Date of search: Aug 2020

Recently identified or confirmed forms of hereditary ataxias

Designation	Less common movement phenotype	Disease entity and clinical features	OMIM	MOI
Autosomal dominant forms				
ATX-*CACNA1G*[1, 2]	Spasticity	Ataxia with gait instability, variable age at onset, additional signs including dysarthria, nystagmus, and less commonly pyramidal signs and cognitive impairment; phenotype can also be much more severe with neurodevelopmental deficits and early-onset ataxia and (OMIM 618087)[3]	604065 (SCA42)	AD
ATX-*CCDC88C*[4, 5]	Tremor, parkinsonism	Adult-onset cerebellar ataxia with action tremor, parkinsonism, pyramidal signs and less frequently with impaired vertical gaze and cognitive impairment	616053 (SCA40)	AD
ATX-*DAB1*[6-8]		Adult-onset, slowly progressive, relatively pure cerebellar ataxia with gait instability, frequent falls, dysarthria, and ocular abnormalities	615945 (SCA37)	AD
ATX-*EBF3*[9-11]		Hypotonia, ataxia, and delayed development syndrome (HADDS); neurodevelopmental syndrome characterized by congenital hypotonia, delayed psychomotor development, variable intellectual disability with speech delay, variable dysmorphic facial features, and ataxia (often associated with cerebellar hypoplasia)	617330	AD
ATX-*ELOVL4*[12, 13]		Relatively pure ataxia, slowly progressive, usually young adult onset, less common additional signs including ocular abnormalities, pyramidal tract signs, or autonomic symptoms, one family with skin abnormalities (erythrokeratodermia)	133190 (SCA34)	AD
ATX-*KCNC3*[14]		Slowly progressive cerebellar ataxia with variable age at onset and variable additional features including cognitive impairment and developmental delay	605259 (SCA13)	AD
ATX-*LMNB1*[15, 16]		Autosomal dominant, adult-onset demyelinating leukodystrophy (ADLD); slowly progressive and fatal disorder characterized clinically by early autonomic abnormalities, pyramidal and cerebellar dysfunction, and symmetric demyelination of the central nervous system	169500	AD
ATX-*PUM1*[17, 18]	Chorea, spasticity	Variable phenotypic presentation ranging from adult-onset, slowly progressive cerebellar ataxia without additional signs to early-onset ataxia with variable additional signs including developmental delay, chorea, spasticity, seizures, and dysmorphic facial features	617931 (SCA47)	AD
ATX-*SAMD9L*[19, 20]		Ataxia-pancytopenia syndrome (ATXPC); cerebellar ataxia, variable hematologic	159550	AD

		cytopenias, and predisposition to bone marrow failure and myeloid leukemia		
ATX-*SNAP25b*[21-23]	Tremor	Early-onset fatigable muscle weakness with ataxia, developmental delay, intellectual disability, seizures, craniofacial dysmorphism and rarely resting and intention tremor	616330	AD
ATX-*TUBB2A*[A,24, 25]	Spasticity	Broad phenotypic spectrum including ataxia, spasticity, developmental delay, seizures, distal amyotrophy, and rarely optic atrophy		AD
Autosomal recessive forms				
ATX-*ABCA2*[26, 27]		Intellectual developmental disorder with poor growth and with or without seizures or ataxia (IDPOGSA): highly variable phenotype including developmental delay, intellectual disability, hypotonia, poor overall growth, intellectual disability, sometimes borderline microcephaly, and seizures. Cases have been reported with ataxia as the predominant manifestation	618808	AR
ATX-*ADPRHL2*[28, 29]	Tremor, dystonia	Stress-induced childhood-onset neurodegeneration with variable ataxia and seizures (CONDSIAS): highly variable phenotype including cyclic episodic deterioration in response to stress, developmental delay, intellectual disability, ataxia, muscle weakness, seizures, neuropathy, and rarely tremor, dystonia, strabismus, nystagmus, hearing loss, and microcephaly	618170	AR
ATX-*BRAT1*[B,30, 31]		Neurodevelopmental disorder with cerebellar atrophy and with or without seizures (NEDCAS); hypotonia, developmental delay, intellectual disability, oculomotor apraxia, saccadic smooth pursuit, gaze-evoked nystagmus. Cases have been reported with ataxia as the predominant manifestation	618056	AR
ATX-*CACNA2D2*[30, 32, 33]	Tremor, myoclonus, chorea	Cerebellar atrophy with seizures and variable developmental delay (CASVDD): ataxia with variable seizures and/or developmental delay (epileptic encephalopathy), tremor, and also myoclonus and choreic movements in some patients	618501	AR
ATX-*COA7*[34, 35]	Tremor	Ataxia, distal muscle weakness and atrophy, peripheral neuropathy, tremor, developmental delay, and intellectual disability	618387 (SCAN3)	AR
ATX-*COG5*[36, 37]		Congenital disorder of glycosylation, type IIi (CDG IIi): variable phenotype including developmental delay, intellectual disability, hypotonia, seizures, microcephaly, and hypotonia. Cases have been reported with ataxia as the predominant manifestation	613612	AR
ATX-*DOCK3*[38-40]		Neurodevelopmental disorder with impaired intellectual development, hypotonia, and ataxia	618292	AR
ATX-*ERCC4*[41-44]	Chorea, tremor	Xeroderma pigmentosum group, type F/Cockayne syndrome: skin photosensitivity, intellectual disability, short stature, microcephaly, and in some patients chorea and	278760	AR

		tremor. Cases have been reported with ataxia as the predominant manifestation		
ATX-*GDAP2*[45-47]	Spasticity, dystonia	Adult-onset cerebellar ataxia, dysarthria, and cognitive impairment, pyramidal signs and spasticity, cervical dystonia reported in one patient	618369 (SCAR27)	AR
ATX-*MTCL1*[*,48, 49]	Tremor, spasticity	Slowly progressive cerebellar ataxia, developmental delay, intellectual disability, seizures, nystagmus, slow saccadic eye movements, dysarthria, hyperreflexia, spasticity, and tremor	615766	AR
ATX-*NFASC*[50-52]	Tremor, myoclonus	Neurodevelopmental disorder with central and peripheral motor dysfunction (NEDCPMD): Highly variable severity and phenotypic spectrum including hypotonia, developmental delay, ataxia, pyramidal signs, and demyelinating peripheral neuropathy. Tremor and myoclonus were reported in some patients	618356	AR
ATX-*PIBF1*[53-55]		Joubert syndrome type 33: hypotonia, ataxia, and developmental delay. Additional features like retinal dystrophy, cystic kidney disease, liver fibrosis, and dysmorphism in a subset of patients. Spastic tetraparesis was reported in one patient	617767	AR
ATX-*PNK*[C,56-60]	Dystonia	Ataxia-oculomotor apraxia type 4 (AOA4): early-onset progressive ataxia, dystonia, oculomotor apraxia, peripheral neuropathy, and cognitive impairment	616267	AR
ATX-*RFC1*[61-65]		Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS): adult onset, slowly progressive. In addition to the 3 cardinal features (cerebellar impairment, bilateral vestibulopathy, and a somatic sensory deficit), patients may have autonomic dysfunction, chronic spasmodic dry cough, and action tremor. More rarely: bradykinesia, orofacial dyskinesia or dystonia and limb chorea	614575	AR
ATX-*TANGO2*[66-68]	Spasticity	Recurrent metabolic encephalomyopathic crises with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (MECRCN): developmental delay followed by acute encephalomyopathic features, including rhabdomyolysis, hypotonia, and neurologic regression; during disease course progressive neurodegeneration with seizures, intellectual disability, pyramidal, ataxia, loss of expressive language, as well as cardiac involvement with severe arrhythmias	616878	AR
ATX-*TBC1D23*[69-71]	Stereotypies	Pontocerebellar hypoplasia type 11 (PCH11): neurodevelopmental disorder with severe developmental delay, intellectual disability, ataxia, hypotonia, behavioral abnormalities, microcephaly, dysmorphic features, and recurrent respiratory infections. Stereotypies and spasticity were reported in some patients.	617695	AR

ATX-*TSEN54*[D,72, 73]		Ataxia, dysarthria, intellectual disability, peripheral neuropathy, and pyramidal signs	608755	AR
ATX-*XRCC1*[74, 75]		Ataxia with dysarthria, intellectual disability, slow and hypometric saccadic eye movements, nystagmus, oculomotor apraxia, and peripheral neuropathy	617633 (SCAR26)	AR
Dominant and/or recessive forms				
ATX-*MSTO1*[76-78]		Mitochondrial myopathy and ataxia (MMYAT); complex neurologic disorder with variable manifestation including early-onset global developmental delay, mitochondrial myopathy, ataxia and variable additional features like growth impairment, cognitive impairment, muscle weakness, elevated creatine kinase, and psychiatric comorbidities	617675	AR (AD)
ATX-*STUB1*[#,E, 79-86]	Parkinsonism, chorea, dystonia, tremor, myoclonus	Ataxia with cognitive-affective symptoms, such as depression, anxiety, or apathy, and variable additional features like parkinsonism, tremor, chorea, dystonia, myoclonus, dysarthria, and dysphagia	618093 (SCA48), 615768 (SCAR16)	AD and AR
Mitochondrial				
ATX-*MT-ATP6*[87-90]	Myoclonus	MT-ATP6-mitochondrial disease: neuropathy, ataxia, and retinitis pigmentosa (NARP); Leigh syndrome; mitochondrial encephalomyopathy; variable phenotype including ataxia, cognitive dysfunction, neuropathy, seizures, and retinopathy	551500	mt
X-linked				
ATX-*AIFM1*[91-94]		Ataxia, peripheral neuropathy, hearing loss, pyramidal signs, behavioral disorder, and intellectual disability		XL
Combined phenotypes: where ataxia coexists with another movement disorder as a prominent consistent feature				
ATX/HSP-*KCNA2*[95-98]	Tremor, myoclonus, dystonia, chorea	Developmental and epileptic encephalopathy-32 (DEE32): variable phenotypic spectrum including (myoclonic) seizures, (episodic) ataxia, HSP, action tremor, myoclonus, dystonia, chorea, dysarthria, developmental delay, and intellectual disability	616366	AD
ATX/HSP-*VPS13D*[99-102]	Dystonia, myoclonus, chorea, tremor	Variable phenotype including ataxia, HSP, other pyramidal signs, dystonia, myoclonus, chorea, tremor, dysarthria, oculomotor abnormalities, distal sensory impairment, hypotonia, sometimes global developmental delay or mild intellectual disability	607317 (SCAR4)	AR
HSP/ATX-*CAPN1*[103, 104]		Pure or complex HSP, cerebellar ataxia, dysarthria, foot deformities, ocular movement abnormalities, peripheral neuropathy, amyotrophy	616907	AR
ATX/MYC-*NUS1*[F,105-107]	Tremor, parkinsonism, dystonia[108, 109]	Mental retardation 55 with seizures (MRD55); broad phenotypic spectrum including developmental delay, intellectual disability, ataxia, myoclonus, (myoclonic) seizures, resting and intention tremor, and rarely parkinsonism	617831	AD
ATX/DYT-*SQSTM1*[110-113]	Chorea	Neurodegeneration with ataxia, dystonia, and gaze palsy (NADGP): ataxia, dystonia, chorea,	617145	AR

		gaze palsy, cognitive decline, nystagmus, pyramidal signs, dysarthria and hypergonadotropic hypogonadism		
Disorders that usually present with other phenotypes but can have (prominent) ataxia				
Gene	**Disease**	**Clinical phenotype**	**OMIM**	**MOI**
C9orf72	Frontotemporal dementia (FTD) and/or Amyotrophic Lateral Sclerosis (ALS)	Broad phenotypic spectrum including frontotemporal dementia and features of motor neuron disease, parkinsonism (mostly atypical, e.g., PSP-like, MSA or CBS), and dystonia, cerebellar signs, or chorea	105550	AD, repeat expansion
PSEN1[114-117]	Alzheimer's disease	Gene is linked to Alzheimer's disease; a few cases with prominent (spastic) ataxia have been described.	607822	AD

AD = autosomal dominant, AR = autosomal recessive, HSP = hereditary spastic paraplegia, MOI = mode of inheritance, mt = mitochondrial, OMIM = Online Mendelian Inheritance in Man (https://www.omim.org/about), SCA = autosomal dominant spinocerebellar ataxia, SCAN = spinocerebellar ataxia with axonal neuropathy, SCAR = autosomal recessive spinocerebellar ataxia, XL = x-linked

* Comment: Evidence is limited as only two patients in total were reported in two independent publications.

Comment: This gene is already included in the previous list of autosomal-recessive ataxias[118] (SCAR16, OMIM: 615768). It has now also been confirmed as a dominant ataxia gene.

A Gene mutations can also cause complex cortical dysplasia with other brain malformations 5 (OMIM: 615763)

B Gene mutations can also cause the lethal neonatal rigidity and multifocal seizure syndrome (OMIM: 614498)

C Gene mutations can also cause autosomal recessive microcephaly, seizures, and developmental delay (OMIM: 613402)

D Gene mutations can also cause pontocerebellar hypoplasia types 5 (OMIM: 610204), 2A (OMIM: 277470) and 4 (OMIM: 225753)

E Gene mutations can also cause the Gordon Holmes syndrome[119]

F Gene mutations can also cause congenital disorder of glycosylation, type 1AA (OMIM: 617082)

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