REVIEW OPEN ACCESS

Review of the Genetic Spectrum of Hereditary Spastic Paraplegias in the Middle East and North Africa Regions

Mehri Salari,[1] Fatemeh Hojjatipour,[2] Masoud Etemadifar,[3] and Sevim Soleimani[2]

Neurol Genet 2025;11:e200250. doi:10.1212/NXG.0000000000200250

Correspondence
Dr. Soleimani
sevim.soleimani@gmail.com

Abstract

Background and Objectives

Hereditary spastic paraplegias (HSPs) are inherited neurodegenerative disorders, and their classification is based on inheritance mode, allelic variants, and clinical presentation. Despite global occurrence, research, especially in the Middle East and North Africa (MENA) regions, is lacking, underscoring the need for further investigation. The objective of this study was to improve the regions' clinical practice and public health, and this study aims to gather data on HSP prevalence, pathogenic variants, and patient characteristics in MENA countries.

Methods

A systematic literature review encompassing PubMed, MEDLINE, and Google Scholar was conducted. Quality assessment was performed on the included studies. Data extraction and analysis provided insights into HSP's current status in the region.

Results

Iran had the highest number of patients with HSP, followed by Tunisia. SPG11 (19.8%), FA2H (8.5%), and ZFYVE26 (7.7%) were the most frequently found genes in the cases. Autosomal recessive HSP with thin corpus callosum was common among the affected patients, with SPG11 identified as the primary cause.

Discussion

Our analysis highlights genetic diversity and regional prevalence variations. Despite limited research in MENA countries, we stress the importance of further investigation to address gaps in understanding and improve patient care and public health initiatives.

MORE ONLINE

Supplementary Material

Introduction

Hereditary spastic paraplegias (HSPs) are a group of inherited neurodegenerative disorders characterized by spasticity and weakness of the lower extremities, along with other motor sensory engagements. These symptoms result from axonal degeneration of the lateral corticospinal tract, progressing slowly and potentially leading to the need for a cane or wheelchair.[1]

The prevalence of HSP is estimated at 1.2 to 9.6 per 100,000.[2] HSP is classified by inheritance mode (autosomal dominant, autosomal recessive, x-linked, and mitochondrial inheritance), mutant gene, phenotype (pure and complex), and clinically as complicated and uncomplicated. Uncomplicated HSP involves progressive lower extremity weakness and spasticity, while complicated HSP includes extraneurologic disturbances.[3]

[1]Physical Medicine & Rehabilitation Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Student Research Committee, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; and [3]School of Medicine, Isfahan University of Medical Sciences, Iran.

The Article Processing Charge was funded by the authors.

Glossary

AGS = Aicardi-Goutières syndrome; **ARHSP** = autosomal recessive HSP; **ENTPD1** = ectonucleoside triphosphate diphosphohydrolase 1; **ER** = endoplasmic reticulum; **HSPs** = hereditary spastic paraplegias; **ID** = intellectual disability; **LL** = lower limbs; **MENA** = Middle East and North Africa; **MERC** = mitochondria-ER contact site; **MTHFR** = methylenetetrahydrofolate reductase; **SPG** = spastic paraplegia genes; **TCC** = thin corpus callosum; **TECPR2** = tectonin beta-propeller repeat containing 2; **TMEM63C** = transmembrane protein 63C; **VPS37A** = vacuolar protein sorting 37A; **WES** = whole-exome sequencing.

Complex HSP is diagnosed when these symptoms occur without another identifiable diagnosis.[4] Symptoms often present symmetrically but can be asymmetric or unilateral. Urinary urgency is common in later stages. Additional signs include lower extremity paresthesia, vibration impairment, loss of light touch, and subtle cognitive impairment, particularly in dominantly inherited HSP.[4]

Diagnosis relies on identifying specific genes or chromosomal locations, designated as spastic paraplegia genes (SPG). HSP is highly genetically diverse, with more than 80 genes identified to cause the condition, and the number is expected to rise with advances in DNA sequencing.[5] Next-generation sequencing-based gene panels are commonly used but have limitations. Several SPG genes have been identified within single families, suggesting potential HSP candidates. However, 51%–71% of patients with suspected HSP do not show genetic abnormalities, indicating that diagnosis is based on HSP gene panels, neuroimaging, and clinical features.[6]

A systematic analysis of HSP prevalence worldwide found Tunisia has the highest reported cases of autosomal recessive HSP (ARHSP), particularly SPG11 and SPG15 variants. SPG4 is most common in autosomal dominant HSP, followed by SPG3A.[7] Southern Norway and Portugal have the highest values for autosomal dominant HSP. Prevalence ranges from 0.5 to $5.5/10^5$ for autosomal dominant HSP and 0.0 to $5.3/10^5$ for ARHSP, with variability within nations.[7]

Despite observations in numerous countries, HSP prevalence has not been thoroughly investigated in various regions. There are no patient reviews regarding this disorder for Middle East and North Africa (MENA) countries. There is also a lack of research on case numbers, clinical signs, diagnosis techniques, and imaging in these areas.

This study reviews current literature and gathers data on HSP in MENA countries to evaluate pathogenic variants, prevalence, and patient characteristics. The goal is to compile data from multiple nations to determine common symptoms, indicators, and prevalent genes in these families. This study aims to highlight the need for further research and its implications for clinical practice and regional public health.

Methods

A highly sensitive systematic search of the literature up to August 2022 was conducted in online databases, including PubMed, MEDLINE, and Google Scholar. We used a combination of text and Medical Subject Heading Terms (MeSH). The search query included "Hereditary Spastic Paraplegia," OR "HSP," OR "Spastic Paraplegia," AND "Algeria," OR "Bahrain," OR "Egypt," OR "Iraq," OR "Iran," OR "Israel," OR "Jordan," OR "Kuwait," OR "Lebanon," OR "Libya," OR "Morocco," OR "Oman," OR "Palestine," OR "Qatar," OR "Saudi Arabia," OR "Sudan," OR "Syria," OR "Tunisia," OR "United Arab Emirates," OR "Yemen," OR "MENA," OR "Middle East," OR "North Africa." Studies focusing on hereditary spastic paraplegia within the MENA countries that mentioned clinical manifestation and genetic aspects were included. There were no time limitations for articles. However, studies were excluded if the patient's homeland was not specifically mentioned, even if they were born somewhere in Africa or Asia. In addition, studies not written in English, lacking sufficient information, or without full-text access were excluded. Studies that did not discuss individual patients and grouped multiple patients were also excluded. Duplicates were removed using EndNoteX20.

The search and extraction were conducted by 2 independent researchers. They assessed the titles and abstracts of the searched articles, excluding those that did not meet the inclusion criteria or lacked sufficient information. If the title and abstract did not provide enough information to determine suitability, the full text was reviewed. Included observational studies underwent quality assessment using the Newcastle-Ottawa Scale checklist. Since our results were primarily derived from case reports or case series that evaluated each patient individually, the findings are robust and specific. Relevant data, including patient demographics, genetic pathogenic variants, presentations, and other crucial information, were extracted by 2 independent researchers using a predefined table in Microsoft Excel. These data were then imported into SPSS 27 for analysis to summarize key findings, trends, and variations across MENA countries. The gathered data and results were reviewed by experts in neurology, genetics, and other relevant specialists to validate the findings and provide insights into the current state of HSP in the region. Our research was authorized by the Ethics Committee of Shahid Beheshti University of Medical Sciences, under the ethical code IR.SBMU.RETECH.REC.1403.542, and throughout the review process, all ethical standards and guidelines were strictly followed.

Results

Based on the review of the included studies, Iran had the most reported HSP patients with 53 cases (16.7%), followed by Tunisia with 45 cases (14.2%), and Iraq and Pakistan had the

least cases reported. The baseline characteristics with the frequency for each of the countries are presented in Table.

The most common pathogenic variants observed among the cases were SPG11 (19.8%) followed by FA2H (8.5%) and ZFYVE26 (7.7%).

The Figure separately demonstrates the types of genes reported in each country.

Pure

SPAST

This gene encodes a protein named Spastin, and it is responsible for the SPG4 phenotype; this protein belongs to the ATPase associated with various intracellular functions and plays a role in regulating the microtubule dynamics.[8] Alterations such as missense, nonsense, splice-site alterations, and deletions were all evident in this gene's pathogenic variant,[9] and it is demonstrated that mutation in this gene can cause intracellular organelle trafficking dysfunction.[10] A p.Glu442-Lys mutation in the SPAST gene in a female member of a family from Morocco was associated with gait spasticity, hyperreflexia of the lower limbs (LL), and mental deficiency.[11] In addition, this HSP type is considered pure.[11]

CYP7B1

Using direct sequencing in several families, researchers identified missense and nonsense alterations in the gene encoding cytochrome P450 oxysterol 7-alpha hydroxylase (*CYP7B1*) in 2 families from Tunisia and Algeria. CYP7B1, expressed in both liver and brain tissue, plays a key role in neurosteroid metabolism.[12]

This type of HSP, called SPG5, is a rare AR neurodegenerative disorder characterized by LL spasticity, weakness, and gait abnormalities. In the Tunisian family, white matter hyperintensities were observed.[13]

The SPG5 locus, located on chromosome 8q12,[14,15] has been refined through various studies. In an Algerian family with pure HSP and additional cerebellar features, linkage to chromosome 8 was confirmed with a high logarithm of the odds score, narrowing the locus to a 3.8 cM interval.[16]

A specific variant (c.1081C>T; p.R361*) was found in a Tunisian family, with affected members displaying spastic gait, urinary symptoms, and visual disturbances, although symptoms varied among family members.[17]

DDHD1

A Moroccan family experiencing early-onset pure spastic paraplegia underwent genetic analysis, revealing a locus on chromosome 14q associated with AR inheritance. Three family members were affected, initially displaying gait instability followed by spasticity and weakness in the LL, eventually leading to dependency on assistance for walking. The locus, identified as SPG28, was investigated, excluding SPG3A and GCH1 due to a lack of pathogenic variants found through direct sequencing.[18]

CYP2U1

Homozygous missense alteration of the *CYP2U1* gene is linked to SPG56, an ARHSP in Iranian families with intellectual disability (ID) and dystonia with evidence of delayed myelination in MRI.[19] Exome sequencing of 2 affected Arab siblings demonstrated a homozygous change, causing a pure ARHSP limited to pyramidal signs.[20]

Complex

SPG7

SPG7 gene on chromosome 16q24.3 encodes paraplegin.[21] The SPG7 gene was evaluated by direct sequencing of all exons and found to have a compound c.850_851delTTinsC and c.1742_1744delTGG heterozygous alterations in a Moroccan family with complex ARHSP, the symptoms of the affected members included instability and spasticity of the limbs, pes cavus and impaired pin-prick in 2 members. In addition, single deleterious heterozygous mutations in 4 families were detected that one of the families from Algeria demonstrated a c.244_246delACA alteration on exon 2 of the *SPG7* gene.[22]

ALDH18A1

A novel heterozygous alteration in the *ALDH18A1* gene which is located on chromosome 10q24.1, linked to the SPG9A phenotype. The whole exome revealed an affected patient from Iran who manifested gait disturbances, spasticity, and weakness of the LL along with upper motor neuron signs and alterations in vibration sense.[23]

The *ALDH18A1* gene is associated with SPG9A and 9B, which are rare metabolic dysfunctions. This gene produces an enzyme called delta1-pyrroline-5-carboxylate synthetase (P5CS). It was demonstrated that insufficient P5CS can cause spastic paraplegia type 9A and 9B.[24]

SPG11

A study on a family from Egypt revealed alterations in the *SPG11* gene that encodes Spatacsin, leading to a homozygous premature stop codon, and recessive inheritance. Symptoms included slowly progressive spasticity and dysarthria, with 2 patients exhibiting thin corpus callosum (TCC) and hyperdensity of the white matter in MRI scans.[25]

The *SPG11* gene situated on chromosome 15q21.1[26] is associated with ARHSP-TCC, which typically manifests as spastic paraparesis, cognitive decline, and axonal neuropathy[27,28]; However, 2 siblings from Saudi Arabia exhibited LL spasticity, weakness, and unsteadiness, with no apparent evidence of TCC in their MRI scans.[27] However, not all cases display TCC, and other symptoms such as seizure, ataxia, dysarthria, dysphagia, and extrapyramidal signs may be present.[28]

Table Patient Demographics According to Each Country

Country	Cases (No.)			Mean age	Mean age at onset	Consanguinity		Family history		Gene inheritance		Mean disease duration	HSP form	
	All	Male	Female			Yes	No	Positive	Negative	Recessive	Dominant		Pure	Complex
Iran	54	30	24	21	10.44	30	NA	8	5	45	2	11.41	3	22
Tunisia	45	22	23	30	9.53	35	4	35	0	45	0	20	2	33
Saudi Arabia	36	17	16	19.32	9.46	33	1	16	0	36	0	11.28	NA	22
Israel	43	17	26	21.4	9.1	35	6	9	2	37	0	13.1	NA	33
Kuwait	5	1	4	33.8	7	5	0	NA	NA	5	0	26.8	NA	1
Algeria	28	21	7	24.43	11.89	23	2	1	0	26	0	13.6	4	15
Palestine	10	4	6	22	11	10	0	NA	NA	10	0	13.17	3	7
Egypt	12	4	5	18.79	9	12	0	9	0	12	0	8.43	NA	3
Arab	29	10	10	24.55	4.9	29	0	9	0	29	0	26	NA	1
Oman	24	14	10	16.53	4.9	22	0	11	0	18	0	9.1	NA	16
Qatar	5	3	2	5.8	1.3	4	0	2	0	3	0	4.8	2	1
Libya	4	3	1	10.25	2.62	4	0	2	0	4	0	7.75	0	2
Morocco	26	14	10	30.48	18.1	15	6	6	3	25	0	13.6	4	14
Iraq	1	0	1	8	3	NA	NA	NA	NA	1	0	5	0	1
Syria	11	8	3	17.1	6.67	7	0	7	0	8	0	10.67	NA	NA
Pakistan	1	0	1	31	4	1	0	1	0	1	0	27	0	1
North Africa	2	1	1	10	1.12	0	1	0	2	2	0	8.5	NA	NA
Sudan	25	9	16	24.58	9.49	25	0	25	0	21	3	NA	3	22
Yemen	3	3	0	11.3	4.93	3	0	3	0	3	0	NA	NA	NA

Abbreviations: HSP = hereditary spastic paraplegia; NA = not assessed; TCC = thin corpus callosum.

A Saudi Arabian family with a mutation in SPG11 exhibited cystic kidneys and median nerve entrapments, expanding the range of associated symptoms. The higher prevalence of SPG11 ARHSP-TCC in Saudi Arabia is attributed to consanguineous marriages.

Exome sequencing in 8 families from Iran revealed homozygous and heterozygous alterations in SPG11 genes, associated symptoms included leg stiffness and weakness, brisk tendon reflexes, and distal amyotrophy. Thus, SPG11 pathogenic variant can cause symptoms consistent with both ARHSP and juvenile amyotrophic lateral sclerosis.[29]

SPG11 is also associated with the KIAA1840 gene (FLJ21439), mainly expressed in the cerebellum and cerebral cortex.[26]

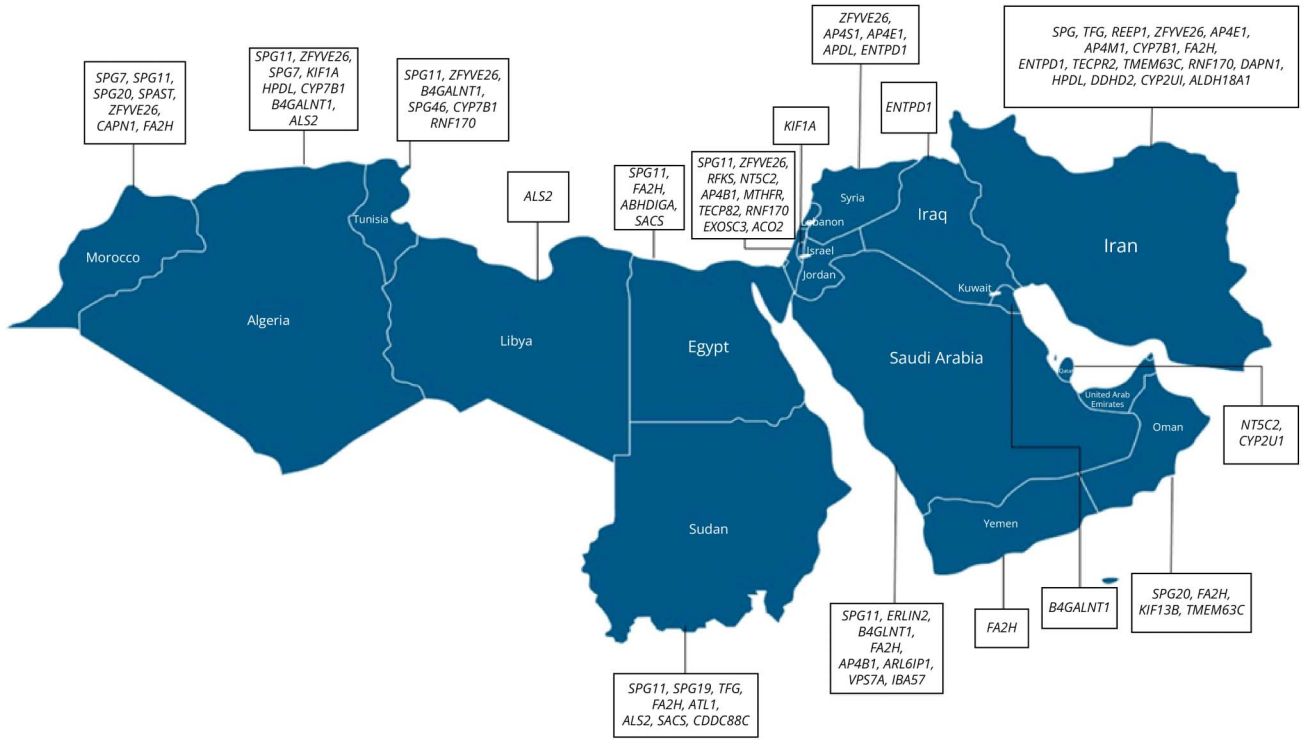
ZFYVE26

SPG15, located on chromosome 14q22-q24, is an ARHSP associated with Kjellin syndrome which is initially described as spastic paraplegia, mental retardation, macular pigmentation, psychosis, and distal amyotrophy.[30] In a Tunisian family harboring this pathogenic variant, the affected members manifested early-onset progressive spastic paraparesis and mental impairment.[31] SPG15 can also be associated with TCC.[32] Another family from Algeria linked to SPG15 with cerebellar signs, cognitive impairment, TCC, and white matter abnormalities, but no maculopathy was detected in the patients in contrast to Kjellin syndrome.[33] Truncating alterations within the *ZFYVE26* gene can also lead to SPG15, characterized by early-onset progressive HSP, mental impairment, and TCC.[34]

ERLIN2

ERLIN2 plays a crucial role as part of the endoplasmic reticulum (ER) degradation pathway, facilitating the removal of abnormal proteins.[35] An extended consanguineous family from Saudi Arabia with 5 affected members presented with progressive tightening of lower extremities, and they also had ID. The 8-year-old boy also presented with seizures a year before. The autozygosity mapping and linkage analysis on the family members revealed an affected interval on 8p12-8q11.22 that was a nullimorphic deletion of ERLIN2 compatible with the analysis of the genes concerning SPG18.[36,37] A splice site mutation

Figure Pathogenic Variants Reported in the Middle East and North African Countries



The Middle East and North Africa regions exhibit a notable diversity in the genetic landscape of hereditary spastic paraplegias. Among the various genes implicated, SPG11, FA2H, and ZFYVE26 are the most frequently identified in affected populations. The presence of these genes indicates a regional pattern of inheritance and clinical manifestations.

within ERLIN2 was also identified in a family exhibiting ARHSP, along with cognitive, speech, and motor impairments.[35]

SPG20

Troyer syndrome presents a set of symptoms including progressive stiffness and weakness in the LL, difficulty with speech, pseudobulbar palsy, weakening of muscles in the hands and feet, reduced height, and abnormalities in skeletal structure.[38] Initially identified in the Amish community of the traditional order, where individuals exhibited short height, speech difficulties, and delayed development.[39] Troyer syndrome, also known as SPG20, is attributed to mutations in the *SPG20* gene located on chromosome 13q13. Various pathogenic variant patterns have been documented, such as a specific single-nucleotide substitution (c.988A>G, p.Met330Val) observed in an Israeli-Arab family and the presence of a stop codon mutation (c.1369C>T, p.Arg457∗) in a Moroccan family, resulting in the interruption of normal gene function.[38,40]

RIPK5

In a consanguineous Arab Israeli family with 4 affected members, spastic paraparesis and weakness primarily affected the LL, accompanied by cutaneous pigmentation abnormalities. A genome-wide linkage screen identified a candidate region on chromosome 1q24-q32. The pigmentation abnormalities included depigmented and hyperpigmented skin lesions, as well as patchy hair depigmentation. Some siblings also exhibited micrognathia, microcephaly, and mild cognitive impairment. These findings suggest a specific type of complicated HSP known as SPG23, where in addition to spasticity, other systems, mainly the skin, are affected.[41]

B4GALNT1

Complex glycosphingolipids such as GM1 and GD1a gangliosides are vital in nervous tissue, aiding cell interactions and regulating membrane proteins. B4GALNT1 adds the third glucan in their biosynthesis. Homozygous B4GALNT1 mutations cause HSP26, leading to progressive neurologic decline, marked by absent GM2 ganglioside and elevated GM3 levels.

SPG26 manifests as early-onset spastic paraparesis, cognitive decline, cerebellar ataxia, extrapyramidal symptoms, and peripheral neuropathy.[42] In a Saudi family, common symptoms included spastic paraparesis and muscle weakness, with additional febrile ataxia and myokymia. Abnormal glycosphingolipid profiles in peripheral samples can aid in diagnosis and monitoring treatment.[43] SPG26, identified in a consanguineous Kuwaiti family, involves progressive spastic paraparesis, speech difficulty, distal amyotrophy, and ID, linked to chromosome 12p11.1-12q14 via the genome-wide scan.[44]

KIF1A

In an affected family of Algerian descent, a genome-wide scan established a connection between the disease and a newly

identified complex ARHSP locus situated on chromosome 2q37.3. The phenotype of SPG30 is associated with spastic gait and progressive spastic paraparesis with saccadic ocular pursuit and cerebellar signs including the impaired finger-to-nose test.[14]

Exome sequencing in an affected family identified the p.R350G variant in the KIF1A gene, associated with the SPG30 phenotype of ARHSP. This variant affects a conserved amino acid in the motor domain crucial for nervous system axonal transport. In addition, whole-genome analysis in a Palestinian family revealed a homozygous region and a missense mutation on chromosome 2q, both within unaffected domains of the KIF1A protein, implicating it in SPG30.[45,46]

REEP1

The *REEP1* gene on chromosome 2p11.2 contains the genetic instructions for producing receptor expression-enhancing protein 1.[47] Its alteration was initially associated with SPG31 through direct sequencing. The prevalent form of SPG31 observed in a cohort of affected Europeans with this subtype of HSP was predominantly pure autosomal dominant.[48,49] The phenotype included pyramidal signs of the LL.[48] Additional complex features of axonal peripheral neuropathy, cerebellar ataxia, and tremor were also evident.[49] A variant in the REEP1 gene, specifically the c.601G>A p.Ala201Thr alteration, was identified in a 55-year-old man who exhibited symptoms including muscular weakness, pes cavus, spasticity in gait, sensory impairment, and axonal sensorimotor polyneuropathy.[50]

FA2H

A 250K gene chip SNP analysis identified a 20.4 Mb homozygous locus on chromosome 16q21-q23.1, known as SPG35, involving 198 genes.[51] Alterations in the FA2H gene—c.703C>T in an Omani family and p.Arg53_Ile58del in a Pakistani family—impair enzyme activity, linking them to SPG35.[52]

SPG35 was initially associated with spasticity, cognitive dysfunction, and white matter abnormalities.[53] It was recognized as a contributor to neurodegeneration related to brain iron accumulation.[54] But not consistently linked to it.[55]

The Omani family exhibited symptoms of increased tone, weakness, hyperreflexia in the LL, gait disturbances, dysarthria, seizures, and progressive cognitive decline.[56] Similarly, a Pakistani family displayed the SPG35 phenotype, with white matter hyperintensities observed in the MRI, indicative of leukodystrophy.[52,56]

NT5C2

SPG45 is associated with complex ARHSP characterized by delayed walking, gait disturbances, ID, increased deep tendon reflexes, and extensor plantar reflexes. A pathogenic variant in cytosolic II 5′-nucleotidase (NT5C2) on chromosome 10q24.3-q25.1 is identified as the causative gene using homozygosity mapping.[57] In a Qatari family, whole-genome sequencing revealed a novel homozygous NT5C2 splice site mutation causing severe LL spasticity, truncal hypotonia, unsteady gait, dysarthria alongside TCC, and white matter hyperintensities and cystic changes.[58] Whole-genome sequencing in an Iranian family with 3 affected members identified a 1954 bp NT5C2 deletion as the cause of their disease, attributed to exon rearrangement.[59]

In addition, homozygous truncating alterations—including frameshift, nonsense, splice site, and a missense alteration (c.1379T>C; p.Leu460Pro) in NT5C2—were linked to attention-deficit hyperactivity disorder and corpus callosum atrophies in 3 Arab families.[60]

AP4B1

A frameshift mutation within the AP4B1 gene, leading to an early termination codon in exon 5, was identified via exome sequencing. The mode of inheritance appears recessive, evidenced by the presence of homozygous-affected offspring born to heterozygous parents.[e1] Two Saudi siblings were diagnosed with complex HSP, displaying lower limb pyramidal symptoms, mental retardation, seizures, and MRI changes in TCC and periventricular white matter. Genome-wide scanning and linkage analysis pinpointed a 7.3 megabase homozygous segment on chromosome 1p13.2-1p12, suggesting a novel locus for SPG47.[e2]

TECPR2

SPG49 is linked to alterations in tectonin beta-propeller repeat containing 2 (TECPR2), which encodes a protein featuring 2 primary domains: tryptophan-aspartic acid repeats and TECPR. These domains play essential roles in the autophagy process.[51]

The autophagy process contributes to cellular homeostasis with protein degradation,[e3] and its dysfunction is responsible for some of the neurodegenerative diseases.[e4]

A homozygous frameshift deletion in exon 16 of TECPR2 in 3 Jewish families identified by exome sequencing presented with HSP complicated with severe ID, generalized hypotonia, recurrent pulmonary infections, and dysmorphic features.[e5] In a family from Iran, a frameshift variant in exon 9 of TECPR2 was found. The afflicted family members exhibited a Griscelli syndrome appearance attributed to an additional alteration in the Melanophilin gene.[51]

DDHD2

Exome sequencing has unveiled frameshift and nonsense alterations within the phospholipase *DDHD2* gene in families afflicted with complex ARHSP. Typical indications of this variant encompass advancing spastic gait irregularities, spasticity, cognitive impairment, diminished stature, and TCC.[e6] DDHD2 plays a pivotal role in membrane trafficking and can catalyze the breakdown of phosphatidic acid and other phospholipids. Phosphatidic acid is involved in various biological processes and is especially important for forming lipid droplets. DDHD2's catalytic activity links it to other genes involving HSP such as

SPG17[e7] and SPG20[e8] associated with lipid metabolism. The known HSP pathogenesis is membrane trafficking, mitochondrial metabolism, myelin formation, and lipid metabolism.[e9]

TFG

Two Iranian families exhibited homozygous missense variants, within the tropomyosin-receptor kinase fused gene (TFG).[e10] TFG is associated with SPG57 which can present as a complex form with symptoms such as muscle wasting, ID, short stature, nystagmus, and visual impairments such as optic atrophy.[e10]

ARL6IP1

The *ARL6IP1* gene on chromosome 16p12.3 leads to encoding tetraspan membrane protein known as ADP ribosylation factor such as GTPase 6 interacting protein 1 (*ARL6IP1*). It operates within the ER and plays a crucial role in intracellular trafficking processes.[e11]

Using whole-exome sequencing (WES), a truncating variant of the *ARL6IP1* gene was found in an Arabian family presenting with developmental delay, leukoencephalopathy, generalized hypotonia, jejunal stricture, and respiratory distress overall causing neonatal death in the siblings.[e12]

IBA57

Genome linkage analysis in a consanguineous Arab family found a specific splice-site alteration (c.678A>G) on chromosome 1q, leading to a decrease in the normal levels of IBA57, and the creation of an abnormal transcript. This decreases complex I and complex II, essential mitochondrial proteins that engage in respiratory chain activity.[e13] The decreased IBA57 level also affects several other mitochondrial iron/sulfur proteins such as pyruvate dehydrogenase, a-ketoglutarate dehydrogenase, and mitochondrial aconitase enzymes. The mutation lead to a clinical phenotype associated with childhood-onset of gait abnormalities, spastic paraparesis, distal sensory deficits and peripheral neuropathy, and optic atrophy.[e14]

CAPN1

WES in a Moroccan family demonstrated homozygous alterations in the CAPN1 gene, which is situated on chromosome 11q13, and encodes Calpain 1; it plays a role in neural plasticity at synapses and axonal maturation in the CNS.[e15] In the affected family members of the ARHSP, indications of spasticity, muscle weakness, and exaggerated reflexes in the LL alongside dysarthria, ataxia, and foot deformity were observed.[e16]

ABHD16A

Abhydrolase domain-containing protein 16A (*ABHD16A*) is a gene located on chromosome 6p21.33 that produces a phospholipase responsible for breaking down a specific lipid called phosphatidylserine in the brain.

Homozygous variants in this gene cause a phenotype associated with developmental delay, ID, and white matter abnormalities with TCC.[e17]

AP4

Adaptor protein complexes (AP) are heterotetrameric complexes, including AP1-4, involved in intracellular vesicle transport. AP4 specifically facilitates the transport of glutamate receptors from the trans-Golgi network to postsynaptic areas in cerebellar Purkinje cells and hippocampal neurons.[e18] Deficiency in AP4 can affect neuronal function and development. Eight patients from 3 families in Israel and Syria, all with AP4 mutations in different subunits, exhibited severe ID, progressive spasticity, reserved personalities, and short stature. Other symptoms included hyperreflexia, hypotonia progressing to hypertonia, and sphincter control issues.[e19] Three families from Iran, with similar phenotypes, had homozygous pathogenic variants in AP4M1 and AP4E1 causing various genetic alterations.[e20]

KIF13B

A genome-wide investigation in 2 consanguineous Omani families revealed an anomaly in 8p12-p11.21. Neuregulin and KIF13B alterations likely cause their complicated HSP. The first family showed delayed development, atypical walking, ID, and MRI abnormalities. The second family had walking difficulties, falls, lower limb spasticity, and epilepsy in 2 individuals.[36]

ACO2

In a family with 2 siblings affected by complex HSP, characterized by moderate to severe ID and microcephaly, a genome-wide scan and exome sequencing identified 2 potential homozygous missense variants. The *ACO2* variant, linked to cerebellar ataxia and expressed in the human brain, was identified as the probable cause. *ACO2* encodes the aconitase 2 enzyme, which converts citrate to isocitrate in the tricarboxylic acid cycle. This pathogenic variant disrupts mitochondrial respiration and reduces aconitase activity in lymphoblast-derived cell lines, suggesting *ACO2* as a causative gene for complex ARHSP.[e21]

ALS2

It is demonstrated that early-onset spastic paraplegia and weakness during the first year of life with an ascending progression causing tetraplegia, anarthria, and slow eye movements are linked to ALS2 or alsin gene on chromosome 2q33-35. Linkage and haplotype analysis in a consanguineous family from Algeria exhibited a homozygous deletion of a single base pair in exon 22 of the ALS2 gene. This phenotype is called infantile-onset ascending hereditary spastic paralysis.[e22]

EXOSC3

WES in affected ARHSP families demonstrated missense and nonsense alterations in the EXOSC3 gene. This gene produces a noncatalytic subunit of the exosome complex, which is highly conserved throughout evolution. Symptoms included a spastic gait, motor developmental delay, impaired cognition, and cerebellar manifestations such as nystagmus, intention tremor, and dysmetria. Enlarged cisterna magna was the key finding in the imaging diagnosis of the patients.[e23]

HPDL

Homozygous alterations in the 4-hydroxyphenylpyruvate dioxygenase-like (HPDL) gene, revealed by exome sequencing, primarily cause spastic paraplegia and neonatal-onset motor developmental delay in the MENA region. Some cases also exhibit seizures, microcephaly, white matter abnormalities, and corpus callosum atrophy. As a single-exon gene, HPDL pathogenic variants likely lead to protein loss, particularly affecting the CNS.[e24]

MTHFR

Methylenetetrahydrofolate reductase (*MTHFR*) pathogenic variants consisting of compound heterozygous and homozygous in addition to hyperhomocysteinemia and hypomethioninemia are associated with complex HSP symptoms involving spastic paraparesis, unsteady gait, distal sensory deficit, cognitive impairments, seizure, and psychosis.[e25]

ENTPD1

Ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1) that encodes ENTPDase-1 protein causes ID and cognitive impairment in an AR pattern.[e26] WES indicated several homozygous variants in the *ENTPD1* gene causing frameshift deletion, missense, and nonsense alterations in families from middle east; the phenotype evident in the affected members was consistent and ranged from spasticity, gait disturbances, and cognitive decline to more complex forms that involved visual disturbances.[e26-e29]

TMEM63C

The transmembrane protein 63C (TMEM63C) belongs to the osmosensitive calcium-permeable cation channel family, situated on chromosome 14q24.[e30,e31] It is linked to motor neuron degenerative diseases due to disrupted lipid metabolism in the ER and mitochondria, connected via mitochondria-ER contact sites (MERCs). These sites are crucial for cellular homeostasis and lipid transfer.[e32] Proteins at MERCs affect mitochondrial morphology, leading to certain HSP.[e33,e34] TMEM63C, located on ER and MERCs, helps maintain mitochondrial structure and dynamics.[e35] Alterations in TMEM63C can result in abnormal organelle morphology and increased MERCs.[e31]

RNF170

Calcium is released from the ER by inositol 1,4,5-trisphosphate receptor(IP3R). Alterations in IP3R and genes involved in its degradation which are ERLIN1 and ERLIN2 are associated with HSP.[35,37,e27] Biallelic mutations in the *RNF170* gene that encodes ring finger protein 170 (RNF170), a ubiquitin E3 ligase, also have a role in IP3R degradation, thus causing accumulation of IP3R and IP3R degradation impairment.[e36] The RNF170 pathogenic variant is responsible for an HSP phenotype with symptoms such as spastic paraparesis in the LL, ataxia, delayed motor development, optic atrophy, and saccadic pursuit in some affected cases.[e36]

VPS37A

Vacuolar protein sorting 37A (*VPS37A*) is involved in upper motor neuron disease and is a component of the endosomal sorting complex required for transport (ESCRT) system; this system plays a significant role in intracellular trafficking.[e37] VPS37A, encoding a subunit of the ESCRT-1 complex, a specific homozygous missense mutation in Vps37A, caused a complex HSP in 2 Arab families presenting with early-onset spastic paraparesis, mild ID, kyphosis, pectus carinatum, and hypertrichosis.[e38]

RNASEH2B

Aicardi-Goutières syndrome (AGS) is an inflammatory response affecting the CNS and skin, driven by an abnormal immune response involving type 1 interferon. Pathogenic variants in AGS-related genes can manifest as spastic paraplegia phenotype. In one Egyptian family with 2 affected siblings, the older sister initially presented with an abnormal gait, while the younger experienced recurrent falling, later developing muscle weakness and hypertonic LL with brisk reflexes. A male patient from nonconsanguineous North African parents also exhibited frequent falling at 21 months, followed by increased reflexes in the lower limbs. Exome sequencing in both families revealed a c.529G>A alteration in the RNASEH2B gene, specifically the p.Ala177Thr amino acid substitution, commonly observed in AGS patients with RNASEH2B pathogenic variant.[e39]

Discussion

Overall, the findings present a comprehensive analysis of various genetic pathogenic variants associated with HSP, revealing the molecular mechanisms underlying HSP and providing insights into the phenotypic variability associated with different gene mutations. We found that the AR type of HSP with complex features was the most common form of HSP among the affected cases in the MENA region. Consanguinity may be the main underlying factor because consanguineous marriages are common in MENA countries.

As stated earlier in the article, HSP has a global prevalence ranging from less than 10 cases per 100,000 individuals, with the dominant form being AD, especially in North American and European populations, often associated with SPAST mutations. Conversely, AR forms are more common in populations with a history of consanguineous marriages, notably, in the MENA region.

Key contributors to ARHSPs include SPG11 and SPG15 characterized by various clinical features such as TCC, parkinsonism, cognitive decline, ataxia, and paraplegia. In addition, FA2H and SPG45 are prevalent AR forms, while SPG5A and SPG7 play lesser roles in the disease.

The prevalence of ADHSP varies from 0.5 to 5.5 cases per 10 people, with the highest rates observed in southeast Norway,

followed by Portugal. SPG4 is the predominant cause of HSP globally, while SPG3A and SPG31 are less common.

The occurrence of ARHSP ranges from 0.3 to 5.3 cases per 10 individuals. Tunisia exhibits the highest prevalence, likely due to increased consanguinity in Northern Africa. SPG11 is the most prevalent form, followed by SPG15 and SPG5.

ARHSP-TCC was common among the total affected patients, and the main cause was SPG11.

An extensive report of HSP families from Arabic and North African backgrounds, determined that AR-complicated HSP emerges as the most common subtype with clinical and genetic diversity, with SPG11 and SPG15 being the primary genes involved. The relationship between phenotype and genotype suggests that when dealing with complex forms of early-onset spastic paraplegia accompanied by severe progression and mental deterioration, particularly when MRI reveals a TCC, testing for these 2 genes in ARHSP is advisable.[e40]

The study on 24 Egyptian families with clinically diagnosed HSP revealed that all the subtypes were AR, with 70.83% being the complex form. The SPG11 was the most prevalent causative gene, and other identified gene mutations were CYP7B1, FA2H, PNPLA6, DDHD2, CAPN1, SPG7, and SOD1.[e41]

Recently, there have been significant advancements regarding the understanding of the molecular pathways and identifications of genes associated with HSP. However, the available treatments mainly focus on managing symptoms, and these treatments aim to reduce muscle spasticity, enhance strength, and improve walking ability.[17]

Overall, the article provides valuable insights into the genetic landscape of HSP within the MENA region. However, it is important to acknowledge its limitations, particularly regarding the representation of reported cases vs actual prevalence. While the review compiles reported cases from various sources, including scientific literature and databases, it may not accurately reflect the true prevalence of HSP within the region. Factors such as underreporting, misdiagnosis, and lack of access to health care services in certain areas could skew the data and lead to an incomplete picture of the genetic spectrum of HSP in MENA.

Another significant limitation highlighted in the article is the constrained availability and accessibility of genetic testing in the region. Limited infrastructure, resources, and expertise for genetic testing pose challenges in accurately identifying and diagnosing individuals with HSP. This limitation hampers efforts to comprehensively understand the genetic basis of the condition and impedes the development of targeted interventions and therapies. Without widespread access to genetic testing, many cases of HSP may go undetected or misdiagnosed, hindering both clinical management and research initiatives aimed at addressing this neurodegenerative disorder in the MENA region. Addressing these limitations through improved health care infrastructure, enhanced diagnostic capabilities, and broader access to genetic testing services is crucial for advancing our understanding and management of HSP in the region.

Ethical Compliance Statement

This study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. In addition, informed patient consent was not necessary for this work. All authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Author Contributions

M. Salari: major role in the acquisition of data; study concept or design. F. Hojjatipour: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M. Etemadifar: study concept or design; analysis or interpretation of data. S. Soleimani: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* September 9, 2024. Accepted in final form December 23, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Alexandra Durr, MD, PhD.

References

1. Murala S, Nagarajan E, Bollu PC. Hereditary spastic paraplegia. *Neurol Sci*. 2021;42(3):883-894. doi:10.1007/s10072-020-04981-7
2. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. *Acta Neuropathol*. 2013;126(3):307-328. doi:10.1007/s00401-013-1115-8
3. Parodi L, Fenu S, Stevanin G, Durr A. Hereditary spastic paraplegia: more than an upper motor neuron disease. *Rev Neurol (Paris)*. 2017;173(5):352-360. doi:10.1016/j.neurol.2017.03.034
4. Fink JK. Hereditary spastic paraplegia. *Neurol Clin*. 2002;20(3):711-726. doi:10.1016/s0733-8619(02)00007-5
5. Boutry M, Morais S, Stevanin G. Update on the genetics of spastic paraplegias. *Curr Neurol Neurosci Rep*. 2019;19(4):18. doi:10.1007/s11910-019-0930-2
6. Shribman S, Reid E, Crosby AH, Houlden H, Warner TT. Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol*. 2019;18(12):1136-1146. doi:10.1016/s1474-4422(19)30235-2
7. Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. *Neuroepidemiology*. 2014;42(3):174-183. doi:10.1159/000358801
8. Errico A, Ballabio A, Rugarli EI. Spastin, the protein mutated in autosomal dominant hereditary spastic paraplegia, is involved in microtubule dynamics. *Hum Mol Genet*. 2002;11(2):153-163. doi:10.1093/hmg/11.2.153
9. Fonknechten N, Mavel D, Byrne P, et al. Spectrum of SPG4 mutations in autosomal dominant spastic paraplegia. *Hum Mol Genet*. 2000;9(4):637-644. doi:10.1093/hmg/9.4.637
10. Tarrade A, Fassier C, Courageot S, et al. A mutation of spastin is responsible for swellings and impairment of transport in a region of axon characterized by changes in microtubule composition. *Hum Mol Genet*. 2006;15(24):3544-3558. doi:10.1093/hmg/ddl431

11. Ribaï P, Depienne C, Fedirko E, et al. Mental deficiency in three families with SPG4 spastic paraplegia. *Eur J Hum Genet* 2008;16(1):97-104. doi:10.1038/sj.ejhg.5201922
12. Roos P, Svenstrup K, Danielsen ER, Thomsen C, Nielsen JE. CYP7B1: novel mutations and magnetic resonance spectroscopy abnormalities in hereditary spastic paraplegia type 5A. *Acta Neurol Scand*. 2014;129(5):330-334. doi:10.1111/ane.12188
13. Goizet C, Boukhris A, Durr A, et al. CYP7B1 mutations in pure and complex forms of hereditary spastic paraplegia type 5. *Brain*. 2009;132(Pt 6):1589-1600. doi:10.1093/brain/awp073
14. Hentati A, Pericak-Vance MA, Hung WY, et al. Linkage of 'pure' autosomal recessive familial spastic paraplegia to chromosome 8 markers and evidence of genetic locus heterogeneity. *Hum Mol Genet*. 1994;3(8):1263-1267. doi:10.1093/hmg/3.8.1263
15. Coutinho P, Barros J, Zemmouri R, et al. Clinical heterogeneity of autosomal recessive spastic paraplegias: analysis of 106 patients in 46 families. *Arch Neurol*. 1999;56(8):943-949. doi:10.1001/archneur.56.8.943
16. Klebe S, Durr A, Bouslam N, et al. Spastic paraplegia 5: locus refinement, candidate gene analysis and clinical description. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144B(7):854-861. doi:10.1002/ajmg.b.30518
17. Saban M, Shachar T. Autosomal recessive hereditary spastic paraplegia: a rare case of a family with phenotypic variation. *Curr Pharmacogenomics Person Med*. 2021;17(3):211-215. doi:10.2174/1875692117999201211142908
18. Bouslam N, Benomar A, Azzedine H, et al. Mapping of a new form of pure autosomal recessive spastic paraplegia (SPG28). *Ann Neurol*. 2005;57(4):567-571. doi:10.1002/ana.20416
19. Kariminejad A, Schöls L, Schüle R, et al. CYP2U1 mutations in two Iranian patients with activity induced dystonia, motor regression and spastic paraplegia. *Eur J paediatric Neurol*. 2016;20(5):782-787. doi:10.1016/j.ejpn.2016.05.013
20. Mohammed EEA, Elsaid MF, Aleem AKA. CYP2U1 recessive recurrent missense mutation in a Gulf family with hereditary spastic paraplegia (SPG56). *Middle East J Med Genet*. 2019;8(2):96.
21. De Michele G, De Fusco M, Cavalcanti F, et al. A new locus for autosomal recessive hereditary spastic paraplegia maps to chromosome 16q24.3. *Am J Hum Genet*. 1998;63(1):135-139. doi:10.1086/301930
22. Elleuch N, Depienne C, Benomar A, et al. Mutation analysis of the paraplegin gene (SPG7) in patients with hereditary spastic paraplegia. *Neurology*. 2006;66(5):654-659. doi:10.1212/01.wnl.0000201185.91110.15
23. Komachali SR, Siahpoosh Z, Salehi M. Two novel mutations in ALDH18A1 and SPG11 gene found by whole-exome sequencing in spastic paraplegia disease patients in Iran. *Genomics Inform*. 2022;20(3):e30. doi:10.5808/gi.22030
24. Koh K, Ishiura H, Beppu M, et al. Novel mutations in the ALDH18A1 gene in complicated hereditary spastic paraplegia with cerebellar ataxia and cognitive impairment. *J Hum Genet*. 2018;63(9):1009-1013. doi:10.1038/s10038-018-0477-0
25. Abdel Aleem A, Abu-Shahba N, Swistun D, et al. Expanding the clinical spectrum of SPG11 gene mutations in recessive hereditary spastic paraplegia with thin corpus callosum. *Eur J Med Genet*. 2011;54(1):82-85. doi:10.1016/j.ejmg.2010.10.006
26. Stevanin G, Santorelli FM, Azzedine H, et al. Mutations in SPG11, encoding spatacsin, are a major cause of spastic paraplegia with thin corpus callosum. *Nat Genet*. 2007;39(3):366-372. doi:10.1038/ng1980
27. Alfaidi N, Kurdi K, Basindwah A, Al Said Y, Cupler E. Case report: SPG11 hereditary spastic paraplegia with no thinning in the corpus callosum. *J Neurol Sci*. 2019;405:38-39. doi:10.1016/j.jns.2019.10.1623
28. Alfaidi N, Sobahy T, Ali Q, et al. Pattern reversal visual evoked potentials (prVEPs) in autosomal recessive hereditary spastic paraplegia with thin corpus callosum (ARHSPTCC) patients with SPG 11 mutations in Saudi Arabia, cross section hospital base study. *J Neurol Sci*. 2022;434:120144. doi:10.1016/j.jns.2022.120144
29. Khani M, Shamshiri H, Fatehi F, et al. Description of combined ARHSP/JALS phenotype in some patients with SPG11 mutations. *Mol Genet Genomic Med*. 2020;8(7):e1240. doi:10.1002/mgg3.1240
30. Kjellin K. Familial spastic paraplegia with amyotrophy, oligophrenia, and central retinal degeneration. *Arch Neurol*. 1959;1:133-140. doi:10.1001/archneur.1959.03840020007002
31. Boukhris A, Feki I, Denis E, et al. Spastic paraplegia 15: linkage and clinical description of three Tunisian families. *Mov Disord*. 2008;23(3):429-433. doi:10.1002/mds.21848
32. Boukhris A, Stevanin G, Feki I, et al. Hereditary spastic paraplegia with mental impairment and thin corpus callosum in Tunisia: SPG11, SPG15, and further genetic heterogeneity. *Arch Neurol*. 2008;65(3):393-402. doi:10.1001/archneur.65.3.393
33. Elleuch N, Bouslam N, Hanein S, et al. Refinement of the SPG15 candidate interval and phenotypic heterogeneity in three large Arab families. *Neurogenetics*. 2007;8(4):307-315. doi:10.1007/s10048-007-0097-x
34. Goizet C, Boukhris A, Maltete D, et al. SPG15 is the second most common cause of hereditary spastic paraplegia with thin corpus callosum. *Neurology*. 2009;73(14):1111-1119. doi:10.1212/wnl.0b013e3181bacf59
35. Wakil SM, Bohlega S, Hagos S, et al. A novel splice site mutation in ERLIN2 causes hereditary spastic paraplegia in a Saudi family. *Eur J Med Genet*. 2013;56(1):43-45. doi:10.1016/j.ejmg.2012.10.003
36. Al-Yahyaee S, Al-Gazali L, De Jonghe P, et al. A novel locus for hereditary spastic paraplegia with thin corpus callosum and epilepsy. *Neurology*. 2006;66(8):1230-1234. doi:10.1212/01.wnl.0000208501.52849.dd
37. Alazami AM, Adly N, Al Dhalaan H, Alkuraya FS. A nullimorphic ERLIN2 mutation defines a complicated hereditary spastic paraplegia locus (SPG18). *Neurogenetics*. 2011;12(4):333-336. doi:10.1007/s10048-011-0291-8
38. Dardour L, Roelens F, Race V, Souche E, Holvoet M, Devriendt K. SPG20 mutation in three siblings with familial hereditary spastic paraplegia. *Cold Spring Harbor Mol Case Stud*. 2017;3(4):a001537. doi:10.1101/mcs.a001537
39. Cross HE, McKusick VA. The Troyer syndrome. A recessive form of spastic paraplegia with distal muscle wasting. *Arch Neurol*. 1967;16(5):473-485. doi:10.1001/archneur.1967.00470230025003
40. Manzini MC, Rajab A, Maynard TM, et al. Developmental and degenerative features in a complicated spastic paraplegia. *Ann Neurol*. 2010;67(4):516-525. doi:10.1002/ana.21923
41. Blumen SC, Bevan S, Abu-Mouch S, et al. A locus for complicated hereditary spastic paraplegia maps to chromosome 1q24-q32. *Ann Neurol*. 2003;54(6):796-803. doi:10.1002/ana.10768
42. Boukhris A, Schule R, Loureiro JL, et al. Alteration of ganglioside biosynthesis responsible for complex hereditary spastic paraplegia. *Am J Hum Genet*. 2013;93(1):118-123. doi:10.1016/j.ajhg.2013.05.006
43. Dad R, Walker S, Scherer SW, et al. Febrile ataxia and myokymia broaden the SPG26 hereditary spastic paraplegia phenotype. *Neurol Genet*. 2017;3(3):e156. doi:10.1212/nxg.0000000000000156
44. Wilkinson P, Simpson M, Bastaki L, et al. A new locus for autosomal recessive complicated hereditary spastic paraplegia (SPG26) maps to chromosome 12p11. 1-12q14. *J Med Genet*. 2005;42(1):80-82. doi:10.1136/jmg.2004.020172
45. Erlich Y, Edvardson S, Hodges E, et al. Exome sequencing and disease-network analysis of a single family implicate a mutation in KIF1A in hereditary spastic paraparesis. *Genome Res*. 2011;21(5):658-664. doi:10.1101/gr.117143.110
46. Klebe S, Lossos A, Azzedine H, et al. KIF1A missense mutations in SPG30, an autosomal recessive spastic paraplegia: distinct phenotypes according to the nature of the mutations. *Eur J Hum Genet*. 2012;20(6):645-649. doi:10.1038/ejhg.2011.261
47. Züchner S, Kail ME, Nance MA, et al. A new locus for dominant hereditary spastic paraplegia maps to chromosome 2p12. *Neurogenetics*. 2006;7(2):127-129. doi:10.1007/s10048-006-0029-1
48. Beetz C, Schüle R, Deconinck T, et al. REEP1 mutation spectrum and genotype/phenotype correlation in hereditary spastic paraplegia type 31. *Brain*. 2008;131(Pt 4):1078-1086. doi:10.1093/brain/awn026
49. Goizet C, Depienne C, Benard G, et al. REEP1 mutations in SPG31: frequency, mutational spectrum, and potential association with mitochondrial morpho-functional dysfunction. *Hum Mutat*. 2011;32(10):1118-1127. doi:10.1002/humu.21542
50. Taghizadeh S, Vazehan R, Beheshtian M, et al. Molecular diagnosis of hereditary neuropathies by whole exome sequencing and expanding the phenotype spectrum. *Arch Iranian Med*. 2020;23(7):426-433. doi:10.34172/aim.2020.39
51. Edizadeh M, Chegeninejad N, Akbari S, et al. Two novel biallelic variants in TECPR2 and FA2H genes causing complicated hereditary spastic paraplegia in Iranian families from Lur ethnicity: case series. *Clin Case Rep*. 2021;9(6):e04293. doi:10.1002/ccr3.4293
52. Dick KJ, Eckhardt M, Paisán-Ruiz C, et al. Mutation of FA2H underlies a complicated form of hereditary spastic paraplegia (SPG35). *Hum Mutat*. 2010;31(4):E1251-E1260. doi:10.1002/humu.21205
53. Edvardson S, Hama H, Shaag A, et al. Mutations in the fatty acid 2-hydroxylase gene are associated with leukodystrophy with spastic paraparesis and dystonia. *Am J Hum Genet*. 2008;83(5):643-648. doi:10.1016/j.ajhg.2008.10.010
54. Kruer MC, Paisán-Ruiz C, Boddaert N, et al. Defective FA2H leads to a novel form of neurodegeneration with brain iron accumulation (NBIA). *Ann Neurol* 2010;68(5):611-618. doi:10.1002/ana.22122
55. Marelli C, Salih MA, Nguyen K, et al. Cerebral iron accumulation is not a major feature of FA2H/SPG35. *Mov Disord Clin Pract*. 2015;2(1):56-60. doi:10.1002/mdc3.12118
56. Dick K, Al-Mjeni R, Baskir W, et al. A novel locus for an autosomal recessive hereditary spastic paraplegia (SPG35) maps to 16q21-q23. *Neurology*. 2008;71(4):248-252. doi:10.1212/01.wnl.0000319610.29522.8a
57. Dursun U, Koroglu C, Kocasoy Orhan E, Ugur SA, Tolun A. Autosomal recessive spastic paraplegia (SPG45) with mental retardation maps to 10q24.3-q25.1. *Neurogenetics*. 2009;10(4):325-331. doi:10.1007/s10048-009-0191-3
58. Elsaid MF, Ibrahim K, Chalhoub N, Elsotouhy A, El Mudehki N, Abdel Aleem A. NT5C2 novel splicing variant expands the phenotypic spectrum of Spastic Paraplegia (SPG45): case report of a new member of thin corpus callosum SPG-Subgroup. *BMC Med Genet*. 2017;18(1):33-37. doi:10.1186/s12881-017-0395-6
59. Darvish H, Azcona LJ, Tafakhori A, Ahmadi M, Ahmadifard A, Paisán-Ruiz C. Whole genome sequencing identifies a novel homozygous exon deletion in the NT5C2 gene in a family with intellectual disability and spastic paraplegia. *NPJ Genomic Med*. 2017;2(1):20-24. doi:10.1038/s41525-017-0022-7
60. Straussberg R, Onoufriadis A, Konen O, et al. Novel homozygous missense mutation in NT5C2 underlying hereditary spastic paraplegia SPG45. *Am J Med Genet A*. 2017;173(11):3109-3113. doi:10.1002/ajmg.a.38414

eReferences are available as supplementary material at Neurology.org/NG.