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Nomenclature of Genetically Determined Myoclonus Syndromes: Recommendations of the International Parkinson and Movement Disorder Society Task Force

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ABSTRACT: Genetically determined myoclonus disorders are a result of a large number of genes. They have wide clinical variation and no systematic nomenclature. With next-generation sequencing, genetic diagnostics require stringent criteria to associate genes and phenotype. To improve (future) classification and recognition of genetically determined movement disorders, the Movement Disorder Society Task Force for Nomenclature of Genetic Movement Disorders (2012) advocates and renews the naming system of locus symbols. Here, we propose a nomenclature for myoclonus syndromes and related disorders with myoclonic jerks (hyperekplexia and myoclonic epileptic encephalopathies) to guide clinicians in their diagnostic approach to patients with these disorders. Sixty-seven genes were included in the nomenclature. They were divided into 3 subgroups: prominent myoclonus syndromes, 35 genes; prominent myoclonus syndromes combined with another prominent movement disorder, 9 genes; disorders that present usually with other phenotypes but

can manifest as a prominent myoclonus syndrome, 23 genes. An additional movement disorder is seen in nearly all myoclonus syndromes: ataxia (n = 41), ataxia and dystonia (n = 6), and dystonia (n = 5). However, no additional movement disorders were seen in related disorders. Cognitive decline and epilepsy are present in the vast majority. The anatomical origin of myoclonus is known in 64% of genetic disorders: cortical (n = 34), noncortical areas (n = 8), and both (n = 1). Cortical myoclonus is commonly seen in association with ataxia, and noncortical myoclonus is often seen with myoclonus-dystonia. This new nomenclature of myoclonus will guide diagnostic testing and phenotype classification. © 2019 The Authors. *Movement Disorders* published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

Key Words: genetics; hyperekplexia; myoclonic epilepsy; myoclonus; nomenclature

Myoclonus is a hyperkinetic movement disorder characterized by sudden, brief, involuntary jerks of a single or multiple muscles.¹⁻³ It can be caused by muscle

contraction (positive myoclonus) or sudden interruption of muscle activity during intended isometric contraction (negative myoclonus).⁴ The myoclonic jerks can be difficult

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to distinguish from other hyperkinetic movement disorders.⁵ Electrophysiological testing has proven helpful for discriminating myoclonus from other hyperkinetic movement disorders and for classifying the myoclonus subtype.⁶ Myoclonus can be classified based on anatomical origin: cortical, subcortical (or noncortical⁷), spinal, and peripheral myoclonus.⁶ So far, in genetic myoclonus syndromes only cortical (CM) and subcortical subtypes have been described.⁸

Determination of the etiology of myoclonus is challenging, and recently, a novel diagnostic 8-step algorithm was proposed to help clinicians accurately, efficiently, and cost-effectively diagnose myoclonus.⁸ Once the acquired forms and late-onset neurodegenerative disorders (such as Alzheimer's disease and parkinsonian disorders) of myoclonus are excluded in this diagnostic workup, a large number of genetically determined disorders with wide clinical variation remain. In almost all genetic syndromes, myoclonus is not the sole feature, but it is accompanied or even overshadowed by another movement disorder.⁵ This is likely the reason systematic nomenclature similar to PARK (for parkinsonism) or DYT (for dystonia) has not been established for myoclonus. In many of the suspected genetic myoclonus syndromes, the genetic cause is (still) unknown, but next-generation sequencing (NGS) has revolutionized molecular genetic diagnosis and has produced an exponential increase in known genetic causes and expansion of movement disorder phenotypes, including myoclonus. However, NGS frequently produces genetic variants for which pathogenicity is unclear. This emphasizes the importance of good clinical phenotyping and weighting of NGS results in the context of the presenting clinical syndrome.

In 2012, the International Parkinson and Movement Disorder Society Task Force for Nomenclature of Genetic Movement Disorders was established to revise the system of locus symbols, as the current movement disorders system had become outdated with the advances in NGS, the lack of established criteria for conferring locus symbols, or ongoing revision of the list.⁹

Here we present a new myoclonus nomenclature. We also include groups of related disorders that can present in the outpatient clinic of a movement disorder specialist with *jerks* as a prominent symptom. First, there are the hyperekplexias, as the excessive startle reflex closely resembles reticular reflex myoclonus, both clinically and neurophysiologically.¹⁰ Second are the genetic epilepsy syndromes with myoclonic jerks, specifically the epileptic encephalopathies. Patients with myoclonic epilepsy encephalopathies exhibit, next to their clear epileptic attacks, often spontaneous, reflex or action myoclonus, with evidence of a cortical origin. These cortically driven epileptic jerks resemble isolated cortical myoclonus, as both are characterized by short-lasting (<100-millisecond) jerks with a cortical discharge on the electroencephalogram (EEG). Historically, it is not clear if there is a neurobiological distinction between

the 2 phenomena, and therefore we decided to include them both in the current myoclonus nomenclature.

The first 2 papers of the task force included the proposed nomenclature for genetic parkinsonism, dystonia, autosomal-dominant and -recessive cerebellar ataxia, hereditary spastic paraplegia, paroxysmal movement disorders, neurodegeneration with brain iron accumulation, and primary familial brain calcification.^{1,2} Here, we present the genetically determined myoclonus syndromes nomenclature based on the same principles, criteria, and recommendations.

Methods

Inclusion

Our recommendations are based on a systematic literature search. All articles regarding genetic causes of myoclonus syndromes were identified by a PubMed, Online Mendelian Inheritance in Man, and Textbook search, including all the additional relevant references cited in the articles found. The key search terms “myoclonus,” “myoclonic epilepsy,” and “startle” were used in combination with the term “genetic causes.” For the period to June 2015, we used our previously published systematic review with the same search terms.⁸ In addition, an identical search was performed for the period between June 2015 and October 2018 to identify newly discovered genes. All reviewed articles and abstracts were restricted to those published in English.

Following the recommendations of the task force, the criteria for gene inclusion are that mutations in the gene must be causative (ie, risk factor genes were excluded), and myoclonus must be a prominent feature. In determining the pathogenicity, no specific threshold for the level of penetrance of a mutation was designated by the Movement Disorder Society (MDS) Task Force and was determined for each gene based on standards prevailing in the field. In the field of myoclonus, we decided that genes related to myoclonus or myoclonic epilepsy with medium or low penetrance were excluded. In Table 1 we included genetic disorders DYT-ANO3 and CHOR-NKX2-1, although the penetrance of these genes is reduced. The reason to include them is that the previous nomenclature of the MDS Task Force decided to include lower penetrance, as it is more common in dystonic syndromes and these 2 genes present with the clinical syndrome of myoclonus-dystonia.

Prominent myoclonus was present if either (1) the literature stated that myoclonic jerks were a prominent feature of the phenotype, (2) the myoclonic jerks were the main reason for disability, and/or (3) the myoclonic jerks were the main focus of treatment. In addition to this, the predominance of myoclonus in the disorder had to be confirmed in the literature by a second independent group of researchers.¹

TABLE 1. The proposed new list of genetically determined myoclonus syndromes

| New designation | Name | Myoclonus | Ataxia | Dystonia | Epilepsy | Cognitive problems | Clinical clues | Myoclonic subtype | OMIM | Inheritance pattern | Locus symbol |
|--------------------------------------|--------------------------------------|-----------|--------|----------|----------|--------------------|--|-------------------|--------|---------------------|--------------|
| Prominent myoclonus syndromes | | | | | | | | | | | |
| MYC-CLN3 ¹¹ | CLN3 disease | + | -/+ | - | ++ | ++ | Juvenile onset, parkinsonian signs, retinal degeneration, neuropsychiatric symptoms | CM ^a | 607042 | AR | CLN3 |
| MYC-CLN5 ¹² | CLN5 disease | ++ | -/+ | - | ++ | ++ | Late-infantile onset, blindness | CM ^a | 608102 | AR | CLN5 |
| MYC-CLN6 ¹³ | CLN6 disease | ++ | +;++ | - | ++ | ++ | Early juvenile or adult ¹⁴ onset, visual failure | CM ^a | 606725 | AR | CLN6 |
| MYC-CLN8 ¹⁵ | CLN8 disease | ++ | +;++ | - | ++ | ++ | Late infantile onset, retinopathy | CM ^a | 607837 | AR | CLN8 |
| MYC-DNAJC5 ¹⁶ | CLN4 disease | ++ | +;++ | - | ++ | ++ | Adult-onset | CM ^a | 611203 | AD | CLN4 |
| MYC-GLRA1 ¹⁷ , | Hyperplexia | + | - | - | - | - | Generalized stiffness at birth and following | BSM | 138491 | AD, AR | HKPX1 |
| MYC-SLC6A5 ¹⁸ , | | | | | | | startle, neonatal tonic cyanotic attacks, | | 604159 | AD, AR | HKPX3 |
| MYC-GLRB ¹⁹ | | | | | | | periodic limb movement during sleep, and hypnagogic myoclonus | | 138492 | AR | HKPX2 |
| MYC-KCNC1 ²⁰ | MEAK | ++ | ++ | - | + | -/+ | - | CM | 176258 | AD | None |
| MYC-PRICKLE1 ²¹ | EPM 1B | ++ | ++ | - | + | -/+ | Upward gaze palsy | UN | 608500 | AR | None |
| MYC-SAMD12 ^c | FCMTE | + | - | - | +;++ | -/+ | Adult-onset, anxiety, and depression ²³ | CM | 618073 | AD | None |
| MYC-RAPGEF2 ²² | | | | | | | | | 609530 | | |
| MYC-SCARB2 ²⁴ | AMRF syndrome | ++ | +;++ | - | +;++ | -/+ | Tremor, renal failure, peripheral neuropathy | CM | 602257 | AR | None |
| ATX/HSP-FOLR1 ²⁵ | Cerebral folate transport deficiency | -/+ | ++ | - | ++ | ++ | Chorea, drop attacks ²⁶ | UN | 136430 | AR | None |
| CARS ²⁷ | | -/+ | - | - | ++ | ++ | Tetraparesis, visual and hearing impairment, areflexia, hypotonia ²⁸ | UN | 612800 | AR | None |
| CHD2 ²⁹ | CHD2 encephalopathy | - | - | - | +;++ | +;++ | Photosensitivity, multiple seizure types of which atonic-myoclonic-absence is most common ³⁰ | CM | 602119 | AD | None |
| CUX2 ³¹ | Myoclonic DEE | - | - | - | ++ | ++ | Infantile-onset myoclonic and absence seizures, stereotypies and dyskinesias | CM | 610648 | AD | None |
| GLDC ³² , | Classic non-ketotic hyperglycinemia | - | - | - | ++ | ++ | Neonatal onset: progressive lethargy, hypotonia | CM | 238300 | AR | None |
| AIMT ³³ , | | | | | | | | | 238310 | | |
| mt-MTTK ^{34d} | MERRF | - | + | - | ++ | -/+ | Muscle weakness, hearing loss, peripheral neuropathy, optic atrophy, axial lipomas, and variable other neurological manifestations (heterogeneous disease, multiple genes associated with phenotype) ³⁵ | CM | 590060 | Mt | None |
| PIGA ³⁶ | MCAHS2 | - | - | - | ++ | ++ | Dysmorphic features, neonatal hypotonia | CM | 311770 | XLR | None |
| POLG ³⁷ | POLG-related disorders | -/+ | -/+ | -/+ | ++ | ++ | Parkinsonism, chorea, migraine, stroke-like episodes, hearing and visual impairment, myopathy, neuropathy, endocrine and gastrointestinal disorders | UN | 174763 | AD or AR | None |
| SCN1A ^{38e} | Dravet syndrome | -/+ | -/+ | - | ++ | +;++ | Febrile and prolonged seizures with alternating pattern | CM | 607208 | AD | None |
| SERPINI7 ^{39,40} | FENIB | - | -/+ | - | ++ | ++ | - | CM | 602445 | AD | None |
| SLC6A1 ⁴¹ | Doose syndrome | - | - | - | ++ | + | Atonic drop attacks | CM | 137165 | AD | None |

(Continues)

TABLE 1. Continued

| New designation | Name | Myoclonus | Ataxia | Dystonia | Epilepsy | Cognitive problems | Clinical clues | Myoclonic subtype | OMIM | Inheritance pattern | Locus symbol |
|---|-------------------------------|-----------|--------|----------|----------|--------------------|--|-------------------|--------|---------------------|--------------|
| <i>TBC1D24</i> ⁴² | TBC1D24-related disorders | -/+ | -/+ | -/+ | + /+++ | + /++ | Variable types of seizures, muscle hypotonia, extrapyramidal signs, hearing and visual loss ⁴³ | UN | 613577 | AR | None |
| Combined myoclonus syndromes ¹ | | | | | | | | | | | |
| <i>MYC/ATX-CS7B</i> ⁴⁴ | Unverricht-Lundborg | ++ | ++ | - | + | -/+ | Periodicity of symptoms ⁴⁵ | CM | 601145 | AR | None |
| <i>MYC/ATX-EPM2A</i> ⁴⁶ | Lafora disease | ++ | ++ | - | ++ | ++ | Focal visual seizures, drop attacks, psychosis ⁴⁷ | CM | 607566 | AR | None |
| <i>MYC/ATX-GOSR2</i> ⁴⁸ | North Sea PME | ++ | ++ | - | + /+++ | -/+ | Scoliosis, areflexia, pes cavus, syndactyly, drop attacks | CM | 614018 | AR | None |
| <i>MYC/ATX-KCTD7</i> ⁴⁹ | EPM 3 | ++ | ++ | - | ++ | ++ | Pyramidal signs, microrcephaly ⁵⁰ | UN | 611726 | AR | None |
| <i>MYC/ATX-NEUF</i> ⁵¹ | Sialidosis | ++ | ++ | - | - /+ | + /+++ | Cherry-red spots ⁵² | CM | 608272 | AR | None |
| <i>MYC/ATX-MHLRC1</i> ⁵³ | Lafora disease | ++ | ++ | - | ++ | ++ | See MYC-EPM2A | CM | 608072 | AR | None |
| <i>MYC/ATX-TPP1</i> ⁵⁴ | CLN2 disease | ++ | ++ | - | ++ | ++ | Late infantile onset, retinopathy, spasticity, hypotonia, extended vegetative state | CM ^a | 204500 | AR | CLN2 |
| <i>MYC/DYT-SGCE</i> ⁵⁵ | Myoclonus-dystonia (M-D) | + | - | + | - | - | M-D predominantly in upper body, psychiatric disorders | SCM | 604149 | AD | DYT11 |
| <i>MYC/DYT-KCTD17</i> ⁵⁶ | Myoclonus-dystonia | + | - | + | - | - | M-D predominantly in upper body, laryngeal involvement can occur, psychiatric symptoms | SCM | 616386 | AD | None |
| Disorders that usually present with other phenotypes but can manifest as a prominent myoclonus syndrome | | | | | | | | | | | |
| <i>ATX-ATM</i> ⁶⁷ | Variant Ataxia-telangiectasia | + | + | ++ | - | - /+ | M-D phenotype, chorea ⁵⁸ Systemic abnormalities: immunodeficiency, malignancies, and oculocutaneous telangiectasias | SCM | 607585 | AR | None |
| <i>ATX-ATN1</i> ⁵⁹ | DRPLA, PME phenotype | + /++ | ++ | - | + /+++ | ++ | PME phenotype especially in patients with age of onset < 20 years. Other phenotypes are an ataxochoreoathetoid form and a pseudo-Huntington form | CM | 607462 | AD | None |
| <i>ATX-MPC</i> ⁶⁰ | Niemann-Pick type C | ++ | ++ | - /+ | - /+ | + /+++ | PMA-phenotype, chorea, and tremor. ⁶¹ hepatosplenomegaly, vertical supranuclear gaze palsy | CM | 607623 | AR | None |
| <i>ATX-PRKCG</i> ⁶² | SCA 14 | + | + | - /+ | - | - /+ | M-D phenotype, sensory loss, hyperactive tendon reflexes, depression ⁶³ | SCM | 176980 | AD | SCA14 |
| <i>DYT-ANO3</i> ⁶⁴ | Tremorous cervical dystonia | + | - | ++ | - | - | M-D predominantly in upper body, tremor | SCM | 610110 | AD | DYT24 |
| <i>CHOR/DYT-ADCY5</i> ⁶⁵ | FDFM | + | - | + | - | - /+ | M-D phenotype with episodic mixed hyperkinetic disorder of the face characterized by myoclonus-chorea, ⁶⁶ axial hypotonia | UN | 600293 | AD | None |
| <i>CHOR-HTT</i> ⁶⁷ | Juvenile Huntington's disease | ++ | ++ | - | - /+ | + /++ | Behavioral symptoms and parkinsonian signs ⁶⁸ | CM | 613004 | AD | None |

(Continues)

TABLE 1. Continued

| New designation | Name | Myoclonus | Ataxia | Dystonia | Epilepsy | Cognitive problems | Clinical clues | Myoclonic subtype | OMIM | Inheritance pattern | Locus symbol |
|---------------------------|---|-----------|--------|----------|----------|--------------------|---|-------------------|--------|---------------------|--------------|
| CHOR-MKX2-1 ⁶⁹ | Benign hereditary chorea | ++ | + | + / ++ | - | + | M-D phenotype, chorea more prominent at young age, in adult life myoclonus most disabling if present. Tics, brain-lung-thyroid syndrome. | UN | 600635 | AD | None |
| HSP-KIF5A ⁷⁰ | Neonatal myoclonus | ++ | - | - | - / + | ++ | Neonatal onset. Eye movement abnormalities, apnea, ptosis, optic nerve pallor, hypotonia. Leukoencephalopathy may be seen. ⁷¹ | UN | 602821 | AD | SFG10 |
| HSP-SACS ²⁰ | ARSACS | ++ | ++ | - | ++ | ++ | Pyramidal signs ⁷² | CM ^a | 604490 | AR | None |
| PARK-GBA ³ | Neuronopathic Gaucher disease | + / ++ | + / ++ | - | ++ | ++ | Spasticity, horizontal gaze abnormalities, visceral involvement ⁷⁴ | CM ^a | 606463 | AR | None |
| APP ⁵ | Familial Alzheimer's disease | + | - / + | - | + | ++ | - | CM | 104760 | AD | None |
| ASAH1 ⁷⁶ | Spinal muscular atrophy | ++ | - | - | ++ | - / + | Progressive lower motor neuron disease manifestations | CM ^{a,h} | 613468 | AR | None |
| CSMK2B ⁷⁷ | CSMK2B-related disorders | - | - | - | ++ | + | Infantile onset of myoclonic seizures. Speech and language disorder. | CM | 115441 | AD | None |
| CTSA ⁷⁸ | Galactosialidosis | ++ | ++ | - | + / ++ | ++ | Coarse facies, vertebral changes, cherry-red spots, corneal clouding, absence of visceromegaly, angiokeratoma ⁷⁹ | CM | 613111 | AR | None |
| FARS2 ⁸⁰ | FARS2-related disorders | - | - | - | ++ | ++ | Early infantile onset of myoclonic seizures, GTCS, and infantile spasms. | CM | 611592 | AR | None |
| PRNP ⁸¹ | Familial Creutzfeldt-Jakob disease | ++ | ++ | - | - / + | ++ | Chorea, visual impairment, aknetic mutism, sleep disturbances, psychiatric disorders, peripheral neuropathy ⁸² | CM & SCM | 176640 | AD | None |
| PSEN1 ⁸³ | Familial Alzheimer's disease | + | - / + | - | + | ++ | Spastic paraparesis, rigidity, behavioral symptoms, language and dysexecutive deficits ⁸⁴ | CM | 104311 | AD | None |
| RPS6KA3 ⁸⁵ | Coffin-Lowry syndrome | + | - | - | - | + | Stimulus-induced drop episodes, ⁸⁶ dysmorphism, progressive skeletal changes, hearing loss, mitral valve deformity | UN | 300075 | XLD | None |
| SLC2A1 ⁸⁷ | Glucose transport type 1 deficiency | - | - / + | - | ++ | + / ++ | Myoclonic, myoclonic-astatic. GTCS, and absence seizures starting in early up to middle childhood. Other phenotypes include paroxysmal exertion-induced dyskinesia, absence epilepsy or episodic choreoathetosis, and spasticity. ⁸⁸ | CM | 138140 | AD | None |
| SYNGAP1 ⁸⁹ | SYNGAP1-associated intellectual disability and epilepsy | - | - / + | - | + / ++ | + / ++ | Early infantile onset of drop attacks, massive myoclonic jerks, and (myoclonic)-absence seizures. Hypotonia, behavioral disorder, ASD, orthopedic problems. | CM | 603384 | AD | None |

(Continues)

TABLE 1. Continued

| New designation | Name | Myoclonus | Ataxia | Dystonia | Epilepsy | Cognitive problems | Clinical clues | Myoclonic subtype | OMIM | Inheritance pattern | Locus symbol |
|----------------------------|-------------------------|-----------|--------|----------|----------|--------------------|--|-------------------|--------|---------------------|--------------|
| <i>UBE3A</i> ⁸⁰ | Angelman syndrome | + | -/+ | - | ++ | ++ | Myoclonic, myoclonic absence, and myoclonic-tonic seizures in early childhood; nonepileptic myoclonus first presenting in adolescence. Sleep dysfunction, absent or limited expressive language. ⁹¹ | CM ^a | 601623 | b | None |
| mJUDP ⁷⁹² | Silver-Russell syndrome | + | - | + | - | - | Growth retardation, dysmorphism, M-D predominantly located in upper body | UN | 180860 | IC | None |

++, Severe/progressive presentation of symptom; +, mild presentation of symptom; -/+ , symptom can be present or absent; - , symptom is absent. AMRF, action myoclonus renal failure; ARSACS, autosomal-recessive spastic ataxia of Charlevoix-Saguenay; BSM, brain stem myoclonus; CM, cortical origin of myoclonus; DEE, developmental and epileptic encephalopathy; DRPLA, dentate-rubro-pallido-luysianatrophy; EPM, progressive myoclonus epilepsy; FCMTE, familial cortical myoclonic tremor with epilepsy; FDFM, familial dyskinesia with facial myokymia; FENIB, familial encephalopathy with neuroserpin inclusion bodies; ICs, isolated cases; MCAHS2, multiple congenital anomalies-hypotonia-seizures syndrome-2; M-D, myoclonus-dystonia; MEAK, myoclonus epilepsy and ataxia from potassium (K⁺) channel mutation; MERRF, myoclonic epilepsy with ragged red fibers; SCM, subcortical origin of myoclonus; UN, myoclonic subtype is unknown; XLD, X-linked dominant; XLR, X-linked recessive.

^aMyoclonic subtype could not be assigned according to the official criteria stated by Zutt et al (2018)⁸³; therefore, the subtype stated in the literature was adopted but accentuated as presumed using an asterisk.

^bLoss of the maternally inherited *UBE3A* gene.

^cRecently, authors have proven the pentanucleotide repeat TTTCA (and TTTTA) to be causative of FCMTE in the intron of *MYC-SAMD12* and *MYC-RAPGEF2*.¹² Although the authors believe the intronic pentanucleotide repeat to be pathogenic irrespective of the gene, we have stated the 2 genes that have been confirmed in the literature.

^dThe following additional genetic mutations are able to cause MERRF: mt-*MTTL11* (OMIM 590050), mt-*MTTH1* (OMIM 590040), mt-*MTTS11* (OMIM 590080), mt-*MTTS21* (OMIM 590085), mt-*MTTF1* (OMIM 590070), mt-*MTTW* (OMIM 590095).

^eThe following genes have been reported to cause a DS-like phenotype by at 2 independent research groups: *SCN1B* (OMIM 600235), *PCDH19* (OMIM 300460), *GABRA1* (OMIM 615744).

^fThe phenotype of a combined myoclonus syndrome is characterized by multiple predominant movement disorders including myoclonus.

^gBecause of recent suggestions of the Task Force Nomenclature, the previously proposed prefix SCA for autosomal-dominant ataxias was replaced by ATX, resulting in the replacement of prefixes of 2 genes, *ATN1* and *PRCKG*. *SCA-ATN1* has been changed to *ATX-ATN1* and *SCA-PRCKG* to *ATX-PRCKG*.

^hPatients diagnosed with a genetic defect of *ASAH1* were described by Topaloglu et al (2016) as having subcortical myoclonic epileptiform abnormalities. However, based on the clinical characteristics we suspect a cortical origin of the myoclonic jerks and have classified this gene accordingly.

ⁱOpposed to the previously assigned prefix CHOR in *CHOR-PRNP*, the prefix CHOR was removed, and the name was altered to *PRNP*, as this gene causes multiple phenotypes including myoclonus and in which chorea only dominates in a minority of cases.

Cognitive problems include both cognitive decline and psychomotor retardation. The myoclonic subtype was determined unknown if neither an official myoclonic subtype could be assigned or a myoclonic subtype was stated in the literature.

This adjudication process included 2 persons (S.V. and R.Z.). All genes included in the new nomenclature were reviewed by 6 experts within the field of myoclonus to reach a broadly supported consensus (H.S., J.C., S.B., P.T., T.K., M.T.).

Classification

Following the recommendation of the task force and to guide clinicians in daily practice, the genetic disorders were allocated based on clinical presentation into 1 of the following 3 groups: (1) *prominent myoclonus syndromes*, genetic disorders that present with prominent myoclonus in the majority of cases; (2) *combined myoclonus syndromes*, genetic disorders that present with prominent myoclonus and another prominent movement disorder (eg, dystonia/ataxia) in the majority of cases; and (3) *disorders that usually present with other phenotypes but can manifest as a prominent myoclonus syndrome*, genetic disorders that present with prominent myoclonus only in a minority of cases as part of the phenotypic spectrum of this disorder.

Prefixes

In accordance with the recommendations of the task force, the prefix MYC was given to genes in which myoclonus is a prominent feature in the majority of the patients. In addition, we added a second prefix to genes and consequently allocated it to the subgroup *combined myoclonus syndromes*, in which another movement disorder is an additional prominent feature, resulting in a double prefix if both movement disorders are prominent (eg, MYC/ATX-GOSR2). Overlapping genes with double prefixes were discussed among the appropriate experts from the MDS Task Force to reach consensus. The symbol prefix is followed by the gene name. For clarity and to allow comparison with former classifications, we provided the old locus symbol (eg, DYT11) in the last column of Table 1, when appropriate. Genes that present with myoclonic epilepsy were not given any prefix, because the dominant feature of the phenotype is epilepsy rather than a movement disorder.

Additional Clinical and Electrophysiological Items

A brief description of the clinical presentation of disorders linked to each gene is listed in Table 1 with special emphasis on the most common accompanying signs and symptoms including ataxia, dystonia, cognitive problems, or epilepsy. Furthermore, we added the myoclonic anatomical subtype, cortical or subcortical (ie, non-cortical), if known, for each genetic disorder based on reported clinical and electrophysiological features to further improve the classification of myoclonus. Experts have argued against the term “subcortical” myoclonus, as its anatomical origin is still undetermined; however,

the term “subcortical” myoclonus will still be used in the new nomenclature because of the absence of a widely supported alternative.⁷ See Supplementary Table 1 for the anatomical classification criteria for myoclonus.⁹³

Results

Gene Selection

One hundred sixty-six genes linked to a myoclonus syndrome were found in the systematic literature review. An extensive overview of all genes associated with myoclonus with reason for inclusion or exclusion can be found in Supplementary Table 3, and see Figure 1 for an overview. Ninety-nine genes were excluded because of the absence of prominent myoclonus (n = 45), lack of confirmation of the phenotype with prominent myoclonus by a second independent research group (n = 31), and questionable pathogenicity (n = 23).

Sixty-seven genes were included in the new nomenclature for myoclonus syndromes (see Table 1). (1) In the subgroup *prominent myoclonus syndromes*, 35 genes were included; (2) in the subgroup *combined myoclonus syndromes*, 9 genes were included; and (3) in the subgroup *disorders that usually present with other phenotypes but can manifest as a prominent myoclonus syndrome*, 23 genes were included.

Prefix Allocation

The locus symbol prefix MYC was assigned to 22 genes. Genes in which the predominant phenotype showed wide heterogeneity or was dominated by epileptic or nonmotor symptoms were not assigned any prefix. For myoclonus epilepsy with ragged red fibers syndrome, only the most frequent causative gene (mt-*MTTK*) is listed. The remaining causative genes are stated in the caption of Table 1, as they are associated with a similar phenotype as mt-*MTTK*.

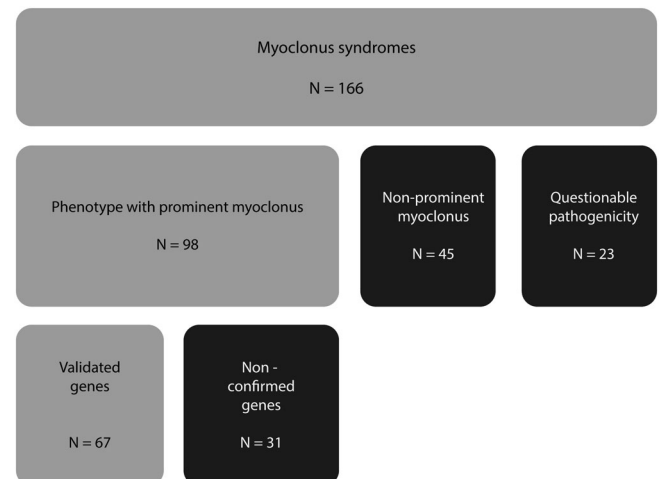


FIG. 1. In and exclusion of genes associated with myoclonus syndromes.

Additional Clinical and Electrophysiological Clues

The following most common accompanying signs and symptoms observed overall were cognitive decline in 90% (n = 60), epilepsy in 82% (n = 55), ataxia in 61% (n = 41), ataxia and dystonia in 9% (n = 6), and dystonia in 7% (n = 5). The anatomical location of myoclonic origin could be allocated in 64% of genes (n = 43) because of support of strong electrophysiological data, and in the cortex in 51% (n = 34), noncortical areas in 12% (n = 8), and both cortical and noncortical areas in 1% (n = 1) of all genes. Three of the 8 genes with jerks originating from noncortical areas were classified as originating from the brain stem (hyperekplexia).

Discussion

In this article we propose a nomenclature of genetically determined myoclonus according to the new naming system presented by the MDS Task Force.¹ This myoclonus list currently includes 67 genes. Thirty-five genes presented with prominent myoclonus syndromes, 9 with combined myoclonus syndromes, and 23 with disorders that usually present with other phenotypes but can manifest as a prominent myoclonus syndrome. Co-occurrence of movement disorders, especially ataxia and dystonia, was seen in almost all except for familial cortical myoclonus tremor with epilepsy (FCMTE, or BAFME, benign adult familial myoclonus epilepsy), hyperekplexia, and (myoclonic) epileptic encephalopathies. Epilepsy and cognitive decline were the most frequently observed accompanying clinical features for the disorders listed in this new nomenclature.

The literature search detected 166 genes linked to a myoclonus syndrome, but only 67 were used for the nomenclature list. Filtering using strict criteria (independent confirmation and predominant myoclonus) to arrive at a list of confirmed entities that can present with predominant myoclonus is meant to help the clinician with the selection of test procedures and assist in the interpretation of results of genetic testing.² In our opinion, the requirement for independent confirmation by a second research group is an important criterion, as it diminishes erroneous genotype-phenotype linkages. At present, with the widespread use of NGS in research and clinical diagnostics, many potentially new myoclonus genes are reported. Still, we had to exclude 31 genes (19%) that require validation. A significant proportion of patients with myoclonus syndromes still remain unsolved (progressive myoclonus ataxias in 36%⁹⁴ and progressive myoclonus epilepsies in 28%⁹⁵), in which excluded genes could be considered.

A new clinical diagnostic approach in patients with myoclonus has recently been described.⁸ After establishing that the myoclonus in a patient has a genetic cause, Table 1 can be used as a diagnostic framework for

physicians in clinical practice to select candidate genes for individual patients based on the absence or presence of accompanying signs and symptoms.

FCMTE/BAFME is the only genetically determined myoclonus syndrome with relatively pure myoclonus, although it is accompanied by infrequent epilepsy in a majority of but not all patients. This genetic disorder is caused by 2 recently confirmed genes (*MYC-SAMD12* and *MYC-RAPGEF2*) with intronic expansions of non-coding TTTCA and TTTTA pentanucleotide repeats. It presents with a phenotype of benign CM with infrequent tonic-clonic and sometimes focal seizures. RNA-mediated toxicity resulting in diffuse loss of Purkinje cells in the cerebellum is suggested to be the underlying pathogenesis of this disorder.^{96,97} The potential role of the cerebellum in CM has been pointed out multiple times in the literature, supported by the frequent phenotypical co-occurrence of CM and cerebellar ataxia.⁹⁸

Ataxia is the most common accompanying movement disorder in myoclonus syndromes (24 genes). Almost all patients in whom the genetic disorder consists of a combination of ataxia and myoclonus present with the clinical syndrome of progressive myoclonus ataxia (PMA) or progressive myoclonus epilepsy (PME). The most common and best characterized are Unverricht-Lundborg disease (*MYC/ATX-CSTB*), Lafora disease (*MYC/ATX-EMP2A*), neuronal ceroid lipofuscinosis (multiple genes), sialidosis (*MYC/ATX-NEU1*), and dentatorubral pallidolusian atrophy (*ATX-ATN1*).⁹⁹

The anatomical origin of myoclonus in most patients with ataxia is thought to be cortical. Clinically, cortical myoclonic jerks present typically in the distal limbs and face, jerks are provoked by action and are stimulus sensitive.⁹³ Of the genetic disorders in which ataxia and myoclonus co-occur, we found that cortical origin was supported by strong electrophysiological evidence in 54% (n = 14), and it was suspected in 33% (n = 8). Mechanistic hypotheses for cortical myoclonus include: (1) loss of Purkinje cells with astrocytosis, resulting in disinhibition via the cerebello-thalamico-cortical pathway, (2) neuronal cell loss in the dentate nuclei leading to impaired cerebellar projections to the cortex, or (3) a reduction in the concentration of γ -aminobutyric acid (GABA)-ergic synapses in the sensory-motor cortex.¹⁰⁰ On a molecular level, most genetic disorders presenting with both ataxia and myoclonus have impaired posttranslational modification of proteins to which certain neuronal groups might be particularly vulnerable compared with others.¹⁰⁰ This could play a role in the characteristic phenotype of PMA, including a fixed order of signs, starting with ataxia, subsequently CM, and eventually by infrequent epilepsy.⁹⁴

Dystonia is the second type of prominent movement disorder accompanying myoclonus. The combination of myoclonus and dystonia is known as myoclonus-dystonia syndrome (M-D). The classical myoclonus-dystonia phenotype is based on genetic defects in the *MYC/DYT*-

SGCE gene in about 50% of cases.¹⁰¹ Other disorders that can give rise to a myoclonus-dystonia phenotype include *MYC/DYT-KCTD17*, *DYT-ANO3*, *ATX-PRKCG*, *ATX-ATM*, *CHOR/DYT-ADCY5*, *CHOR-NKX2-1*, and maternal uniparental disomy with regions of heterodisomy and isodisomy on chromosome 7 (mUPD7), which is based on the loss of function of the *SGCE* gene.

The anatomical locus of myoclonus in M-D is subcortical. Clinically, the myoclonus and dystonia in M-D are located mainly in the trunk and proximal upper limbs, and the myoclonus is not stimulus sensitive. The noncortical origin of the myoclonus is supported electrophysiologically in 5 genetic disorders presenting with M-D (*MYC/DYT-SGCE*, *MYC/DYT-KCTD17*, *DYT-ANO3*, *ATX-ATM*, *ATX-PRKCG*) and unknown in 2 others (*CHOR/DYT-ADCY5* and *CHOR-NKX2-1*). The pathophysiology of subcortical myoclonus includes circuit abnormalities in the basal ganglia and involvement of the cerebellum. Disruptions in neurotransmission pathways have been hypothesized to play a role, particularly the unbalanced homeostasis of GABA, serotonin, and dopamine-related pathways.¹⁰² In contrast to myoclonus of cortical origin, cortical excitability and intracortical inhibition were found to be normal or less profoundly disturbed.¹⁰³

The overlap between types of accompanying movement disorders and the anatomical origins of the myoclonic jerks is remarkable. Currently, the anatomical origin can be assigned in only 64% of genetic disorders. We encourage movement disorder specialists to classify the subtype of myoclonus by a thorough clinical description (eg, distribution, stimulus sensitivity) of the myoclonic jerks and if possible electrophysiological testing (eg, corticomuscular coherence or jerk-locked back-averaging). We realize that availability of the tests varies considerably between centers and countries.⁶ However, the myoclonic subtype guides the clinician toward a more precise differential diagnosis (see Table 1) and effective treatment strategy,¹⁰⁴ and it helps to unravel the pathogenesis of myoclonus by creating homogenous groups.

Epilepsy is an additional feature in 82% of myoclonus syndromes, presenting either as CM in combination with epilepsy or myoclonic jerks as part of a myoclonic seizure. It is only described in genes with jerks originating from the cortex, as mutations in genes linked to noncortical myoclonus (hyperekplexia, all M-D syndromes, and Coffin-Lowry syndrome) rarely present with epileptic manifestations. The distinction between myoclonus and (myoclonic) epilepsy can be difficult to make, and seemingly minor differences in terminology can create confusion. *Myoclonus* epilepsy is a condition in which CM, often continuously present, and epilepsy occur independently, whereas *myoclonic* epilepsy is an attack of generalized convulsions starting with myoclonic jerks or predominantly characterized by myoclonic jerks. Jerks in both CM and myoclonic epilepsy are associated with EEG polyspikes or spike/

polyspike-wave complexes before the onset of an EMG burst.¹⁰⁵ Confusion is not only the case in clinical practice but also in the literature, making it difficult to interpret many of the clinical presentations described. For instance, the phenotype associated with *MYC/ATX-GOSR2* has been called an epileptic syndrome with myoclonic seizures (progressive myoclonus epilepsy type 6) in articles from the field of epilepsy,¹⁰⁶ as opposed to a syndrome with prominent cortical myoclonus in combination with epilepsy (progressive myoclonus ataxia) in articles from the field of movement disorders.¹⁰⁷ Particularly in the fields of movement disorders and epilepsy, the phenotype is a decisive factor for further diagnostics, and inaccuracy of descriptions can lead to erroneous genotype-phenotype relationships. Ongoing discussion and consensus meetings between experts in both fields are necessary to accomplish a consistent terminology with clear definitions that could easily be implemented in clinical practice.

Cognitive problems including cognitive decline and psychomotor retardation have been reported in all but 5 genetic disorders, *MYC/DYT-SGCE*, *MYC/DYT-KCTD17*, mUPD7 (based on loss of *SGCE*-gene), *DYT-ANO3*, and the hyperekplexias. Other nonmotor features, particularly psychiatric disorders and behavioral problems, are also being recognized as part of the phenotype of certain movement disorders (eg, dystonia). In disorders with cortical myoclonus, almost half the patients experience symptoms of depression or anxiety.¹⁰⁸ Underestimation of these nonmotor features is likely, as we have only recently started considering this to be part of the phenotype. Future case descriptions of myoclonus syndromes should include details on cognition, psychiatric symptoms, and behavioral changes. The clinician should be aware of the high occurrence of nonmotor features in patients with myoclonus syndromes. These are features that impact the patient's life and his or her family, and they require proper guidance and counseling.¹⁰⁹

Just as the presence of accompanying signs and symptoms can guide clinicians to a refined differential diagnosis, absence of an accompanying movement disorder proves a useful observation, as it points toward the related disorders, *hyperekplexia* and *myoclonic epileptic encephalopathies*. Hyperekplexia is characterized by 3 clinical symptoms: generalized stiffness at birth, excessive startle reflexes, and generalized stiffness following a startle. Genetic studies have shown mutations in different parts of the inhibitory glycine receptor complex, located in the postsynaptic membrane of glycinergic and mixed GABAergic neurons. Synaptic inhibition in the brain stem and spinal cord is impaired as a result of a defect in 1 of these 3 genes.¹⁰ With regard to the genes identified in epileptic encephalopathies with prominent myoclonic jerks, a majority of these disorders share a phenotype that includes early disease onset (in the first 18 months of life) and a progressive course resulting in refractory epilepsy

and severe cognitive decline. However, some genetic disorders are extremely rare (eg, *CARS2*), and those phenotypes are likely to be expanded in the coming years.

Conclusion

In collaboration with the MDS Task Force, we present a new nomenclature that includes 67 genetically determined myoclonus syndromes. As is apparent from this current list, numerous genes are linked to myoclonus syndromes, and prioritizing putative causative genes based on corresponding accompanying signs or symptoms and clinical clues could accelerate the identification of a molecular diagnosis in individual cases. Furthermore, it shows the additional value of electrophysiological testing in patients with myoclonus syndromes, as it may lead to a more refined differential diagnosis and therapeutic strategy. The current nomenclature can be used as a framework to add newly discovered genes in a systematic way and can be used for movement disorder (myoclonus) next-generation sequencing diagnostics. In the near future, genetically determined myoclonus syndromes can be uploaded in the searchable online database, the Movement Disorder Society Genetic Mutation Database, MDSGene (www.MDSGene.org), to provide an online, browsable database of hereditary myoclonus syndromes.¹¹⁰ ■

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References

- Marras C, Lang A, van de Warrenburg BP, et al. Nomenclature of genetic movement disorders: Recommendations of the international Parkinson and movement disorder society task force. *Mov Disord* 2016;31:436–457.
- Rossi M, Anheim M, Durr A, et al. The genetic nomenclature of recessive cerebellar ataxias. *Mov Disord* 2018;33:1056–1076.
- Caviness JN. Myoclonus. *Mayo Clin Proc* 1996;71:679–688.
- Shibasaki H, Hallett M. *The Neurological Examination: Scientific Basis for Clinical Diagnosis*. New York: Oxford University Press; 2016.
- Van Egmond ME, Elting JWJ, 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.
- Zutt R, Elting JW, van Zijl JC, et al. Electrophysiologic testing aids diagnosis and subtyping of myoclonus. *Neurology* 2018;90:e647–e657.
- Shibasaki H, Thompson PD. Milestones in myoclonus. *Mov Disord* 2011;26:1142–1148.
- Zutt R, van Egmond ME, Elting JW, et al. A novel diagnostic approach to patients with myoclonus. *Nat Rev Neurol* 2015;11:687–697.
- Marras C, Lohmann K, Lang A, Klein C. Fixing the broken system of genetic locus symbols: Parkinson disease and dystonia as examples. *Neurology* 2012;78:1016–1024.
- Dreissen YEM, Tijssen MAJ. The startle syndromes: Physiology and treatment. *Epilepsia* 2012;53:3–11.
- Munroe PB, Mitchison HM, O'Rawe AM, et al. Spectrum of mutations in the Batten disease gene, *CLN3*. *Am J Hum Genet* 1997;61:310–316.
- Peltonen L, Savukoski M, Klockars T, Holmberg V, Santavuori P, Lander ES. *CLN5*, a novel gene encoding a putative transmembrane protein mutated in Finnish variant late infantile neuronal ceroid lipofuscinosis. *Nat Genet* 1998;19:286–288.
- Gao H, Boustany R-MN, Espinola JA, et al. Mutations in a novel *CLN6*-encoded transmembrane protein cause variant neuronal ceroid lipofuscinosis in man and mouse. *Am J Hum Genet* 2002;70:324–335.
- 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.
- Ranta S, Zhang Y, Ross B, et al. The neuronal ceroid lipofuscinoses in human EPMR and *mnd* mutant mice are associated with mutations in *CLN8*. *Nat Genet* 1999;23:233–236.
- Cadioux-Dion M, Andermann E, Lachance-Touchette P, et al. Recurrent mutations in *DNAJC5* cause autosomal dominant Kufs disease. *Clin Genet* 2013;83:571–575.
- Shiang R, Ryan SG, Zhu Y-Z, Hahn AF, O'Connell P, Wasmuth JJ. Mutations in the alpha-1 subunit of the inhibitory glycine receptor cause the dominant neurologic disorder, hyperkplexia. *Nat Genet* 1993;5:351–357.
- Rees MI, Harvey K, Pearce BR, et al. Mutations in the gene encoding GlyT2 (*SLC6A5*) define a presynaptic component of human startle disease. *Nat Genet* 2006;38:801–806.
- Rees MI, Lewis TM, Kwok JBJ, et al. Hyperkplexia associated with compound heterozygote mutations in the beta-subunit of the human inhibitory glycine receptor (*GLRB*). *Hum Mol Genet* 2002;11:853–860.
- 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.
- Bassuk AG, Wallace RH, Buhr A, et al. A Homozygous Mutation in Human *PRICKLE1* Causes an Autosomal-Recessive Progressive Myoclonus Epilepsy-Ataxia Syndrome. *Am J Hum Genet* 2008;83:572–581.
- Ishiura H, Doi K, Mitsui J, et al. Expansions of intronic TTTCA and TTTTA repeats in benign adult familial myoclonic epilepsy. *Nat Genet* 2018;50:581–590.
- Lei XX, Liu Q, Lu Q, et al. TTTCA repeat expansion causes familial cortical myoclonic tremor with epilepsy. *Eur J Neurol* 2018;26(3):513–518.
- Berkovic SF, Dibbens LM, Oshlack A, et al. Array-Based Gene Discovery with Three Unrelated Subjects Shows *SCARB2/LIMP-2* Deficiency Causes Myoclonus Epilepsy and Glomerulosclerosis. *Am J Hum Genet* 2008;82(3):673–684.
- Steinfeld R, Grapp M, Kraetzner R, et al. Folate Receptor Alpha Defect Causes Cerebral Folate Transport Deficiency: A Treatable Neurodegenerative Disorder Associated with Disturbed Myelin Metabolism. *Am J Hum Genet* 2009;85:354–363.
- Ortigoza Escobar JD, Pérez Dueñas B. Treatable Inborn Errors of Metabolism Due to Membrane Vitamin Transporters Deficiency. *Semin Pediatr Neurol* 2016;23:341–350.
- Hallmann K, Zsurka G, Moskau-Hartmann S, et al. A homozygous splice-site mutation in *CARS2* is associated with progressive myoclonic epilepsy. *Neurology* 2014;83:2183–2187.
- Coughlin CR, Scharer GH, Friederich MW, et al. Mutations in the mitochondrial cysteinyl-tRNA synthase gene, *CARS2*, lead to a severe epileptic encephalopathy and complex movement disorder. *J Med Genet* 2015;52:532–540.
- Carvill GL, Heavin SB, Yendle SC, et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in *CHD2* and *SYNGAP1*. *Nat Genet* 2013;45:825–830.
- Thomas RH, Zhang LM, Carvill GL, et al. *CHD2* myoclonic encephalopathy is frequently associated with self-induced seizures. *Neurology* 2015;84:951–958.

31. Chatron N, Møller RS, Champaigne NL, et al. The epilepsy phenotypic spectrum associated with a recurrent CUX2 variant. *Ann Neurol* 2018;83:926–934.
32. Tada K, Kure S, Kume A, Hiraga K. Genomic Analysis of Non-ketotic Hyperglycinaemia: A Partial Deletion of P-protein Gene. *J Inher Metab Dis* 1990;13(5):766–770.
33. Nanao K, Takada G, Takahashi E-I, et al. Structure and Chromosomal Localization of the Aminomethyltransferase Gene (AMT). *Genomics* 1994;19:27–30.
34. Shoffner JM, Lott MT, Lezza a M, Seibel P, Ballinger SW, Wallace DC. Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNA(Lys) mutation. *Cell* 1990;61:931–937.
35. Tranchant C, Anheim M. Movement disorders in mitochondrial diseases. *Rev Neurol* 2016;172:524–529.
36. Johnston JJ, Gropman AL, Sapp JC, et al. The Phenotype of a Germline Mutation in PIGA: The Gene Somatic Mutated in Paroxysmal Nocturnal Hemoglobinuria. *Am J Hum Genet* 2012;90:295–300.
37. Van Goethem G, Dermaut B, Löfgren A, Martin J-J, Van Broeckhoven C. Mutation of POLG is associated with progressive external ophthalmoplegia characterized by mtDNA deletions. *Nat Genet* 2001;28:211–212.
38. Claes L, Del-Favero J, Ceulemans B, Lagae L, Broeckhoven C Van, De Jonghe P. De Novo Mutations in the Sodium-Channel Gene SCN1A Cause Severe Myoclonic Epilepsy of Infancy. *Am J Hum Genet* 2001;68:1327–1332.
39. Davis RL, Shrimpton A E, Holohan PD, et al. Familial dementia caused by polymerization of mutant neuroserpin. *Nature* 1999;401:376–379.
40. Davis RL, Shrimpton AE, Carrell RW, et al. Association between conformational mutations in neuroserpin and onset and severity of dementia. *Lancet* 2002;359:2242–2247.
41. Carvill GL, McMahan 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.
42. Falace A, Filipello F, La Padula V, et al. TBC1D24, an ARF6-Interacting Protein, Is Mutated in Familial Infantile Myoclonic Epilepsy. *Am J Hum Genet* 2010;87:365–370.
43. Balestrini S, Milh M, Castiglioni C, et al. TBC1D24 genotype – phenotype correlation Epilepsies and other neurologic features. *Neurology* 2016:77–87.
44. Pennacchio LA, Lehesjoki AE, Stone NE, et al. Mutations in the gene encoding cystatin B in progressive myoclonus epilepsy (EPM1). *Science* 1996;271:1731–1734.
45. Crespel A, Ferlazzo E, Franceschetti S, et al. Unverricht-Lundborg disease. *Epileptic Disord* 2016;18:28–37.
46. Minassian BA, Lee JR, Herbrick JA, et al. Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy. *Nat Genet* 1998;20:171–174.
47. Turnbull J, Tiberia E, Striano P, et al. Lafora disease. *Epileptic Disord* 2016;18:S38–S62.
48. 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.
49. Van Bogaert P, Azizieh R, Désir J, et al. Mutation of a potassium channel-related gene in progressive myoclonic epilepsy. *Ann Neurol* 2007;61:579–586.
50. Van Bogaert P. KCTD7-related progressive myoclonus epilepsy. *Epileptic Disord* 2016;18:115–119.
51. Bonten E, Van Der Spoel A, Fornerod M, Grosveld G, D’Azzo A. Characterization of human lysosomal neuraminidase defines the molecular basis of the metabolic storage disorder sialidosis. *Genes Dev* 1996;10:3156–3169.
52. Franceschetti S, Canafoglia L. Sialidoses. *Epileptic Disord* 2016;18: 89–93.
53. Chan EM, Young EJ, Ianzano L, et al. Mutations in NHLRC1 cause progressive myoclonus epilepsy. *Nat Genet* 2003;35:125–127.
54. Rawlings ND, Barrett AJ. Tripeptidyl-peptidase I is apparently the CLN2 protein absent in classical late-infantile neuronal ceroid lipofuscinosis. *Biochim Biophys Acta* 1999;1429:496–500.
55. Zimprich A, Grabowski M, Asmus F, et al. Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. *Nat Genet* 2001;29:66–69.
56. Mencacci NE, Rubio-Agusti I, Zdebek A, et al. A missense mutation in KCTD17 causes autosomal dominant myoclonus-dystonia. *Am J Hum Genet* 2015;96:938–947.
57. Savitsky K, Bar-shira A, Gilad S, et al. A Single Ataxia Telangiectasia Gene with a Product Similar to PI-3 Kinase. *Science* 1995;268: 1749–1753.
58. Pearson TS. More Than Ataxia: Hyperkinetic Movement Disorders in Childhood Autosomal Recessive Ataxia Syndromes. *Tremor Other Hyperkinet Mov (N Y)* 2016;6:368.
59. Koide R, Ikeuchi T, Onodera O, et al. Unstable expansion of CAG repeat in hereditary dentatorubral-pallidolusian atrophy (DRPLA). *Nat Genet* 1994;6:9–13.
60. Carstea ED, Morris JA, Coleman KG, et al. Niemann-Pick C1 disease gene: homology to mediators of cholesterol homeostasis. *Science* 1997;277:228–231.
61. Anheim M, Lagha-Boukhiba O, Fleury-Lesaunier M-C, et al. Heterogeneity and frequency of movement disorders in juvenile and adult-onset Niemann-Pick C disease. *J Neurol* 2014;261:174–179.
62. Chen DH, Brkanac Z, Verlinde CLMJ, et al. Missense mutations in the regulatory domain of PKC gamma: a new mechanism for dominant nonepisodic cerebellar ataxia. *Am J Hum Genet* 2003;72: 839–849.
63. Miura S, Nakagawara H, Kaida H, et al. Expansion of the phenotypic spectrum of SCA14 caused by the Gly128Asp mutation in PRKCG. *Clin Neurol Neurosurg* 2009;111:211–215.
64. Stamelou M, Charlesworth G, Cordvari C, et al. The phenotypic spectrum of DYT24 due to ANO3 mutations. *Mov Disord* 2014; 29:928–934.
65. Chen YZ, Matsushita MM, Robertson P, et al. Autosomal dominant familial dyskinesia and facial myokymia: single exome sequencing identifies a mutation in adenylyl cyclase 5. *Arch Neurol* 2012;69:630–635.
66. Tunc S, Brüggemann N, Baaske MK, et al. Facial twitches in ADCY5-associated disease — Myokymia or myoclonus? An electromyography study. *Parkinsonism Relat Disord* 2017;40:73–75.
67. Anon. The Huntington’s Disease Collaborative Researches Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington’s disease chromosome. *Cell* 1993;72: 971–983.
68. Rossi Sebastiano D, Soliveri P, Panzica F, et al. Cortical myoclonus in childhood and juvenile onset Huntington’s disease. *Parkinsonism Relat Disord* 2012;18:794–797.
69. Breedveld GJ, van Dongen JWF, Danesino C, et al. Mutations in TITF-1 are associated with benign hereditary chorea. *Hum Mol Genet* 2002;11:971–979.
70. Duis J, Dean S, Applegate C, et al. KIF5A mutations cause an infantile onset phenotype including severe myoclonus with evidence of mitochondrial dysfunction. *Ann Neurol* 2016;80:633–637.
71. Rydzanicz M, Jagla M, Kosinska J, et al. KIF5A de novo mutation associated with myoclonic seizures and neonatal onset progressive leukoencephalopathy. *Clin Genet* 2017;91:769–773.
72. Nascimento FA, Canafoglia L, Aljaafari D, et al. Progressive myoclonus epilepsy associated with SACS gene mutations. *Neurol Genet* 2016;2:e83.
73. Tsuji S, Choudary P V., Martin BM, et al. A Mutation in the Human Glucocerebrosidase Gene in Neuronopathic Gaucher’s Disease. *N Engl J Med* 1987;316:570–575.
74. Park JK, Orvisky E, Tayebi N, et al. Myoclonic epilepsy in Gaucher disease: Genotype-phenotype insights from a rare patient subgroup. *Pediatr Res* 2003;53:387–395.
75. Goate A, Chartier-Harlin M-C, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer’s disease. *Nature* 1991;349:704–706.
76. Zhou J, Tawk M, Tiziano FD, et al. Spinal Muscular Atrophy Associated with Progressive Myoclonic Epilepsy Is Caused by Mutations in ASAH1. *Am J Hum Genet* 2012 91:5–14.

77. Poirier K, Hubert L, Viot G, et al. CSNK2B splice site mutations in patients cause intellectual disability with or without myoclonic epilepsy. *Hum Mutat* 2017;932–941.
78. Takano T, Shimmoto M, Fukuhara Y, et al. Galactosialidosis: clinical and molecular analysis of 19 Japanese patients. *Brain Dysfunct* 1991;4:271–280.
79. Annunziata I and d’Azzo A. Galactosialidosis: historic aspects and overview of investigated and emerging treatment options. *Expert Opin Orphan Drugs* 2017;5:131–141.
80. Elo JM, Yadavalli SS, Euro L, et al. Mitochondrial phenylalanyl-tRNA synthetase mutations underlie fatal infantile Alpers encephalopathy. *Hum Mol Genet* 2012;21:4521–4529.
81. Goldgaber D, Goldfarb LG, Brown P, et al. Mutations in familial Creutzfeldt-Jakob disease and Gerstmann-Sträussler-Scheinker’s syndrome. *Exp Neurol* 1989;106:204–206.
82. Manix M, Kalakoti P, Henry M, et al. Creutzfeldt-Jakob disease: updated diagnostic criteria, treatment algorithm, and the utility of brain biopsy. *Neurosurg Focus* 2015;39:E2.
83. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer’s disease. *Nature* 1995;375:754–760.
84. Ryan NS, Nicholas JM, Weston PSJ, et al. Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer’s disease: a case series. *Lancet Neurol* 2016;15:1326–1335.
85. Trivier E, De Cesare D, Jacquot S, et al. Mutations in the kinase Rsk-2 associated with Coffin-Lowry syndrome. *Nature* 1996;384:567–570.
86. Van Egmond ME, Elting JWJ, 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.
87. Mullen SA, Marini C, Suls A, et al. Glucose Transporter 1 Deficiency as a Treatable Cause of Myoclonic Astatic Epilepsy. *Arch Neurol* 2011;68:1152.
88. Koch H and Weber YG. The glucose transporter type 1 (Glut1) syndromes. *Epilepsy Behav* 2018;1:4–7.
89. Vissers LELM, de Ligt J, Gilissen C, et al. A de novo paradigm for mental retardation. *Nat Genet* 2010;42:1109–1112.
90. Kishino T, Lalande M, Wagstaff J. UBE3A/E6-AP mutations cause Angelman syndrome. *Nat Genet* 1997;15:70–73.
91. Pollack SF, Grocott OR, Parkin KA, Larson AM, Thibert RL. Myoclonus in Angelman syndrome. *Epilepsy Behav* 2018;82:170–174.
92. Kotzot D, Schmitt S, Bernasconi F, et al. Uniparental disomy 7 in Silver-Russell syndrome and primordial growth retardation. *Hum Mol Genet* 1995;4:583–587.
93. Zutt R, Elting JW, van der Hoeven JH, Lange F, Tijssen MAJ. Myoclonus subtypes in tertiary referral center. Cortical myoclonus and functional jerks are common. *Clin Neurophysiol* 2017;128:253–259.
94. Van der Veen S, Zutt R, Becker CE, Elting JWJ, De Koning TJ, Tijssen MAJ. Progressive Myoclonus Ataxia Time for a New Definition? *MovDisord* 2018;33:1281–1286.
95. Franceschetti S, Michelucci R, Canafoglia L, et al. Progressive myoclonic epilepsies Definitive and still undetermined causes. *Neurology* 2014;82:405–411.
96. Ishiura H, Doi K, Mitsui J, et al. Expansions of intronic TTTCA and TTTTA repeats in benign adult familial myoclonic epilepsy. *Nat Genet* 2018;50:581–590.
97. Van Rootselaar AF, Van Der Salm SMA, Bour LJ, et al. Decreased cortical inhibition and yet cerebellar pathology in “familial cortical myoclonic tremor with epilepsy.” *Mov Disord* 2007;22:2378–2385.
98. Ganos C, Kassavetis P, Erro R, Edwards MJ, Rothwell J and Bhatia KP. The role of the cerebellum in the pathogenesis of cortical myoclonus. *Mov Disord* 2014;29:437–443.
99. Bhat S and Ganesh S. New discoveries in progressive myoclonus epilepsies: a clinical outlook. *Expert Rev Neurother* 2018;18:649–667.
100. 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.
101. Nardocci N, Zorzi G, Barzaghi C, et al. Myoclonus-dystonia syndrome: clinical presentation, disease course, and genetic features in 11 families. *Mov Disord* 2008;23:28–34.
102. Roze E, Lang AE, Vidailhet M. Myoclonus-dystonia: classification, phenomenology, pathogenesis, and treatment. *Curr Opin Neurol* 2018;31:484–490.
103. Eberhardt O, Topka H. Myoclonic disorders. *Brain Sci* 2017;7(8): pii: E103.
104. Dijk JM, Tijssen MAJ. Management of patients with myoclonus: Available therapies and the need for an evidence-based approach. *Lancet Neurol* 2010;9:1028–1036.
105. Apartis E and Vercueil L. To jerk or not to jerk: A clinical pathophysiology of myoclonus. *Rev Neurol (Paris)* 2016;172:465–476.
106. Boissé Lomax L, Bayly MA, Hjalgrim H, et al. “North Sea” progressive myoclonus epilepsy: phenotype of subjects with GOSR2 mutation. *Brain* 2013;136:1146–1154.
107. 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.
108. Zutt R, Gelauff JM, Smit M, Zijl JC Van, Stone J and Tijssen MAJ. The presence of depression and anxiety do not distinguish between functional jerks and cortical myoclonus. *Parkinsonism Relat Disord* 2017;45:90–93.
109. Skorvanek M, Rosenberger J, Minar M, et al. Relationship between the non-motor items of the MDS-UPDRS and Quality of Life in patients with Parkinson’s disease. *J Neurol Sci* 2015;353:87–91.
110. Lill CM, Mashychev A, Hartmann C, et al. Launching the movement disorders society genetic mutation database (MDSGene). *Mov. Disord* 2016;31:607–609.

Supporting Data

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