REVIEW

The Genetic Nomenclature of Recessive Cerebellar Ataxias

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ABSTRACT: The recessive cerebellar ataxias are a large group of degenerative and metabolic disorders, the diagnostic management of which is difficult because of the enormous clinical and genetic heterogeneity. Because of several limitations, the current classification systems provide insufficient guidance for clinicians and researchers. Here, we propose a new nomenclature for the genetically confirmed recessive cerebellar ataxias according to the principles and criteria laid down by the International Parkinson and Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders. We apply stringent criteria for considering an association between gene and phenotype to be established. The newly proposed list of recessively inherited cerebellar ataxias includes 62 disorders that were assigned an ATX prefix, followed by the gene name, because these typically present with ataxia as a predominant and/or consistent feature. An additional 30 disorders that often combine ataxia with a predominant or consistent other movement disorder received a double prefix (e.g., ATX/HSP). We also identified a group of 89 entities that usually present with complex nonataxia phenotypes, but may occasionally present with cerebellar ataxia. These are listed separately without the ATX prefix. This new, transparent and adaptable nomenclature of the recessive cerebellar ataxias will facilitate the clinical recognition of recessive ataxias, guide diagnostic testing in ataxia patients, and help in interpreting genetic findings.

Key Words: genetics; recessive ataxias; movement disorders; nomenclature

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The recessive cerebellar ataxias are a large group of clinically and genetically heterogeneous degenerative and metabolic disorders.[1] Although cerebellar ataxia is the shared clinical theme, the phenotype is often complex as other neurological features and sometimes systemic manifestations co-occur. The enormous heterogeneity complicates clinical management, particularly in the diagnostic phase. The currently used classification systems have several limitations and are therefore of limited use in terms of both providing guidance for clinicians in the diagnostic process and making understandable the field of recessive cerebellar ataxias as well as its boundaries. For example, the classification of autosomal recessive spinocerebellar ataxias's (SCAR) (for SCA-recessive) is far from complete, mainly consisting of relatively newer entities (the most common recessive ataxia, Friedreich ataxia, is not included) and also contains unconfirmed entities. Moreover, this SCAR classification is partly paralleled and duplicated, yet with different numbers, by another autosomal recessive cerebellar ataxia (ARCA) classification, the ARCA classification (for a recent criticism of these autosomal recessive ataxia nomenclatures, see the review by Synofzik and Schule[2]). These problems of existing incomplete, inconsistent, and partly parallel nomenclatures are not unique to recessive ataxias, as the classifications of other genetic movement disorders are similarly flawed.[3] For this reason, the International Parkinson and Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders was installed to take on the task of designing a uniform, adaptable, and phenotype-first nomenclature for genetic movement disorders. A certain genetic entity is included only after stringent, predefined criteria are met.[4] Although the review process and the classification procedure incorporate clinical data, the proposed nomenclature does not constitute a new clinical classification of the recessive ataxias. The first paper of this task force included the proposed nomenclature for genetic parkinsonism, dystonia, autosomal dominant cerebellar ataxia, hereditary spastic paraplegia, paroxysmal movement disorder, neurodegeneration with brain iron accumulation, and primary familial brain calcification.[4]

Here we present the proposed nomenclature for the recessive cerebellar ataxias, based on the same principles, criteria, and recommendations as provided by the task force.

Search Strategy

The search aimed to have a fully comprehensive list of all autosomal and X-linked recessive diseases that have been reported to present with ataxia. The Online Mendelian Inheritance in Man database was searched using the term "recessive ataxia." Each disease that was identified was then checked in PubMed, GeneReviews, OrphaNet, and the Washington University in St. Louis neuromuscular section webpage (http://neuromuscular.wustl.edu/ataxia/recatax.html). To ensure that no diseases were missed, the same search strategy without time restrictions was applied in PubMed using the terms "recessive ataxia" or "cerebellar ataxia" and updated to August 2017. Only publications written in English were reviewed. Additional publications were identified by using the respective gene name as keyword, for example, SYNE1. A complete list of publications reviewed can be found in the supplementary material.

Review Process

In total, 355 recessive, genetic entities were identified in which ataxia had been reported. A total of 48 disorders for which a causative gene had not been identified were excluded from further analysis. We applied the following criteria that lend support to causality according to the U.S. National Human Genome Research Institute: (1) the presence of the variant in multiple, unrelated affected individuals; (2) evidence for segregation or statistical association of the variant with disease; (3) the variant should be conserved across different species; and (4) the variant should be predicted to alter the normal biochemical effect of a gene product as supported by functional evidence in human tissue, well-established cellular or animal models, or other biochemical or histological abnormalities, if possible. The members of the recessive ataxias working group (MA, AD, MK, MS and BW) each reviewed a subset of entities assigned to them. The review process consisted of selecting those diseases in which cerebellar ataxia was associated with mutations in the gene of interest in at least 2 independent reports. The review process was focused on cerebellar ataxias and not on purely sensory ataxias or those disorders with mainly cerebellar hypoplasia as a cardinal feature without the clinical presence of cerebellar ataxia. Congenital ataxias, Joubert syndrome, and primary metabolic diseases, such as peroxisomal and lysosomal disorders, were included if cerebellar ataxia was documented at any disease stage.

During the early stages of the process, it was decided to use the ataxia (ATX) prefix for both dominantly and recessively inherited ataxias. The first paper that had proposed a classification for the dominant ataxias[4] used spinocerebellar ataxias (SCA) as the prefix. However, to be consistent with the classification of other movement disorders,[4] we propose the same prefix independent of the mode of inheritance, in particular, as several ataxias can be inherited in both a autosomal dominant or autosomal recessive fashion (eg, *SPTBN2, AFG3L2, ITPR1, OPA1*; for a review, see ref. 5). As

the term *SCA* is quite strongly associated with dominant ataxias, we decided to use the ATX prefix instead. In the International Parkinson and Movement Disorder Society Genetic Mutation Online Database[6] (MDSGene; available at http://www.mdsgene.org), which systematically links reported mutations to movement disorder phenotypes, the dominant ataxias will also carry the ATX prefix.

According to the recommendations of the International Parkinson and Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders,[4] the ATX prefix was assigned to those disorders that included ataxia as a prominent and/or consistent feature. When another movement disorder was also a prominent feature that generally coexisted with ataxia in several patients, a double prefix was assigned (e.g., ataxia (ATX)/Hereditary spastic paraplegia (HSP)). For those genes (eg, TPP1) that gave rise to allelic disorders (autosomal recessive spinocerebellar ataxia type 7 with pure ataxia and without myoclonus as well as neuronal ceroid lipofuscinosis type 2 with myoclonus and ataxia) that both present with prominent and consistent ataxia, a double prefix was established of which the order reflects the phenotype of the more prevalent or common presentation (in this case, ATX/MYC-TPP1). However, when another phenotype (eg, myoclonic epilepsy in POLG mutations) was the most common presentation or if ataxia was not usually predominant, the disease would appear in the proposed new list for the recessive ataxias, but would not receive the ATX prefix. To be considered for an ATX prefix, the association with ataxia must have been reported by more than one group of investigators. Last, a prefix was not assigned for complex or mixed phenotypes that usually showed a different predominant, nonmovement disorder clinical presentation (eg, mental retardation or epilepsy), as these probably would require a nonmovement disorder prefix that has not been established.

An initial draft list was prepared along with any doubts or queries, which were then reviewed by a working group member who had not initially reviewed the entity. At various stages of the process, all authors of this work held telephone conferences to discuss the criteria, discrepancies, and open issues. A cross-check with members of the chorea, myoclonus and hereditary spastic paraplegia working groups was done to ensure that the disorders that received the ATX prefix were referred to in a similar way with respect to the entities listed in the new nomenclature lists of the abovementioned disorders. Discrepancies were resolved by discussion until consensus was reached.

The Proposed New List for the Recessive Cerebellar Ataxias

The newly proposed list of recessively inherited cerebellar ataxias is shown in Table 1. This list includes 62 disorders that usually present with ataxia as a predominant and/or consistent feature, which were assigned the ATX prefix (group A, Table 1). It also lists 30 diseases that usually combine ataxia with other predominant and/or consistent movement disorders (eg, spastic paraparesis) and that received a mixed prefix (eg, ATX/HSP or HSP/ATX, depending on the phenotype that is consistent with the majority of cases; group B, Table 1). A group of 89 entities that usually present with other complex and/or nonataxia phenotypes but that may occasionally manifest cerebellar ataxia were not assigned an ATX prefix (group C, Table 1). Supplementary Table 1 lists the recessive diseases that appeared in our initial list following the abovementioned search strategy, but that upon review were classified as diseases with only occasional ataxia presentation, or diseases for which the presence of ataxia or the genetic finding itself remains unconfirmed. The posterior column ataxia with retinitis pigmentosa, a purely sensory ataxia as a result of mutations in the FLVCR1 gene, was excluded.

Discussion

Here we propose a new nomenclature of the genetically confirmed recessive cerebellar ataxias according to the principles and criteria of the International Parkinson and Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders.

We identified and listed almost 100 different, confirmed genetic entities that present with ataxia as a dominant or relevant phenotype. We also provided a list of a similar number of entities that more commonly have nonataxia presentations but that may present with ataxia. We believe that this resource is a useful guide for the selection and interpretation of genetic testing when confronted with a patient with ataxia. A unique feature of our work is separating out those entities for which the genetic association remains unconfirmed. An important limitation of the previous nomenclature was the potential for perpetuating spurious associations.[3] Requiring independent confirmation of associations before assigning prefixes should minimize such occurrences.

There have been earlier attempts to classify recessive cerebellar ataxias, a complex task because of the large clinical and genetic heterogeneity. Previous classifications have used phenotypic precision (ie, a list of the recessive ataxia genes per phenotypic category), for example, by separating Friedreich from non-Friedreich ataxias or by distinguishing those with from those without a peripheral neuropathy.[1,7] However, this system does not reflect the within-genotype heterogeneity and is also difficult to update as it might not be clear what the consistent phenotype is for a new ataxia

TABLE 1. The proposed new list for the recessive cerebellar ataxias[a]

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
		A. Disorders that present with ataxia as a predominant or consistent feature			
ATX-ABCB7[12]	Sideroblastic anemia with spinocerebellar ataxia	Intention tremor, pyramidal signs, hypochromic, microcytic anemia, abnormal pigmentation, skin atrophy	301310	XR	None
ATX-ABHD12[13]	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC)	Retinopathy, cataract, hearing loss, intention tremor, pyramidal signs, peripheral neuropathy, pes cavus	612674	AR	None
ATX-ADCK3[14,15]		Developmental delay, muscle weakness, pes cavus, exercise intolerance, myoclonus, dystonia, headache, stroke-like episodes, seizures	612016	AR	SCAR9, ARCA2
ATX-AHI1[16,17]		Developmental delay, morphological abnormalities, oculomotor apraxia, nystagmus, retinopathy, spasticity, scoliosis, seizures, renal failure, respiratory dysfunction	608629	AR	JBTS3
ATX-ALDH5A1[18]	Succinic semialdehyde dehydrogenase deficiency	Developmental delay, mental retardation, hyperkinesis, hyporeflexia, psychiatric symptoms, abnormal eye movements, seizures	271980	AR	None
ATX-ALG6[19]		Developmental delay, psychiatric symptoms, nystagmus, strabismus, peripheral neuropathy, muscle weakness, seizures, skeletal deformities, coagulation anomalies	603147	AR	None
ATX-ANO10[20]		Cognitive impairment, nystagmus, hypermetric saccades, tortuous conjunctival vessels, pyramidal signs, intention tremor, proximal lower limbs atrophy, fasciculations, seizures, pes cavus	613728	AR	SCAR10, ARCA3
ATX-APTX[21,22]		Hypometric saccades, oculomotor apraxia, nystagmus, ophthalmoplegia, peripheral neuropathy, scoliosis, pes cavus, choreoathetosis, tremor, dystonia, cognitive decline	208920	AR	AOA1
ATX-ARL13B[23]		Developmental delay, oculomotor apraxia, retinopathy, respiratory dysfunction	612291	AR	JBTS8
ATX-ATM[24]	Ataxia-telangiectasia (including variant ataxia-telangiectasia)	Telangiectases and other skin alterations, oculomotor apraxia, dystonia, chorea, myoclonus, tremor, peripheral neuropathy, distal muscular atrophy, short stature, hypogonadism, respiratory dysfunction, immunodeficiency, predisposition to neoplasia, glucose intolerance	208900	AR	None
ATX-BCKDHB[25]	Maple syrup urine disease	Maple syrup urine odor, life-threatening metabolic decompensation, lethargy, coma, hypoglycemia, ketosis, lactic acidosis, hallucinations, seizures,mental retardation if untreated, vomiting, pancreatitis	248600	AR	None
ATX-BTD4[26]	Biotinidase deficiency	Developmental delay, optic atrophy, vision and hearing loss, seizures, metabolic ketoacidosis, organic aciduria, skin problems, alopecia, hepatosplenomegaly, breathing problems	253260	AR	None
ATX-C10orf2[27]	Hepatocerebral type of Mitochondrial DNA depletion syndrome	Psychomotor retardation, psychiatric symptoms, ophthalmoplegia, nystagmus, optic atrophy, hearing loss, peripheral neuropathy, myopathy, status epilepticus, epileptic encephalopathy, headaches, liver disease, hypergonadotrophic hypogonadism	271245	AR	None
ATX-CA84[28]	Cerebellar ataxia and mental retardation with or without quadrupedal locomotion type 3	Mental retardation, dysarthria, quadrupedal gait, tremor	613227	AR	None
ATX-CEP290[29,30]		Mental retardation, congenital amaurosis, oculomotor apraxia, retinopathy, retinal coloboma, nystagmus, nephronophthisis, neonatal breathing dysregulation	610188	AR	JBTS5
ATX-COX20[31]	Mitochondrial complex IV deficiency or cytochrome c oxidase deficiency	Developmental delay, mental retardation, pyramidal signs, peripheral neuropathy, dystonia, lactic acidosis retinopathy, optic atrophy, respiratory insufficiency	220110	AR/Mi	None
ATX-CWF19L1[32]		Developmental delay, intellectual disability, tremor, hyperreflexia in lower limbs	616127	AR	SCAR17
ATX-CYP27A1[33]	Cerebrotendinous xanthomatosis (CTX)	Tuberous skin and tendon xantomas, xanthelasmas, cataracts, chronic diarrhea, cognitive decline, psychiatric symptoms, peripheral neuropathy, parkinsonism, dystonia, myoclonus, spastic paraplegia, pseudobulbar palsy, seizures	213700	AR	None

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
ATX-DNAJC194[34]	3-methylglutaconic aciduria, type V	Developmental delay, mental retardation, growth retardation, optic atrophy, muscle weakness, dilated cardiomyopathy, long Q-T syndrome, genitourinary deformities	610198	AR	None
ATX-FXN[35,36]	Friedreich ataxia (FRDA)	Nystagmus, square wave jerks, optic atrophy, hearing loss, peripheral sensory neuropathy, pes cavus, hammertoes, muscle weakness, amyotrophy, extensor plantar responses, spasticity, spastic ataxia, chorea, scoliosis, hypertrophic cardiomyopathy, diabetes	229300	AR	None
ATX-GRID2[37]		Developmental delay, cognitive impairment, esotropia, nystagmus, oculomotor apraxia, tonic upgaze, pale optic discs, retinopathy, pyramidal signs, muscle atrophy, joint contractures, scoliosis	616204	AR	SCAR18
ATX-GRN[38]		Dementia, myoclonic retinopathy, optic atrophy, seizures	614706	AR	CLN11
ATX-ITPR1[39]	Gillespie syndrome	Developmental delay, mental retardation, aniridia or iris hypoplasia, scalloped pupillary margins of iris, nystagmus, visual impairments, postural tremor	206700	AR	None
ATX-KCNJ10[40]	Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SESAME syndrome)	Developmental delay, mental retardation, sensorineural deafness, intention tremor, peripheral neuropathy, seizures,short stature, salt craving, enuresis, polydipsia, polyuria, electrolyte imbalance	612780	AR	None
ATX-KIAA0226[41]	Salih ataxia	Developmental delay, mental retardation, nystagmus, abnormal saccadic eye movements, seizures	615705	AR	SCAR15
ATX-L2HGDH[42]	L-2-hydroxyglutaric aciduria or academia	Psychomotor regression, mental retardation, cognitive impairment, hearing loss, strabismus, optic atrophy, nystagmus, spastic tetraparesis, facial dyskinesia, rigidity, dystonia, intention tremor, action-induced negative myoclonus, pyramidal signs, seizures, macrocephaly	236792	AR	None
ATX-MAN2B1[43]	Alpha-mannosidosis	Developmental delay, mental retardation, growth retardation, sensorineural deafness, nystagmus, pyramidal signs, macrocephaly, facial dysmorphism, skeletal deformities, hepatosplenomegaly	248500	AR	None
ATX-MRE11A[44]	Ataxia-telangiectasia-like disorder type 1	Hypometric saccades, oculomotor apraxia, nystagmus, chorea, dystonia, myoclonus, tremor, hyporeflexia, distal muscle atrophy	604391	AR	None
ATX-MSTO1[45]		Myopathy, developmental delay, growth impairment, pigmentary retinopathy with papillary pallor, tremor, skeletal abnormalities, pes cavus, dysmoprhism	617619	AR	None
ATX-NPC1[46]	Niemann-Pick disease type C1	Developmental regression, cognitive impairment, psychiatric symptoms, loss of speech, vertical supranuclear gaze palsy, dystonia, intention tremor, spasticity, seizures, hepatosplenomegaly, cholestatic jaundice, gelastic cataplexy	257220	AR	None
ATX-NPC2[47]	Niemann-Pick disease type C2	Similar than ATX-NPC1 with severe pulmonary involvement and respiratory failure	607625	AR	None
ATX-OFD1[48]		Developmental delay, mental retardation, recurrent infections, hirsutism, postaxial polydactyly, cystic renal disease, facial dysmorphism, macrocephaly	300804	XR	JBTS10
ATX-OPHN1[49]	X-linked mental retardation with cerebellar hypoplasia and distinctive facial appearance	Developmental delay, mental retardation, spasticity, psychiatric symptoms, seizures, macrocephaly, facial dysmorphism, microphaly, hypoplastic scrotum, cryptorchidism, strabismus	300486	XR	None
ATX-OTC[50] (Heterozygous females)	Ornithine transcarbamylase deficiency	Episodic extreme irritability, episodic vomiting and lethargy, protein avoidance, coma, delayed growth, developmental delay, seizures	311250	XR	None
ATX-PEX7[51]	Peroxisome biogenesis disorder 9B or Zellweger spectrum disorder	Developmental delay, cognitive impairment, cataracts, retinopathy, anosmia, hearing loss, muscle weakness, pes cavus, peripheral neuropathy	614879	AR	None
ATX-PEX10[52]	Peroxisome biogenesis disorder 6B or Zellweger spectrum disorder	Mental retardation, intention tremor, peripheral neuropathy, pyramidal signs, distal muscle atrophy, pes cavus, dysmetric saccades, impaired smooth pursuit, nystagmus, diabetes	614871	AR	None

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
ATX-PHYH[53]	Refsum disease or or hereditary motor and sensory neuropathy type IV	Muscle weakness and atrophy, peripheral neuropathy, sensory impairment, pes cavus, anosmia, sensorineural deafness, retinopathy, ichthyosis, shortening of the metacarpals and metatarsals, multiple epiphyseal dysplasia, cardiomyopathy, sudden death	266500	AR	None
ATX-PMM2[54]	Congenital disorder of glycosylation type Ia (CDGIa) or Jaeken syndrome	Developmental delay, psychomotor retardation, cognitive impairment, strabismus, nystagmus, retinopathy, peripheral neuropathy, stroke-like episodes, seizures, microcephaly, morphological abnormalities, abnormal subcutaneous fat tissue distribution, pericardial effusion, hepatomegaly, liver steatosis, diarrhea, renal cysts, nephrotic syndrome, thrombotic events, hypothyroidism, hypergonadotropic hypogonadism, scoliosis, osteoporosis	212065	AR	None
ATX-PMPCA[55]		Developmental delay, mental retardation, visuospatial defects, nystagmus, dysmetric saccades, pes cavus, hyperreflexia, spasticity, tremor, short stature	213200	AR	SCAR2
ATX-POLR3B[56]	Hypomyelinating leukodystrophy type 8 with or without oligodontia and/or hypogonadotropic hypogonadism	Developmental delay, cognitive decline, mental retardation, nystagmus, abnormal saccades, vertical gaze palsy, myopia, spasticity, tremor, oligodontia, hypodontia, delayed dentition, short stature, hypogonadism	614381	AR	None
ATX-PRKCG[57]		Peripheral neuropathy, pyramidal signs, cognitive impairment, depression, myoclonus, tremor	605361	AR	None
ATX-PTRH2[58]	Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD)	Developmental delay, failure to thrive, poor postnatal growth, poor expressive speech, peripheral neuropathy, distal muscle weakness, foot and hand deformities, hypothyroidism, pancreatic endocrine insufficiency, facial dysmorphism, brachycephaly, short stature	616263	AR	None
ATX-RNF168[59]	RIDDLE syndrome	Learning difficulties, immunodeficiency, dry skin, progressive pulmonary fibrosis and failure, ocular telangiectasia, short stature, microcephaly, dysmorphic features	611943	AR	None
ATX-RNF216[60]	Gordon Holmes syndrome	Mental retardation, dementia, psychiatric symptoms, chorea, sensorineural deafness, hypogonadism	212840	AR	None
ATX-SETX[61]		Saccadic pursuit, oculomotor apraxia, nystagmus, strabismus, intention tremor, head tremor, dystonia, chorea, pyramidal signs, peripheral neuropathy, distal muscle atrophy and weakness, pes cavus, scoliosis	606002	AR	SCAR1, AOA2
ATX-SIL1[62]	Marinesco-Sjögren syndrome	Developmental delay or regression, mental retardation, growth retardation, microcephaly, facial dysmorphism, short stature, congenital cataracts, nystagmus, strabismus, spasticity, muscle weakness and atrophy, peripheral neuropathy, scoliosis, skeletal deformities, hypogonadism	248800	AR	None
ATX-SLC17A5[63]	Salla disease or Finnish type sialuria and the variant syndrome of infantile form of sialic acid storage disorder	Developmental delay, mental retardation, rigidity, spasticity, seizures, visceromegaly, facial dysmorphism, hypopigmented skin	604369 and 269920	AR	None
ATX-SLC33A1[64]	Congenital cataracts, hearing loss, and neurodegeneration (CCHLND)	Psychomotor retardation, nystagmus, congenital cataracts, hearing loss, seizures	614482	AR	None
ATX-SLC52A2[65,66] (allelic with Brown-Vialetto-Van Laere syndrome type 2)		Optic atrophy, blindness, cochlear degeneration, deafness	271250	AR	SCAR3
ATX-SNX14[67]		Developmental delay, mental retardation, autistic behavior, macrocephaly, sensorineural hearing loss, nystagmus, apraxia, spasticity, extensor plantar responses, hyporeflexia, seizures, hypertrichosis, scoliosis, distal skeletal deformities, brachycamptodactyly, facial dysmorphism	616354	AR	SCAR20
ATX-SPTBN2[68]		Developmental delay, cognitive impairment, speech delay, intention tremor, spasticity, hyperreflexia, hypometric saccades, nystagmus, abnormal eye movements with convergent squint	615386	AR	SCAR14

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
ATX-SRD5A3[69]	Congenital disorder of glycosylation, type Iq	Developmental delay, mental retardation, coloboma, nystagmus, facial dysmorphism, hypertrichosis, skin abnormalities, coagulation defects, microcytic anemia	612379	AR	None
ATX-STUB1[70]		Nystagmus, external ophthalmoplegia, pyramidal signs, tremor, myoclonus, cognitive impairment, peripheral neuropathy, reduced vibration sense in lower limbs, hypogonadism	615768	AR	SCAR16
ATX-SYNE1[71]		Nystagmus, abnormal saccades and slow or jerky pursuit, hyperreflexia in lower limbs, motor neuron involvement, respiratory dysfunction due to multisystemic neuromuscular compromise, mental retardation	610743	AR	SCAR8, ARCA1
ATX-TTPA[72]	Ataxia with vitamin E deficiency	Nystagmus, retinopathy, propioception loss, areflexia in lower limbs, peripheral neuropathy, extensor plantar response, head titubation or tremor, dystonia, hypoacusia, tendon xanthomas, pes cavus, hammer toes, kyphoscoliosis	277460	AR	None
ATX-TMEM216[73]		Developmental delay, failure to thrive, mental retardation, impaired saccades, oculomotor apraxia, nystagmus, optic nerve coloboma, chorioretinal coloboma, retinopathy, esotropia, polydactyly, nephronophthisis, renal cysts, hypoplastic genitalia, episodic hyperpnea or apnea, facial dysmorphism, macrocephaly	608091	AR	JBTS2
ATX-TMEM67[74,75], ATX-RPGRIP1L[76-78] ATX-CC2D2A[79]	COACH syndrome (cerebellar vermis hypo/aplasia, oligophrenia, ataxia, ocular coloboma, and hepatic fibrosis) and allelic disorders	Developmental delay, mental retardation, oculomotor apraxia, ocular coloboma, retinopathy, nystagmus, facial dysmorphism, polydactyly, pyramidal signs, seizures, splenomegaly, renal failure, liver disease, breathing dysregulation	216360, 611560, 610688	AR	JBTS6, JBTS7
ATX-TMEM231[80]		Developmental delay, oculomotor apraxia, psychiatric symptoms, polydactyly, syndactyly, renal cysts, retinopathy	614970	AR	JBTS20
ATX-TTC19[81]	Mitochondrial complex III deficiency nuclear type 2	Developmental delay, cognitive impairment, apraxia, psychiatric symptoms, dysphonia, nystagmus, bradykinesia, dystonia, muscle atrophy and weakness, pyramidal signs	615157	AR	None
ATX-VLDLR[82]	Cerebellar ataxia, mental retardation, and dysequilibrium syndrome type 1	Developmental delay, mental retardation, lack of speech development, strabismus, postnatal cataracts, nystagmus, saccadic visual pursuit, quadrupedal gait, intention tremor, hyperreflexia, seizures, pes planus, short stature	224050	AR	None
ATX-WDR73[83]	Galloway-Mowat syndrome	Delayed psychomotor development, mental retardation, oculomotor apraxia, optic atrophy, retinopathy, seizures, spastic quadriplegia, dystonia, hyperreflexia, skin abnormalities (osmiophilic skin vessels), skeletal deformities, genitourinary affectation, facial dysmorphias, microcephaly, short stature, intrauterine growth retardation	251300	AR	SCAR5
ATX-WDR81[84]	Cerebellar ataxia, mental retardation, and dysequilibrium syndrome type 2	Developmental delay, mental retardation, strabismus, facial dysmorphism, quadrupedal locomotion, poor or absence language development, tremor, hyporeflexia, hirsutism, small hands and feet, thoracic kyphosis, short stature	610185	AR	None
	B. Combined ataxias (disorders where ataxia frequently coexists with other predominant or consistent movement disorders)				
ATX/HSP-AFG3L2[85]		Spastic paraparesis, oculomotor apraxia, dystonia, myoclonus, myoclonic epilepsy, generalized tonic-clonic seizures, distal muscle atrophy, peripheral neuropathy	614487	AR	SPAX5
ATX/HSP-DARS2[86]	Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation	Spastic paraparesis, developmental delay, cognitive decline, nystagmus, tremor, peripheral neuropathy, sensation deficits, muscle weakness and atrophy, joint contractures	611105	AR	None
ATX/HSP-FOLR1[87]	Neurodegeneration as a result of cerebral folate transport deficiency	Spastic paraparesis, developmental regression, mental retardation, visual disturbances, sensorineural hearing loss, chorea, generalized tonic-clonic, atonic and myoclonic seizures	613068	AR	None

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
ATX/HSP-GJC2[88]	Hypomyelinating leukodystrophy-2 or Pelizaeus-Merzbacher-like disease	Spastic paraparesis, developmental delay, mental retardation, lack of independent ambulation, poor head and trunk control in infancy, optic atrophy, rotary nystagmus, myopia, facial weakness, tremor, head titubation, dystonia, spasticity, seizures, peripheral neuropathy	608804	AR	None
ATX/HSP-HEXA[89]	Tay-Sachs disease or GM2-gangliosidosis type I	Spastic paraparesis, cognitive decline, psychiatric symptoms, late spasticity, dystonia, peripheral neuropathy, macular pallor with prominence of fovea centralis (cherry red spot), blindness, muscular weakness and atrophy, seizures	272800	AR	None
ATX/HSP-HEXB[90]	Sandhoff disease or GM2-Gangliosidosis type II	Spastic paraparesis, progressive mental and motor deterioration, macrocephaly, macular pallor with prominence of fovea centralis (cherry red spot), blindness, dysmorphic features, startle reaction, hyperreflexia, muscular atrophy, fasciculations, cardiomegaly, episodic abdominal pain, chronic diarrhea, hepatosplenomegaly, macroglossia, high lumbar gibbus	268800	AR	None
ATX/HSP-PNPLA6[91-95]	PNPLA6-related disorders: Boucher-Neuhauser syndrome, Laurence-Moon syndrome and Oliver-McFarlane syndrome	Visual impairment due to chorioretinal dystrophy, nystagmus, distal muscle atrophy, intention tremor, spastic paraparesis, cognitive impairment, peripheral neuropathy, hypogonadism, trichomegaly, short stature	215470, 215470, 245800, 275400, 612020	AR	SPG39
ATX/HSP-POLR3A[96]	Hypomyelinating leukodystrophy type 7 with or without oligodontia and/or hypogonadotropic hypogonadism or 4H syndrome	Spastic paraparesis, developmental delay, cognitive decline, mental retardation, optic atrophy, nystagmus, abnormal saccades, vertical gaze palsy, pyramidal signs, postural tremor, dystonia, seizures, peripheral neuropathy, oligodontia, hypodontia, delayed dentition, hypogonadotropic hypogonadism, short stature	607694	AR	None
ATX/HSP-SACS[97]	Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) or autosomal recessive spastic ataxia type 6	Spastic paraparesis, delayed walking development, retinal striation, nystagmus, impaired smooth pursuit, pes cavus, hammertoes, finger deformities, hyperreflexia, ankle areflexia, spasticity, extensor plantar responses, scoliosis, distal muscle weakness and atrophy, peripheral neuropathy, dystonia, erectile dysfunction	270550	AR	SPAX6
HSP/ATX-B4GALNT1[98]		Spastic paraparesis, distal amyotrophy, nonprogressive cognitive impairment, sensory polyneuropathy, pes cavus, stereotypies, emotional lability, psychiatric symptoms, seizures	609195	AR	SPG26
HSP/ATX-CAPN1[99]		Spasticity in lower and upper limbs, other pyramidal signs, peripheral neuropathy, pes cavus, pes valgus, nystagmus	616907	AR	SPG76
HSP/ATX-CLCN2[100]	Leukoencephalopathy with ataxia	Spastic paraparesis, learning disabilities, headache, optic neuropathy, chorioretinopathy, visual field defects	615651	AR	None
HSP/ATX-CYP7B1[101]		Spastic paraparesis, other pyramidal signs besides spasticity, cognitive impairment, nystagmus, optic atrophy, cataracts, altered saccadic eye movements, pes cavus, sensation deficits	270800	AR	SPG5A
HSP/ATX-GAN[102]		Spastic paraparesis, distal limb muscle weakness and atrophy as a result of peripheral neuropathy, distal sensory impairment, kinky or curly hair, foot or hand deformities, scoliosis, nystagmus, facial weakness	256850	AR	None
HSP/ATX-GBA2[103]		Spastic paraparesis, other pyramidal signs, muscle weakness, pseudobulbar dysarthria, cognitive impairment, mental retardation, congenital cataracts, nystagmus, hearing loss, head tremor, peripheral neuropathy, pes cavus, scoliosis, infertility, small testicles, hypogonadism in males	614409	AR	SPG46
HSP/ATX-KIF1C[104,105]		Spastic paraparesis, chorea, myoclonus, dystonia, developmental delay, mild mental retardation, hypodontia, ptosis, short stature, sensorineural deafness, pes planus	611302	AR	SPAX2, SPG58
HSP/ATX-MLC1[106]	Megalencephalic leukoencephalopathy with subcortical cysts	Spastic paraparesis, developmental delay, mental retardation, seizures, macrocephaly, spasticity	604004	AR	None

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
HSP/ATX-PLP1[107]		Spastic paraparesis, lower limb weakness, other pyramidal signs, mental retardation, upper limb spasticity, pes cavus, joint contractures, nystagmus, optic atrophy, tremor	312920	XR	None
HSP/ATX-SPG7[108]		Spastic paraparesis, optic atrophy, chronic external ophthalmoplegia-like phenotype, nystagmus, decreased vibratory sense in the lower limbs, pes cavus, scoliosis	607259	AR/AD	SPG7
HSP/ATX-UCHL1[109]	Childhood-onset neurodegeneration with optic atrophy	Spastic paraparesis, other pyramidal signs, myotonia, myokymia, head titubation, intellectual impairment, impaired distal sensation to vibration and position, optic atrophy, nystagmus	615491	AR	None
HSP/ATX/NBIA-FA2H[110]	Fatty acid hydroxylase-associated neurodegeneration (FAHN)	Spastic paraparesis, cognitive decline, optic nerve atrophy, seizures, dystonia, parkinsonism	612319	AR	SPG35
ATX/MYC-TPP1[111,112] (allelic disorders: Neuronal ceroid lipofuscinosis type 2 and autosomal recessive spinocerebellar ataxia type 7)		Myoclonus, developmental regression, speech and language difficulties, nystagmus, diplopia, hypermetric saccades, progressive vision loss, retinopathy, postural tremor, pyramidal signs, spastic paraparesis, decreased vibration sense, fasciculations, seizures	609270, 204500	AR	SCAR7, CLN2
MYC/ATX-CSTB[113]	Myoclonic epilepsy of Unverricht and Lundborg	Myoclonic epilepsy, stimulus sensitive segmental or generalized myoclonus, action myoclonus, generalized tonic-clonic or absence seizures, mental and motor deterioration	254800	AR	None
MYC/ATX-EPM2A[114]	Lafora disease	Myoclonic or other types of seizures, focal visual seizures, drop attacks cognitive decline, psychosis, myoclonus	607566	AR	None
MYC/ATX-GOSR2[115]		Myoclonic, absence and tonic-clonic seizures, drop attacks, action myoclonus, tremor, areflexia, scoliosis, pes cavus, syndactyly	614018	AR	None
MYC/ATX-KCTD7[116]	Progressive myoclonic epilepsy type 3 with or without intracellular inclusions	Myoclonic epilepsy, secondary generalization seizures, neurologic regression following seizure onset, mental retardation, hyperreflexia, opsoclonus, optic atrophy, visual loss, microcephaly	611726	AR	None
MYC/ATX-NEU1[117]	Neuraminidase deficiency or sialidosis type I and II	Myoclonus, mental retardation, seizures, hyperreflexia, muscle atrophy, skeletal malformations, hepatosplenomegaly, cardiomyopathy, progressive vision loss, cherry-red spots, cataracts, nystagmus, sensorineural hearing loss, short stature, dysmorphic features	256550	AR	None
MYC/ATX-NHLRC1[118]	Lafora disease	Myoclonic or other types of seizures, focal visual seizures, drop attacks cognitive decline, psychosis, myoclonus	608072	AR	None
DYT/ATX-ATP7B[119]	Wilson disease	Dystonia, occasionally parkinsonism, chorea, flapping tremor, rest, action, and intention tremor, orofacial dyskinesias, liver disease, Kayser Fleischer rings, psychiatric symptoms	277900	AR	None
PxMD-DYT-ATX-PRRT2[120] (Biallelic mutations)		Paroxysmal non-kinesigenic dyskinesia, prolonged episodes of ataxia, motor tics, seizures, hemiplegic migraine, learning difficulties, psychiatric symptoms	614386	AR	None
		C. Disorders that usually present with other phenotypes but can have occasionally ataxia (no ATX prefix)			
HSP-ACP33[121]		Spastic paraparesis, other pyramidal signs, apraxia, bulbar dysfunction, developmental delay, cognitive impairment, akinetic mutism, dykinesias, peripheral neuropathy	248900	AR	SPG21
HSP-DDHD2[122]		Spastic paraparesis, other pyramidal signs, developmental delay, mental retardation, lower limbs weakness, strabismus, facial dysmorphism, short stature, optic nerve hypoplasia	615033	AR	SPG54
HSP-KIAA0415[123]		Spastic paraparesis, lower limb weakness, dystonia, myoclonus, parkinsonism, peripheral neuropathy	613647	AR	SPG48
HSP- KIAA1840[124]		Spastic paraparesis, lower limb atrophy, weakness, peripheral neuropathy, pes cavus, parkinsonism, cognitive impairment, mental retardation, retinopathy, pigmented macular degeneration, nystagmus	604360	AR	SPG11

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
HSP-KIF1A[125]		Spastic paraparesis, lower limb atrophy and weakness, peripheral neuropathy, saccadic ocular pursuit	610357	AR	SPG30
HSP-SPARTIN[124]		Spastic paraplegia and upper limb spasticity, distal muscle atrophy, pes cavus, hammertoes, short stature, dysmorphism, developmental delay	275900	AR	SPG20
HSP-ZFYVE26[126]		Spastic paraparesis, mental retardation, cognitive impairment, psychiatric symptoms, parkinsonism, distal amyotrophy, pes cavus, peripheral neuropathy, retinopathy, hearing loss, pigmentary maculopathy	270700	AR	SPG15
MYC-CLN5[127]		Myoclonus, tremor, mental retardation, cognitive decline, visual loss, glaucoma, retinopathy, nystagmus, hyperreflexia, seizures	256731	AR	CLN5
MYC-CLN6[128]		Myoclonus, dystonia, bradykinesia, myoclonic epilepsy, dementia, mental retardation, psychiatric symptoms, blindness	204300	AR	CLN6
MYC-SCARB2[129]	Progressive myoclonic epilepsy type 4 with or without renal failure	Action and resting myoclonus, intention and postural tremor, horizontal saccades, seizures, nephrotic syndrome, renal failure	254900	AR	None
DYT/PARK-GLB1[130]		Dystonia, parkinsonism, pyramidal signs, cognitive deficits, skeletal abnormalities, short stature, corneal clouding, cardiomyopathy	230600	AR	None
DYT/PARK-SPR[131]	Sepiapterin reductase deficiency	Dystonia, parkinsonism, motor and speech delay, truncal hypotonia, limb hypertonia and hyperreflexia, oculogyric crises, psychiatric symptoms, autonomic dysfunction, diurnal fluctuation	612716	AR	None
NBIA/DYT/PARK-CP[132]	Aceruloplasminemia	Dystonia, parkinsonism, chorea, cognitive impairment, retinopathy, blepharospasm, systemic hemosiderosis, diabetes, anemia	604290	AR	None
NBIA/DYT-PANK2[133]	Pantothenate kinase-associated neurodegeneration (PKAN)	Dystonia, parkinsonism, chorea, tremor, spasticity, cognitive decline, apraxia of eyelid opening, retinopathy, optic atrophy, psychiatric symptoms, muscle atrophy	234200	AR	NBIA1
NBIA/DYT/PARK-PLA2G6[134]	PLA2G6-associated neurodegeneration or Infantile neuroaxonal dystrophy type 1	Dystonia, parkinsonism, cognitive decline, pyramidal signs, psychiatric symptoms (adult phenotype), ataxia (childhood phenotype)	256600/610217	AR	NBIA2, PARK14
AAAS[135]	Achalasia-addisonianism-alacrimia syndrome or Triple-A syndrome or Allgrove syndrome	Developmental delay, mental retardation, pyramidal signs, distal muscle weakness and atrophy, achalasia, autonomic dysfunction, anisocoria, peripheral neuropathy, adrenal insufficiency, alacrima, optic atrophy, short stature, hyperpigmentation, hyperkeratosis of the palms and soles	231550	AR	None
AARS2[136]	Progressive leukoencephalopathy with ovarian failure	Dystonia, tremor, developmental delay, cognitive decline, apraxia, psychiatric symptoms, nystagmus, spasticity, premature ovarian failure	615889	AR	None
ABCD1[137]	X-linked adrenoleukodystrophy	Visual disturbances, sensation deficits, spastic paraplegia, autonomic failure, adrenal dysfunction	300100	XR	None
ARX[138]	Partington syndrome	Dystonia, mental retardation, spasticity, seizures, morphological abnormalities	309510	XR	None
ATAD3A[139,140]	Harel-Yoon syndrome	Developmental delay, intellectual disability, optic atrophy, nystagmus, spasticity, distal limb muscle atrophy, peripheral neuropathy, scoliosis, dysmorphism, hypertrophic cardiomyopathy	617183	AR/AD	None
AUH[141]	3-methylglutaconic aciduria type I	Dystonia, developmental delay, failure to thrive, mental retardation, spastic quadriplegia, cognitive impairment, hyperreflexia, metabolic acidosis, febrile seizures, optic atrophy	250950	AR	None
BCS1L, COX10, COX15, FOXRED1, NDUFAF2, NDUFS3, NDUFS4, NDUFAF6, NDUFS7, NDUFS8, NDUFA10, SDHA, SURF1) [142]	Leigh syndrome	Dystonia, failure to thrive, psychomotor retardation, mental retardation, pyramidal signs, seizures, psychiatric symptoms, lactic acidosis, hypertrochosis, respiratory failure, pigmentary retinopathy, ptosis, strabismus, nystagmus, optic atrophy, ophthalmoplegia	256000	Mi/AR	None
C5orf42[143]		Developmental delay, oculomotor apraxia, polydactyly, syndactyly, abnormal breathing pattern	614615	AR	JBTS17

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
CTC1[144]	Cerebroretinal microangiopathy with calcifications and cysts or Coats plus syndrome	Dystonia, tremor, intrauterine growth retardation, growth retardation, seizures, spasticity, hemiplegia, cognitive decline, pyramidal signs, bone marrow failure, skin and hair abnormalities, intracranial calcifications, skeletal deformities, intestinal bleeding, retinopathy, optic atrophy, blindness	612199	AR	None
CTDP1[145]	Congenital cataracts with facial dysmorphism and neuropathy	Chorea, developmental delay, congenital cataracts, nystagmus, cognitive impairment, pyramidal signs, peripheral neuropathy, hypo- or hypergonadotrophic hypogonadism, acute rhabdomyolysis, pes cavus, talipes equinovarus, skeletal deformities, facial dysmorphism	604168	AR	None
CTSA[146]	Galactosialidosis	Myoclonus, mental retardation, seizures, angiokeratoma, facial dysmorphism, conjunctival telangiectases, macular cherry red spot, hearing loss, hemangiomas, hepatosplenomegaly, dysostosis multiplex, cardiac valvular disease	256540	AR	None
CTSF[147]		Myoclonus, tremor, dementia, perioral dyskinesias, pyramidal signs, seizures, psychiatric symptoms	615362	AR	CLN13
CUL4B[148]	Cabezas type of X-linked syndromic mental retardation	Tremor, mental retardation, speech delay, hypogonadism, short stature, facial dysmorphism, skeletal abnormalities, seizures, psychiatric symptoms, central obesity, macrocephaly	300354	XR	None
DKC1[149]	X-linked dyskeratosis congenital (ataxia reported in the severe variant: Hoyeraal-Hreidarsson syndrome)	Intrauterine growth retardation, developmental delay, mental retardation, microcephaly, multisystem involvement, bone marrow failure resulting in immunodeficiency, enteropathy, strabismus, cataracts, optic atrophy, sparse eyelashes, conjunctival leukoplakia, short stature, pulmonary fibrosis, liver failure, skin atrophy, nail dystrophy, carcinomas, leukemia	305000	XR	None
DLD[150]	Dihydrolipoamide dehydrogenase deficiency or Maple syrup urine disease type II	Dystonia, developmental delay, episodic encephalopathy, seizures, lactic or metabolic acidosis, recurrent vomiting, hepatomegaly, liver dysfunction, hypertrophic cardiomyopathy, microcephaly	246900	AR	None
EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5[151]	Leukoencephalopathies with vanishing white matter	Mental and motor retardation or regression, cognitive impairment, psychiatric symptoms, optic atrophy, pyramidal signs, seizures, ovarian failure, clinical features worsened by head trauma or fever, macrocephaly, lethargy	603896	AR	None
ERCC4[152,153]	XFE progeroid syndrome and the allelic entity Xeroderma pigmentosum complementation group F/Cockayne syndrome	Dwarfism, cachexia, microcephaly, photosensitivity, wizened appearance, scoliosis, delayed sexual maturity, chorea, tremor, mental retardation, cognitive decline, nystagmus, astigmatism, deep-set eyes, hearing impairment, short stature, seborrheic keratosis-like papules, abnormal pigmentation, skin cancer susceptibility, plantar warts	610965, 278760	AR	None
EXOSC3[154]	Pontocerebellar hypoplasia type 1B	Tremor, developmental delay, poor growth, axial hypotonia, spasticity, hyperreflexia, lack of speech, seizures, peripheral neuropathy, muscle atrophy and weakness, tongue atrophy and fasciculations, foot deformities, joint contractures, respiratory insufficiency, oculomotor apraxia, nystagmus, strabismus, retinopathy, microcephaly	614678	AR	None
GALC[155]	Krabbe disease or galactocerebrosidase deficiency	Failure to thrive, developmental delay or regression, deafness, blindness, optic atrophy, nystagmus, hypersensitive to stimuli, irritability, spastic tetraparesis, seizures, muscular, decerebrate posturing, peripheral neuropathy, pes cavus, tongue atrophy, episodic fever	245200	AR	None
GBA[156]	Gaucher disease type III or subacute neuronopathic type	Myoclonus, developmental delay, dementia, psychiatric symptoms, spastic paraparesis, horizontal supranuclear gaze palsy, abnormal saccade eye movements, strabismus, seizures, short stature, hepatosplenomegaly, pancytopenia	231000	AR	None
GJC2[157]		Tremor, slow saccades, sensorineural hearing loss, strabismus, spastic paraparesis, other pyramidal signs, pes cavus, scoliosis, seizures, cognitive impairment	613206	AR	SPG44
GPR56 or ADGRG1[158]	Bilateral frontoparietal polymicrogyria	Developmental delay, mental retardation, pyramidal signs, esotropia, exotropia, strabismus, nystagmus, seizures	606854	AR	None

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
HEPACAM[159]	Autosomal recessive megalencephalic leukoencephalopathy with subcortical cysts type 2A	Developmental delay, mental retardation, cognitive decline, spasticity, seizures, macrocephaly	613925	AR	None
HIBCH[160]	3-hydroxyisobutyrl-CoA hydrolase deficiency	Dystonia, myoclonus, developmental delay or regression, seizures, nystagmus, strabismus, facial dysmorphism, head titubation, persistent vomiting	250620	AR	None
HSD17B4[161]	Perrault syndrome type 1 (allelic with Peroxisomal D-bifunctional protein deficiency)	Sensorineural deafness, ovarian dysgenesis, primary amenorrhea, developmental delay, mental retardation, spastic diplegia, pes cavus, pes equinovarus, peripheral neuropathy, nystagmus, short stature, scoliosis	233400	AR	None
LRPPRC[162]	French Canadian type of Leigh syndrome	Tremor, developmental delay, mental retardation, failure to thrive, language delay, seizures, lactic acidosis, metabolic crises, strabismus, facial dysmorphism, liver dysfunction	220111	AR	None
LYST[163]	Chediak-Higashi syndrome	Parkinsonism, tremor, mental retardation, cranial nerve palsies, spastic paraparesis, peripheral neuropathy, foot drop, seizures, anemia, recurrent cutaneous and systemic pyogenic infections, severe immune deficiency, hair hypopigmentation, reduced visual acuity, nystagmus, strabismus, reduced iris pigmentation, macular hypoplasia, hepatosplenomegaly, jaundice	214500	AR	None
MAG[164]		Developmental delay, cognitive impairment, impaired distal vibration sense, peripheral neuropathy, distal muscle atrophy in lower limbs, spastic paraplegia, optic atrophy, nystagmus, visual impairment	616680	AR	SPG75
MECP2[165]	Lubs X-linked mental retardation syndrome	Chorea, psychomotor retardation, macro- or microcephaly, facial dysmoprhism, seizures, spasticity, recurrent respiratory infections, cryptorchidism, asymmetric skull, stereotypic hand movements, autistic features, depression, compulsions, psychosis	300260	XR	None
MFSD8[166]		Developmental regression, mental retardation, cognitive impairment, optic atrophy, retinopathy, blindness, seizures, myoclonus	610951	AR	CLN7
MKS1[167]		Developmental delay, intellectual disability, nystagmus, oculomotor apraxia, retinopathy	617121	AR	JBTS28
MMACHC[168]	cblC type of combined methylmalonic aciduria and homocystinuria	Tremor, failure to thrive, developmental delay, mental retardation, dementia, retinopathy, visual deficits, nystagmus, facial dysmorphism, seizures, hypergonadotropic hypogonadism, anemia, renal failure, microcephaly	277400	AR	None
MPV17[169]	Mitochondrial DNA depletion syndrome-6 or Navajo neurohepatopathy	Dystonia, neonatal jaundice, failure to thrive, developmental delay, peripheral neuropathy, hypo-areflexia, pain insensitivity, acral ulceration and osteomyelitis leading to autoamputation, painless fractures due to injury, distal muscle weakness, lactic acidosis, systemic infections, liver dysfunction, Reye syndrome-like episodes, short stature	256810	AR	None
MTFMT[170]	Combined oxidative phosphorylation deficiency type 15	Tremor, developmental delay, cognitive impairment, pyramidal signs, seizures, strabismus, nystagmus, optic atrophy, short stature, obesity, cardiopathy	614947	AR	None
MTTP[171]	Abetalipoproteinemia	Peripheral neuropathy, retinopathy, acanthocytosis, steatorrhea (celiac-like syndrome), hepatic steatosis	200100	AR	None
MVK[172]	Mevalonic aciduria	Developmental delay, psychomotor retardation, failure to thrive, recurrent febrile crises with lymphadenopathy, hepatosplenomegaly, anemia, morbilliform rash, kyphoscoliosis, arthralgias, facial dysmorphism, nystagmus, central cataracts, retinal dystrophy, microcephaly	610377	AR	None
NPHP1[173]		Developmental delay, mental retardation, congenital head tilt, abnormal eye movements, nystagmus, oculomotor apraxia, hypometric saccades, tubulointerstitial medullary cystic kidney disease, nephronophthisis, renal failures	609583	AR	JBTS4
NUBPL[174]	Mitochondrial complex I deficiency	Developmental delay, strabismus, nystagmus, contractures, spasticity, cognitive decline	252010	AR/Mi/AD	None

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
OPA1[175]	Behr syndrome or infantile hereditary optic atrophy with neurologic abnormalities	Tremor, developmental delay, mental retardation, optic atrophy, progressive visual loss, nystagmus, spasticity, pyramidal signs, myopathy, posterior column sensory loss, peripheral neuropathy, tendon and muscular contractures	210000	AR	None
OPA3[176]	3-methylglutaconic aciduria type III or Costeff syndrome	Chorea, cognitive impairment, optic atrophy, visual loss, cataracts, nystagmus, pyramidal signs	258501	AR	None
PDHX or PDX1[177]	Lactic acidemia due to PDX1 deficiency	Dystonia, developmental delay, mental retardation, microcephaly, optic atrophy, hypertelorism, facial dysmorphism, spastic quadriplegia, seizures, lactic or metabolic acidosis	245349	AR	None
PEX2[178]	Peroxisome biogenesis disorder 5B or Zellweger spectrum disorders	Tremor, developmental delay, peripheral neuropathy, pes cavus, hypoacusia, slow saccades, oculomotor apraxia, nystagmus, retinopathy, strabismus	614867	AR	None
PEX6[25]		Optic atrophy, blindness, cochlear degeneration, deafness	271250	AR	SCAR3
PNKP[179-181]	Microcephaly, seizures, and developmental delay and allelic disorders (eg, autosomal recessive axonal Charcot-Marie-Tooth)	Dystonia, developmental delay, mental retardation, cognitive impairment, oculomotor apraxia, tetraplegia, impaired vibration sense, peripheral neuropathy, pes cavus, hammertoes, distal muscle weakness and atrophy, seizures, microcephaly	616267, 613402, 605610	AR	AOA4
PNP[182]	Purine nucleoside phosphorylase deficiency or Nucleoside phosphorylase deficiency	Tremor, developmental delay, failure to thrive, mental retardation, spastic diplegia, tetraparesis, behavioral disorder, autoimmune hemolytic anemia, frequent infections, splenomegaly, pneumonia	613179	AR	None
POLG[183-186]	Allelic disorders: Mitochondrial recessive ataxia syndrome (MIRAS) or sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO), Autosomal recessive progressive external ophthalmoplegia with mitochondrial DNA deletions type 1 and Mitochondrial DNA depletion syndrome 4A (Alpers-Huttenlocher syndrome) and 4B (MNGIE type)	Myoclonus, parkinsonism, dystonia, tremor, developmental delay, cognitive impairment, psychiatric symptoms, dysarthria, nystagmus, upward gaze paresis, blepharoptosis, ophthalmoparesis, cataracts, progressive external ophthalmoplegia, optic atrophy, dyschromatopsia, cortical blindness, migraine, seizures, peripheral neuropathy, muscle weakness and atrophy, hypogonadism, seizures, stroke-like episodes, gastroparesis, intestinal pseudo-obstruction, cardiomyopathy, hepatic dysfunction	607459, 258450, 203700, 613662	AR	None
POLR1C[187]	Hypomyelinating leukodystrophy type 11 (allelic with Treacher Collins syndrome type 3)	Tremor, developmental delay, intellectual disability, spasticity, myopia, dental abnormalities, head titubation	616494	AR	None
PRF1[188,189]	Familial hemophagocytic lymphohistiocytosis type 2 and the allelic disorder of recurrent immune-mediated neurodegeneration	Developmental delay, failure to thrive, meningitis, encephalitis, hemiplegia, tetraplegia, seizures, coma, pancytopenia, coagulation abnormalities, lymphadenopathy, fever, edema, liver dysfunction Neurodegeneration triggered by infections, recurrent subacute post-viral onset of ataxia, primary immunodeficiency	603553, 170280	AR	None

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
PRPS1[190-192]	Allelic disorders or continuum with Arts syndrome, X-linked recessive Charcot-Marie-Tooth disease-5 or Rosenberg-Chutorian syndrome and Hyperuricemia, mental retardation and sensorineural deafness with PRPS1 superactivity	Developmental delay, mental retardation, poor growth, sensorineural hearing loss, optic atrophy, retinopathy, nystagmus, muscle weakness, hyperreflexia, peripheral neuropathy, distal muscle weakness and atrophy, distal sensory impairment, pes cavus, flaccid tetraplegia, immune deficiency, recurrent respiratory tract infections, uric acid urolithiasis, secondary renal insufficiency, gout, gouty arthritis	301835, 300661, 311070	XR	None
PRX[193]		Distal and proximal lower limb muscle weakness and atrophy, peripheral neuropathy, pes cavus, scoliosis, delayed motor development	614895	AR	None
RARS[194]		Tremor, developmental delay, mental retardation, pyramidal signs, nystagmus, altered smooth pursuit, microcephaly	616140	AR	None
RELN[195]	Norman-Roberts type of Lissencephaly	Microcephaly, facial dysmorphism, mental retardation, nystagmus, seizures, congenital lymphedema	257320	AR	None
ROGDI[196]	Kohlschutter-Tonz syndrome	Developmental delay, mental retardation, cognitive impairment, spasticity, seizures, amelogenesis imperfecta, enamel hypoplasia, discolored teeth	226750	AR	None
RRM2B[197]	Mitochondrial DNA depletion syndrome 8B (MNGIE type)	Failure to thrive, lactic acidosis, proximal renal tubulopathy, seizures, external ophthalmoplegia, ptosis, gastrointestinal dysmotility, cachexia, peripheral neuropathy	612075	AR	None
RTN4IP1[198]	Optic atrophy type 10 with or without ataxia, mental retardation, and seizures	Mental retardation, photophobia, nystagmus, reduced visual acuity, color vision impairment of red/green axis, optic atrophy, central scotoma seizures	616732	AR	None
SLC2A1[199]		Dystonia, developmental delay, seizures, myoclonic epilepsy, spasticity	606777	AR/AD	None
SLC6A19[200]	Hartnup disease	Delayed cognitive development, psychiatric symptoms, seizures, hypertonia, light-sensitive dermatitis, atrophic glossitis	234500	AR	None
SLC16A2[201]	Allan-Herndon-Dudley syndrome or monocarboxylate transporter type 8 deficiency	Dystonia, developmental delay, mental retardation, pyramidal signs, amyotrophy, behavior disorders, scoliosis, nystagmus, facial dysmorphism, microcephaly, pectus excavatum	300523	XR	None
SLC19A3[202]	Thiamine metabolism dysfunction syndrome type 2 or biotin-thiamine-responsive basal ganglia disease	Dystonia, psychomotor retardation, encephalopathy, coma, psychiatric symptoms, external ophthalmoplegia, nystagmus, ptosis, gaze palsy, seizures, pyramidal signs, paraparesis, rigidity	607483	AR	None
SLC25A15[203]	Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome	Psychomotor retardation, failures to thrive, mental retardation, lethargy, episodic confusion, acute encephalopathy, coma, pyramidal signs, myoclonic epilepsy, decreased vibration sense, coagulopathy as a result of liver dysfunction	238970	AR	None
SLC25A46[204]	Hereditary motor and sensory neuropathy type VIB or Charcot-Marie-Tooth disease type 6B	Myoclonus, delayed development, optic atrophy, pyramidal signs, peripheral neuropathy, distal sensory impairment, pes cavus, morphological abnormalities	616505	AR	None
SLC52A2[205]	Brown-Vialetto-Van Laere syndrome type 2	Cranial nerve palsies, bulbar palsy, optic atrophy, nystagmus, visual loss, absent pupillary reflex, sensorineural hearing loss, peripheral neuropathy, muscle weakness and atrophy, tongue fasciculations, psychiatric symptoms, claw hands, scoliosis, respiratory insufficiency	614707	AR	None
SNORD118[206]	Leukoencephalopathy, brain calcifications, and cysts	Dystonia, tremor, seizures, spasticity, hemiplegia, cognitive decline, pyramidal signs	614561	AR	None

(Continued)

TABLE 1. *Continued*

New designation	Alternate name	Main clinical features	OMIM	Inheritance pattern	Locus symbol
SUOX[207]	Sulfocysteinuria or sulfite oxidase deficiency	Dystonia, developmental delay, infantile hemiplegia, seizures, behavior disorders, fine hair, eczema, delayed teething, ectopia lentis	272300	AR	None
SURF1[208]		Peripheral neuropathy, distal muscle weakness and atrophy, kyphoscoliosis, nystagmus, sensorineural hearing loss	616684	AR	None
TCTN1[209]		Cognitive impairment, limb abnormalities	614173	AR	JBTS13
TCTN2[210]		Developmental delay, absent speech, pyramidal signs, nystagmus, hyperopia, polydactyly, talipes equinovarus	616654	AR	JBTS24
TCTN3[211]		Mental retardation, abnormal eye movements, facial dysmorphism, scoliosis, polydactyly, camptodactyly, breathing anomalies, ventricular septal defect, horseshoe kidney	614815	AR	JBTS18
TRAPPC11[212]	Limb-girdle muscular dystrophy type 2S	Dystonia, chorea, tremor, developmental delay, proximal muscle weakness, muscle cramps, scapular winging, scoliosis, hip dysplasia, cataracts, strabismus, myopia, microcephaly, short stature	615356	AR	None
TRNT1[213]	Congenital sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay	Severe sideroblastic anemia, developmental delay, growth retardation, lactic acidosis, recurrent fevers, brittle hair, nephrocalcinosis, cardiomyopathy, retinopathy, sensorineural hearing loss seizures	616084	AR	None
VARS2[214]	Combined oxidative phosphorylation deficiency type 20	Developmental delay, ptosis, progressive external ophthalmoplegia, seizures, facial dysmorphism, microcephaly	615917	AR	None
VRK1[215]		Psychomotor retardation, mental retardation, microcephaly, nystagmus, muscle weakness, distal spinal muscular atrophy, fasciculations, peripheral neuropathy, hyperreflexia, foot deformities, skeletal contractures, arthrogryposis, scoliosis, respiratory insufficiency	607596	AR	None
WFS1[216]	Wolfram syndrome-1 or Diabetes insipidus and mellitus with optic atrophy and deafness	Parkinsonism, tremor, myoclonus, mental retardation or dementia, poor growth, optic atrophy, retinopathy, ptosis, nystagmus, sensorineural hearing loss, hyposmia, seizures, peripheral neuropathy, stroke-like episodes, psychiatric symptoms, diabetes mellitus and diabetes insipidus, hypothyroidism, hydronephrosis, testicular atrophy, cardiomiopathy	222300	AR	None
XRCC4[217]	Short stature, microcephaly, and endocrine dysfunction syndrome	Intrauterine growth failure, developmental delay, cognitive impairment, apraxia, pyramidal signs, peripheral neuropathy, dyslipidemia, diabetes mellitus, hypothyroidism, anemia, acanthosis nigricans, cryptorchidism, renal dysgenesis, malpositioned teeth, facial dysmorphism, short stature, microcephaly	616541	AR	None

AR, autosomal recessive; AD, autosomal dominant; Mi, mitochondrial; OMIM, Online Mendelian Inheritance in Man; XR, X-linked recessive.
[a]A complete reference list can be found in the Supplementary Material.

gene. Recessive cerebellar ataxias have also been classified according to their presumed molecular pathogenesis, such as metabolic alterations, mitochondrial dysfunction, altered calcium signaling, defective DNA repair, abnormal protein folding, and chaperone dysfunction.[2,8,9] This is a useful approach for ataxia researchers and for future therapeutic targeting but is of limited value to clinicians. Last, more recently the field has begun to refer to recessive ataxias as SCAR's (for SCA recessive). However, this list is incomplete (only 26 entities so far) and also contains unconfirmed entities, such as SCAR11 (SYT14), SCAR12 (WWOX), SCAR19 (SLC9A1), SCAR21 (SCYL1), SCAR22 (VWA3B), SCAR23 (TDP2) and SCAR24 (UBA5), which did not meet our criteria to be part of the final list (Table 1). Moreover, this SCAR classification partly parallels and duplicates the ARCA classification, yet with different numbers. For example, ATX-SYNE1 is dubbed ARCA1 in 1 nomenclature system, but SCAR8 in the other.

A recently conducted systematic review of autosomal recessive ataxias conducted by Beaudin and colleagues[10] identified 45 genetically confirmed disorders that have ataxia as a core feature. An important difference from their approach is that we included genetic entities that present with ataxia as part of a more complex phenotype. Recently, the comprehensive features of 67 recessively inherited entities that may present with ataxia were gathered within a knowledgebase that was the basis of an automated algorithm for the diagnosis of recessive cerebellar ataxias.[11] During the review process of our working group, we have applied strict criteria. In part related to this inclusive principle, we encountered classification difficulties for certain entries, for example, in relation to the criteria of prominent or consistent ataxia. Also, in some cases, it was difficult to distinguish purely sensory ataxias (eg, the posterior column ataxia with retinitis pigmentosa as a result of mutations in the FLVCR1 gene) from disorders that combine sensory and cerebellar ataxia, such as Friedreich ataxia, ataxia with vitamin E deficiency, or ataxia as a result of mutations in the MTTP gene (also known as abetalipoproteinemia) or in the POLG gene (sensory ataxic neuropathy, dysarthria, and ophthalmoparesis). If there was a clear cerebellar contribution to the clinical manifestation of ataxia, such an entity was included in the final list.

Prefix designation is work in progress, as prefixes may change over time when further clinical descriptions or case reports have been published. Also, for the system to be fully comprehensive, prefixes need to be defined for nonmovement disorder phenotypes. This requires other subspecialties within neurology and neurogenetics to adopt this system. We specifically designed our system with adaptability in mind. This also requires periodic updating, which is facilitated by the availability of an online tool, the International Parkinson and Movement Disorder Society genetic mutation database (http://www.mdsgene.org), which is a more suitable medium than static publications of this new genetic nomenclature of the recessive cerebellar ataxias. The updated lists will also be accessible on the Task Forces section of the MDS website (https://www.movementdisorders.org/MDS/About/Committees–Other-Groups/MDS-Task-Forces/Task-Force-on-Nomenclature-in-Movement-Disorders.htm).

We encourage all neurologists, particularly movement disorders specialists and pediatric neurologists, and researchers in the field of ataxia to adopt and use this newly transparent and adaptable nomenclature system of the recessive cerebellar ataxias as it will facilitate the clinical recognition of numerous recessive ataxias, guide diagnostic testing in ataxia patients, and help in interpreting genetic findings. ■

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Supporting Data

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