Genetic types of HSP*

Autosomal dominant HSP			
Spastic gait (SPG) locus	**OMIM#**		**Clinical Syndrome**
SPG3A	182600	Atlastin	Uncomplicated HSP: symptoms usually begin in childhood (and may be non-progressive); symptoms may also begin in adolescence or adulthood and worsen insidiously. Genetic non-penetrance reported. De novo mutation reported presenting as spastic diplegic cerebral palsy.
SPG4	182601	Spastin	Uncomplicated HSP, symptom onset in infancy through senescence, single most common cause of autosomal dominant HSP (~40%); some subjects have late onset cognitive impairment.
SPG6	600363	NIPA1	Uncomplicated HSP: prototypical late-adolescent, early-adult onset, slowly progressive uncomplicated HSP. Rarely complicated by epilepsy or variable peripheral neuropathy. One subject with uncomplicated HSP later died from amyotrophic lateral sclerosis.
SPG8	603563	KIAA0196 (Strumpellin)	Uncomplicated HSP, adult-onset.
SPG9A	601162	ALDH18A1	Complicated spastic paraplegia associated with cataracts, gastroesophageal reflux, peripheral neuropathy, variably accompanied by dysarthria, ataxia, cognitive impairment. Onset in adolescence to adulthood (one subject with infantile onset). Subjects from several unrelated families and two “apparently sporadic” subjects reported.
SPG10	604187	Kinesin heavy chain (KIF5A)	Uncomplicated HSP or complicated by distal muscle atrophy
SPG12	604805	Reticulon 2 (RTN2)	Uncomplicated HSP
SPG13	605280	Chaperonin 60 (HSP60)	Uncomplicated HSP: adolescent and adult onset
SPG17	270685	BSCL2/seipin	Complicated: spastic paraplegia associated with amyotrophy of hand muscles (Silver Syndrome)
SPG19	607152	Unknown	Uncomplicated HSP
SPG29	609727	Unknown	Complicated: spastic paraplegia associated with hearing impairment; persistent vomiting due to hiatal hernia inherited
SPG31	610250	REEP1	Uncomplicated HSP or occasionally associated with peripheral neuropathy
SPG33	610244	ZFYVE27	Uncomplicated HSP
SPG36	613096	Unknown	Complicated HSP: onset age 14 to 28 years, associated with motor sensory neuropathy
SPG37	611945	Unknown	Uncomplicated HSP
SPG38	612335	Unknown	One family, 5 affected subjects, onset age 16-21 years. Subjects had atrophy of intrinsic hand muscles (severe in one subject at age 58)
SPG41	613364	Unknown	Single Chinese family with adolescent onset, spastic paraplegia associated with mild weakness of intrinsic hand muscles
SPG42	612539	Acetyl CoA transporter (SLC33A1)	Uncomplicated spastic paraplegia reported in single kindred, onset age 4-40 years, possibly one instance of incomplete penetrance.
		ATP2B4 (PMCA4)	Uncomplicated spastic paraplegia with onset in teenage years through third decade; six members of a two-generation Chinese kindred reported.
SPG73	616282	CPT1C	Three-generation Italian family with uncomplicated, progressive spastic paraplegia beginning between 19 and 48 years
Chromosome 21q22.3: gene not yet			Complicated spastic paraplegia: 8 individuals in an American family of European descent, mean age of onset 44.6 (SD ± 8.9), with progressive spastic paraplegia later associate with axonal sensory-motor neuropathy

identified			
No SPG designation	612438	Tubb4A	Complicated spastic paraplegia associated with ataxia and brain white matter abnormality (hypomyelination); five affected subjects from a consanguineous family with heterozygous TubbA4 mutation c.568C>T (p.H190Y) were reported. Possible incomplete genetic penetrance: unaffected mother had the same mutation. Mode of inheritance uncertain. Tubb4A mutations also cause hypomyelinating leukodystrophy (HLD6; 612438) and autosomal dominant torsion dystonia (torsion dystonia (DYT4; 128101)
No SPG designation		IFIH1	One patient reported with early childhood onset, uncomplicated spastic paraplegia with heterozygous IF1H1 mutation c.1483G>A pGly495Arg. FIH1 gene mutations also cause Aicardi-Guiterrez syndrome (615846), see above, ADAR1 mutation).
No SPG designation	214500	ADAR1	Uncomplicated, early childhood-onset reported in one patient of Hispanic descent with non-consanguineous parents. Subjects had heterozygous mutation in ADAR1, mutations in which cause Aicardi Guiterrez syndrome: a genetically heterogeneous inflammatory syndrome affecting skin and brain, due to mutation in either TREX1, RNaseH2 components, and SAMHD1, and ADAR1, or IFIH1/MDA5 genes. Pathogenesis is thought to involve neurotoxicity from type 1 interferons and abnormal induction of type 1 interferon-mediated immune response.

Autosomal recessive HSP			
Spastic gait (SPG) locus	**OMIM #**		**Clinical Syndrome**
SPG5A	270800	CYP7B1	Uncomplicated or complicated by axonal neuropathy, distal or generalized muscle atrophy, and white matter abnormalities on MRI
SPG7	607259	Paraplegin	Uncomplicated or complicated: variably associated with mitochondrial abnormalities on skeletal muscle biopsy and dysarthria, dysphagia, optic disc pallor, axonal neuropathy, and evidence of "vascular lesions", cerebellar atrophy, or cerebral atrophy on cranial MRI. SPG7 may be transmitted as either autosomal dominant or autosomal recessive disorder
SPG9B	616586	ALDH18A1	Complicated spastic paraplegia associated with cataracts, gastroesophageal reflux, peripheral neuropathy, variably accompanied by dysarthria, ataxia, cognitive impairment. Onset in adolescence to adulthood (one subject with infantile onset). Subjects from several unrelated families and two "apparently sporadic" subjects reported. May be transmitted as an autosomal dominant disorder (SPG9A)
SPG11	604360	Spatacsin (KIAA1840)	Uncomplicated or complicated: spastic paraplegia variably associated with thin corpus callosum, mental retardation, upper extremity weakness, dysarthria, and nystagmus; may have "Kjellin syndrome": childhood-onset, progressive spastic paraplegia accompanied by pigmentary retinopathy, mental retardation, dysarthria, dementia, and distal muscle atrophy; juvenile, slowly progressive ALS reported in subjects with SPG11 HSP; 50% of autosomal recessive HSP is considered to be SPG11
SPG14	605229	Unknown	Single consanguineous Italian family, 3 affected subjects, onset age ~30 years; Complicated spastic paraplegia with mental retardation and distal motor neuropathy (sural nerve biopsy was normal).
SPG15	270700	Spastizin/ZFYVE26	Complicated: spastic paraplegia variably associated with associated with pigmented maculopathy, distal amyotrophy, dysarthria, mental retardation, and further intellectual deterioration (Kjellin syndrome).
SPG18	611225	ERLIN2	Two families described with spastic paraplegia complicated by mental retardation and thin corpus callosum. ERLIN2 mutations also identified in subjects with juvenile primary lateral sclerosis
SPG20	275900	Spartin	Complicated: spastic paraplegia associated with distal muscle wasting (Troyer syndrome)
SPG21	248900	Maspardin	Complicated: spastic paraplegia associated with dementia, cerebellar and extrapyramidal signs, thin corpus callosum, and white matter abnormalities (Mast syndrome)
SPG23	270750	Unknown	Complicated: childhood onset spastic paraplegia associated with skin pigment abnormality (vitiligo), premature graying, characteristic facies; Lison syndrome
SPG24	248900	Unknown	Complicated: childhood onset spastic paraplegia variably complicated by spastic dysarthria and deafness; one consanguineous Saudi Arabian family reported.
SPG25)	608220	Unknown	Consanguineous Italian family, four subjects with adult (30-46 years) onset back and neck pain related to disk herniation and spastic paraplegia; surgical correction of disk herniation ameliorated pain and reduced spastic paraplegia. Peripheral neuropathy also present.
SPG26	609195	B4GALNT1	Complicated spastic paraplegia, variably associated with muscle atrophy, intellectual impairment, and variably with scoliosis, dyskinesia, dystonia, cataracts, ataxia, axonal sensorimotor neuropathy, and abnormal appearing white matter on brain MRI; onset between ages 2 and 19; Affected subjects from six families from Spain, Tunisia, Brazil, Portugal, Germany, and Kuwait.
SPG27	609041	Unknown	Complicated or uncomplicated HSP. Two families described. In one family (7 affected subjects) uncomplicated spastic paraplegia began between ages 25 and 45 years. In the second family (three subjects described) the disorder began in childhood and included spastic paraplegia, ataxia, dysarthria; mental retardation, sensorimotor polyneuropathy, facial dysmorphism and short stature.
SPG28	609340	DDHD1	Uncomplicated: pure spastic paraplegia, onset in infancy, childhood, or adolescence, either as an uncomplicated spastic paraplegia syndrome; or variable associated with axonal neuropathy, distal sensory loss, and cerebellar eye movement disturbance
SPG29	609727	Unknown	Uncomplicated HSP, childhood onset
SPG30	610357	KIF1A	Complicated: spastic paraplegia, distal wasting, saccadic ocular pursuit, peripheral neuropathy, mild cerebellar signs
SPG32	611252	Unknown	Complicated spastic paraplegia, onset in childhood (ages 6 to 7), associated with mild mental retardation, and MRI evidence of brainstem dysgraphia, think corpus callosum, cortical and cerebellar atrophy
SPG35	612319	Fatty acid 2-hydroxylase (FA2H)	Childhood onset (6 -11 years), spastic paraplegia with extrapyramidal features, progressive dysarthria, dementia, seizures. Brain white matter abnormalities and brain iron accumulation; an Omani and a Pakistani kindred reported.
SPG39	612020	PNPLA6 (Neuropathy target	Complicated: spastic paraplegia associated with wasting of distal upper and lower extremity muscles

		esterase, NTE)	
SPG43	615043	C19orf12	Two sisters from Mali, symptom onset 7 and 12 years, progressive spastic paraplegia with atrophy of intrinsic hand muscles and dysarthria (one sister)
SPG44	613206	Gap junction protein GJA12/GJC2, also known as connexin47 (Cx47)	Allelic with "Pelizeaus-Merzbacher-like disease " (PMLD), early onset dysmyelinating disorder with nystagmus, psychomotor delay, progressive spasticity, ataxia). GJA/GJC2 mutation causes a milder phenotype: late-onset (first and second decades), cognitive impairment, slowly progressive, spastic paraplegia, dysarthria, and upper extremity involvement. MRI and MR spectroscopy imaging consistent with a hypomyelinating leukoencephalopathy
SPG45	613162	Unknown	Single consanguineous kindred from Turkey, five subjects described: affected subjects had mental retardation, infantile onset lower extremity spasticity and contractures, one subject with optic atrophy, two subjects with pendular nystagmus; MRI in one subject was normal.
SPG46	614409	GBA2	Progressive spastic paraplegia, complicated by ataxia and variable degrees of progressive cognitive decline, upper extremity spasticity, neuropathy, cataract, and thin corpus callosum; onset in childhood and adolescence.
SPG47	614066	AB4B1	Two affected siblings from consanguineous Arabic family with early childhood onset slowly progressive spastic paraparesis, mental retardation, and seizures; one subject had ventriculomegaly; the other subject had thin corpus callosum and periventricular white matter abnormalities
No SPG designation		KLC4 (Kinesin light chain 4 protein)	Complicated spastic paraplegia progressing to involve all extremities with four-limb contractures (tetraplegia), muscle atrophy, blindness, and deafness. One consanguineous family with two affected children, childhood onset spastic reported.
SPG48	613647	*AP5Z1* (KIAA0415)	Spastic paraplegia, onset in childhood through sixth decade, variably complicated by thin corpus callosum, cognitive impairment (usually), white matter abnormalities, and neuropathy. One subject had spastic paraplegia onset age ~60 accompanied by ataxia, retinopathy, neuropathy and parkinsonism. Five spastic paraplegia subjects with AP5Z1 mutations reported.
SPG49	615031	TECPR2	5 subjects from three apparently unrelated families (Jewish Bukharian ancestry) had infantile onset hypotonia, developmental delay with severe cognitive impairment, dysmorphic features (short stature, brady-microcephaly, oral, facial, dental, nuchal abnormalities). Spastic, ataxic, rigid gait developed in childhood; additional features included gastroesophageal reflux, recurrent apneic episodes, mild dysmorphic features. Two subjects had epilepsy and MRI of two subjects showed thin corpus callosum and cerebellar atrophy.
SPG50	612936	AP4M1	Five subjects from one consanguineous Moroccan family exhibited infantile onset, nonprogressive spastic quadriplegic with severe cognitive impairment; variably associated with adducted thumbs. Ventriculomegaly, white matter abnormalities and variable cerebellar atrophy noted on neuroimaging. Neuroaxonal abnormalities, gliosis, and reduced myelin noted on post mortem examination.
SPG51	613744	AP4E1	Two siblings from a consanguineous Palestinian Jordanian family and two siblings from a consanguineous Syrian family exhibited microcephaly, hypotonia, psychomotor delay, spastic tetraplegia, marked cognitive impairment with severe language impairment, facial dysmorphic features, abnormal brain MRI showed (including atrophy and diffuse white matter loss). Seizures were variably present.
SPG52	614067	AP4S1	5 affected subjects from consanguineous Syrian family exhibited neonatal hypotonia and severe cognitive impairment and progressive, early childhood onset, spastic paraplegia with contracturdes, microcephaly, short stature, facial dysmorphism, and microcephaly.
SPG53	614898	VSP37A	9 subjects from two Arab Moslem families exhibited developmental delay, progressive lower extremity spasticity, and subsequently progressive upper extremity involvement; associated with skeletal dysmorphism (kyphosis and pectus carinatum); mild to moderate cognitive impairment; and variable hypertrichosis and impaired vibration sensation.
SPG54	615033	DDHD2	Affected subjects reported from four unrelated families exhibited psychomotor delay, cognitive impairment, progressive spasticity (onset before age 2 years), thin corpus callosum, periventricular white matter abnormalities. Additional clinical features include foot contractures, dysarthria, dysphagia, strabismus, optic hypoplasia
SPG55	615035	C12ORF65	2 Japanese brothers from consanguineous parents exhibited early onset spastic paraplegia variably associated with reduced visual acuity (with central scotoma and optic atrophy), reduced upper extremity strength and dexterity, lower extremity muscle atrophy, and motor sensory neuropathy.
SPG56	615030	CYP2U1	5 unrelated families were reported with early childhood onset spastic paraplegia, variable upper extremity involvement, upper extremity dystonia, cognitive impairment, thin corpus callosum, brain white matter disturbance, axonal neuropathy, basal ganglia calcifications
SPG57	615658	TFG	Early childhood onset, uncomplicated spastic paraplegia (subjects from one consanguineous family); or early childhood-onset spastic paraplegia complicated by optic atrophy, axonal-demyelinating neuropathy, muscle atrophy (two families).
2q31.1	605363	GAD1	Four siblings in consanguineous Pakistani family with spastic cerebral palsy, and moderate to severe mental retardation
No SPG designation	609541	KLC2	"SPOAN" syndrome: complicated, childhood-onset, spastic paraplegia associated with optic atrophy, neuropathy (SPOAN); 25 subjects from a large consanguineous Brazilian kindred, 44 subjects from the same geographic area, and 2 individuals of Egyptian descent

No SPG designation	256840	Cct5	Complicated spastic paraplegia associated with mutilating sensory neuropathy.
No SPG designation	214500	LYST	Complicated, progressive spastic paraplegia associated with peripheral neuropathy, dementia, ataxia, cerebellar atrophy, beginning in the fourth and fifth decades in two Japanese brothers. Peripheral blood examination showed peroxidase-positive giant granules in granulocytes and reduced natural killer cell activity Chediak-Higashi syndrome (autosomal recessive, hypopigmentation, severe immune deficiency, hemorrhagic diathesis, neurologic degeneration).
No SPG designation	610181	RNASEH2B	Slowly progressive spastic paraplegia, early childhood onset in two siblings, complicated by mild upper extremity spasticy and in one subject, unilateral optic atrophy. These subjects were homozygous RNAseH2B mutation c.529G > A (p.Ala177Thr) mutation in RNASEH2B, the most frequent mutation seen in patients with RNASEH2B-associated Aicardi-Guiterrez syndrome (see above, ADAR1 mutation). One additional, unrelated subject, also homozygous for this same RNASEH2B mutation, had early childhood onset, uncomplicated spastic paraplegia, associated with abnormal appearing brain white matter on MRI, lateral ventricle dilatation, and CSF lymphocytosis.
SPG74	616451	IBA57	Complicated spastic paraplegia associated with optic atrophy and peripheral neuropathy beginning in late-childhood; 11 individuals in one consanguineous Arab family
SPG75	616680	MAG	Complicated spastic paraplegia described in two affected subjects in one family and three affected subjects in another family. Subjects had onset in infancy and early childhood of spastic gait associated with ataxia, dysarthria, peripheral neuropathy, optic atrophy, and mild to moderate cognitive impairment; brain MRI showed cerebellar and corpus callosal atrophy and white matter disturbance.
SPG76	616907	CAPN1	Spastic paraplegia complicated beginning between 19 and 39 years, variably accompanied by dysarthria, ataxia, muscle atrophy, peripheral neuropathy; nine individuals from three families reported.
SPG77	617046	FARS2	*Uncomplicated spastic paraplegia, childhood-onset, reported in one consanguineous family.*
SPG78	617225	ATP13A2	Complicated spastic paraplegia: onset in late-adolescence to adulthood of slowly progressive spastic gait, variably accompanied by ataxia, peripheral neuropathy, tremor, dementia, supranuclear gaze disturbance. ATP13A2 mutations also cause Kufor-Rakeb syndrome (also known as Parkinsonism-9 [PARK9]), a degenerative neurologic disorder associated with basal ganglia iron accumulation.
No SPG designation	607485	GRN	Complicated spastic paraplegia: spastic ataxia, cognitive impairment, psychiatric symptoms, and epilepsy. Heterozygous mutations in this gene cause autosomal dominant frontotemporal dementia
No SPG designation	611105	DARS2	One subject with adolescent onset spastic gait. Brain MRI showed leukoencephalopathy with brainstem and spinal cord involvement; elevated serum lactate elevation

X-linked HSP

Spastic gait (SPG) locus	OMIM #		Clinical Syndrome
SPG1	303350	L1 cell adhesion molecule (L1CAM)	Complicated: associated with mental retardation, and variably, hydrocephalus, aphasia, and adducted thumbs
SPG2	312920	Proteolipid protein	Complicated: variably associated with MRI evidence of CNS white matter abnormality; may have peripheral neuropathy
SPG16	300266	Unknown	Uncomplicated; or complicated: associated with motor aphasia, reduced vision, nystagmus, mild mental retardation, and dysfunction of the bowel and bladder
SPG22	300523	Monocarboxylate transport 8 (MCT8)	Complicated (Allan-Herndon-Dudley syndrome): congenital onset, neck muscle hypotonia in infancy, mental retardation, dysarthria, ataxia, spastic paraplegia, abnormal facies
SPG34			Uncomplicated , onset 12 to 25 years
No SPG designation	300100	ABCD1	Insidiously progressive spastic paraparesis, onset in adolescence through adulthood, often accompanied by peripheral neuropathy and mild dorsal column impairment; may be accompanied by clinical or laboratory evidence of adrenal insufficiency; plasma very long chain fatty acids are typically elevated in males but may be normal in affected females.

Maternally (mitochondrial) inherited HSP

Spastic gait (SPG) locus			

	OMIM #		Clinical Syndrome
No SPG designation		Mitochondrial ATP6 gene	Adult onset, progressive spastic paraplegia, mild to severe symptoms, variably associated with axonal neuropathy, late-onset dementia, and cardiomyopathy.

* updated from reference 8, 9 and https://www.ncbi.nlm.nih.gov/books/NBK1509/

#OMIM numbers refer to “Online Mendelian Inheritance in Man” (www.omim.org), an online database of human genes and genetic disorders. Please refer to this site for references.