Turkish Journal of Neurology

Turk J Neurol 2024;30(4):236-243
Doi: 10.55697/tnd.2024.12

ORIGINAL ARTICLE

The role of spastin and paraplegin genes in primary progressive multiple sclerosis

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ABSTRACT

Objectives: This study aimed to detect the presence of mutations in the spastin (SPG4) and paraplegin (SPG7) genes in patients with primary progressive multiple sclerosis (PPMS) to determine the role of hereditary spastic paraplegia (HSP) genes on the susceptibility to PPMS, clinical course, and severity and to reveal its potential role on motor pathways leading to spastic paraparesis clinic.

Patients and methods: The descriptive study was conducted with 25 patients with PPMS. The patients were divided into two groups: those presenting with (n=16; 8 males, 8 females; mean age: 47.2±8.4 years; range, 32 to 58 years) and without (n=9; 5 males, 4 females; mean age: 42.8±5.8 years; range, 34 to 49 years) spastic paraparesis. The SPG4 and SPG7 genes from the purified DNAs, which were isolated from blood samples, were sequenced to include all exons and introns. The variations detected as a result of the analysis were evaluated in terms of the suitability of the reading parameters. The frequency of variants in populations and the number of homozygous variants in individuals were analyzed with the gnomAD (Genome Aggregation Database). Of the detected variants, only pathogenic and possibly pathogenic variants that could be clinically associated were reported.

Results: In the genotyping of the two groups with PPMS, both with and without spastic paraparesis, no pathogenic or probable pathogenic variant was observed in terms of SPG4 and SPG7 genes.

Conclusion: We found no evidence that the SPG4 and SPG7 genes were involved in the pathogenesis, clinical course, and severity of PPMS. However, the question of what kind of effects these genes have on susceptibility to multiple sclerosis and the course remains unclear.

Keywords: Hereditary spastic paraplegia, multipl sclerosis, paraplegin (SPG7), spastin (SPG4).

Several single gene disorders share clinical and radiologic characteristics with multiple sclerosis (MS) and have the potential to be overlooked in the differential diagnostic evaluation of both adult and pediatric patients with MS.[1] Primary progressive multiple sclerosis (PPMS) is characterized by a gradual accumulation of disability that may occur from the onset of the disease. The underlying disease mechanisms of PPMS are complex and involve a variety of different mechanisms and pathways, including inflammation, axonal degeneration, microglial activation/oxidation byproducts, mitochondrial damage, and glutamate excitotoxicity.[2] In addition, a genetic predisposition is thought to play a role in the pathogenesis and phenotypic expression of PPMS, and in some cases, pathogenic genes that could contribute to progressive disability independent of immune system-mediated mechanisms were also identified.[3]

Hereditary spastic paraplegia (HSP) is a rare group of neurodegenerative diseases characterized by high genetic heterogeneity and progressive spasticity and weakness in the lower extremities.[4] The emergence

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Received: January 05, 2024 **Accepted:** September 18, 2024 **Published online:** December 20, 2024
Cite this article as: Çopuroğlu B, Uca AU, Zamani AG, Yıldırım MS, Altaş M, Okur Altındaş B. The role of spastin and paraplegin genes in primary progressive multiple sclerosis. Turk J Neurol 2024;30(4):236-243. doi: 10.55697/tnd.2024.12.

of white matter lesions in the central nervous system in some HSP variants and additional symptoms such as cognitive dysfunction, ataxia, and optic neuropathy with spastic paraplegia may complicate the differential diagnosis with PPMS.[5] In recent years, beyond clinical and radiological similarity, the detection of HSP-related spastin (SPG4) and paraplegin (SPG7) gene mutations in some PPMS has raised questions about whether this represents comorbidity or a pathogenic relationship.[6,7]

Mutations in the SPG4 locus mapped to chromosome 2p22.[3] cause the most common autosomal dominant form of HSP.[8] The SPG4 gene encodes spastin, a 795 amino acid protein, a member of the AAA (ATPase associated with various cellular activities) protein family. By sharing an ATPase domain, spastin plays important roles in a variety of cellular critical processes, including membrane trafficking, intracellular motility, organelle biogenesis, protein folding, and proteolysis.[9] It is also an ATPase microtubule severing enzyme that promotes cytoskeletal remodeling associated with membrane remodeling.[10] In addition, spastin has key functions in axonal transport and regeneration in neurons.[11]

The SPG7 locus mapped to chromosome 16q24.3 is responsible for an autosomal recessive HSP.[12,13] The SPG7 gene encodes paraplegin, a member of the AAA protein family.[13,14] Paraplegin is located in the mitochondrial inner membrane and plays a role in proteolytic and chaperone-like functions.[13] Studies showed that loss of paraplegia caused complex I deficiency and increased sensitivity to oxidative stress.[15] Paraplegin is also required for ribosome assembly and translation in mitochondria.[16]

The fact that PPMS and HSP show similar progressive degeneration in the corticospinal tract axons, coupled with the association of some MS cases with HSP, has led to the hypothesis of a pathogenetic relationship between these two diseases. Hence, this study aimed to examine the presence of SPG4 and SPG7 gene mutations in patients with PPMS to determine the role of HSP genes on the susceptibility, clinical course, and severity of PPMS, as well as to reveal the possibility of their effects on the motor pathways that lead to spastic paraparesis.

PATIENTS AND METHODS

The descriptive study was conducted with 25 patients diagnosed with PPMS in accordance with Polman et al.'s[17] diagnostic criteria for MS, a revision to the McDonald criteria. The patients were followed in the neurology outpatient clinic of the Necmettin Erbakan University, Meram Faculty of Medicine Hospital, between September 2020 and February 2021. The patients were divided into two groups: those with spastic paraparesis similar to HSP (Group 1, n=16; 8 males, 8 females; mean age: 47.2±8.4 years; range, 32 to 58 years) and those without spastic pareparesis (Group 2, n=9; 5 males, 4 females; mean age: 42.8±5.8 years; range, 34 to 49 years). Patients diagnosed with clinically isolated syndrome, radiologically isolated syndrome, relapsing-remitting MS (RRMS), or secondary progressive MS (SPMS) were excluded from the study. A control group was not formed since pathogenic variants were not expected in the normal population for the SPG4 and SPG7 genes. The study protocol was approved by the Necmettin Erbakan University, Meram Faculty of Medicine Ethics Committee for Non-Pharmaceutical and Medical Device Research (2020/2800 decision number). Written informed consent was obtained from all participants before the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Neurological and physical examinations of all patients were performed by the same neurologist. Demographic characteristics, age at onset of disease, age at diagnosis, duration of disease, disability score measured by the Expanded Disability Status Scale (EDSS), and other associated clinical features were recorded.

The remnants of blood taken routinely during the examinations were included in the study. After the blood samples were taken into EDTA tubes, they were kept in a cooler at –20°C in the genetics laboratory.

Peripheral blood samples taken from the patient group were automatically isolated using the MagPurix Blood DNA Extraction Kit 200 with the MagPurix 12A Automated Nucleic Acid Purification Instrument (Zinexts Life Science Corporation, New Taipei City, Taiwan). It was confirmed that the DNA samples of all individuals were isolated with quality control. Obtained samples were amplified by polymerase chain reaction using appropriate temperature regulation with the SimpliAmp Thermal Cycler device (Thermo Fisher Scientific Inc., Waltham, MA, USA). After preparing the cDNA library from the purified DNAs obtained, SPG4 and SPG7 genes were extracted using previously described workflows with the Celemics Neuromuscular Diseases Kit

TABLE 1
Comparative statistical analyzes of demographic, clinical, and genetic data

	Group 1 (n=16)			Group 2 (n=9)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			47.2±8.4			42.8±5.8	0.112**
Sex							0.790*
Male	8	50.0		5	55.6		
Female	8	50.0		4	44.4		
Onset age (year)			35.75±7.20			35.22±6.72	0.977**
Diagnosis age (year)			36.87±7.35			37.22±6.38	0.755**
Disease duration (year)			11.44±6.02			7.56±5.25	0.099**
EDSS score			5.44±1.38			3.33±0.71	**0.001****
HSP family history							
Existent	0	0.0		0	0.0		
Nonexistent	16	100.0		9	100.0		
Spastin (SPG4) mutation							
Existent	0	0.0		0	0.0		
Nonexistent	16	100.0		9	100.0		
Paraplegin (SPG7) mutation							
Existent	0	0.0		0	0.0		
Nonexistent	16	100.0		9	100.0		

Group 1: pwPPMS with spastic paraparesis; Group 2: pwPPMS without spastic paraparesis; SD: Standard deviation; EDSS: expanded disability status scale; HSP: Herediter spastic paraplegia; * Statistical significance in the Pearson's Chi-squared test; ** Statistical significance in the Mann-Whitney U test; Bold: Statistically significant results.

(Celemics, Inc., Geumcheon-gu, Seoul, Korea) and the Illumina Miniseq Platform (Illumina, San Diego, CA, USA). Sequencing included all exons and introns.

Data analyses

The raw data obtained from sequencing were analyzed after confirming that more than 95% of the targeted genes were covered at a read depth of 20×. The variations detected as a result of the analysis were evaluated in terms of the suitability of the reading parameters using the Integrative Genomics Viewer version 2.8.6 application with the contributions of research assistant doctors and lecturers of the Department of Medical Genetics. The frequency of variants in populations and the number of homozygous variants in individuals were analyzed with the gnomAD (Genome Aggregation Database). The evaluations in the ClinVar database, the American College of Medical Genetics and Genomics (ACMG) classifications in the Franklin and Varsome databases, the estimates of in silico prediction tools such as MutationAssessor, SIFT, PolyPhen2, MutationTaster, FATHMM, Dann, and REVEL, the evolutionary conservation degree of these regions, the conservation status of the amino

TABLE 2
Population frequency values and number of homozygous individuals of the SPG7 gene c.1032 C>T (rs116319889) variant specified on the gnomAD

	Single nucleotide variant 16-89598356-C-T		
	Exomes	Genomes	Total
Allele count	1240	127	1367
Allele number	250820	31394	282214
Allele frequency	0.004944	0.004045	0.004844
Number of homozygotes	10	0	10
Popmax filtering AF (95% confidence)	0.007329	0.005631	

AF: Allele frequency.

TABLE 3
Results of studies on HSP genes in patients with MS

	HSP genes	Patients (n)	Mutations
Boucher et al.[6] (2020)	Spastin	PPMS (1)	Spastin c.926G>A / heterozygous variant / SPG4 gene / 1 PPMS patient
Bellinvia et al.[7] (2020)	Paraplegin	PPMS (1)	Paraplegin c.2162A>G / homozygous variant / SPG7 gene / 1 PPMS patient
DeLuca et al.[21] (2007)	Paraplegin, NIPA1, KIF5A, HSPD1, Atlastin, Spartin, Spastin, PLP1, L1CAM, Maspardin and BSCL2	Benign MS (112), Malignant MS (51)	The results from genotyping paraplegin, NIPA1, KIF5A, HSPD1, atlastin, spartin, PLP1, L1CAM, maspardin and BSCL2 showed that these genes do not appear to play a role in MS disease pathogenesis. Spastin (SPG4) appeared to be a strong susceptibility locus for MS.
Jia et al.[22] (2018)	KIF5A, REEP1	PPMS (38)	KIF5A p.Ala361Val / pathogenic variant / SPG10 gene / 1 PPMS patient REEP1 c.606 + 43G> T / pathogenic variant / SPG31 gene / 1 PPMS patient
Criscuolo et al.[23] (2015)	CYP7B1	43 PPMS (43), PRMS (22), RRMS (26), SPMS (26)	Direct sequencing of CYP7B1 gene revealed no homozygous mutations. CYP7B1 c.806delA / pathogenic heterozygous variant/ SPG5 gene / 1 PPMS patient CYP7B1 c.614A>G / heterozygous variant / SPG5 gene / 1 PPMS patient CYP7B1 c.-35 C>T / heterozygous variant/ SPG5 gene / 1 SPMS patient
Rubegni et al.[24] (2017)	PLP1	PPMS (2)	PLP1 c.210T >G / heterozygous variant/ SPG2 gene / 2 PPMS patient
Warshawsky et al.[25] (2005)	PLP1	PPMS (1)	PLP1 c.89T >G / heterozygous variant/ SPG2 gene / 1 PPMS patient
Cloake et al.[26] (2018)	PLP1	PPMS (22)	PLP1 c.89T >G / heterozygous variant/ SPG2 gene / 1 PPMS patient
Mead et al.[27] (2001)	Spastin	MS (2)	Spastin 1406delT / heterozygous variant / SPG4 gene / 2 MS patient
Yazıcı et al.[28] (2013)	Spastin	RRMS (1)	Spastin c.310_311 insA / heterozygous variant / SPG4 gene / 1 RRMS patient
Laurencin et al.[29] (2016)	Spatacsin	RRMS (1)	Spatacsin c.5255delT and c.6754+2_6754+3dupTG / heterozygous variant / SPG11 gene / 1 RRMS patient
Mukai et al.[30] (2018)	Spatacsin	RRMS(1)	Spatacsinc.208C>A, c.2450C>T and c.6809_6810delCT / heterozygous variant / SPG11 gene / 1 RRMS patient
Our study	Spastin, paraplegin	PPMS (25)	Paraplegin c.1032 C>T (rs116319889) / benign variant / SPG7 gene / 2 PPMS patient In the genotyping of the with PPMS no pathogenic or possibly pathogenic variants were observed in terms of spastin (SPG4) and paraplegin (SPG7) genes involved in the pathogenesis of HSP.

HSP: Hereditary spastic paraplegia; MS: Multiple sclerosis; PPMS: Primary progressive multiple sclerosis.

acid change in the identified variant (if present), the clinical data of the patients, and the literature information available on PubMed were all assessed together. These variants were classified according to the rules of the Human Genome Variation Society and the ACMG criteria.[18] It was deemed appropriate to report only pathogenic and possibly pathogenic variants that could be clinically associated.

Statistical analysis

Data were analyzed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequency (n) and percentages (%). The Pearson chi-square test was used to compare categorical variables between the two groups, and the Mann-Whitney U test was used to compare continuous variables. A p-value <0.05 was considered statistically significant.

RESULTS

In Group 1, the mean age of onset was 35.75±7.20 years, and the mean age at diagnosis was 36.87±7.35. In Group 2, the mean age of onset was 35.22±6.72 years, and the mean age at diagnosis was 37.22±6.38. There was no statistically significant difference between Group 1 and Group 2 in terms of sex, age, age at onset, age at diagnosis, and disease duration (p=0.790, p=0.112, p=0.977, p=0.755, and p=0.099, respectively). The mean EDSS score was 5.44±1.38 in Group 1 and 3.33±0.71 in Group 2, and the EDSS score was statistically significantly higher in Group 1 (p<0.001). None of the patients had a family history of HSP, PPMS, or undiagnosed spastic paraparesis. In the genotyping of the two groups with PPMS, both with (Group 1) and without (Group 2) spastic paraparesis, no pathogenic or possible pathogenic variants were observed in terms of genes involved in the pathogenesis of HSP (SPG4 and SPG7). The comparison of demographic, clinical, and genetic data of the participants in Group 1 and Group 2 is given in Table 1.

The gene coverage rates of SPG4 and SPG7 genes of the patients included in the study were over 95%. Synonymous benign c.1032 C>T (rs116319889) variant was detected in the SPG7 gene of two patients in Group 1 (Figure 1).

The SPG7 gene c1032. C>T synonymous variant was analyzed according to the ACMG classification in the VarSome and Franklin databases. A benign variant was found in both databases. This benign variant was not compatible with significant clinical

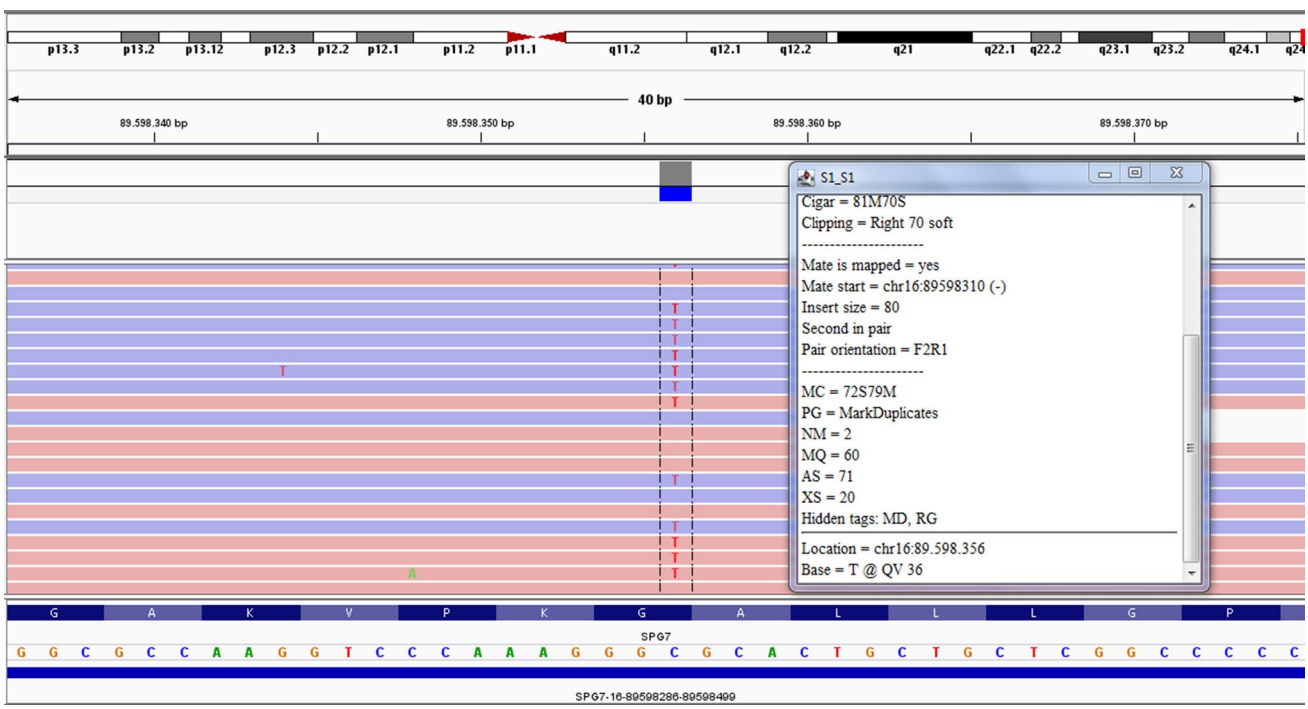

Figure 1. Image of the c.1032 C>T (rs116319889) variant in the paraplegia (SPG7) gene in IgV 2.8.6. with read quality parameters.

change. Additionally, these variants had no effect on disease severity and clinical status in PPMS (Table 2).

DISCUSSION

Multiple sclerosis is characterized by marked clinical heterogeneity. Symptoms are variable, and the long-term course is often difficult to predict. However, the progressive phase of the disease is associated with the accumulation of irreversible functional disability. In all phenotypes of MS, an ongoing pathological process in the form of inflammation, demyelination, remyelination, axonal loss, and glial scar formation is observed.[19,20] It is suggested that progressive forms of MS represent a largely neurodegenerative process and that the infiltrative inflammation evident in RRMS is relatively rare in progressive forms.[21] Recently, genes responsible for the protection of axons in the corticospinal and sensory pathways have started to attract attention among the factors that will affect the clinical process in MS. However, it remains unclear whether genetic variations affect the course of the disease. Hereditary spastic paraplegia is a retrograde distal axonopathy of the longest descending motor fibers of the corticospinal tract and dorsal columns with clinical and radiological features similar to PPMS.[5] The notion that patients with PPMS may be rich in HSP-related mutations that cause progressive axonal damage is consistent with the observation that the most common clinical presentation in PPMS is a progressive spastic paraparesis. From this point of view, we investigated the relationship of two genes (SPG4 and SPG7), which are best known to cause HSP, with PPMS susceptibility and clinical outcomes. We did not detect homozygous mutations with next-generation direct sequencing of the SPG4 and SPG7 genes in any of the 25 patients with PPMS. A synonymous benign c.1032 C>T (rs116319889) variant was detected in the SPG7 gene in only two patients with PPMS with spastic paraparesis. Although the proposed hypothesis was strong and logical, the results obtained from SPG4 and SPG7 genotyping revealed that these genes did not contribute to the pathogenesis of PPMS.

DeLuca at al.[22] investigated single nucleotide polymorphisms in a cohort of 112 patients with benign MS and 51 patients with malignant MS to detect variants in 11 genes known to be involved in the pathogenesis of HSP, including SPG4 and SPG7. Although SPG4 appeared to be a strong susceptibility locus for MS in this study, the results obtained did not show any relationship between the eleven genes involved in the pathogenesis of HSP and MS susceptibility or disease severity. In contrast, Jia et al.[23] emphasized that potentially pathogenic HSP mutations (e.g., SPG7, SPG10, and SPG31) were significantly enriched in 315 patients with PPMS compared to 987 controls in their meta-analysis with three replication cohorts. However, they did not find a significant enrichment in patients with RRMS compared to controls, although they observed a trend towards enrichment of HSP-related variants in patients with PPMS compared to those with SPMS, but this was not considered statistically significant. In addition, they did not observe a significant difference between patients with PPMS, patients with SPMS carrying the HSP variant, and those not carrying the variant. They stated that the enrichment of spastic paraplegia variants was specific to patients with a progressive disease course and was not present in all forms of MS and that rare HSP-related variants modulated the risk of developing a progressive disease course independent of the overall genetic burden associated with the risk of developing MS. Criscuolo et al.[24] evaluated whether CYP7B1 gene changes played a role in the MS phenotype by screening for mutations in the CYP7B1 (SPG5) gene in 117 patients with MS (43 PPMS, 22 progressive-relapsing MS, 26 RRMS, and 26 SPMS). While the researchers did not find SPG5 patients (homozygous mutations) in their cohort, they identified three heterozygous carriers for CYP7BI variations among patients with MS. The common feature of these three carriers, of which two were PPMS and one was SPMS, was a family history of HSP and some autoimmune diseases.

The similarity of clinical and radiological presentations of PPMS and HSP from time to time may cause confusion and misdiagnosis. In addition, although rarely, there are reports of patients with PPMS with SPG2,[25-27] SPG4,[6,28,29] SPG7,[7] and SPG11[30,31] gene mutations in the literature. The most important feature in these patients with MS with comorbid HSP was the presence of a family history of HSP in the majority. This is likely because, unlike PPMS, more than seventy different genetic forms were identified in HSP, including all patterns of Mendelian inheritance (autosomal dominant, autosomal recessive, and X-linked) and non-Mendelian mitochondrial maternal transmission.[22]

Leptomeningeal inflammation, oxidative stress directing mitochondrial damage, chronic microglial activation causing oligodendrocyte dysfunction and axonal damage, and age-related iron accumulation are the putative mechanisms in the pathogenesis of PPMS.[21,22,32] The absence of pathogenic and possibly pathogenic SPG4 and SPG7 gene mutations in our PPMS patient group showed that there was no relationship between PPMS and HSP in terms of pathogenesis. In addition, there was no family history suggestive of HSP or undiagnosed spastic paraparesis among our patients. We believe that in cases where a patient with a clinically evident PPMS diagnosis with spastic paraparesis is misdiagnosed or HSP comorbidity is suspected, an in-depth analysis of the family history will lead the clinician to the correct diagnosis, avoiding unnecessary and expensive genetic studies. Our study demonstrated the importance of laboratory (blood tests for differential diagnosis, brainstem evoked potentials, and cerebrospinal fluid examination) and neuroradiological evaluation, together with a comprehensive medical history and neurological examination, and that the McDonald criteria are sufficient for diagnosis. Moreover, the results showed that PPMS was not misdiagnosed in the population we studied.

This study had some limitations. Some forms of MS, such as RRMS and SPMS, were not included in the study. In addition, the other gene mutations observed in HSP were not evaluated. The single-center design and the low sample size limited the generalizability of the results. Therefore, studies with larger samples are needed to confirm our results. Given that axonal degeneration is important in progression in MS and that irreversible clinical disability is associated with such axonal loss, MS-associated variants of genes involved in maintaining axonal integrity should be explored. These efforts will also guide the development of effective treatments that slow and prevent disability in patients with progressive forms of MS.

In conclusion, the absence of SPG4 and SPG7 gene mutations indicated that there was no relationship between PPMS and HSP in terms of pathogenesis and that these gene mutations did not have an effect on the motor pathways that led to the spastic paraparesis phenotype in patients with PPMS.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conception and design of the work, acquisition, analysis, and inter-pretation of data: B.Ç., A.U.U., A.G.Z., M.S.Y., M.M., B.O.; Drafting the manuscript and critical revision for intellectual content: B.Ç., A.U.U., M.A.; Each author listed on the manuscript has seen and approved the final version of the manuscript.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: This study was supported by Necmettin Erbakan University.

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