Updated complete list of hereditary spastic paraplegia

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| **Designation** | **Less common movement phenotype** | **Clinical clues** | **OMIM** | **MOI** |
| **Autosomal dominant forms** |
| HSP-*BSCL2*881 |  | Complex; Silver syndrome\*, these mutations may also cause distal hereditary neuropathy type 5 | 270685 | AD |
| HSP-*CPT1C882, 883* |  | Pure HSP, variable age at onset (infantile to adulthood), slowly progressive disease course | 616282 | AD |
| HSP-*HSPD1*884 |  | Pure or complex; dystonia | 605280 | AD |
| HSP-*WASHC5/KIAA0196*885 |  | Pure spastic paraplegia  | 603563 | AD |
| HSP-*KIF5A*140 |  | Pure or complex; allelic to Charcot Marie Tooth Neuropathy Type 2, Silver syndrome\*, mental retardation, parkinsonism, deafness, retinitis, dysautonomia, sensory spinal cord-like syndrome.  | 604187 | AD |
| HSP-*NIPA1*141 |  | Pure or complex; Peripheral neuropathy, spinal cord atrophy, spastic dysarthria, facial dystonia, atrophy of the small hand muscles, upper limb spasticity, epilepsy.  | 600363 | AD |
| HSP-*REEP1*703 | Ataxia704 | Pure or complex; distal motor neuronopathy, axonal Peripheral neuropathy, Silver-like syndrome\*, cerebellar ataxia, tremor, dementia.  | 610250 | AD |
| HSP-*RTN2*886 |  | Pure spastic paraplegia  | 604805 | AD |
| HSP-*SPAST*887 |  | Pure or complex; dementia, epilepsy, Peripheral neuropathy, tremor, ataxia, TCC, cerebellar atrophy  | 182601 | AD |
| HSP-*UBAP1888-892* |  | Typically pure; juvenile-onset, toe-walking, sometimes complicated by cerebellar signs or mild cognitive impairment, eventual association with parkinsonism and learning difficulties (needs to be confirmed) | 618418 | AD |
| ATX/HSP-*VAMP1*519 |  | Spastic ataxia, supranuclear upgaze limitation  | 108600 | AD |
| HSP-*ZFYVE27*893 |  | Pure spastic paraplegia  | 610244 | AD |
| **Autosomal Recessive forms** |
| HSP-*ACP33*697 |  | Pure or complex; Mast syndrome, Dementia, cerebellar involvement, dyskinesias, athetoid movements, TCC, white matter lesions | 248900 | AR |
| HSP- *ALDH3A2*894 |  | Sjogren-Larrson syndrome; spastic paraparesis, mental retardation, ichthyosis, macular dystrophy, and leukoencephalopathy | 270200 | AR |
| HSP-*ALSIN*895  |  | Complex; infantile-onset ascending spastic paralysis, generalized dystonia, no speech | 607225 | AR |
| HSP-*APAM1*896 |  | Complex; cerebral palsy, intellectual disability, reduction of cerebral white matter and atrophy of the cerebellum | 612936 | AR |
| HSP-*AP4B1*897 |  | Complex; intellectual disability, seizures, TCC, white matter lesions | 614066 | AR |
| HSP-*AP4E1*898 |  | Complex; cerebral palsy, intellectual disability and microcephaly | 613744 | AR |
| HSP-*AP4M1*896, 899  |  | Complex; neonatal hypotonia that progresses to hypertonia and spasticity, and severe mental retardation with poor or absent speech development | 612936 | AR |
| HSP-AP4S1900, 901  |  | Complex; neonatal hypotonia progressing to hypertonia and spasticity, cognitive and speech impairment, developmental delay, seizures, short stature, microcephaly, dysmorphic features, brain imaging abnormalities such as nonprogressive hydrocephalus | 614067 | AR |
| HSP-*B4GALNT*653 |  | Complex; progressive dysarthria, distal amyotrophy, non-progressive cognitive impairment, cerebellar signs, sensory polyneuropathy, pes cavus, stereotypies, emotional lability, psychiatric illness, seizures | 609195 | AR |
| HSP-*BICD2902* |  | SMA like phenotype |  | AR |
| HSP-*MTRFR*/*C12orf65*903 |  | Complex; optic atrophy, peripheral neuropathy | 615035 | AR |
| HSP-*C19orf12*-(NBIA)356 | Dystonia, parkinsonism | Mitochondrial membrane protein-associated neurodegeneration (MPAN)357: progressive spastic paresis, dystonia, parkinsonism, and variable additional clinical features including dysarthria, dysphagia, cognitive decline/dementia, motor axonal neuropathy, optic nerve atrophy, psychiatric symptoms, bowel/bladder incontinenceIron accumulation: GP - hyperintense streaking of medial medullary lamina between GPi and GPe; SN | 614298 | AR |
| HSP-*CYP2U1904, 905*  |  | Pure or complex; cognitive impairment, dystonia, cerebellar ataxia, visual impairment, subclinical axonal neuropathy, white matter lesions and thin corpus callosum on MRI | 615030 | AR |
| HSP-*CYP7B1*658 |  | Pure or complex; white matter lesions, optic atrophy, cerebellar ataxia, sensory ataxia | 270800 | AR |
| HSP-*DDHD1*905 |  | Pure and complex; cerebellar oculomotor disturbance, peripheral neuropathy | 609340 | AR |
| HSP-*DDHD2*698 |  | Complex; mental retardation, dysmorphism, short stature and dysgenesis of the corpus callosum906  | 615033 | AR |
| HSP-*DSTYK*907 |  | Complicated HSP with skin and hair dyspigmentation | 270750 | AR |
| HSP-*ENTPD1908, 909* |  | Complex; infancy or childhood onset with white matter change, intellectual impairment, dysarthria, and gait ataxia | 615683 | AR |
| HSP-*ERLIN1*284 |  | Pure and complex; thoracic kyphosis, borderline intelligence | 611604 | AR |
| HSP-*ERLIN2*910 |  | Complex; intellectual decline, speech involvement, seizures, congenital hip dislocation | 611225 | AR |
| HSP/ATX-*FA2H*-(NBIA)362 | Dystonia, parkinsonism, ataxia363  | Fatty Acid Hydroxylase-associated Neurodegeneration (FAHN)363: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  | 612319 | AR |
| HSP-*GBA2*911 |  | Complex; mental impairment, cataract, hypogonadism in males, TCC and cerebellar atrophy on brain imaging911 | 614409 | AR |
| HSP-*HPDL912, 913* |  | 1) Pure; mostly juvenile onset, sometimes myalgia or mild dysarthria 2) Severe neurodevelopmental disorder with progressive spasticity and brain white matter abnormalities (NEDSWMA; OMIM: 619026) | 619027 | AR |
| HSP-*AP5Z1*/*KIAA0415*699 |  | Pure or complex; cervical cord hyperintensities  | 613647 | AR |
| HSP-*KIAA1840*358 | Parkinsonism359 | Pure or complex; May cause Kjellin syndrome\*\*; TCC, mental retardation, sensory neuropathy, amyotrophy, dysarthria, nystagmus, ataxia, maculopathy, white matter lesions, occasional parkinsonism | 640360 | AR |
| HSP-*KIF1A*701 |  | Pure or complex; cerebellar signs, PNP, allelic to hereditary sensory and autonomic neuropathy | 610347 | AR |
| HSP-*MAGB, 914* |  | Complex; infantile-onset Pelizaeus-Merzbacher disease-like phenotype, mental retardation, dysarthria, optic atrophy, peripheral neuropathy, demyelinating leukodystrophy | 616680 | AR |
| HSP-*NT5C2*284 |  | Complex; learning disability, mental retardation, optic atrophy, squint, glaucoma, congenital cataract, TCC, white matter lesions, cystic occipital leukomalacia  | 613162 | AR |
| HSP-*PCYT2915, 916* |  | Complex; infancy-onset global developmental delay, motor impairment, and progressive spasticity of mainly lower limbs, severe gait impairment or inability to walk (never achieved or lost), additional features including impaired intellectual development with language difficulties, ocular anomalies, and seizures; frequently brain imaging abnormalities (cerebral and cerebellar atrophy and white matter hyperintensities) | 618770 | AR |
| HSP-*PNPLA6/NT*702 |  | Complex; axonal peripheral neuropathy, spinal cord atrophy, learning disability, speech impairment, cerebellar signs, allelic with Boucher-Neuhäuser and Gordon Holmes syndrome | 612020 | AR |
| HSP-*RNF170C, 142, 143* |  | Complex; predominantly lower limb spastic paraparesis with mild upper limb involvement, age at onset before 5 years, optic atrophy, variable features include cerebellar involvement, mild cervical dystonia, and axonal sensorimotor polyneuropathy |  | AR |
| HSP-*SACSIN*917 |  | Spastic ataxia |  | AR |
| HSP-SPART/*SPARTIN*918 |  | Complex; Troyer-syndrome. Early onset dysarthria, distal muscle wasting with contractures and cerebellar signs in some, delayed cognition and dysmorphism | 275900 | AR |
| HSP-*SPG7*683 |  | Pure or complex; optic atrophy, cerebellar atrophy, dysarthria, dysphagia, TCC, CPEO-like phenotype, mitochondrial abnormalities on muscle biopsy  | 607249 | AR or AD# |
| HSP-*TECPR2*919 |  | Complex; severe intellectual disability, fluctuating central hypoventilation, gastroesophageal reflux disease, awake apnea, areflexia, dysmorphic features | 615031 | AR |
| HSP-*TFG920, 921* |  | Complex; optic atrophy, axonal demyelinating sensorimotor neuropathy, facial atrophy, nystagmus, hyperelastic skin, cryptorchidism, hirsutism, kyphoscoliosis, pectus excavatum. | 615658 | AR |
| HSP-*ZFYVE26*360 | Parkinsonism359 | Complex; Kjellin syndrome\*\*; TCC, WMLs, mental retardation, dysarthria, pigmentary maculopathy, peripheral neuropathy, distal amyotrophy, occasional parkinsonism361  | 270700 | AR |
| **Autosomal dominant or recessive forms** |
| HSP-*ALDH18A1D, 922, 923* |  | Dominant form: Pure or complex HSP, 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 deficiencyRecessive form: Complex HSP, early-onset, delayed psychomotor development, cognitive impairment, variable additional features including dysmorphic facial features, tremor, and urinary incontinence | 601162 (AD), 616586 (AR) | AD or AR |
| HSP-*ATL1*138 |  | Pure or complex; Silver syndrome\*, allelic with hereditary sensory neuropathy type 1, cerebral palsy (infantile onset)  | 182600 | AD or AR |
| **X-linked**  |
| HSP-*L1CAM*924 |  | Complex; MASA-syndrome, hydrocephalus, TCC | 312920 | XLR |
| HSP-*PLP1E,* 692 |  | Pure or complex; optic atrophy, ataxia, nystagmus, peripheral neuropathy, aphasia, mental retardation  | 312920 | XLR |
| HSP-*SLC16A2*775, 925-928 | Dystonia | Complex; Allan-Herndon-Dudley syndrome (ADHS); abnormal thyroid function (elevated T3 and low T4 levels), severely intellectual impairment, delayed developmental milestones, dysmorphic facies, dysarthria, athetoid movements, muscle hypoplasia, and spastic paraplegia  | 300523 | XLR |
| **Combined phenotypes: where HSP coexists with another movement disorder as a prominent consistent feature** |
| HSP/ATX-*CAPN1654, 655* |  | Pure or complex; cerebellar ataxia, dysarthria, foot deformities, ocular movement abnormalities, peripheral neuropathy, amyotrophy | 616907 | AR |
| HSP/ATX-*KIF1CA,* 463, 464 | Dystonia, ataxia464 | Pure and complicated; chorea, myoclonus, dysarthria, developmental delay, mild mental retardation, hypodontia, ptosis, short stature, sensorineural deafness, pes planus, white matter lesions | 611302 | AR |
| HSP/ATX-*UCHL1662, 929, 930* |  | Complex; progressive visual loss and optic atrophy may be an early and prominent manifestation, variable additional features as peripheral neuropathy, cerebellar ataxia, cognitive impairment, axonal sensorimotor polyneuropathy, facial dysmorphism, microcephaly, fasciculations (tongue and limb muscles), and abnormal MRI findings including cerebellar and mild cerebral atrophy | 615491 | AR |
| ATX/HSP-*KCNA2F,517, 931* | myoclonus | Variable phenotypic spectrum including complex HSP, ataxia, intellectual and learning disability, developmental delay, dysarthria, sensory-motor peripheral neuropathy, abnormal EEG without clinical seizures |  | AD |
| ATX/HSP-*VPS13D651* | dystonia, myoclonus, chorea | Variable phenotypic spectrum ranging from adult-onset pure form of HSP to childhood-onset complicated form of HSP with additional cerebellar ataxia, dystonia, cataracts, and chorioretinal dystrophy |  | AR |
| **Disorders that usually present with other phenotypes but can have predominant spastic paraparesis** |
| ***Gene*** | **Associated disease** | **OMIM** | **Clinical phenotype** | **MOI** |
| ATX-*ATXN1*932 | Spinocerebellar ataxia | 164400 | Marked non-ataxia features; can have dominant choreapyramidal features, spasticity, peripheral neuropathy, ophthalmoplegia  | AD |
| ATX-*ATXN3460-462* | Spinocerebellar ataxia (Machado-Joseph Disease) | 109150 | Marked non-ataxia features; can have predominant parkinsonism, dystonia, chorea, spasticity, neuropathy, lower motor neuron involvement  | AD |
| DYT-*TUBB4AG,* 436 | Dystonia | 128101 | Spasmodic dysphonia is most common dystonic presentation, spasticity in a minority437, 438 | AD |

AD = autosomal dominant, AR = autosomal recessive, CPEO = chronic progressive external ophthalmoplegia, GP = Globus pallidus, GPe = External globus pallidus, GPi = Internal globus pallidus, HSP = Hereditary spastic paraplegia, MASA = mental retardation, aphasia, shuffling gait and adducted thumbs, MOI = mode of inheritance, OMIM = Online Mendelian Inheritance in Man (<https://www.omim.org/about>), SACS = Spastic Ataxia of Charlevoix-Saguenay, SMA = Spinal Muscular Atrophy, SN = Subthalamic nucleus, SPG = spastic paraplegia, TCC = thinning of the corpus callosum, WML = White matter lesions, XLR = x-linked recessive

A Allelic with autosomal recessive spastic ataxia at the SAX2 locus.

B Allelic with Pelizaeus-Merzbacher disease.

C Mutations in this gene can also cause autosomal-dominant sensory ataxia (OMIM 608984).

D Mutations in this gene can also cause autosomal dominant cutis laxa type 3 (OMIM 616603) and autosomal recessive cutis laxa type IIIA (OMIM 219150).

E Allelic with Pelizaeus-Merzbacher disease.

F Mutations in this gene can also cause developmental and epileptic encephalopathy 32 (DEE32, OMIM 616366).

G Mutations in this gene more commonly cause hypomyelinating leukodystrophy with developmental delay, dystonia, choreoathetosis, rigidity, opisthotonus, oculogyric crises, progressive spastic tetraplegia, ataxia, and, more rarely, seizures (OMIM: 612438).

\* 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.

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