

Supplemental Table 1. HSP loci and known genes, divided into functional groups

(compiled from [OMIM](#) and [1-3])

	Inheritance	Locus	Protein	Clinical features	Frequency	Models
Endosome and Membrane traffic related						
SPG3A (<i>Atlastin-1</i>)	AD	14q12-q21	Atlastin-1	Early-onset pure, slow progression HSP	<10% AD HSP	<i>C. elegans</i> [4], Zebrafish [5], <i>drosophila</i> [6, 7], mouse [8], iPSC-derived neurons [9]
SPG4 (<i>SPAST</i>)	AD	2p22	Spastin	Variable-onset mainly pure HSP	40% of AD HSP	Zebrafish [10, 11], <i>drosophila</i> [12, 13], mouse [14], iPSC-derived neurons[15, 16]
SPG6 (<i>NIPA1</i>)	AD	15q11.2-q12	Non-imprinted in Prader-Willi/Angelman syndrome region protein 1) NIPA1	Adult-onset pure HSP	~10 families	<i>C. elegans</i> [17], <i>drosophila</i> [18]
SPG8 (<i>KIAA0196</i>)	AD	8q24	Strumpellin	Adult-onset pure HSP, marked spasticity	<10 families	<i>Drosophila</i> [19], Zebrafish [20]
SPG10 (<i>KIF5A</i>)	AD	12q13	Kinesin family member 5A	Early-onset pure HSP, can be complicated with distal amyotrophy	<10 families	<i>Drosophila</i> [21], Mouse [21]
SPG11 (<i>KIAA1840</i>)	AR	15q	Spatacsin	Childhood to early adult onset, thin corpus callosum, cognitive impairment, neuropathy	Many families	Zebrafish [22, 23], iPSC-derived neurons [24]
SPG12 (<i>RTN2</i>)	AD	19q13	Reticulon-2	Early-onset pure HSP	<10 families	
SPG15 (<i>ZFYVE26</i>)	AR	14q	Spastizin	Kjellin syndrome: adolescent onset, pigmented retinopathy, cerebellar signs, mental retardation	<10 families	
SPG17 (<i>BSCL2</i>)	AD	11q12-q14	Seipin	Silver syndrome: variable onset, distal amyotrophy in hands more than in feet	<20s families	
SPG18 (<i>ERLIN2</i>)	AR	8p11.23	Endoplasmic reticulum, lipid raft associated protein 2	Severe complex HSP, psychomotor retardation, thin corpus callosum, intellectual disability	5 families	
SPG20	AR	13q	Spartin	Troyer syndrome: childhood onset, amyotrophy, cerebellar signs, developmental delay	>10 families	
SPG21 (<i>ACP33</i>)	AR	15q	Maspardin	Mast syndrome: early adult onset, thin corpus callosum, cognitive decline, extrapyramidal features, cerebellar signs	>10 families	Mouse [25]
SPG33 (<i>ZFYVE27</i>)	AD	10q24.2	Protrudin	Uncomplicated HSP	1 family	Zebrafish [26]
SPG30 (<i>KIF1A</i>)	AR	2q37.2	KIF1A	Adolescent-onset pure HSP, sensory neuropathy	1 family	<i>C. elegans</i> [27], Mouse [28]
SPG31 (<i>REEP1</i>)	AD	2p12	Receptor expression-enhancing protein 1	Variable-onset pure HSP	8% of AD pure HSP	Mouse [29]
SPG51 (<i>AP4E1</i>)	AR	15q21.2	Adaptor protein complex 4 eta 1	Complicated, microcephaly, hypotonia, white matter loss, cognitive impairment	2 families	

SPG53 (VPS37A)	AR	8p22	Vacuolar protein sorting 37A	Complicated early-onset HSP, cognitive impairment, impaired vibration sensitivity	2 families	Zebrafish [30]
SPG58 (KIF1C)	AR	chr17:49 04143	Kinesin family member 1C	Complicated and uncomplicated, early childhood onset, increased deep tendon reflexes, white matter abnormalities	2 families	
SPG59 (USP8)	AR	chr15:50 769124	Ubiquitin specific peptidase 8	Complicated, early childhood onset, increased deep tendon reflexes, positive clonus	1 family	
SPG60 (WDR48)	AR	chr3:391 35498	WD repeat domain 48	Complicated, early onset, Increased patellar and absent Achilles tendon Reflexes, peripheral neuropathy	1 family	
SPG61(AR L6IP1)	AR	chr16:18 804609	ADP-ribosylation factor-like 6 interacting protein 1	Complicated, early onset, increased patellar and absent Achilles tendon reflexes	1 family	
SPG62 (ERLIN1)	AR	chr10:10 1914679	<i>ER lipid raft associated 1</i>	Uncomplicated, early onset, increased deep tendon reflexes	1 family	
Mitochondrial						
SPG13 (HSPDI)	AD	2q24-q34	Heat shock protein 60	Adult-onset pure HSP	<10 families	Mouse [31]
SPG7	AR	16q	Paraplegin	Variable onset, cerebellar signs, optic atrophy, neuropathy	~30 families	Mouse [32]
Lipid/Myelination						
SPG2 (PLP1)	X-linked	Xq21	Proteolipoprotein 1	Quadriplegia, nystagmus, mental retardation, seizures	<100 familial cases	Mouse [33]
SPG5 (CYP7B1)	AR	8p	Cytochrome P450-7B1	Variable-onset pure and complicated HSP	~20 families	Mouse [34]
SPG28 (DDHD1)	AR	14q22.1	Phospholipase DDHD1	Early-onset pure HSP	3 families	
SPG35	AR	16q21-q23	Fatty acid 2-hydroxylase	Childhood onset, intellectual decline, seizures	1 family	
SPG66 (ARS1)	AR	chr5:149 676845	Arylsulfatase family member I	Complicated, early onset, absent deep tendon reflexes	1 family	
SPG54 (DDHD2)	AR	chr8:381 03473	DDHD domain-containing protein 2	Complicated, early onset, intellectual disability	6 families	<i>Drosophila</i> [35]
SPG67 (PGAP1)	AR	chr2:197 712670	Post-GPI attachment to proteins 1	Complicated, early onset, increased deep tendon reflexes,	1 family	
Axon guidance/synapse related						
SPG1 (L1CAM)	X-linked	Xq28	L1 cell adhesion molecule	Mental retardation, hypoplasia of corpus callosum, adducted thumbs, hydrocephalus	Over 100 familial cases	<i>C. elegans</i> [36], mouse [32]
SPG68 (FLRT1)	AR	chr11:63 885762	Fibronectin leucine rich transmembrane protein 1	Complicated, early onset, increased deep tendon reflexes, patellar clonus, peripheral neuropathy	1 family	
SPG69 (RAB3GAP 2)	AR	chr1:220 357421	RAB3 GTPase activating protein subunit 2	Complicated, early onset, increased deep tendon reflexes, positive clonus, intellectual disability, deafness, cataract	1 family	
Nucleotide metabolism						

SPG63 (AMPD2)	AR	chr1:110 167989	Adenosine monophosphate deaminase 2	Complicated, early childhood onset, increased deep tendon reflexes	1 family	
SPG64 (ENTPD1)	AR	chr10:97 605168	Ectonucleoside triphosphate diphosphohydro- lase 1	Complicated, early onset, increased deep tendon reflexes	2 families	
SPG65 (NT5C2)	AR	chr10:10 4899162	5'-nucleotidase, cytosolic II	Complicated and uncomplicated, both early and adult onset, increased deep tendon reflexes	5 families	
Miscellaneous						
SPG9	AD	10q23.3- q24.2	..	Cataracts, motor neuropathy, skeletal abnormalities, gastro- oesophageal reflux	1 family	
SPG14	AR	3q27-q38	..	Variable onset, motor neuropathy, mental retardation	1 family	
SPG16	X- linked	Xq11.2	..	HSP with onset in infancy, aphasia, sphincter disturbance, mental retardation	1 family	
SPG19	AD	9q33-q34	..	Adult-onset pure HSP	1 family	
SPG23	AR	1q24-q32	..	Lison syndrome: childhood onset, pigmentation abnormalities, facial and skeletal dysmorphism, cognitive decline, tremor	4 families	
SPG24	AR	13q14	..	Childhood-onset pure HSP, pseudobulbar signs	1 family	
SPG25	AR	6q23-q23	..	Adult onset, cataracts, prolapsed intervertebral discs	1 family	
SPG26	AR	12p11.1- q14	..	Complicated HSP, adult onset, neuropathy and distal wasting, intellectual impairment	6 families	
SPG27	AR	10q22.1- q24.1	..	Variable onset, cerebellar signs, neuropathy, mental retardation, microcephaly	2 families	
SPG29	AD	1p31-p21	..	Early adolescence onset, sensorineural deafness, hiatus hernia, pes cavus, hyperbilirubinaemia	1 family	
SPG32	AR	14q12- q21	..	Childhood onset, mental retardation, thin corpus callosum, pontine dysraphism	1 family	
SPG34	X- linked (R)	Xq24-q25	..	Pure HSP, late childhood onset	1 family	
SPG36	AD	12q23- q24	..	Complicated HSP, lower limb sensory deficits	1 family	
SPG37	AD	8p21.1- q13.3	..	Pure HSP, variable onset, hyperreflexia of the upper limbs, decreased vibration sensitivity	1 family	
SPG38	AD	4p16-p15	..	Distal amyotrophy (Silver syndrome)	1 family	
SPG39	AR	19p13	Neuropathy target esterase	Childhood onset, marked distal wasting in all four limbs	2 families	<i>Drosophila</i> [37], Mouse [38]
SPG41	AD	11p14.1- p11.2	..	Pure HSP, urinary urgency, adolescent onset	1 family	

SPG42 (SLC33A1)	AD	3q25.31	acetyl-CoA transporter	Early onset	1 family	Zebrafish [39]
SPG43 (C19orf12)	AR	19p13.11 -q12	C19orf12	Associated with amyotrophy	1 family	
SPG44 (GJC2)	AR	1q42.13	Gap junction protein 12	Seizures and spasticity	1 family	
SPG45 (NT5C2)	AR	10q24.32 -q24.33	5'-nucleotidase, cytosolic II	Very early onset , mental retardation and ocular signs	1 family	
SPG70 (MARS)	AR	chr12:57 908741	Cytosolic methionyl-tRNA synthetase	Complicated, early onset, increased deep tendon reflexes	1 family	Zebrafish [3]
SPG71 (ZFR1)	AR	chr5:324 06955	ZFR	Uncomplicated, early onset, increased deep tendon reflexes, positive clonus, thin corpus callosum	1 family	

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