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Review

Hereditary spastic paraplegia: Clinical-genetic characteristics and evolving molecular mechanisms

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ABSTRACT

Hereditary spastic paraplegia (HSP) is a group of clinically and genetically heterogeneous neurological disorders characterized by pathophysiologic hallmark of length-dependent distal axonal degeneration of the corticospinal tracts. The prominent features of this pathological condition are progressive spasticity and weakness of the lower limbs. To date, 72 spastic gait disease-loci and 55 spastic paraplegia genes (*SPGs*) have been identified. All modes of inheritance (autosomal dominant, autosomal recessive, and X-linked) have been described. Recently, a late onset spastic gait disorder with maternal trait of inheritance has been reported, as well as mutations in genes not yet classified as spastic gait disease. Several cellular processes are involved in its pathogenesis, such as membrane and axonal transport, endoplasmic reticulum membrane modeling and shaping, mitochondrial function, DNA repair, autophagy, and abnormalities in lipid metabolism and myelination processes. Moreover, recent evidences have been found about the impairment of endosome membrane trafficking in vesicle formation and about the involvement of oxidative stress and mtDNA polymorphisms in the onset of the disease. Interactome networks have been postulated by bioinformatics and biological analyses of spastic paraplegia genes, which would contribute to the development of new therapeutic approaches.

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Abbreviations: AAA, ATPases associated with diverse cellular activities; AD, autosomal dominant; AEPs, auditory evoked potentials; AP, adaptor protein complex; AR, autosomal recessive; BiP, binding immunoglobulin protein; BMP, bone morphogenetic protein; CMT, Charcot–Marie–Tooth disease; DCVs, dense core vesicles; DTI, diffusion tensor imaging; ER, endoplasmic reticulum; EGFR, epidermal growth factor receptor; ERAD, ER-associated degradation; ESCRT, endosomal sorting complex required for transport; HSP, hereditary spastic paraplegia; JALS, juvenile amyotrophic lateral sclerosis; MEPs, motor evoked potentials; MIT, microtubule interacting and transport (domain); NBIA, neurodegeneration with brain iron accumulation; RHD, reticulon homology domain; UPR, unfolded protein response; SCA, spinocerebellar ataxias; SEPs, sensory evoked potentials; SMA, spinal muscolar atrophy; SPG, spastic paraplegia gene; TCC, thin *corpus callosum*; VEPs, visual evoked potentials; WASH, Wiskott-Aldrich syndrome protein and scar homolog (complex); WMLs, white matter lesions; XL, X-linked.

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Introduction

Hereditary spastic paraplegias (HSPs) constitute a heterogeneous group of neurodegenerative diseases characterized by genetic mutations that cause distal neuropathy of the longest corticospinal tract axons (Harding, 1993) ; ascending fibers (column of Goll and spinocerebellar tracts) are also often involved (reviewed in Blackstone, 2012; Deluca et al., 2004; reviewed in Orlacchio et al., 2006). As a result of corticospinal dysfunction, progressive weakness and spasticity, extensor plantar responses, and hyperreflexia of deep tendon reflexes in lower limbs are common clinical features in pure forms. *Iliopsoas*, *quadriceps femoris,* and *tibialis anterior* are the muscles most affected by spasticity and weakness. Hypertonic bladder and lower limb sensory disturbances (generally mild, regarding vibration and joint position sense) may be present in pure forms too.

Other manifestations may occur in complicated forms, including above all cognitive impairment, cerebellar atrophy, polyneuropathy, thin *corpus callosum* (TCC), epilepsy, skeletal abnormalities, amyotrophy, and optic atrophy.

Age of onset is early childhood through 70 years. A recent systematic review from 12 studies performed since 1985 in European, Asian, and North African countries, estimated a global average prevalence of $1.8/10^5$ for both ADHSP and ARHSP (reviewed in Ruano et al., 2014). Pure forms are more prevalent in Northern Europe, Japan, and North America (Braschinsky et al., 2009; Ishiura et al., 2014). Complicated forms are generally inherited as autosomal recessive traits (Coutinho et al., 1999). In Mediterranean countries, these forms are more common due to the increased frequency of consanguinity.

To date, 72 different spastic gait disease-loci have been identified, and 55 spastic paraplegia genes (*SPGs*) have already been cloned. Other HSP causative genes are not in the SPG classification yet.

This review focuses on the clinical features and diagnostic clues for each genetic subtype of HSP, and on molecular pathogenesis including mitochondrial dysfunctions, the involvement of mitochondrial DNA polymorphisms/haplogroups and of oxidative stress in the disease. The recent discoveries of new causative genes also highlight the importance of ER function, morphogenesis, membrane shaping and endosome membrane trafficking, and vesicle formation in HSP pathophysiology.

Genetic classification of HSP

HSP can be transmitted in an autosomal dominant (AD), autosomal recessive (AR), X-linked (XL), or mitochondrial manner (reviewed in Finsterer et al., 2012; reviewed in Schüle and Schöls, 2011). Nonetheless, sporadic HSP due to true *de novo* mutations, genealogical censure, non-penetrant AD mutations, or singleton in unrecognized AR kindred, is common. Fig. 1 shows the most frequent HSP causative genes. HSP forms and putative protein function of each HSP gene product are summarized in Table 1. Inheritance and clinical features of each HSP form are described in Table 2.

ADHSP

To date, 20 genetic SPG loci for ADHSP have been identified, but only 12 genes are known. There are at least eight identified ADHSP loci with an uncloned gene associated with the disease in both pure and complicated forms (Tables 1 and 2): SPG9 (Panza et al., 2008; Seri et al., 1999), SPG19 (Valente et al., 2002), SPG29 (Orlacchio et al., 2005a), SPG36 (Schüle et al., 2009a), SPG37 (Hanein et al., 2007), SPG38 (Orlacchio et al., 2008b), SPG40 (Subramony et al., 2009), and SPG41 (Zhao et al., 2008).

SPG3A

SPG3A/*ATL1* mutations represent approximately 10% of ADHSP patients and are the most frequent cause of HSP with onset before age 10 years (Namekawa et al., 2006).

ATL1 encodes atlastin-1, a member of the dynamin family of large guanosine triphosphatases, implicated in neurite outgrowth, intracellular membrane trafficking, but mainly in ER and Golgi morphogenesis, and in axon elongation during neuronal development (Byrnes and Sondermann, 2011; Rismanchi et al., 2008).

Mutations are predominantly of missense type and whole genome and in-frame deletions have also been reported. Whole genome deletion of *ATL1* was found in an SPG4 family, which did not co-segregate with the disease (Beetz et al., 2007). A patient carrying the in-frame deletion of residue 436 (436delN) showed decreased atlastin-1 levels in lymphoblasts, but normal levels of mRNA, normal GTPase activity, and normal protein interactions. These features indicate that the pathogenic

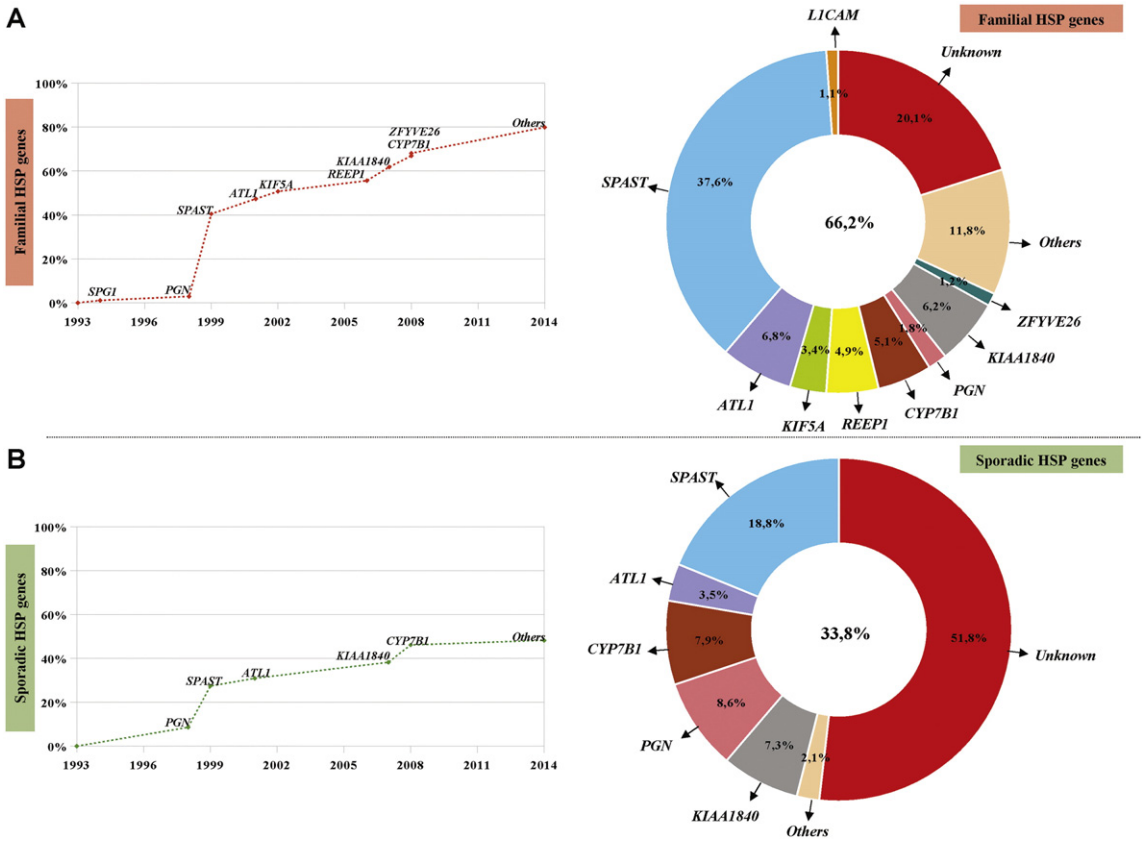

Fig. 1. Timeline of gene discoveries and frequencies of the most frequent causative genes in familial (A) and sporadic (B) HSP. Epidemiological data of the HSP Italian network (total of 1707 affected subjects from all over the world).

mechanism for SPG3A is not simply due to haploinsufficiency. A dominant-negative loss-of-function mechanism has been postulated (Meijer et al., 2007).

The age of onset is around 4 years or, more rarely, later than that age. Very early onset cases develop severe spastic gait, contrary to late onset. Pure forms are the most common; additional symptoms include axonal polyneuropathy of small hand muscles (Silver syndrome) and TCC (Al-Maawali et al., 2011; Fusco et al., 2010; reviewed in Hedera, 2010; Orlacchio et al., 2011).

SPG4

About 40% of ADHSP and about 20% of sporadic HSP are caused by mutations in SPG4/*SPAST* (Fig. 1), encoding spastin (Hazan et al., 1999). Spastin is a member of the ATPases associated with diverse cellular activities (AAA) family, with roles in microtubule dynamics and membrane trafficking. Four kinds of *SPAST* mRNA have been discovered, depending on the translation initiation codon used and alternative splicing of the exon 4 (reviewed in Salinas et al., 2007). Spastin has two main structural domains: the microtubule interacting and transport (MIT) domain at the N-terminus, and the AAA catalytic domain in C-terminus. Over 300 mutations, including partial deletions, have been described; all pathogenic gene variants appear to affect the AAA domain, and act by a loss-of-function mechanism (haploinsufficiency) (Beetz et al., 2006). Recently, intragenic copy-number variations have been found to cause the disease (Depienne et al., 2007). The high concentration of *Alu* (highly homologous non low-copy repeats interspersed repetitive sequences) family members in the introns and flanking sequence of *SPAST* may predispose to intragenic rearrangements.

Most SPG4-patients show a pure phenotype, with average onset in the fourth decade of life, variably accompanied by column sensory deficits and, in about one third of cases, bladder disturbance (McDermott et al., 2006; Orlacchio et al., 2008a; Schulte et al., 2003). SPG4 embraces a wide phenotypic variation, including the Silver syndrome (Orlacchio et al., 2008b). The excess of males in published reports suggests that penetrance or severity may be sex-dependent (Orlacchio et al., 2005b; Proukakis et al., 2011). Phenotypes complicated by cognitive impairment in executive functions (Ribaï et al., 2008) and by posterior fossa abnormalities (congenital arachnoid cysts) (Orlacchio et al., 2004a) have been reported.

SPG6

SPG6 is caused by mutations in *NIPA1* (Kaneko et al., 2006; Munhoz et al., 2006; Rainier et al., 2003). It comprises five exons encoding the non-imprinted in Prader-Willi/Angelman syndrome region protein 1.

Pure forms, with severe and rapidly progressive spasticity, are the majority. Polyneuropathy, cognitive impairment, and epilepsy are also reported (Du et al., 2011; Klebe et al., 2007; Svenstrup et al., 2011).

SPG8

SPG8/*KIAA0196* encodes strumpellin, a protein ubiquitously expressed and localized in cytoplasm and endoplasmic reticulum (ER). KIAA0196 mutations, reported in a few families with pure HSP (de Bot et al., 2013; Rocco et al., 2000), lead to reduction of axonal outgrowth with a loss-of-function mechanism (Clemen et al., 2010) disrupting the endosome membrane trafficking (Freeman et al., 2013).

SPG10

SPG10 is caused by mutations in *KIF5A* (Reid et al., 2002). This gene codes for kinesin HC5A, a kinesin heavy chain. Most of *KIF5A* mutations are located in the highly conserved kinesin motor domain. Functional analyses showed an altered axonal transport, reducing the cargo flux and leading to deficient supply of the synapse (Ebbing et al., 2008).

A recent study of ADHSP Western European families reported that SPG10 accounts for about 10% of complicated forms (Goizet et al., 2009c). Moreover, a new phenotype present in SPG10 includes dysautonomia (Collongues et al., 2013).

SPG12

SPG12/*RTN2* encodes reticulon 2, a protein belonging to a large and diverse group of membrane-associated proteins found throughout the eukaryotic kingdom and named reticulons. These proteins regulate ER structure and functions and contain a uniquely conserved C-terminal domain (reticulon homology domain, RHD). RHD contains two putative transmembrane domains (TM1 and TM2), a loop region and a short N-terminus (reviewed in Chiurchiù et al., 2014). Reticulon 2 interacts with spastin. Mutations can be frameshift, missense, and whole gene deletion, presumably leading to haploinsufficiency. SPG12 is a pure and rapid progressive HSP (Montenegro et al., 2012; Orlacchio et al., 2002).

SPG13

SPG13/*HSPD1* encodes a mitochondrial protein, the heat shock protein 60 chaperone (Hsp60), which assists the folding of several proteins localized in mitochondria.

SPG13 occurs between 1 and 60 years of age; in addition to pure form with loss of vibratory sensation, it was associated with dystonia, which improves upon deep brain stimulation (Gilbert et al., 2009; Hansen et al., 2002).

SPG17

SPG17/*BSCL2* encodes seipin, an ER integral membrane protein whose function is unknown. The two identified missense mutations affect its glycosylation and result in an accumulation of unfolded protein in the ER. This probably triggers the unfolded protein response (UPR) and cell death, suggesting that these diseases are tightly associated with ER stress.

SPG17 causes Silver syndrome that includes amyotrophy of small hand muscles. Nerve conduction studies often disclose severe reduction of compound muscle action potentials (CMAPs) (Windpassinger et al., 2004).

SPG17 is allelic to congenital generalized lipodystrophy type 2 (also termed Berardinelli–Seip congenital lipodystrophy), distal hereditary motor neuropathy type V (dHMN V), and Charcot–Marie–Tooth disease 2 (CMT2) (reviewed in Ito and Suzuki, 2009).

SPG31

SPG31/*REEP1* encodes the receptor expression-enhancing protein 1, a mitochondrial protein that might be involved in chaperon-like activities. Missense, splice site, nonsense, insertion and deletion mutations are known. Loss of function and haploinsufficiency are the major mechanisms of action in SPG31 (Battini et al., 2011). Functional studies showed abnormal mitochondrial network organization in fibroblasts of one patient, in addition to defective mitochondrial energy production (Goizet et al., 2011).

Only a few patients show a complicated HSP form (Beetz et al., 2008; Goizet et al., 2011).

SPG33

SPG33 was reported in a single German family with complicated HSP and mutation (p.G191V) in *ZFYVE27* (Mannan et al., 2006). It encodes a specific spastin-binding protein, protrudin, a member of the FYVE-finger family of proteins. The mutated protein shows an aberrant intracellular pattern in its tubular structure impairing its interaction with spastin and affecting neuronal intracellular trafficking in the corticospinal tract.

The disease-related role remains unsettled (Martignoni et al., 2008).

SPG42

SPG42/*SLC33A1* encodes the acetyl-CoA transporter, a multiple transmembrane protein in the ER. It carries acetyl-CoA into the lumen of Golgi apparatus, where it is transferred to the sialyl residues of gangliosides and glycoproteins. This modification may play a critical role in the outgrowth

Table 1
HSP loci/*genes* and protein putative function of each HSP form.

Type	Location[a]	*Gene*/Protein	Exons[b]	TOM	OMIM Gene/locus	Phenotype	PPF	References [c]
SPG1	Xq28	*L1CAM*/NCAM	29	PM	MIM308840	MIM303350	Neuronal cell adhesion and signaling	Jouet et al. (1994)
SPG2	Xq22.2	*PLP1*/MPLP	8	PM, del, dupl	MIM300401	MIM312920	Myelination and axonal survival	Saugier-Veber et al. (1994)
SPG3A	14q22.1	*ATL1*/ATLASTIN-1	14	PM	MIM606439	MIM182600	Neurite outgrowth, membrane trafficking, ER and Golgi morphogenesis	Zhao et al. (2001)
SPG4	2p22.3	*SPAST*/SPASTIN	17	PM, ss, del, dupl, ins	MIM604277	MIM182601	Microtubule dynamics, membrane trafficking, ER morphogenesis, BMP signaling	Hazan et al. (1999)
SPG5A	8q12.3	*CYP7B1*/OAH1	6	PM	MIM603711	MIM270800	Brain cholesterol metabolism	Tsaousidou et al. (2008)
SPG6	15q11.2	*NIPA1*/NIPA1	5	PM	MIM608145	MIM600363	Cellular magnesium ion metabolism, endosomal/ER morphogenesis, protein folding	Rainier et al. (2003)
SPG7	16q24.3	*PGN*/PARAPLEGIN	17	PM, del, ins	MIM602783	MIM607259	Mitochondrial protease, ribosome maturation	Casari et al. (1998)
SPG8	8q24.13	*KIAA0196*/STRUMPELLIN	29	PM, del	MIM610657	MIM603563	Endosomal morphogenesis, protein folding	Valdmanis et al. (2007)
SPG9	10q23.3–24.2	–	–	–		MIM601162	Unknown	Seri et al. (1999)
SPG10	12q13.3	*KIF5A*/KINESIN HC5A	29	PM	MIM602821	MIM604187	Microtubule-based motor protein	Reid et al. (2002)
SPG11	15q21.1	*KIAA1840*/SPATACSIN	40	PM, dupl, ins, del, ss	MIM610844	MIM604360	Vesicles sorting	Stevanin et al. (2007b)
SPG12	19q13.32	*RTN2*/RETICULON 2	11	PM, ins, del	MIM603183	MIM604805	ER morphogenesis	Montenegro et al. (2012)
SPG13	2q33.1	*HSPD1*/HSP60	12	PM	MIM118190	MIM605280	Protein folding and assembly in mitochondria	Hansen et al. (2002)
SPG14	3q27–q28	–	–	–		MIM605229	Unknown	Vazza et al. (2000)
SPG15	14q24.1	*ZFYVE26*/SPASTIZIN	42	PM, del, ss	MIM612012	MIM220700	Endosomal trafficking, authophagy, cytokinesis	Hanein et al. (2008)
SPG16	Xq11.2	–	–	–		MIM300266	Unknown	Steinmuller et al. (1997)
SPG17	11q12.3	*BSCL2*/SEIPIN	12	PM	MIM606158	MIM270685	Lipid metabolism, ER stress response	Windpassinger et al. (2004)
SPG18	8p11.23	*ERLIN2*/SPFH2	12	Del	MIM611605	MIM611225	Regulation of ERAD pathway	Alazami et al. (2011)
SPG19	9q	–	–	–		MIM607152	Unknown	Valente et al. (2002)
SPG20	13q13.3	*SPG20*/SPARTIN	9	PM, del	MIM607111	MIM2759002	Protein folding, turnover in mitochondria and microtubule dynamics	Patel et al. (2002)
SPG21	15q22.31	*ACP33*/MASPARDIN	9	PM, ins	MIM608181	MIM248900	Endosomal trafficking and sorting	Simpson et al. (2003)
SPG22	Xq13.2	*SLC16A2*/MCT8	6	PM, del, ins	MIM30095	MIM300523	Membrane transporter (axon development)	Schwartz et al. (2005)
SPG23	1q24–q32	–	–	–		MIM270750	Unknown	Blumen et al. (2003)
SPG24	13q14	–	–	–	MIM607584		Unknown	Hodgkinson et al. (2002)
SPG25	6q23–q24.1	–	–	–		MIM608220	Unknown	Zortea et al. (2002)
SPG26	12p11.1–q14	*B4GALNT1*/B4GALNT1	11	PM, del, dupl	MIM601873	MIM609195	Ganglioside biosynthesis	Boukhris et al. (2013)
SPG27	10q22.1–q24.1	–	–	–		MIM609041	Unknown	Meijer et al. (2004)
SPG28	14q22.1	*DDHD1*/PAPLA1	13	PM, del	MIM614603	MIM609340	Fatty-acid and/or phospholipid metabolism	Tesson et al. (2012)
SPG29	1p31.1–p21.1	–	–	–		MIM609727	Unknown	Orlacchio et al. (2005a)
SPG30	2q37.3	*KIF1A*/KINESIN3	50	PM	MIM601255	MIM610357	Anterograde transport	Erlich et al. (2011)
SPG31	2p11.2	*REEP1*/REEP1	7	PM, del, ss, ins	MIM609139	MIM610250	Chaperon-like activities, ER morphogenesis	Züchner et al. (2006)
SPG32	14q12–q21	–	–	–		MIM611252	Unknown	Stevanin et al. (2007a)
SPG33	10q24.2	*ZFYVE27*/PROTRUDIN	12 13	PM[d]	MIM610243	MIM610244	Specific spastin binding protein	Mannan et al. (2006)
SPG34	Xq24–q25	–	–			MIM300750	Unknown	Macedo-Souza et al. (2008)
SPG35	16q23.1	*FA2H*/FA2H	7	PM, del	MIM611026	MIM612319	Sphingolipids synthesis	Dick et al. (2010)
SPG36	12q23–q24	–	–	–		MIM613096	Unknown	Schüle et al. (2009a)
SPG37	8p21.1–q13.3	–	–	–		MIM611945	Unknown	Hanein et al. (2007)
SPG38	4p16–p15	–	–	–		MIM612335	Unknown	Orlacchio et al. (2008b)
SPG39	19p13.2	*NTE*/PNPLA6	34	PM, ins	MIM603197	MIM612020	Maintain the integrity of motor neurons, phospholipid homeostasis	Rainier et al. (2008)
SPG40	Reserved	–	–	–	–		–	Subramony et al. (2009)
SPG41	11p14.1–p11.2	–	–	–		MIM613364	Unknown	Zhao et al. (2008)
SPG42	3q25.31	*SLC33A1*/ACoA CARRIER	6	PM	MIM603690	MIM612539	Acetyl-CoA transporter	Lin et al. (2008)

SPG43	19p13.11–q12	*C19orf12*/C19ORF12	3	PM, del	MIM614297	MIM615043	Unknown	Landouré et al. (2013)
SPG44	1q42.13	*GJC2*/CONNEXIN 47	2	PM	MIM608803	MIM613206	Formation of gap junctions, direct cell-to cell diffusion of ions and small molecules	Orthmann-Murphy et al. (2009)
SPG45	10q24.3–q25.1	–	–	–		MIM613162	Unknown	Dursun et al. (2009)
SPG46	9p13.3	*GBA2*/GBA2	18	PM, dupl	MIM609471	MIM614409	Ganglioside biosynthesis	Martin et al. (2013)
SPG47	1p13.2	*AP4B1*/AP4B1	10	Ins, del	MIM607245	MIM614066	Vesicle formation, molecular cargo	Abou Jamra et al. (2011)
SPG48	7p22.1	*KIAA0415*/AP5Z1	17	Indel	MIM613653	MIM613647	Helicase that repair DNA double-strand break and interacts with spatacsin and spastizin	Słabicki et al. (2010)
SPG49	14q32.31	*TECPR2*/KIAA0329	20		MIM615000	MIN615031	Intracellular autophagy	Oz-Levi et al. (2012)
SPG50	7q22.1	*AP4M1*/AP4M1	15	Ss	MIM602296	MIM612936	Vesicle formation, molecular cargo	Abou Jamra et al. (2011)
SPG51	15q21.2	*AP4E1*/AP4E1	21	Ss	MIM607244	MIM613744	Vesicle formation, molecular cargo	Abou Jamra et al. (2011)
SPG52	14q12	*AP4S1*/AP4S1	6	PM	MIM607243	MIM614067	Vesicle formation, molecular cargo	Abou Jamra et al. (2011)
SPG53	8p22	*VPS37A*/VPS37A	12	PM	MIM609927	MIM614898	Sorting of ubiquitinated transmembrane proteins into internal vesicles	Zivony-Elboum et al. (2012)
SPG54	8p11.23	*DDHD2*/DDHD2	18	PM, ins, ss	MIM615003	MIM615033	Intracellular phospholipase	Schuurs-Hoeijmakers et al. (2012)
SPG55	12q24.31	*C12orf65*/C12ORF65	3	PM	MIM613541	MIM615035	Peptide chain termination in the mitochondrial translation machinery	Shimazaki et al. (2012)
SPG56	4q25	*CYP2U1*/CYP2U1	5	PM, del	MIM610670	MIM615030	Fatty acids hydroxylation	Tesson et al. (2012)
SPG57	3q12.2	*TFG*/TFG	8	PM	MIM602498	MIM604484	Oncogenesis and vesicle biogenesis and trafficking	Beetz et al. (2013)
SPG58	17p13.2	*KIF1C*/KINESIN FAMILY MEMBER 1C	23	PM, del	MIM603060 MIM611302		Retrograde Golgi to ER transport	Novarino et al. (2014)
SPG59	15q21.2	*USP8*/UBIQUITIN-SPECIFIC PROTEASE 8	21	PM	MIM603158		Deubiquitinating enyzme	Novarino et al. (2014)
SPG60	3p22.2	*WDR48*/WD REPAET DOMAIN 48	19	Del	MIM612167		Regulator of deubiquitination	Novarino et al. (2014)
SPG61	16p12.3	*ARL6IP1*/ADP-RIBOSYLATION FACTOR-LIKE 6 INTERACTING PROTEIN 1	6	Del	MIM607669		Protein transport	Novarino et al. (2014)
SPG62	10q24.31	*ERLIN1*/ER LIPID RAFT ASSOCIATED 1	11	PM	MIM611604		ER-associated degradation	Novarino et al. (2014)
SPG63	1p13.3	*AMPD2*/ADENOSINE MONOPHOSPHATE DEAMINASE 2	18	Del	MIM102771		Deaminates AMP to IMP in purine nucleotide metabolism	Novarino et al. (2014)
SPG64	10q24.1	*ENTPD1*/ECTONUCLEOSIDE TRIPHOSPHATE DIPHOSPHOHYDROLASE 1	10	PM	MIM601752		Hydrolyzes ATP and other nucleotides to regulate purinergic transmission	Novarino et al. (2014)
SPG65	10q24.32–q24.33	*NT5C2*/5′-NUCLEOTIDASE, CYTOSOLIC II	18	PM, ss	MIM600417		Preferentially hydrolyzes IMP, in both purine/pyrimidine nucleotide metabolism	Novarino et al. (2014)
SPG66	5q32	*ARSI*/ARYLSULFATASE FAMILY, MEMBER I	2	Ins	MIM610009		Hydrolyze sulfate esters, hormone biosynthesis	Novarino et al. (2014)
SPG67	2q33.1	*PGAP1*/POST-GPI ATTACHMENT TO PROTEINS 1	27	Ss	MIM611655		GPI biosynthesis	Novarino et al. (2014)
SPG68	11q13.1	*FLRT1*/FIBRONECTIN LEUCINE RICH TRANSMEMBRANE PROTEIN 1	2	PM	MIM604806		Cell adhesion and receptor signaling	Novarino et al. (2014)
SPG69	1q41	*RAB3GAP2*/RAB3 GTPASE ACTIVATING PROTEIN SUBUNIT 2 (NON-CATALYTIC)	35	PM	MIM609275		Exocytosis of neurotransmitters and hormones	Novarino et al. (2014)
SPG70	12q13	*MARS*/METHIONYL-TRNA SYNTHETASE	21	PM	MIM156560		Cytosolic methionyl-tRNA synthetase	Novarino et al. (2014)
SPG71	5p13.3	*ZFR*/ZINC FINGER RNA-BINDING PROTEIN	20	PM	-		RNA localization?	Novarino et al. (2014)
SPG72	5q31	*REEP2*/RECEPTOR EXPRESSION-ENHANCING PROTEIN 2	8	PM	MIM609347		ER-shaping protein	Esteves et al. (2014), Novarino et al. (2014)
Ua	2q31.1	*GAD1*/GLUTAMATE DECARBOXYLASE 1	17	PM	MIM605363	MIM603513	GABA synthesis	Lynex et al. (2004)
Ua	5p15.2	*CCT5*/ε SUBUNIT OF THE CYTOSOLIC CHAPERONIN CONTAINING T-COMPLEX PEPTIDE-1	11	PM	MIM610150	MIM256840	Proteins folding and cytosolic proteins assembly	Bouhouche et al. (2006)
Ua	19q13.32	*OPA3*/OPTIC ATROPHY 3 PROTEIN	3	PM	MIM606580	MIM258501	Regulator of mitocondrial activity	Arif et al. (2013)
Ua	9q22.31	*BICD2*/BICAUDAL D HOMOLOG 2	7	PM	MIM609797		Protein transport	Novarino et al. (2014)
Ua	19q13.1	*MAG*/MYELIN ASSOCIATED GLYCOPROTEIN	12	PM	MIM159460		Component of myelin	Novarino et al. (2014)
Ua	1q42.3	*LYST*/LYSOSOMAL TRAFFICKING REGULATOR	53	PM	MIM214500		Lysosomal trafficking regulator	Shimazaki et al. (2014)
Ua	Mit	*MT-ATP6*/ATP SYNTHASE 6	-	PM	MIM516060		Mitochondrial ATP production	Verny et al. (2011)
SPOAN	11q13	–	–	–	MIM609541		Unknown	Macedo-Souza et al. (2005)

BMP = bone morphogenic protein; del = deletion; dupl = duplication; ER = endoplasmic reticulum; ERAD = ER-associated degradation; indel = insertion/mutation; ins = insertion; Mit = mitochondrial; PM = point mutation; PPF = protein putative function; TOM = type of mutation; ss = splice site mutation; Ua = unassigned SPGs.

[a] Loci from http://www.ncbi.nlm.nih.gov/omim/ (OMIM).

[b] Total exons, including UTR.

[c] Locus or gene discovery.

[d] Mutation/polymorphism (see the text).

Table 2
Inheritance and clinical features of HSP patients.

Type	MI	NOF	Onset	Phenotype	Additional features
SPG1	X-linked	~20	EO	C	Mental retardation, aphasia, shuffling gait, and adducted thumbs, hydrocephalus, ACC
SPG2	X-linked	~10	VO	P or C	Seizures, mental retardation, nystagmus, ataxia, WMLs, PNP
SPG3A	AD	~35	EO	P or C	Lower limb muscle atrophy, seizures, ataxia, OA, spasticity in the upper limbs, sensorimotor axonal PNP, CI, cranial nerve impairment, intellectual disability, *pes cavus*, TCC
SPG4	AD	~130	VO	P or C	CI, epilepsy, ataxia, psychosis, upper limb spasticity, *pes cavus*, posterior fossa abnormalities, PNP, hand tremor, WMLs, amyotrophy of small hand muscles
SPG5A	AR	~35	VO	P or C	OA, WMLs, cerebellar ataxia
SPG6	AD	11	TO	P or C	IGE, dysarthria, PNP, CI, facial dystonia, atrophy of the small hand muscles, upper limbs spasticity, *pes cavus*
SPG7	AR	~30	VO	P or C	CS, cerebellar atrophy, PNP, OA, supranuclear palsy, CI of attention and executive functions, TCC, scoliosis, *pes cavus*
SPG8	AD	10	AO	P	-
SPG9	AD	1	TO	C	Cataracts, motor PNP, skeletal abnormalities, gastrooesophageal reflux
SPG10	AD	17	EO	P or C	Distal amyotrophy in the upper extremities, CI, PNP, dysautonomia, parkinsonism, deafness, retinitis pigmentosa
SPG11	AR	~35	VO	C	CS, PNP, WMLs, cerebellar atrophy, TCC, seizures, CI, abnormal eye signs, amyotrophy, parkinsonism, maculopathy, action tremor, mental retardation, upper limbs weakness
SPG12	AD	4	EO	P	–
SPG13	AD	2	VO	P or C	Dystonia
SPG14	AR	1	AO	C	Motor PNP, mental retardation
SPG15	AR	20	EO	C	Pigmentary retinopathy, CS, PNP, amyotrophy, seizures, mental retardation, TCC
SPG16	X-linked	2	EO	P or C	Aphasia, ipovision, nystagmus, mental retardation
SPG17	AD	13	TO	C	Amyotrophy of small hand and feet muscles, lower motor neuron disease
SPG18	AR	3	EO	C	Epilepsy, mental retardation, congenital hip dislocation, multiple joint contractures
SPG19	AD	1	AO	P	-
SPG20	AR	~25	EO	C	Mental retardation, dysarthria, upper limbs spasticity, CS, euphoria, crying, WMLs
SPG21	AR	2	EO	C	Dementia, TCC, WMLs, CS, extrapyramidal features, callosal disconnection syndrome
SPG22	X-linked	~10	EO	C	Mental retardation, muscle atrophy, distal wasting, dyskinesia, nystagmus, ataxia
SPG23	AR	4	EO	C	CI, pigmentary abnormalities, facial and skeletal dysmorphism, tremor
SPG24	AR	1	EO	C	Pseudobulbar signs
SPG25	AR	1	AO	C	Cataracts, PNP, disc erniation
SPG26	AR	5	EO	C	Intellectual disability, cortical atrophy, PNP, distal atrophy. cerebellar ataxia, WMLs
SPG27	AR	2	VO	C	Dysarthria, mental retardation, PNP
SPG28	AR	3	EO	P or C	Saccadic eye pursuit, axonal PNP
SPG29	AD	1	TO	C	*Pes cavus*, hearing loss, hiatal hernia, hyperbilirubinaemia
SPG30	AR	3	TO	P or C	Sensory PNP, CS, hypoacusis, distal muscle wasting
SPG31	AD	~30	EO	P or C	PNP, cerebellar ataxia, tremor, dementia, amyotrophy of small hand muscles, *pes cavus*
SPG32	AR	1	EO	C	Mental retardation, pontine dysraphism, TCC
SPG33	AD	1	AO	C	*Pes equinus*
SPG34	X-linked	1	VO	P	–
SPG35	AR	2	EO	P or C	CI, epilepsy
SPG36	AD	1	VO	C	Sensory PNP
SPG37	AD	1	VO	P	-
SPG38	AD	1	VO	C	Amyotrophy of small hand muscles, PNP
SPG39	AR	2	EO	C	Distal wasting in upper limbs, axonal PNP
SPG40	AD	1	AO	P or C	Hyperrreflexia of upper limbs, CI
SPG41	AD	1	TO	P	-
SPG42	AD	1	VO	P	-
SPG43	AR	1	VO	C	Amyotrophy of small hand muscles, bilateral OA, axonal sensory and motor PNP, brain iron deposits in the *globus pallidus*
SPG44	AR	1	AO	C	CI, CS, dysarthria, WMLs, *pes cavus,* TCC, scoliosis, upper limbs involvement
SPG45	AR	1	EO	C	Mental retardation, pendular nystagmus, OA
SPG46	AR	4	EO	C	Mental retardation, cataract, cerebellar atrophy, TCC, hypogonadism in males
SPG47	AR	2	EO	C	Periventricular WMLs, TCC, microcephaly, epilepsy, waddling gait, joint hyperlaxity
SPG48	AR	1	AO	P or C	Spinal cord hyperintensities
SPG49	AR	3	EO	C	Delayed psychomotor development, mental retardation, TCC, cerebral and cerebellar dysfunction, dysmorphic features, central apnea
SPG50	AR	1	EO	C	Tetraplegic cerebral palsy, mental retardation, reduction of cerebral white matter, atrophy of the cerebellum
SPG51	AR	2	EO	C	Microcephaly, growth and intellectual retardation
SPG52	AR	1	EO	C	Delayed speech, stereotypic laughter, growth retardation
SPG53	AR	3	EO	C	Spasticity in upper extremities, delays in cognition and speech, kyphosis, *pectus carinatum,* hypertrichosis
SPG54	AR	6	EO	C	Mental retardation, strabismus, dysarthria, dysphagia, optic-nerve hypoplasia, short stature, TCC, laterally deviated feet, abnormal lipid peak on brain spettroscopy, WMLs
SPG55	AR	1	EO	C	OA, PNP *pes equinovarus*
SPG56	AR	5	EO	P or C	TCC, CI, upper limbs involvement, basal-ganglia calcification. dystonic postures, WMLs
SPG57	AR	1	EO	C	OA, PNP
SPG58	AR	3	EO	P or C	Chorea, myoclonus, ataxia, hypodontia, deafness, short stature, *pes planus,* ptosis, developmental delay, mental retardation, WMLs
SPG59	AR	1	EO	C	Nystagmus, borderline intelligence
SPG60	AR	1	EO	C	PNP in lower limbs, nystagmus
SPG61	AR	1	EO	C	Loss of terminal digits, acromutilation, PNP
SPG62	AR	3	EO	P	–
SPG63	AR	1	EO	C	TCC, WMLs, underweight, short stature
SPG64	AR	2	EO	C	*Pes equinovarus*, aggressiveness, delayed puberty, microcephaly, borderline intelligence
SPG65	AR	5	EO	P or C	TCC, defective myelination, small bilateral cystic occipital leukomalacia, learning disability, *pes equinovarus*
SPG66	AR	1	EO	C	*Corpus callosum* and cerebellar hypoplasia, colpocephaly, borderline intelligence, PNP, *pes equinovarus*

Table 2 (*continued*)

Type	MI	NOF	Onset	Phenotype	Additional features
SPG67	AR	1	EO	C	Distended abdomen, borderline intelligence, ACC, vermis hypoplasia, defective myelination
SPG68	AR	1	EO	C	Nystagmus, OA, PNP, amyotrophy, foot drop
SPG69	AR	1	EO	C	Intellectual disability, deafness, cataract
SPG70	AR	1	EO	C	Scoliosis, bilateral Achilles contracture, borderline intelligence, nephrotic syndrome
SPG71	AR	1	EO	C	TCC
SPG72	AD and AR	3	EO	P	-
GAD1 gene	AR	1	EO	C	Spastic cerebral palsy, mental retardation
Cct5 gene	AR	1	EO	C	Mutilating sensory neuropathy
OPA3 gene	AR	1	EO	C	OA, chorea, cerebellar ataxia, dementia
BICD2 gene	AR	1	EO	P	-
MAG gene	AR	1	EO	C	Nystagmus, poor school achievement
LYST gene	AR	1	AO	C	PNP, cerebellar ataxia
ATPase6 gene	Maternal	1	AO	C	Diabetes mellitus, hypertrophic cardiomyopathy, supraventricular arrhythmia, cerebellar syndrome
SPOAN	AR	2	EO	C	OA, PNP, dysarthria, exacerbated acoustic startle response, joint retractions, spine deformities, fixation nystagmus, distal amyotrophy, extrapiramidal signs

ACC = *agenesis corpus callosum*; AO = adult onset; AD = autosomal dominant; AR = autosomal recessive; C = complicated; CI = cognitive impairment; CS = cerebellar signs; EO = early onset (infancy); IGE = idiopathic generalized epilepsy; MI = mode of inheritance; NOF = number of families; OA = optic atrophy; P = pure; PNP = polyneuropathy; TCC = thin *corpus callosum*; TO = teenage onset; VO = variable onset (infancy, teenage, or adult); WMLs = white matter lesions.

and maintenance of axons in motor neurons. Inadequate supply of acetyl-CoA, caused by a reduced flow of acetyl-CoA into the Golgi apparatus, can result in misprocessing of gangliosides and glycoproteins.

A single, large Chinese family, harboring the missense p. S113R, has been reported with a possible loss of function (Lin et al., 2008).

SPG72

In affected members of a large French family with ADHSP, it has been identified a heterozygous missense mutation in the REEP2 gene (Esteves et al., 2014) (Tables 1 and 2).

ARHSP

Forty-eight SPG loci and 41 genes responsible for ARHSP have been identified so far. Several other ARHSP loci, namely SPG14 (Vazza et al., 2000), SPG23 (Blumen et al., 2003), SPG24 (Hodgkinson et al., 2002), SPG25 (Zortea et al., 2002), SPG27 (Meijer et al., 2004; Ribaï et al., 2006), SPG32 (Stevanin et al., 2007a), and SPG45 (Dursun et al., 2009), have been identified but pathological genes are yet unknown (Tables 1 and 2).

SPG5A

SPG5A/*CYB7B1* encodes cytochrome P450 oxysterol 7-hydroxylase, implicated in biosynthesis, storage and catabolism of brain cholesterol metabolites. The gene product of *CYP7B1* also participates in the "acidic" pathway of bile acid synthesis (Arnoldi et al., 2012). The role of 27-hydroxy-cholesterol blood accumulation in SPG5A-patients, its role as pathogenetic player and its utility in clinical practice is still debated (Schüle et al., 2010).

More than 20 different mutations were reported (Goizet et al., 2009a; Schüle et al., 2009b; Tsaousidou et al., 2008). Pure form is the most common; periventricular and subcortical white matter lesions (WMLs) are observed in many patients (Biancheri et al., 2009). Electrophysiological investigations revealed pathologic motor evoked potentials (MEPs), sensory evoked potentials (SEPs), visual evoked potentials (VEPs), and auditory evoked potentials (AEPs), in contrast with normal nerve conduction study and EMG (Manganelli et al., 2011).

SPG7

SPG7/*PGN* encodes paraplegin, one of the proteins forming the m-AAA protease complex located in the mitochondrial membrane. This protein is constituted by two peptide regions, a metallo-peptidase domain and an ATPase domain (reviewed in Langer, 2000). *PGN* variants identified to date are almost all nonsense loss-of-function mutations or missense mutations in the metallo-peptidase domain (Casari et al., 1998); however, some mutations cause an amino acid substitution mapping in the AAA-domain. Paraplegin is involved in the removal of damaged or misfolded proteins, the proteolytic activation of essential mitochondrial proteins and ribosome maturation; ultrastructural studies showed abnormal shaping of mitochondria (Nolden et al., 2005).

Patients may show cerebellar signs or cerebellar atrophy (Brugman et al., 2008; Elleuch et al., 2006) that, in addition to optic neuropathy (or abnormalities on optical coherence tomography), are key features for the diagnosis of SPG7 (Klebe et al., 2012b).

SPG11

SPG11/*KIAA1840* mutations are the most common cause of ARHSP (Stevanin et al., 2007b, 2008). Genetic analyses of *KIAA1840* revealed several types of mutations leading to protein loss of function. Recent identification of repeated *Alu* elements should be linked to SPG11 locus instability, making this genomic region prone to large gene rearrangements (Conceição Pereira et al., 2012). *KIAA1840*, encoding spatacsin, is expressed ubiquitously in the nervous system, but most prominently in the cerebellum, cerebral cortex, hippocampus and pineal gland. The specific role of peptide remains unknown, though it seems to be essential to the survival of neurons (Crimella et al., 2009; Southgate et al., 2010).

KIAA1840 mutations have been identified as a genetic cause of juvenile amyotrophic lateral sclerosis type 5 (ALS5) in 40% of patients (Orlacchio et al., 2010) and Kjellin syndrome (Orlén et al., 2009) characterized by central retinal degeneration, mental retardation and amyotrophy in addition to ARHSP-TCC.

On average, patients become wheelchair-bound 16 years after disease onset. Cognitive impairment and TCC are reliable phenotype predictors of SPG11; other common features are axonal polyneuropathy and cerebellar signs (Del Bo et al., 2007; Pippucci et al., 2009; Stevanin et al., 2006). Hehr et al. (2007) hypothesized that phenotype results from the combined degeneration of central and peripheral axons and neuronal loss within cortical and thalamic regions and in the spinal cord.

SPG15

Patients carrying mutations in SPG15/*ZFYVE26*, encoding spastizin, show similar symptoms to those observed in SPG11 (Table 2). Mutations lead to loss of protein or mutated forms of protein with defective autophagy (Vantaggiato et al., 2013).

Originally mapped in families with Kjellin syndrome (Hanein et al., 2008; Kjellin, 1959), SPG15 is the second most common cause of HSP-TCC (Goizet et al., 2009b). Being relatively rarer than SPG11, genetic test is recommended in SPG11 negative patients only.

SPG18

ERLIN2 in the SPG18 locus encodes SPFH2 protein that contains a characteristic SPFH (stomatin–prohibitin–flotillin–HflC/K) domain. This peptidic region makes the protein capable of assembling into an oligomeric structure anchored to the cellular membrane. SPFH2 has been shown to regulate the ER-associated degradation (ERAD) pathway by interacting with endogenous proteins and resulting in their polyubiquitination and proteasome degradation (Pearce et al., 2007).

Three loss-of-function mutations in *ERLIN2* have been reported in families from Saudi Arabia (Alazami et al., 2011; Wakil et al., 2013; Yildirim et al., 2011). Patients carrying a nullimorphic *ERLIN2* mutation showed additional features of mental retardation, late epilepsy and hip dislocation (Alazami et al., 2011).

SPG20

Troyer syndrome is a complicated ARHSP that occurs with high frequency in Amish people and it was also reported in two Omani families: a frameshift mutation due to a single base deletion producing a truncated SPG20/spartin protein and two null mutations were reported in *SPG20* (Bakowska et al., 2008; Manzini et al., 2010; Patel et al., 2002). The encoded protein, spartin, has been considered as a multifunctional protein, playing a role in protein folding and turnover, both in mitochondria and ER. It seems to have a crucial function in the ubiquitination and degradation of lipid droplet-associated proteins (Milewska et al., 2009). Spartin contains several distinct domains including an N-terminal MIT region, which is responsible for its interaction with microtubule and trafficking molecules (Ciccarelli et al., 2003).

Troyer syndrome is characterized by mental retardation, distal muscle wasting, dysarthria, and quadriparesis. Cerebellar signs, choreoathetosis, euphoria, crying, and WMLs on brain MRI may also be observed (Proukakis et al., 2004).

SPG21

Mast syndrome, initially described by Cross and McKusick (1967), is a complicated form of ARHSP associated with dementia and other CNS abnormalities, that is present at high frequency among the Old Order Amish. It is caused by SPG21/*ACP33* mutations. The single base-pair insertion reported in an Amish pedigree results in the premature termination of the encoded product maspardin. This protein has been shown to localize in vesicle of the endosomal/trans-Golgi network, highlighting a possible role of this protein in cellular transport and sorting, and its role in neuronal cells has been confirmed in *SPG21*$^{-/-}$ knockout mice, which also showed alterations in axon branching (Soderblom et al., 2010).

SPG21-patients, in addition to slowly progressive pure phenotype that develops in early adulthood, may show cerebellar and extrapyramidal signs in the advanced disease. Most of patients have TCC and WMLs on MRI (Simpson et al., 2003). Recently, a missense mutation (p.A108P) in *APC33* was identified in a Japanese family (Ishiura et al., 2014).

SPG26

SPG26/*B4GALNT1* encodes β-1,4-N-acetyl-galactosaminyl transferase 1, involved in ganglioside biosynthesis. Gangliosides belong to the family of glycosphingolipids, which are components of the synaptic plasma involved in synaptic plasticity, signal transduction, and endocytosis. B4GALNT1 catalyzes the transfer of N-acetyl-galactosamine into GM3, GD3, and globotriaosylceramide by a β-1,4 linkage. The reverse reaction is performed by β-hexosaminidase and its cofactor (GM2 activator). Molecular defects in the degradation of glycosphingolipids lead to lysosomal storage diseases.

Truncating, missense mutations, and deletions of *B4GALNT1* cause complicated early onset ARHSP (Boukhris et al., 2013). It is worthy of note that SPG26 is the second disorder of ganglioside biosynthesis after SPG46 (Martin et al., 2013). These findings confirm the increasing interest of lipid metabolism in HSP.

Patients carrying the *B4GALNT1* mutation had an early onset (2 to 19 years) spastic paraplegia with intellectual impairment. About a third of such patients also had mild upper limb involvement. Other features were more variable (Boukhris et al., 2013).

SPG28

Truncating mutations in SPG28/*DDHD1*, encoding PAPLA1 (phosphatidic-acid-preferring phospholipase A1), are reported in pure and complicated HSP.

PAPLA1 is involved in the maintenance of the ER and Golgi structures. *DDHD1* mutations also cause mitochondrial dysfunction, including reduced respiration and ATP production that might result from the accumulation of PA in mitochondria. Therefore, DDHD1 might also be involved in similar functions in the maintenance of organelle membranes and intracellular trafficking (Higgs et al., 1998; Nakajima et al., 2002; Tani et al., 1999).

The discovery of *DDHD1* mutations in three additional SPG28-affected subjects extended the clinical spectrum of this disease, compared to the pure phenotype originally described in a single Moroccan family (Bouslam et al., 2005; Tesson et al., 2012).

SPG30

SPG30/*KIF1A* encodes the kinesin 3 protein. The protein belongs to the kinesin-3 family that is involved in intracellular anterograde transport of dense core vesicles (DCVs), containing neuropeptide cargos, along microtubules to the pre- and post-synaptical cellular regions: gene deletion determines a reduction of DCVs at synapses, followed by an accumulation of such vesicles in the cell body and neuronal death (Lo et al., 2011).

Missense mutations have been reported (Erlich et al., 2011; Klebe et al., 2012a), causing early onset and slow progressive HSP. Nonsense mutations in the same gene cause hereditary sensory neuropathy type IIC (HSN2C) (Rivière et al., 2011).

SPG35

FA2H enzyme catalyzes the synthesis of sphingolipids containing 2-hydroxy fatty acids; these biochemical compounds participate in several biological processes. In particular, SPG35/*FA2H* null mice suggested that the protein is necessary in long-term maintenance of myelin (Zöller et al., 2008).

SPG35 is generally characterized by childhood onset of gait difficulties, dysarthria, cognitive impairment, and leukodystrophy on MRI (Dick et al., 2010). *FA2H* mutations are involved in other two neurodegenerative diseases: leukodystrophy with spastic paraparesis and dystonia (Edvardson et al., 2008) and neurodegeneration with brain iron accumulation (NBIA). Kruer et al. (2010) referred to this phenotypic spectrum of disorders as fatty acid hydroxylase associated neurodegeneration (FAHN).

SPG39

The gene at the SPG39 locus has been identified in a novel HSP, designated NTE-related motor neuron disease (NTE-MND) (Rainier et al., 2008): it is the neuropathy target esterase gene (*NTE*), encoding PNPLA6. The protein plays a role in axonopathy produced by organophosphorus compounds; moreover, knockdown experiments show that it is also implicated in survival of developing embryos (Moser et al., 2004).

Reported point mutations, disrupting the catalytic domain, decrease hydrolysis activities and alter the ability to be reactivated by nucleophiles (Hein et al., 2010). An insertion mutation, causing frameshift and protein truncation, is also reported in compound heterozygosity (Synofzik et al., 2014).

The affected phenotype in each family conformed both to organophosphorus compound-induced delayed neuropathy (OPIDN) and to Troyer-like syndrome. In childhood, patients exhibit features of the pure form later associated with wasting of distal leg and intrinsic hand

muscles. Electrophysiological studies were consistent with a motor axonopathy affecting upper and lower limbs. Single SPG39-patient showed atrophy of the spinal cord, particularly in the thoracic region on MRI (Rainier et al., 2008).

SPG43

SPG43, previously described in two Malian sisters (Meilleur et al., 2010), is caused by missense mutation or nucleotides deletion in *C19orf12* (Landouré et al., 2013). Mutations in the same gene are also reported in a series of patients with NBIA (Hartig et al., 2011).

In addition to Silver syndrome, patients may have bilateral optic atrophy or axonal sensory motor polyneuropathy and MRI evidenced iron deposits in the *globus pallidus* of Brazilian patients, linking with SPG43 and NBIA (Landouré et al., 2013).

SPG44

SPG44 is caused by a homozygous point mutation in *GJC2*, encoding connexin-47 (Orthmann-Murphy et al., 2009). Recessive mutations in this gene also cause Pelizaeus–Merzbacher-like disease (PMLD), which is characterized by severe CNS demyelination (Orthmann-Murphy et al., 2007). Connexin-47 is constituted by four transmembrane, two extracellular, and three cytoplasmic domains. This protein belongs to the connexin family and it forms gap junctions (intercellular channels), allowing direct cell-to-cell diffusion of ions and small molecules.

SPG44-related patients (three members of a large Italian family) had *pes cavus* and a late onset slowly progressive paraplegia. Brain MRI showed a hypomyelinating leukodystrophy and TCC in all three patients. Other features in individual patients include dysarthria, loss of finger dexterity, dysmetria, intention tremor, scoliosis, upper limb involvement, and cognitive impairment (Orthmann-Murphy et al., 2009).

SPG46

Four different mutations in *GBA2* (glucosidase beta bile acid 2), three truncating variants, and one missense variant, were identified in four unrelated SPG46 families (Martin et al., 2013). This is a complicated form with slowly progressive spastic paraplegia and cerebellar signs. Some patients show cerebral and cerebellar atrophy and TCC on brain MRI (Boukhris et al., 2008, 2010; Martin et al., 2013). Homozygous mutations in *GBA2* were also found in patients with autosomal recessive cerebellar ataxia and spasticity (Hammer et al., 2013).

GBA2 encodes a microsomal non-lysosomal glucosylceramidase, localized in the endoplasmic reticulum and at the cell surface, which catalyzes the conversion of glucosylceramide to free glucose and ceramide and the hydrolysis of bile acid 3-O-glucosides. Ceramides formed by this enzyme are rapidly converted into sphingomyelin (Yildiz et al., 2006). The missense variant was also found at the homozygous state in a single patient, in whom no residual glucocerebrosidase activity of GBA2 was proven in blood cells, opening the way to a possible measurement of this enzyme activity in clinical practice (Martin et al., 2013).

SPG47, SPG50–SPG52

These neurodegenerative disorders are characterized by neonatal hypotonia of all limbs that progresses to spasticity and severe mental retardation with poor or absent speech development (Abou Jamra et al., 2011).

Mutations in genes encoding heterotetrameric adaptor protein 4 complex (AP4) subunits were identified: a frameshift mutation (Abou Jamra et al., 2011) and a truncating mutation (Bauer et al., 2012) in SPG47/*AP4B1*, a splice mutation in SPG51/*AP4E1* (Abou Jamra et al., 2011) and a nonsense mutation in SPG52/*AP4S1* (Abou Jamra et al., 2011). Two mutations affecting SPG50/*AP4M1* and *AP4E1* have recently been found to cause cerebral palsy associated with severe intellectual disability (Verkerk et al., 2009).

Moreno-De-Luca et al. (2011) proposed the designation of 'AP4 deficiency syndrome' to refer to disorders caused by disruption of any of the four AP4 subunits.

SPG48

An insertion/deletion has been found in SPG48/*KIAA0415* in two HSP siblings; *KIAA0415* encodes a putative helicase (AP5Z1), with both nuclear and cytoplasmic localization, involved in DNA double-strand break repair processes and known to be a spatacsin and spastizin interactor. In particular, spatacsin is phosphorylated upon DNA damage by protein kinases ATM (ataxia telangiectasia mutated) or ATR (ATM and Rad3-related) (Słabicki et al., 2010). A recent study showed that the protein is a member of the adaptor protein 5 complex (AP5) that is implicated in vesicle formation and sorting (as AP4) (Hirst et al., 2011).

The two siblings, in the single French family reported, presented spastic paraplegia associated with urinary incontinence. One had spinal hyperintensities on MRI in the cervical spine. The unaffected parents were from two neighboring villages (Słabicki et al., 2010).

SPG49

Oz-Levi et al. (2012) identified a homozygous truncating mutation in SPG49/*TECPR2* (tectonin beta-propeller repeat containing 2) in a form of complicated HSP. This HSP is characterized by onset of spastic paraplegia in the first decade, delayed psychomotor development, mental retardation, dysmorphic features (such as short stature, mild brachycephalic microcephaly, round face, low anterior hairline, dental crowding, short broad neck, a chubby appearance), dysarthria, dysmetria, TCC on brain imaging and episodes of central apnea.

SPG53

A homozygous mutation in SPG53/*VPS37A* (vacuolar protein sorting 37A), a member of the endosomal sorting complex required for transport (ESCRT) system, has been described in a complicated HSP (Zivony-Elboum et al., 2012). The system plays a central role in intracellular trafficking, maturation of multivesicular bodies, and sorting of ubiquitinated membrane proteins into internal luminal vesicles (Raiborg and Stenmark, 2009).

Disease progresses from onset in infancy of delayed motor development to upper and lower limb spasticity. Affected individuals also show mild to moderate cognitive and speech delay.

SPG54

Biallelic or homozygous frameshift and missense mutations of SPG54/*DDHD2* were identified in a complicated early onset HSP (Schuurs-Hoeijmakers et al., 2012).

The DDHD2 protein belongs to the mammalian intracellular phospholipase A_1, implicated in organelle biogenesis and membrane trafficking. DDHD2 preferentially hydrolyzes phosphatidic acid but also exhibits activity toward phosphatidylethanolamine. RNA-interference experiments in cellular systems indicated a role of DDHD2 in transport from the Golgi to the plasma membrane. In view of this, it was hypothesized that DDHD2 facilitates membrane and vesicle fusion by the modification of membranes through phospholipid hydrolysis (Inoue et al., 2012; Morikawa et al., 2009; Nakajima et al., 2002; Sato et al., 2010; Tani et al., 1999).

Phenotype among all six families was relatively homogeneous (Table 2) with mental retardation and early onset of progressive spasticity before the age of 2 years. In line with the function in lipid metabolism, an abnormal lipid peak indicating accumulation of lipids was detected with cerebral magnetic resonance spectroscopy (MRS) with the highest intensity around the basal ganglia and thalamus. This can be an applicable diagnostic biomarker to distinguish the SPG54 phenotype from other complicated HSP (Schuurs-Hoeijmakers et al., 2012).

SPG55

A nonsense mutation in SPG55/*C12orf65* was identified in two patients with HSP complicated by optic atrophy and polyneuropathy in a Japanese family (Shimazaki et al., 2012).

The C12ORF65 protein belongs to the mitochondrial class I peptide release factors. Its function is still not clear. It might play a role in recycling abortive peptidyl-tRNAs that were prematurely released from ribosomes during polypeptide elongation (Antonicka et al., 2010; Richter et al., 2010). This mutation causes marked reduction of mitochondrial protein synthesis, followed by functional and structural defects in respiratory complexes I and IV. A study in cultured neurons showed that complex I deficiency could increase mitochondrial reactive oxygen species leading to neuronal death (Abramov and Duchen, 2010).

SPG56

CYP2U1 is a cytochrome P450 protein implicated in ω- and ω − 1 fatty-acid (C16–C22) hydroxylation. CYP2U1 is able to catalyze the hydroxylation of arachidonic acid and related long-chain fatty acids such as eicosapentaenoic and docosahexaenoic acids. Two known metabolites, 19- and 20-hydroxyeicosatetraenoic acids, are local mediators of signal transduction (Carroll and McGiff, 2000; Chuang et al., 2004).

Missense and deletion mutations in SPG56/*CYP2U1* are reported in five unrelated families with ARHSP (Tesson et al., 2012). Affected individuals developed spastic paraplegia with a range from birth to 8 years. Symptom severity varied widely: complicated phenotype includes upper limbs involvement, dystonic posturing of the upper limbs, mental retardation, subclinical axonal polyneuropathy, WMLs on brain MRI, calcifications in the *globus pallidus* and TCC (Citterio et al., 2014).

SPG57

In two siblings with early onset spastic paraplegia, optic atrophy, and polyneuropathy, a genetic analysis revealed a homozygous variant, p.R106C, in Trk-fused (*TFG*) as the only plausible mutation (Beetz et al., 2013). Intriguingly, a heterozygous mutation, p.P285L, was demonstrated in a distinct phenotype called hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P) (Ishiura et al., 2012).

Native TFG functions affect vesicle biogenesis on the ER, the formation of a matrix between ER exit sites and the ER–Golgi intermediate compartment, a sorting hub for secretory cargoes in metazoan cells (Witte et al., 2011). Mutant protein lacks its ability to self-assemble into an oligomeric complex, which is a critical phase for normal TFG function. In cell lines, TFG inhibition slows protein secretion from the ER and alters ER morphology, disrupting organization of peripheral ER tubules and causing collapse of the ER network onto the underlying microtubule cytoskeleton (Beetz et al., 2013).

SPG58–SPG72

Very recently, 15 candidate genes for ARHSP were reported and the assigned locus for HSP increased up to SPG72 (Esteves et al., 2014; Novarino et al., 2014) (Fig. 2, Tables 1 and 2). Based on the putative biological function, most of these genes can be stratified into the functional modules described below.

XLHSP

To date, five X-linked SPG loci, named SPG1, SPG2, SPG16, SPG22, and SPG34, and three genes (*L1CAM, PLP1,* and *SLC16A2*) have been identified. Gene identity at the SPG16 (Steinmuller et al., 1997) and SPG34 (Macedo-Souza et al., 2008) loci are unknown (details in Tables 1 and 2).

SPG1

X-linked *hydrocephalus*, MASA (mental retardation, aphasia, shuffling gait, and adducted thumbs) syndrome, X-linked complicated SPG1 and X-linked partial agenesis of the *corpus callosum* are the four diseases usually referred to L1 syndrome, caused by mutations in SPG1/*L1CAM* (Jouet et al., 1994). Its product (NCAM) is a transmembrane glycoprotein mainly expressed in neurons and Schwann cells.

SPG2

SPG2 is caused by mutations in *PLP1* (proteolipid protein 1), encoding myelin proteolipid protein (MPLP), the major myelin protein responsible for stabilization and maintenance of the myelin sheath. *PLP1* variants also lead to Pelizaeus–Merzbacher disease, a hypomyelination disorder having onset in infancy and death in young adulthood (Saugier-Veber et al., 1994). Several mutations in *PLP1* have been identified ranging from entire gene duplications, deletions, and intragenic sequence variants (Cailloux et al., 2000).

Only males are affected, exhibiting slowly progressive paraplegia; some patients have nystagmus, ataxia, cerebral or spinal WMLs, polyneuropathy, and, in a single case, dementia (Suzuki et al., 2011).

SPG22

This HSP is caused by mutations in SPG22/*SLC16A2* encoding monocarboxylate transporter 8 (MCT8) (Schwartz et al., 2005). The protein is essential in triiodothyronine transport into neurons, and contributes to axon pathfinding (reviewed in Blackstone et al., 2011); its abnormal function is reflected in elevated free triiodothyronine and lowered free thyroxine levels in the blood (Friesema et al., 2003).

Clinical manifestations in complex form (Allan–Herndon–Dudley syndrome) include severe mental retardation, dysarthria, athetoid movements, muscle hypoplasia, and spastic paraplegia (Boccone et al., 2010; Schwartz et al., 2005).

Unassigned SPGs

GAD1 gene

A homozygous nonsense mutation in glutamic acid decarboxylase 1(*GAD1*) leading to a protein truncation has been identified in patients from consanguineous Pakistan families; affected subjects had cerebral palsy and mental retardation (Lynex et al., 2004).

*GAD*1 encodes for the 67 kDa isoform of L-glutamate decarboxylase (GAD_{67}), which is involved in conversion of the excitatory neurotransmitter glutamate to the inhibitory neurotransmitter GABA. The glutamatergic excitotoxicity may play a role in this context too.

Cct5 gene

Cct5 encodes the epsilon subunit of the cytosolic chaperonin-containing t-complex peptide-1 (CCT): a homozygous missense mutation p.H147R was identified in this gene in four patients from a consanguineous Moroccan family, displaying mutilating sensory neuropathy associated with spastic paraplegia (Bouhouche et al., 2006).

Molecular chaperones play an important role in the folding of many proteins and the CCT complex is a member of the two major chaperone systems that promote folding and assembly of a wider range of cytosolic substrates (actin and tubulin in particular).

OPA3 gene

Mutations in this gene cause 3-methylglutaconic aciduria type III (Costeff optic atrophy syndrome) (Anikster et al., 2001) and autosomal dominant optic atrophy and cataract (Reynier et al., 2004). In a recent study, two cousins from consanguineous parents showed, in addition to optic atrophy, motor symptoms from the age of 3 to 4 years including chorea, cerebellar ataxia, dystonia, and pyramidal tract signs of lower limbs. Exome sequencing revealed 2 homozygous variants (c.32 T>A [p.L11Q] in *OPA3* and c.941 C>G [p.A314G] in *TSHZ3*) that segregated with the disease. Only the *OPA3* variant was absent in the control subjects and predicted to be damaging (Arif et al., 2013).

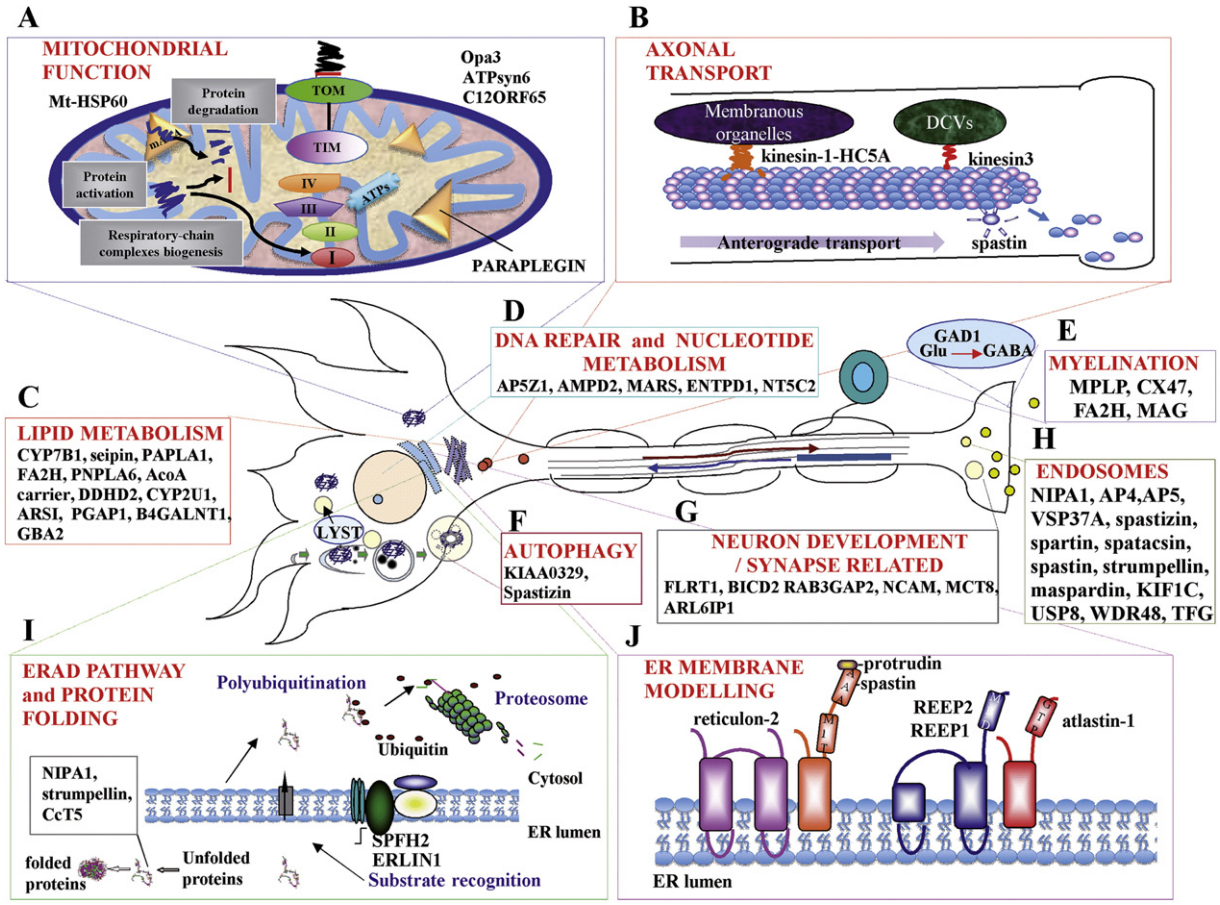

Fig. 2. HSP proteins involved in cellular functions divided into major functional modules. (A) Paraplegin (m-AAA protein) and HSP60 control the removal of damaged or misfolded proteins in mitochondria, respectively; TIM (translocase of the inner membrane) and TOM (translocase of the outer membrane) are mitochondrial membrane transporters for mitochondria-destined proteins. (B) In the axonal transport, spastin is responsible for the disassembly of microtubules acting on the kinesin HC5A and kinesin 3 function in the transport of anterograde cargoes. (C) Proteins implicated in synthesis, metabolism, and distribution of lipids and sterols; ACoA carrier carries acetyl-CoA into the lumen of Golgi apparatus and then it is transferred to the sialyl residues of gangliosides and glycoproteins. (D) AP5Z1 is implicated in DNA double-strand break repair. The other proteins are involved in nucleotide metabolism. (E) MPLP, connexin (Cx) 47, FA2H, and MAG are involved in the stabilization and maintenance of the myelin sheath. (F) KIAA0329 and spastizin participate in the degradation of unnecessary or dysfunctional cellular components through the actions of lysosomes (autophagy). (G) Proteins involved in axon development. (H) Other proteins, such as NIPA1 and AP4 subunits, are involved in the endosomal pathway. (I) The ERAD pathway is regulated by ERLIN1 and SPFH2. Proteins involved in protein folding are in the left of the box. (J) Reticulon-2, spastin, REEP1, and REEP2 are involved in membrane modeling and shaping by interacting each other. In synaptic terminals, GAD1 converts glutamic acid (Glu) into GABA; LYST is a lysosomal trafficking regulator (circles in turquoise).

The function of the OPA3 protein is important for mitochondrial dynamics and respiratory chain complex protein stability (Grau et al., 2013).

BICD2, MAG, and LYST genes

These three genes were lately found mutated in ARHSP patients (Novarino et al., 2014; Shimazaki et al., 2014) (Fig. 2, Tables 1 and 2).

HSP with maternal inheritance

A late onset HSP due to m.9176 T>C mtDNA mutation in *MT-ATP6* in five members of a large family is the first and sole maternally-inherited form of HSP described to date (Verny et al., 2011). Variable clinical presentation is the hallmark of mtDNA mutations: for example, like the more common m.8993 T>G, the m.9176 T>C change is associated with the severe neonatal-onset Leigh syndrome (Dionisi-Vici et al., 1998; Hung and Wang, 2007).

Phenotypic variability (Table 2) in this family cannot be explained by the mutant load, and other factors (nuclear modifying genes or the mtDNA background) may be involved in the phenotypic expression of the disease. Moreover, three additional mitochondrial encoded genes have been identified in HSP (*PGN, HSPD1,* and *OPA3*), focusing on the importance of mitochondrial dysfunction (reviewed in Salinas et al., 2008).

Other phenotypes

SPOAN syndrome (complicated spastic paraplegia associated with optic atrophy and neuropathy) linked to 11q13 (Macedo-Souza et al., 2005), a complex phenotype in a Japanese family (Hattori et al., 2010), and a complex HSP related to oligodendropathy (Woehrer et al., 2012) await molecular definition.

Functional modules

HSP is characterized by clinical and genetic heterogeneity, caused by a large number of loci/genes involved. Proteins implicated in the onset of the disease are part of specific molecular pathways or perform similar functions and the same protein can be implicated in several functions.

Ten principal functional modules (Fig. 2) have been summarized, which are also presumed to create interactome networks (Novarino et al., 2014).

Oxidative stress in HSP pathogenesis

PGN mutations determine the lack of the paraplegin/AFG3L2 complex, responsible for a specific quality control of proteins that are localized in the inner mitochondrial membrane; moreover, this complex is also involved in a chaperone-like activity on the OXPHOS (oxidative phosphorylation pathway) protein complexes (Maltecca et al., 2009). The impairment in complex I activity has been observed in SPG7 subjects and an increased sensitivity to oxidative stress has been measured in their fibroblasts (reviewed in Rugarli and Langer, 2006). Paraplegin-deficient mice showed axonal degeneration with an abnormal mitochondrial morphology and impairment in axonal transport (Ferreirinha et al., 2004), indicating a role for paraplegin in axon maintenance. A recent work has underlined the crucial role of both AFG3L2 and paraplegin in preventing neuronal death and, in particular, their ability to inhibit cerebellar degeneration (Martinelli et al., 2009).

HSP60 functions only in combination with HSP10, forming a barrel-like structure. Compared to controls, no particular mitochondrial dysfunction has been observed in SPG13-patients; however, it has been demonstrated that their cells show a decreased expression of two quality control mitochondrial proteases Lon and ClpP (Hansen et al., 2008). Instead, an abnormal functioning of mitochondrial respiratory chain complex I and IV has been found in a patient carrying a mutation in *REEP1* (Hewamadduma et al., 2009).

MT-ATP6 encodes a subunit of ATP synthase (Complex V). It leads to complex V instability, impaired assembly, and function. Phenotypic similarity has been observed between patients carrying mitochondrial DNA (mtDNA) mutations and

HSP patients. On the basis of these observations, a recent work evaluated the possible involvement of common mitochondrial polymorphisms/haplogroups on the risk of developing HSP (Sánchez-Ferrero et al., 2011).

Dysfunction of axonal transport

Axonal transport is believed to be primarily impaired in several HSP forms. Well-characterized proteins will be focused on: spastin, kinesin HC5A, and kinesin 3.

Spastin has a complex subcellular localization based on its different isoforms (Lumb et al., 2012). The full-length isoform is mainly localized on the early secretory pathway, at the ER and probably also at the very early ER-to-Golgi intermediate compartment. In contrast, the isoform that lacks the first 87 amino acids stretch exists in a cytosolic pool and can be recruited to endosomes and to the cytokinetic midbody during cell division. This isoform has also been described in the nucleus due to two nuclear localization signals. While the wild-type over-expressed form of spastin causes disassembly of microtubules, the mutated form localizes with them (Errico et al., 2002). With reference to the disassembly of microtubules, the spastin seems to act in a hexameric form that binds polymerized tubulin and induces a conformational change responsible for breaking microtubules. A recent work has described a post-translational glutamylation of tubulin (the generation of long glutamate side chains) that is a necessary step for spastin-dependent microtubule disassembly (Lacroix et al., 2010). The spastin MIT domain also mediates the interaction with the charged multi vesicular body proteins. These proteins form a complex named ESCRT-III, involved in viral budding, formation, and sorting of cargoes into the late endosomes, as well as in the resolution of the midbody membrane (Raiborg and Stenmark, 2009). Spastin also interacts with protrudin. The lack of protrudin in cultured neurons inhibits neurite extension, whereas its over-expression promotes neurite extension (Shirane and Nakayama, 2006). Moreover, a loss of spastin is suggested to reduce the rate of axonal branching in cultured primary neurons (Riano et al., 2009). *Post mortem* analysis of SPG4 reported abnormalities in the distribution of mitochondria in spinal motor neurons, emphasizing the spastin involvement in organelles axonal movement (McDermott et al., 2003).

In mammals, kinesin HC5A is necessary for anterograde axonal transport of neurofilament subunits and it plays a role in the transport of other anterograde cargoes, for example membrane vesicles (Reid et al., 2002). Experimental data suggested that when *KIF5A* is mutated, cargo transport to the distal axon is slowed, or microtubules binding affinity is decreased. Consequently, the frequency of anterograde transport is lowered, and the arrival of the cargo to the synapse is largely delayed. Alternatively, axonal degeneration in patients with HSP subtypes may be caused by impaired slow axonal transport. Indeed, the lack of neurofilament supply to the synapsis is a plausible reason for neurodegeneration (Ebbing et al., 2008).

Kinesin 3 is a highly processive and fast motor protein belonging to the homonymous family of microtubule-associated proteins involved in intracellular transport (Lo et al., 2011). It is responsible for fast axonal transport of DCVs, implicated in carrying organelles in neurons responsible for transporting and secreting neuropeptides, but it remains associated with them during retrograde axonal transport too. This protein contains multiple protein–protein interaction domains that facilitate differential cargo binding. Additionally, Park et al. (2008) demonstrated that the complex containing dynactin–kinesin 2/kinesin 3 interacts with carboxypeptidase E, which plays an important role in the transport of pituitary hormones vesicles; yet, the exact mechanism of binding to DCVs is not known.

Abnormal lipid metabolism

Some proteins involved in HSP play a role in lipid metabolism at various levels.

CYP7B1 is one of two CYP7 family members, which is expressed in several tissues (liver, kidney, and brain) (Siam et al., 2012). In the brain, this hydroxylase is implicated in steroid hormone metabolism, acting toward two neurosteroids, pregnenolone and dehydroepiandrosterone (DHEA), (Lorbek et al., 2012). CYP7B1 is also important for the 7-hydroxylation of DHEA-related hydroxysteroids. Some data suggest that this group of neurosteroids act as neuroprotective factors and they can reduce ischemia-induced neurodegeneration. Consequently, neurodegeneration associated with *CYP7B1* mutation may also be associated with a loss of neuroprotective function of DHEA-related neurosteroids (Arnoldi et al., 2012).

PNPLA6 is a phospholipase/lysophospholipase and its activity may be regulated by cAMP. The protein participates in the regulation of phospholipid homeostasis necessary for maintaining cellular membrane integrity. In particular, it acts as a phospholipase B promoting phospatidylcholine conversion to glycerophosphocholine. Knockout experiments show that it is indispensable for survival of the embryo and maintenance of axons in adults; acetylation of gangliosides and glycoproteins may also play a significant role (Moser et al., 2004).

Abnormal DNA repair

AP5Z1 is a putative helicase with both nuclear and cytoplasmic localization (Słabicki et al., 2010). It interacts with four proteins, probably forming a complex required for an efficient homologous recombination DNA double-strand break repair. Two of the interaction partners, spatacsin and spastizin, are proteins associated with spastic paraparesis. Indeed, spatacsin is phosphorylated upon DNA damage by protein kinases ATM (ataxia telangiectasia mutated) or ATR (ATM and Rad3-related).

Dysregulation of myelination

MPLP is involved in myelin sheath stabilization and axon–myelin interactions, whereas DM20, its splicing variant, is involved in oligodendrocyte maturation (Inoue, 2005). The large part of misfolded MPLP/DM20 is retained in the ER. The presence of misfolded proteins induces a cascade of protein interactions and dissociations. The chaperone binding immunoglobulin protein (BiP) associates with three stress sensors (PERK, IRE1, and ATF6), maintaining these proteins in an inactive state. Upon stress induction, BiP dissociates, translocates to the ER lumen to assist in protein folding, and the sensor proteins adopt an active status. The activated proteins induce a series of interacting pathways constituting the UPR that leads to apoptosis of oligodendrocytes (Swanton et al., 2003).

FA2H is an NADPH-dependent monooxygenase highly expressed in oligodendrocytes and it is involved in the biosynthesis of mammalian sphingolipids (Lamari et al., 2013). FA2H synthesizes 2-hydroxy fatty acids: these are incorporated into ceramide, a precursor of galactosylceramide and one of the major constituents of the myelin sheath. 2-hydroxylation stabilizes lateral interactions between sphingolipids and membrane–membrane interactions (Zöller et al., 2008). An alteration of this mechanism suggests that transport and/or degradation of myelin components might be affected.

GJC2 mutations disrupt junction channels between astrocytes and oligodendrocytes causing cell–cell communication impairment in maintenance of CNS myelin (Orthmann-Murphy et al., 2009).

Autophagy

It was hypothesized that the truncated KIAA0329 protein would lead to dysregulation of the intracellular autophagy pathway, with reduced delivery of two targeted autophagocytic proteins (SQSTM1 and MAP1LC3B) to lysosomes (Oz-Levi et al., 2012).

Spastizin has been suggested to be associated with the AP5 complex in endolysosomal function (Khundadze et al., 2013). In lymphoblast and fibroblast cells derived from spastizin mutated patients, it has been demonstrated an impairment of autophagosome maturation with accumulation of immature autophagosomes (Vantaggiato et al., 2013).

Axon development

Neural cell adhesion molecule (NCAM) plays an important role in the development of the nervous system, promoting neuron–neuron adhesion and axon outgrowth. These crucial cellular events are permitted by NCAM interactions with other cell adhesion molecules (CAMs). NCAM molecular partners determine its function; in fact, NCAM-integrin binding modulates adhesion to extracellular matrix proteins, whereas the interaction between NCAM and TAG1 (transient axonal glycoprotein-1) is necessary for NCAM–NCAM mediated neurite outgrowth (Kenwrick et al., 2000).

MCT8 is expressed in neurons and cerebral microvessels in all species; its role in the transport of T4 from the blood into the cerebrospinal fluid and in efflux of thyroid hormones or their inactive metabolites from the cerebrospinal fluid to blood was also suggested as a cause of axon impairment (Roberts et al., 2008).

Endosome membrane trafficking and vesicle formation

Adaptor protein complexes (AP1–4) are ubiquitously expressed and mediate different types of vesicle formation and their molecular cargo selection from the trans-Golgi compartment to the endosomal–lysosomal system. AP4-mediated trafficking can be involved in brain development and functioning (Abou Jamra et al., 2011). It is also involved in the transport of amyloid precursor protein (APP) from the trans-Golgi network to early endosomes (Burgos et al., 2010).

VPS37A is a component and an upstream regulator of the ESCRT-I; its depletion delays EGF receptor degradation (Bache et al., 2004).

Strumpellin is a component of the Wiskott–Aldrich syndrome protein and scar homolog (WASH) complex, an actin-regulating complex present at the surface of endosomes, which regulates the correct subcellular distribution of the β-2-adrenergic receptor; corticospinal neurons are especially vulnerable to reductions in functional WASH (Freeman et al., 2013).

Abnormal cellular signaling in protein morphogenesis

Atlastin-1, NIPA1, spastin, and spartin have been shown to inhibit bone morphogenetic protein (BMP) signaling (Tsang et al., 2009). This suggests that the up-regulation of BMP pathway by loss-of-function mutation in these genes could be a common pathogenic mechanism in the disease.

Atlastin-1 regulates the axons architecture by down-regulating BMP signaling during zebrafish development (Fassier et al., 2010). As a matter of fact, the early depletion of this protein leads to severe defects in axons, with consequent marked decrease of larval mobility. Functional studies have demonstrated that atlastin-1 partially co-localizes with BMP receptor type I in late endosomes, probably regulating the receptor trafficking.

NIPA1 protein is mainly expressed in early endosomes and cell surface. It contains nine transmembrane domains and it is suggested to partake in cellular magnesium metabolism. Recent evidences show that NIPA1 and atlastin-1 are direct binding partners, since cellular distribution of atlastin-1/NIPA1 complexes is dramatically altered by

HSP-causing mutations (Botzolakis et al., 2011). In addition, NIPA1 inhibits BMP signaling by promoting endocytosis and lysosomal degradation of the type II BMP receptor (BMPRII). Mutant NIPA1 is retained in the ER and alters BMPRII trafficking (Tsang et al., 2009).

Spartin is involved in epidermal growth factor receptor (EGFR) intracellular trafficking and an impaired endocytosis of EGFR by mutant spartin would cause the onset of Troyer syndrome. Low levels of EGF cause the internalization of EGFR via clathrin-mediated endocytosis. Spartin knockdown decreases the rate of EGFR degradation and affects EGFR internalization, recycling, or both. Conversely, spartin over-expression results in a prominent decrease in EGFR degradation. The molecular mechanisms leading to the redistribution of spartin are unknown. It is believed that EGFR activation might induce the phosphorylation of spartin, leading to its translocation to the plasma membrane (Bakowska et al., 2007).

SPFH2 is a protein with the ability to assemble into oligomeric structures and localize in cholesterol-rich membranes (Pearce et al., 2009). As previously mentioned, it is involved in the ER degradation pathway that target both aberrant and normal proteins to maintain homeostasis. SPFH2 depletion causes impaired degradation of inositol-1,4,5-trisphosphate (IP3); it leads to a persistent activation of IP3 signaling and channel opening, determining neuronal hyperactivity (Alazami et al., 2011).

Abnormal membrane traffic and organelle shaping

Spastin, atlastin, REEP1, and reticulon 2 take part in ER membrane modeling and shaping. These proteins share similar hairpin loops that control ER membrane shaping.

Reticulon 2 overexpression determines the formation of tubular ER membrane structures. It acts together with DP1/Yop1 proteins in stabilizing the ER membrane curvature at the sheets edges. Moreover, the different quantitative expression of these proteins is responsible for ER morphology (Shibata et al., 2010). Atlastin controls ER tubules fusion in order to create the ER network; it is noteworthy that morphology of the tubular ER depends on microtubules dynamics that, in turn, depend on spastin function. Mutual interactions between spastin, REEP1, and atlastin-1 make these peptides responsible for the ER network formation and membrane bending. A truncated REEP1 protein causes the disruption

of ER morphology by interfering with REEP1-microtubules binding; this hypothesis expects that these three proteins cooperate in protein trafficking along microtubules and the loss of function of these peptides leads to a damage of the long axons of the corticospinal tract (Park et al., 2010).

Diagnosis

HSP can be suspected when the following differential diagnoses have been excluded: leukodystrophies, subacute combined degeneration of spinal cord (vitamin B12 deficiency), multiple sclerosis (absence of oligoclonal bands in CSF in HSP), acyl-CoA dehydrogenase deficiency (VLCAD), copper deficiency, Segawa disease (DYT5), HTLV-1-associated myelopathy, amyotrophic lateral sclerosis, primary lateral sclerosis, arginase deficiency, Friedreich's ataxia, mitochondrial disorders, early onset Alzheimer disease with spastic paraparesis caused by presenilin 1 mutations, structural abnormalities of brain and spinal cord, and lumbar vertebral stenosis. Also, spinocerebellar ataxias (SCA) can mimic HSP: SCA3 (*ATXN3*) and autosomal recessive SCA (*APTX*, *SETX*, *POLG*, *TDP1*, *SACS*, *SYNE1*, *C10orf2*, *SCAR3*, and *SCAR7*) should be excluded in selected patients.

Diagnostic steps include individual and family history to detect the type of transmission. A careful neurological examination, neurophysiological testing, and instrumental investigations (MEPs, SEPs, VEPs, AEPs, electroneurography/EMG, MRI, EEG, and cystometry) are needed in diagnosis; pure and complex forms shall be identified before starting genetic testing. Prolonged central conduction time in MEPs and SEPs indicates the central long tract impairment. Neuroimaging analyses would provide early clues to the diagnosis of HSP. Thinning or atrophy of *corpus callosum* as well as cervical and thoracic spinal cord has been observed on conventional MRI studies (Lan et al., 2014; Orlacchio et al., 2011). Diffusion tensor imaging (DTI) successfully showed HSP-related microstructural alterations in white matter. DTI could reveal abnormality of white matter integrity, especially at the corticospinal tract, in the early stage of SPG4 (Duning et al., 2010). Specific statistical analyses clearly showed alterations in multiple DTI indices, such as decreased fractional anisotropy and increased radial diffusivity, indicating loss of myelin integrity in HSP patients, including SPG3, SPG4, SPG5, SPG7, and SPG10. Intriguingly, a decreased fractional anisotropy was observed in the frontal circuitry, suggesting subtle disruption of the frontal connections (Aghakhanyan et al., 2014). Neuropathological investigations may detect axonal degeneration of the corticospinal tract, loss of anterior horn cells, or demyelination consistent with axonal degeneration (Deluca et al., 2004).

Screening for *SPG* mutations is usually carried out by direct Sanger sequencing coupled with multiplex ligation-dependent probe amplification (Battini et al., 2011). The improvement of nucleotide sequencing has recently demonstrated the possibility of accelerating and improving cost-effectiveness of genetic diagnosis using an array-based amplification strategy after generation of amplicon libraries of all currently known HSP genes followed by a pooled next-generation sequencing (NGS) (Chase, 2014; Novarino et al., 2014; Schlipf et al., 2011). Besides, modern methodologies of re-sequencing have been reported (Kumar et al., 2013) as well as a gene chip screening (Luo et al., 2013).

Being molecular genetic testing available on a routine basis only for a few HSP forms (SPG3A, SPG4, SPG6, SPG7, SPG10, SPG11, SPG17, and SPG31) we propose two algorithms (Fig. 3) for genetic testing.

Treatment

Treatment is exclusively symptomatic. Spasticity benefits from daily physical therapy (swimming, in particular), baclofen or tizanidine. If ineffective, intramuscular injections of botulinum toxins A or B can be considered, especially in cases associated with dystonia (Geva-Dayan et al., 2010). Long-term intrathecal baclofen therapy can be administered via a surgically implanted programmable pump (Motta and Antonello, 2014). A recent study focused on gait and hydrotherapy treatment in patients with late onset HSP demonstrating increased walking speed mediated by compensatory strategies (Zhang et al., 2014). Deep brain stimulation has also been used in dystonia (Gilbert et al., 2009). Hypertonic bladder benefits from anticholinergic drugs and neuropathic pain from gabapentin or pregabalin. Parkinsonism, dementia, and epilepsy are treated according to the respective guidelines. Hearing devices in SPG29 and shunt implantations in SPG1 developing *hydrocephalus* are often used. Regular clinical revaluations of patients once or twice yearly are recommended to assess progression and complications.

Potential therapies

The availability of HSP animal models, including mouse, rat, zebrafish, cattle, *Drosophila*, and *C. elegans* (reviewed in Fink, 2013), not only allows the exploration of disease mechanisms, but also of potential treatments. Future prospects will allow a rational approach to intracellular transport defects (Soderblom and Blackstone, 2006), in particular microtubules dysfunction in SPG4 *Drosophila* models in which mutated spastin leads to an excessive stabilization of microtubules in the neuromuscular junction synapse: agents destabilizing microtubules, like nocodazole (Trotta et al., 2004) and vinblastine (Orlacchio et al., 2004b; Orso et al., 2005), seem to attenuate HSP-like phenotypes in vivo.

If 27-hydroxycholesterol was a major factor in the degeneration of corticospinal tracts in SPG5-patients, an effective therapeutic approach should aim at reducing its levels. A possible therapeutic strategy might be a statin treatment. It has been observed that the levels of 27-hydroxycholesterol and cholesterol decrease in parallel during statin therapy, limiting the synthesis (CYP27A1 activity) by a substrate availability (Schüle et al., 2010). Recent findings of moderate reductions of serum 27-hydroxycholesterol upon simvastatin administration in a SPG5-patient led to interesting possibilities on SPG5 treatment (Mignarri et al., 2014).

A gene transfer study showed that adenoassociated virus-mediated (AAV-mediated) intramuscular delivery of paraplegin halts the progression of neuropathological changes and rescues mitochondrial morphology in the peripheral nerves of paraplegin-deficient mice, suggesting that viral vectors can be the key to treat genetic diseases (Pirozzi et al., 2006).

Food for thought

Pure and late onset HSP forms are generally inherited following an AD pattern, whereas ARHSPs often associate with early, more severe onset, and complex phenotypes.

The evidence that degeneration may also regard shorter axons, for example in the *cerebellum, neocortex, corpus callosum,* and optic nerve, suggests that length-dependent distal axon degeneration is not the only pathogenetic mechanism involved (White et al., 2000).

Different clinical features reflect genetic heterogeneity in HSP. Many genes are implicated in selective clinical manifestations, while the same gene is mutated in various diseases (see among others, the ample allelisms of *BSCL2* and *FA2H*). It is well known that mutated genes alter specific intracellular (or cell-to-cell) mechanisms bringing different clinical features. The identification of causative genes in HSP revealed that the common axonal degeneration has different pathogenetic mechanisms. This overlaps with other neurodegenerative diseases, in particular distal spinal muscolar atrophy (SMA), juvenile amyotrophic lateral sclerosis (JALS), and CMT. Indeed, *BICD2* mutations, encoding a key adaptor protein involved in trafficking of cellular cargos, are reported in patients showing both HSP and autosomal dominant congenital SMA (DCSMA) (Oates et al., 2013). Lower motor neuron degeneration in HSP overlaps with JALS, as evidenced by the identification of *KIAA1840* mutations in 40% of JALS-patients (Orlacchio et al., 2010) and by the dysfunction of

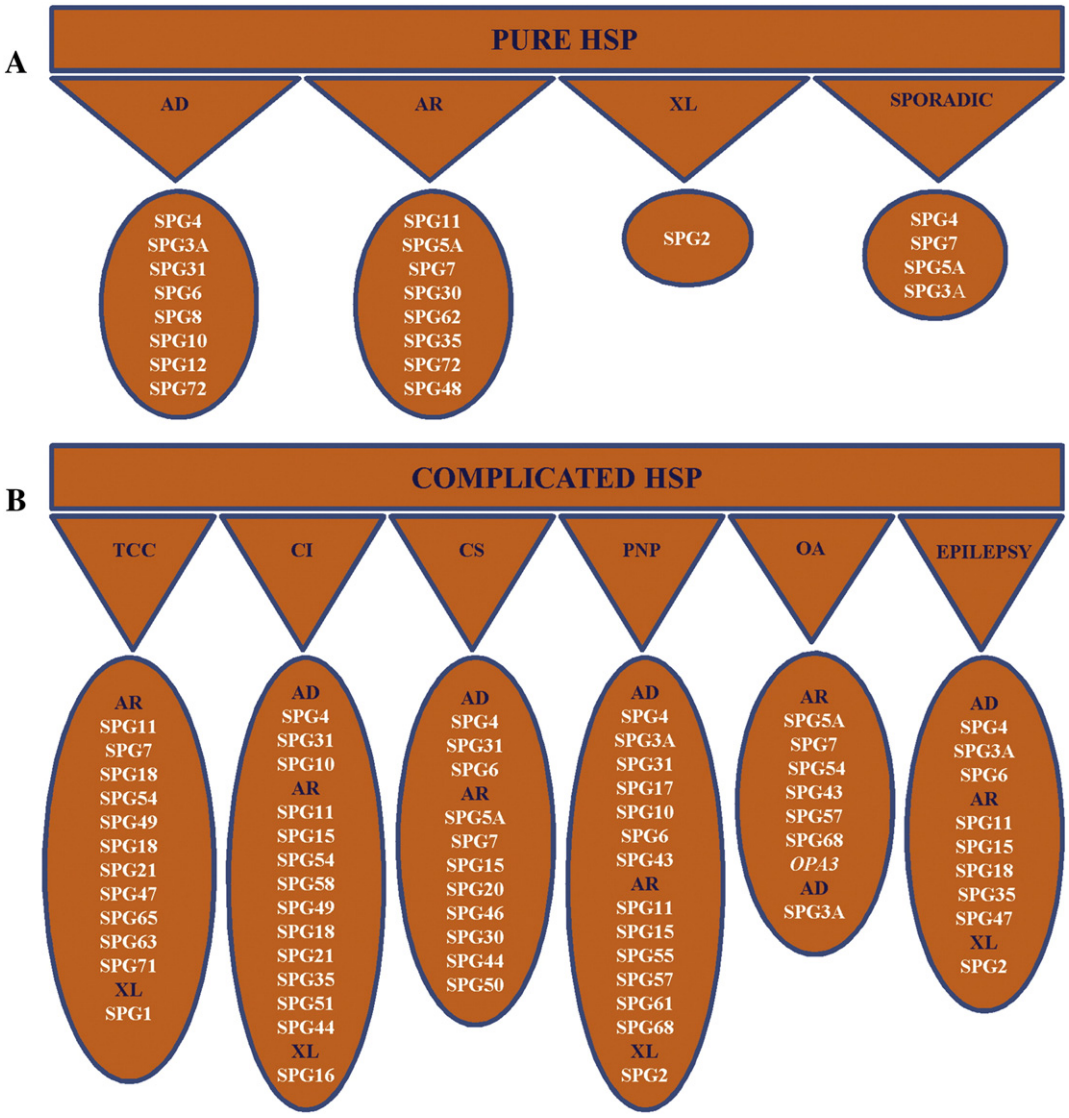

Fig. 3. Algorithms for genetic testing in pure (A) and complicated (B) HSP. SPG forms in ovals are reported following their relative frequencies from top to bottom. AD = autosomal dominant; AR = autosomal recessive; CI = cognitive impairment; CS = cerebellar signs; OA = optic atrophy; PNP = polyneuropathy; TCC = thin *corpus callosum*; XL = X-linked.

endosomal trafficking in *ALS2* mutated JALS-patients (Hadano et al., 2007). This concept also concerns CMT neuropathies (primarily CMT2), which show many similarities with HSP (reviewed in Timmerman et al., 2013) in terms of clinical presentation, molecular genetics, and cellular pathology. In particular, a *KIF5A* mutation, p.G235E, has been found in a patient affected by axonal CMT and member of an HSP family; this suggests that SPG10 and CMT may be the extreme phenotypes resulting from mutations in the same gene (Crimella et al., 2012). Finally, by using the random walk distance algorithm in HSP genes network, Novarino et al. (2014) linked HSP to amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease.

Therefore, the recognition of common molecular themes in motor neuron diseases could clarify the bases of neurodegeneration and justify therapeutic strategies, which are not limited to individual subtypes, but rather based on pathway/module impairment.

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