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REVIEW

Nomenclature of Genetic Movement Disorders: Recommendations of the International Parkinson and Movement Disorder Society Task Force – An Update

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on behalf of the Task Force on Genetic Nomenclature in Movement Disorders

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ABSTRACT: In 2016, the Movement Disorder Society Task Force for the Nomenclature of Genetic Movement Disorders presented a new system for naming genetically determined movement disorders and provided a criterion-based list of confirmed monogenic movement disorders. Since then, a substantial number of novel disease-causing genes have been described, which warrant classification using this system. In addition, with this update, we further refined the system and propose dissolving the imaging-

based categories of Primary Familial Brain Calcification and Neurodegeneration with Brain Iron Accumulation and reclassifying these genetic conditions according to their predominant phenotype. We also introduce the novel category of Mixed Movement Disorders (MxMD), which includes conditions linked to multiple equally prominent movement disorder phenotypes. In this article, we present updated lists of newly confirmed monogenic causes of movement disorders. We found a total of 89 different newly

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identified genes that warrant a prefix based on our criteria; 6 genes for parkinsonism, 21 for dystonia, 38 for dominant and recessive ataxia, 5 for chorea, 7 for myoclonus, 13 for spastic paraplegia, 3 for paroxysmal movement disorders, and 6 for mixed movement disorder phenotypes; 10 genes were linked to combined phenotypes and have been assigned two new prefixes. The updated lists represent a resource for clinicians and researchers alike and they have also been published on the website of the Task Force for the Nomenclature of Genetic Movement Disorders on the

homepage of the International Parkinson and Movement Disorder Society (<https://www.movementdisorders.org/MDS/About/Committees-Other-Groups/MDS-Task-Forces/Task-Force-on-Nomenclature-in-Movement-Disorders.htm>). © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson Movement Disorder Society.

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Originally, locus symbols (eg, *DYT1*) were used to specify chromosomal regions that had been linked to a familial disorder or a specific phenotype with an as yet unknown gene.¹ These symbols were systematically assigned in a numerical order (eg, *PARK1*, *PARK2*, etc.) and were regularly used by clinicians and researchers in lieu of the name for the condition (eg, *DYT1* dystonia), even when the disease-causing gene (eg, *TOR1A* for *DYT1*) had been identified. This system has a number of weaknesses, making it unsuitable to use as a reference.^{2,3} Therefore, the International Parkinson and Movement Disorder Society (MDS) initiated the Task Force for the Nomenclature of Genetic Movement Disorders to fix this “broken system.” Thus, new recommendations and lists of monogenic movement disorders based on these recommendations were published in 2016.³ Since then, both our knowledge and techniques of gene discovery have evolved enormously. Next-generation sequencing techniques have found their way into clinical and research settings, resulting in a large number of newly identified (potentially) disease-causing genes and genetic variants reported in the literature. The interpretation of these genes and novel gene variants, particularly their pathogenicity, remains challenging. Some newly identified genes are just reported in a few individuals or small families, and sometimes the same variants are also found in controls and healthy family members, albeit at a lower frequency, whereas large families with convincing segregation are often missing. Further, reduced penetrance and phenocopies are used to explain imperfect segregation. Another challenge relates to the distinction between variants that are disease-causing versus variants that confer an increased risk, as the boundaries are often blurred. Unconfirmed genes may be rapidly included in multigene panels for a given phenotype, which carries a risk of diagnostic results that are often difficult to interpret. Thus, a systematic approach to critically evaluate newly reported genes and updated lists of monogenic movement disorders based on our standardized criteria appear warranted.

What’s Known?

The MDS Task Force for the Nomenclature of Genetic Movement Disorders and its Mandate

When the MDS Task Force first convened, its initial mandate was to revise the naming system of genetic movement disorders. For this, a team of clinical neurologists and genetic experts from the field of movement disorders, supported by additional input from journal editors, medical experts from fields with already existing naming systems, representatives from GeneReviews, and the MDS membership developed rules for a new naming system and created lists for single-gene disorders known to cause several movement disorder phenotypes. This article expands these previously created lists and improves the naming system further. To achieve this, the newly published literature was systemically screened and curated. The recommendations were applied to newly reported gene–disease associations, carefully evaluated, and extensively discussed among the Task Force members and external experts when needed. Eventually, genes with convincing evidence were added by consensus to the respective phenotype lists. Genes that have yet to be confirmed are listed in the Supplementary tables.

Rules and Recommendations for the Nomenclature of Genetic Movement Disorders

Recommendations of the MDS Task Force for the revised naming system of genetic movement disorders have been described previously.³ Briefly: (1) The list only includes disorders for which a causative gene has been identified. (2) Genes will be assigned a movement disorder prefix if the phenotype (eg, parkinsonism for *PARK*) is a prominent feature of the disease linked to pathogenic variants (also referred to as mutations) in that gene in the majority of cases. If two different movement disorders generally coexist with equal prominence or if a gene causes two different movement disorder phenotypes not necessarily coexisting but both as a prominent feature in about half of the patients, a double prefix should be assigned (eg, *DYT/PARK-*

ATP1A3). If an additional movement disorder is present but less prevalent, no additional prefix is assigned but a cross reference is made between lists. (3) In addition to the phenotype-driven prefix, the naming system for each listed genetic disorder requires the name of the mutated gene (eg, *DYT-TOR1A* for dystonia caused by mutations in the *TOR1A* gene. (4) A prefix will only be assigned to disease-causing genes (as in monogenic disorders) and not to genetic risk factors. (5) Before including a gene in the list and assigning a prefix, a certain level of evidence for a genotype–phenotype association must be met (for details see Methods section).

What's New?

In this update, we focused on the three areas outlined below

(1) We updated the previously published³⁻⁵ lists of monogenic movement disorders. Through an extensive literature search, newly discovered disease-causing genes were identified and added for all movement disorder phenotypes covered by this Task Force. We identified 6 genes for parkinsonism (Table 1), 21 for dystonia (Table 2), 38 for dominant and recessive ataxia (Table 3), 5 for chorea (Table 4), 7 for myoclonus (Table 5), 13 for spastic paraplegia (Table 6), 3 for paroxysmal movement disorders (Table 7), and 6 for mixed movement disorder phenotypes (Table 8). As stated earlier, whenever a gene caused two different types of movement disorders with similar prevalence, a double prefix was assigned. When, however, a gene caused more than two different movement disorders and it was impossible to identify a consistent “core phenotype”, we placed this gene in the newly added group of Mixed Movement Disorders (MxMD).

(2) Even after applying the previously developed criteria,³ evaluating the evidence to support a causal gene–disease association was challenging, particularly for a more common disorder such as Parkinson's disease (PD). We thus piloted the application of an evidence-based framework developed by the Clinical Genome Resource (ClinGen)^{6,7} to evaluate gene–disease associations using PD as an example (for details refer to the Methods section).

(3) Our initial set of recommendations assigned the prefixes *NBIA* for Neurodegeneration with Brain Iron Accumulation (NBIA) and *PFBC* for Primary Familial Brain Calcifications (PFBC) to genes linked to a movement disorder phenotype and characteristic imaging findings (evidence of brain iron accumulation for NBIA and cerebral calcification for PFBC). With this update, we decided to classify genes and phenotypes exclusively based on their clinical presentation and avoid the use of ancillary tests, such as imaging findings. This led to the reclassification of the genes

previously assigned an NBIA or PFBC according to their predominant movement disorder phenotype. Nonetheless, since we acknowledge that imaging can be a distinguishing factor for these entities, we have added the suffix NBIA or PFBC and highlighted the imaging findings in the clinical features column where appropriate (eg, *DYT-PANK2*-(NBIA), *PARK-SLC20A2*-(PFBC)).

Methods

Literature Search

We performed a systematic literature search using standardized search terms (Table S1) and the National Center for Biotechnology Information's PubMed database (<https://www.ncbi.nlm.nih.gov/pubmed>). We searched for articles published until August 31, 2020 that reported patients with different movement disorders carrying genetic variants in newly identified and potentially disease-causing genes. We also evaluated relevant papers cited in the included articles. All listed articles were screened stepwise by title, abstract, and full text. All articles reporting at least one patient with a movement disorder carrying a potentially pathogenic variant in a newly identified gene were evaluated in detail. Another brief literature search focusing on unconfirmed candidate genes was conducted in May 2021 (search term: “[name of the gene] AND [disease in question]”) and again in September 2021 in order to update previously curated lists.

Data Collection Process

We collected information on the number of affected and unaffected mutation carriers for each identified gene. For affected individuals, we further extracted data on the predominant phenotype as well as associated movement disorders or other non-movement disorder features. To evaluate the pathogenicity of variants in a gene, we additionally collected evidence for segregation, as well as additional molecular and functional evidence (see later).

Evaluation of Pathogenicity and Gene–Disease Association

To evaluate the involvement of a gene in causing a movement disorder, we assessed the previously described criteria³: (1) the presence of variants within one gene in multiple, unrelated affected individuals, reported by at least two independent groups; (2) evidence for segregation or a statistical association of the gene with disease proven by gene-wide burden analysis; and (3) variants with an in silico prediction to alter the normal biochemical effect of a gene product, further supported by functional evidence in human tissue, well-established cellular or animal models, or other biochemical or histological abnormalities. Once this information was extracted, all available data were discussed and evaluated by Task

TABLE 1 Recently identified or confirmed forms of hereditary parkinsonism

Designation	Clinical features	OMIM	MOI
Classical parkinsonism			
PARK- <i>CHCHD2</i> ¹⁸⁻²⁵	Typical levodopa-responsive parkinsonism	616710	AD ^a
Atypical parkinsonism or complex phenotypes			
PARK- <i>DCTN1</i> ²⁶⁻²⁹	Adult-onset (atypical) parkinsonism with depression or apathy, followed by weight loss and respiratory hypoventilation/failure (referred to as Perry syndrome); some cases reported with PSP-like phenotype	168605	AD
PARK- <i>RAB39B</i> ³⁰⁻³²	Early-onset (atypical) parkinsonism, delayed psychomotor development, impaired intellectual development (referred to as Waisman syndrome)	311510	XLR
PARK- <i>VPS13C</i> ^{29,33-37}	Early-onset parkinsonism with often rapid and severe progression and loss of response to levodopa during disease course, early cognitive impairment potentially leading to dementia	616840	AR
Reclassified primary familial brain calcification genes			
PARK- <i>JAM2</i> -(PFBC) ³⁸⁻⁴⁰	Atypical parkinsonism with cognitive deficits, brain imaging: calcifications in basal ganglia, cerebellum, and white matter	618824	AR
PARK- <i>SLC20A2</i> -(PFBC) ^{40,41}	Atypical parkinsonism, commonly with cognitive deficits and headaches, less commonly dystonia, chorea, and ataxia, brain imaging: calcifications in basal ganglia, thalamus, cerebellum, and white matter	213600	AD
Disorders that usually present with other phenotypes but can have (prominent) parkinsonism			
Gene	Disease	OMIM	MOI
<i>DYT-DNAJC12</i> ^{42,43}	Hyperphenylalaninemia	617384	Increased serum phenylalanine and highly variable neurological defects including movement disorder phenotypes; many cases with dystonia and variable impairment of intellectual development; phenotype can also include non-progressive or mild levodopa-responsive parkinsonism
<i>MYC/ATX-EPM2A</i> ^{44,45}	Progressive myoclonus epilepsy (Lafora disease)	254780	Early-onset progressive neurodegeneration with myoclonus, generalized seizures, often visual hallucinations and cognitive decline, phenotype can also include ataxia or rarely parkinsonism
<i>C9orf72</i> ^{46,47}	Frontotemporal dementia (FTD) and/or amyotrophic lateral sclerosis (ALS)	105550	Broad phenotypic spectrum including frontotemporal dementia and features of motor neuron disease, parkinsonism (mostly atypical, eg, PSP-like, MSA, or CBS), and also dystonia, cerebellar signs, or chorea

(Continues)

TABLE 1 *Continued*

Disorders that usually present with other phenotypes but can have (prominent) parkinsonism				
Gene	Disease	OMIM	Clinical phenotype	MOI
<i>GRN</i> ^{a,49}	Primary progressive aphasia (PPA) Frontotemporal lobar degeneration with ubiquitin-positive inclusions, and neuronal ceroid lipofuscinosis type 11	607485 607485, 614706	Phenotypic spectrum includes atypical parkinsonism (PSP-like, CBS, and DLB)	AD or AR
<i>MAPT</i> ^{23,47,50-55}	Frontotemporal dementia with or without parkinsonism, Pick disease, progressive supranuclear palsy, progressive atypical supranuclear palsy	600274, 172700, 601104, 260540	Broad phenotypic spectrum including mostly atypical parkinsonism (PSP-like, CBS) but also features of motor neuron disease (eg, ALS); susceptibility locus for PD (OMIM 168600)	AD or AR
<i>PDE8B</i> ⁵⁶⁻⁶⁰	Autosomal dominant striatal degeneration	609,161	Neurological disorder with variable movement abnormalities due to striatal dysfunction; phenotypic spectrum includes slowly progressive parkinsonism (mainly bradykinesia and rigidity, usually no tremor) without response to levodopa, as well as dysarthria, gait disturbances, and brisk (lower limb) reflexes	AD
<i>PDGFRB</i> -(PFBC) ^{b,61}	Idiopathic basal ganglia calcification-4 (IBGC4)	615007	Many asymptomatic carriers, prominent late-onset parkinsonism and cognitive impairment in a minority of patients, brain imaging: calcification most commonly in basal ganglia	AD
<i>XPR1</i> -(PFBC) ^{b,62}	Idiopathic basal ganglia calcification-6 (IBGC6)	616413	Neurodegenerative disorder with adult onset neuropsychiatric and movement disorders including parkinsonism, dystonia, gait abnormalities, chorea, psychosis, and dementia, brain imaging: calcification most commonly in basal ganglia	AD

OMIM, Online Mendelian Inheritance in Man (<https://www.omim.org/about>); MOI, mode of inheritance; AD, autosomal dominant; XLR, X-linked recessive; AR, autosomal recessive; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; CBS, corticobasal syndrome; DLB, dementia with Lewy bodies.

^aIn addition to pathogenic variants as monogenic causes of the disease, some of the reported variants in *CHCHD2* represent genetic risk factors also occurring in a considerable but lower number of control individuals when compared to PD patients.

^bThese genes were previously included in the list of primary familial brain calcification.

TABLE 2 Recently identified or confirmed forms of hereditary dystonia

Designation	Less common movement phenotype	Clinical clues	OMIM	MOI
Isolated dystonia				
DYT-ANO3 ^{63,64}	(Head) tremor, myoclonus	Cranial-cervical dystonia, variable age at onset	615034	AD
DYT-EIF2AK2 ⁶⁵⁻⁶⁷		Early-onset, mostly generalized dystonia including laryngeal involvement, may be accompanied by leukoencephalopathy, spasticity, and developmental delay	618877	AD, AR
DYT-HPCA ^{64,68,69}		Childhood-onset generalized dystonia and adolescence-onset segmental dystonia; first affecting the distal limbs and later involving neck, orofacial and craniocervical regions, dysarthria, febrile seizures, and developmental delay in one case	224500	AR
DYT-KMT2B ^{64,70,71}		Childhood-onset, generalized dystonia, usually first affecting the lower limbs, variable additional signs including developmental delay, microcephaly, intellectual disability, facial dysmorphia	617284	AD
DYT-VPS16 ⁷²⁻⁷⁵		Early-onset generalized dystonia, mild to moderate intellectual disability and neuropsychiatric symptoms in a subset of patients	619291	AD
Combined dystonia				
DYT-COX20 ⁷⁶⁻⁷⁸	Ataxia	Mitochondrial complex IV deficiency nuclear type 11; hypotonia, gait ataxia, dysarthria, and sensory neuropathy	619054	AR
DYT-DNAJC12 ^{42,79,80}	Parkinsonism	Hyperphenylalaninemia and developmental delay. Phenotype can also include non-progressive or mild levodopa-responsive parkinsonism	617384	AR
DYT-SLC39A14 ⁸¹⁻⁸⁴	Parkinsonism	Hypermagnesemia, dysarthria, and generalized dystonia, MRI: T1 hyperintense, diffuse, non-enhancing signal of basal ganglia	617013	AR
DYT/CHOR-GNAO1 ^{85,86}	Myoclonus	Hypotonia and motor delay, exacerbated by febrile illness, stress, high ambient temperature	617493	AD
MYC/DYT-KCTD17 ⁸⁷⁻⁹⁰		Onset of mild myoclonic symptoms in the first or second decade of life, followed by later onset of progressive dystonia with predominant involvement of the cranial and laryngeal muscles; dystonia dominates the clinical picture	616398	AD
Complex dystonia				
DYT-MECR ^{91,92}		Dystonia, childhood-onset, with optic atrophy and basal ganglia abnormalities (DYTOABG); MRI: basal ganglia signal abnormalities, T2 hyperintense signal in putamen and globus pallidus, cystic changes in putamen	617282	AR

(Continues)

TABLE 2 Continued

Designation	Less common movement phenotype	Clinical clues	OMIM	MOI
DYT- <i>OPA1</i> ^{93,94}	Ataxia	Optic atrophy, peripheral neuropathy, myopathy, and progressive external ophthalmoplegia		AD
DYT/CHOR- <i>ADAR</i> ^{95,96}	Spasticity	Aicardi–Goutières syndrome, includes dystonia and spastic paraparesis, MRI may reveal isolated bilateral striatal necrosis, adult-onset psychological difficulties, linked to characteristic interferon signature (upregulation of interferon-stimulated genes)	615010	AR, rarely AD
ATX/DYT- <i>SQSTM1</i> ^{97,98}	Chorea	Neurodegeneration with ataxia, dystonia, and gaze palsy (NADGP): gait ataxia, cognitive decline, oculomotor abnormalities including vertical gaze palsy and nystagmus, dysarthria and hypergonadotropic hypogonadism	617145	AR
<i>Dystonia presenting with deafness</i>				
DYT- <i>ACTB</i> ⁹⁹⁻¹⁰²		Sensorineural hearing loss, generalized dystonia, skeletal abnormalities	607371	AD
DYT- <i>BCAP31</i> ¹⁰³⁻¹⁰⁹		Deafness, central hypomyelination, microcephaly, ophthalmoplegia, intellectual disability	300475	XLD
DYT- <i>FITM2</i> ¹¹⁰⁻¹¹²		Global developmental delay, sensorineural hearing loss, poor growth, and low body mass index	618635	AR
DYT- <i>SERAC1</i> ¹¹³⁻¹¹⁵		3-Methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome (MEGDEL); sensorineural hearing loss, delayed psychomotor development, increased excretion of 3-methylglutaconic acid, transient liver dysfunction in the neonatal period, MRI: bilateral basal ganglia hyperintensities	614739	AR
<i>Dystonia presenting with developmental delay</i>				
DYT- <i>IRF2BPL</i> ¹¹⁶⁻¹¹⁹		Developmental delay, hypotonia, seizures, pyramidal signs, dysarthria	618088	AD
DYT- <i>VAC14</i> ¹²⁰⁻¹²³	Ataxia	Neurodegeneration, ataxia, dysarthria, hypotonia	617054	AR
DYT/CHOR- <i>FOXG1</i> ¹²⁴⁻¹²⁶	Dyskinesia	Rett-like phenotype (with congenital encephalopathy)	613454	AD

OMIM, Online Mendelian Inheritance in Man (<https://www.omim.org/about>); MOI, mode of inheritance; AD, autosomal dominant; AR, autosomal recessive; MRI, magnetic resonance imaging; XLD, X-linked dominant.

^aThis gene has also been linked to Baraitser–Winter syndrome 1 (OMIM 243310).

Force members. In the few cases where uncertainty remained, external experts were consulted.

Recently, an evidence-based framework for evaluating gene–disease associations has been developed by the United States’ National Institutes of Health-supported ClinGen program.^{6,7} We decided to employ these previously published criteria to evaluate ambiguous, newly reported PD genes, since here interpreting the pathogenicity was particularly challenging due to the frequently observed reduced penetrance^{8,9} and high rate of phenocopies (5%).¹⁰ The proposed

framework is based on the evaluation of relevant genetic and experimental evidence supporting or contradicting a gene–disease relationship, leading to a qualitative classification: “Definitive Evidence”, “Strong Evidence”, “Moderate Evidence”, “Limited Evidence”, “No Reported Evidence”, or “Conflicting Evidence” (for details see ClinGen’s Standard Operating Procedure (SOP) https://clinicalgenome.org/site/assets/files/5391/gene_curation_sop_pdf-1.pdf). Only genes with a strong or definitive gene–disease association were included in our list of genes causing PD.

TABLE 3 Recently identified or confirmed forms of hereditary ataxias

Designation	Less common movement phenotype	Disease entity and clinical features	OMIM	MOI
Autosomal dominant forms				
ATX-CACNA1G ^{127,128}	Spasticity	Ataxia with gait instability, variable age at onset, additional signs including dysarthria, nystagmus, and less commonly pyramidal signs and cognitive impairment; phenotype can also be much more severe with neurodevelopmental deficits and early-onset ataxia (and OMIM 618087) ¹²⁹	604065 (SCA42)	AD
ATX-CCDC88C ^{130,131}	Tremor, parkinsonism	Adult-onset cerebellar ataxia with action tremor, parkinsonism, pyramidal signs and less frequently with impaired vertical gaze and cognitive impairment	616053 (SCA40)	AD
ATX-DAB1 ¹³²⁻¹³⁴		Adult-onset, slowly progressive, relatively pure cerebellar ataxia with gait instability, frequent falls, dysarthria, and ocular abnormalities	615945 (SCA37)	AD
ATX-EBF3 ¹³⁵⁻¹³⁷		Hypotonia, ataxia, and delayed development syndrome (HADDS); neurodevelopmental syndrome characterized by congenital hypotonia, delayed psychomotor development, variable intellectual disability with speech delay, variable dysmorphic facial features, and ataxia (often associated with cerebellar hypoplasia)	617330	AD
ATX-ELOVL4 ^{138,139}		Relatively pure ataxia, slowly progressive, usually young adult onset, less common additional signs including ocular abnormalities, pyramidal tract signs, or autonomic symptoms, one family with skin abnormalities (erythrokeratoderma)	133190 (SCA34)	AD
ATX-KCNC3 ¹⁴⁰		Slowly progressive cerebellar ataxia with variable age at onset and variable additional features including cognitive impairment and developmental delay	605259 (SCA13)	AD
ATX-LMNB1 ^{141,142}		Autosomal dominant, adult-onset demyelinating leukodystrophy (ADLD); slowly progressive and fatal disorder characterized clinically by early autonomic abnormalities, pyramidal and cerebellar dysfunction, and symmetric demyelination of the central nervous system	169500	AD
ATX-PUM1 ^{143,144}	Chorea, spasticity	Variable phenotypic presentation ranging from adult-onset, slowly progressive cerebellar ataxia without additional signs to early-onset ataxia with variable additional signs including developmental delay, chorea, spasticity, seizures, and dysmorphic facial features	617931 (SCA47)	AD
ATX-SAMD9L ^{145,146}		Ataxia-pancytopenia syndrome (ATXPC); cerebellar ataxia, variable hematologic cytopenias, and predisposition to bone marrow failure and myeloid leukemia	159550	AD
ATX-SNAP25b ¹⁴⁷⁻¹⁴⁹	Tremor	Early-onset fatigable muscle weakness with ataxia, developmental delay, intellectual disability, seizures, craniofacial dysmorphism and rarely resting and intention tremor	616330	AD

(Continues)

TABLE 3 Continued

Designation	Less common movement phenotype	Disease entity and clinical features	OMIM	MOI
ATX-TUBB2A ^{a, 150,151}	Spasticity	Broad phenotypic spectrum including ataxia, spasticity, developmental delay, seizures, distal amyotrophy, and rarely optic atrophy		AD
Autosomal recessive forms				
ATX-ABCA2 ^{152,153}		Intellectual developmental disorder with poor growth and with or without seizures or ataxia (IDPOGSA): highly variable phenotype including developmental delay, intellectual disability, hypotonia, poor overall growth, intellectual disability, sometimes borderline microcephaly, and seizures. Cases have been reported with ataxia as the predominant manifestation	618808	AR
ATX-ADPRHL2 ^{154,155}	Tremor, dystonia	Stress-induced childhood-onset neurodegeneration with variable ataxia and seizures (CONDSIAS): highly variable phenotype including cyclic episodic deterioration in response to stress, developmental delay, intellectual disability, ataxia, muscle weakness, seizures, neuropathy, and rarely tremor, dystonia, strabismus, nystagmus, hearing loss, and microcephaly	618170	AR
ATX-BRAT1 ^{b, 156,157}		Neurodevelopmental disorder with cerebellar atrophy and with or without seizures (NEDCAS); hypotonia, developmental delay, intellectual disability, oculomotor apraxia, saccadic smooth pursuit, gaze-evoked nystagmus. Cases have been reported with ataxia as the predominant manifestation	618056	AR
ATX-CACNA2D2 ^{156,158,159}	Tremor, myoclonus, chorea	Cerebellar atrophy with seizures and variable developmental delay (CASVDD): ataxia with variable seizures and/or developmental delay (epileptic encephalopathy), tremor, and also myoclonus and choreic movements in some patients	618501	AR
ATX-CO4 ^{160,161}	Tremor	Ataxia, distal muscle weakness and atrophy, peripheral neuropathy, tremor, developmental delay, and intellectual disability	618387 (SCAN3)	AR
ATX-COG5 ^{162,163}		Congenital disorder of glycosylation, type IIi (CDG IIi): variable phenotype including developmental delay, intellectual disability, hypotonia, seizures, microcephaly, and hypotonia. Cases have been reported with ataxia as the predominant manifestation	613612	AR
ATX-DOCK3 ¹⁶⁴⁻¹⁶⁶		Neurodevelopmental disorder with impaired intellectual development, hypotonia, and ataxia	618292	AR
ATX-ERCC4 ¹⁶⁷⁻¹⁷⁰	Chorea, tremor	Xeroderma pigmentosum group, type F/Cockayne syndrome: skin photosensitivity, intellectual disability, short stature, microcephaly, and in some patients chorea and tremor. Cases have been reported with ataxia as the predominant manifestation	278760	AR

(Continues)

TABLE 3 *Continued*

Designation	Less common movement phenotype	Disease entity and clinical features	OMIM	MOI
ATX- <i>GDAP2</i> ¹⁷¹⁻¹⁷³	Spasticity, dystonia	Adult-onset cerebellar ataxia, dysarthria, and cognitive impairment, pyramidal signs and spasticity, cervical dystonia reported in one patient	618369 (SCAR27)	AR
ATX- <i>MTCL1</i> ^{c:174,175}	Tremor, spasticity	Slowly progressive cerebellar ataxia, developmental delay, intellectual disability, seizures, nystagmus, slow saccadic eye movements, dysarthria, hyperreflexia, spasticity, and tremor	615766	AR
ATX- <i>NFASC</i> ¹⁷⁶⁻¹⁷⁸	Tremor, myoclonus	Neurodevelopmental disorder with central and peripheral motor dysfunction (NEDCPMD): Highly variable severity and phenotypic spectrum including hypotonia, developmental delay, ataxia, pyramidal signs, and demyelinating peripheral neuropathy. Tremor and myoclonus were reported in some patients	618356	AR
ATX- <i>PIBF1</i> ¹⁷⁹⁻¹⁸¹		Joubert syndrome type 33: hypotonia, ataxia, and developmental delay. Additional features like retinal dystrophy, cystic kidney disease, liver fibrosis, and dysmorphism in a subset of patients. Spastic tetraparesis was reported in one patient	617767	AR
ATX- <i>PNK</i> ^{d:182-186}	Dystonia	Ataxia-oculomotor apraxia type 4 (AOA4): early-onset progressive ataxia, dystonia, oculomotor apraxia, peripheral neuropathy, and cognitive impairment	616267	AR
ATX- <i>RFC1</i> ¹⁸⁷⁻¹⁹¹		Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS): adult onset, slowly progressive. In addition to the three cardinal features (cerebellar impairment, bilateral vestibulopathy, and a somatic sensory deficit), patients may have autonomic dysfunction, chronic spasmodic dry cough, and action tremor. More rarely: bradykinesia, orofacial dyskinesia or dystonia and limb chorea	614575	AR
ATX- <i>TANGO2</i> ¹⁹²⁻¹⁹⁴	Spasticity	Recurrent metabolic encephalomyopathic crises with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (MECRCN): developmental delay followed by acute encephalomyopathic features, including rhabdomyolysis, hypotonia, and neurologic regression; during disease course progressive neurodegeneration with seizures, intellectual disability, pyramidal, ataxia, loss of expressive language, as well as cardiac involvement with severe arrhythmias	616878	AR
ATX- <i>TBC1D23</i> ¹⁹⁵⁻¹⁹⁷	Stereotypies	Pontocerebellar hypoplasia type 11 (PCH11): neurodevelopmental disorder with severe developmental delay, intellectual disability, ataxia, hypotonia, behavioral abnormalities, microcephaly, dysmorphic features, and recurrent respiratory infections. Stereotypies and spasticity were reported in some patients	617695	AR
ATX- <i>TSEN5A</i> ^{f:198,199}		Ataxia, dysarthria, intellectual disability, peripheral neuropathy, and pyramidal signs	608755	AR

(Continues)

TABLE 3 Continued

Designation	Less common movement phenotype	Disease entity and clinical features	OMIM	MOI
ATX-XRCC1 ^{200,201}		Ataxia with dysarthria, intellectual disability, slow and hypometric saccadic eye movements, nystagmus, oculomotor apraxia, and peripheral neuropathy	617633 (SCAR26)	AR
Dominant and/or recessive forms				
ATX-MSTO1 ²⁰²⁻²⁰⁴		Mitochondrial myopathy and ataxia (MMYAT); complex neurologic disorder with variable manifestation including early-onset global developmental delay, mitochondrial myopathy, ataxia and variable additional features like growth impairment, cognitive impairment, muscle weakness, elevated creatine kinase, and psychiatric comorbidities	617675	AR (AD)
ATX-STUB1 ^{148,205-212}	Parkinsonism, chorea, dystonia, tremor, myoclonus	Ataxia with cognitive-affective symptoms, such as depression, anxiety, or apathy, and variable additional features like parkinsonism, tremor, chorea, dystonia, myoclonus, dysarthria, and dysphagia	618093 (SCA48), 615768 (SCAR16)	AD and AR
Mitochondrial				
ATX-MT-ATP6 ²¹³⁻²¹⁶	Myoclonus	MT-ATP6-mitochondrial disease: neuropathy, ataxia, and retinitis pigmentosa (NARP); Leigh syndrome; mitochondrial encephalomyopathy; variable phenotype including ataxia, cognitive dysfunction, neuropathy, seizures, and retinopathy	551500	mt
X-Linked				
ATX-AIFM1 ²¹⁷⁻²²⁰		Ataxia, peripheral neuropathy, hearing loss, pyramidal signs, behavioral disorder, and intellectual disability		XL
Combined phenotypes: where ataxia coexists with another movement disorder as a prominent consistent feature				
ATX/HSP-KCNA2 ²²¹⁻²²⁴	Tremor, myoclonus, dystonia, chorea	Developmental and epileptic encephalopathy-32 (DEE32): variable phenotypic spectrum including (myoclonic) seizures, (episodic) ataxia, HSP, action tremor, myoclonus, dystonia, chorea, dysarthria, developmental delay, and intellectual disability	616366	AD
ATX/HSP-IPPS13D ²²⁵⁻²²⁸	Dystonia, myoclonus, chorea, tremor	Variable phenotype including ataxia, HSP, other pyramidal signs, dystonia, myoclonus, chorea, tremor, dysarthria, oculomotor abnormalities, distal sensory impairment, hypotonia, sometimes global developmental delay or mild intellectual disability	607317 (SCAR4)	AR
HSP/ATX-CAPN1 ^{229,230}		Pure or complex HSP, cerebellar ataxia, dysarthria, foot deformities, ocular movement abnormalities, peripheral neuropathy, amyotrophy	616907	AR

(Continues)

TABLE 3 Continued

Designation	Less common movement phenotype	Disease entity and clinical features	OMIM	MOI
ATX/MYC-NUS ^{1h,231-233}	Tremor, parkinsonism, dystonia ^{234,86}	Mental retardation 55 with seizures (MRD55); broad phenotypic spectrum including developmental delay, intellectual disability, ataxia, myoclonus, (myoclonic) seizures, resting and intention tremor, and rarely parkinsonism	617831	AD
ATX/DYT-SQSTM1 ^{98,97,235,236}	Chorea	Neurodegeneration with ataxia, dystonia, and gaze palsy (NADGP); ataxia, dystonia, chorea, gaze palsy, cognitive decline, nystagmus, pyramidal signs, dysarthria and hypergonadotropic hypogonadism	617145	AR
Disorders that usually present with other phenotypes but can have (prominent) ataxia				
Gene	Disease	Clinical phenotype	OMIM	MOI
<i>C9orf72</i>	Frontotemporal dementia (FTD) and/or amyotrophic lateral sclerosis (ALS)	Broad phenotypic spectrum including frontotemporal dementia and features of motor neuron disease, parkinsonism (mostly atypical, eg, PSP-like, MSA, or CBS), and dystonia, cerebellar signs, or chorea	105550	AD, repeat expansion
<i>PSEN1</i> ²³⁷⁻²⁴⁰	Alzheimer's disease	Gene is linked to Alzheimer's disease; a few cases with prominent (spastic) ataxia have been described.	607822	AD

OMIM, Online Mendelian Inheritance in Man (<https://www.omim.org/about>); MOI, mode of inheritance; AD, autosomal dominant; AR, autosomal recessive; mit, mitochondrial; XL, X-linked; HSP, hereditary spastic paraplegia; SCA, autosomal dominant spinocerebellar ataxia; SCAN, spinocerebellar ataxia with axonal neuropathy; SCAR, autosomal recessive spinocerebellar ataxia; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; CBS, corticobasal syndrome.

^aGene mutations can also cause complex cortical dysplasia with other brain malformations 5 (OMIM: 615763).

^bGene mutations can also cause the lethal neonatal rigidity and multifocal seizure syndrome (OMIM: 614498).

^cComment: Evidence is limited as only two patients in total were reported in two independent publications.

^dGene mutations can also cause autosomal recessive microcephaly, seizures, and developmental delay (OMIM: 613402).

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

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

^gGeGene mutations can also cause the Gordon Holmes syndrome¹¹⁹.

^hGene mutations can also cause congenital disorder of glycosylation, type 1AA (OMIM: 617082).

Genes that have been associated with a movement disorder-predominant phenotype but did not meet the criteria for a confirmed genotype–phenotype relationship are listed as unconfirmed candidate genes (Supplementary material).

Results

Applying the Recommendations

A full list of all genes, including genes previously included³ (<https://www.movementdisorders.org/MDS/About/Committees-Other-Groups/MDS-Task-Forces/Task-Force-on-Nomenclature-in-Movement-Disorders.htm>) as well as yet unconfirmed candidate genes can be found in the Supplementary material (Tables S2–S7). Here we describe newly confirmed genes that cause movement disorders.

Genetically Determined Parkinsonism

The literature search for hereditary parkinsonism yielded >5000 publications in which genetic variants

that are potentially associated with monogenic PD have been reported in over 80 genes. The majority of these genes have been reported only once, often in single sporadic cases, and thus remain to be confirmed (see Supplementary material). Twenty genes were already known causes of other non-parkinsonian disease entities; however, predominant features of typical or atypical parkinsonism have been described in several patients, indicating that the phenotypic spectrum of these entities should be expanded to include parkinsonism. Based on our criteria, these genes do not warrant a PARK prefix; however, for six of these genes, typical or atypical parkinsonism has been repeatedly reported to be a predominant feature in a subset of patients. Thus, we list *C9orf72*, *DNAJC12*, *EPM2A*, *GRN*, *MAPT*, and *PDE8B* in the category of genes that usually show a different phenotype but can have predominant parkinsonism in a subset of patients. Finally, 18 genes (Table 1 and Table S2) have been reported repeatedly in several unrelated patients or families, or by independent research groups, and were therefore classified as potential novel monogenic causes of parkinsonism.

TABLE 4 Recently identified or confirmed forms of hereditary chorea

Designation	Less common movement phenotype	Clinical clues	OMIM	MOI
CHOR- <i>PDE10A</i> ^{242,243}		Recessive form: childhood onset axial hypotonia, chorea, ballism, variable orofacial dyskinesia, variable cognition, and normal brain MRI Dominant form: slowly progressive chorea with normal cognition, brain MRI with bilateral T2 striatal hyperintensity	616921 (AR), 616922 (AD)	AR and AD, often de novo
Combined phenotypes: where chorea coexists with (an)other movement disorder(s) as a prominent and consistent feature				
DYT/CHOR- <i>ADAR</i> ^{95,96}	Spasticity	Aicardi–Goutières syndrome, includes dystonia and spastic paraparesis, MRI may reveal isolated bilateral striatal necrosis, adult-onset psychological difficulties, linked to characteristic interferon signature (upregulation of interferon-stimulated genes)	615010	AR, rarely AD
DYT/CHOR- <i>FOXG1</i> ¹²⁴⁻¹²⁶	Dyskinesia	Rett-like phenotype (with congenital encephalopathy)	613454	AD
DYT/CHOR- <i>GNAO1</i> ^{244,245}	Myoclonus	Hypotonia, motor delay. Exacerbated by febrile illness, stress, high ambient temperature	617493	AD
ATX/CHOR- <i>RNF216</i> ²⁴⁶⁻²⁴⁸		Huntington-like disorder, chorea develops in second or third decade, gait ataxia, nystagmus, dysarthria and dysmetria. Hypogonadotropic hypogonadism	212840	AR

OMIM, Online Mendelian Inheritance in Man (<https://www.omim.org/about>); MOI, mode of inheritance; AD, autosomal dominant; AR, autosomal recessive; MRI, magnetic resonance imaging.

TABLE 5 Recently identified or confirmed forms of hereditary myoclonus

New designation	Less common movement phenotype	Disease entity and clinical features	OMIM	MOI
Prominent myoclonus syndromes				
MYC-DHDDS ^{231,249}	Ataxia, dystonia, tremor	Developmental delay and seizures with or without movement abnormalities (DEDSM); global developmental delay, variable intellectual disability, early-onset seizures, and myoclonic component (can be prominent)	617836	AD
MYC-GRJA3 ²⁵⁰⁻²⁵²	Chorea ^a	Syndromic intellectual disability disorder (MRXSW); broad phenotypic spectrum including mental retardation and seizures, myoclonus, and variable motor and behavioral impairment	300699	XLR
MYC-MFSD8 ^{253,254}		Neuronal ceroid lipofuscinosis 7 (CLN7); neurodegenerative disease with variable phenotypic features including seizures, myoclonus, mental regression, speech impairment, loss of vision, and personality disorder	610951	AR
MYC-SEMA6B ²⁵⁵⁻²⁵⁹		Progressive myoclonic epilepsy-11 (EPM11); neurodegenerative disease with infancy-onset of developmental regression and seizures, followed by additional neurological symptoms, eg, spasticity, loss of independent ambulation, myoclonus, tremor, ataxia, and severe cognitive impairment in the first and second decade	618876	AD
MYC/PxMD-SCN8A ^{b,260-262}	Ataxia	Familial myoclonus with childhood-onset of isolated action-induced nonepileptic myoclonus affecting the upper limbs, nonprogressive; also epilepsy or developmental and epileptic encephalopathy phenotypes	618364	AD
Combined phenotypes: where myoclonus coexists with another movement disorder as a prominent consistent feature				
MYC/DYT-KCTD17 ⁸⁷⁻⁹⁰		Onset of mild myoclonic symptoms in the first or second decade of life, followed by later onset of progressive dystonia with predominant involvement of the cranial and laryngeal muscles; dystonia dominates the clinical picture	616398	AD
ATX/MYC-NUS1 ^{231,259}	Tremor, parkinsonism, dystonia ^{86,234}	Mental retardation 55 with seizures (MRD55); broad phenotypic spectrum including developmental delay, intellectual disability, ataxia, myoclonus, (myoclonic) seizures, resting and intention tremor, and rarely parkinsonism	617831	AD

(Continues)

TABLE 5 Continued

New designation	Less common movement phenotype	Disease entity and clinical features	OMIM	MOI
Disorders that usually present with other phenotypes but can have dominant myoclonus				
Gene	Disease	OMIM	Clinical phenotype and comment	MOI
ATX/PxMD-CACNA1A ^{6,263,264}	Episodic ataxia type 2 (EA2)	108500	Gene linked to EA2, but recent publications report phenotypes including progressive myoclonus epilepsy	AD
ATX-MT-ATP6 ^{215,265}	See Table 3 (ATX list)	551500	Variable phenotype predominantly including ataxia in the majority, but also myoclonus in a minority, for details see Table 3	mt
EEF1A2 ²⁶⁶⁻²⁶⁸	Developmental and epileptic encephalopathy 33 (DEE33), mental retardation (MRD38)	616409, 616393	Epilepsy phenotype with various types of seizures in the first month of life and severe global developmental delay with impaired intellectual development and poor or absent speech, sometimes prominent myoclonic epilepsy	AD
RORB ^{269,270}	Susceptibility to idiopathic generalized epilepsy 15 (EIG15)	618357	Epilepsy phenotype with various types of seizures in the first decade (most commonly absence seizures), majority with developmental delay with impaired intellectual development, predominant eyelid myoclonus	AD
SCN2A ²⁷¹⁻²⁷⁴	Developmental and epileptic encephalopathy 11 (DEE11), Episodic ataxia type 9 (EA9), Benign familial infantile seizures 3	613721, 618924, 607745	Gene linked to multiple diseases and therefore with a broad and overlapping phenotypic spectrum including developmental delay, seizures and various movement disorders, myoclonus can be a dominant feature	AD
SETD1B ²⁷⁵	Intellectual developmental disorder with seizures and language delay	619000	Global developmental delay with speech and language impairment and seizures, mostly myoclonic (absence) seizures as predominant feature, often accompanying behavioral abnormalities (autism spectrum disorder or anxiety), sometimes additional features like facial dysmorphism, tapering fingers, and pigmentary skin changes	AD

OMIM, Online Mendelian Inheritance in Man (<https://www.omim.org/about>); MOI, mode of inheritance; AD, autosomal dominant; XLR, X-linked recessive; AR, autosomal recessive; mt, mitochondrial.

^aChorea is rather equally prominent in respective cases, but this finding needs to be independently confirmed. This gene is currently in the list of unconfirmed candidate genes of hereditary chorea (Table S5).

^bMutations in this gene can also cause autosomal dominant cognitive impairment with or without cerebellar ataxia (OMIM 614306), autosomal dominant developmental and epileptic encephalopathy 13 (DEE13, OMIM 614558), and/or autosomal dominant benign familial infantile seizures type 5 (OMIM 617080).

^cMutations in this gene can also cause autosomal dominant spinocerebellar ataxia type 6 (OMIM 183086), autosomal dominant familial hemiplegic migraine with or without progressive cerebellar ataxia (OMIM 141500), and/or autosomal dominant developmental and epileptic encephalopathy type 41 (OMIM 617106).²⁷⁶

TABLE 6 Recently identified or confirmed forms of hereditary spastic paraplegia

New designation	Less common movement phenotype	Clinical clues/clinical phenotype and comment	OMIM	MOI
Autosomal dominant forms				
HSP- <i>CPT1C</i> ^{277,278}		Pure HSP, variable age at onset (infantile to adulthood), slowly progressive disease course	616282	AD
HSP- <i>UBAP1</i> ²⁷⁹⁻²⁸³		Typically pure HSP, juvenile-onset, toe-walking, sometimes complicated by cerebellar signs or mild cognitive impairment, eventual association with parkinsonism and learning difficulties (needs to be confirmed)	618418	AD
Autosomal recessive forms				
HSP- <i>ENTPDI</i> ^{284,285}		Complex HSP, infancy or childhood onset with white matter change, intellectual impairment, dysarthria, and gait ataxia	615683	AR
HSP- <i>HPDL</i> ^{286,287}		(1) Pure HSP, mostly juvenile onset, sometimes myalgia or mild dysarthria (2) Severe neurodevelopmental disorder with progressive spasticity and brain white matter abnormalities (NEDSWMA; OMIM 619026)	619027	AR
HSP- <i>MAG</i> ^{a,288}		Complex HSP, infantile-onset Pelizaeus–Merzbacher disease-like phenotype, mental retardation, dysarthria, optic atrophy, peripheral neuropathy, demyelinating leukodystrophy	616680	AR
HSP- <i>PCYT2</i> ^{289,290}		Complex HSP, infancy-onset global developmental delay, motor impairment, and progressive spasticity of mainly lower limbs, severe gait impairment or inability to walk (never achieved or lost), additional features including impaired intellectual development with language difficulties, ocular anomalies, and seizures; frequently brain imaging abnormalities (cerebral and cerebellar atrophy and white matter hyperintensities)	618770	AR
HSP- <i>RNF170</i> ^{b,291,292}		Complex HSP, predominantly lower limb spastic paraparesis with mild upper limb involvement, age at onset before 5 years, optic atrophy, variable features include cerebellar involvement, mild cervical dystonia, and axonal sensorimotor polyneuropathy		AR
Autosomal dominant or recessive forms				
HSP- <i>ALDH18A1</i> ^{c,293,294}		Dominant form: pure or complex HSP, cognitive impairment, congenital cataract, dysarthria, cerebellar signs, neuropathic pain, epilepsy, infantile psychosis, sensorineural hearing loss, vomiting, biochemical features of delta-1-pyrroline-5-carboxylate synthase deficiency	601162 (AD), 616586 (AR)	AD or AR

(Continues)

TABLE 6 Continued

New designation	Less common movement phenotype	Clinical clues/clinical phenotype and comment	OMIM	MOI
Recessive form: complex HSP, early-onset, delayed psychomotor development, cognitive impairment, variable additional features including dysmorphic facial features, tremor, and urinary incontinence				
X-Linked forms				
HSP- <i>SLC16A2</i> ²⁹⁵⁻²⁹⁸	Dystonia	Complex HSP; Allan–Herndon–Dudley syndrome (ADHS); abnormal thyroid function (elevated T3 and low T4 levels), severely intellectual impairment, delayed developmental milestones, dysmorphic facies, dysarthria, athetoid movements, muscle hypoplasia, and spastic paraplegia	300523	XL
Combined phenotypes: where HSP coexists with another movement disorder as a prominent consistent feature				
HSP/ATX- <i>CAPN1</i> ^{229,230}		Pure or complex HSP, cerebellar ataxia, dysarthria, foot deformities, ocular movement abnormalities, peripheral neuropathy, amyotrophy	616907	AR
HSP/ATX- <i>UCHL1</i> ²⁹⁹⁻³⁰¹		Complex HSP, progressive visual loss and optic atrophy may be an early and prominent manifestation, variable additional features as peripheral neuropathy, cerebellar ataxia, cognitive impairment, axonal sensorimotor polyneuropathy, facial dysmorphism, microcephaly, fasciculations (tongue and limb muscles), and abnormal MRI findings including cerebellar and mild cerebral atrophy	615491	AR
ATX/HSP- <i>KCNA2</i> ^{d,222,302}	Myoclonus	Variable phenotypic spectrum including complex HSP, ataxia, intellectual and learning disability, developmental delay, dysarthria, sensory-motor peripheral neuropathy, abnormal EEG without clinical seizures		AD
ATX/HSP- <i>VPS13D</i> ²²⁷	Dystonia, myoclonus, chorea	Variable phenotypic spectrum ranging from adult-onset pure form of HSP to childhood-onset complicated form of HSP with additional cerebellar ataxia, dystonia, cataracts, and chorioretinal dystrophy		AR

OMIM, Online Mendelian Inheritance in Man (<https://www.omim.org/about>); MOI, mode of inheritance; HSP, hereditary spastic paraplegia; AD, autosomal dominant; AR, autosomal recessive; XL, X-linked; MRI, magnetic resonance imaging; EEG, electroencephalogram.

^aAllelic with Pelizaeus–Merzbacher disease.

^bMutations in this gene can also cause autosomal dominant sensory ataxia (OMIM 608984).

^cMutations in this gene can also cause autosomal dominant cutis laxa type 3 (OMIM 616603) and autosomal recessive cutis laxa type IIIA (OMIM 219150).

^dMutations in this gene can also cause developmental and epileptic encephalopathy 32 (DEE32, OMIM 616366).

Notably, several of these genes had already been assigned a PARK locus designation (by the previous ad hoc locus system). However, over time, follow-up studies and expert reviews have raised doubts and the evidence for many of these genes has been questioned.¹¹⁻¹³ For the majority of these genes, some of which were initially

reported several years ago, the evidence is still not fully convincing or even became conflicting. A full list of genes still under debate can be found in the Supplementary material (Table S2). Based on our interpretation, supported by the ClinGen gene–disease curation criteria, we added four genes to the list of confirmed monogenic

causes of parkinsonism. One of these genes, *CHCHD2*, causes typical levodopa-responsive parkinsonism very similar to idiopathic PD, whereas the other three, *DCTN1*, *RAB39B*, and *VPS13C*, cause a rather atypical parkinsonian phenotype with additional clinical features (Table 1). Interestingly, biallelic variants in the *VPS13C* gene have also been reported in patients with early-onset and autopsy-confirmed dementia with Lewy bodies (DLB), however, further research is necessary to confirm this association.¹⁴

Additionally, four of the six genes that were previously listed as primary familial brain calcification genes were reclassified, and are now included in our updated list of hereditary parkinsonism (Table 1). Two of these genes, *JAM2* and *SLC20A2*, cause a phenotype with predominant atypical parkinsonism in the majority of cases and have therefore been assigned a PARK prefix, whereas another two, *PDGFRB* and *XPR1*, can include parkinsonian features but are insufficiently prominent to warrant a PARK prefix.

Genetically Determined Dystonia

We identified 21 new genes that warrant classification as causing dystonia (DYT). These genes have been organized into isolated dystonia, combined dystonia, and complex dystonia in accordance with the most recent guidelines³ (Table 2). Within the complex dystonias, we highlight those genes associated with dystonia-deafness and dystonia with developmental delay since these combinations may be helpful genotype–phenotype relationships to consider when evaluating patients from a

diagnostic standpoint. The frequent association of dystonia and neurodevelopmental disorders reflects the role of several of these genes in central nervous system development, and it is debatable whether to assign a DYT prefix (highlighting dystonia as a prominent feature) in the context of a neurodevelopmental disorder with developmental delay and/or intellectual disability. We suggest a DYT classification for three forms where dystonia is a predominant sign (*IRF2BPL*, *VAC14*, and *FOXG1*; Table 2). There are several genetic conditions where less prominent dystonia can be encountered in the setting of a predominant developmental disorder or epileptic encephalopathy. This combination can be diagnostically helpful, and we have designated these forms as “Neurodevelopmental disorder with dystonia” (Table S3A).

Finally, six additional genes have been reported in the literature as potential dystonia genes, namely *TOMM70*, *COL6A3*, *NR4A2*, *POLR1C*, *NUBPL*, and *DEGS1*; however, they currently lack independent confirmation and are therefore not (yet) included in our updated list of genetically determined dystonia (Table S3B).

Genetically Determined Ataxia

The ataxias are a clinically and genetically heterogeneous group of movement disorders. They can present as pure cerebellar ataxias with ataxia as the only or predominant feature or can be accompanied by variable additional signs and symptoms. We identified a total of 38 new genes known to cause monogenic ataxia and therefore assigned an ATX prefix. We categorized them

TABLE 7 Recently identified or confirmed forms of paroxysmal movement disorders

Designation	Less common movement phenotype	Clinical clues	OMIM	MOI
Predominant dyskinesia				
PxMD- <i>KCNMA1</i> ^{303,304}		Paroxysmal non-kinesigenic dyskinesia including dystonic and choreiform movements of mouth, tongue and extremities. Triggered by alcohol, fatigue, or stress, although no clear trigger in some individuals. Developmental delay, generalized epilepsy	609446	AD
Predominant dystonia				
PxMD- <i>ECHS1</i> ^{17,305-308}	Ataxia, spasticity	Leigh syndrome; onset before age 10 years, paroxysmal dystonia triggered by high metabolic demand (exercise, fever, low calorie intake), developmental delay, acute episodes of encephalopathy, increased plasma lactate, and urinary excretion of organic acids	616277	AR
Disorders that usually present with other phenotypes but can have predominant paroxysmal dyskinesias				
MYC/PxMD- <i>SCN8A</i> ^{a,309}	Ataxia	Paroxysmal kinesigenic dyskinesia, seizure disorder (wide spectrum with benign infantile seizures in some and epileptic encephalopathy in others), intellectual disability	617080	AD

OMIM, Online Mendelian Inheritance in Man (<https://www.omim.org/about>); MOI, mode of inheritance; AD, autosomal dominant; AR, autosomal recessive.

^aMutations in this gene can also cause familial myoclonus type 2 (OMIM 618364; Table 5), autosomal dominant cognitive impairment with or without cerebellar ataxia (OMIM 614306), and/or autosomal dominant developmental and epileptic encephalopathy 13 (DEE13, OMIM 614558).

TABLE 8 Confirmed forms of mixed movement disorders

Designation	Clinical clues	OMIM	MOI
MxMD- <i>ADCY5</i> ³¹⁰	Pleiotropic dyskinesia (choreatic, myoclonic, dystonic) mainly involving the limbs, neck, and/or face, paroxysmal worsening triggered by anxiety or drowsiness, axial hypotonia, developmental delay, abnormal saccades, spasticity	600293	AD
MxMD- <i>ATP13A2</i> ^a	Broad and variable clinical spectrum including several movement disorders: (1) Kufor-Rakeb syndrome ³¹¹⁻³¹³ : juvenile-onset atypical dystonia-parkinsonism, supranuclear gaze palsy, pyramidal signs, dementia, dysphagia, dysarthria and olfactory dysfunction; (2) HSP ³¹⁴⁻³¹⁷ : adult-onset, characterized by spasticity, lower limb weakness, cognitive impairment, psychiatric symptoms, axonal neuropathy, thin corpus callosum and “ears of the lynx” sign on MRI; (3) adult-onset progressive ataxia ³¹⁸⁻³²⁰ and action myoclonus ³¹⁸⁻³²³	606695 (PARK), 617225 (HSP)	AR
MxMD- <i>MYORG</i> -(PFBC) ³²⁴⁻³²⁷	Dysarthria, cognitive deficits, and depression, headaches and psychosis in a lower percentage, imaging abnormalities include basal ganglia and cerebellum calcification	618317	AR
MxMD- <i>OPA3</i> ³²⁸⁻³³³	3-Methylglutaconic aciduria type 3 (MGCA3; many alternative names); neuro-ophthalmological syndrome with early-onset bilateral optic atrophy with progressive decrease in visual acuity and horizontal nystagmus, choreoathetoid movements before age 10 years, which can restrict ambulation, spastic paraparesis in second decade, pyramidal dysfunction, ataxia, and variable cognitive impairment	258501	AR
MxMD- <i>PDGFB</i> -(PFBC) ^{334,335}	Parkinsonism, ataxia, or chorea with possible additional headache and cognitive deficits, imaging abnormalities include thalamus, cerebellum, white matter, and basal ganglia calcifications	615483	AD
MxMD- <i>POLG</i> ³³⁶⁻³³⁸	Multiple syndromes often with progressive external ophthalmoparesis and variable other neurological manifestations; rarely prominent parkinsonism	174763	AD or AR

OMIM, Online Mendelian Inheritance in Man (<https://www.omim.org/about>); MOI, mode of inheritance; MxMD, mixed movement disorders; AD, autosomal dominant; HSP, hereditary spastic paraplegia; MRI, magnetic resonance imaging; AR, autosomal recessive; PFBC, primary familial brain calcifications.

^aMutations in this gene also cause neuronal ceroid lipofuscinosis (CLN12).³²¹

based on their mode of inheritance: 11 genes are inherited in an autosomal dominant manner, 18 are inherited in an autosomal recessive fashion, and one each shows mitochondrial and X-linked inheritance. Further, another gene that was already known to cause autosomal recessive ataxia (*ATX-STUB1*, also known as SCAR16) and had therefore already been assigned a prefix,⁴ has now also been confirmed as a dominant ataxia gene (also known as SCA48). Lastly, in *ATX-MSTO1* also both autosomal dominant and recessive inheritance have been reported. The variable phenotypic spectrum of the listed genes is highlighted in Table 3. For five genes, a double prefix was assigned.

In addition to these confirmed genes, 95 genes have been reported as potential novel ataxia genes or genes causing a phenotype that can include ataxia. These await further confirmation (Table S4).

Genetically Determined Chorea

We expand our list of genetically determined chorea by adding five genes. Notably, four of these are related to combined phenotypes, specifically *DYT* and *ATX* (Table 4). One salient aspect of our literature review is the combination of chorea and developmental delay. Indeed, several entities characterized by motor, language,

global delay, or epileptic encephalopathy are also associated with chorea, albeit in some cases in a less prominent manner. This is similar to our findings for dystonia genes and highlights the evolving spectrum of epilepsy-dyskinesia syndromes.¹⁵ Table S5A lists genes linked to a neurodevelopmental disorder that can have chorea as part of their phenotype. Finally, three genes have been reported in the literature as potential chorea genes, *PDE2A*, *GRIA3*, and *MRPL24*; however, they lack independent confirmation (Table S5).

Genetically Determined Myoclonus

Myoclonus is a hyperkinetic movement disorder that is characterized by sudden, brief, involuntary jerks of single or multiple muscles.^{5,16} In addition, there are genetic myoclonic epilepsy syndromes, specifically the progressive myoclonus epilepsies and epileptic encephalopathies, where myoclonic jerks co-occur with epilepsy. There are many genetic disorders that include myoclonus but not as the only or most prominent feature.

Our literature review led us to assign a MYC-prefix to seven additional genes (Table 5), *DHDDS*, *GRIA3*, *MFSD8*, *SEMA6B*, *SCN8A*, and *NUS1*, three of which (*SCN8A*, *KCTD17*, and *NUS1*) have been assigned a combined prefix since paroxysmal movements, dystonia, and ataxia frequently coexist with myoclonus in these disorders. Notably, all these genes can cause a broad clinical phenotypic spectrum. Table 5 includes a list of genetic disorders that more commonly present with other phenotypes and do not warrant a MYC-prefix. A list of all genes which we identified for which myoclonus has been repeatedly reported, but neither as the prominent feature in the majority nor as the sole feature even in the minority of patients, can be found in the Supplementary material (Table S6A). Finally, another five genes have been reported in the literature as potential newly identified myoclonus genes, namely *BOLA3*, *HCN4*, *KCNN2*, *MT-TN*, and *NUP214*; however, they lack independent confirmation (Table S6B).

Hereditary Spastic Paraplegia (HSP)

The hereditary spastic paraplegias (HSP) can present as pure or complicated/complex forms with variable additional associated features such as cerebellar signs, neuropathy, cognitive impairment, seizures, optic nerve atrophy, or ophthalmoplegia. Our literature review resulted in the addition of 13 newly confirmed HSP genes (Table 6). Two of them (*CPT1C* and *UBAP1*) are inherited in an autosomal dominant fashion and present as pure forms, whereas the others, except for one X-linked gene (*SLC16A2*), are inherited in an autosomal recessive fashion and present with a complex phenotype (*ENTPD1*, *HPDL*, *MAG*, *PCYT2*, and

RNF170). One form, *ALDH18A1*, has both autosomal dominant and autosomal recessive inheritance. Further, four genes have been assigned a combined prefix, all of which can cause a broad and variable phenotypic spectrum including two predominant movement disorder phenotypes each; specifically ataxia and spastic paraplegia in *HSP/ATX-CAPN1*, *HSP/ATX-UCHL1*, *ATX/HSP-KCNA2*, and *ATX/HSP-VPS13D*. Additionally, another 20 genes have been reported in the literature as potential HSP genes; however, they lack independent confirmation and are therefore not (yet) included in our updated list. The list of unconfirmed candidate genes can be found in the Supplementary material (Table S7).

Genetically Determined Paroxysmal Movement Disorders

In our 2016 review, we introduced the category of Paroxysmal Movement Disorders (PxMD) which describes cases where movement disorders occur in an episodic manner. These disorders often include a mixed and overlapping phenomenology. Table 7 shows the proposed list of additional genetic paroxysmal movement disorders. We have conferred a PxMD prefix to the *KCNMA1* gene which causes dystonic and choreiform movements. In some individuals, episodes happen without a clear trigger. We also included the *ECHS1* gene that has been reported to cause episodic dystonia triggered by fever, stress, and physical activity.¹⁷ Additionally, for *SCN8A* a double prefix has been assigned as mutations in this gene can either cause paroxysmal movements within a broad phenotypic spectrum of seizure disorders or familial myoclonus (Tables 5 and 7).

Genetically Determined Neurodegeneration with Brain Iron Accumulation (NBIA) and Primary Familial Brain Calcification (PFBC)

As stated above, we decided to reclassify genes that have previously been assigned a NBIA or PFBC prefix according to their most prominent movement disorder phenotype. Two of these genes, *XPR1* and *PDGFRB*, have lost their preceding prefix since the current evidence shows a movement disorder is present in a minority of individuals only. For both genes, however, parkinsonism has been described as a prominent feature in a subset of patients (see Table 1). Table S8 shows a complete list of all reclassified entities and summarizes all genes with a PBFC and NBIA suffix, respectively.

Genetically Determined Mixed Movement Disorders

Some genes display a mixed and overlapping phenomenology, without a clear predominance of a specific movement disorder. Given this, we propose a new

category of Mixed Movement Disorders (MxMD). This list includes *ATP13A2*, *OPA3*, as well as *POLG*, and further also *PDGFB* and *MYORG*, both of which were in the previously existing category of primary familial brain calcification. Finally, *ADCY5* was moved to this category; it was previously listed with three prefixes (CHOR/DYT/PxMD-*ADCY5*; <https://www.movementdisorders.org/MDS/About/Committees-Other-Groups/MDS-Task-Forces/Task-Force-on-Nomenclature-in-Movement-Disorders.htm>).

Discussion

We here provide updated lists of hereditary movement disorders following the established procedure of the MDS Task Force for the Nomenclature of Genetic Movement Disorders. Our update covers the past 5 years and we have identified 89 new genes that warrant a movement disorder-related prefix. We believe that this is a helpful resource for clinicians and researchers, and we encourage the field to continue to adopt and use this nomenclature system. Along these lines, this project remains a moving target with need for continuous updates. We expect that many additional disease-causing genes will be identified and will need to be evaluated. We also expect that genes already assigned a prefix will need to be reassessed and may be reclassified over time. We will strive to continue to expand and improve our recommendations as the Task Force continues its assigned mandate, and yearly updates will be made available on the MDS Task Force website (<https://www.movementdisorders.org/MDS/About/Committees-Other-Groups/MDS-Task-Forces/Task-Force-on-Nomenclature-in-Movement-Disorders.htm>).

Challenges and Limitations

One of the main challenges we encountered when preparing these updated lists was determining the predominant phenotype in a given condition. This becomes especially challenging in very complex genetic syndromes and disorders with a broad phenotypic spectrum, for example, neurodevelopmental disorders or in the case of pronounced phenotypic variability (chameleon-like gene–disease relationships). From a clinical perspective, one might argue that genes should only be included if the respective movement disorder is the most prominent phenotype. Otherwise, the lists might get too extensive and then fail to usefully highlight any particular disorder. However, from a genetics perspective, it might make sense to include all genes that may present with a movement disorder in broader genetic testing efforts, even if it is not the predominant phenotype or if it is just in the minority of cases. This would ensure that physicians are aware of the phenotypic spectrum of a mutated gene and would be of more practical use to

physicians seeing patients first presenting with movement disorders independent of whether this is a common or rare manifestation of the disorder. Recognizing the advantages of both approaches, we provide both a concise list that highlights those disorders where movement disorders predominate and a more comprehensive list of genes that usually present with other phenotypes or are even confirmed genes for a different disease entity, but where a movement disorder has been described. To distinguish the two, the latter genes were not assigned a prefix. We acknowledge that some of these “less predominant” cases may be the ones that are referred to a movement disorders specialist. Nonetheless, we believe that including them as part of the Supplementary material still provides a useful resource for the clinician. In this current update, we started by highlighting conditions that predominantly present as a neurodevelopmental disorder but can also have dominant dystonia and chorea. For future updates, it might be useful to apply this categorization also to other movement disorders, for example, ataxia and HSP. Additionally, in the future, we may consider assigning a special prefix to these genes. For example, to distinguish phenotypic presentations occurring in more than 50% and less than 50% of cases, one option under consideration is to retain the uppercase phenotype designation (eg, *PARK*, *DYT*, *ATX*, etc.) followed by the gene name for the former situation (as in the current classification) and to use a lowercase symbolization (eg, *park*, *dyt*, *atx*) for the latter.

Further, especially for newly identified genes, the initial publications often include patients with a broad phenotype and only over time, the “pure movement disorder phenotypes” or “core phenotypes” become apparent. In some cases, initial publications may report a pure movement disorder phenotype, and only over time and additional cases recurrent additional features may be identified. Finally, even with considerable further experience, for some genetic disorders it may remain impossible to define only a single (core) phenotype if great heterogeneity remains present.

Another challenge that arose in the preparation of this update was the evaluation of pathogenicity and what to consider to be convincing evidence for a causal gene–disease association. Our evaluation of pathogenicity was based on numerous criteria, the most important of which was an independent confirmation of a causal role of a gene in multiple unrelated patients or families and, in addition, the lack of evidence that refutes a causal gene–disease relationship. In general, this approach works well for rare diseases, which comprise the majority of genetic movement disorders described here. A particular challenge, however, was the evaluation of newly identified genes causing parkinsonism. PD is a common neurodegenerative disease. Thus, even two independent groups reporting variants in the same gene

in single(ton) cases with typical PD and absence of specific additional features would not necessarily constitute enough evidence to be convincing as a monogenic cause of PD. Evidence of segregation in extended families and gene-specific functional studies on the other hand can help to support a causal relationship.

To overcome this obstacle, we employed standardized, previously published criteria.⁶ These criteria served as presumably objective guidance in the interpretation of evidence for a gene–disease association based on currently available data; however, there remained room for subjective interpretation. Of note, these criteria set a high threshold, especially regarding the number of reported mutation carriers, to confirm a causal relationship. Given this, our list of unconfirmed genes (Table S2) serves as an important adjunct resource. Several genes already designated as PARK by the previous ad hoc locus system, for example, *UCHL1*, *GIGYF2*, *HTRA2*, *EIF4G1*, and *DNAJC13* (termed as *PARK5*, *PARK11*, *PARK13*, *PARK18*, and *PARK21*, respectively), could not be confirmed. Of note, these genes are already being widely and mostly controversially discussed in the literature.^{11,12} After the initial nomination of these genes as “novel PD genes”, additional studies failed to confirm a causative role and pointed out that the existing evidence was conflicting (for details see Table S2). It has even been suggested to remove the PARK designation for these genes.¹³ This experience reinforces the importance of standard criteria for inclusion in the PARK list. Based on these criteria, *CHCHD2* and *VPS13C* (also known as *PARK22* and *PARK23*, respectively) are now listed as confirmed causes of monogenic parkinsonism due to several reported patients, often with clearly truncating variants, especially in *VPS13C* (see Table 1).

With the support of the Parkinson’s Foundation in the US, a PD Gene Curation Expert Panel (GCEP) comprising experts in clinical and molecular genetics of PD has been officially convened as a ClinGen Clinical Domain Working Group (<https://clinicalgenome.org/affiliation/40079/>). The PD GCEP has already begun to curate the well-established PD genes such as *LRRK2* and *VPS35* using the ClinGen framework and will additionally evaluate genes with a lower confidence of gene–disease association. As the work of the PD GCEP continues and more data become available in the literature, we will evaluate any potential discrepancies within the PD GCEP with our determinations and address them collaboratively before including them on the Task Force’s homepage. Indeed, several of our Task Force members are also members of the PD GCEP, which will facilitate this dialogue. With respect to other movement disorders with a particular focus on rare movement disorders, the utility and feasibility of using the ClinGen framework still need to be determined. If deemed helpful, we may seek to establish new GCEPs for these conditions.

What’s Next?

We expect that the list of newly identified genes linked to a movement disorder phenotype will continue to expand and simultaneously hopefully also our understanding of gene–disease associations. Therefore, it remains important to re-evaluate the literature periodically and update the lists of (confirmed) monogenic causes of movement disorders. These updated lists will then be published on the MDS Task Force website (<https://www.movementdisorders.org/MDS/About/Committees-Other-Groups/MDS-Task-Forces/Task-Force-on-Nomenclature-in-Movement-Disorders.htm>). To make this easier, we have already started to prepare lists of yet unconfirmed candidate genes for the future.

To further define the phenotypic spectrum and genotype–phenotype correlations of these movement disorder genes, the Movement Disorder Society Genetic Mutation Database (MDSGene; <https://www.mdsgene.org>) provides the infrastructure for a systematic collection, curation, and descriptive analysis of phenotypic and genotypic data. Each of these newly defined movement disorders genes are candidates for inclusion in MDSGene and can provide new insights into the phenotype through the comprehensive individual-level nature of the data collection. We aim to expand the number of included genes in the MDSGene database and will start this effort by prioritizing novel monogenic causes of parkinsonism and dystonia. ■

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Task Force on Genetic Nomenclature in Movement Disorders

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Employment	University Health Network
Contracts	None
Royalties	None
Other	None