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Recently identified or confirmed forms of hereditary spastic paraplegia

New designation	Less common movement phenotype	Clinical clues / Clinical phenotype and comment	OMIM	MOI
Autosomal dominant forms				
HSP-*CPT1C*[1, 2]		Pure HSP, variable age at onset (infantile to adulthood), slowly progressive disease course	616282	AD
HSP-*UBAP1*[3-7]		Typically pure HSP, 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
Autosomal recessive forms				
HSP-*ENTPD1*[8, 9]		Complex HSP, infancy or childhood onset with white matter change, intellectual impairment, dysarthria, and gait ataxia	615683	AR
HSP-*HPDL*[10, 11]		1) Pure HSP, 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-*MAG*[A, 12]		Complex HSP, infantile-onset Pelizaeus-Merzbacher disease-like phenotype, mental retardation, dysarthria, optic atrophy, peripheral neuropathy, demyelinating leukodystrophy	616680	AR
HSP-*PCYT2*[13, 14]		Complex HSP, 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-*RNF170*[B, 15, 16]		Complex HSP, 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
Autosomal dominant or recessive forms				
HSP-*ALDH18A1*[C, 17, 18]		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 deficiency Recessive 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
X-linked forms				

HSP-*SLC16A2*[19-22]	Dystonia	Complex HSP; 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	XL
Combined phenotypes: where HSP coexists with another movement disorder as a prominent consistent feature				
HSP/ATX-*CAPN1*[23, 24]		Pure or complex HSP, cerebellar ataxia, dysarthria, foot deformities, ocular movement abnormalities, peripheral neuropathy, amyotrophy	616907	AR
HSP/ATX-*UCHL1*[25-27]		Complex HSP, 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-*KCNA2*[D,28, 29]	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-*VPS13D*[30]	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

AD = autosomal dominant, AR = autosomal recessive, MOI = mode of inheritance, OMIM = Online Mendelian Inheritance in Man (https://www.omim.org/about), SPG = spastic paraplegia, XL = x-linked

[A] Allelic with Pelizaeus-Merzbacher disease.

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

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

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

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