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CLINICAL AND GENETIC HETEROGENEITY IN HEREDITARY SPASTIC PARAPLEGIAS: FROM SPG1 TO SPG72 AND STILL COUNTING

Stephan KLEBE¹, Giovanni STEVANIN²⁻⁵, Christel DEPIENNE^{2, 3, 5}

1. Department of Neurology, University Hospital Würzburg, Würzburg, Germany
2. Sorbonne Universités, UPMC Université Paris 06, Paris, France
3. ICM, CNRS UMR 7225, INSERM U 1127, Paris, France
4. Ecole Pratique des Hautes Etudes, Paris, France.
5. Département de génétique et cytogénétique, APHP, Hôpital Pitié-Salpêtrière, Paris, France

Correspondence should be addressed to:

Stephan KLEBE, Department of Neurology, University Hospital Würzburg, Würzburg, Germany. Tel: +49 (0)93120123169. Email: Klebe_S@ukw.de.

Christel DEPIENNE, Institut du cerveau et de la moelle épinière, Hôpital Pitié-Salpêtrière, Paris, France. Tel: +33 (0)1 57 27 46 69. Email: christel.depienne@upmc.fr.

Abstract

Hereditary spastic paraplegias (HSPs) are genetically determined neurodegenerative disorders characterized by progressive weakness and spasticity of lower limbs, which are among the most clinically and genetically heterogeneous human diseases. All modes of inheritance have been described, and, due to the recent technological revolution in molecular genetics, 76 different spastic gait disease-loci (SPG) with 59 corresponding spastic paraplegia genes (SPG) have been identified. Autosomal recessive HSP are usually associated with diverse additional features (referred as complicated forms) contrary to autosomal dominant HSP, which are mostly pure. However, the identification of additional mutations and families has considerably enlarged of the clinical spectra and has revealed a huge clinical variability for almost all HSP, and complicated forms have been described for primary pure HSP subtypes, making therefore genotype-phenotype more complex. In addition, the introduction of next generation sequencing (NGS) in clinical practice has revealed a genetic and phenotypic overlap with other neurodegenerative disorders (amyotrophic lateral sclerosis, neuropathies, cerebellar ataxias...) or neurodevelopmental disorders including intellectual disability. This review aims to describe the most recent advances in the field and to provide genotype-phenotype correlations that could help making clinical diagnoses of this heterogeneous group of disorders.

Keywords: Hereditary Spastic Paraplegia, Genetic heterogeneity, Clinical variability, Diagnosis.

Résumé en français

Les paraplégies spastiques héréditaires (PSH) sont des maladies neurodégénératives d'origine génétique caractérisées par une spasticité progressive et une faiblesse des membres inférieurs. Les PSH font partie des affections les plus hétérogènes d'un point de vue clinique mais également génétique, avec plus de 76 loci différents et 59 gènes (SPG) connus rapportés dans la littérature, dont les mutations se transmettent selon tous les modes de transmissions connus. Les PSH autosomiques récessives sont généralement des formes complexes, *i.e.* associant d'autres symptômes neurologiques ou extra-neurologiques, contrairement aux formes autosomiques dominantes qui ont été décrites comme des formes habituellement pures. Toutefois, un élargissement phénotypique s'est opéré avec la description de familles et mutations additionnelles pour quasiment tous les sous-types de PSH et des formes complexes ont été décrites également dans les formes initialement pures, compliquant ainsi considérablement la visibilité des différentes entités cliniques pour les cliniciens. Par ailleurs, l'introduction du séquençage de nouvelle génération dans la pratique clinique a récemment révélé un chevauchement génétique et phénotypique important entre les PSH et d'autres types de maladies neurodégénératives comme la sclérose latérale amyotrophique, les neuropathies héréditaires, ou encore les ataxies cérébelleuses. Ce chevauchement s'est étendu également à des maladies neuro-développementales comme la déficience intellectuelle. Dans ce contexte, cette revue a pour but de décrire les avancées les plus récentes du domaine et de fournir aux cliniciens un aperçu des corrélations génotype-phénotypes qui peuvent aider à établir un diagnostic moléculaire dans ce groupe de pathologies hétérogènes.

Mots-Clés : Paraplégies spastiques héréditaires, hétérogénéité génétique, variabilité phénotypique, diagnostic.

1. Introduction

Hereditary spastic paraplegias (HSPs) are neurodegenerative disorders characterized by progressive weakness and spasticity of lower limbs. These symptoms are due to progressive degeneration or distal axonopathy of the corticospinal tract, which conducts the nervous information from the cerebral cortex to the spinal cord and allows the control of motor functions. HSP are genetically determined and they are among the most clinically and genetically heterogeneous human diseases. All modes of inheritance (autosomal dominant (ADHSP), autosomal recessive (ARHSP), X-linked (XHSP) and more rarely mitochondrial inheritance) have been described. Due to the considerable progress in molecular diagnostics for neurodegenerative diseases over the last decade, 76 different spastic gait disease-loci (SPG) with 59 corresponding spastic paraplegia genes (SPG) have been identified. This number does not even take into account genes involved in complex forms not referred as HSP or causative genes that are not yet part of the SPG classification¹.

The onset of HSP ranges from early childhood to more than 70 years. The age at onset depends on the underlying genetic defect, but is also highly variable between family members with a same mutation for almost all HSP subtypes. Besides, the onset of the first symptoms is sometimes difficult to precise and is probably often underestimated, as most HSP forms are slowly progressive and patients complain about their disability a long period of time after the onset. It might therefore be helpful to ask about physical activity in childhood or adolescence because poor performance or lack of interest in sport might indicate a long-lasting motor disturbance. In general, most HSP patients report a slow progression of their motor symptoms. However, the worsening of functional disability is also highly variable between affected individuals, ranging from fairly static, non-worsening cases to inexorable and rapid deterioration. In many patients a functional plateau is reached after a continuous aggravation. The prevalence of HSP has recently been reviewed and estimated to $1.8/10^5$ for both ADHSP and ARHSP². Most of the 22 reviewed studies were performed in Europe or Asia. Epidemiological studies for rare diseases have to be viewed with a critical eye due to a couple of limitations, including in particular the different methods used for patients' inclusion, diagnosis and classification. These studies do not usually take into account the fact that specific geographic regions can show a cluster of the disease and areas with very low prevalence of the disease are rarely reported. Additionally, founder effects in isolated populations and the level of consanguineous marriages in some populations can contribute to a higher or lower prevalence of ADHSP or ARHSP in specific geographic regions³. Due to these limitations, the prevalence could easily be overestimated or underestimated depending

on the population.

The clinical classification, based on the historic description by Anita Harding in 1983⁶, distinguishes between pure and complex forms of HSP. Patients with pure HSP show isolated pyramidal signs, *i.e.* brisk reflexes, Babinski sign, spasticity, and motor deficit, which can be associated with sphincter disturbances and deep sensory loss. The severity of the motor symptoms is assessed by the Spastic Paraplegia Rating Scale (SPRS)⁴. Complex forms consist of a multitude of clinical entities in which HSP is associated with variable combinations of other neurological or extra-neurological signs, such as cerebellar ataxia, dysarthria, mental retardation, peripheral neuropathy, optic atrophy, *retinitis pigmentosa*, hearing loss, or thin *corpus callosum*⁵.

Recently, the advances in molecular diagnosis have revealed a large clinical and genetic overlap within different HSP subtypes⁷, and between HSP and other neurodegenerative diseases like hereditary ataxia, amyotrophic lateral sclerosis (ALS)⁸, primary lateral sclerosis (PLS)⁹, Charcot-Marie-Tooth disease (CMT)¹⁰ and elusive clinical syndromes like Boucher-Neuhäuser and Gordon Holmes or Kjellin syndrome¹¹⁻¹³ (Figure 1). Although the distinction between pure and complex forms serves in daily routine, this classification could lead to overlook the cause of the disease since pure and complex phenotypes have been described for almost all HSP subtypes. In addition, a single or a few families have been described in many newly described HSP forms. The experience of the last two decades has taught us that the phenotypical spectrum is usually broadened when additional mutated patients are reported. The current challenge for neurologists is then to link the clinical and molecular results to a specific neurogenetic disease. Discussions with specialized movement disorder centers and geneticists are thus becoming important, especially in the time of next-generation sequencing (NGS) and gene panel analyses. In this context, this review will focus on a rational clinical based diagnostic of the heterogeneous genetic group of HSP. We will try to guide the reader through the most relevant phenotype/genotype correlations for diagnostic clues and to have a red line for HSP diagnostics.

2. Clinical diagnosis of HSP and differential diagnoses

The elicitation of family history is a crucial step in HSP diagnosis. It is often more difficult to clinically and genetically assess patients without family history or without reliable information. In these sporadic cases, HSP is essentially a diagnosis of exclusion.

The technical examinations in HSP patients comprise a magnetic resonance imaging (MRI) of the head and the spinal cord, which usually shows no particular damage, a normal lumbar

puncture and an electrophysiological examination, including transcranial magnetic stimulation (TMS) and somatosensory evoked potentials (SEP) of the upper limbs (UL) and lower limbs (LL), nerve conduction studies and electromyography (EMG). TMS of the LL typically shows an elevated cortical motor threshold, reduced amplitudes and a prolonged central motor conduction time (CMCT). However, TMS of the LL in pure HSP forms can also be normal^{14, 15}, due for example to primarily axonal damages or selective affection of thinner motoneurons and other motor pathways (*i.e.* reticulospinal or vestibulo-spinal tracts) that omit the fastest conducting thick fibers investigated by TMS. SEP of the LL are frequently prolonged or even absent^{16, 17}, whereas SEP of the UL are often normal in pure HSP cases¹⁷. The UL are typically spared from clinical symptoms especially in pure forms, even after several decades of disease duration. Nonetheless, the UL often display hyperreflexia and conflicting electrophysiological results have been shown^{15, 18}. In a recent published electrophysiological study, TMS of the UL showed pathological results in about one third of the patients¹⁵. Clinical signs of peripheral neuropathy are frequently observed with affected sensory and motor nerves of the UL, LL or both¹⁵ and reflects the clinical overlap between HSP and CMT. An ophthalmological examination including a funduscopy and optical coherence tomography (OCT) should be part of the examination if possible to detect subclinical optic atrophy (see SPG7). Regarding the bladder dysfunction, two systematic studies have revealed a urinary dysfunction in up to 78% of patients with urgency or incontinence as the most dominant complaint in HSP patients with a pure phenotype^{19, 20}. HSP patients do not seem to have a higher risk of developing upper urinary tract complications even after a long-term follow up of two decades²⁰.

In sporadic patients, additional evaluation includes the analysis of very long chain fatty acids (VLCFA), white cell enzymes, plasma amino acids, lipoprotein analysis, vitamin B12, homocysteine, methionine, vitamin E, copper, ceruloplasmin, treponema pallidum, human T-cell leukemia virus 1 (HTLV1) and HIV. Treatment by low doses of L-dopa can also be valuable to rule out the possibility of GTP cyclohydrolase I deficiency (DOPA-responsive dystonia, due to mutations in *GCHI*), since patients with this disorder sometimes present with spastic paraplegia at the beginning of the disease²¹. In young onset forms and obvious autosomal-recessive cases a neurometabolic screening (Krabbe disease, metachromatic leukodystrophy, GM1-gangliosidosis, GM2-gangliosidosis Tay Sachs and Sandhoff, Gaucher disease) should be considered and excluded by serum and/or cerebrospinal fluid (CSF) diagnostic. An overview of the differential diagnoses of HSP is given in Table 1.

3. Spastic Paraplegia Genes (SPGs)

The first SPGs were identified in the late 1990s using genome-wide linkage in the largest families, followed by cloning of the causal gene. This approach, which has usually taken several years, was mainly based on candidate gene prioritization. In several cases, a genomic region has been reported but the corresponding gene still remains unknown. For this reason, a total of 76 genomic regions and 59 genes have been described to date in HSP.

In the last few years, an acceleration of gene discovery consecutive to the development of new technologies, including microarrays and next generation sequencing (NGS), has occurred. These technologies, which respectively allow detecting copy number variations (CNVs) and small variants present all over the genome, have completely revolutionized the strategies used for gene identification, making in particular possible the analysis of small families and sporadic cases at an individual scale. The NGS techniques commonly used for research or diagnostic purposes are whole exome sequencing (WES, *i.e.* sequencing of all the coding regions of a genome) and sequencing of selected genes (gene panels). These techniques have led to the identification of many new genes in which mutations are extremely rare and account for only a few families worldwide. Another consequence of the use of NGS in clinical practice was the description of mutations in known genes associated with unusual phenotypes and the demonstration that there is a continuum between HSP and other neurodegenerative disorders (Figure 1).

Nineteen SPGs follow an autosomal dominant mode of inheritance and are more commonly associated with pure or mixed (*i.e.* pure and complex) forms of HSP. Among those, 11 genes have been identified (Table 2). These genes include *SPAST* (SPG4), *ATL1* (SPG3), *REEP1* (SPG31), *KIF5A* (SPG10), *NIPA1* (SPG6), *KIAA0196* (SPG8), *RTN2* (SPG12) and *BSCL2* (SPG17). SPG4 is the main dominant form, accounting for ~40% of ADHSP families. The frequency of all other ADHSP subtypes is much lower, ranging from 5-10% to less than 1%. The list of published ADHSP genes also includes *HSPD1* (SPG13), *ZFYVE27* (SPG33) and *SLC33A1* (SPG42) although those genes were not validated by further studies and it therefore remains controversial whether mutations of these genes are truly pathogenic.

The field of the ARHSP has recently known a real revolution, with 15 new genes identified in a single study¹. To date, 52 different loci and 45 genes with AR inheritance have been described (Table 2). Contrary to ADHSP, ARHSP are mostly complicated forms and are very diverse from one subtype to another regarding both age at onset, disease evolution and the nature of the associated clinical features. In extreme cases such as Troyer syndrome (SPG20) or Mast syndrome (SPG21), pyramidal signs only constitute a sign among many other clinical

characteristics (see Table 2). The main SPGs causing ARHSP to date are *SPG7*, *SPG11*, and *SPG15*. *SPG7*, encoding the mitochondrial paraplegin protein, is the first ARHSP gene identified in 1998²². Mutations in *SPG11* and *SPG15* cause a similar complex HSP form characterized by progressive *corpus callosum* atrophy concomitant with a cognitive decline, which are amongst the most frequent features associated with ARHSP^{7, 23, 24}.

X-linked HSP subtypes are more exceptional, with only 5 loci and 3 genes reported so far (Table 2). Like ARHSP, mutations in X-linked genes usually cause early-onset, complex phenotypes, such as MASA or CRASH syndromes (both related to mutations in *LICAM/SPG1*), Pelizaeus-Merzbacher disease (due to mutations in *PLP1/SPG2*), and Allan-Herndon-Dudley syndrome (due to mutations in *SLC16A2/SPG22*), but their expression is usually restricted to hemizygous males.

An interesting recent observation is the increasing evidence that mutations in some SPGs can be inherited according to different modes of inheritance: this is for example the case of *ATL1* (SPG3), in which recessive mutations causing HSP have recently been described²⁵; *REEP2* (SPG72), in which both a dominant mutation leading to a dominant negative effect on the WT allele and a recessive mutations causing a loss of function have been reported²⁶; and *KIF1A* (SPG30), in which recessive mutations were initially described, while *de novo* dominant mutations associated with complex HSP including cognitive impairment were recently reported^{27, 28}.

Finally, mutations in mitochondrial genes, such as *MT-ATP6*²⁹ or *MT-TT*³⁰, could occasionally account for patients with pure or complex forms of HSP depending on the heteroplasmy rate and affected tissues. These unusual forms could be easily overlooked unless the presentation of the disease, usually very variable from one family member to the other, suggests a mitochondrial involvement in at least some of them.

4. Phenotype/genotype correlations in HSP

The objective of the following section is to focus on the frequent and well-characterized HSP subtypes, which are the most relevant forms in daily clinical practice, and to establish correlations according to the clinical presentation. For the complete list of HSP subtypes described to date, please refer to Table 2.

4.1 Pure or mixed HSP with AD inheritance

Pure HSP consists of clinical signs of an upper motor neuron syndrome affecting the LL, which can further be associated with electrophysiological alterations, sphincter disturbances

and deep sensory loss. The MRI and lumbar puncture usually show no specific abnormalities in pure HSP patients. The clinical signs include spasticity, an extensor plantar response, hyperreflexia, crossed adductor signs and a slight weakness most prominent in iliopsoas, hamstring and tibialis anterior muscles. With the exception of SPG17, all ADHSP with a known gene have initially been described as pure forms. However, the identification of additional mutated families has systematically revealed that most HSP subtypes can also occur as complicated phenotypes in some individuals. There are two main nonexclusive reasons accounting for this variability: the patients could present with a pure form at the beginning of the disease and evolve toward a complicated phenotype over time. It is also possible that genetic or environmental modifiers play a determinant role in determining the age at onset, presentation and evolution of the disease. The different pure / mixed ADHSP presented below are sorted according their known prevalence.

SPG4 (Spastin)

SPG4 is by far the most frequent ADHSP subtype, especially in patients with a pure phenotype, accounting for ~40% of ADHSP and 10-20% of apparently sporadic cases^{5, 31-33}. The mean age at onset is typically between the third and fourth decade of life^{34, 35}, although symptoms may start as early as infancy or as late as 70 years, and vary even between members of a same family. Usually, SPG4 patients show a slowly progressive disorder, many of them being able to walk several decades after the first symptoms. Besides the clinically affected LL, UL hyperreflexia, decreased vibration sense, and a slight muscle wasting in the lower limbs are consistently found. Some mutation carriers can remain unaffected or very mildly affected all their lives. TMS of the UL is typically normal^{15, 18} and TMS of the LL is normal in up to 48%^{14, 15}. The axonal integrity of corticospinal projections to the UL in SPG4 patients has been investigated using the triple stimulation technique (TST)¹⁸ and has not shown pathological changes. TST is considered to be two or three times more sensitive than standard TMS procedures to detect corticospinal conduction deficits and is especially suited for the detection and quantification of small changes of central motor conduction¹⁸. A slightly delayed P40 latency of the SEP has often been reported for the LL, contrary to the SEP of the UL, which is normal¹⁵.

SPG4 HSP is caused by mutations in *SPAST*, encoding spastin, a member of the AAA family of ATPases³³. All types of mutations (missense³³, nonsense, splice site mutations, small deletions and insertions, as well as rare large scale deletions or duplications) have been identified. This large spectrum is compatible with haploinsufficiency (*i.e.* loss of function of

one allele) as the main pathogenic mechanism. Mutations have been reported in all exons of the gene with the exception of exon 4, which is alternatively spliced in blood and brain. Recurrent mutations are exceptional, and, with only a few exceptions, missense mutations are always located in the AAA cassette.

SPG3 (Atlastin)

SPG3 is characterized by a clinically pure phenotype that progresses very slowly over time^{36, 37}. It is the most frequent ADHSP in patients with a disease onset <10 years^{37, 38}, with a mean age at onset of 5 years³⁷. Very occasionally, a late onset or complex or more severe phenotypes have been reported in SPG3 patients³⁹⁻⁴⁷. SPG3 HSP is due to mutations in *ATL1*, encoding atlastin 1, a dynamin-related GTPase. Most of the dominant mutations described so far are missense mutations supposed to lead to a gain of function of atlastin 1^{48, 49}.

SPG31 (REEP31)

SPG31 is responsible for approximately 2-8% of ADHSP depending on the population^{35, 50-53}. The symptoms of the disease usually appear in the first two decades of life. However, patients with an adult-onset also exist and the age at onset varies between affected family members. Like SPG4 individuals, patients can remain unaffected, even at advanced ages^{50, 52}. Although most SPG31 patients have a pure phenotype, complicated forms including lower motor neuron involvement mimicking a Silver syndrome and abnormal white matter signals have been described (see 4.4)^{50, 52, 54}. Mutations in *REEP1* are of all types (missense or truncating mutations) and exon deletions have also been reported^{35, 50-53}.

SPG10 (KIF5A)

SPG10 accounts for 2-10% of AD families and sporadic patients in Europe⁵⁵⁻⁵⁸. The age at onset is usually late (>35 years) although early infantile onset has also been described^{58, 59}. The phenotype of SPG10 has first been classified as pure ADHSP⁶⁰. However, in European countries, SPG10 accounts for up to 10% of complicated ADHSP cases⁵⁷. The complicated phenotype of SPG10 patients is often associated with CMT2 and Silver syndrome^{57, 61} (see 4.4). The phenotype has recently broadened to include sensory spinal cord-like syndrome, dysautonomia, severe axonal polyneuropathy and symmetric cerebral demyelination and spinal cord atrophy on the MR in some patients⁶².

Like *ATL1*, mutations in *KIF5A*, encoding the neuronal kinesin 5A heavy chain involved in anterograde axonal transport, are mainly missense mutations located in the motor domain of

the protein^{55-58, 63}.

SPG6 (NIPAI)

Mutations in *NIPAI* are a rare cause (<1%) of ADHSP^{64, 65}. In the literature, less than 20 pedigrees with *NIPAI* mutations have been reported with a worldwide distribution⁶⁵⁻⁶⁸. The mean age at onset varies between early childhood and late adulthood⁶⁵. Most of the patients have a pure phenotype with a slow disease progression^{65, 69} but an intrafamilial clinical heterogeneity also exists for this HSP subtype^{65, 69}. In some families, a mild memory deficit has been reported. Only a few recurrent missense mutations have been identified in *NIPAI*. Interestingly, *NIPAI* is located on chromosome 15, in a region with variable copy number. Deletion of the four genes comprised in this region (including *NIPAI*) predisposes to various neurodevelopmental disorders⁷⁰ but is almost never associated with HSP, indicating that haploinsufficiency of *NIPAI* does not cause HSP.

4.2 Pure or mixed HSP with AR inheritance

SPG7 (Paraplegin)

The frequency of SPG7 HSP, initially thought to be rare⁷¹, has recently been reevaluated and might be as high as 8-10% of all HSP including sporadic cases³⁵. This change is partly due to the fact that a recurrent missense variant (Ala510Val), first considered as a polymorphism, finally turned out to be pathogenic⁷²⁻⁷⁴. SPG7 HSP is slowly progressive and usually pure at the beginning of the disease, with an age at onset ranging from 10 to 63 years^{71-73, 75-77}. An onset in childhood or adolescence is rare⁷³, which is quite uncommon for a recessive disorder. During the course of the disease, atrophy of the cerebellum observed by MRI, followed or accompanied by cerebellar signs frequently appear: these signs can be observed in up to 57% of the patients^{71-73, 75, 76}. Another feature characteristic of SPG7 HSP is bilateral optic disc pallor, which has been observed in several SPG7-positive families^{22, 73, 77, 78}. A very useful tool to determine optic neuropathy is optical coherence tomography (OCT). In a recent study, all SPG7-positive patients who underwent OCT had detectable pathology of the optic nerve⁷³. The identification of a dominant *SPG7* mutation segregating with clinically isolated optic neuropathy in a large multigenerational pedigree supports the view that the loss of retinal ganglion cells in patients with hereditary spastic paraplegia with *SPG7* mutations is not coincidental⁷³. Therefore, patients might have a pure phenotype on examination, but *in fine*, if cerebellar atrophy is detected by brain MRI or optic neuropathy by OCT, they have to be

reclassified to complex HSP. The diagnostic accuracy can hence be increased if patients are selected on the basis of their phenotype for SPG7 testing⁷³.

Mutations in *SPG7* are of all types, also including large exon or whole gene deletion^{22, 71, 73}. Several mutations such as p.Ala510Val and p.Arg485_Glu487del are recurrently found. Interestingly, heterozygous mutations in *SPG7* were associated with late-onset neurologic signs including cerebellar signs, neuropathy or gait instability⁷³.

SPG5 (CYP7B1)

SPG5 is an ARHSP with a frequency up to 8% of ARHSP families and 3% in apparently sporadic cases^{79, 80}. Age at onset shows both an interfamilial and intrafamilial variability, with a range from early childhood to the 5th decade of life⁷⁹⁻⁸¹. Most SPG5 patients show a slowly progressive pure form, but complicated courses with/or without periventricular and subcortical white matter lesions at brain MRI have been reported in patients with a long disease duration^{79, 80, 82}. A cerebellar involvement and/or optical atrophy have been described in a few patients⁷⁹⁻⁸². Electrophysiological investigations have reported profound dorsal column deficits with severe disturbed SEP of the UL and LL with normal nerve conduction study and EMG¹⁶. SPG5 is due to nonsense or missense mutations in the *CYP7B1* gene, encoding the oxysterol 7-alpha-hydroxylase, a steroid-metabolizing enzyme belonging to the cytochrome P450 family involved in bile acid and neurosteroid biosynthetic pathways. As a consequence of the loss of function of this enzyme, an accumulation of 27-hydroxycholesterol occurs in the serum and CSF⁸³. The aforementioned molecule may serve as therapeutic target and could act as first biomarker in this HSP subtype.

SPG30 (KIF1A)

SPG30 is a rare ARHSP form with an age at onset between 10 and 39 years and a slow disease progression^{84, 85}. Cerebellar signs, or cerebellar atrophy and axonal sensorimotor peripheral neuropathy are frequently associated signs. Recently, autosomal dominant mutations mostly occurring *de novo* were identified in patients with a more complex and severe phenotype including intellectual deficit, axonal neuropathy and cerebellar atrophy^{27, 86}.

SPG49/SPG56 (CYP2U1) and SPG28 (DDHD1)

SPG49 (nomenclature source: HUGO Gene Nomenclature Committee (HGNC)) or SPG56 (nomenclature source: National Center for Biotechnology Information (NCBI)) is a rare ARHSP with very early onset (birth to age 8 years) that can present either as pure or complex

forms. Contrary to other HSP, UL are also frequently affected. Additional features in complicated forms include dystonic posturing of the upper limbs, cognitive impairment, subclinical axonal neuropathy, thin corpus callosum, white-matter abnormalities, and/or calcification of the basal ganglia⁸⁷. SPG28 is a rare early-onset, slowly progressive and usually pure form. Some patients also have distal sensory impairment⁸⁷. SPG49/56 is caused by biallelic mutations in *CYP2U1*, a member of the P450 enzyme family, while SPG28 is due to mutations in *DDHDI*, which encodes a lipase that catalyzes degradation of phosphatidic acid. Both enzymes are involved in fatty-acid metabolism.

4.3 HSP with abnormalities in neuroimaging

Neuroimaging abnormalities in the MRI are commonly present in complicated HSP forms. The most frequent abnormality is a thin *corpus callosum* (TCC) present in about one-third of ARHSP index cases²⁴. Other MRI abnormalities frequently associated with HSP include white matter lesions (WML) or white matter abnormalities (WMA), and cerebellum atrophy, often concomitant with a cerebellar phenotype.

A TCC has been reported in at least 15 different HSP subtypes, and is almost always associated with cognitive deterioration or intellectual disability (ID)³⁵. By far, the most frequent HSP form associating TCC, cognitive impairment and/or WML is the SPG11 ARHSP subtype, followed by SPG15^{88, 89}, SPG49/56⁸⁷ and SPG46⁹⁰. TCC and WML have also been observed in patients with SPG21⁹¹, SPG44⁹², SPG47⁹³, SPG54⁹⁴ and SPG63 HSPs¹. An agenesis of the *corpus callosum* (ACC) has been reported in the SPG1 X-linked HSP⁹⁵ and the recently published SPG67 ARHSP¹.

WML are frequent in complicated phenotypes and are occasionally also described in pure HSP forms (*e.g.* SPG4, SPG5). The clinical overlap between HSP and other forms of metabolic and neurodegenerative diseases with specific WML has become evident since the identification of neurodegeneration with brain iron accumulation (NBIA) on MRI in patients with *FA2H* (SPG35) mutations⁹⁶ (Figure 1).

SPG11 (Spatacsin)

The *SPG11* gene, encoding spatacsin, has been identified in 2007⁹⁷. *SPG11* mutations are responsible for up to 60% of patients with TCC and cognitive impairment and 4.5% of cases with spastic paraplegia, cognitive impairment and WML without TCC⁸⁸. Overall, *SPG11* mutations account for approximately 20% of ARHSP^{88, 98}. The age at onset ranges from early childhood to the third decade of life, although late onset is more occasional^{88, 97, 99, 100}. TCC

with or without WML is present in the vast majority (>90%) of mutated individuals^{88, 97}. ID or cognitive deterioration are observed in >80% of SPG11 patients^{88, 97}. Other frequent associated clinical signs include axonal sensory-motor neuropathy, cerebellar symptoms (nystagmus, dysarthria, saccadic pursuit) and, to a lesser extent, extrapyramidal symptoms and retinopathy^{13, 70, 88, 101}. The progression of motor symptoms in SPG11 HSP is more severe than in pure phenotypes since two-third of patients are wheelchair bound or need assistance for walking after mean disease duration of 15 years⁸⁸. Several studies have shown that some SPG11 patients can present with juvenile ALS (jALS, also classified as ALS5) and that 40% of families with jALS and long-term survival (>25 years after disease onset) are SPG11 positive^{8, 102}. Strikingly, these SPG11 positive ALS patients have bulbar symptoms, clinical signs typical of ALS, and normal nerve conduction analyses, but no TCC, WMA and/or cognitive deficits. However, the existence of an intrafamilial phenotypic heterogeneity with an atypical ALS and a classical HSP-TCC phenotype in some families is very evocative of SPG11 mutations^{8, 102}.

With rare exceptions, *SPG11* mutations all introduce a premature termination codon (*i.e.* nonsense mutations, splice site mutations, frameshifts and microrearrangements deleting one or more exons) leading to the absence of the spastacin protein in the patients' cells.

SPG15 (Spastizin)

SPG15, initially identified as a complicated ARHSP associated with pigmentary maculopathy (Kjellin syndrome)^{11, 103}, is due to mutations in *ZFYVE26*, encoding spastizin. *ZFYVE26* mutations are responsible for ~12% of subjects with ARHSP and TCC and ~4% of all ARHSP⁸⁹. Age at onset ranges from 4 to 18 years^{89, 104}. Brain imaging shows TCC and white matter signal abnormalities in about 80% of SPG15 patients and cerebellar atrophy in 25% of the cases⁸⁹. A clinical distinction between SPG11 and SPG15 is difficult as both ARHSP are associated cognitive impairment and peripheral axonal neuropathy and a similar disease progression. However, SPG15 patients suffer more often from cerebellar signs and hearing loss^{89, 104}. Like those in *SPG11*, biallelic mutations in *ZFYVE26* lead to a loss of function of the gene.

4.4 HSP associated with peripheral motor neuropathy and/or distal muscle atrophy

The differential diagnosis of HSP *versus* amyotrophic lateral sclerosis (ALS) is often based on the observation of an affected lower motor neuron in ALS. There is growing evidence in the literature that the combination of upper and lower motor tract impairment by itself is not

indicating only of ALS but is a common feature of HSP as well. As discussed earlier (see 4.2), SPG11 is a good example of ARHSP in which mutations can also cause juvenile ALS (ALS5)⁸. Mutations in the same gene may lead to a damage of the upper motor neuron, peripheral motor neuron or sensory nerves, explaining the variability of the phenotype, which can appear as HSP and/or spinal muscular atrophy (SMA), distal hereditary motor neuropathy (dHMN), hereditary sensory neuropathy (HSN), hereditary sensory autonomic neuropathy (HSAN) or CMT. Examples of genes associated with such variability are *ALSIN* (ALS2)^{105, 106}, *SETX* (ALS4)^{107, 108}, *BSCL2* (SPG17; dHMN-V, see below)¹⁰⁹⁻¹¹¹, *KIF1A* (SPG30; HSAN-II)^{112, 113}, *REEP1* (SPG31; Silver like syndrome, dHMN-V)^{52-54, 114}, *KIF5A* (SPG10; Silver like syndrome; CMT2)^{57, 61}, *ATLI* (SPG3; HSN-I)^{39, 40}, and *NIPA1* (SPG6) (although the association with ALS is exceptional)¹¹⁵. An atrophy of the small hand muscles or a wasting of the UL has been reported for the complicated HSP forms SPG10, SPG17, SPG22, SPG30, SPG38 and SPG43³⁵.

SPG17 (BSCL2)

The complicated SPG17 ADHSP, also known as Silver syndrome, is caused by two mutations in *BSCL2*, encoding seipin¹¹⁰. These two mutations (p.Asn88Ser and p.Ser90Leu) affect glycosylation of seipin and result in aggregate formation leading to neurodegeneration¹¹⁶, contrary to mutations leading to a loss of function of the gene, which cause two AR allelic disorders: congenital generalized lipodystrophy type 2 and progressive encephalopathy with or without lipodystrophy^{109, 117}. Silver syndrome was first described in 1966 in two families with spastic paraplegia in which a wasting and atrophy of the small hands muscles was the first and most marked manifestation^{110, 118}. The phenotype has later been extended to dHMN-V, CMT and even to pure HSP^{111, 119, 120}. A reduced penetrance and patients with only subclinical signs have been described¹²⁰. The age at onset is again variable and ranges from 2 to 60 years^{111, 119-122}. *BSCL2* mutations could be the most common cause of dHMN¹²². The phenotype and the disease progression seem to depend on the mutation. Patients with the p.Asn88Ser mutation usually have a rather slow progression, more often a dHMN phenotype and relatively mild impact on daily live functioning despite an onset of disease in the first or second decade of life^{120, 121}. Patients with the p.Ser90Leu mutation mostly have a prominent amyotrophy of the intrinsic hand muscles in association with a marked spasticity of the lower limbs and the presence of additional pyramidal tract signs¹²², corresponding to Silver syndrome. A detailed electrophysiological study in four Austrian families has revealed that Silver syndrome is not only caused by impairment of upper motor neurons but is also due to a

peripheral motor neuropathy closely resembling clinically to dHMN-V¹²³. This study has reported a conduction block of the tibial nerve in two patients¹²³, which we have also observed in one SPG17 patient (unpublished data). This observation suggests that *SPG17* should be included in the diagnostic workup of Multifocal Motor Neuropathy (MMN). The aforementioned implicates that a careful and detailed family history in MMN is of great importance.

4.5 HSP and cerebellar ataxia

The association of an upper motoneuron syndrome and cerebellar signs (dysarthria, nystagmus, coordination problems in finger-nose dysmetria, tandem walk ect.) and/or cerebellar atrophy on MRI imaging is common in complicated HSP subtypes. The ataxia can be the most prominent sign as in SPG46 (*GBA2*)^{90, 124}, SPG58/*SAX2* (*KIF1C*) ARHSP^{1, 125} and ARSACS (*SACS*)^{126, 127}, or only an associated sign, such as in SPG1 (*LICAM*), SPG7 (see 4.2), SPG11, SPG15 (*ZFYVE26*), SPG26 (*B4GALNT1*), SPG30 (*KIF1A*), SPG31 (*REEPI*), SPG44 (*GJC2*), SPG49/SPG56 (*CYP2U1*), SPG50 (*AP4M1*), SPG54 (*DDHD2*) SPG66 (*ARSI*), and SPG67 (*PGAPI*)³⁵.

One important differential diagnostic of HSP with cerebellar ataxia is Friedreich Ataxia (*FRDA*). *FRDA* is the most common autosomal recessive ataxia in Europe with an estimated prevalence of 3-4/10⁵^{128, 129}. *FRDA* can mimic HSP in particular in patients with a late onset (>25 years). In these patients, an affected upper motoneuron syndrome might be the most prominent sign at the beginning of the disorder.

The classification between HSP associated with cerebellar involvement and spastic ataxias (SPAX) is sometimes confusing and the reason why some HSP are not classified as SPAX and *vice versa* is not obvious. Autosomal recessive spastic ataxias include ARSAL (*MARS2*; SPAX3)¹³⁰ and ARSACS (*SACS*; SPAX6)¹²⁷. Some genes even belong different classifications, such as the autosomal dominant spastic ataxia due to *AFG3L2* mutations (SPAX5 = SPG28)¹³¹, or the recently published ARHSP due to *KIF1C* mutations (SPG58 = SPAX2)^{125, 132}. In addition, a cerebellar involvement has also rarely been reported for primarily pure phenotypes including SPG3, SPG4 and SPG6.

4.6 HSP and intellectual deficiency (ID)

As previously discussed in section 4.3, the most frequent cause of HSP and intellectual disability (ID) known so far is mutations in SPG11⁷. Cognitive impairment in SPG11 HSP is usually noticed in childhood and progresses insidiously to severe functional disability of a

frontal type over a period of 10-20 years¹³³. An age at onset in early childhood and/or delayed psychomotor development exists in some individuals¹³⁴, although motor signs preceding mental deterioration can appear much later in other individuals.

The association of HSP and ID (or cognitive decline) is frequent in complicated ARHSPs, including SPG15 (*ZFYVE26*), SPG18 (*ERLIN2*), SPG20 (*KIAA0610*), SPG21 (*ACP33*), SPG26 (*B4GALNT1*), SPG35 (*FA2H*), SPG44 (*GJC2*), SPG46 (*GBA2*), SPG47 (*AP4B1*), SPG48 (*AP5Z1*), SPG49 (*TECPR2*), SPG50 (*AP4MI*), SPG51 (*AP4E1*), SPG52 (*AP4SI*), SPG53 (*VPS37A*), SPG54 (*DDHD2*), SPG55 (*C12ORF65*), SPG49/SPG56 (*CYP2U1*), SPG58 (*KIF1C*), SPG59 (*USP8*), SPG64 (*ENTPD1*), SPG65 (*NT5C2*), SPG69 (*RAB3GAP2*), and the X-linked HSP SPG1 (*LICAM*), SPG2 (*PLP1*), SPG22 (*SLC16A2*) and is also present in homocystinuria due to methylenetetrahydrofolate reductase deficiency (mutations in the *MTHFR* gene), a disorder potentially treatable by betaine supplementation¹³⁵.

In addition, recurrent duplications or triplications of a region comprising 16 genes (including *RPL10*, *ATP6AP1* and *GDII*) on chromosome Xq28 have been shown to cause HSP and ID whose severity is dependent on the copy number¹³⁶. More generally, the association of HSP and ID is an indication to search for genomic rearrangements using microarrays.

5. Molecular genetic testing of HSP

5.1 Identification of the causative gene/mutation in a family

Until very recently, molecular screening of SPGs in index cases was done sequentially (*i.e.* one gene at a time) using Sanger Sequencing. The choice of the tested genes was driven by the phenotype (pure/complex forms), age at onset of the first symptoms and mode of inheritance observed in the family. For example, in patients with pure ADHSP, molecular testing of *SPAST* was prioritized in patients with an age at onset >10-15 years whereas *ATLI* was first analyzed in patients with early-onset (< 10 years). If the analysis of these genes was negative, other genes (*REEP1*, *KIF5A*, *NIPAI* *ect.*) were further screened. Since Sanger sequencing does not allow detecting heterozygous microrearrangements altering the gene such as exon deletions, a method measuring the quantity of each exon (Multiplex ligation-dependent probe amplification / MLPA, quantitative PCR) was recommended in parallel to Sanger sequencing.

However, the introduction of NGS has transformed the strategies used for molecular testing of HSP. By drastically reducing the cost of DNA sequencing and allowing fast and efficient sequencing of millions or even billions of bases in a single experiment, the new sequencers now offer the possibility of analyzing all genes involved in a pathology at the same time. This

method, referred to as gene panel analysis, has become available in diagnostic laboratories and tends to totally replace Sanger sequencing^{137, 138}.

5.2 Molecular testing in sporadic cases

As discussed in section 2, HSP is mainly a diagnosis of exclusion in patients with spastic paraplegia or spastic paraparesis without family history of the disease. After exclusion of non-genetic causes and other genetic disorders that can mimic HSP, molecular testing of HSP genes has to be considered in sporadic HSP cases, especially if age at onset is early and before the age of 50 years. Many different reasons account for the absence of family history: incomplete penetrance, genealogical censure³⁴, and more rarely *de novo* mutations for dominant forms, or absence of recurrence of an AR or X-linked disease in small families. The main genetic causes of isolated HSP patients are mutations in *SPAST*³¹, *SPG7*^{71, 73}, *KIF5A*⁵⁷ and *CYP7B1*⁷⁹, and more rarely, mutations in *REEP1* and *ATLI* (personal communication). Mutations in *SPG11* are also very frequent in sporadic HSP-TCC⁸⁸.

5.3 Genetic counseling and molecular testing of at-risk individuals

Since the first symptoms of many HSP subtypes, especially those of AD inheritance, can occur at any time from infancy to adulthood, asymptomatic individuals may be carrier of a mutation and therefore at-risk to develop HSP. The proportion of mutated individuals who exhibit clinical symptoms is called penetrance. In ADHSP, penetrance is typically incomplete and age-dependent, *i.e.* mutated individuals have a risk of developing HSP symptoms increasing with age.

The identification of the causative mutation in a family has thus important consequences for family members: it allows precisely appraising the risk of each of them, and performing a predictive molecular test in adult at-risk asymptomatic individuals who wish to know their status. In addition, the possibility of performing prenatal diagnosis can be considered for the more severe forms.

6. Pathophysiological mechanisms underlying HSP

The identification of SPGs has been a crucial step to understanding the pathophysiological mechanisms involved in HSPs. Although many different genes have been identified, it is now recognized that they encode proteins functioning in a limited number of cellular pathways, including axonal transport, intracellular trafficking, mitochondrial function, lipid metabolism and developmental processes and myelination¹³⁹ (Figure 2). Moreover, many of the encoded

proteins altered in HSP interact together or belong to a large interconnected network¹.

HSP is due to a length-dependent distal axonopathy of the fibers constituting the corticospinal tract. Since the axons of the upper motor neuron are the longest of the human body, it has been postulated that the processes impairing paths or connections between the cellular body and the axon terminals (synapses) will lead to a dysfunction of the axon and therefore be pathogenic. Cargo protein regularly travel at high velocities on specific cytoskeletal structures (microtubules) within the axon to deliver proteins and intracellular organelles such as elements of the endoplasmic reticulum (ER), mitochondria, endosomes, or synaptic vesicle precursors from the cell body towards the axonal terminals (anterograde transport) or *vice versa* (retrograde transport). Kinesins are the main microtubule motor proteins involved in anterograde transport. SPG10 (*KIF5A*), SPG30 (*KIF1A*) and SPG58 (*KIF1C*) are all HSP subtypes due to mutations in kinesin chains^{55, 125, 139, 140}. For example, missense mutations in *KIF5A* located in the kinesin motor domain have been shown to impair microtubule affinity or gliding properties on microtubules or both⁶³. Spastin (*SPAST*, SPG4) also binds microtubules and regulate their dynamics and organization by performing ATP-dependent severing^{141, 142}. Spastin interacts with atlastin 1 (*ATL1*, SPG3)^{143, 144}, REEP1 (SPG31)¹⁴⁵, and reticulon 2 (*RTN2*, SPG12)¹⁴⁶ and all four proteins contribute to the shaping of tubular ER network by inducing a membrane curvature¹⁴⁵⁻¹⁴⁸. Atlastin 1 also mediates homotypic fusion of ER tubules^{149, 150}, and *ATL1* mutations were shown to alter vesicle trafficking between ER and Golgi apparatus as well as Golgi morphogenesis^{49, 148}. Spatacsin (SPG11) and spastizin (*ZFYVE26*, SPG15) interact together and co-localize with protein-trafficking vesicles, endoplasmic reticulum and microtubules¹⁵¹. They also interact with AP5Z1 (SPG48), one of the subunit forming the adaptor protein (AP) 5 complex¹⁵². AP4B1 (SPG47), AP4M1 (SPG50), AP4E1 (SPG51) and AP4S1 (SPG52) form the AP4 complex⁹³. AP complexes mediate the sorting of membrane proteins in the secretory and endocytic pathways¹⁵². *SPG7* encodes paraplegin, a protein that forms together with AFG3L2 (SPAX5) the mAAA complex present at the inner mitochondrial membrane¹⁵³. mAAA is a protease essential for mitochondrial biogenesis and function, which contributes in particular to the processing of regulatory proteins and quality control surveillance¹⁵⁴. In agreement with paraplegin function, mitochondrial abnormalities, including complex I deficiency and increased sensitivity to oxidative stress are detectable in SPG7 patients' cells^{22, 153}. Interestingly, REEP1 also partially localizes to the mitochondria or at the mitochondrial surface⁵³, and patients with *REEP1* mutations also show mitochondrial dysfunction⁵². Strikingly, although spastin and paraplegin have different function and localization, the consequences of the loss of function

of the two proteins appear similar in mouse models, and mainly consist in the accumulation of organelles and neurofilaments in synaptic terminals and distal regions of axons, suggestive of an impairment of anterograde axonal transport, and leading to the apparition of axonal swellings^{155, 156}.

Finally, increasing evidence suggests that lipid metabolism is an important issue in HSP physiopathology. In addition of their role in metabolism and energy storage, lipids play a crucial role in membrane composition. The composition of the membranes in lipids and sterols controls membrane fluidity as well as compartmentalization into specialized membrane microdomains. Unsurprisingly, lipid metabolism and membrane lipid structural composition are therefore linked to several cellular functions, including intracellular membrane trafficking among many others¹⁵⁷. Several genes mutated in HSP enter in the category of lipid metabolism, such as *CYP7B1* (SPG5), *CYP2U1* (SPG49/56), *DDHD1* (SPG28) and *DDHD2* (SPG54), *GBA2* (SPG46), *PNPLA6* (SPG44), *FA2H* (SPG35), and *B4GALNT1* (SPG26). However, the precise mechanism by which alteration of these genes leads to HSP still remains unclear. Altogether, these data suggest that HSP would in many cases results from disturbance in intracellular membrane trafficking or organelle transport, either related to defects in cytoskeletal dynamics, membrane properties or composition, organelle structure and/or the connection between cytoskeleton and organelles.

HSP due to abnormalities of development or myelination (e.g. *SPG1/LICAM*, *SPG2/PLP1*, *SPG42/GJC2* or *SPG67/PGAP1*) are usually complex forms since these processes also affect many other neurons than the upper motor neurons.

7. Treatment of HSP and future therapeutic perspectives

To date, no causal therapy of an underlying genetic defect in HSP is available. The treatment remains therefore exclusively symptomatic and focuses on the main symptoms. The common strategy for treating spasticity and cerebellar ataxia is regular physiotherapy. In complex HSP subtypes, speech and occupational therapy might also be useful. The spasticity also benefits from oral medication like baclofen, tolperisone or tizanidine. Intramuscular injections of botulinum toxin A is then a therapeutic option to reduce the increased muscle tone^{158, 159} although this treatment is considered as an off label procedure for the LL in most countries. Intrathecal baclofen therapy (ITB) can also alleviate spasticity in HSP. Most HSP patients are still able to work even after long disease duration. Therefore ITB therapy in HSP has the special requirement of reducing spasticity but preserving gait function^{160, 161}. ITB can be

administered via a surgically implanted programmable pump. HSP patients that undergo an intrathecal baclofen pump implantation have to be carefully selected by applying one or several preoperative ITB testing doses^{160, 161}. For the rare HSP patients with significant weakness in the LL the proposed symptomatic treatment of spasticity offers much less functional improvement. In HSP patients with a young onset in early childhood or adolescence orthopedic options such as special shoes for pes cavus, or achille tenotomy for equinovarus are also proposed to allow a longer autonomous gait. Anticholinergic drugs like oxybutinine chlorhydrate or trospium chlorure are used for the recurrent symptom of a detrusor overactivity and detrusor sphincter dyssynergia as expression of a central neurogenic bladder^{19, 20}. Parkinsonism, dementia, and epilepsy are treated according to their respective guidelines. A hydrocephalus in X-chromosomal SPG1 patients shunt implantations is often performed.

In HSP patients with an identified mutation the socio-medical assistance in terms of familial counseling, especially for the risk of transmission and questions dealing with prenatal and presymptomatic testing, is also an important issue for the attending neurologist and/or geneticist.

8. Conclusion

The recent discoveries of new pathophysiological pathways like genes involved in fatty-acid (SPG28, SPG49, SPG54)^{87, 94} or steroid metabolism (*e.g.* SPG5, SPG18)^{79-81, 162, 163} may open new treatment strategies and useful distinguishing biomarker for diagnostic and disease progression purposes in HSP. It also underlines the importance of clinical and genetic studies in HSP. In SPG5 HSP, a reduction of the 27-hydroxycholesterol levels might be achieved by statin therapy. Indeed, the observation of moderate decreases of plasmatic 27-hydroxycholesterol after simvastatin intake in a SPG5 patient are encouraging results¹⁶⁴, and further clinical studies are currently under way. It remains however unclear whether a reduction in the 27-hydroxycholesterol levels in the serum and/or CSF will correlate with a clinical improvement. Particularly in slowly progressive forms like SPG5, the measurement of the clinical outcome after a metabolic treatment will be difficult to undertake. Finally, the identification of environmental and/or genetic modifiers constitutes an important challenge in HSP in order to understand the huge phenotypic variability of these disorders, predict the evolution and outcome and ultimately develop new therapeutic strategies.

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Figure 1. Overview of the clinical and genetic overlap between HSP and other neurodegenerative disorders

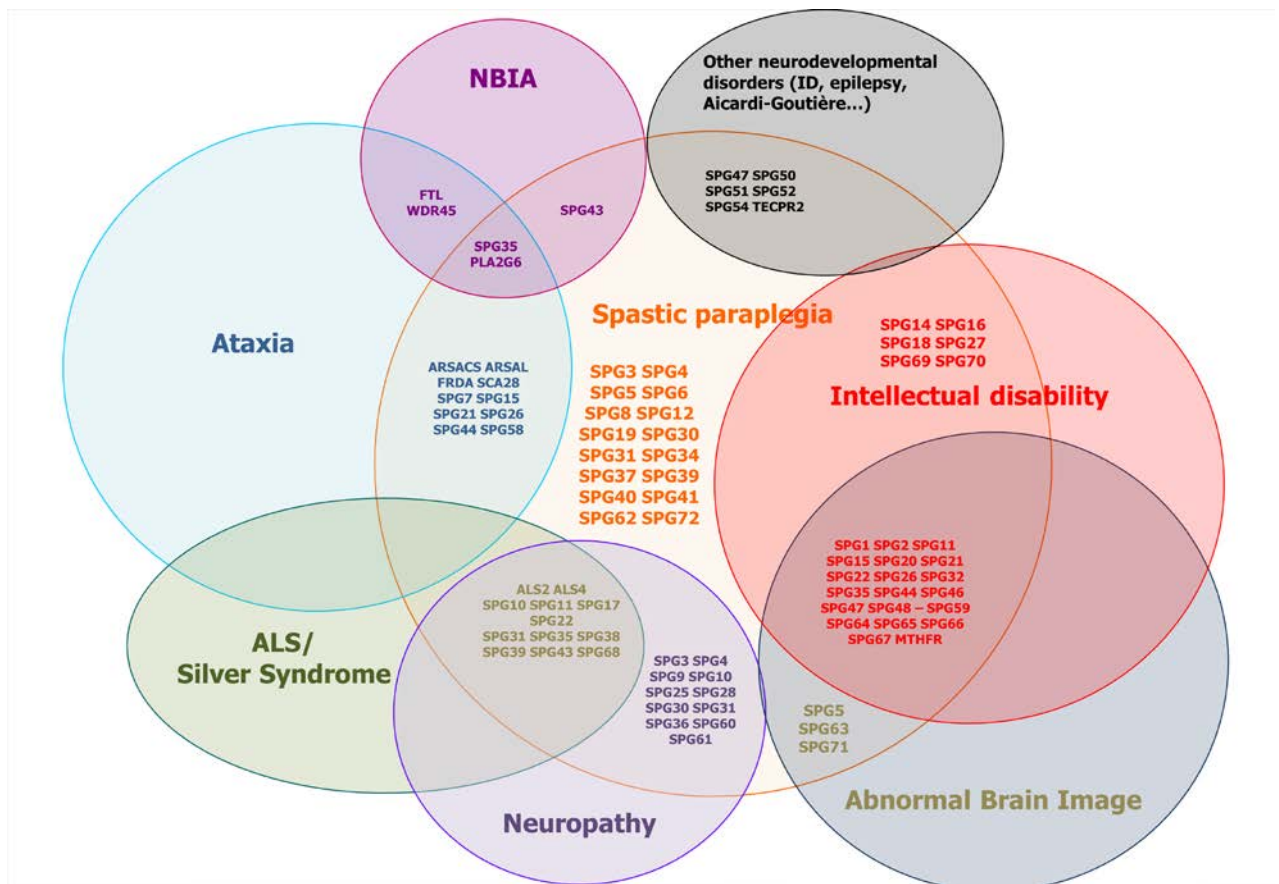


Figure 2. Overview of the pathophysiological mechanisms involved in HSP

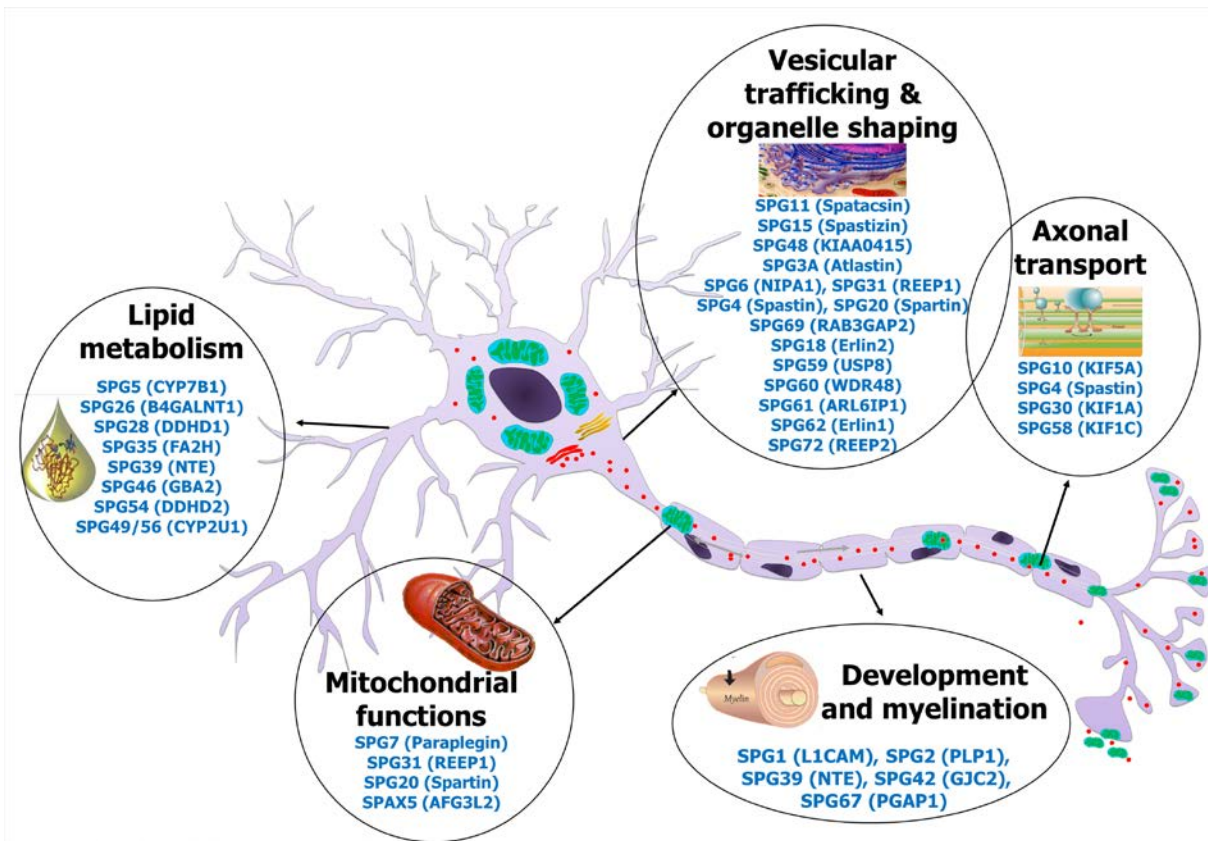


Table 1. Differential diagnoses of HSP

Metabolic disorders	Structural damage	Autoimmune and infectious diseases	Other degenerative diseases
Abetalipoproteinaemia	Cerebral palsy	Myelitis	Motoneuron disease
Arginase Deficiency	Chiari malformation	HTLV1	SCA
Krabbe's disease	Atlanto-axial subluxation	HIV	Spastic ataxias
Adrenoleucodystrophy	Cervical spine degeneration	Syphilis	
GM1/GM2 gangliosidosis	CNS tumor	Multiple sclerosis	
Gaucher disease	Dural arteriovenous malformation		
Vitamin deficiency (B12, E)			
MTHFR deficiency			
Copper deficiency			
Lathyrism			

L-dopa-responsive dystonia

HTLV1: human T-cell leukemia virus 1; HIV: Human immunodeficiency virus; MTHFR: methylenetetrahydrofolate reductase; SCA: Spinocerebellar Ataxia; CNS: central nervous system; L-dopa: Levodopa

Table 2. Loci and genes involved in HSP and their associated phenotypes.

Inheritance	SPG (NCBI)	SPG (HGNC)	Gene	Chromosome	Protein (Uniprot)	Reference	Frequency	Age at onset (yrs)	Pure (P) / Complex (C)	Associated clinical features OMIM N°	MRI
AD (AR)	SPG3A	SPG3 SPG3A	<i>ATL1</i>	14q22.1	Atlastin 1	40	Second most frequent AD form, most frequent form in early-onset [5-20%]	Usually before age 10 [1-51]	P (C)	Rarely: axonal neuropathy 182600	Normal
AD	SPG4	SPG4	<i>SPAST</i>	2p22.3	Spastin	33	Most frequent AD form [10-40%]	Mean age at onset: 30 years [1-80]	P (C)	rarely: neuropathy, cognitive impairment 182601	Normal
AD	SPG6	SPG6	<i>NIPA1</i>	15q11.2	NIPA1	64	Rare	Variable [8-37]	P (C)	rarely: neuropathy 600363	Normal
AD	SPG8	SPG8	<i>KIAA0196</i>	8q24.13	Strumpellin	165	Rare	Variable [18-60]	P (C)	603563	Normal
AD	SPG9	SPG9	-	10q23.3-q24.2		166	2 families	Variable [1-30], possible anticipation	P or C	Bilateral cataracts, gastro-esophageal reflux with persistent vomiting, peripheral motor and sensory neuropathy, amyotrophy. 601162	Normal
AD	SPG10	SPG10	<i>KIF5A</i>	12q13.3	Kinesin heavy chain isoform 5A (KIF5A)	55	2-10%	Variable [2-51]	P (C)	Neuropathy, Silver syndrome 604187	Normal
AD	SPG12	SPG12	<i>RTN2</i>	19q13.32	Reticulon 2	146	Rare	Variable [5-24]	P	604805	Normal
AD	SPG13	SPG13	<i>HSPD1</i>	2q33.1	Chaperonin	167	1 family	variable [17-68]	P	605280	Normal
AD	SPG17	SPG17	<i>BSCL2</i>	11q12.3	Seipin	110	Rare	Variable [2-60]	C (P)	Silver syndrome, neuropathy 270685	Normal

AD	SPG19	SPG19	-	9q33-q34		168	1 family	Adulthood [36-55]	P	607152	Normal
AD	SPG29	SPG29	-	1p31.1-21.1		169	1 family	Infancy	C	Neonatal hyperbilirubinemia, hearing impairment due to auditory neuropathy, persistent vomiting due to hiatal hernia. 609727	Normal
AD	SPG31	SPG31	<i>REEP1</i>	2p11.2	Receptor expression-enhancing protein 1 (REEP1)	53	2-10%	Variable [2-45]	P (C)	Neuropathy 610250	Normal
AD	SPG33	SPG33	<i>ZFYVE27</i>	10q24.2	Protrudine	170	1 family	Adulthood [42-50]	P	610248	
AD	SPG36	SPG36	-	12q23-24		171	1 family	Variable [14-33]	C	Peripheral sensorymotor neuropathy 613096	Normal
AD	SPG37	SPG37	-	8p21.1-q13.3		172	1 family	Variable [8-60]	P	611945	Normal
AD	SPG38	SPG38	-	4p16-p15		173	1 family	[16-19]	P	612335	
AD	SPG41	SPG41	-	11p14.1-11p.2		174	1 family	Mean: 17 yrs	P	613364	Normal
AD	SPG42	SPG42	<i>SLC33A1</i>	3q25.31	Acetyl-coenzyme A transporter 1 (SLC33A1)	175	1 family	Variable [4-42]	P	612539	Normal
AR	SPG5	SPG5A	<i>CYP7B1</i>	8q12.3	25-hydroxycholesterol 7-alpha-hydroxylase	163	3-8%	Variable [4-47]	P or C	Cerebellar sign, nystagmus, amyotrophy, cognitive impairment 270800	Normal or WMA
AR	SPG7	SPG7	<i>SPG7</i>	16q24.3	Paraplegin	22	2-10%	Variable [4-42]	P or C	optic neuropathy, cerebellar ataxia. 607259	Cerebellar atrophy

AR	SPG11	SPG11	<i>SPG11</i>	15q21.1	Spatacsin	97	Most frequent form of HSP-TCC (60%), most frequent AR form (20%)	Early with variability [1-30]	C	Cognitive decline, neuropathy, retinopathy, (Kjellin syndrome), cerebellar signs, ALS 604360	TCC, WMA, cerebellar atrophy
AR	SPG14	SPG14	-	3q27-q28		176	1 family		C	Distal motor neuropathy, mild mental retardation, visual agnosia, memory deficiency 605229	Normal
AR	SPG15	SPG15	<i>ZFYVE26</i>	14q24.1	Spastizin	177	HSP-TCC [5-11%], ARHSP [2-5%]	Early [4-19]	C	Cognitive decline, neuropathy, retinopathy, (Kjellin syndrome), cerebellar signs 270700	TCC, WMA, cerebellar atrophy
AR	SPG18	SPG18	<i>ERLIN2</i>	8p11.23	Erlin 2	178	Rare	Infancy	C	Intellectual disability, contracture, juvenile primary lateral sclerosis 611225	Normal
AR	SPG20	SPG20	<i>SPG20</i>	13q12.3	Spartin	179	Rare, founder effect in Amish and Omani populations	Infancy	C	Troyer Syndrome: Dysarthria, distal amyotrophy in the hands and feet, cerebellar sign, mild intellectual deficit and various skeletal abnormalities especially short stature 275900	WMA
AR	SPG21	SPG21	<i>SPG21 (ACP33)</i>	15q22.31	Maspardin	91	Rare, founder effect in the Ohio Amish population	Adulthood, with variability	C	Mast Syndrome : Speech decline leading to akinetic mutism, psychotic episodes, cognitive decline and cerebellar dysfunction 248900	TCC, WMA

AR	SPG23	SPG23	-	1q24-q32		180	Rare	Infancy	C	Lison syndrome : Abnormal pigmentation of the skin and hair. Some cases present facial dysmorphisms, skeletal deformities, mental retardation or sensorimotor neuropathy. 270750	Normal or slight enlargement of the ventricles
AR	SPG24	SPG24	-	13q14		181	1 family	Infancy	P	607584	Normal
AR	SPG25	SPG25	-	6q23-24.1		182	1 family	Adulthood [30-46]	C	Mild sensorimotor neuropathy. 608220	Spinal disc herniations
AR	SPG26	SPG26	<i>B4GALNT1</i>	12q13.3	Beta-1,4 N-acetylgalactosaminyltransferase 1	183	Rare	Early with variability [2-19]	C	Intellectual disability, cerebellar ataxia, peripheral neuropathy and one family present behavioral problems 609195	Normal or after long disease duration cortical and subcortical atrophy and/or white matter hyperintensities
AR	SPG27	SPG27	-	10q22.1-q24.1		184	Rare	Variable [2-45] C 2-7	P or C	Sensorimotor polyneuropathy and sometimes with mental retardation, cerebellar signs and skeletal abnormalities 609041	Normal or mild cortical and cerebellar atrophy
AR	SPG28	SPG28	<i>DDHD1</i>	14q22.1	Phospholipase DDHD1	87	Rare	Early [7-15]	P or C	Pure or complex with cerebellar oculomotor disturbance or axonal neuropathy 609340	Normal

AR	SPG30	SPG30	<i>KIF1A</i>	2q37.3	Kinesin-like protein KIF1A	84, 85	Rare	Variable [10-39]	P or C	Pure or Complex with sensory neuropathy and cerebellar ataxia 610357	Normal or cerebellar atrophy
AR	SPG32	SPG32	-	14q12-q21		185	1 family	6-7	C	Mild mental retardation. 611252	Cerebellar atrophy, pontine dysraphia, moderate TCC
AR	SPG35	SPG35	<i>FA2H</i>	16q23.1	Fatty acid 2-hydroxylase	96	Rare	2-17 one family with late onset	C	Dystonia, LL amyotrophy, seizures, cerebellar signs, cognitive decline and optic atrophy. 612319	Leukodystrophy, hypointensities of globus pallidus, TCC, cerebellar atrophy.
AR	SPG39	SPG39	<i>PNPLA6</i>	19p13.2	Neuropathy target esterase (NTE)	186	Rare	Early with variability	C	Muscle wasting and motor axonopathy of the LL and UL 612020	Normal
AR	SPG43	SPG43	<i>C19ORF12</i>	19p13.11-q12	Protein C19orf12	187	1 family	Childhood [7-12]	C	Neuropathy and severe atrophy and decreased sensation in the arms and legs 615043	Normal
AR	SPG44	SPG44	<i>GJC2</i>	1q42.13	Gap junction gamma-2 protein	92	1 family	Early with variability	C	Dysarthria, cerebellar ataxia, mental impairment. 613206	WMA
AR	SPG45	SPG45	-	10q24.3-q25.1		188	1 family	Infancy	C	Mental retardation and ocular signs 613162	
AR	SPG46	SPG46	<i>GBA2</i>	9p13.3	Non-lysosomal glucosylceramidase	90	Rare	Early [1-16]	C	Cerebellar ataxia, cataract and mental impairment. 614409	TCC, WMA, cerebellar atrophy
AR	SPG47	SPG47	<i>AP4B1</i>	1p13.2	AP-4 complex subunit beta-1	93	Rare	Infancy	C	Severe intellectual disability, absent speech, shy character, stereotypic laughter, muscular hypotonia, microcephaly, foot deformity, decreased muscle mass and growth retardation	TCC, WMA

										614066	
AR	SPG48	SPG48	<i>AP5Z1</i>	7p22.1	AP-5 complex subunit zeta-1	189	Rare	Variable [2-50]	P or C	Pure or complex with cognitive impairment or mental retardation 613647	Normal or TCC, WMA
AR	SPG56	SPG49	<i>CYP2U1</i>	4q25	Cytochrome P450 2U1	87	Rare	Infancy	P or C	Pure or complex with mental impairment, dysarthria, dystonia, infraclinical axonal neuropathy 615030	Normal or TCC, WMA, basal ganglion calcification
AR	SPG49	No SPG	<i>TECPR2</i>	14q32.31	Tectonin beta-propeller repeat-containing protein 2	190	Rare	Infancy	C	Severe intellectual disability, rigid ataxic gait, brachycephalic microcephaly, fluctuating central hypoventilation, gastroesophageal reflux disease, wake apnea, areflexia, dysmorphic features 615031	Ventriculomegaly, TCC, cerebellar atrophy
AR	SPG50	SPG50	<i>AP4M1</i>	7q22.1	AP-4 complex subunit mu-1	191	Rare	Infancy	C	Tetraplegic cerebral palsy, mental retardation, 612936	WMA, cerebellar atrophy
AR	SPG51	SPG51	<i>AP4E1</i>	15q21.2	AP-4 complex subunit epsilon-1	93, 192	Rare	Infancy	C	Neonatal hypotonia progressing to hypertonia, spasticity, mental retardation, poor or absent speech development 613744	

AR	SPG52	SPG52	<i>AP4S1</i>	14q12	AP-4 complex subunit sigma-1	93	1 family	Infancy	C	Severe intellectual disability, absent speech, shy character, stereotypic laughter, muscular hypotonia, microcephaly, foot dformity, decreased muscle mass and growth retardation 614067	
AR	SPG53	SPG53	<i>VPS37A</i>	8p22	Vacuolar protein sorting 37 homolos A	193	Rare	Infancy	C	Developmental and motor delay, delays in cognition and speech, marked kyphosis 614898	Normal or WMA, mild ventriculomegalgy
AR	SPG54	SPG54	<i>DDHD2</i>	8p11.23	Phospholipase DDHD2	94	Rare	Infancy	C	Intellectual disability or developmental delay, dysarthria cerebellar sign, short stature 615033	TCC, WMA
AR	SPG55	SPG55	<i>C12ORF6</i> 5	12q24.31	Probable peptide chain release factor C12orf65, mitochondrial	194	Rare	Childhood [2-7]	C	Optic atrophy, muscle atrophy and neuropathy or intellectual disability, neuropathy, opthalmoplegia 615035	Normal or Thin corpus callosum and white matters abnormalities
AR	SPG57	SPG57	<i>TFG</i>	3q12.2	Protein TFG	195 196	1 family	Infancy	C	Optic atrophy, axonal demyelinating motor neuropathy. 615658	Normal
AR	SPG58	SPG58	<i>KIF1C</i>	17p13.2	Kinesin-like protein KIF1C	125 1	Rare	Infancy	P or C	Pure or complex with ataxia, dysarthria, extrapyramidal chorea, hypodonita, developmental delay or mental retardation	Normal or WMA
AR	SPG59	SPG59	<i>USP8</i>	15q21.2	Ubiquitin carboxyl-terminal hydrolase 8	1	1 family	Infancy	C	Nystagmus, pes equinovarus, mild mental retardation	Normal
AR	SPG60		<i>WDR48</i>	3p22.2	WD repeat-containing protein 48	1	1 family	Infancy	C	Nystagmus, neuropathy	Normal

AR	SPG61	SPG61	<i>ARL6IP1</i>	16p12.3	ADP-ribosylation factor-like protein 6-interacting protein 1	1	1 family	Infancy	C	Motor and sensory polyneuropathy with acromutilation 615685	Normal or mild dilatation of lateral ventricles
AR	SPG62	SPG62	<i>ERLIN1</i>	10q24.31	Erlin 1	1	Rare	Infancy	P		Normal
AR	SPG63	SPG63	<i>AMPD2</i>	1p13.3	AMP deaminase 2	1	1 family	Infancy	C	Short stature 615686	TCC, WMA
AR	SPG64	SPG64	<i>ENTPD1</i>	10q24.1	Ectonucleosidase triphosphate diphosphorilase 1	1	Rare	Infancy	C	Amyotrophy, cerebellar sign, moderate intellectual disability, agressiveness, delayed puberty, microcephaly 615683	WMA
AR	SPG65	SPG65	<i>NT5C2</i>	10q24.32 q24.33	Cytosolic purine 5'-nucleotidase	1	Rare	Infancy	P or C	Amyotrophy, pes equinovarus, learning disability 613162	TCC, WMA
AR	SPG66	SPG66	<i>ARSI</i>	5q32	Arylsulfatase I	1	1 family	Infancy	C	Amyotrophy, pes equinovarus, sensory/motor polyneuropathy	TCC, cerebellar hypoplasia
AR	SPG67	SPG67	<i>PGAP1</i>	2q33.1	GPI inositol-deacylase	1	1 family	Infancy	C	Amyotrophy	ACC, vermis hypoplasia, defective myelination, prominent cortical sulci & widened sylvian fissures
AR	SPG68	SPG68	<i>FLRT1</i>	11q13.1	Leucine-rich repeat transmembrane protein FLRT1	1	1 family	Infancy	C	Optic atrophy, nystagmus, mild amyotrophy, péripheral neuropathy	Normal

AR	SPG69	SPG69	<i>RAB3GAP2</i>	1q31	Rab3 GTPase-activating protein non-catalytic subunit	1	1 family	Infancy	C	Dysarthria, cataract, deafness, intellectual disability	Normal
AR	SPG70	SPG70	<i>MARS</i>	12q13.3	Methionine--tRNA ligase, cytoplasmic	1	1 family	Infancy	C	Amyotrophy, bilateral achilles contractures	
AR	SPG71	SPG71	<i>ZFR</i>	5p13.3	Zinc finger RNA-binding protein	1	1 family	Infancy	P		TCC
AD AR	SPG72	SPG72	<i>REEP2</i>	5q31.2	Receptor expression-enhancing protein 2 (REEP2)	26	Rare	Infancy	P	615625	
AR	-	-	<i>LYST</i>	1q42.3	Lysosomal-trafficking regulator	197	1 family	Late [48-58]	C	Cerebellar ataxia, peripheral neuropathy Mutations in this gene also cause Chediak-Higashi syndrome 214500	Cerebellar atrophy
AR	-	-	<i>MAG</i>	19q13.1	Myelin-associated glycoprotein	1	1 family	Infancy	C	Cerebellar sign, nystagmus, and amyotrophy	Normal
AR	-	-	<i>CCT5</i>	5p15.2	T-complex protein 1 subunit epsilon	198	1 family	Infancy	C	mutilating sensory neuropathy 256840	
AR	-	-	<i>EXOSC3</i>	9p13.2	Exosome component 3	199, 200	1 family	Infancy	C	Cognitive disability, cerebellar signs, distal amyotrophy Mutations in this genes also cause Pontocerebellar hypoplasia, type 1B 614678	Enlarged cisterna magna, cerebellar atrophy
AD AR	-	-	<i>BICD2</i>	9q22.32	Protein bicaudal D homolog 2	201 1	Rare	Infancy	C	Spinal muscular atrophy Mutations in this gene also cause Spinal muscular atrophy, lower extremity-predominant, 2, AD 615290	Normal

X linked	SPG1	SPG1	<i>LICAM</i>	Xq28	Neural cell adhesion molecule L1	202	Rare	Infancy	C	Mutations in this gene also cause MASA syndrome (Mental retardation Aphasia Shuffling gait and Adducted thumb) or CRASH syndrom (Corpus callosum hypoplasia Retardation Adducted thumb Spastic paraplegia and Hydrocephalus) 303350	ACC, hydrocephalus
X linked	SPG2	SPG2	<i>PLP1</i>	Xq22.2	Myelin proteolipid protein	203	Rare	Infancy or Childhood	P or C	nystagmus, cerebellar dysfunction, hypotonia, mental retardation, dementia or seizures 312920	WMA
X linked		SPG22	<i>SLC16A2</i>	Xq13.2	Monocarboxylate transporter 8	204	Rare	Infancy	C	Mutations in this gene also cause Allan-Herndon-Dudley syndrom : spastic quadriplegia, mental retardation, lack of head support, central hypotonia, muscle hypoplasia, dystonia, ataxia 300523	Delayed myelination, TCC, cortical atrophy
X linked	SPG16	SPG16	-	Xq11.2		205	Rare	Infancy	P or C	quadriplegia, motor aphasia, reduced vision, mild mental retardation 300266	Delayed myelination
X linked	SPG34	SPG34	-	Xq24-q25		206	1 family	Adulthood	P	300750	
Mitochondrial			<i>MT-TI</i>		Transfer RNA, Mitochondrial, Isoleucine	30	1 family	Adulthood	P or C	ataxia, deafness, epilepsy, cardiomyopathy hypogonadism	

Mitochondrial		<i>MT-ATP6</i>	Complex V, ATP synthase, subunit ATPase 6	29	1 family	Adulthood	P or C	axonal neuropathy, cerebellar signs, cardiomyopathy
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