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The proposed new list of hereditary spastic paraplegias

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **New designation** | **Less common movement phenotype** | **Clinical clues** | | **Inheri-tance** | | **Locus Symbol** | |
| **Autosomal dominant forms** | | | | | | | |
| HSP-*ATL11* |  | Pure or complex; Silver-syndrome, allelic with hereditary sensory neuropathy type 1, cerebral palsy (infantile onset).  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK45978/  OMIM 182600 | | AD/AR | | SPG3A | |
| HSP-*SPAST2* |  | Pure or complex; dementia, epilepsy, Peripheral neuropathy, tremor, ataxia, TCC, cerebellar atrophy.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1160/  OMIM 182601 | | AD | | SPG4 | |
| HSP-*NIPA13* |  | Pure or complex; Peripheral neuropathy, spinal cord atrophy, spastic dysarthria, facial dystonia, atrophy of the small hand muscles, upper limb spasticity, epilepsy.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 600363 | | AD | | SPG6 | |
| HSP-*KIAA01964* |  | Pure spastic paraplegia  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1827/  OMIM 603563 | | AD | | SPG8 | |
| HSP-*KIF5A5* |  | Pure or complex; allelic to Charcot Marie Tooth Neuropathy Type 2, Silver-syndrome, mental retardation, parkinsonism, deafness, retinitis, dysautonomia, sensory spinal cord-like syndrome.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 604187 | | AD | | SPG10 | |
| HSP-*RTN26* |  | Pure spastic paraplegia  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 604805 | | AD | | SPG12 | |
| HSP-*HSPD17* |  | Pure or complex; dystonia.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 605280 | | AD | | SPG13 | |
| HSP-*BSCL28* |  | Complex; Silver syndrome, these mutations may also cause distal hereditary neuropathy type 5.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1307/  OMIM 270685 | | AD | | SPG17 | |
| HSP-*REEP19* | Ataxia10 | Pure or complex; distal motor neuronopathy, axonal Peripheral neuropathy, Silver-like syndrome, cerebellar ataxia, tremor, dementia.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 610250 | | AD | | SPG31 | |
| HSP-*ZFYV32711* |  | Pure spastic paraplegia  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 610244 | | AD | | SPG33 | |
| SCA/HSP-*VAMP112* |  | Spastic ataxia, supranuclear upgaze limitation  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1138/  OMIM 108600 | | AD | | SPAX1 | |
| HSP-ALDH18A113, 14 |  | Autosomal dominant  Pure or complex; cognitive impairment, congenital cataract, dysarthria, cerebellar signs, neuropathic pain, epilepsy, infantile psychosis, sensorineural hearing loss, vomiting, biochemical features of delta-1-pyrroline-5-carboxylate synthase deficiency.  GeneReviews  https://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 601162  Autosomal recessive  Complex; cognitive impairment.  OMIM 616586  GeneReviews  <https://www.ncbi.nlm.nih.gov/books/NBK1509/>  Alternative phenotype: Cutis laxa, autosomal dominant 3 (OMIM 616603) and Cutis laxa, autosomal recessive, type IIIA (OMIM 219150). | | AD/AR | | SPG9A, autosomal dominant  SPG 9B, autosomal recessive | |
| **Autosomal Recessive forms** | | | | | | | |
| HSP-*CYP7B115* |  | | Pure or complex; white matter lesions, optic atrophy, cerebellar ataxia, sensory ataxia.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 270800 | | AR | | SPG5A |
| HSP-*SPG716* |  | | Pure or complex; optic atrophy, cerebellar atrophy, dysarthria, dysphagia, TCC, CPEO-like phenotype, mitochondrial abnormalities on muscle biopsy.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1107/  OMIM 607249 | | AR/AD\* | | SPG7 |
| HSP-*KIAA184017* | Parkinsonism18 | | Pure or complex; May cause Kjellin syndrome; TCC, mental retardation, sensory neuropathy, amyotrophy, dysarthria, nystagmus, ataxia, maculopathy, white matter lesions. Occasional parkinsonism.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1210/  OMIM 640360 | | AR | | SPG11 |
| HSP-*ZFYVE2619* | Parkinsonism18 | | Complex; Kjellin syndrome. TCC, WMLs, mental retardation, dysarthria, pigmentary maculopathy, peripheral neuropathy, distal amyotrophy. Occasional parkinsonism.51  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 270700 | | AR | | SPG15 |
| HSP-*ERLIN220* |  | | Complex; intellectual decline, speech involvement, seizures, congenital hip dislocation.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 611225 | | AR | | SPG18 |
| HSP-*SPARTIN21* |  | | Complex; Troyer-syndrome. Early onset dysarthria, distal muscle wasting with contractures and cerebellar signs in some. Delayed cognition and dysmorphism.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 275900 | | AR | | SPG20 |
| HSP-*ACP3322* |  | | Pure or complex; Mast syndrome, Dementia, cerebellar involvement, dyskinesias, athetoid movements, TCC, white matter lesions.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 248900 | | AR | | SPG21 |
| HSP-*B4GALNT23* |  | | Complex; progressive dysarthria, distal amyotrophy, non-progressive cognitive impairment, cerebellar signs, sensory polyneuropathy, pes cavus, stereotypies, emotional lability, psychiatric illness, seizures.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 609195 | | AR | | SPG26 |
| HSP-*DDHD124* |  | | Pure and complex; cerebellar oculomotor disturbance, Peripheral neuropathy.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 609340 | | AR | | SPG28 |
| HSP-*KIF1A25* |  | | Pure or complex; cerebellar signs, PNP, allelic to hereditary sensory and autonomic neuropathy.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 610347 | | AR | | SPG30 |
| HSP/NBIA-*FA2H26* | Dystonia, parkinsonism, ataxia27 | | Fatty Acid Hydroxylase-associated Neurodegeneration (FAHN) 27:  Iron accumulation: GP (more subtle than other NBIAs)  Additional clinical features: Spastic tetraparesis, cognitive decline, cerebellar and brainstem atrophy, dysarthria, dysphagia, optic nerve atrophy, seizures  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 612319 | | AR | | SPG35 |
| HSP-*PNPLA6/NT28* |  | | Complex; axonal peripheral neuropathy, spinal cord atrophy, learning disability, speech impairment, cerebellar signs, allelic with Boucher-Neuhäuser and Gordon Holmes syndromes.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK247161/  OMIM 612020 | | AR | | SPG39 |
| HSP/NBIA-*C19orf1229* | Dystonia, parkinsonism | | Mitochondrial membrane protein-associated neurodegeneration (MPAN) 30: Dystonia, parkinsonism  Iron accumulation: GP - hyperintense streaking of medial medullary lamina between GPi and GPe; SN  Additional clinical features: Progressive spastic paresis, dysarthria, dysphagia, cognitive decline/dementia, motor axonal neuropathy, optic nerve atrophy, psychiatric symptoms, bowel/bladder incontinenceGeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK185329/  OMIM 614298 | | AR | | NBIA4/SPG43 |
| HSP-*NT5C231* |  | | Complex; mental retardation, ocular signs  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 613162 | | AR | | SPG45 |
| HSP-*GBA232* |  | | Complex; mental impairment, cataract, hypogonadism in males, TCC and cerebellar atrophy on brain imaging.32  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 614409 | | AR | | SPG46 |
| HSP-*AP4B33* |  | | Complex; intellectual disability, seizures, TCC, white matter lesions.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 614066 | | AR | | SPG47 |
| HSP-*KIAA041534* |  | | Pure or complex; cervical cord hyperintensities.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 613647 | | AR | | SPG48 |
| HSP-*TECPR235* |  | | Complex; severe intellectual disability, fluctuating central hypoventilation, gastresophageal reflux disease, awake apnea, areflexia, dysmorphic features.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 615031 | | AR | | SPG49 |
| HSP-*APAM136* |  | | Complex; cerebral palsy, intellectual disability, reduction of cerebral white matter and atrophy of the cerebellum.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 612936 | | AR | | SPG50 |
| HSP-*AP4E137* |  | | Complex; cerebral palsy, intellectual disability and microcephaly.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 613744 | | AR | | SPG51 |
| HSP-*DDHD238* |  | | Complex; mental retardation, dysmorphism, short stature and dysgenesis of the corpus callosum.39  GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 615033 | | AR | | SPG54 |
| HSP-*C12orf6540* |  | | Complex; optic atrophy, peripheral neuropathy.  GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 615035 | | AR | | SPG55 |
| HSP-*KIF1C41*  Allelic with autosomal recessive spastic ataxia at the SAX2 locus. | Dystonia, ataxia41 | | Pure and complicated, chorea, myoclonus, dysarthria, developmental delay, mild mental retardation, hypodontia, ptosis, short stature, sensorineural deafness, pes planus, white matter lesions.  GeneReviews: http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 611302 | | AR | | SPG58 |
| HSP-*ERLIN131* |  | | Pure and complex; thoracic kyphosis, borderline intelligence.  GeneReviews: n/a  OMIM 611604 | | AR | | SPG62 |
| HSP-*NT5C231* |  | | Complex; learning disability, optic atrophy, squint, glaucoma, congenital cataract, TCC, white matter lesions, cystic occipital leukomalacia.  GeneReviews: http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 613162 | | AR | | SPG65 |
| HSP-*ALSIN42* |  | | Complex, generalized dystonia, no speech  GeneReviews  OMIM | | AR | | Alsin |
| HSP-*SACSIN43* |  | | Spastic ataxia  GeneReviews  OMIM | | AR | | SACS |
| HSP- *ALDH3A244* |  | | RM, ichtyosis, macular dystrophy, leukoencephalopathy  GeneReviews  OMIM | | AR | | Sjögren-Larsson syndrome |
| HSP-*BICD245* |  | | SMA like  GeneReviews  OMIM | | AR | |  |
| HSP-MAG46  Allelic with Pelizaeus-Merzbacher disease. |  | | Complex; infantile-onset Pelizaeus-Merzbacher disease-like phenotype, mental retardation, dysarthria, optic atrophy, peripheral neuropathy, demyelinating leukodystrophy  GeneReviews  https://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM [616680](https://www.omim.org/entry/616680) | | AR | | SPG75 |
|  |  | |  | |  | |  |
| **X-linked recessive** | | | | | | | |
| HSP-*L1CAM47* |  | Complex; MASA-syndrome, hydrocephalus, TCC.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1182/  OMIM 312920 | | XR | | SPG1 | |
| HSP-*PLP148*  Allelic with Pelizaeus-Merzbacher disease. |  | Pure or complex; optic atrophy, ataxia, nystagmus, peripheral neuropathy, aphasia, mental retardation.  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1182/  OMIM 312920 | | XR | | SPG2 | |
| HSP-*SLC16A249* |  | Complex; Allan-Herndon-Dudley syndrome  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM 300523 | | XR | | SPG22 | |
|  |  |  | |  | |  | |
| **Disorders that usually present with other phenotypes but can have predominant spastic paraparesis** | | | | | | | |
| SCA-*ATXN1* | HSP50 | Marked non-ataxia features; can have dominant choreapyramidal features, peripheral neuropathy, ophthalmoplegia  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1184/  OMIM 164400 | | AD | | SCA1 | |
| SCA-*ATXN3* | HSP, dystonia51, 41 | Marked non-ataxia features; can have predominant parkinsonism, dystonia, chorea, spasticity, neuropathy, lower motor neuron involvement  GeneReviews  http://www.ncbi.nlm.nih.gov/books/NBK1196/  OMIM 109150 | | AD | | SCA3 | |
| DYT\*\*-*TUBB4A52* | HSP53, 54 | Spasmodic dysphonia is most common dystonic presentation. Alternative, phenotype: Hypomyelinating leukodystrophy (see footnote)  GeneReviews n/a  OMIM: 128101 | | AD | | TUBB4A | |
| HSP/ATX-CAPN155, 56 |  | Hereditary spastic paraplegia: pure or complex; cerebellar dysarthria, cerebellar ataxia, foot deformity, ocular movement abnormalities, peripheral neuropathy, amyotrophy.  GeneReviews  https://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM: [616907](https://www.omim.org/entry/616907) | | AR | | SPG76 | |
| HSP/ATX-KCNA257, 58 |  | Hereditary spastic paraplegia: complex; learning disability, global developmental delay, autism spectrum disorder, sensory-motor peripheral neuropathy, seizures, ataxia.  Alternative phenotype: Epileptic encephalopathy, early infantile, 32  OMIM: [616366](https://www.omim.org/entry/616366)  GeneReviews  https://www.ncbi.nlm.nih.gov/books/NBK1509/  OMIM: not assigned | | AD | |  | |

TCC=thinning of the corpus callosum, SACS=Spastic Ataxia of Charlevoix-Saguenay, SMA=Spinal Muscular Atrophy

Silver syndrome: Complex HSP involving amyotrophy of the hand muscles

Kjellin syndrome: Complex HSP including thinning of the corpus callosum and central retinal degeneration

**\*** Note that some studies have suggested that some SPG7 mutations may have an autosomal dominant effect, particularly autosomal dominant optic atrophy.

\*\* Mutations in this gene more commonly cause a hypomyelinating leukodystrophy

with developmental delay, dystonia,choreoathetosis, rigidity, opisthotonus, andoculogyric crises, progressive spastic tetraplegia, ataxia, and, more rarely, seizures.

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