2010; Papoff et al. 2024; Jin et al. 2023; Wei et al. 2019; Schlipf et al. 2014).

To the best of our knowledge, only 16 cases of *AP5Z1*-related spastic paraplegia have been described in the literature (Pensato et al. 2014; Hirst et al. 2015; Hirst et al. 2016; Slabicki et al. 2010; Papoff et al. 2024; Jin et al. 2023; Wei et al. 2019; Schlipf et al. 2014; D'Amore et al. 2018; Maruta et al. 2020). Here, we report the 17th known case of *AP5Z1*-related spastic paraplegia: a case from Turkey presenting with spasticity and carrying compound heterozygous variants in the *AP5Z1* gene, further expanding the current understanding of the phenotypic variability and genetic heterogeneity associated with this rare neurodegenerative disorder.

2 | Materials and Methods

The case file, detailed anamnesis, family history, pedigree analysis, neurological and ophthalmological examination findings, brain magnetic resonance imaging (MRI), electromyography, optical coherence tomography (OCT) and genetic results were evaluated.

Genomic DNA was isolated from peripheral blood leukocytes. DNA extraction was performed using the HiPurA prefilled clinical multipurpose nucleic acid purification kit and the HIMEDIA InstaN Mag-96 system. DNA concentrations were measured using the Qubit fluorometer (Thermo Fisher Scientific, USA). Whole-exome sequencing (WES) was performed for the proband. WES was conducted using the Roche KAPA HyperExome 96 rxn kit and sequenced on the MGI DNBSEQ-G400 platform. Raw sequencing data (FastQ files) were analysed using the Genomize SEQ platform (version 8.7.0; https://seq.genomize.com). Variant filtering involved two major steps: filtering out all nonsense, missense, frameshift, splice site, indel, in-frame and synonymous variants and retention of variants with a minor allele frequency (MAF) < 1.0% in population databases including 1000 Genomes (1000G), the Exome Sequencing Project (ESP), the Exome Aggregation Consortium (ExAC) and the Genome Aggregation Database (gnomAD). Visualization of sequencing data was performed using the Integrative Genomics Viewer (IGV). The novel variant was queried in the Human Gene Mutation Database (HGMD), Mastermind Genomic Search Engine (Genomenon Inc.), ClinVar (http://ncbi.nlm.nih.gov/clinvar) and literature. Pathogenicity predictions were made using in silico tools such as MutationTaster and Combined Annotation Dependent Depletion (CADD). Variant classification followed the guidelines of the American College of Medical Genetics and Genomics (ACMG) (Richards et al. 2015). The identified variants were validated, and familial segregation analysis was carried out using Sanger sequencing and next-generation sequencing (NGS).

Informed consent was obtained from the case prior to the collection of clinical, radiological and genetic data for this study. Ethical approval for the study was obtained from the local ethics committee (decision number: 2025/271, date: 01/07/2025).

3 | Case Presentation

A 72-year-old male case was referred to our medical genetics outpatient clinic by the department of neurology, with complaints of progressive difficulty in walking. His symptoms began approximately 7 years ago with pain in the lower extremities, followed by weakness. He has been suffering with numbness in the soles of his feet for the past 5 years. He described a progressive worsening of his symptoms over the past 2 years. Medical history revealed hypertension and diabetes mellitus, mild hearing loss and spastic bladder. Although the parents were not known to be consanguineous, they originate from the same small town, raising the possibility of distant or unrecognized consanguinity (Figure 1).

On physical examination, proximal muscle strength of the lower extremities was bilaterally 4/5. Bilateral Babinski signs were positive, and deep tendon reflexes were increased in the lower

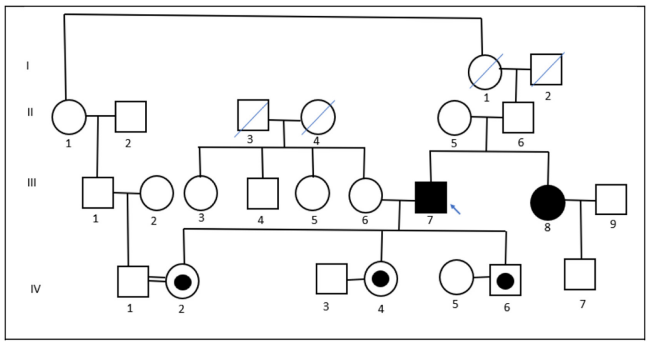

FIGURE 1 | Pedigree of the family. The squares indicate males, and the circles indicate females. The proband (III-7) is indicated by a blue arrow. The patient's son (IV-6) and daughters (IV-2, IV-4) were characterized by heterozygous variations. The patient's affected sister refused to be tested.

extremities. Sensory examination revealed hypoesthesia below the knees, bilaterally. Spasticity was detected in the left lower extremity. No myoclonus was observed. No cognitive deficit or dysmetria was observed.

The patient was able to walk short distances with single support. The Spastic Paraplegia Rating Scale (SPRS) score was 30. Electroneuromyography (ENMG) revealed a prominent mixed-type sensorimotor polyneuropathy in the lower extremities. There were no findings suggestive of seizures in the case's history. Electroencephalography (EEG) was normal. Abdominal and thoracic computed tomography (CT) scans were normal. A 24-h urine copper and the paraneoplastic panel results were negative.

Brain MRI showed a mild brain atrophy with periventricular white matter hyperintensities on fluid-attenuated inversion recovery (FLAIR) sequences (Figure 2).

In the comprehensive ophthalmological examination of the case, the visual acuity with the Snellen chart was 0.6 in the right eye and counting fingers at 2 m in the left eye due to bilateral severe pterygium. Bilateral retinal pigmentary changes and symmetrical cupping on the optic disc were detected. The intraocular pressure measured with Goldmann applanation tonometry was 11 mmHg in both eyes. Evaluation with OCT (RTVue-XR Avanti, Optovue, Fremont, CA, USA) revealed the parafoveal atrophic areas in the macular ganglion cell complex (GCC, which includes the axons, cell bodies and dendrites of ganglion cells; the retinal nerve fibre layer; the ganglion cell layer; and the inner plexiform layer) (Figure 3), but the peripapillary retinal nerve fibre thickness could not be measured due to pterygium.

4 | Genetic Results

WES performed in the proband identified two disease-causing variants (c.1322G > A and c.857_866del) in the *AP5Z1* gene. The c.1322G > A, p.(Trp441Ter) variant is a nonsense variant that has been reported in the ClinVar database (Variation ID: 375313) and is classified as pathogenic (PVS1, PM2_sup, PM3) according to ACMG criteria. The c.857_866del, p.(Leu286ProfsTer25) variant is a novel frameshift variant not previously reported in the ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and gnomAD (https://gnomad.broadinstitute.org/) databases and

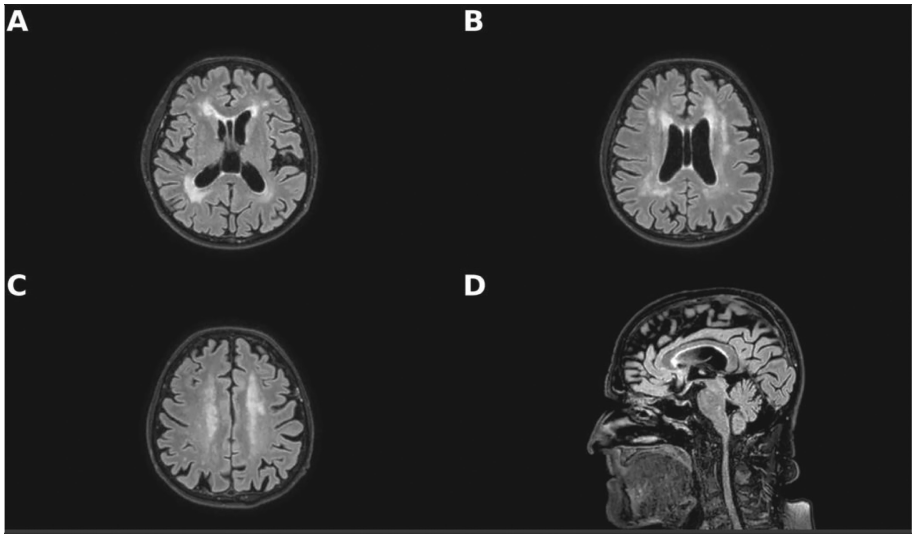

FIGURE 2 | Brain magnetic resonance imaging of the case. (A–C) FLAIR sequences reveal high signal changes in the periventricular white matter and mild brain atrophy. (D) The corpus callosum appears to be of normal thickness on the sagittal FLAIR sequence.

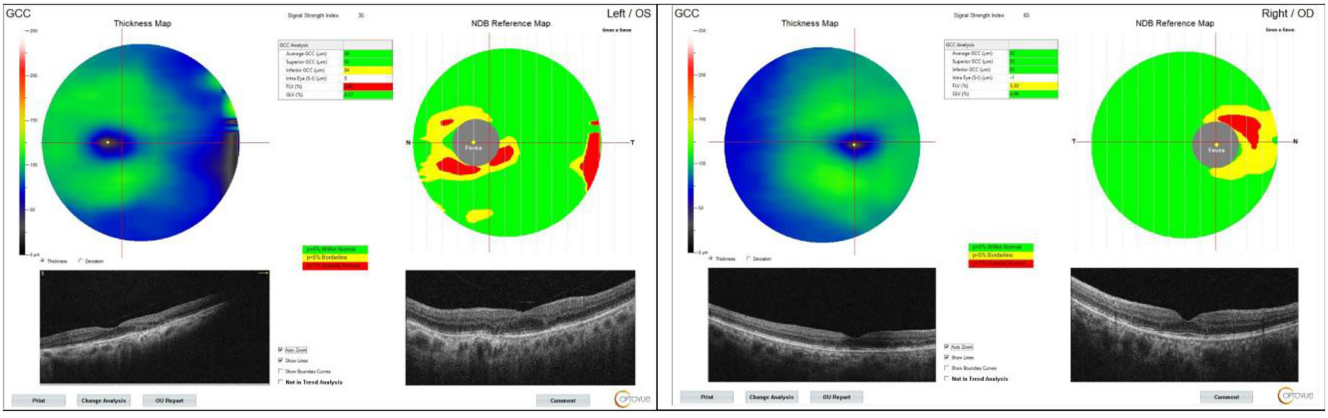

FIGURE 3 | The macular ganglion cell complex thickness map of the case's optical coherence tomography shows parafoveal thinning.

TABLE 1 | Literatüre review of *AP5Z1*-related SPG48 cases.

References	Our case	Slabicki et al. (2010)	Slabicki et al. (2010)	Pensato et al. (2014)	Pensato et al. (2014)	Schlipf et al. (2014)	Hirst et al. (2016)	Hirst et al. (2016)	Hirst et al. (2016)
Sex/age at onset	M/65 years	F/50 years	M/49 years	F/47 years	F/1 year	F/43 years	M/60y	M/39y	F/40y
Nationality	Turkish	French	French	Italian	Moroccan	German	German	Belgian	Belgian
Genotype	c.857_866del (p.Leu286ProfsTer25) and c.1322G > A(p.Trp441Ter), compound heterozygous	c.80_83del4, homozygous	79_84ins22(p.R27Lfs*3), homozygous	c.412C > T(p.Arg138*) and c.1322G > A(p.Trp441*), compound heterozygous	c.616C > T(p.R206W), homozygous	c.874C > T(p.R292W) and c.2267C > T(p.T756I), heterozygous	c.1732C > T(p.Q578*), homozygous	c.412C > T(p.R138*) and c.1033C > T(p.R345*), heterozygous	c.412C > T(p.R138*) and c.1033C > T(p.R345*), heterozygous
Neurologic signs	Spastic paraplegia, hyperreflexia and Babinski sign, hypoesthesia below the knees bilaterally, lower limb spasticity, lower limb weakness, spastic gait, wide-based gait, sensorimotor polyneuropathy	Spastic paraplegia	Spastic paraplegia	Spastic paraplegia, wide-based gait, mild dysmetria at upper limbs	Spastic paraplegia, mild intellectual disability, psychomotor delay and walking abnormalities (tiptoes gait), spastic paraparesis	Spastic paraplegia, cerebellar dysfunction, myokymia	Spastic paraplegia, spastic dysarthria, parkinsonism, limb ataxia, mild motor and sensory polyneuropathy, foot dystonia, mild distal muscle weakness	Spastic paraplegia, parkinsonism, limb ataxia, moderate axonal mixed polyneuropathy/distal amyotrophy, mild intellectual disability, spastic and ataxic gait, exaggerated deep tendon reflexes, positive Babinski sign, distal lower limb weakness, cerebellar speech and hypomimia	Spastic paraplegia, parkinsonism, limb ataxia, dysarthria, moderate axonal mixed polyneuropathy, mild intellectual disability, limb dystonia, spastic ataxic gait, limb dysmetria, brisk lower limbs reflexes, bilaterally positive Babinski sign
Ophthalmological finding	Bilaterally retinal pigmentary changes, mild decreased visual acuity, symmetrical cupping of the optic disc, parafoveal atrophic areas in the macular ganglion cell complex, mild cataract	NA	NA	NA	NA	Bilateral congenital nystagmus	Bilaterally pigmentary retinopathy, macular degeneration, posterior subcapsular cataracts, choroidal depigmentation and pigment clumping around the optic nerves, partial macular hole in the left eye	Pigmentary retinopathy, cataracts, bilaterally lens sclerosis	Bilateral pigmentary retinopathy, mild cataracts, lens sclerosis, hypometric saccades, glaucoma

(Continues)

TABLE 1 | (Continued)

References	Our case	Slabicki et al. (2010)	Slabicki et al. (2010)	Pensato et al. (2014)	Pensato et al. (2014)	Schlipf et al. (2014)	Hirst et al. (2016)	Hirst et al. (2016)	Hirst et al. (2016)
Genitourinary	Urinary incontinence	Urinary incontinence	Urinary incontinence	Urinary incontinence	NA	NA	Spastic bladder	Spastic bladder	Spastic bladder
Brain MRI	Periventricular white matter hyperintensities, mild brain atrophy	Normal	Spinal hyperintensities at C3–C4 and C7	Severe narrowing of corpus callosum and hyperintense white matter lesions at the frontal horns of lateral ventricles	Mild narrowing of corpus callosum at the isthmus part with periventricular hyperintense white matter lesions	Normal	Periventricular T2 hyperintense white matter lesions 'ears of the lynx' sign, mild cortical atrophy and	Hyperintense white matter lesions, focal atrophy of the corpus callosum	Hyperintense white matter lesions
Other clinical symptoms	Mild hearing loss	NA	NA	NA	NA	NA	Mild hearing loss	NA	NA

References	Hirst et al. (2016)	Hirst et al. (2016)	Hirst et al. (2016)	D'Amore et al. (2018)	Wei et al. (2019)	Maruta et al. (2020)	Jin et al. (2023)	Papoff et al. (2024)
Sex/age at onset	M/52y	F/Childhood	M/13 years	NA	M/58 years	F/47 years	M/53 years	F/5 years
Nationality	Belgian	NA	Kuwaitis	Italian	Chinese	Japanese	Chinese	NA
Genotype	c.412C > T(p.R138*) and c.1033C > T(p.R345*), heterozygous	c.1364C > T(p.P455L), homozygous	c.500C > A(p.T167N) and c.2010C > A(p.F670L), heterozygous	c.1302-1G > T and c.2287G > A(p.V763M), heterozygous	c.164C > T(p.T55M) and c.923G > C(p.S308T), heterozygous	c.1662_1672del(p.Q554Hfs*15), homozygous	c.1133-345_1311 + 249del (p.G378Vfs*93X), homozygous	c.622–2A > T; c.1132G > A (p.Gly378Arg)
Neurologic signs	Spastic paraplegia, limb ataxia, spastic ataxic gait, mild intellectual disability, accentuated lower limb reflexes, bilaterally extensor toe response, dysdiadochokinesis in both hands, slow saccades	Spastic paraplegia sensory-motor polyneuropathy, amyotrophy, absent deep tendon reflexes	Spastic paraplegia, limb ataxia, mild intellectual disability, intellectual regression at age 13, myoclonus, limb dystonia, brisk reflexes, ankle clonus, positive Babinski sign on the left	Spastic paraplegia	Spastic paraplegia, peripheral neuropathy, brisk patellar reflexes, ankle clonus, unilaterally Hoffmann sign, enhanced reflexes of upper limbs	Spastic paraplegia, cramps in foot and hands, spastic gait, weakness in the lower limbs, brisk reflexes in all limbs	Spastic paraplegia, cognitive impairment, peripheral neuropathy, weakness at lower limbs, bilateral spastic gait, tendon hyperreflexia, ankle clonuses, bilateral pyramidal signs, positive Romberg's test, spastic dysarthria	Spastic paraplegia, language delay, hyperreflexia, positive Babinski sign, clumsy gait, brisk deep tendon reflexes with ankle clonus, borderline intellectual functioning
Ophthalmological finding	Pigmentary retinopathy, cataracts	NA	Hypometric saccades	NA	NA	NA	NA	'Round-the-house' sign in vertical saccades, ptosis
Genitourinary	Spastic bladder	No	Spastic bladder	NA	NA	NA	NA	NA

(Continues)

TABLE 1 | (Continued)

References	Hirst et al. (2016)	Hirst et al. (2016)	Hirst et al. (2016)	D'Amore et al. (2018)	Wei et al. (2019)	Maruta et al. (2020)	Jin et al. (2023)	Papoff et al. (2024)
Brain MRI	Hyperintense white matter lesions	Normal	Hyperintense white matter lesions, mild leukoencephalopathy and thinning of corpus callosum	NA	Normal	Hyperintense white matter lesions and narrowing of corpus callosum	Hyperintense white matter lesions and mild brain atrophy	Hyperintense white matter lesions at the apices of the frontal horns of the lateral ventricles
Other clinical symptoms	NA	NA	NA	NA	NA	NA	Hearing loss sensorineural deafness, azoospermia, mild	Normal

is classified as pathogenic (PVS1, PM2_sup, PM3) according to ACMG criteria. Segregation analysis revealed heterozygosity for the c.1322G > A variant in the patient's son, while both daughters showed heterozygosity for the c.857_866del variant.

The clinical findings of our case and 16 previously reported cases are summarized in Table 1. Among neurological features, spastic paraplegia and spasticity were observed in all patients (17/17, 100%), while exaggerated deep tendon reflexes were present in 29% (5/17), clonus in 23% (4/17), parkinsonism in 17% (3/17), cerebellar dysfunction in 41% (7/17) and intellectual disability in 41% (7/17). Brain MRI findings included white matter lesions in 68% (11/16), thin corpus callosum in 31% (5/16) and mild brain atrophy in 18% (3/16). Ophthalmological abnormalities were reported in a subset of patients: pigmentary retinal changes in 62% (5/8) and cataracts in 62% (5/8). Urinary incontinence was documented in 44% of cases (4/9) and spastic bladder in 55% (5/9).

To the best of our knowledge, 17 variants in the *AP5Z1* gene have been reported in the literature as being associated with the disease. A schematic representation of the reported variants across the exons is shown in Figure 4.

5 | Discussion

HSPs are genetically and clinically a heterogeneous group of neurodegenerative disorders characterized primarily by progressive lower limb spasticity and weakness. Biallelic pathogenic variants in the *AP5Z1* gene have been associated with SPG48 (*OMIM* #613653). Our case contributes new insights into the phenotypic spectrum and genetic landscape of this condition.

AP5Z1, the gene implicated in SPG48, encodes the ζ subunit of the adaptor protein complex 5 (AP-5), which is thought to be involved in intracellular vesicular trafficking and the regulation of autophagic flux (Hirst et al. 2013). AP-5, in coordination with other HSP-related proteins, such as spatacsin and spastizin, facilitates the recruitment of late endosomes and lysosomes. These proteins are also functionally linked to the mTORC1 signalling pathway, collectively contributing to autophagic lysosome reformation (Chang et al. 2014). Papoff et al. (2024) performed Western blot analysis on cultured skin fibroblasts from a patient with SPG48 and reported decreased expression of the AP5Z1 and spastizin proteins, increased levels of core autophagy-related proteins such as ATG9A and ATG5–ATG12 and reduced expression of lysosomal function markers including LAMP1 and NPC1. In AP-4 complex disorders, abnormalities in the key autophagy regulators ATG5–ATG12 and ATG9A have also been reported. Dysfunctions in this family of proteins are associated with both neurodevelopmental and neurodegenerative disorders (Davies et al. 2018).

Although SPG48 typically manifests during adulthood, literature data indicate a considerable variability in age at onset, ranging from early childhood to late adulthood (Pensato et al. 2014; Hirst et al. 2016; Papoff et al. 2024). The majority of reported cases presented with symptoms in the fourth to sixth decades of life, with onset ages between 39 and 60 years (Pensato et al. 2014; Slabicki et al. 2010; Jin et al. 2023; Wei et al. 2019; Schlipf et al. 2014; Maruta et al. 2020). A paediatric onset has also been described, as in a Moroccan case who presented since the first

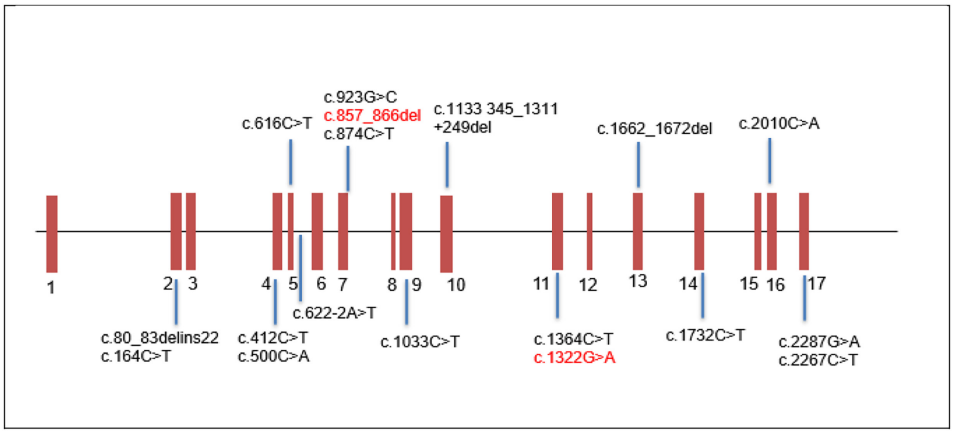

FIGURE 4 | Schematic representation of the *AP5Z1* gene. Variants identified in the present study are highlighted in red, including one previously reported pathogenic variant, c.1322G > A, p.(Trp441Ter), and one novel variant, c.857_866del, p.(Leu286ProfsTer25), while other previously reported pathogenic variants are depicted in black.

year of life with mild psychomotor delay and walking abnormalities and developed spastic paraparesis at the age of 3 (Pensato et al. 2014). Despite this variability, symptom onset beyond the age of 60 has not been previously reported in the literature. Our case presented with initial symptoms of lower limb pain and weakness at the age of 65, representing the oldest reported onset of SPG48 to date. The proband's affected sister declined genetic testing. According to the available clinical information, she is 65 years old and developed gait difficulties at approximately 63 years of age. Although molecular confirmation is lacking, this observation suggests a similarly late-onset phenotype within the family. However, further phenotypic comparison could not be performed due to the absence of detailed clinical data.

When compared with previously published cases, our case shares several common features, such as spastic paraplegia, urinary incontinence and hyperintense white matter lesions on neuroimaging (Pensato et al. 2014; Hirst et al. 2016; Slabicki et al. 2010; Papoff et al. 2024; Jin et al. 2023; Wei et al. 2019; Schlipf et al. 2014; D'Amore et al. 2018; Maruta et al. 2020). Similar MRI findings have been described by Pensato et al. and Hirst et al., including periventricular white matter lesions (Pensato et al. 2014; Hirst et al. 2016; Papoff et al. 2024; Jin et al. 2023; Maruta et al. 2020). Unlike most previous cases, our case did not exhibit cognitive impairment or overt ataxia, suggesting a relatively pure motor presentation with selective extrapyramidal involvement. This variability has also been noted in earlier studies, with some cases displaying parkinsonism, myoclonus and intellectual disability, while others presented with isolated spasticity.

In the series reported by Hirst et al. (2013, 2015, 2016), ophthalmological findings were described in five out of six cases. These findings included bilateral congenital nystagmus, pigmentary retinopathy, macular degeneration, bilateral posterior subcapsular cataracts, choroidal depigmentation, peripapillary pigment clumping, partial macular hole, lens sclerosis, glaucoma, hypometric saccades and optic disc cupping (Hirst et al. 2016). In our case, ophthalmological evaluation revealed reduced visual acuity due to bilateral severe pterygium. Bilateral retinal pigmentary changes and symmetrical optic disc cupping were observed. Although intraocular pressure was within normal limits, OCT imaging demonstrated parafoveal atrophic changes in the macular GCC, including the retinal nerve fibre layer, ganglion cell layer and inner plexiform layer. Compared to the more severe ocular phenotypes reported by Hirst et al., the absence of lens involvement and oculomotor signs in our case may indicate a milder or distinct variant within the same clinical spectrum. The variability of these ocular manifestations across cases underscores the phenotypic heterogeneity of ocular involvement in this disorder. Moreover, features such as cataracts, observed in our case, have also been reported in the cohort described by Hirst et al. (2016), further supporting the phenotypic overlap.

Pensato et al. (2014) reported a case harbouring the same previously described heterozygous c.1322G > A variant in the *AP5Z1* gene, along with a second variant, c.412C > T. When the clinical features of their case are compared to ours, notable similarities and differences emerge. Adult-onset spastic paraplegia and urinary dysfunction were common findings in both cases, suggesting a shared core phenotype. However, the age of onset was 47 years in the case reported by Pensato et al. (2014), whereas our case presented at 65 years of age, indicating a potentially milder or more slowly progressive disease course. Furthermore, while our case exhibited marked sensorimotor polyneuropathy on ENMG, the previously reported case had normal peripheral nerve conduction studies but showed significantly abnormal motor evoked potentials (MEPs), pointing to differing levels of central and peripheral nervous system involvement. In our case, a brain MRI revealed mild atrophy and periventricular white matter hyperintensities, in contrast to the anterior thinning of the corpus callosum and frontal white matter changes observed in the other case. In addition, ophthalmological findings unique to our case, such as pigmentary retinopathy and macular GCC atrophy, may reflect the modifying effects of the second variant or other genetic and/or environmental factors. Comparative analyses such as this contribute valuable insights into the genotype–phenotype correlations in this disorder.

6 | Conclusion

In conclusion, this case represents the 17th reported instance of *AP5Z1*-related SPG48 and currently the patient with the latest-onset presentation described in the literature, further emphasizing the rarity of this neurodegenerative condition.

The identification of the previously reported pathogenic variant c.1322G > A, p.(Trp441Ter), together with the novel variant c.857_866del, p.(Leu286ProfsTer25), broadens the variant spectrum of *AP5Z1* and supports continued molecular investigation in similar presentations.

Clinical findings in our patient highlight the considerable phenotypic variability of SPG48. Age of onset is variable, brain MRI findings are non-specific and routine neurological and ophthalmological evaluations alone are often insufficient to distinguish HSP subtypes. Moreover, the absence of comprehensive systemic assessments, particularly ophthalmological examinations reported in previous cases, suggests that relevant clinical features may be underrecognized. These factors increase the risk of missed or delayed diagnosis.

Given the autosomal recessive inheritance pattern and potential consanguinity in some regions, comprehensive genetic testing, including WES, remains essential for accurate diagnosis, prognostic counselling and family planning. Because AP5Z1 dysfunction impairs autophagy, patients with SPG48 may become candidates for future targeted therapeutic approaches as autophagy-modulating treatments evolve.

This report reinforces the clinical value of molecular confirmation and careful variant interpretation in rare HSPs and supports broader surveillance for underdiagnosed adult-onset cases.

7 | Limitations

Limitations of this study include the absence of a PRISMA-guided systematic literature review and the lack of functional assays to validate the pathogenicity and biological consequences of the identified variants.

Author Contributions

Z.E. performed and interpreted the genetic tests and clinical examinations, wrote the manuscript and collected data. E.B. collected the data and wrote the manuscript. S.S. and G.E.K. made neurological evaluations. D.A. provided support for ophthalmological evaluation.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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