Myoclonus-Ataxia Syndromes: A Diagnostic Approach

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Abstract: Background: A myriad of disorders combine myoclonus and ataxia. Most causes are genetic and an increasing number of genes are being associated with myoclonus-ataxia syndromes (MAS), due to recent advances in genetic techniques. A proper etiologic diagnosis of MAS is clinically relevant, given the consequences for genetic counseling, treatment, and prognosis.

Objectives: To review the causes of MAS and to propose a diagnostic algorithm.

Methods: A comprehensive and structured literature search following PRISMA criteria was conducted to identify those disorders that may combine myoclonus with ataxia.

Results: A total of 135 causes of combined myoclonus and ataxia were identified, of which 30 were charted as the main causes of MAS. These include four acquired entities: opsoclonus-myoclonus-ataxia syndrome, celiac disease, multiple system atrophy, and sporadic prion diseases. The distinction between progressive myoclonus epilepsy and progressive myoclonus ataxia poses one of the main diagnostic dilemmas.

Conclusions: Diagnostic algorithms for pediatric and adult patients, based on clinical manifestations including epilepsy, are proposed to guide the differential diagnosis and corresponding work-up of the most important and frequent causes of MAS. A list of genes associated with MAS to guide genetic testing strategies is provided. Priority should be given to diagnose or exclude acquired or treatable disorders.

Syndromes that combine dystonia and parkinsonism, dystonia and myoclonus, and dystonia and ataxia have been extensively reviewed.^{1,2} The association of myoclonus and ataxia has received less attention in the literature. The combination of myoclonus and ataxia can be the manifestation of a plethora of diseases.^{3,4} In clinical practice, recognition of these entities and orchestrating the appropriate work-up are often challenging.

Within the genetically determined myoclonus syndromes, ataxia is the most common associated movement disorder and a highly frequent accompanying clinical feature, only surpassed by epilepsy and cognitive decline.³ Traditionally, the combination of these two movement disorders is linked to the syndrome of progressive myoclonus ataxia (PMA), previously referred to as Ramsay Hunt syndrome. The PMA share overlapping clinical

features with the progressive myoclonus epilepsies (PME).⁵ According to the new refined definition,⁵ PMA is mainly separated from PME by the considerably lower frequency of seizures, less frequent mental deterioration, and often slower progression. PMA will often be of genetic origin, but still in many cases the etiology remains unclear despite the wide use of next generation sequencing (NGS) diagnostics.

In this systematic review, we will list the disorders that may combine myoclonus and ataxia, capture the causes of progressive myoclonus ataxia (PMA) and propose diagnostic algorithms and clinical clues for the most important and frequent causes of myoclonus-ataxia syndromes (MAS). In addition, we will provide a list of genes associated with MAS for guidance in diagnostic NGS strategies.

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TABLE 1 Myoclonus-ataxia syndromes

Entity or Designation	Age of Onset	Main Additional Clinical Features	Myoclonus		Epilepsy
			Myoclonus subtype; Distribution; Activation Mode; Additional Information	Electrophysiological Characteristics of Myoclonus (Polymyography)	Seizure Types; Frequency; Therapy Response
1) <i>Non-genetic or acquired</i> Opsoclonus-myoclonus-ataxia syndrome ⁶⁻¹² Celiac disease ³³⁻²²	Infancy, childhood, adulthood	Opsoclonus, behavioral changes, insomnia, neoplasms, infections	BM ^a Extremities, axial muscles; Spontaneous, action	Burst duration <100 ms; No EMG-EEG correlates	Normal
Celiac disease ³³⁻²²	Adulthood	Peripheral neuropathy, gastrointestinal symptoms	CM ^a Multifocal; Spontaneous, action and stimulus sensitive	Cortical reflex myoclonus	Multi-focal epileptiform discharges
Multiple system atrophy ³³⁻²⁷	Adulthood	Parkinsonism, autonomic dysfunction, orofacial dystonia, disproportionate ataxia, inspiratory sighs, severe dysphonia, dysarthria	CM Stimulus-sensitive, action- or posture induced myoclonus. Small - Polymini-myoclonus	Positive J/LBA, Giant SSEP	Not described
Acquired or sporadic prion diseases (iatrogenic, variant and sporadic Creutzfeldt-Jakob disease) ²⁸⁻³³	Adulthood	Dementia, aphasia, behavioral disorders, parkinsonism, ophthalmoparesis	CM, SCM ^a Multifocal Both positive and negative jerks Spontaneous	Either short burst of 54.1 ± 15.8 ms or long burst of >200 ms. In most cases a positive jerk-locked back-averaging was present. Giant SSEP	Diffuse slow activity. Typical periodic sharp wave discharges and paroxysmal discharges
2) <i>Autosomal recessive diseases</i> Myoclonic epilepsy of Unverricht and Lundborg (MYC/ATX-CSTB) ³⁴⁻³⁴ #MIM 254800	Childhood, adolescence	Cognitive decline, hallucinations	CM Multifocal; Action and stimulus sensitive (stress, touch, PS)	Cortico-muscular coherence present	Normal to slightly slow background; Brief and rare epileptiform discharges
Myoclonic epilepsy of Lafora ³⁴⁻⁴⁹ - #MIM 254780 and MYC/ATX-NHLRC1 ⁵⁰⁻⁵³ #MIM 254780	Childhood, adolescence	Cognitive decline, hallucinations	CM Multifocal; Spontaneous, action and stimulus sensitive (stress, sound, touch, PS) Positive and negative jerks	Brief and small bursts; Cortico-muscular coherence present	Slow and poor topographic organization of background; Diffuse epileptiform discharges
North Sea progressive myoclonic epilepsy (MYC/ATX-GOSR2) ⁵⁴⁻⁵⁸ #MIM 614018	Infancy	Scoliosis, areflexia, pes cavus, syndactyly, dysarthria, cognitive decline (rare)	CM Multifocal; Spontaneous, action and stimulus sensitive (stress, PS)	Burst duration <100 ms; Time-locked association between cortex and bursts; Giant SSEP	Slow background; Generalized epileptiform discharges Photoparoxysmal responses
Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6) ⁵⁹⁻⁶⁶ #MIM 204300	Adolescence adulthood	Dystonia, bradykinesia, dementia, mental retardation, behavioral disorders	CM Multifocal; Spontaneous, action and stimulus sensitive Positive and negative jerks	Time-locked association between cortex and bursts; Giant SSEP	Background can be preserved; Interictal epileptiform discharges; Photoparoxysmal responses
Progressive myoclonic epilepsy type 3 or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) ⁶⁷⁻⁷¹ #MIM 611726	Infancy	Neurologic regression following seizure onset, mental retardation, pyramidal signs, microcephaly, scoliosis	Myoclonus of unknown origin Multifocal; Spontaneous, action and stimulus sensitive (stress) Positive and negative jerks	No association with epileptic discharges on EEG and myoclonic bursts on EMG; No giant SSEP	Slow background; Prominent epileptic activity; Photoparoxysmal response
Myoclonus epilepsy and ataxia due to potassium channel mutation (KCNC1) ⁷²⁻⁷⁴ #MIM 616187	Infancy, childhood, adolescence	Cognitive decline	CM Multifocal; Spontaneous, action and stimulus sensitive (stress, sound, startle, senses) Positive and negative jerks	Cortico-muscular coherence present. Giant SSEP Enhanced C reflexes	Preservation of background; Generalized epileptiform discharges
Progressive myoclonic epilepsy type 4 with or without renal failure (MYC-SCAR82) ⁷⁵⁻⁸⁶ #MIM 254906	Adolescence, early adulthood	Tremor, renal failure, peripheral neuropathy	CM Multifocal; Spontaneous, action, stimulus-induced (auditory, visual, touch, stress, fever, menses) Positive and negative jerks	Burst duration <50 ms; Positive cortical spike back-averaging	Slow background; Fast epileptiform discharges Photoparoxysmal response

(Continues)

TABLE 1 Continued

Entity or Designation	Age of Onset	Main Additional Clinical Features	Myoclonus		Epilepsy	
			Myoclonus subtype; Distribution; Activation Mode; Additional Information	Electrophysiological Characteristics of Myoclonus (Polymyography)	Seizure Types; Frequency; Therapy Response	Electrophysiological Characteristics of Epilepsy (EEG)
Ataxia-telangiectasia, including variant ataxia-telangiectasia (ATX-ATM) ⁸⁷⁻⁹⁴ #MIM 208900	Neonatal, infancy	Telangiectasias and other skin alterations, oculomotor apraxia, dystonia, chorea, tremor, peripheral neuropathy, distal muscular atrophy, short stature, immunodeficiency, predisposition to neoplasia	SCM Multifocal; Spontaneous, action, not stimulus-sensitive	Burst duration 20-385 ms; No cortical correlation No giant SSEP	Not described	Not described.
Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) ⁹⁵⁻⁹⁸ #MIM 615768	Variable	Nystagmus, external ophthalmoplegia, pyramidal signs, tremor, dystonia, cognitive impairment, peripheral neuropathy, hypogonadism	CM ^h Multifocal; Spontaneous, action	Not described	Not described	Not described
Neuraminidase deficiency or sialidosis type I and II (MVC/ATX-NEU1) ⁹⁹⁻¹⁰⁶ #MIM 256550	Variable	Cognitive decline, cherry-red spots, dysmorphic features, hearing loss, cataracts, hepatosplenomegaly, cardiomyopathy, skeletal malformations, short stature	CM Multifocal; Spontaneous, action, stimulus sensitive (sound, touch, PS) Positive and negative jerks	Highly frequent and rhythmic bursts; Positive cortical spike back-averaging; Cortico-muscular coherence present; Giant SSEP	M, GTC; Frequent; Usually treatment-responsive	Normal EEG in majority present; In some cases epileptiform discharges
Neuronal ceroid lipofuscinosis type 2 (MVC/ATX-TPI1) ^{107,108} #MIM 204500	Infancy	Developmental regression, speech and language difficulties, progressive vision loss with retinopathy, dystonia	Not described	Not described	M, GTC, Ab; Frequent; Intractable	Slow background; Focal or generalized epileptiform discharges
POLG-ataxia and allied disorders: MIRAS, SANDO, and Alpers'-Huttenlocher syndrome (POLG) ¹⁰⁹⁻¹¹⁴ #MIM 607459, #MIM 613662	Infancy, childhood, adulthood	Cognitive decline, developmental delay, peripheral neuropathy, muscle weakness and atrophy, behavioral disorders, parkinsonism, dystonia, tremor, dysarthria, nystagmus, ophthalmoparesis, cataracts, optic atrophy, hypogonadism, stroke-like episodes, gastroparesis, cardiomyopathy, hepatic dysfunction	Myoclonus of unknown origin Multifocal; Stimulus sensitive Positive and negative jerks	Not described	M, motor, Visual, G; Frequent; Refractory	Slow background; Epileptiform discharges
Pr-m3y coenzyme Q10 deficiency, Type 4 (ATX-ADCK3) ¹¹⁵⁻¹²⁰ #MIM 612016	Childhood, (early adulthood onset is rare)	Muscle weakness, exercise intolerance, episodes of vomiting, hypotonia, pes cavus, developmental delay, cognitive impairment, dystonia	SCM ^a Not described; Not action-induced or stimulus sensitive	Low amplitude jerks; Burst duration 80-135 ms; No cortical correlation	M, GTC; Infrequent	Normal background; Interictal epileptiform discharges
Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2) ^{121,122} #MIM 614487	Infancy or early childhood	Spastic paraparesis, oculomotor apraxia, ptosis, dystonia, distal muscle atrophy and weakness, peripheral neuropathy	Myoclonus of unknown origin Multifocal; Spontaneous, action, stimulus sensitive; Interictal myoclonus	Not described	GTC; Infrequent	Normal or epileptiform discharges on EEG
Congenital disorder of glycosylation, Type Ic (ATX-ALGG) ^{123,124} #MIM 603147	Infancy or early childhood	Developmental delay, hypotonia, behavioral disorders, strabismus, retinopathy, cataracts, peripheral neuropathy, proximal muscle weakness	-	Not described	M or infantile spasms; Frequent; Refractory	Slowed background; Generalized epileptiform discharges
Neuronal ceroid lipofuscinosis type 7 (MFSDB) ¹²⁵⁻¹²⁸ #MIM 610951	Infancy or early childhood	Developmental regression, cognitive decline, speech impairment, optic atrophy, retinopathy	-	Not described	M, GTC; Frequent; Poorly responsive to therapy	Slow background; Focal or generalized epileptiform discharges
Progressive myoclonic epilepsy type 1B (PRCKLE1) ¹²⁹⁻¹³² #MIM 612437	Infancy or early childhood	Developmental delay, reduced upward gaze, action tremor, pyramidal signs, peripheral neuropathy	Myoclonus of unknown origin Multifocal; Not described	Delayed cortical response during SSEP	GTC; Infrequent; Usually treatment-responsive	Generalized epileptiform discharges
3) Autosomal dominant diseases Dentatorubral pallidoluysian atrophy (ATX-ATX18) ¹³³⁻¹⁴⁰ #MIM 125370	Adulthood	Chorea, cognitive decline, behavioral disorders, pyramidal signs	Myoclonus of unknown origin Multifocal; Stimulus sensitive	No giant SSEP	GTC, M, A; Intractable	Diffuse epileptiform discharges; Photoparoxysmal response
Spinocerebellar ataxia type 2 (ATX-ATX2) ¹⁴¹⁻¹⁴⁵ #MIM 183890	Adulthood	Altered saccadic eye movements, ophthalmoparesis, parkinsonism, behavioral disorders, muscle atrophy, autonomic dysfunction	SCM Multifocal; Spontaneous, action, stimulus-sensitive (touch)	High-amplitude bursts; Burst duration 40-60 ms	Not described	Not described
Spinocerebellar ataxia type 4 (ATX-PRKCG) ¹⁴⁶⁻¹⁶³ #MIM: 605361	Adulthood	Nystagmus, saccadic intrusions, cognitive decline, behavioral disorders, dystonia, pyramidal signs	SCM Multifocal; Spontaneous, action-induced	Normal SEP, no cortical correlates	Not described	Not described

(Continues)

TABLE 1 Continued

Entity or Designation	Age of Onset	Main Additional Clinical Features	Myoclonus		Epilepsy	
			Myoclonus subtype; Distribution; Activation Mode; Additional Information	Electrophysiological Characteristics of Myoclonus (Polymyography)	Seizure Types; Frequency; Therapy Response	Electrophysiological Characteristics of Epilepsy (EEG)
Neuronal ceroid lipofuscinosis type 4B (MYC-DNAJC5) ¹⁶⁴⁻¹⁶⁵ MIM #162350	Adulthood	Cognitive impairment, parkinsonism, behavioral disorders, dysarthria	Myoclonus of unknown origin	Not described	M, GTC; Frequent; Intractable	Generalized epileptic discharges
Prion disease: Familial Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease and familial fatal insomnia (PRNP) ^{20,33,166-177} MIM #123400, MIM #137440, MIM #600072	Adulthood	Cognitive decline, behavioral disorders, parkinsonism, pyramidal signs, ophthalmoparesis, refractory insomnia, apraxia, mutism	CM ^a or SCM ^a Multifocal; Spontaneous, action and stimulus sensitive (touch) Positive and negative jerks Polymorphic presentation of myoclonic jerks (rhythmic, dystonic and periodic)	Either burst duration of 54.1 ± 15.8 ms or > 200 ms; Positive cortical spike back-averaging; Giant SSEP	GTC	Slow background; Epileptic discharges
Autosomal dominant mental retardation type 5 (SYNGAP1) ¹⁷⁸⁻¹⁸¹ MIM #612621	Infancy	Developmental delay or regression, mental retardation, hypotonia, behavioral disorders, autism spectrum disorder, facial dysmorphism, orthopedic abnormalities, sleeping problems, microcephaly	-	Not described	M, A, Ab, GTC, febrile, reflex (eating, sound, touch); Frequent	Slow background; Focal or multifocal epileptic discharges; Photoparoxysmal response
SCN1A-related disorder (SCN1A) ¹⁸²⁻¹⁸⁶ #MIM 607208	Infancy	Psychomotor retardation, pyramidal signs	CM Multifocal; Spontaneous, action; Interictal myoclonus	EMG bursts in beta frequency during active movements, brief ranging from 24-48 ms. Giant SEPs. Presence of cortico-muscular coherence and jerk-locked backaveraging.	M, GTC, A, Ab; Frequent; Refractory	Interictal generalized, focal, and multifocal epileptic discharges; Photoparoxysmal response is rare
SLC6A1-related disorder (SLC6A1) ¹⁸⁷⁻¹⁹⁰ #MIM 616421	Infancy	Developmental delay, mental retardation, autistic features, tremor	-	Not described	M, A, Ab; Treatment-responsive	Generalized epileptic discharges; Photoparoxysmal response
4) Mitochondrial diseases MERRF and MELAS syndromes (MTTK) ¹⁹¹⁻¹⁹⁸ MIM #590060	Adulthood (Infancy and childhood is rare)	Cognitive impairment or mental regression, hearing loss, muscle weakness, behavioral disorders, dysarthria, dysphagia, short stature, stroke-like episodes, cardiac abnormalities, migraine, respiratory dysfunction, gastrointestinal symptoms	CM ^a Not described; Action and stimulus sensitive	Giant SSEP	GTC	Slow background; Epileptic discharges

Genes or conditions fulfilling criteria for progressive myoclonus ataxia (PMA) are shown in bold.

Abbreviations: CM, cortical myoclonus; SCM, subcortical myoclonus; BM, brainstem myoclonus; EEG, electroencephalogram; EMG, electromyography; M, myoclonic seizures, GTC, generalized tonic-clonic seizures; A, atonic seizures, Ab, absence seizures, V, visual seizures; ms, milliseconds; SEPs, somatosensory evoked potentials, MIRAS, Mitochondrial recessive ataxia syndrome; SANDO, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; MERRF, Myoclonic epilepsy associated with ragged-red fibers; MELAS, Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; PS, photosensitive.

^aOfficial myoclonus subtype is unknown.

TABLE 2 Clinical clues associated with main myoclonus-ataxia syndromes

Clinical Features	Disease (Gene Name)
Developmental delay or regression	Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6) Progressive myoclonic epilepsy type 3, or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) Neuronal ceroid lipofuscinosis type 2 (MYC/ATX-TPP1) POLG-ataxia and allelic disorders (POLG) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Neuronal ceroid lipofuscinosis type 7 (MFSD8) Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3) SCN1A-related disorder (SCN1A) SLC6A1-related disorder (SLC6A1) Autosomal dominant mental retardation type 5 (SYNGAP1)
Cognitive decline or mental retardation (usually mild and/or infrequent)	Myoclonic epilepsy of Unverricht and Lundborg (MYC/ATX-CSTB) North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2) Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) Myoclonus epilepsy and ataxia due to potassium channel mutation (KCNC1) Progressive myoclonic epilepsy type 1B (PRICKLE1) Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3) Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1)
Cognitive impairment or mental retardation (usually moderate or severe)	Myoclonic epilepsy of Lafora (MYC/ATX-EPM2A) Myoclonic epilepsy of Lafora (MYC/ATX-NHLRC1) Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6) Progressive myoclonic epilepsy type 3, or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) Neuronal ceroid lipofuscinosis type 2 (MYC/ATX-TPP1) POLG-ataxia and allelic disorders (POLG) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Neuronal ceroid lipofuscinosis type 7 (MFSD8) Autosomal dominant mental retardation type 5 (SYNGAP1) Neuronal ceroid lipofuscinosis type 4B (MYC-DNAJC5) SLC6A1-related disorder (SLC6A1) SCN1A-related disorder (SCN1A) Spinocerebellar ataxia type 2 (ATX-ATXN2) Dentatorubral-pallidoluysian atrophy (ATX-ATN1) Prion diseases (PRNP) MERRF and MELAS syndrome (mt-MTTK)
Behavioral disorders	Opsoclonus-myoclonus-ataxia syndrome Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6) POLG-ataxia and allelic disorders (POLG) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Dentatorubral-pallidoluysian atrophy (ATX-ATN1) Prion diseases (PRNP) Neuronal ceroid lipofuscinosis type 4B (MYC-DNAJC5) Autosomal dominant mental retardation type 5 (SYNGAP1) MERRF and MELAS syndrome (mt-MTTK)
Autistic features	SLC6A1-related disorder (SLC6A1) Autosomal dominant mental retardation type 5 (SYNGAP1)
Insomnia	Opsoclonus-myoclonus-ataxia syndrome Prion diseases: familial fatal insomnia (PRNP) Autosomal dominant mental retardation type 5 (SYNGAP1)
Hallucinations	Myoclonic epilepsy of Lafora (MYC/ATX-EPM2A) Myoclonic epilepsy of Lafora (MYC/ATX-NHLRC1)
Opsoclonus	Opsoclonus-myoclonus-ataxia syndrome
Oculomotor apraxia	Ataxia-telangiectasia (ATX-ATM) Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2)
Ophthalmoparesis	Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) POLG-related ataxias (sensory ataxic neuropathy, dysarthria, and ophthalmoparesis - SANDO) Progressive myoclonic epilepsy type 1B (PRICKLE1) Prion diseases (PRNP)
Nystagmus	Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) POLG-ataxia and allelic disorders (POLG)
Retinopathy (cherry-red spots)	Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1)

(Continues)

TABLE 2 Continued

Clinical Features	Disease (Gene Name)
Retinopathy	Neuronal ceroid lipofuscinosis type 2 (MYC/ATX-TPP1) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Neuronal ceroid lipofuscinosis type 7 (MFSD8)
Optic atrophy	Neuronal ceroid lipofuscinosis type 7 (MFSD8) POLG-ataxia and allelic disorders (POLG)
Cataracts	POLG-ataxia and allelic disorders (POLG) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1)
Hearing loss	Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) MERRF and MELAS syndrome (mt-MTTK)
Peripheral neuropathy	Progressive myoclonic epilepsy type 4 with or without renal failure (MYC-SCARB2) North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2) Ataxia-telangiectasia (ATX-ATM) Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) POLG-ataxia and allelic disorders (POLG) Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Progressive myoclonic epilepsy type 1B (PRICKLE1) Celiac disease
Muscle atrophy and weakness	MERRF and MELAS syndrome (mt-MTTK) POLG-ataxia and allelic disorders (POLG) Ataxia-telangiectasia (ATX-ATM) Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2) Congenital disorder of glycosylation, type Ic (ATX-ALG6) Spinocerebellar ataxia type 2 (ATX-ATXN2) Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3)
Parkinsonism	Spinocerebellar ataxia type 2 (ATX-ATXN2) POLG-ataxia and allelic disorders (POLG) Prion diseases (PRNP) Neuronal ceroid lipofuscinosis type 4B (MYC-DNAJC5) Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6)
Tremor	Progressive myoclonic epilepsy type 4 with or without renal failure (MYC-SCARB2) Ataxia-telangiectasia (ATX-ATM) Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) Progressive myoclonic epilepsy type 1B (PRICKLE1) SLC6A1-related disorder (SLC6A1) Myoclonus epilepsy and ataxia due to potassium channel mutation (KCNC1) POLG-ataxia and allelic disorders (POLG)
Dystonia	Neuronal ceroid lipofuscinosis type 6 or Kufs disease (MYC-CLN6) Ataxia-telangiectasia (ATX-ATM) Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) Neuronal ceroid lipofuscinosis type 2 (MYC/ATX-TPP1) POLG-ataxia and allelic disorders Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3) Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2)
Chorea	Ataxia-telangiectasia (ATX-ATM) Dentatorubral-pallidoluysian atrophy (ATX-ATN1)
Pyramidal signs	Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) Progressive myoclonic epilepsy type 3, or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) Progressive myoclonic epilepsy type 1B (PRICKLE1) SCN1A-related disorder (SCN1A) Dentatorubral-pallidoluysian atrophy (ATX-ATN1) Autosomal recessive spastic ataxia type 5 (ATX/HSP-AFG3L2) Prion diseases (PRNP)
Hypogonadism	Autosomal recessive spinocerebellar ataxia type 16 (ATX-STUB1) POLG-ataxia and allelic disorders (POLG)
Telangiectasias	Ataxia-telangiectasia (ATX-ATM)
Pes cavus	North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2) Primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3)

(Continues)

TABLE 2 Continued

Clinical Features	Disease (Gene Name)
Scoliosis or other skeletal deformations	Progressive myoclonic epilepsy type 3, or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2) Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) Autosomal dominant mental retardation type 5 (SYNGAP1)
Dysmorphic features	Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2) Autosomal dominant mental retardation type 5 (SYNGAP1)
Microcephaly	Progressive myoclonic epilepsy type 3, or neuronal ceroid lipofuscinosis type 14 (MYC/ATX-KCTD7) Autosomal dominant mental retardation type 5 (SYNGAP1)
Stroke-like episodes	MERRF and MELAS syndrome (mt-MTTK) POLG-ataxia and allelic disorders (POLG)
Short stature	MERRF and MELAS syndrome (mt-MTTK) Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) Ataxia-telangiectasia (ATX-ATM)
Neoplasia	Ataxia-telangiectasia (ATX-ATM) Opsoclonus-myoclonus-ataxia syndrome
Immunodeficiency	Ataxia-telangiectasia (ATX-ATM)
Renal failure	Progressive myoclonic epilepsy type 4 with or without renal failure (MYC-SCARB2)
Cardiac abnormalities	Neuraminidase deficiency or sialidosis type I and II (MYC/ATX-NEU1) POLG-ataxia and allelic disorders (POLG) MERRF and MELAS syndrome (mt-MTTK)

Methods

A comprehensive and structured search in PubMed following PRISMA was performed by two independent reviewers (MR, SV) to identify those diseases that may combine myoclonus with ataxia. Disorders that presented with either myoclonus or myoclonic seizures were included, for it is historically unclear whether, despite a clear clinical difference, a neurobiological distinction exists between cortical myoclonus and myoclonic epilepsy with both cortically driven jerks. The following search strategy was conducted: (“myoclonus”[tiab] OR “myoclonus”[Mesh] OR myoclonic disorder*[tiab]) AND (“ataxia”[tiab] OR “ataxia”[Mesh] OR ataxic disorder*[tiab]) AND (gene*[tiab] OR acquired cause*[tiab] OR metabolic disease*[tiab] OR “inborn errors of metabolism”[tiab] OR etiolog*[tiab] OR “causality”[tiab] OR “drug-induced”[tiab] OR “toxin”[tiab] OR autoimmune*[tiab] OR paraneoplastic*[tiab]) AND English[LA]. Publications written in English and published up to December 31, 2018 (without a start date as limitation) were reviewed. To ensure that no genetic diseases would be missed, the key words “myoclonus” and “ataxia” were also applied in OMIM and GeneReviews.

Results

A total of 30 disorders shown in Table 1 were identified as the main MAS because of the high frequency of combined myoclonus and ataxia, of which four were acquired and 26 genetic.

Hundred-and-five other disorders were either only occasionally associated with a combined myoclonus and ataxia presentation, or had an unconfirmed genetic cause; these are listed in Table S1.

An extensive review of series and cases confirmed that most MAS present as PMA or PME.³ In general, PMA are conditions presenting first with ataxia, with the subsequent development of myoclonus, and eventually drug-responsive epilepsy with infrequent seizures. In contrast, PME disorders were characterized by frequent and refractory epilepsy with severe cognitive decline.⁵ Applying the new refined definition of PMA,⁵ a total of 12 entities could be classified as such (shown in bold in Table 1), of which celiac disease, prion diseases, North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2), sialidosis type I (MYC/ATX-NEU1), and spinocerebellar ataxias types 2 (ATX-ATXN2) and 14 (ATX-PRKCG) were the most relevant. One should keep in mind that these genetic disorders show variability in the clinical presentation; severe and frequent seizures can be present in some patients, in whom the clinical syndrome would be classified as PME. However, in the aforementioned 12 entities, this is true in the minority of cases. In addition, conditions like myoclonic epilepsy of Unverricht-Lundborg (MYC/ATX-CSTB)¹⁹⁹ and Kufs disease (MYC-CLN6)²⁰⁰ are considered as PME; however, they can sometimes present as PMA.

Some PMA disorders showed ataxia as the predominant clinical sign, as was the case of ataxia-telangiectasia (ATX-ATM),²⁰¹ the spinocerebellar ataxias type 2 (ATX-ATXN2),^{202,203} type 3 (ATX-ATXN3),²⁰³ type 14 (ATX-PRKCG),^{204,205} the dentatorubral-pallidolysian atrophy (ATX-ATN1)²⁰⁶ or ATX-STUB1,²⁰⁷ whereas in other conditions, such as, North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2),²⁰⁸ and

FIG 1. Clinical diagnostic algorithm for myoclonus-ataxia syndromes with onset in infancy or childhood. For didactic purposes, this figure includes the main myoclonus-ataxia syndromes (entities where myoclonus and ataxia are prominent and frequent features) and which therefore should be suspected first, before considering disorders where the combination of myoclonus and ataxia is found only occasionally. In addition, next-generation sequencing techniques can be the first step in the diagnostic process in many cases and the genetic finding can be matched or validated with the clinical features displayed in both figures. Conditions with (possible) faster disease progression are shown in bold. CMA: chromosomal microarray analysis; Del/dupl: deletions and duplications; REA: repeat expansion analysis; SGS: single gene sequencing; TGP: targeted gene panels; WES: whole exome sequencing; LH: luteinizing hormone; FSH: follicle stimulating hormone; CK: creatine kinase. Conditions with (possible) faster disease progression are shown in bold.

FIG 2. Clinical diagnostic algorithm for myoclonus-ataxia syndromes with onset in adulthood. For didactic purposes, this figure includes the main myoclonus-ataxia syndromes (entities where myoclonus and ataxia are prominent and frequent features) and which therefore should be suspected first, before considering disorders where the combination of myoclonus and ataxia is found only occasionally. In addition, next-generation sequencing techniques can be the first step in the diagnostic process in many cases and the genetic finding can be matched or validated with the clinical features displayed in both figures. Conditions with (possible) faster disease progression are shown in bold. CMA: chromosomal microarray analysis; Del/dupl: deletions and duplications; REA: repeat expansion analysis; RRFs: ragged red fibers; SGS: single gene sequencing; TGP: targeted gene panels; WES: whole exome sequencing; FLAIR: fluid attenuated inversion recovery; DWI: diffusion-weight imaging; LH: luteinizing hormone; FSH: follicle stimulating hormone. Conditions with (possible) faster disease progression are shown in bold.

myoclonus epilepsy and ataxia due to KCNC1 gene mutations,²⁰⁹ myoclonus was often the main clinical feature.

In some cases, it is difficult to separate the effects of action myoclonus from ataxia on motor examination.²¹⁰ In children with PME, negative myoclonic jerks causing a loss of isotonic muscle activity and atonic seizures can interrupt smooth movement, affect balance and produce “pseudoataxia”.²¹¹ These presumed ataxic features may improve or cease when myoclonus is controlled by appropriate treatment.^{212,213} The use of electrophysiological techniques, especially a combined electroencephalography and polymyography, can be of additional value in identifying myoclonic jerks and determine the origin of these jerks.²¹⁴

Different types of myoclonus were described in the MAS (Table 1). In relation to the anatomical origin of myoclonus, cortical myoclonus was the most frequent type of myoclonus and presented typically as action-induced and stimulus-sensitive myoclonus, predominantly in distal limbs and face.^{215,216} Cortical myoclonus was present in several conditions, such as myoclonic epilepsy of Unverricht-Lundborg, myoclonic epilepsy of Lafora or North Sea progressive myoclonus epilepsy (MYC/ATX-GOSR2). Subcortical myoclonus was present in ataxia-telangiectasia (ATX-ATM),²⁰¹ the spinocerebellar ataxias types 2 (ATX-ATXN2) and 14 (ATX-PRKCG)^{204,217} and in primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3).²¹⁸ A brainstem origin of subcortical myoclonic jerks was presumed in prion diseases (although a cortical component or origin could not be completely excluded)²¹⁹ and in opsoclonus-myoclonus-ataxia syndrome.²²⁰ Of importance, the electrophysiological interpretation of jerky movements was sometimes problematic because the myoclonic discharges were superimposed in body parts also affected by dystonia, tremor or chorea.^{11,24,201,204,217}

Specific clinical forms of myoclonus can be present. First, polyminimyoclonus, characterized by small amplitude, jerky abnormal movements in the hands and fingers, which is suggestive of multiple system atrophy²¹⁶ or opsoclonus-myoclonus-ataxia syndrome.²²¹ Second, excessive fragmentary myoclonus, a sleep disorder characterized by subtle and fine movements at the fingertips, feet, or lips that persist throughout all stages of sleep, which can be particularly frequent in spinocerebellar ataxia type 3 (ATX-ATXN3).²²²

Diagnostic Approach

The large number of causes of MAS as well as the phenotypic overlap of these disorders obviously poses a challenge in clinical practice to establish a proper (genetic) diagnosis. Still, certain clinical manifestations are highly suggestive of specific diseases, such as the presence of hallucinations in myoclonic epilepsy of Lafora, opsoclonus in opsoclonus-myoclonus-ataxia syndrome, oculomotor apraxia or telangiectasias in ataxia-telangiectasia, cherry-red spots in the retina in sialidosis type 1, hypogonadotropic hypogonadism in ATX-STUB1 or hypergonadotropic hypogonadism in POLG-ataxia and dysmorphic features in sialidosis type 2. These and other clinical clues than can help reducing the

number of entities to consider when facing a patient with a MAS are listed in Table 2.

Diagnostic algorithms for childhood- and adult-onset MAS are illustrated in Figures 1 and 2, respectively. Acquired disorders should be initially ruled out both in adults and children as these are more common than the genetically determined MAS. These include celiac disease, multiple system atrophy type C and prion diseases in adulthood (Table 1), and the clinical syndrome of opsoclonus-myoclonus-ataxia, often associated with a neoplasm or autoimmune disease in children, and which can also be seen in adults.

Biochemical markers could be screened before genetic testing when there is a high clinical suspicion of specific disorders, such as celiac disease antibodies, alpha-fetoprotein for ataxia-telangiectasia, and neuraminidase activity or urinary sialyl-oligosaccharides for sialidosis type I. Conversely, these could be used as confirmatory markers in case genetic testing was done first.

As many of the MAS are of genetic origin, NGS techniques, i.e. targeted gene panels (TGP) or whole exome sequencing (WES), will often be needed to establish a diagnosis given the genetic heterogeneity and clinical overlap. In children with MAS, WES or TGP (preferentially including copy number variation analysis, to avoid missing some cases of myoclonic epilepsy of Lafora) could be considered first-tier genetic tests. If negative, this could be followed by repeat expansions analysis (REA) to detect myoclonic epilepsy of Unverricht-Lundborg (Fig. 1). In the pediatric population, the diagnostic and clinical utility of WES has been shown to be greater than CMA.²²³ In adults with MAS, REA could be considered first-tier genetic tests if a spinocerebellar ataxia, such as ATX-ATXN2 or ATX-ATN1 is suspected. If mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome and/or myoclonic epilepsy associated with ragged-red fibers (MERRF) syndrome or the MERRF/MELAS overlap syndrome is suspected, TGP or WES of blood leukocyte DNA is suggested, taking into account the occurrence of heteroplasmy in mitochondrial disorders, which may require testing DNA isolated from other tissues, such as skeletal muscle, buccal mucosa, or cultured skin fibroblasts.

In Table S2, a total of 123 genes involved in disorders that combine myoclonus and ataxia are listed, which could be used for the development of specific TGP or for dedicated exome strategies that prioritize those genes that are associated with overlap phenotypes of myoclonus and ataxia.

The fact that numerous disorders present with the combination of myoclonus and ataxia, points to the possible pathophysiological link between the origin of myoclonus and cerebellar alterations, such as disruption of the cerebello-thalamo-cortical pathway due to loss of Purkinje cells or dentate nuclei neurons, as well as a reduction in the concentration of γ -aminobutyric acid (GABA)-ergic synapses in the sensori-motor cortex leading to cortical disinhibition.²²⁴ In addition, most MAS have impaired posttranslational modification of proteins to which certain neuronal groups might be particularly vulnerable compared with others.²²⁴

It is important to early recognize the treatable acquired or metabolic disorders, such as opsoclonus-myoclonus-ataxia syndrome, celiac disease, and primary coenzyme Q10 deficiency, type 4 (ATX-ADCK3). Patients will obviously benefit from an early diagnosis and timely treatment.

Conclusions

The MAS are a clinically and etiologically heterogeneous group of disorders. We have provided diagnostic algorithms for children and adults based on clinical manifestations that will guide diagnostic procedures. However, NGS techniques can be the first diagnostic step in many cases and the genetic finding can be matched or validated with the clinical features displayed in the diagnostic algorithms. Targeted gene panels or exome filters to genetically characterize MAS could be developed based on the list of genes associated with MAS that is provided.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

M.R.: 1A, 1B, 1C, 2A.

S.v.d.V.: 1A, 1B, 1C, 2A.

M.M.: 1A, 1B, 1C, 2B.

M.T.: 1A, 1B, 1C, 2B.

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Disclosures

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References

- Balint B, Bhatia KP. Isolated and combined dystonia syndromes - an update on new genes and their phenotypes. *Eur J Neurol* 2015;22: 610-617.
- Rossi M, Balint B, Millar Vernetti P, Bhatia KP, Merello M. Genetic dystonia-ataxia syndromes: Clinical Spectrum, diagnostic approach, and treatment options. *Mov Disord Clin Pract* 2018;5:373-382.
- van der Veen S, Zutt R, Klein C, et al. Nomenclature of genetically determined myoclonus syndromes: recommendations of the International Parkinson and Movement Disorder Society task force. *Mov Disord* 2019;34:1602-1613.
- Rossi M, Anheim M, Durr A, et al. The genetic nomenclature of recessive cerebellar ataxias. *Mov Disord* 2018;33:1056-1076.
- van der Veen S, Zutt R, Elting JWJ, Becker CE, de Koning TJ, Tijssen MAJ. Progressive myoclonus ataxia: Time for a new definition? *Mov Disord* 2018;33:1281-1286.
- Hersh B, Dalmau J, Dangond F, Gultekin S, Geller E, Wen PY. Paraneoplastic opsoclonus-myoclonus associated with anti-Hu antibody. *Neurology* 1994;44:1754-1755.
- Nasri A, Kacem I, Jerdak F, et al. Paraneoplastic opsoclonus-myoclonus-ataxia syndrome revealing dual malignancy. *Neurol Sci* 2016;37: 1723-1725.
- Oh SY, Kim JS, Dieterich M. Update on opsoclonus-myoclonus syndrome in adults. *J Neurol* 2018.
- Pranzatelli MR, Tate ED, McGee NR. Demographic, Clinical, and Immunologic Features of 389 Children with Opsoclonus-Myoclonus Syndrome: A Cross-sectional Study. *Front Neurol* 2017;8:468.
- Van Diest D, De Raeye H, Claes J, Parizel PM, De Ridder D, Cras P. Paraneoplastic Opsoclonus-Myoclonus-Ataxia (OMA) syndrome in an adult patient with esthesioneuroblastoma. *J Neurol* 2008;255:594-596.
- van Toorn R, Rabie H, Warwick JM. Opsoclonus-myoclonus in an HIV-infected child on antiretroviral therapy--possible immune reconstitution inflammatory syndrome. *Eur J Paediatr Neurol* 2005;9:423-426.
- Gwinn KA, Caviness JN. Electrophysiological observations in idiopathic opsoclonus-myoclonus syndrome. *Mov Disord* 1997;12:438-442.
- Gordon N. Cerebellar ataxia and gluten sensitivity: a rare but possible cause of ataxia, even in childhood. *Dev Med Child Neurol* 2000;42: 283-286.
- Bhatia KP, Brown P, Gregory R, et al. Progressive myoclonic ataxia associated with coeliac disease. The myoclonus is of cortical origin, but the pathology is in the cerebellum. *Brain* 1995;118(Pt 5):1087-1093.
- Fung VS, Duggins A, Morris JG, Lorentz IT. Progressive myoclonic ataxia associated with celiac disease presenting as unilateral cortical tremor and dystonia. *Mov Disord* 2000;15:732-734.
- Khwaja GA, Bohra V, Duggal A, Ghuge VV, Chaudhary N. Gluten Sensitivity - A Potentially Reversible Cause of Progressive Cerebellar Ataxia and Myoclonus - A Case Report. *J Clin Diagn Res* 2015;9: OD07-OD08.
- Sarrigiannis PG, Hoggard N, Aeschlimann D, et al. Myoclonus ataxia and refractory coeliac disease. *Cerebellum Ataxias* 2014;1:11.
- Borg M. Symptomatic myoclonus. *Neurophysiol Clin* 2006;36:309-318.
- Lu CS, Thompson PD, Quinn NP, Parkes JD, Marsden CD. Ramsay Hunt syndrome and coeliac disease: a new association? *Mov Disord* 1986;1:209-219.
- Javed S, Safdar A, Forster A, et al. Refractory coeliac disease associated with late onset epilepsy, ataxia, tremor and progressive myoclonus with giant cortical evoked potentials--a case report and review of literature. *Seizure* 2012;21:482-485.
- Tison F, Arne P, Henry P. Myoclonus and adult coeliac disease. *J Neurol* 1989;236:307-308.
- Chinnery PF, Reading PJ, Milne D, Gardner-Medwin D, Turnbull DM. CSF antigliadin antibodies and the Ramsay Hunt syndrome. *Neurology* 1997;49:1131-1133.
- Wenning GK, Ben Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. *Brain* 1994;117(Pt 4):835-845.
- Tzoulis C, Engelsens BA, Telstad W, et al. The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 cases. *Brain* 2006;129:1685-1692.
- Okuma Y, Fujishima K, Miwa H, Mori H, Mizuno Y. Myoclonic tremulous movements in multiple system atrophy are a form of cortical myoclonus. *Mov Disord* 2005;20:451-456.
- Rodriguez ME, Artieda J, Zubieta JL, Obeso JA. Reflex myoclonus in olivopontocerebellar atrophy. *J Neurol Neurosurg Psychiatry* 1994;57: 316-319.
- Batla A, De Pablo-Fernandez E, Ero R, et al. Young-onset multiple system atrophy: Clinical and pathological features. *Mov Disord* 2018;33: 1099-1107.

28. Baiardi S, Magherini A, Capellari S, et al. Towards an early clinical diagnosis of sporadic CJD VV2 (ataxic type). *J Neurol Neurosurg Psychiatry* 2017;88:764–772.
29. Binelli S, Agazzi P, Canafoglia L, et al. Myoclonus in Creutzfeldt-Jakob disease: polygraphic and video-electroencephalography assessment of 109 patients. *Mov Disord* 2010;25:2818–2827.
30. Cooper SA, Murray KL, Heath CA, Will RG, Knight RS. Sporadic Creutzfeldt-Jakob disease with cerebellar ataxia at onset in the UK. *J Neurol Neurosurg Psychiatry* 2006;77:1273–1275.
31. Rudge P, Jaunmuktane Z, Adlard P, et al. Iatrogenic CJD due to pituitary-derived growth hormone with genetically determined incubation times of up to 40 years. *Brain* 2015;138:3386–3399.
32. Shi Q, Zhou W, Chen C, et al. The Features of Genetic Prion Diseases Based on Chinese Surveillance Program. *PLoS One* 2015;10:e0139552.
33. Spacey SD, Pastore M, McGillivray B, Fleming J, Gambetti P, Feldman H. Fatal familial insomnia: the first account in a family of Chinese descent. *Arch Neurol* 2004;61:122–125.
34. Andrade DM, Ackerley CA, Minett TS, et al. Skin biopsy in Lafora disease: genotype-phenotype correlations and diagnostic pitfalls. *Neurology* 2003;61:1611–1614.
35. Berkovic SF, Mazarib A, Walid S, et al. A new clinical and molecular form of Unverricht-Lundborg disease localized by homozygosity mapping. *Brain* 2005;128:652–658.
36. Genton P. Unverricht-Lundborg disease (EPM1). *Epilepsia* 2010;51 (Suppl 1):37–39.
37. Kalviainen R, Khyuppenen J, Koskenkorva P, Eriksson K, Vanninen R, Mervaala E. Clinical picture of EPM1-Unverricht-Lundborg disease. *Epilepsia* 2008;49:549–556.
38. Kasai K, Onuma T, Kato M, et al. Differences in evoked potential characteristics between DRPLA patients and patients with progressive myoclonic epilepsy: preliminary findings indicating usefulness for differential diagnosis. *Epilepsy Res* 1999;37:3–11.
39. Laloti MD, Scott HS, Buresi C, et al. Dodecamer repeat expansion in cystatin B gene in progressive myoclonus epilepsy. *Nature* 1997;386:847–851.
40. Mazarib A, Xiong L, Neufeld MY, et al. Unverricht-Lundborg disease in a five-generation Arab family: instability of dodecamer repeats. *Neurology* 2001;57:1050–1054.
41. Magaouda A, Ferlazzo E, Nguyen VH, Genton P. Unverricht-Lundborg disease, a condition with self-limited progression: long-term follow-up of 20 patients. *Epilepsia* 2006;47:860–866.
42. Franceschetti S, Canafoglia L, Rotondi F, Visani E, Granvillano A, Panzica F. The network sustaining action myoclonus: a MEG-EMG study in patients with EPM1. *BMC Neurol* 2016;16:214.
43. Avanzini G, Shibasaki H, Rubboli G, et al. Neurophysiology of myoclonus and progressive myoclonus epilepsies. *Epileptic Disord* 2016;18:11–27.
44. Panzica F, Canafoglia L, Franceschetti S, et al. Movement-activated myoclonus in genetically defined progressive myoclonic epilepsies: EEG-EMG relationship estimated using autoregressive models. *Clin Neurophysiol* 2003;114:1041–1052.
45. Ganesh S, Delgado-Escueta AV, Suzuki T, et al. Genotype-phenotype correlations for EPM2A mutations in Lafora's progressive myoclonus epilepsy: exon 1 mutations associate with an early-onset cognitive deficit subphenotype. *Hum Mol Genet* 2002;11:1263–1271.
46. Harirchian MH, Shandiz EE, Turnbull J, Minassian BA, Shahsiah R. Lafora disease: a case report, pathologic and genetic study. *Indian J Pathol Microbiol* 2011;54:374–375.
47. Jara-Prado A, Ochoa A, Alonso ME, et al. Late onset Lafora disease and novel EPM2A mutations: breaking paradigms. *Epilepsy Res* 2014;108:1501–1510.
48. Schorlemmer K, Bauer S, Belke M, et al. Sustained seizure remission on perampanel in progressive myoclonic epilepsy (Lafora disease). *Epilepsy Behav Case Rep* 2013;1:118–121.
49. Singh S, Sethi I, Franceschetti S, et al. Novel NHLRC1 mutations and genotype-phenotype correlations in patients with Lafora's progressive myoclonic epilepsy. *J Med Genet* 2006;43:e48.
50. Casciato S, Gambardella S, Mascia A, et al. Severe and rapidly-progressive Lafora disease associated with NHLRC1 mutation: a case report. *Int J Neurosci* 2017;127:1150–1153.
51. Gomez-Abad C, Gomez-Garre P, Gutierrez-Delgado E, et al. Lafora disease due to EPM2B mutations: a clinical and genetic study. *Neurology* 2005;64:982–986.
52. Satishchandra P, Sinha S. Progressive myoclonic epilepsy. *Neurol India* 2010;58:514–522.
53. Striano P, Ackerley CA, Cervasio M, et al. 22-year-old girl with status epilepticus and progressive neurological symptoms. *Brain Pathol* 2009;19:727–730.
54. Boisse Lomax L, Bayly MA, Hjalgrim H, et al. 'North Sea' progressive myoclonus epilepsy: phenotype of subjects with GOSR2 mutation. *Brain* 2013;136:1146–1154.
55. Prasherberger R, Balint B, Mencacci NE, et al. Expanding the Phenotype and Genetic Defects Associated with the GOSR2 Gene. *Mov Disord Clin Pract* 2015;2:271–273.
56. van der Veen S, Zutt R, Elting JWJ, Becker CE, de Koning TJ, Tijssen MAJ. Progressive myoclonus ataxia: Time for a new definition? *Mov Disord* 2018;33:1281–1286.
57. van Egmond ME, Verschuuren-Bemelmans CC, Nibbeling EA, et al. Ramsay Hunt syndrome: clinical characterization of progressive myoclonus ataxia caused by GOSR2 mutation. *Mov Disord* 2014;29:139–143.
58. van Egmond ME, Weijenberg A, van Rijn ME, et al. The efficacy of the modified Atkins diet in North Sea Progressive Myoclonus Epilepsy: an observational prospective open-label study. *Orphanet J Rare Dis* 2017;12:45.
59. Andrade DM, Paton T, Turnbull J, Marshall CR, Scherer SW, Minassian BA. Mutation of the CLN6 gene in teenage-onset progressive myoclonus epilepsy. *Pediatr Neurol* 2012;47:205–208.
60. Arsov T, Smith KR, Damiano J, et al. Kufs disease, the major adult form of neuronal ceroid lipofuscinosis, caused by mutations in CLN6. *Am J Hum Genet* 2011;88:566–573.
61. Berkovic SF, Oliver KL, Canafoglia L, et al. Kufs disease due to mutation of CLN6: clinical, pathological and molecular genetic features. *Brain* 2019;142:59–69.
62. Bouhouche A, Regragui W, El Fahime E, et al. CLN6 p.L154del mutation causing late infantile neuronal ceroid lipofuscinosis in a large consanguineous Moroccan family. *Indian J Pediatr* 2013;80:694–696.
63. Canafoglia L, Gilioli I, Invernizzi F, et al. Electroclinical spectrum of the neuronal ceroid lipofuscinoses associated with CLN6 mutations. *Neurology* 2015;85:316–324.
64. Lv Y, Zhang N, Liu C, Shi M, Sun L. Occipital epilepsy versus progressive myoclonic epilepsy in a patient with continuous occipital spikes and photosensitivity in electroencephalogram: A case report. *Medicine (Baltimore)* 2018;97:e0299.
65. Ozkara C, Gunduz A, Coskun T, et al. Long-term follow-up of two siblings with adult-onset neuronal ceroid lipofuscinosis, Kufs type A. *Epileptic Disord* 2017;19:147–151.
66. Sato R, Inui T, Endo W, et al. First Japanese variant of late infantile neuronal ceroid lipofuscinosis caused by novel CLN6 mutations. *Brain Dev* 2016;38:852–856.
67. Blumkin L, Kivity S, Lev D, et al. A compound heterozygous missense mutation and a large deletion in the KCTD7 gene presenting as an opsoclonus-myoclonus ataxia-like syndrome. *J Neurol* 2012;259:2590–2598.
68. Farhan SM, Murphy LM, Robinson JF, et al. Linkage analysis and exome sequencing identify a novel mutation in KCTD7 in patients with progressive myoclonus epilepsy with ataxia. *Epilepsia* 2014;55:e106–e111.
69. Kousi M, Anttila V, Schulz A, et al. Novel mutations consolidate KCTD7 as a progressive myoclonus epilepsy gene. *J Med Genet* 2012;49:391–399.
70. Moen MN, Fjaer R, Hamdani EH, et al. Pathogenic variants in KCTD7 perturb neuronal K⁺ fluxes and glutamine transport. *Brain* 2016;139:3109–3120.
71. Van Bogaert P, Azizieh R, Desir J, et al. Mutation of a potassium channel-related gene in progressive myoclonic epilepsy. *Ann Neurol* 2007;61:579–586.
72. Kim H, Lee S, Choi M, et al. Familial cases of progressive myoclonic epilepsy caused by maternal somatic mosaicism of a recurrent KCNC1 p.Arg320His mutation. *Brain Dev* 2018;40:429–432.
73. Muona M, Berkovic SF, Dibbens LM, et al. A recurrent de novo mutation in KCNC1 causes progressive myoclonus epilepsy. *Nat Genet* 2015;47:39–46.
74. Oliver KL, Franceschetti S, Milligan CJ, et al. Myoclonus epilepsy and ataxia due to KCNC1 mutation: Analysis of 20 cases and K(+) channel properties. *Ann Neurol* 2017;81:677–689.

75. Balreira A, Gaspar P, Caiola D, et al. A nonsense mutation in the LIMP-2 gene associated with progressive myoclonic epilepsy and nephrotic syndrome. *Hum Mol Genet* 2008;17:2238–2243.
76. Dardis A, Filocamo M, Grossi S, et al. Biochemical and molecular findings in a patient with myoclonic epilepsy due to a mistarget of the beta-glucosidase enzyme. *Mol Genet Metab* 2009;97:309–311.
77. Dibbens LM, Karakis I, Bayly MA, Costello DJ, Cole AJ, Berkovic SF. Mutation of SCARB2 in a patient with progressive myoclonus epilepsy and demyelinating peripheral neuropathy. *Arch Neurol* 2011;68:812–813.
78. Dibbens LM, Michelucci R, Gambardella A, et al. SCARB2 mutations in progressive myoclonus epilepsy (PME) without renal failure. *Ann Neurol* 2009;66:532–536.
79. Fu YJ, Aida I, Tada M, et al. Progressive myoclonus epilepsy: extraneuronal brown pigment deposition and system neurodegeneration in the brains of Japanese patients with novel SCARB2 mutations. *Neuropathol Appl Neurobiol* 2014;40:551–563.
80. Guerrero-Lopez R, Garcia-Ruiz PJ, Giraldez BG, et al. A new SCARB2 mutation in a patient with progressive myoclonus ataxia without renal failure. *Mov Disord* 2012;27:1826–1827.
81. He J, Lin H, Li JJ, et al. Identification of a Novel Homozygous Splice-Site Mutation in SCARB2 that Causes Progressive Myoclonus Epilepsy with or without Renal Failure. *Chin Med J (Engl)* 2018;131:1575–1583.
82. He M, Tang BS, Li N, et al. Using a combination of whole-exome sequencing and homozygosity mapping to identify a novel mutation of SCARB2. *Clin Genet* 2014;86:598–600.
83. Perandones C, Pellene LA, Micheli F. A new SCARB2 mutation in a patient with progressive myoclonus ataxia without renal failure. *Mov Disord* 2014;29:158–159.
84. Rubboli G, Franceschetti S, Berkovic SF, et al. Clinical and neurophysiologic features of progressive myoclonus epilepsy without renal failure caused by SCARB2 mutations. *Epilepsia* 2011;52:2356–2363.
85. Tian WT, Liu XL, Xu YQ, et al. Progressive myoclonus epilepsy without renal failure in a Chinese family with a novel mutation in SCARB2 gene and literature review. *Seizure* 2018;57:80–86.
86. Zeigler M, Meiner V, Newman JP, et al. A novel SCARB2 mutation in progressive myoclonus epilepsy indicated by reduced beta-glucocerebrosidase activity. *J Neurol Sci* 2014;339:210–213.
87. Cummins G, Jawad T, Taylor M, Lynch T. Myoclonic head jerks and extensor axial dystonia in the variant form of ataxia telangiectasia. *Parkinsonism Relat Disord* 2013;19:1173–1174.
88. Levy A, Lang AE. Ataxia-telangiectasia: A review of movement disorders, clinical features and genotype correlations – Addendum. *Mov Disord* 2018;33:1372.
89. Liu XL, Wang T, Huang XJ, et al. Novel ATM mutations with ataxia-telangiectasia. *Neurosci Lett* 2016;611:112–115.
90. Meneret A, Ahmar-Beaugendre Y, Rieunier G, et al. The pleiotropic movement disorders phenotype of adult ataxia-telangiectasia. *Neurology* 2014;83:1087–1095.
91. Nakayama T, Sato Y, Uematsu M, et al. Myoclonic axial jerks for diagnosing atypical evolution of ataxia telangiectasia. *Brain Dev* 2015;37:362–365.
92. Teive HAG, Camargo CHF, Munhoz RP. More than ataxia – Movement disorders in ataxia-telangiectasia. *Parkinsonism Relat Disord* 2018;46:3–8.
93. Termsarasab P, Yang AC, Frucht SJ. Myoclonus in ataxia-telangiectasia. *Tremor Other Hyperkinet Mov (N Y)* 2015;5:298.
94. van Egmond ME, Elting JW, Kuiper A, et al. Myoclonus in childhood-onset neurogenetic disorders: The importance of early identification and treatment. *Eur J Paediatr Neurol* 2015;19:726–729.
95. Bettencourt C, de Yébenes JG, Lopez-Sendon JL, et al. Clinical and Neuropathological Features of Spastic Ataxia in a Spanish Family with Novel Compound Heterozygous Mutations in STUB1. *Cerebellum* 2015;14:378–381.
96. Cordoba M, Rodriguez-Quiroga S, Gatto EM, Alurralde A, Kauffman MA. Ataxia plus myoclonus in a 23-year-old patient due to STUB1 mutations. *Neurology* 2014;83:287–288.
97. Kawai T, Miyamoto R, Shimatani Y, Orlacchio A, Kaji R. Choreoathetosis, Dystonia, and Myoclonus in 3 Siblings With Autosomal Recessive Spinocerebellar Ataxia Type 16. *JAMA Neurol* 2016;73:888–890.
98. Synofzik M, Schule R, Schulze M, et al. Phenotype and frequency of STUB1 mutations: next-generation screenings in Caucasian ataxia and spastic paraplegia cohorts. *Orphanet J Rare Dis* 2014;9:57.
99. Ahn JH, Kim AR, Lee C, et al. Type 1 Sialidosis Patient With a Novel Deletion Mutation in the NEU1 Gene: Case Report and Literature Review. *Cerebellum* 2019.
100. Canafoglia L, Robbiano A, Pareyson D, et al. Expanding sialidosis spectrum by genome-wide screening: NEU1 mutations in adult-onset myoclonus. *Neurology* 2014;82:2003–2006.
101. Gowda VK, Srinivasan VM, Benakappa N, Benakappa A. Sialidosis Type 1 with a Novel Mutation in the Neuraminidase-1 (NEU1) Gene. *Indian J Pediatr* 2017;84:403–404.
102. Hu SC, Hung KL, Chen HJ, Lee WT. Seizure remission and improvement of neurological function in sialidosis with perampanel therapy. *Epilepsy Behav Case Rep* 2018;10:32–34.
103. Lai SC, Chen RS, Wu Chou YH, et al. A longitudinal study of Taiwanese sialidosis type 1: an insight into the concept of cherry-red spot myoclonus syndrome. *Eur J Neurol* 2009;16:912–919.
104. Mohammad AN, Bruno KA, Hines S, Atwal PS. Type 1 sialidosis presenting with ataxia, seizures and myoclonus with no visual involvement. *Mol Genet Metab Rep* 2018;15:11–14.
105. Sekijima Y, Nakamura K, Kishida D, et al. Clinical and serial MRI findings of a sialidosis type I patient with a novel missense mutation in the NEU1 gene. *Intern Med* 2013;52:119–124.
106. Franceschetti S, Canafoglia L. Sialidoses. *Epileptic Disord* 2016;18:89–93.
107. Chang X, Huang Y, Meng H, et al. Clinical study in Chinese patients with late-infantile form neuronal ceroid lipofuscinoses. *Brain Dev* 2012;34:739–745.
108. Di Giacomo R, Cianetti L, Caputo V, et al. Protracted late infantile ceroid lipofuscinosis due to TPP1 mutations: Clinical, molecular and biochemical characterization in three sibs. *J Neurol Sci* 2015;356:65–71.
109. Hunter MF, Peters H, Salemi R, Thorburn D, Mackay MT. Alpers syndrome with mutations in POLG: clinical and investigative features. *Pediatr Neurol* 2011;45:311–318.
110. Janssen W, Quaegebeur A, Van Goethem G, et al. The spectrum of epilepsy caused by POLG mutations. *Acta Neurol Belg* 2016;116:17–25.
111. Papandreou A, Rahman S, Fratter C, et al. Spectrum of movement disorders and neurotransmitter abnormalities in paediatric POLG disease. *J Inher Metab Dis* 2018;41:1275–1283.
112. Rajakulendran S, Pitceathly RD, Taanman JW, et al. A Clinical, Neuropathological and Genetic Study of Homozygous A467T POLG-Related Mitochondrial Disease. *PLoS One* 2016;11:e0145500.
113. Spiegler J, Stefanova I, Hellenbroich Y, Sperner J. Bowel obstruction in patients with Alpers-Huttenlocher syndrome. *Neuropediatrics* 2011;42:194–196.
114. Synofzik M, Srujies K, Godau J, Berg D, Schols L. Characterizing POLG ataxia: clinics, electrophysiology and imaging. *Cerebellum* 2012;11:1002–1011.
115. Aure K, Benoist JF, Ogier de Baulny H, Romero NB, Rigal O, Lomès A. Progression despite replacement of a myopathic form of coenzyme Q10 defect. *Neurology* 2004;63:727–729.
116. Horvath R, Czermin B, Gulati S, et al. Adult-onset cerebellar ataxia due to mutations in CABC1/ADCK3. *J Neurol Neurosurg Psychiatry* 2012;83:174–178.
117. Liu YT, Hersheson J, Plagnol V, et al. Autosomal-recessive cerebellar ataxia caused by a novel ADCK3 mutation that elongates the protein: clinical, genetic and biochemical characterisation. *J Neurol Neurosurg Psychiatry* 2014;85:493–498.
118. Sun M, Johnson AK, Nelakuditi V, et al. Targeted exome analysis identifies the genetic basis of disease in over 50% of patients with a wide range of ataxia-related phenotypes. *Genet Med* 2018.
119. Gerards M, van den Bosch B, Calis C, et al. Nonsense mutations in CABC1/ADCK3 cause progressive cerebellar ataxia and atrophy. *Mitochondrion* 2010;10:510–515.
120. Mignot C, Apartis E, Durr A, et al. Phenotypic variability in ARCA2 and identification of a core ataxic phenotype with slow progression. *Orphanet J Rare Dis* 2013;8:173.
121. Mancini C, Orsi L, Guo Y, et al. An atypical form of AOA2 with myoclonus associated with mutations in SETX and AFG3L2. *BMC Med Genet* 2015;16:16.
122. Pierson TM, Adams D, Bonn F, et al. Whole-exome sequencing identifies homozygous AFG3L2 mutations in a spastic ataxia-neuropathy syndrome linked to mitochondrial m-AAA proteases. *PLoS Genet* 2011;7:e1002325.

123. Miller BS, Freeze HH, Hoffmann GF, Sarafoglou K. Pubertal development in ALG6 deficiency (congenital disorder of glycosylation type Ic). *Mol Genet Metab* 2011;103:101–103.
124. Morava E, Tiemes V, Thiel C, et al. ALG6-CDG: a recognizable phenotype with epilepsy, proximal muscle weakness, ataxia and behavioral and limb anomalies. *J Inher Metab Dis* 2016;39:713–723.
125. Kousi M, Siintola E, Dvorakova L, et al. Mutations in CLN7/MFSD8 are a common cause of variant late-infantile neuronal ceroid lipofuscinosis. *Brain* 2009;132:810–819.
126. Siintola E, Topcu M, Aula N, et al. The novel neuronal ceroid lipofuscinosis gene MFSD8 encodes a putative lysosomal transporter. *Am J Hum Genet* 2007;81:136–146.
127. Patino LC, Battu R, Ortega-Recalde O, et al. Exome sequencing is an efficient tool for variant late-infantile neuronal ceroid lipofuscinosis molecular diagnosis. *PLoS One* 2014;9:e109576.
128. Mandel H, Cohen Katsanelson K, Khayat M, et al. Clinico-pathological manifestations of variant late infantile neuronal ceroid lipofuscinosis (vLINCL) caused by a novel mutation in MFSD8 gene. *Eur J Med Genet* 2014;57:607–612.
129. Mastrangelo M, Tolve M, Martinelli M, Di Noia SP, Parrini E, Leuzzi V. PRICKLE1-related early onset epileptic encephalopathy. *Am J Med Genet A* 2018;176:2841–2845.
130. Straussberg R, Basel-Vanagaite L, Kivity S, et al. An autosomal recessive cerebellar ataxia syndrome with upward gaze palsy, neuropathy, and seizures. *Neurology* 2005;64:142–144.
131. Tao H, Manak JR, Sowers L, et al. Mutations in prickle orthologs cause seizures in flies, mice, and humans. *Am J Hum Genet* 2011;88:138–149.
132. Algahtani H, Al-Hakami F, Al-Shehri M, et al. A very rare form of autosomal dominant progressive myoclonus epilepsy caused by a novel variant in the PRICKLE1 gene. *Seizure* 2019;69:133–139.
133. Becher MW, Rubinstein DC, Leggo J, et al. Dentatorubral and pallidolusian atrophy (DRPLA). Clinical and neuropathological findings in genetically confirmed North American and European pedigrees. *Mov Disord* 1997;12:519–530.
134. Licht DJ, Lynch DR. Juvenile dentatorubral-pallidolusian atrophy: new clinical features. *Pediatr Neurol* 2002;26:51–54.
135. Maruyama S, Saito Y, Nakagawa E, et al. Importance of CAG repeat length in childhood-onset dentatorubral-pallidolusian atrophy. *J Neurol* 2012;259:2329–2334.
136. Ono S, Kaneda K, Suzuki M, Tagawa A, Shimizu N. Dentatorubral-pallidolusian atrophy with chronic renal failure in a Japanese family. *Eur Neurol* 2002;47:222–223.
137. Sunami Y, Koide R, Arai N, Yamada M, Mizutani T, Oyanagi K. Radiologic and neuropathologic findings in patients in a family with dentatorubral-pallidolusian atrophy. *AJNR Am J Neuroradiol* 2011;32:109–114.
138. Tomiyasu H, Yoshii F, Ohnuki Y, Ikeda JE, Shinohara Y. The brainstem and thalamic lesions in dentatorubral-pallidolusian atrophy: an MRI study. *Neurology* 1998;50:1887–1890.
139. Vale J, Bugalho P, Silveira I, Sequeiros J, Guimaraes J, Coutinho P. Autosomal dominant cerebellar ataxia: frequency analysis and clinical characterization of 45 families from Portugal. *Eur J Neurol* 2010;17:124–128.
140. Yam WK, Wu NS, Lo IF, Ko CH, Yeung WL, Lam ST. Dentatorubral-pallidolusian atrophy in two Chinese families in Hong Kong. *Hong Kong Med J* 2004;10:53–56.
141. Abdel-Aleem A, Zaki MS. Spinocerebellar ataxia type 2 (SCA2) in an Egyptian family presenting with polyphagia and marked CAG expansion in infancy. *J Neurol* 2008;255:413–419.
142. Armstrong J, Bonaventura I, Rojo A, et al. Spinocerebellar ataxia type 2 (SCA2) with white matter involvement. *Neurosci Lett* 2005;381:247–251.
143. Boesch SM, Donnemiller E, Muller J, et al. Abnormalities of dopaminergic neurotransmission in SCA2: a combined 123I-betaCIT and 123I-IBZM SPECT study. *Mov Disord* 2004;19:1320–1325.
144. Crum BA, Josephs KA. Varied electrophysiologic patterns in spinocerebellar ataxia type 2. *Eur J Neurol* 2006;13:194–197.
145. De Rosa A, Striano P, Barbieri F, et al. Suppression of myoclonus in SCA2 by piracetam. *Mov Disord* 2006;21:116–118.
146. Durr A, Smadja D, Cancel G, et al. Autosomal dominant cerebellar ataxia type I in Martinique (French West Indies). Clinical and neuropathological analysis of 53 patients from three unrelated SCA2 families. *Brain* 1995;118(Pt 6):1573–1581.
147. Furtado S, Payami H, Lockhart PJ, et al. Profile of families with parkinsonism-predominant spinocerebellar ataxia type 2 (SCA2). *Mov Disord* 2004;19:622–629.
148. Kim JM, Shin S, Kim JY, et al. Spinocerebellar ataxia type 2 in seven Korean families: CAG trinucleotide expansion and clinical characteristics. *J Korean Med Sci* 1999;14:659–664.
149. Matsuura T, Sasaki H, Yabe I, et al. Mosaicism of unstable CAG repeats in the brain of spinocerebellar ataxia type 2. *J Neurol* 1999;246:835–839.
150. Momeni P, Lu CS, Chou YH, et al. Taiwanese cases of SCA2 are derived from a single founder. *Mov Disord* 2005;20:1633–1636.
151. Moro A, Munhoz RP, Moscovich M, Arruda WO, Raskin S, Teive HA. Movement disorders in spinocerebellar ataxias in a cohort of Brazilian patients. *Eur Neurol* 2014;72:360–362.
152. Schols L, Gispert S, Vorgerd M, et al. Spinocerebellar ataxia type 2. Genotype and phenotype in German kindreds. *Arch Neurol* 1997;54:1073–1080.
153. Chelban V, Wiethoff S, Fabian-Jessing BK, et al. Genotype-phenotype correlations, dystonia and disease progression in spinocerebellar ataxia type 14. *Mov Disord* 2018;33:1119–1129.
154. Foncke EM, Beukers RJ, Tijssen CC, Koelman JH, Tijssen MA. Myoclonus-dystonia and spinocerebellar ataxia type 14 presenting with similar phenotypes: trunk tremor, myoclonus, and dystonia. *Parkinsonism Relat Disord* 2010;16:288–289.
155. Ganos C, Zittel S, Minnerop M, et al. Clinical and neurophysiological profile of four German families with spinocerebellar ataxia type 14. *Cerebellum* 2014;13:89–96.
156. Rossi M, Perez-Lloret S, Cerquetti D, Merello M. Movement Disorders in Autosomal Dominant Cerebellar Ataxias: A Systematic Review. *Mov Disord Clin Pract* 2014;1:154–160.
157. Stevanin G, Hahn V, Lohmann E, et al. Mutation in the catalytic domain of protein kinase C gamma and extension of the phenotype associated with spinocerebellar ataxia type 14. *Arch Neurol* 2004;61:1242–1248.
158. van Gaalen J, Giunti P, van de Warrenburg BP. Movement disorders in spinocerebellar ataxias. *Mov Disord* 2011;26:792–800.
159. Verbeek DS, Warrenburg BP, Hennekam FA, et al. Gly118Asp is a SCA14 founder mutation in the Dutch ataxia population. *Hum Genet* 2005;117:88–91.
160. Visser JE, Bloem BR, van de Warrenburg BP. PRKCG mutation (SCA-14) causing a Ramsay Hunt phenotype. *Mov Disord* 2007;22:1024–1026.
161. Vlak MH, Sinke RJ, Rabelink GM, Kremer BP, van de Warrenburg BP. Novel PRKCG/SCA14 mutation in a Dutch spinocerebellar ataxia family: expanding the phenotype. *Mov Disord* 2006;21:1025–1028.
162. Yabe I, Sasaki H, Chen DH, et al. Spinocerebellar ataxia type 14 caused by a mutation in protein kinase C gamma. *Arch Neurol* 2003;60:1749–1751.
163. Yamashita I, Sasaki H, Yabe I, et al. A novel locus for dominant cerebellar ataxia (SCA14) maps to a 10.2-cM interval flanked by D19S206 and D19S605 on chromosome 19q13.4-qter. *Ann Neurol* 2000;48:156–163.
164. Cadieux-Dion M, Andermann E, Lachance-Touchette P, et al. Recurrent mutations in DNAJC5 cause autosomal dominant Kufs disease. *Clin Genet* 2013;83:571–575.
165. Noskova L, Stranecky V, Hartmannova H, et al. Mutations in DNAJC5, encoding cysteine-string protein alpha, cause autosomal-dominant adult-onset neuronal ceroid lipofuscinosis. *Am J Hum Genet* 2011;89:241–252.
166. Butefisch CM, Gambetti P, Cervenakova L, Park KY, Hallett M, Goldfarb LG. Inherited prion encephalopathy associated with the novel PRNP H187R mutation: a clinical study. *Neurology* 2000;55:517–522.
167. Kovacs GG, Ertsey C, Majtenyi C, et al. Inherited prion disease with A117V mutation of the prion protein gene: a novel Hungarian family. *J Neurol Neurosurg Psychiatry* 2001;70:802–805.
168. Kovacs GG, Seguin J, Quadrio I, et al. Genetic Creutzfeldt-Jakob disease associated with the E200K mutation: characterization of a complex proteinopathy. *Acta Neuropathol* 2011;121:39–57.
169. Larue S, Verreault S, Gould P, Coulthart MB, Bergeron C, Dupre N. A case of familial Creutzfeldt-Jakob disease presenting with dry cough. *Can J Neurol Sci* 2006;33:243–245.
170. Rusina R, Fiala J, Holada K, et al. Gerstmann-Straussler-Scheinker syndrome with the P102L pathogenic mutation presenting as familial

- Creutzfeldt-Jakob disease: a case report and review of the literature. *Neurocase* 2013;19:41–53.
171. Samman I, Schulz-Schaeffer WJ, Wohrl JC, Sommer A, Kretzschmar HA, Hennerici M. Clinical range and MRI in Creutzfeldt-Jakob disease with heterozygosity at codon 129 and prion protein type 2. *J Neurol Neurosurg Psychiatry* 1999;67:678–681.
 172. Sasaki K, Doh-ura K, Wakisaka Y, Tomoda H, Iwaki T. Fatal familial insomnia with an unusual prion protein deposition pattern: an autopsy report with an experimental transmission study. *Neuropathol Appl Neurobiol* 2005;31:80–87.
 173. Shi Q, Chen C, Wang XJ, et al. Rare V203I mutation in the PRNP gene of a Chinese patient with Creutzfeldt-Jakob disease. *Prion* 2013;7:259–262.
 174. Sun C, Xia W, Liu Y, et al. Agrypnia excitata and obstructive apnea in a patient with fatal familial insomnia from China: A case report. *Medicine (Baltimore)* 2017;96:e8951.
 175. Takada LT, Kim MO, Metcalf S, Gala II, Geschwind MD. Prion disease. *Handb Clin Neurol* 2018;148:441–464.
 176. Takashima S, Tateishi J, Taguchi Y, Inoue H. Creutzfeldt-Jakob disease with florid plaques after cadaveric dural graft in a Japanese woman. *Lancet* 1997;350:865–866.
 177. Takazawa T, Ikeda K, Ito H, et al. A distinct phenotype of leg hyperreflexia in a Japanese family with Gerstmann-Strausler-Scheinker syndrome (P102L). *Intern Med* 2010;49:339–342.
 178. Mignot C, von Stulpnagel C, Nava C, et al. Genetic and neurodevelopmental spectrum of SYNGAP1-associated intellectual disability and epilepsy. *J Med Genet* 2016;53:511–522.
 179. Parker MJ, Fryer AE, Shears DJ, et al. De novo, heterozygous, loss-of-function mutations in SYNGAP1 cause a syndromic form of intellectual disability. *Am J Med Genet A* 2015;167A:2231–2237.
 180. Sabatini PJB, Ejaz R, Stavropoulos DJ, Mendoza-Londono R, Joseph-George AM. Stable transmission of an unbalanced chromosome 21 derived from chromoanasythesis in a patient with a SYNGAP1 likely pathogenic variant. *Mol Cytogenet* 2018;11:50.
 181. Vlaskamp DRM, Shaw BJ, Burgess R, et al. SYNGAP1 encephalopathy: A distinctive generalized developmental and epileptic encephalopathy. *Neurology* 2018.
 182. Fountain-Capal JK, Holland KD, Gilbert DL, Hallinan BE. When should clinicians order genetic testing for Dravet syndrome? *Pediatr Neurol* 2011;45:319–323.
 183. Kanai K, Hirose S, Oguni H, et al. Effect of localization of missense mutations in SCN1A on epilepsy phenotype severity. *Neurology* 2004;63:329–334.
 184. Mahoney K, Moore SJ, Buckley D, et al. Variable neurologic phenotype in a GEFS+ family with a novel mutation in SCN1A. *Seizure* 2009;18:492–497.
 185. Sugawara T, Mazaki-Miyazaki E, Fukushima K, et al. Frequent mutations of SCN1A in severe myoclonic epilepsy in infancy. *Neurology* 2002;58:1122–1124.
 186. Canafoglia L, Ragona F, Panzica F, et al. Movement-activated cortical myoclonus in Dravet syndrome. *Epilepsy Res* 2017;130:47–52.
 187. Carvill GL, McMahon JM, Schneider A, et al. Mutations in the GABA Transporter SLC6A1 Cause Epilepsy with Myoclonic-Atonic Seizures. *Am J Hum Genet* 2015;96:808–815.
 188. Johannesen KM, Gardella E, Linnankivi T, et al. Defining the phenotypic spectrum of SLC6A1 mutations. *Epilepsia* 2018;59:389–402.
 189. Mattison KA, Butler KM, Inglis GAS, et al. SLC6A1 variants identified in epilepsy patients reduce gamma-aminobutyric acid transport. *Epilepsia* 2018;59:e135–e141.
 190. Palmer S, Towne MC, Pearl PL, et al. SLC6A1 Mutation and Ketogenic Diet in Epilepsy With Myoclonic-Atonic Seizures. *Pediatr Neurol* 2016;64:77–79.
 191. Altmann J, Buchner B, Nadaj-Pakleza A, et al. Expanded phenotypic spectrum of the m.8344A>G "MERRF" mutation: data from the German mitoNET registry. *J Neurol* 2016;263:961–972.
 192. Arenas J, Campos Y, Bornstein B, et al. A double mutation (A8296G and G8363A) in the mitochondrial DNA tRNA (Lys) gene associated with myoclonus epilepsy with ragged-red fibers. *Neurology* 1999;52:377–382.
 193. Casali C, Fabrizi GM, Santorelli FM, et al. Mitochondrial G8363A mutation presenting as cerebellar ataxia and lipomas in an Italian family. *Neurology* 1999;52:1103–1104.
 194. Fang W, Huang CC, Chu NS, et al. Myoclonic epilepsy with ragged-red fibers (MERRF) syndrome: report of a Chinese family with mitochondrial DNA point mutation in tRNA(Lys) gene. *Muscle Nerve* 1994;17:52–57.
 195. Lax NZ, Hepplewhite PD, Reeve AK, et al. Cerebellar ataxia in patients with mitochondrial DNA disease: a molecular clinicopathological study. *J Neuropathol Exp Neurol* 2012;71:148–161.
 196. Liu K, Zhao H, Ji K, Yan C. MERRF/MELAS overlap syndrome due to the m.3291T>C mutation. *Metab Brain Dis* 2014;29:139–144.
 197. Nadeem MS, Ahmad H, Mohammed K, et al. Identification of variants in the mitochondrial lysine-tRNA (MT-TK) gene in myoclonic epilepsy-pathogenicity evaluation and structural characterization by in silico approach. *J Cell Biochem* 2018;119:6258–6265.
 198. Ozawa M, Nishino I, Horai S, Nonaka I, Goto YI. Myoclonus epilepsy associated with ragged-red fibers: a G-to-A mutation at nucleotide pair 8363 in mitochondrial tRNA(Lys) in two families. *Muscle Nerve* 1997;20:271–278.
 199. Lalioti MD, Scott HS, Buresi C, et al. Dodecamer repeat expansion in cystatin B gene in progressive myoclonus epilepsy. *Nature* 1997;386:847–851.
 200. Berkovic SF, Oliver KL, Canafoglia L, et al. Kufs disease due to mutation of CLN6: clinical, pathological and molecular genetic features. *Brain* 2019;142:59–69.
 201. Meneret A, Ahmar-Beaugendre Y, Rieunier G, et al. The pleiotropic movement disorders phenotype of adult ataxia-telangiectasia. *Neurology* 2014;83:1087–1095.
 202. Schols L, Gispert S, Vorgerd M, et al. Spinocerebellar ataxia type 2. Genotype and phenotype in German kindreds. *Arch Neurol* 1997;54:1073–1080.
 203. Lee WY, Jin DK, Oh MR, et al. Frequency analysis and clinical characterization of spinocerebellar ataxia types 1, 2, 3, 6, and 7 in Korean patients. *Arch Neurol* 2003;60:858–863.
 204. Visser JE, Bloem BR, Van de Warrenburg BP. PRKCG mutation (SCA-14) causing a Ramsay hunt phenotype. *Mov Disord* 2007;22:1024–1026.
 205. Vlak MH, Sinke RJ, Rabelink GM, Kremer BP, van de Warrenburg BP, Novel PRKCG. SCA14 mutation in a Dutch spinocerebellar ataxia family: expanding the phenotype. *Mov Disord* 2006;21:1025–1028.
 206. Kasai K, Onuma T, Kato M, et al. Differences in evoked potential characteristics between DRPLA patients and patients with progressive myoclonic epilepsy: preliminary findings indicating usefulness for differential diagnosis. *Epilepsy Res* 1999;37:3–11.
 207. Bettencourt C, de Yébenes JG, Lopez-Sendon JL, et al. Clinical and Neuropathological features of spastic Ataxia in a Spanish family with Novel compound heterozygous mutations in STUB1. *Cerebellum* 2015;14:378–381.
 208. van Egmond ME, Verschuuren-Bemelmans CC, Nibbeling EA, et al. Ramsay hunt syndrome: Clinical characterization of progressive myoclonus ataxia caused by GOSR2 mutation. *Mov Disord* 2014;29:139–143.
 209. Muona M, Berkovic SF, Dibbens LM, et al. A recurrent de novo mutation in KCNC1 causes progressive myoclonus epilepsy. *Nat Genet* 2015;47:39–46.
 210. Canafoglia L, Ferlazzo E, Michelucci R, et al. Variable course of Unverricht-Lundborg disease: Early prognostic factors. *Neurology* 2017;89:1691–1697.
 211. Poretti A, Benson JE, Huisman TA, Boltshauser E. Acute ataxia in children: approach to clinical presentation and role of additional investigations. *Neuropediatrics* 2013;44:127–141.
 212. Crespel A, Ferlazzo E, Franceschetti S, et al. Unverricht-Lundborg disease. *Epileptic Disord* 2016;18:28–37.
 213. Genton P. Unverricht-Lundborg disease (EPM1). *Epilepsia* 2010;51(Suppl 1):37–39.
 214. Zutt R, Elting JW, van Zijl JC, et al. Electrophysiologic testing aids diagnosis and subtyping of myoclonus. *Neurology* 2018;90:e647–e657.
 215. Bhatia KP, Brown P, Gregory R, et al. Progressive myoclonic ataxia associated with coeliac disease. The myoclonus is of cortical origin, but the pathology is in the cerebellum. *Brain* 1995;118(Pt 5):1087–1093.
 216. Okuma Y, Fujishima K, Miwa H, Mori H, Mizuno Y. Myoclonic tremulous movements in multiple system atrophy are a form of cortical myoclonus. *Mov Disord* 2005;20:451–456.

217. Foncke EM, Beukers RJ, Tijssen CC, Koelman JH, Tijssen MA. Myoclonus-dystonia and spinocerebellar ataxia type 14 presenting with similar phenotypes: trunk tremor, myoclonus, and dystonia. *Parkinsonism Relat Disord* 2010;16:288–289.
218. Mignot C, Apartis E, Durr A, et al. Phenotypic variability in ARCA2 and identification of a core ataxic phenotype with slow progression. *Orphanet J Rare Dis* 2013;8:173.
219. Binelli S, Agazzi P, Canafoglia L, et al. Myoclonus in Creutzfeldt-Jakob disease: Polygraphic and video-electroencephalography assessment of 109 patients. *Mov Disord* 2010;25:2818–2827.
220. Gwinn KA, Caviness JN. Electrophysiological observations in idiopathic opsoclonus-myoclonus syndrome. *Mov Disord* 1997;12:438–442.
221. Pranzatelli MR. The neurobiology of the opsoclonus-myoclonus syndrome. *Clin Neuropharmacol* 1992;15:186–228.
222. dos Santos DF, Pedrosa JL, Braga-Neto P, et al. Excessive fragmentary myoclonus in Machado-Joseph disease. *Sleep Med* 2014;15:355–358.
223. Clark MM, Stark Z, Farnaes L, Tan TY, White SM, Dimmock D, Kingsmore SF. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. *NPJ Genom Med* 2018;3:16.
224. Corbett MA, Schwake M, Bahlo M, et al. A mutation in the Golgi Qb-SNARE gene GOSR2 causes progressive myoclonus epilepsy with early ataxia. *Am J Hum Genet* 2011;88:657–663.

Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Diseases with only occasional combined myoclonus and ataxia presentation, or for which the presence of myoclonus or ataxia or the genetic finding itself are unconfirmed.

Table S2. The 123 genes involved in conditions that combine myoclonus and ataxia.