REVIEW

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

Lara M. Lange, MD,[1] Paulina Gonzalez-Latapi, MD, MSc,[2,3] Rajasumi Rajalingam, MD,[2] Marina A.J. Tijssen, MD, PhD,[4] Darius Ebrahimi-Fakhari, MD, PhD,[5,6] Carolin Gabbert, MSc,[1] Christos Ganos, MD,[7] Rhia Ghosh, MD,[8] Kishore R. Kumar, MBBS, PhD, FRACP,[9,10] Anthony E. Lang, MD,[2] Malco Rossi, MD, PhD,[11] Sterre van der Veen, MD,[4] Bart van de Warrenburg, MD, PhD,[12] Tom Warner, MD, PhD,[13] Katja Lohmann, PhD,[1#] Christine Klein, MD,[1#*] Connie Marras, MD, PhD,[2#*] and on behalf of the Task Force on Genetic Nomenclature in Movement Disorders

[1]*Institute of Neurogenetics, University of Lübeck, Lübeck, Germany*
[2]*The Edmond J. Safra Program in Parkinson's Disease and The Morton and Gloria Shulman Movement Disorder Clinic, Toronto Western Hospital, University of Toronto, Toronto, Canada*
[3]*Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA*
[4]*UMCG Expertise Centre Movement Disorders, Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands*
[5]*Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA*
[6]*The Manton Center for Orphan Disease Research, Boston Children's Hospital, Boston, Massachusetts, USA*
[7]*Department of Neurology, Charité University Hospital Berlin, Berlin, Germany*
[8]*Huntington's Disease Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, UK*
[9]*Molecular Medicine Laboratory and Department of Neurology, Concord Repatriation General Hospital, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia*
[10]*Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia*
[11]*Movement Disorders Section, Neuroscience Department, Raul Carrea Institute for Neurological Research (FLENI), Buenos Aires, Argentina*
[12]*Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Center of Expertise for Parkinson and Movement Disorders, Radboud University Medical Center, Nijmegen, the Netherlands*
[13]*Department of Clinical & Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, London, UK*

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

***Correspondence to:** Dr. Connie Marras, The Morton and Gloria Shulman Movement Disorder Centre and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital, McLaughlin Pavilion, 399 Bathurst Street, Toronto ON M5T 2S8, Canada; E-mail: connie.marras@uhnresearch.ca
Dr. Christine Klein, Institute of Neurogenetics, BMF, Building 67, University of Lübeck and University Hospital Schleswig-Holstein, Ratzeburger Allee 160, 23538 Lübeck, Germany; E-mail: christine.klein@neuro.uni-luebeck.de

[#]These authors are shared last authors. They contributed equally to this work.

Relevant conflictsof interest/financial disclosures: There are no financial conflicts of interest.

Funding agencies: The study was supported by the Movement Disorder Society (to C.M., C.K., and K.L.), by the Deutsche Forschungsgemeinschaft (FOR2488) (to C.K. and K.L.), and the Damp Foundation (to K.L.).

Received: 25 November 2021; **Revised:** 28 January 2022; **Accepted:** 14 February 2022

Published online 28 April 2022 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28982

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).

Key Words: genetics; movement disorders; nomenclature

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 published[3-5] 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 criteria[3]: (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-*CHCHD2*[18–25]	Typical levodopa-responsive parkinsonism	616710	AD[a]
Atypical parkinsonism or complex phenotypes			
PARK-*DCTN1*[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-*RAB39B*[30–32]	Early-onset (atypical) parkinsonism, delayed psychomotor development, impaired intellectual development (referred to as Waisman syndrome)	311510	XLR
PARK-*VPS13C*[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-*JAM2*-(PFBC)[38–40]	Atypical parkinsonism with cognitive deficits, brain imaging: calcifications in basal ganglia, cerebellum, and white matter	618824	AR
PARK-*SLC20A2*-(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	Clinical phenotype	MOI
DYT-*DNAJC12*[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	AR
MYC/ATX-*EPM2A*[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	AR
C9orf72[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	AD, repeat expansion

(Continues)

TABLE 1 *Continued*

Disorders that usually present with other phenotypes but can have (prominent) parkinsonism				
Gene	**Disease**	**OMIM**	**Clinical phenotype**	**MOI**
GRN[48,49]	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
MAPT[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
PDE8B[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
PDGFRB-(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
XPR1-(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.

[a]In 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.

[b]These 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-*OPA1*[93,94]	Ataxia	Optic atrophy, peripheral neuropathy, myopathy, and progressive external ophthalmoplegia		AD
DYT/CHOR-*ADAR*[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-*SQSTM1*[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
Dystonia presenting with deafness				
DYT-*ACTB*[a],[99-102]		Sensorineural hearing loss, generalized dystonia, skeletal abnormalities	607371	AD
DYT-*BCAP31*[103-109]		Deafness, central hypomyelination, microcephaly, ophthalmoplegia, intellectual disability	300475	XLD
DYT-*FITM2*[110-112]		Global developmental delay, sensorineural hearing loss, poor growth, and low body mass index	618635	AR
DYT-*SERAC1*[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
Dystonia presenting with developmental delay				
DYT-*IRF2BPL*[116-119]		Developmental delay, hypotonia, seizures, pyramidal signs, dysarthria	618088	AD
DYT-*VAC14*[120-123]	Ataxia	Neurodegeneration, ataxia, dysarthria, hypotonia	617054	AR
DYT/CHOR-*FOXG1*[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.
[a]This 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 (erythrokeratodermia)	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-*COA7*[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-*GDAP2*[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-*MTCL1*[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-*NFASC*[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-*PIBF1*[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-*PNK*[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-*RFC1*[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-*TANGO2*[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-*TBC1D23*[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-*TSEN54*[e,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*[f,g,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-*VPS13D*[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-*NUS1*[h,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**
C9orf72	Frontotemporal dementia (FTD) and/or amyotrophic lateral sclerosis (ALS)	Broad phenotypic spectrum including frontotemporal dementia and features of motor neuron disease, parkinsonism (mostly atypical, eg, PSP-like, MSA, or CBS), and dystonia, cerebellar signs, or chorea	105550	AD, repeat expansion
PSEN1[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; mt, 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.

[a]Gene mutations can also cause complex cortical dysplasia with other brain malformations 5 (OMIM: 615763).

[b]Gene mutations can also cause the lethal neonatal rigidity and multifocal seizure syndrome (OMIM: 614498).

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

[d]Gene mutations can also cause autosomal recessive microcephaly, seizures, and developmental delay (OMIM: 613402).

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

[f]Comment: This gene is already included in the previous list of autosomal-recessive ataxias118 (SCAR16, OMIM: 615768). It has now also been confirmed as a dominant ataxia gene.

[g]GeGene mutations can also cause the Gordon Holmes syndrome119.[241]

[h]Gene 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 included[3] (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-*PDE10A*[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-*ADAR*[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-*FOXG1*[124–126]	Dyskinesia	Rett-like phenotype (with congenital encephalopathy)	613454	AD
DYT/CHOR-*GNAO1*[244,245]	Myoclonus	Hypotonia, motor delay. Exacerbated by febrile illness, stress, high ambient temperature	617493	AD
ATX/CHOR-*RNF216*[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-*GRIA3*[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*[c,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.
[a]Chorea 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).
[b]Mutations 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).
[c]Mutations 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-*CPT1C*[277,278]		Pure HSP, variable age at onset (infantile to adulthood), slowly progressive disease course	616282	AD
HSP-*UBAP1*[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-*ENTPD1*[284,285]		Complex HSP, infancy or childhood onset with white matter change, intellectual impairment, dysarthria, and gait ataxia	615683	AR
HSP-*HPDL*[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-*MAG*[a,288]		Complex HSP, infantile-onset Pelizaeus–Merzbacher disease-like phenotype, mental retardation, dysarthria, optic atrophy, peripheral neuropathy, demyelinating leukodystrophy	616680	AR
HSP-*PCYT2*[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-*RNF170*[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-*ALDH18A1*[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-*SLC16A2*[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-*CAPN1*[229,230]		Pure or complex HSP, cerebellar ataxia, dysarthria, foot deformities, ocular movement abnormalities, peripheral neuropathy, amyotrophy	616907	AR
HSP/ATX-*UCHL1*[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-*KCNA2*[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-*VPS13D*[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.
[a]Allelic with Pelizaeus–Merzbacher disease.
[b]Mutations in this gene can also cause autosomal dominant sensory ataxia (OMIM 608984).
[c]Mutations in this gene can also cause autosomal dominant cutis laxa type 3 (OMIM 616603) and autosomal recessive cutis laxa type IIIA (OMIM 219150).
[d]Mutations 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 guidelines[3] (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-*KCNMA1*[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-*ECHS1*[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-*SCN8A*[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.
[a]Mutations 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-*ADCY5*[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-*ATP13A2*[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-*MYORG*-(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-*OPA3*[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-*PDGFB*-(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-*POLG*[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.
[a]Mutations 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.

Acknowledgments: Lara M. Lange, Carolin Gabbert, Katja Lohmann, Christine Klein, and Connie Marras are members of the ClinGen PD Gene Curation Expert Panel (GCEP) and receive support from the Parkinson's Foundation for PD GCEP gene curation efforts. Lara M. Lange receives support from the Bachmann-Strauss Dystonia and Parkinson Foundation. Open Access funding enabled and organized by Projekt DEAL.

Task Force on Genetic Nomenclature in Movement Disorders

Members

Darius Ebrahimi-Fakhari	**Department of Neurology, Boston Children's Hospital, Boston, MA, USA; Manton Center for Orphan Disease Research, Boston, MA, USA**
Vladimir S. Kostic	Clinic of Neurology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia
Christine Klein (Chair)	Institute of Neurogenetics, University of Lübeck, Lübeck, Germany
Anthony E. Lang	The Edmond J. Safra Program in Parkinson's Disease and The Morton and Gloria Shulman Movement Disorder Clinic, Toronto Western Hospital, University of Toronto, Toronto, Canada
Katja Lohmann	Institute of Neurogenetics, University of Lübeck, Lübeck, Germany

Connie Marras (Co-Chair)	The Edmond J. Safra Program in Parkinson's Disease and The Morton and Gloria Shulman Movement Disorder Clinic, Toronto Western Hospital, University of Toronto, Toronto, Canada
Malco Rossi	Sección Movimientos Anormales, Departamento de Neurociencias, Fleni, Buenos Aires, Argentina; Argentine National Scientific and Technological Research Council (CONICET), Argentina
Carolyn M. Sue	Department of Neurology, Royal North Shore Hospital, Sydney, NSW, Australia; Department of Neurogenetics, Kolling Institute, University of Sydney and Northern Sydney Local Health District, Sydney, New South Wales, Australia
Sara J. Tabrizi	Huntington's Disease Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, UK
Marina A.J. Tijssen	Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
Bart van de Warrenburg	Donders Institute for Brain, Cognition and Behavior, Department of Neurology, Center of Expertise for Parkinson and Movement Disorders, Radboud University Medical Center, Nijmegen, the Netherlands
Tom Warner	Department of Clinical & Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, London, UK

Data Availability Statement

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

References

1. Kramer PL, de Leon D, Ozelius L, et al. Dystonia gene in Ashkenazi Jewish population is located on chromosome 9q32-34. Ann Neurol 1990;27(2):114–120.
2. 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(13):1016–1024.
3. 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(4):436–457.
4. Rossi M, Anheim M, Durr A, et al. The genetic nomenclature of recessive cerebellar ataxias. Mov Disord 2018a;33(7):1056–1076.
5. van der Veen S, Zutt R, Klein C, et al. Nomenclature of genetically determined myoclonus syndromes: recommendations of the International Parkinson and Movement Disorder Society Task Force. Mov Disord 2019;34(11):1602–1613.
6. Strande NT, Riggs ER, Buchanan AH, et al. Evaluating the clinical validity of gene-disease associations: an evidence-based framework developed by the Clinical Genome Resource. Am J Hum Genet 2017;100(6):895–906.
7. Rehm HL, Berg JS, Brooks LD, et al. ClinGen — the Clinical Genome Resource. N Engl J Med 2015;372(23):2235–2242.
8. Cooper DN, Krawczak M, Polychronakos C, Tyler-Smith C, Kehrer-Sawatzki H. Where genotype is not predictive of phenotype: towards an understanding of the molecular basis of reduced penetrance in human inherited disease. Hum Genet 2013;132(10):1077–1130.
9. Zanon A, Pramstaller PP, Hicks AA, Pichler I. Environmental and genetic variables influencing mitochondrial health and Parkinson's disease penetrance. Parkinsons Dis 2018;2018:8684906.
10. Klein C, Chuang R, Marras C, Lang AE. The curious case of phenocopies in families with genetic Parkinson's disease. Mov Disord 2011;26(10):1793–1802.
11. Lunati A, Lesage S, Brice A. The genetic landscape of Parkinson's disease. Rev Neurol (Paris) 2018;174(9):628–643.
12. Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. Lancet Neurol 2020;19(2):170–178.
13. Saini P, Rudakou U, Yu E, et al. Association study of DNAJC13, UCHL1, HTRA2, GIGYF2, and EIF4G1 with Parkinson's disease. Neurobiol Aging 2021;100:119 e117–119 e113.
14. Smolders S, Philtjens S, Crosiers D, et al. Contribution of rare homozygous and compound heterozygous VPS13C missense mutations to dementia with Lewy bodies and Parkinson's disease. Acta Neuropathol Commun 2021;9(1):25.
15. Papandreou A, Danti FR, Spaull R, Leuzzi V, McTague A, Kurian MA. The expanding spectrum of movement disorders in genetic epilepsies. Dev Med Child Neurol 2020;62(2):178–191.
16. Caviness JN. Myoclonus. Mayo Clin Proc 1996;71(7):679–688.
17. Marti-Sanchez L, Baide-Mairena H, Marce-Grau A, et al. Delineating the neurological phenotype in children with defects in the ECHS1 or HIBCH gene. J Inherit Metab Dis 2021a;44(2):401–414.
18. Funayama M, Ohe K, Amo T, et al. CHCHD2 mutations in autosomal dominant late-onset Parkinson's disease: a genome-wide linkage and sequencing study. Lancet Neurol 2015;14(3):274–282.
19. Jansen IE, Bras JM, Lesage S, et al. CHCHD2 and Parkinson's disease. Lancet Neurol 2015;14(7):678–679.
20. Shi CH, Mao CY, Zhang SY, et al. CHCHD2 gene mutations in familial and sporadic Parkinson's disease. Neurobiol Aging 2016;38:217 e219–217 e213.
21. Koschmidder E, Weissbach A, Bruggemann N, Kasten M, Klein C, Lohmann K. A nonsense mutation in CHCHD2 in a patient with Parkinson disease. Neurology 2016;86(6):577–579.
22. Ikeda A, Matsushima T, Daida K, et al. A novel mutation of CHCHD2 p.R8H in a sporadic case of Parkinson's disease. Parkinsonism Relat Disord 2017;34:66–68.
23. Li N, Wang L, Zhang J, et al. Whole-exome sequencing in early-onset Parkinson's disease among ethnic Chinese. Neurobiol Aging 2020a;90:150 e155–150 e111.
24. Zheng R, Jin CY, Chen Y, et al. Analysis of rare variants of autosomal-dominant genes in a Chinese population with sporadic Parkinson's disease. Mol Genet Genomic Med 2020;8(10):e1449.
25. Yang N, Zhao Y, Liu Z, et al. Systematically analyzing rare variants of autosomal-dominant genes for sporadic Parkinson's disease in a Chinese cohort. Neurobiol Aging 2019;76:215 e211–215 e217.
26. Farrer MJ, Hulihan MM, Kachergus JM, et al. DCTN1 mutations in Perry syndrome. Nat Genet 2009;41(2):163–165.
27. Konno T, Ross OA, Teive HAG, Slawek J, Dickson DW, Wszolek ZK. DCTN1-related neurodegeneration: Perry syndrome and beyond. Parkinsonism Relat Disord 2017;41:14–24.

28. Mishima T, Fujioka S, Tomiyama H, et al. Establishing diagnostic criteria for Perry syndrome. J Neurol Neurosurg Psychiatry 2018; 89(5):482–487.
29. Wittke C, Petkovic S, Dobricic V, et al. Genotype–phenotype relations for the atypical parkinsonism genes: MDSGene systematic review. Mov Disord 2021;36(7):1499–1510.
30. Wilson GR, Sim JC, McLean C, et al. Mutations in RAB39B cause X-linked intellectual disability and early-onset Parkinson disease with alpha-synuclein pathology. Am J Hum Genet 2014;95(6): 729–735.
31. Puschmann A. New genes causing hereditary Parkinson's disease or parkinsonism. Curr Neurol Neurosci Rep 2017;17(9):66.
32. Tang BL. Rabs, membrane dynamics, and Parkinson's disease. J Cell Physiol 2017;232(7):1626–1633.
33. Lesage S, Drouet V, Majounie E, et al. Loss of VPS13C function in autosomal-recessive parkinsonism causes mitochondrial dysfunction and increases PINK1/Parkin-dependent mitophagy. Am J Hum Genet 2016;98(3):500–513.
34. Schormair B, Kemlink D, Mollenhauer B, et al. Diagnostic exome sequencing in early-onset Parkinson's disease confirms VPS13C as a rare cause of autosomal-recessive Parkinson's disease. Clin Genet 2018;93(3):603–612.
35. Darvish H, Bravo P, Tafakhori A, et al. Identification of a large homozygous VPS13C deletion in a patient with early-onset Parkinsonism. Mov Disord 2018;33(12):1968–1970.
36. Smaili I, Tesson C, Regragui W, et al. Gene panel sequencing identifies novel pathogenic mutations in Moroccan patients with familial Parkinson disease. J Mol Neurosci 2021;71(1):142–152.
37. Zhao Y, Qin L, Pan H, et al. The role of genetics in Parkinson's disease: a large cohort study in Chinese mainland population. Brain 2020;143(7):2220–2234.
38. Cen Z, Chen Y, Chen S, et al. Biallelic loss-of-function mutations in JAM2 cause primary familial brain calcification. Brain 2020; 143(2):491–502.
39. Schottlaender LV, Abeti R, Jaunmuktane Z, et al. Bi-allelic JAM2 variants lead to early-onset recessive primary familial brain calcification. Am J Hum Genet 2020;106(3):412–421.
40. Balck A, Schaake S, Kuhnke NS, et al. Genotype–phenotype relations in primary familial brain calcification: systematic MDSGene review. Mov Disord 2021;36(11):2468–2480.
41. Wang C, Li Y, Shi L, et al. Mutations in SLC20A2 link familial idiopathic basal ganglia calcification with phosphate homeostasis. Nat Genet 2012;44(3):254–256.
42. Anikster Y, Haack TB, Vilboux T, et al. Biallelic mutations in DNAJC12 cause hyperphenylalaninemia, dystonia, and intellectual disability. Am J Hum Genet 2017a;100(2):257–266.
43. Straniero L, Guella I, Cilia R, et al. DNAJC12 and dopa-responsive nonprogressive parkinsonism. Ann Neurol 2017;82(4):640–646.
44. Lynch DS, Wood NW, Houlden H. Late-onset Lafora disease with prominent parkinsonism due to a rare mutation in EPM2A. Neurol Genet 2016;2(5):e101.
45. Yildiz EP, Yesil G, Ozkan MU, Bektas G, Caliskan M, Ozmen M. A novel EPM2A mutation in a patient with Lafora disease presenting with early parkinsonism symptoms in childhood. Seizure 2017;51:77–79.
46. Wilke C, Pomper JK, Biskup S, Puskas C, Berg D, Synofzik M. Atypical parkinsonism in C9orf72 expansions: a case report and systematic review of 45 cases from the literature. J Neurol 2016; 263(3):558–574.
47. Lin CH, Chen PL, Tai CH, et al. A clinical and genetic study of early-onset and familial parkinsonism inTaiwan: an integrated approach combining gene dosage analysis and next-generation sequencing. Mov Disord 2019a;34(4):506–515.
48. Yabe I, Yaguchi H, Kato Y, et al. Mutations in bassoon in individuals with familial and sporadic progressive supranuclear palsy-like syndrome. Sci Rep 2018;8(1):819.
49. Chang KH, Lee GC, Huang CC, et al. Genetic and functional characters of GRN p.T487I mutation in Taiwanese patients with atypical parkinsonian disorders. Parkinsonism Relat Disord 2018;51: 61–66.
50. Ogaki K, Li Y, Takanashi M, et al. Analyses of the MAPT, PGRN, and C9orf72 mutations in Japanese patients with FTLD, PSP, and CBS. Parkinsonism Relat Disord 2013;19(1):15–20.
51. Strafela P, Plesko J, Magdic J, et al. Familial tauopathy with P364S MAPT mutation: clinical course, neuropathology and ultrastructure of neuronal tau inclusions. Neuropathol Appl Neurobiol 2018;44(6):550–562.
52. Mazzon G, Menichelli A, Fabretto A, Cattaruzza T, Manganotti P. A new MAPT deletion in a case of speech apraxia leading to corticobasal syndrome. Neurocase 2018;24(3):140–144.
53. Nan H, Takaki R, Shimozono K, Ichinose Y, Koh K, Takiyama Y. Clinical and genetic study of the first Japanese FTDP-17 patient with a mutation of +3 in intron 10 in the MAPT gene. Intern Med 2019b;58(16):2397–2400.
54. Nakayama S, Shimonaka S, Elahi M, et al. Tau aggregation and seeding analyses of two novel MAPT variants found in patients with motor neuron disease and progressive parkinsonism. Neurobiol Aging 2019;84:240 e213–240 e222.
55. Tipton PW, Jaramillo-Koupermann G, Soto-Beasley AI, et al. Genetic characterization of Parkinson's disease patients in Ecuador and Colombia. Parkinsonism Relat Disord 2020;75:27–29.
56. Appenzeller S, Schirmacher A, Halfter H, et al. Autosomal-dominant striatal degeneration is caused by a mutation in the phosphodiesterase 8B gene. Am J Hum Genet 2010;86(1):83–87.
57. Bollen E, Prickaerts J. Phosphodiesterases in neurodegenerative disorders. IUBMB Life 2012;64(12):965–970.
58. Barsottini OG, Martins Pde M, Chien HF, et al. Familial striatal degeneration: new mutation and neuroimaging clues. Neurology 2015;85(20):1816–1818.
59. Azuma R, Ishikawa K, Hirata K, et al. A novel mutation of PDE8B gene in a Japanese family with autosomal-dominant striatal degeneration. Mov Disord 2015;30(14):1964–1967.
60. Ni J, Yi X, Liu Z, et al. Clinical findings of autosomal-dominant striatal degeneration and PDE8B mutation screening in parkinsonism and related disorders. Parkinsonism Relat Disord 2019;69: 94–98.
61. Nicolas G, Pottier C, Maltete D, et al. Mutation of the PDGFRB gene as a cause of idiopathic basal ganglia calcification. Neurology 2013;80(2):181–187.
62. Legati A, Giovannini D, Nicolas G, et al. Mutations in XPR1 cause primary familial brain calcification associated with altered phosphate export. Nat Genet 2015;47(6):579–581.
63. Charlesworth G, Plagnol V, Holmstrom KM, et al. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. Am J Hum Genet 2012;91(6):1041–1050.
64. Lange LM, Junker J, Loens S, et al. Genotype–phenotype relations for isolated dystonia genes: MDSGene systematic review. Mov Disord 2021;36(5):1086–1103.
65. Mao D, Reuter CM, Ruzhnikov MRZ, et al. De novo EIF2AK1 and EIF2AK2 variants are associated with developmental delay, leukoencephalopathy, and neurologic decompensation. Am J Hum Genet 2020;106(4):570–583.
66. Kuipers DJS, Mandemakers W, Lu CS, et al. EIF2AK2 Missense Variants Associated with Early Onset Generalized Dystonia. Ann Neurol 2021;89(3):485–497.
67. Musacchio T, Zech M, Reich MM, Winkelmann J, Volkmann J. A recurrent EIF2AK2 missense variant causes autosomal-dominant isolated dystonia. Ann Neurol 2021;89(6):1257–1258.
68. Charlesworth G, Angelova PR, Bartolome-Robledo F, et al. Mutations in HPCA cause autosomal-recessive primary isolated dystonia. Am J Hum Genet 2015;96(4):657–665.
69. Atasu B, Hanagasi H, Bilgic B, et al. HPCA confirmed as a genetic cause of DYT2-like dystonia phenotype. Mov Disord 2018;33(8): 1354–1358.
70. Zech M, Boesch S, Maier EM, et al. Haploinsufficiency of KMT2B, encoding the lysine-specific histone methyltransferase 2B, results in early-onset generalized dystonia. Am J Hum Genet 2016;99(6): 1377–1387.

71. Meyer E, Carss KJ, Rankin J, et al. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet 2017;49(2):223–237.
72. Cai X, Chen X, Wu S, et al. Homozygous mutation of VPS16 gene is responsible for an autosomal recessive adolescent-onset primary dystonia. Sci Rep 2016;6:25834.
73. Steel D, Zech M, Zhao C, et al. Loss-of-function variants in HOPS complex genes VPS16 and VPS41 cause early onset dystonia associated with lysosomal abnormalities. Ann Neurol 2020;88(5):867–877.
74. Li XY, Wang L, Guo Y, Wan XH. Mutations in the VPS16 gene in 56 early-onset dystonia patients. Mov Disord 2021a;36(3):780–781.
75. Ostrozovicova M, Jech R, Steel D, et al. A recurrent VPS16 p.Arg187* nonsense variant in early-onset generalized dystonia. Mov Disord 2021;36(8):1984–1985.
76. Doss S, Lohmann K, Seibler P, et al. Recessive dystonia-ataxia syndrome in a Turkish family caused by a COX20 (FAM36A) mutation. J Neurol 2014;261(1):207–212.
77. Otero MG, Tiongson E, Diaz F, et al. Novel pathogenic COX20 variants causing dysarthria, ataxia, and sensory neuropathy. Ann Clin Transl Neurol 2019;6(1):154–160.
78. Ozcanyuz DG, Incecik F, Herguner OM, Mungan NO, Bozdogan ST. Dysarthria, ataxia, and dystonia associated with COX20 (FAM36A) gene mutation: a case report of a Turkish child. Ann Indian Acad Neurol 2020;23(3):399–401.
79. van Spronsen FJ, Himmelreich N, Rufenacht V, et al. Heterogeneous clinical spectrum of DNAJC12-deficient hyperphenylalaninemia: from attention deficit to severe dystonia and intellectual disability. J Med Genet 2017 Aug 9;jmedgenet-2017-104875. https://doi.org/10.1136/jmedgenet-2017-104875.
80. Veenma D, Cordeiro D, Sondheimer N, Mercimek-Andrews S. DNAJC12-associated developmental delay, movement disorder, and mild hyperphenylalaninemia identified by whole-exome sequencing re-analysis. Eur J Hum Genet 2018;26(12):1867–1870.
81. Tuschl K, Meyer E, Valdivia LE, et al. Mutations in SLC39A14 disrupt manganese homeostasis and cause childhood-onset parkinsonism-dystonia. Nat Commun 2016;7:11601.
82. Juneja M, Shamim U, Joshi A, et al. A novel mutation in SLC39A14 causing hypermanganesemia associated with infantile onset dystonia. J Gene Med 2018;20(4):e3012.
83. Rodan LH, Hauptman M, D'Gama AM, et al. Novel founder intronic variant in SLC39A14 in two families causing Manganism and potential treatment strategies. Mol Genet Metab 2018;124(2):161–167.
84. Namnah M, Bauer M, Mor-Shaked H, et al. Benign SLC39A14 course of dystonia-parkinsonism secondary to inherited manganese accumulation. Mov Disord Clin Pract 2020;7(5):569–570.
85. Kelly M, Park M, Mihalek I, et al. Spectrum of neurodevelopmental disease associated with the GNAO1 guanosine triphosphate-binding region. Epilepsia 2019;60(3):406–418.
86. Wirth T, Tranchant C, Drouot N, et al. Increased diagnostic yield in complex dystonia through exome sequencing. Parkinsonism Relat Disord 2020a;74:50–56.
87. Mencacci NE, Rubio-Agusti I, Zdebik A, et al. A missense mutation in KCTD17 causes autosomal dominant myoclonus-dystonia. Am J Hum Genet 2015a;96(6):938–947.
88. Marce-Grau A, Correa M, Vanegas MI, et al. Childhood onset progressive myoclonic dystonia due to a de novo KCTD17 splicing mutation. Parkinsonism Relat Disord 2019a;61:7–9.
89. Graziola F, Stregapede F, Travaglini L, et al. A novel KCTD17 mutation is associated with childhood early-onset hyperkinetic movement disorder. Parkinsonism Relat Disord 2019a;61:4–6.
90. Todisco M, Gana S, Cosentino G, et al. KCTD17-related myoclonus-dystonia syndrome: clinical and electrophysiological findings of a patient with atypical late onset. Parkinsonism Relat Disord 2020a;78:129–133.
91. Heimer G, Keratar JM, Riley LG, et al. MECR mutations cause childhood-onset dystonia and optic atrophy, a mitochondrial fatty acid synthesis disorder. Am J Hum Genet 2016;99(6):1229–1244.
92. Gorukmez O, Gorukmez O, Havali C. Novel MECR mutation in childhood-onset dystonia, optic atrophy, and basal ganglia signal abnormalities. Neuropediatrics 2019;50(5):336–337.
93. Liskova P, Ulmanova O, Tesina P, et al. Novel OPA1 missense mutation in a family with optic atrophy and severe widespread neurological disorder. Acta Ophthalmol 2013;91(3):e225–e231.
94. Ortega-Suero G, Fernandez-Matarrubia M, Lopez-Valdes E, Arpa J. A novel missense OPA1 mutation in a patient with dominant optic atrophy and cervical dystonia. Mov Disord Clin Pract 2019;6(2):171–173.
95. Livingston JH, Lin JP, Dale RC, et al. A type I interferon signature identifies bilateral striatal necrosis due to mutations in ADAR1. J Med Genet 2014a;51(2):76–82.
96. Rice GI, Kitabayashi N, Barth M, et al. Genetic, phenotypic, and interferon biomarker status in ADAR1-related neurological disease. Neuropediatrics 2017a;48(3):166–184.
97. Muto V, Flex E, Kupchinsky Z, et al. Biallelic SQSTM1 mutations in early-onset, variably progressive neurodegeneration. Neurology 2018a;91(4):e319–e330.
98. Haack TB, Ignatius E, Calvo-Garrido J, et al. Absence of the autophagy adaptor SQSTM1/p62 causes childhood-onset neurodegeneration with ataxia, dystonia, and gaze palsy. Am J Hum Genet 2016a;99(3):735–743.
99. Verloes A, Di Donato N, Masliah-Planchon J, et al. Baraitser-Winter cerebrofrontofacial syndrome: delineation of the spectrum in 42 cases. Eur J Hum Genet 2015;23(3):292–301.
100. Conboy E, Vairo F, Waggoner D, et al. Pathogenic variant in ACTB, p.Arg183Trp, causes juvenile-onset dystonia, hearing loss, and developmental delay without midline malformation. Case Rep Genet 2017;2017:9184265.
101. Zech M, Jech R, Wagner M, et al. Molecular diversity of combined and complex dystonia: insights from diagnostic exome sequencing. Neurogenetics 2017;18(4):195–205.
102. Freitas JL, Vale TC, Barsottini OGP, Pedroso JL. Expanding the phenotype of dystonia-deafness syndrome caused by ACTB gene mutation. Mov Disord Clin Pract 2020;7(1):86–87.
103. Cacciagli P, Sutera-Sardo J, Borges-Correia A, et al. Mutations in BCAP31 cause a severe X-linked phenotype with deafness, dystonia, and central hypomyelination and disorganize the Golgi apparatus. Am J Hum Genet 2013;93(3):579–586.
104. Albanyan S, Al Teneiji A, Monfared N, Mercimek-Mahmutoglu S. BCAP31-associated encephalopathy and complex movement disorder mimicking mitochondrial encephalopathy. Am J Med Genet A 2017;173(6):1640–1643.
105. Vittal P, Hall DA, Dames S, Mao R, Berry-Kravis E. BCAP31 mutation causing a syndrome of congenital dystonia, facial dysorphism and central hypomyelination discovered using exome sequencing. Mov Disord Clin Pract 2016;3(2):197–199.
106. Rinaldi B, Van Hoof E, Corveleyn A, Van Cauter A, de Ravel T. BCAP31-related syndrome: the first de novo report. Eur J Med Genet 2020;63(2):103732.
107. Shimizu K, Oba D, Nambu R, et al. Possible mitochondrial dysfunction in a patient with deafness, dystonia, and cerebral hypomyelination (DDCH) due to BCAP31 mutation. Mol Genet Genomic Med 2020;8(3):e1129.
108. Kao HJ, Chiang HL, Chen HH, et al. De novo mutation and skewed X-inactivation in girl with BCAP31-related syndrome. Hum Mutat 2020;41:1775–1782.
109. Louie RJ, Collins DL, Friez MJ, Skinner C, Schwartz CE, Stevenson RE. Schimke XLID syndrome results from a deletion in BCAP31. Am J Med Genet A 2020;182(9):2168–2174.
110. Zazo Seco C, Castells-Nobau A, Joo SH, et al. A homozygous FITM2 mutation causes a deafness-dystonia syndrome with motor regression and signs of ichthyosis and sensory neuropathy. Dis Model Mech 2017;10(2):105–118.
111. Shakir A, Wadley AF, Purcarin G, Wierenga KJ. The first case of deafness-dystonia syndrome due to compound heterozygous variants in FITM2. Clin Case Rep 2018;6(9):1815–1817.
112. Riedhammer KM, Leszinski GS, Andres S, Strobl-Wildemann G, Wagner M. First replication that biallelic variants in FITM2 cause

a complex deafness-dystonia syndrome. Mov Disord 2018;33(10): 1665–1666.

113. Wortmann SB, de Brouwer APM, Wevers RA, Morava E. SERAC1 deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews((R)). Seattle (WA); University of Washington; 1993.
114. Maas RR, Iwanicka-Pronicka K, Kalkan Ucar S, et al. Progressive deafness-dystonia due to SERAC1 mutations: a study of 67 cases. Ann Neurol 2017;82(6):1004–1015.
115. Giron C, Roze E, Degos B, et al. Adult-onset generalized dystonia as the main manifestation of MEGDEL syndrome. Tremor Other Hyperkinet Mov (N Y) 2018;8:554.
116. Skorvanek M, Dusek P, Rydzanicz M, et al. Neurodevelopmental disorder associated with IRF2BPL gene mutation: expanding the phenotype? Parkinsonism Relat Disord 2019;62:239–241.
117. Ginevrino M, Battini R, Nuovo S, et al. A novel IRF2BPL truncating variant is associated with endolysosomal storage. Mol Biol Rep 2020;47(1):711–714.
118. Ganos C, Zittel S, Hidding U, Funke C, Biskup S, Bhatia KP. IRF2BPL mutations cause autosomal dominant dystonia with anarthria, slow saccades and seizures. Parkinsonism Relat Disord 2019;68:57–59.
119. Prilop L, Buchert R, Woerz S, Gerloff C, Haack TB, Zittel S. IRF2BPL mutation causes nigrostriatal degeneration presenting with dystonia, spasticity and keratoconus. Parkinsonism Relat Disord 2020;79:141–143.
120. Stutterd C, Diakumis P, Bahlo M, et al. Neuropathology of childhood-onset basal ganglia degeneration caused by mutation of VAC14. Ann Clin Transl Neurol 2017;4(12):859–864.
121. de Gusmao CM, Stone S, Waugh JL, Yang E, Lenk GM, Rodan LH. VAC14 gene-related parkinsonism-dystonia with response to deep brain stimulation. Mov Disord Clin Pract 2019; 6(6):494–497.
122. Kaur P, Bhavani GS, Raj A, Girisha KM, Shukla A. Homozygous variant, p. (Arg643Trp) in VAC14 causes striatonigral degeneration: report of a novel variant and review of VAC14-related disorders. J Hum Genet 2019;64(12):1237–1242.
123. Baumann H, Tunc S, Gunther A, Munchau A, Lohmann K, Bruggemann N. Altered homodimer formation and increased iron accumulation in VAC14-related disease: case report and review of the literature. Parkinsonism Relat Disord 2020;80:41–46.
124. Kortum F, Das S, Flindt M, et al. The core FOXG1 syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis. J Med Genet 2011a;48(6):396–406.
125. Cellini E, Vignoli A, Pisano T, et al. The hyperkinetic movement disorder of FOXG1-related epileptic-dyskinetic encephalopathy. Dev Med Child Neurol 2016a;58(1):93–97.
126. Papandreou A, Schneider RB, Augustine EF, et al. Delineation of the movement disorders associated with FOXG1 mutations. Neurology 2016a;86(19):1794–1800.
127. Coutelier M, Blesneac I, Monteil A, et al. A recurrent mutation in CACNA1G Alters Cav3.1 T-type calcium-channel conduction and causes autosomal-dominant cerebellar ataxia. Am J Hum Genet 2015a;97(5):726–737.
128. Morino H, Matsuda Y, Muguruma K, et al. A mutation in the low voltage-gated calcium channel CACNA1G alters the physiological properties of the channel, causing spinocerebellar ataxia. Mol Brain 2015;8:89.
129. Chemin J, Siquier-Pernet K, Nicouleau M, et al. De novo mutation screening in childhood-onset cerebellar atrophy identifies gain-of-function mutations in the CACNA1G calcium channel gene. Brain 2018;141(7):1998–2013.
130. Tsoi H, Yu AC, Chen ZS, et al. A novel missense mutation in CCDC88C activates the JNK pathway and causes a dominant form of spinocerebellar ataxia. J Med Genet 2014;51(9):590–595.
131. Lenska-Mieciek M, Charzewska A, Krolicki L, et al. Familial ataxia, tremor, and dementia in a Polish family with a novel mutation in the CCDC88C gene. Mov Disord 2019;34(1):142–144.
132. Serrano-Munuera C, Corral-Juan M, Stevanin G, et al. New subtype of spinocerebellar ataxia with altered vertical eye movements mapping to chromosome 1p32. JAMA Neurol 2013;70(6): 764–771.
133. Seixas AI, Loureiro JR, Costa C, et al. A Pentanucleotide ATTTC repeat insertion in the non-coding region of DAB1, mapping to SCA37, causes spinocerebellar ataxia. Am J Hum Genet 2017; 101(1):87–103.
134. Corral-Juan M, Serrano-Munuera C, Rabano A, et al. Clinical, genetic and neuropathological characterization of spinocerebellar ataxia type 37. Brain 2018;141(7):1981–1997.
135. Chao HT, Davids M, Burke E, et al. A syndromic neurodevelopmental disorder caused by de novo variants in EBF3. Am J Hum Genet 2017;100(1):128–137.
136. Harms FL, Girisha KM, Hardigan AA, et al. Mutations in EBF3 disturb transcriptional profiles and cause intellectual disability, ataxia, and facial dysmorphism. Am J Hum Genet 2017;100(1): 117–127.
137. Sleven H, Welsh SJ, Yu J, et al. De novo mutations in EBF3 cause a neurodevelopmental syndrome. Am J Hum Genet 2017;100(1): 138–150.
138. Cadieux-Dion M, Turcotte-Gauthier M, Noreau A, et al. Expanding the clinical phenotype associated with ELOVL4 mutation: study of a large French-Canadian family with autosomal dominant spinocerebellar ataxia and erythrokeratodermia. JAMA Neurol 2014;71(4):470–475.
139. Ozaki K, Doi H, Mitsui J, et al. A Novel mutation in ELOVL4 leading to spinocerebellar ataxia (SCA) with the hot cross bun sign but lacking erythrokeratodermia: a broadened spectrum of SCA34. JAMA Neurol 2015;72(7):797–805.
140. Waters MF, Minassian NA, Stevanin G, et al. Mutations in voltage-gated potassium channel KCNC3 cause degenerative and developmental central nervous system phenotypes. Nat Genet 2006;38(4):447–451.
141. Finnsson J, Sundblom J, Dahl N, Melberg A, Raininko R. LMNB1-related autosomal-dominant leukodystrophy: clinical and radiological course. Ann Neurol 2015;78(3):412–425.
142. Zhang Y, Li J, Bai R, et al. LMNB1-related adult-onset autosomal dominant leukodystrophy presenting as movement disorder: a case report and review of the literature. Front Neurosci 2019;13:1030.
143. Gennarino VA, Palmer EE, McDonell LM, et al. A mild PUM1 mutation is associated with adult-onset ataxia, whereas haploinsufficiency causes developmental delay and seizures. Cell 2018;172(5):924–936 e911.
144. Lai KL, Liao YC, Tsai PC, Hsiao CT, Soong BW, Lee YC. Investigating PUM1 mutations in a Taiwanese cohort with cerebellar ataxia. Parkinsonism Relat Disord 2019;66:220–223.
145. Chen DH, Below JE, Shimamura A, et al. Ataxia-pancytopenia syndrome is caused by missense mutations in SAMD9L. Am J Hum Genet 2016;98(6):1146–1158.
146. Tesi B, Davidsson J, Voss M, et al. Gain-of-function SAMD9L mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. Blood 2017;129(16):2266–2279.
147. Shen XM, Selcen D, Brengman J, Engel AG. Mutant SNAP25B causes myasthenia, cortical hyperexcitability, ataxia, and intellectual disability. Neurology 2014;83(24):2247–2255.
148. Fukuda H, Imagawa E, Hamanaka K, et al. A novel missense SNAP25b mutation in two affected siblings from an Israeli family showing seizures and cerebellar ataxia. J Hum Genet 2018;63(5): 673–676.
149. Heyne HO, Singh T, Stamberger H, et al. De novo variants in neurodevelopmental disorders with epilepsy. Nat Genet 2018;50(7): 1048–1053.
150. Sferra A, Fattori F, Rizza T, et al. Defective kinesin binding of TUBB2A causes progressive spastic ataxia syndrome resembling sacsinopathy. Hum Mol Genet 2018;27(11):1892–1904.
151. Cai S, Li J, Wu Y, Jiang Y. De novo mutations of TUBB2A cause infantile-onset epilepsy and developmental delay. J Hum Genet 2020;65(7):601–608.

152. Hu H, Kahrizi K, Musante L, et al. Genetics of intellectual disability in consanguineous families. Mol Psychiatry 2019;24(7):1027–1039.

153. Aslam F, Naz S. Ataxia and dysarthria due to an ABCA2 variant: extension of the phenotypic spectrum. Parkinsonism Relat Disord 2019;64:328–331.

154. Ghosh SG, Becker K, Huang H, et al. Biallelic mutations in ADPRHL2, encoding ADP-ribosylhydrolase 3, lead to a degenerative pediatric stress-induced epileptic ataxia syndrome. Am J Hum Genet 2018;103(3):431–439.

155. Danhauser K, Alhaddad B, Makowski C, et al. Bi-allelic ADPRHL2 mutations cause neurodegeneration with developmental delay, ataxia, and axonal neuropathy. Am J Hum Genet 2018; 103(5):817–825.

156. Valence S, Cochet E, Rougeot C, et al. Exome sequencing in congenital ataxia identifies two new candidate genes and highlights a pathophysiological link between some congenital ataxias and early infantile epileptic encephalopathies. Genet Med 2019;21(3): 553–563.

157. Mahjoub A, Cihlarova Z, Tetreault M, et al. Homozygous pathogenic variant in BRAT1 associated with nonprogressive cerebellar ataxia. Neurol Genet 2019;5(5):e359.

158. Butler KM, Holt PJ, Milla SS, da Silva C, Alexander JJ, Escayg A. Epileptic encephalopathy and cerebellar atrophy resulting from compound heterozygous CACNA2D2 variants. Case Rep Genet 2018;2018:6308283.

159. Punetha J, Karaca E, Gezdirici A, et al. Biallelic CACNA2D2 variants in epileptic encephalopathy and cerebellar atrophy. Ann Clin Transl Neurol 2019;6(8):1395–1406.

160. Martinez Lyons A, Ardissone A, Reyes A, et al. COA7 (C1orf163/RESA1) mutations associated with mitochondrial leukoencephalopathy and cytochrome c oxidase deficiency. J Med Genet 2016;53(12):846–849.

161. Higuchi Y, Okunushi R, Hara T, et al. Mutations in COA7 cause spinocerebellar ataxia with axonal neuropathy. Brain 2018;141(6): 1622–1636.

162. Paesold-Burda P, Maag C, Troxler H, et al. Deficiency in COG5 causes a moderate form of congenital disorders of glycosylation. Hum Mol Genet 2009;18(22):4350–4356.

163. Wang X, Han L, Wang XY, et al. Identification of two novel mutations in COG5 causing congenital disorder of glycosylation. Front Genet 2020;11:168.

164. Wiltrout K, Ferrer A, van de Laar I, et al. Variants in DOCK3 cause developmental delay and hypotonia. Eur J Hum Genet 2019; 27(8):1225–1234.

165. Helbig KL, Mroske C, Moorthy D, Sajan SA, Velinov M. Biallelic loss-of-function variants in DOCK3 cause muscle hypotonia, ataxia, and intellectual disability. Clin Genet 2017;92(4):430–433.

166. Iwata-Otsubo A, Ritter AL, Weckselbatt B, et al. DOCK3-related neurodevelopmental syndrome: biallelic intragenic deletion of DOCK3 in a boy with developmental delay and hypotonia. Am J Med Genet A 2018;176(1):241–245.

167. Marelli C, Guissart C, Hubsch C, et al. Mini-exome coupled to read-depth based copy number variation analysis in patients with inherited ataxias. Hum Mutat 2016;37(12):1340–1353.

168. Carre G, Marelli C, Anheim M, et al. Xeroderma pigmentosum complementation group F: a rare cause of cerebellar ataxia with chorea. J Neurol Sci 2017;376:198–201.

169. Doi H, Koyano S, Miyatake S, et al. Cerebellar ataxia-dominant phenotype in patients with ERCC4 mutations. J Hum Genet 2018; 63(4):417–423.

170. Shanbhag NM, Geschwind MD, DiGiovanna JJ, et al. Neurodegeneration as the presenting symptom in 2 adults with xeroderma pigmentosum complementation group F. Neurol Genet 2018;4(3):e240.

171. Eidhof I, Baets J, Kamsteeg EJ, et al. GDAP2 mutations implicate susceptibility to cellular stress in a new form of cerebellar ataxia. Brain 2018;141(9):2592–2604.

172. Breza M, Bourinaris T, Efthymiou S, et al. A homozygous GDAP2 loss-of-function variant in a patient with adult-onset cerebellar ataxia. Brain 2020;143(6):e49.

173. Dong HL, Cheng HL, Bai G, Shen Y, Wu ZY. Novel GDAP2 pathogenic variants cause autosomal recessive spinocerebellar ataxia-27 (SCAR27) in a Chinese family. Brain 2020;143(6):e50.

174. Krygier M, Kwarciany M, Wasilewska K, et al. A study in a Polish ataxia cohort indicates genetic heterogeneity and points to MTCL1 as a novel candidate gene. Clin Genet 2019;95(3):415–419.

175. Jiao B, Zhou Z, Hu Z, et al. Homozygosity mapping and next generation sequencing for the genetic diagnosis of hereditary ataxia and spastic paraplegia in consanguineous families. Parkinsonism Relat Disord 2020;80:65–72.

176. Anazi S, Maddirevula S, Salpietro V, et al. Expanding the genetic heterogeneity of intellectual disability. Hum Genet 2017;136(11–12):1419–1429.

177. Monfrini E, Straniero L, Bonato S, et al. Neurofascin (NFASC) gene mutation causes autosomal recessive ataxia with demyelinating neuropathy. Parkinsonism Relat Disord 2019;63:66–72.

178. Kvarnung M, Shahsavani M, Taylan F, et al. Ataxia in patients with bi-allelic NFASC mutations and absence of full-length NF186. Front Genet 2019;10:896.

179. Wheway G, Schmidts M, Mans DA, et al. An siRNA-based functional genomics screen for the identification of regulators of ciliogenesis and ciliopathy genes. Nat Cell Biol 2015;17(8):1074–1087.

180. Hebbar M, Kanthi A, Shukla A, Bielas S, Girisha KM. A biallelic 36-bp insertion in PIBF1 is associated with Joubert syndrome. J Hum Genet 2018;63(8):935–939.

181. Ott T, Kaufmann L, Granzow M, et al. The frog Xenopus as a model to study Joubert syndrome: the case of a human patient with compound heterozygous variants in PIBF1. Front Physiol 2019; 10:134.

182. Bras J, Alonso I, Barbot C, et al. Mutations in PNKP cause recessive ataxia with oculomotor apraxia type 4. Am J Hum Genet 2015;96(3):474–479.

183. Tzoulis C, Sztromwasser P, Johansson S, Gjerde IO, Knappskog P, Bindoff LA. PNKP mutations identified by whole-exome sequencing in a Norwegian patient with sporadic ataxia and edema. Cerebellum 2017;16(1):272–275.

184. Schiess N, Zee DS, Siddiqui KA, Szolics M, El-Hattab AW. Novel PNKP mutation in siblings with ataxia-oculomotor apraxia type 4. J Neurogenet 2017;31(1–2):23–25.

185. Rudenskaya GE, Marakhonov AV, Shchagina OA, et al. Ataxia with oculomotor apraxia type 4 with PNKP common "Portuguese" and novel mutations in two Belarusian families. J Pediatr Genet 2019;8(2):58–62.

186. Gatti M, Magri S, Nanetti L, et al. From congenital microcephaly to adult onset cerebellar ataxia: distinct and overlapping phenotypes in patients with PNKP gene mutations. Am J Med Genet A 2019;179(11):2277–2283.

187. Cortese A, Simone R, Sullivan R, et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet 2019;51(4):649–658.

188. Rafehi H, Szmulewicz DJ, Bennett MF, et al. Bioinformatics-based identification of expanded repeats: a non-reference intronic pentamer expansion in RFC1 causes CANVAS. Am J Hum Genet 2019;105(1):151–165.

189. Akcimen F, Ross JP, Bourassa CV, et al. Investigation of the RFC1 repeat expansion in a Canadian and a Brazilian ataxia cohort: identification of novel conformations. Front Genet 2019;10:1219.

190. Cortese A, Tozza S, Yau WY, et al. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. Brain 2020;143(2):480–490.

191. Traschutz A, Cortese A, Reich S, et al. Natural history, phenotypic spectrum, and discriminative features of multisystemic RFC1 disease. Neurology 2021;96(9):e1369–e1382.

192. Lalani SR, Liu P, Rosenfeld JA, et al. Recurrent muscle weakness with rhabdomyolysis, metabolic crises, and cardiac arrhythmia due

to bi-allelic TANGO2 mutations. Am J Hum Genet 2016;98(2): 347–357.

193. Kremer LS, Distelmaier F, Alhaddad B, et al. Bi-allelic truncating mutations in TANGO2 cause infancy-onset recurrent metabolic crises with encephalocardiomyopathy. Am J Hum Genet 2016;98(2): 358–362.

194. Jennions E, Hedberg-Oldfors C, Berglund AK, et al. TANGO2 deficiency as a cause of neurodevelopmental delay with indirect effects on mitochondrial energy metabolism. J Inherit Metab Dis 2019;42(5):898–908.

195. Marin-Valencia I, Gerondopoulos A, Zaki MS, et al. Homozygous mutations in TBC1D23 lead to a non-degenerative form of pontocerebellar hypoplasia. Am J Hum Genet 2017;101(3): 441–450.

196. Ivanova EL, Mau-Them FT, Riazuddin S, et al. Homozygous truncating variants in TBC1D23 cause pontocerebellar hypoplasia and alter cortical development. Am J Hum Genet 2017;101(3): 428–440.

197. Laugwitz L, Buchert R, Groeschel S, et al. Pontocerebellar hypoplasia type 11: does the genetic defect determine timing of cerebellar pathology? Eur J Med Genet 2020;63(7):103938.

198. Qian Y, Wang H, Jin T, et al. A familial lateonset hereditary ataxia mimicking pontocerebellar hypoplasia caused by a novel TSEN54 mutation. Mol Med Rep 2014;10(3):1423–1425.

199. Arslan EA, Oncel I, Ceylan AC, Topcu M, Topaloglu H. Genetic and phenotypic features of patients with childhood ataxias diagnosed by next-generation sequencing gene panel. Brain Dev 2020; 42(1):6–18.

200. Hoch NC, Hanzlikova H, Rulten SL, et al. XRCC1 mutation is associated with PARP1 hyperactivation and cerebellar ataxia. Nature 2017;541(7635):87–91.

201. O'Connor E, Vandrovcova J, Bugiardini E, et al. Mutations in XRCC1 cause cerebellar ataxia and peripheral neuropathy. J Neurol Neurosurg Psychiatry 2018;89(11):1230–1232.

202. Gal A, Balicza P, Weaver D, et al. MSTO1 is a cytoplasmic promitochondrial fusion protein, whose mutation induces myopathy and ataxia in humans. EMBO Mol Med 2017;9(7):967–984.

203. Li K, Jin R, Wu X. Whole-exome sequencing identifies rare compound heterozygous mutations in the MSTO1 gene associated with cerebellar ataxia and myopathy. Eur J Med Genet 2020b;63(1): 103623.

204. Nasca A, Scotton C, Zaharieva I, et al. Recessive mutations in MSTO1 cause mitochondrial dynamics impairment, leading to myopathy and ataxia. Hum Mutat 2017;38(8):970–977.

205. Genis D, Ortega-Cubero S, San Nicolas H, et al. Heterozygous STUB1 mutation causes familial ataxia with cognitive affective syndrome (SCA48). Neurology 2018;91(21):e1988–e1998.

206. De Michele G, Lieto M, Galatolo D, et al. Spinocerebellar ataxia 48 presenting with ataxia associated with cognitive, psychiatric, and extrapyramidal features: a report of two Italian families. Parkinsonism Relat Disord 2019;65:91–96.

207. Lieto M, Riso V, Galatolo D, et al. The complex phenotype of spinocerebellar ataxia type 48 in eight unrelated Italian families. Eur J Neurol 2020;27(3):498–505.

208. Chen DH, Latimer C, Yagi M, et al. Heterozygous STUB1 missense variants cause ataxia, cognitive decline, and STUB1 mislocalization. Neurol Genet 2020a;6(2):1–13.

209. Capitanio GL, Leone M, Croce S, Schiapparelli P. Evaluation of progesterone receptors in epithelial culture of human endometrium using a cytofluorescence method. Boll Soc Ital Biol Sper 1988; 64(7):671–676.

210. Mol MO, van Rooij JGJ, Brusse E, et al. Clinical and pathologic phenotype of a large family with heterozygous STUB1 mutation. Neurol Genet 2020;6(3):e417.

211. Roux T, Barbier M, Papin M, et al. Clinical, neuropathological, and genetic characterization of STUB1 variants in cerebellar ataxias: a frequent cause of predominant cognitive impairment. Genet Med 2020;22(11):1851–1862.

212. Ravel JM, Benkirane M, Calmels N, et al. Expanding the clinical spectrum of STIP1 homology and U-box containing protein 1-associated ataxia. J Neurol 2021;268(5):1927–1937.

213. Ganetzky RD, Stendel C, McCormick EM, et al. MT-ATP6 mitochondrial disease variants: phenotypic and biochemical features analysis in 218 published cases and cohort of 14 new cases. Hum Mutat 2019;40(5):499–515.

214. Ng YS, Martikainen MH, Gorman GS, et al. Pathogenic variants in MT-ATP6: a United Kingdom-based mitochondrial disease cohort study. Ann Neurol 2019;86(2):310–315.

215. Bugiardini E, Bottani E, Marchet S, et al. Expanding the molecular and phenotypic spectrum of truncating MT-ATP6 mutations. Neurol Genet 2020a;6(1):e381.

216. Stendel C, Neuhofer C, Floride E, et al. Delineating MT-ATP6-associated disease: from isolated neuropathy to early onset neurodegeneration. Neurol Genet 2020;6(1):e393.

217. Pandolfo M, Rai M, Remiche G, Desmyter L, Vandernoot I. Cerebellar ataxia, neuropathy, hearing loss, and intellectual disability due to AIFM1 mutation. Neurol Genet 2020;6(3):e420.

218. Bogdanova-Mihaylova P, Alexander MD, Murphy RP, et al. Clinical spectrum of AIFM1-associated disease in an Irish family, from mild neuropathy to severe cerebellar ataxia with colour blindness. J Peripher Nerv Syst 2019;24(4):348–353.

219. Kawarai T, Yamazaki H, Yamakami K, et al. A novel AIFM1 missense mutation in a Japanese patient with ataxic sensory neuronopathy and hearing impairment. J Neurol Sci 2020;409: 116584.

220. Wang Q, Xingxing L, Ding Z, Qi Y, Liu Y. Whole exome sequencing identifies a novel variant in an apoptosis-inducing factor gene associated with X-linked recessive hearing loss in a Chinese family. Genet Mol Biol 2019;42(3):543–548.

221. Syrbe S, Hedrich UBS, Riesch E, et al. De novo loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy. Nat Genet 2015;47(4):393–399.

222. Helbig KL, Hedrich UB, Shinde DN, et al. A recurrent mutation in KCNA2 as a novel cause of hereditary spastic paraplegia and ataxia. Ann Neurol 2016a;80(4):638–642.

223. Corbett MA, Bellows ST, Li M, et al. Dominant KCNA2 mutation causes episodic ataxia and pharmacoresponsive epilepsy. Neurology 2016;87(19):1975–1984.

224. Masnada S, Hedrich UBS, Gardella E, et al. Clinical spectrum and genotype–phenotype associations of KCNA2-related encephalopathies. Brain 2017;140(9):2337–2354.

225. Seong E, Insolera R, Dulovic M, et al. Mutations in VPS13D lead to a new recessive ataxia with spasticity and mitochondrial defects. Ann Neurol 2018;83(6):1075–1088.

226. Gauthier J, Meijer IA, Lessel D, et al. Recessive mutations in VPS13D cause childhood onset movement disorders. Ann Neurol 2018;83(6):1089–1095.

227. Koh K, Ishiura H, Shimazaki H, et al. VPS13D-related disorders presenting as a pure and complicated form of hereditary spastic paraplegia. Mol Genet Genomic Med 2020a;8(3):e1108.

228. Dziurdzik SK, Bean BDM, Davey M, Conibear E. A VPS13D spastic ataxia mutation disrupts the conserved adaptor-binding site in yeast Vps13. Hum Mol Genet 2020;29(4):635–648.

229. Gan-Or Z, Bouslam N, Birouk N, et al. Mutations in CAPN1 cause autosomal-recessive hereditary spastic paraplegia. Am J Hum Genet 2016a;98(5):1038–1046.

230. Wang Y, Hersheson J, Lopez D, et al. Defects in the CAPN1 gene result in alterations in cerebellar development and cerebellar ataxia in mice and humans. Cell Rep 2016a;16(1):79–91.

231. Hamdan FF, Myers CT, Cossette P, et al. High rate of recurrent de novo mutations in developmental and epileptic encephalopathies. Am J Hum Genet 2017a;101(5):664–685.

232. Den K, Kudo Y, Kato M, et al. Recurrent NUS1 canonical splice donor site mutation in two unrelated individuals with epilepsy, myoclonus, ataxia and scoliosis - a case report. BMC Neurol 2019; 19(1):253.

233. Araki K, Nakamura R, Ito D, et al. NUS1 mutation in a family with epilepsy, cerebellar ataxia, and tremor. Epilepsy Res 2020; 164:106371.

234. Gunzler SA, DeBrosse SD. Generalized dystonia as a prominent feature in a case of NUS1 gene mutation. Can J Neurol Sci 2021a; 48(3):433–434.

235. Zuniga-Ramirez C, de Oliveira LM, Kramis-Hollands M, et al. Beyond dystonia and ataxia: expanding the phenotype of SQSTM1 mutations. Parkinsonism Relat Disord 2019;62:192–195.

236. Vedartham V, Sundaram S, Nair SS, Ganapathy A, Mannan A, Menon R. Homozygous sequestosome 1 (SQSTM1) mutation: a rare cause for childhood-onset progressive cerebellar ataxia with vertical gaze palsy. Ophthalmic Genet 2019;40(4):376–379.

237. Appel-Cresswell S, Guella I, Lehman A, Foti D, Farrer MJ. PSEN1 p.Met233Val in a complex neurodegenerative movement and neuropsychiatric disorder. J Mov Disord 2018;11(1):45–48.

238. 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(13):1326–1335.

239. Seliverstov Y, Kanivets I, Illarioshkin S. Spinocerebellar ataxia-like presentation of the M233V PSEN1 mutation. Cerebellum 2020; 19(5):744–747.

240. Testi S, Peluso S, Fabrizi GM, et al. A novel PSEN1 mutation in a patient with sporadic early-onset Alzheimer's disease and prominent cerebellar ataxia. J Alzheimers Dis 2014;41(3):709–714.

241. Hayer SN, Deconinck T, Bender B, et al. STUB1/CHIP mutations cause Gordon Holmes syndrome as part of a widespread multisystemic neurodegeneration: evidence from four novel mutations. Orphanet J Rare Dis 2017;12(1):31.

242. Diggle CP, Sukoff Rizzo SJ, Popiolek M, et al. Biallelic mutations in PDE10A lead to loss of striatal PDE10A and a hyperkinetic movement disorder with onset in infancy. Am J Hum Genet 2016; 98(4):735–743.

243. Mencacci NE, Kamsteeg EJ, Nakashima K, et al. De novo mutations in PDE10A cause childhood-onset chorea with bilateral striatal lesions. Am J Hum Genet 2016;98(4):763–771.

244. Schirinzi T, Garone G, Travaglini L, et al. Phenomenology and clinical course of movement disorder in GNAO1 variants: results from an analytical review. Parkinsonism Relat Disord 2019;61: 19–25.

245. Yamashita Y, Ogawa T, Ogaki K, et al. Neuroimaging evaluation and successful treatment by using directional deep brain stimulation and levodopa in a patient with GNAO1-associated movement disorder: a case report. J Neurol Sci 2020;411:116710.

246. Santens P, Van Damme T, Steyaert W, et al. RNF216 mutations as a novel cause of autosomal recessive Huntington-like disorder. Neurology 2015;84(17):1760–1766.

247. Lieto M, Galatolo D, Roca A, et al. Overt hypogonadism may not be a sentinel sign of RING finger protein 216: two novel mutations associated with ataxia, chorea, and fertility. Mov Disord Clin Pract 2019;6(8):724–726.

248. Chen KL, Zhao GX, Wang H, et al. A novel de novo RNF216 mutation associated with autosomal recessive Huntington-like disorder. Ann Clin Transl Neurol 2020b;7(5):860–864.

249. Togashi N, Fujita A, Shibuya M, et al. Fifteen-year follow-up of a patient with a DHDDS variant with non-progressive early onset myoclonic tremor and rare generalized epilepsy. Brain Dev 2020; 42(9):696–699.

250. Wu Y, Arai AC, Rumbaugh G, et al. Mutations in ionotropic AMPA receptor 3 alter channel properties and are associated with moderate cognitive impairment in humans. Proc Natl Acad Sci U S A 2007;104(46):18163–18168.

251. Piard J, Bereau M, XiangWei W, et al. The GRIA3 c.2477G > A variant causes an exaggerated startle reflex, chorea, and multifocal myoclonus. Mov Disord 2020;35(7):1224–1232.

252. Trivisano M, Santarone ME, Micalizzi A, et al. GRIA3 missense mutation is cause of an x-linked developmental and epileptic encephalopathy. Seizure 2020;82:1–6.

253. Patino LC, Battu R, Ortega-Recalde O, et al. Exome sequencing is an efficient tool for variant late-infantile neuronal ceroid lipofuscinosis molecular diagnosis. PLoS One 2014;9(10):e109576.

254. Kozina AA, Okuneva EG, Baryshnikova NV, et al. A novel MFSD8 mutation in a Russian patient with neuronal ceroid lipofuscinosis type 7: a case report. BMC Med Genet 2018; 19(1):151.

255. Hamanaka K, Imagawa E, Koshimizu E, et al. De novo truncating variants in the last exon of SEMA6B cause progressive myoclonic epilepsy. Am J Hum Genet 2020;106(4):549–558.

256. Herzog R, Hellenbroich Y, Bruggemann N, et al. Zonisamide-responsive myoclonus in SEMA6B-associated progressive myoclonic epilepsy. Ann Clin Transl Neurol 2021;8(7):1524–1527.

257. Li Q, Liu M, Huang DP, et al. A de novo SEMA6B variant in a Chinese patient with progressive myoclonic epilepsy-11 and review of the literature. J Mol Neurosci 2021b;71(9):1944–1950.

258. Xiaozhen S, Fan Y, Fang Y, et al. Novel truncating and missense variants in SEMA6B in patients with early-onset epilepsy. Front Cell Dev Biol 2021;9:633819.

259. Courage C, Oliver KL, Park EJ, et al. Progressive myoclonus epilepsies-residual unsolved cases have marked genetic heterogeneity including dolichol-dependent protein glycosylation pathway genes. Am J Hum Genet 2021;108(4):722–738.

260. Wagnon JL, Mencacci NE, Barker BS, et al. Partial loss-of-function of sodium channel SCN8A in familial isolated myoclonus. Hum Mutat 2018;39(7):965–969.

261. Gardella E, Marini C, Trivisano M, et al. The phenotype of SCN8A developmental and epileptic encephalopathy. Neurology 2018;91(12):e1112–e1124.

262. Denis J, Villeneuve N, Cacciagli P, et al. Clinical study of 19 patients with SCN8A-related epilepsy: two modes of onset regarding EEG and seizures. Epilepsia 2019;60(5):845–856.

263. Hayashida T, Saito Y, Ishii A, et al. CACNA1A-related early-onset encephalopathy with myoclonic epilepsy: a case report. Brain Dev 2018;40(2):130–133.

264. Lv Y, Wang Z, Liu C, Cui L. Identification of a novel CACNA1A mutation in a Chinese family with autosomal recessive progressive myoclonic epilepsy. Neuropsychiatr Dis Treat 2017;13:2631–2636.

265. Mordel P, Schaeffer S, Dupas Q, et al. A 2 bp deletion in the mitochondrial ATP 6 gene responsible for the NARP (neuropathy, ataxia, and retinitis pigmentosa) syndrome. Biochem Biophys Res Commun 2017;494(1–2):133–137.

266. Inui T, Kobayashi S, Ashikari Y, et al. Two cases of early-onset myoclonic seizures with continuous parietal delta activity caused by EEF1A2 mutations. Brain Dev 2016;38(5):520–524.

267. Lam WW, Millichap JJ, Soares DC, et al. Novel de novo EEF1A2 missense mutations causing epilepsy and intellectual disability. Mol Genet Genomic Med 2016;4(4):465–474.

268. De Rinaldis M, Giorda R, Trabacca A. Mild epileptic phenotype associates with de novo eef1a2 mutation: case report and review. Brain Dev 2020;42(1):77–82.

269. Rudolf G, Lesca G, Mehrjouy MM, et al. Loss of function of the retinoid-related nuclear receptor (RORB) gene and epilepsy. Eur J Hum Genet 2016;24(12):1761–1770.

270. Sadleir LG, de Valles-Ibanez G, King C, et al. Inherited RORB pathogenic variants: overlap of photosensitive genetic generalized and occipital lobe epilepsy. Epilepsia 2020;61(4):e23−−e29.

271. Liao Y, Anttonen AK, Liukkonen E, et al. SCN2A mutation associated with neonatal epilepsy, late-onset episodic ataxia, myoclonus, and pain. Neurology 2010;75(16):1454–1458.

272. Huang Q, Yu L, Ma M, Qi H, Wu Y. Novel SCN2A mutation in a family associated with juvenile-onset myoclonus: case report. Medicine (Baltimore) 2019;98(8):e14698.

273. Lee S, Kim SH, Kim B, et al. Genetic diagnosis and clinical characteristics by etiological classification in early-onset epileptic encephalopathy with burst suppression pattern. Epilepsy Res 2020;163: 106323.

274. Tang S, Addis L, Smith A, et al. Phenotypic and genetic spectrum of epilepsy with myoclonic atonic seizures. Epilepsia 2020;61(5): 995–1007.

275. Hiraide T, Hattori A, Ieda D, et al. De novo variants in SETD1B cause intellectual disability, autism spectrum disorder, and epilepsy with myoclonic absences. Epilepsia Open 2019;4(3):476–481.

276. Indelicato E, Boesch S. From genotype to phenotype: expanding the clinical spectrum of CACNA1A variants in the era of next generation sequencing. Front Neurol 2021;12:639994.

277. Rinaldi C, Schmidt T, Situ AJ, et al. Mutation in CPT1C associated with pure autosomal dominant spastic paraplegia. JAMA Neurol 2015;72(5):561–570.

278. Hong D, Cong L, Zhong S, Liu L, Xu Y, Zhang J. A novel CPT1C variant causes pure hereditary spastic paraplegia with benign clinical course. Ann Clin Transl Neurol 2019;6(3):610–614.

279. Farazi Fard MA, Rebelo AP, Buglo E, et al. Truncating mutations in UBAP1 cause hereditary spastic paraplegia. Am J Hum Genet 2019;104(4):767–773.

280. Lin X, Su HZ, Dong EL, et al. Stop-gain mutations in UBAP1 cause pure autosomal-dominant spastic paraplegia. Brain 2019b; 142(8):2238–2252.

281. Nan H, Ichinose Y, Tanaka M, et al. UBAP1 mutations cause juvenile-onset hereditary spastic paraplegias (SPG80) and impair UBAP1 targeting to endosomes. J Hum Genet 2019a;64(11):1055–1065.

282. Gu S, Chen CA, Rosenfeld JA, et al. Truncating variants in UBAP1 associated with childhood-onset nonsyndromic hereditary spastic paraplegia. Hum Mutat 2020;41(3):632–640.

283. Bourinaris T, Smedley D, Cipriani V, et al. Identification of UBAP1 mutations in juvenile hereditary spastic paraplegia in the 100,000 Genomes Project. Eur J Hum Genet 2020;28(12):1763–1768.

284. Novarino G, Fenstermaker AG, Zaki MS, et al. Exome sequencing links corticospinal motor neuron disease to common neurodegenerative disorders. Science 2014;343(6170):506–511.

285. Mamelona J, Crapoulet N, Marrero A. A new case of spastic paraplegia type 64 due to a missense mutation in the ENTPD1 gene. Hum Genome Var 2019;6:5.

286. Husain RA, Grimmel M, Wagner M, et al. Bi-allelic HPDL variants cause a neurodegenerative disease ranging from neonatal encephalopathy to adolescent-onset spastic paraplegia. Am J Hum Genet 2020;107(2):364–373.

287. Wiessner M, Maroofian R, Ni MY, et al. Biallelic variants in HPDL cause pure and complicated hereditary spastic paraplegia. Brain 2021;144(5):1422–1434.

288. Lossos A, Elazar N, Lerer I, et al. Myelin-associated glycoprotein gene mutation causes Pelizaeus-Merzbacher disease-like disorder. Brain 2015;138(Pt 9):2521–2536.

289. Vaz FM, McDermott JH, Alders M, et al. Mutations in PCYT2 disrupt etherlipid biosynthesis and cause a complex hereditary spastic paraplegia. Brain 2019;142(11):3382–3397.

290. Velez-Santamaria V, Verdura E, Macmurdo C, et al. Expanding the clinical and genetic spectrum of PCYT2-related disorders. Brain 2020;143(9):e76.

291. Wagner M, Osborn DPS, Gehweiler I, et al. Bi-allelic variants in RNF170 are associated with hereditary spastic paraplegia. Nat Commun 2019;10(1):4790.

292. de Sainte Agathe JM, Mercier S, Mahe JY, et al. RNF170-related hereditary spastic paraplegia: confirmation by a novel mutation. Mov Disord 2021;36(3):771–774.

293. Coutelier M, Goizet C, Durr A, et al. Alteration of ornithine metabolism leads to dominant and recessive hereditary spastic paraplegia. Brain 2015b;138(Pt 8):2191–2205.

294. Panza E, Escamilla-Honrubia JM, Marco-Marin C, et al. ALDH18A1 gene mutations cause dominant spastic paraplegia SPG9: loss of function effect and plausibility of a dominant negative mechanism. Brain 2016;139(Pt 1):e3.

295. Schwartz CE, May MM, Carpenter NJ, et al. Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene. Am J Hum Genet 2005;77(1):41–53.

296. Namba N, Etani Y, Kitaoka T, et al. Clinical phenotype and endocrinological investigations in a patient with a mutation in the MCT8 thyroid hormone transporter. Eur J Pediatr 2008;167(7): 785–791.

297. Hedera P. Hereditary spastic paraplegia overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews((R)). Seattle (WA); University of Washington; 1993.

298. Kim JH, Kim YM, Yum MS, et al. Clinical and endocrine features of two Allan-Herndon-Dudley syndrome patients with monocarboxylate transporter 8 mutations. Horm Res Paediatr 2015;83(4):288–292.

299. Bilguvar K, Tyagi NK, Ozkara C, et al. Recessive loss of function of the neuronal ubiquitin hydrolase UCHL1 leads to early-onset progressive neurodegeneration. Proc Natl Acad Sci U S A 2013; 110(9):3489–3494.

300. Rydning SL, Backe PH, Sousa MML, et al. Novel UCHL1 mutations reveal new insights into ubiquitin processing. Hum Mol Genet 2017;26(6):1031–1040.

301. Das Bhowmik A, Patil SJ, Deshpande DV, Bhat V, Dalal A. Novel splice-site variant of UCHL1 in an Indian family with autosomal recessive spastic paraplegia-79. J Hum Genet 2018;63(8):927–933.

302. Manole A, Mannikko R, Hanna MG, SYNAPS study group, Kullmann DM, Houlden H. De novo KCNA2 mutations cause hereditary spastic paraplegia. Ann Neurol 2017;81(2):326–328.

303. Du W, Bautista JF, Yang H, et al. Calcium-sensitive potassium channelopathy in human epilepsy and paroxysmal movement disorder. Nat Genet 2005;37(7):733–738.

304. Zhang ZB, Tian MQ, Gao K, Jiang YW, Wu Y. De novo KCNMA1 mutations in children with early-onset paroxysmal dyskinesia and developmental delay. Mov Disord 2015;30(9):1290–1292.

305. Olgiati S, Skorvanek M, Quadri M, et al. Paroxysmal exercise-induced dystonia within the phenotypic spectrum of ECHS1 deficiency. Mov Disord 2016;31(7):1041–1048.

306. Mahajan A, Constantinou J, Sidiropoulos C. ECHS1 deficiency-associated paroxysmal exercise-induced dyskinesias: case presentation and initial benefit of intervention. J Neurol 2017;264(1): 185–187.

307. Masnada S, Parazzini C, Bini P, et al. Phenotypic spectrum of short-chain enoyl-Coa hydratase-1 (ECHS1) deficiency. Eur J Paediatr Neurol 2020;28:151–158.

308. Illsinger S, Korenke GC, Boesch S, et al. Paroxysmal and non-paroxysmal dystonia in 3 patients with biallelic ECHS1 variants: expanding the neurological spectrum and therapeutic approaches. Eur J Med Genet 2020;63(11):104046.

309. Tian WT, Huang XJ, Mao X, et al. Proline-rich transmembrane protein 2-negative paroxysmal kinesigenic dyskinesia: clinical and genetic analyses of 163 patients. Mov Disord 2018;33(3):459–467.

310. 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(5):630–635.

311. Najim al-Din AS, Wriekat A, Mubaidin A, Dasouki M, Hiari M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol Scand 1994;89(5): 347–352.

312. Behrens MI, Bruggemann N, Chana P, et al. Clinical spectrum of Kufor-Rakeb syndrome in the Chilean kindred with ATP13A2 mutations. Mov Disord 2010;25(12):1929–1937.

313. Balint B, Damasio J, Magrinelli F, Guerreiro R, Bras J, Bhatia KP. Psychiatric manifestations of ATP13A2 mutations. Mov Disord Clin Pract 2020;7(7):838–841.

314. Estrada-Cuzcano A, Martin S, Chamova T, et al. Loss-of-function mutations in the ATP13A2/PARK9 gene cause complicated hereditary spastic paraplegia (SPG78). Brain 2017;140(2):287–305.

315. de Bot S, Kamsteeg EJ, Van De Warrenburg BPC. Complicated hereditary spastic paraplegia due to ATP13A2 mutations: what's in a name? Brain 2017;140(12):e73.

316. Wei Q, Dong HL, Pan LY, et al. Clinical features and genetic spectrum in Chinese patients with recessive hereditary spastic paraplegia. Transl Neurodegener 2019;8:19.

317. Estiar MA, Leveille E, Spiegelman D, et al. Clinical and genetic analysis of ATP13A2 in hereditary spastic paraplegia expands the phenotype. Mol Genet Genomic Med 2020;8(3):e1052.

318. Pietrzak A, Badura-Stronka M, Kangas-Kontio T, et al. Clinical and ultrastructural findings in an ataxic variant of Kufor-Rakeb syndrome. Folia Neuropathol 2019;57(3):285–294.

319. De Michele G, Galatolo D, Lieto M, et al. Ataxia-myoclonus syndrome due to a novel homozygous ATP13A2 mutation. Parkinsonism Relat Disord 2020;76:42–43.

320. Miranda M, Harmuth F, Bustamante ML, et al. Intermediate phenotype of ATP13A2 mutation in two Chilean siblings: towards a continuum between parkinsonism and hereditary spastic paraplegia. Parkinsonism Relat Disord 2020;81:45–47.

321. Bras J, Verloes A, Schneider SA, Mole SE, Guerreiro RJ. Mutation of the parkinsonism gene ATP13A2 causes neuronal ceroid-lipofuscinosis. Hum Mol Genet 2012;21(12):2646–2650.

322. Montaut S, Tranchant C, Drouot N, et al. Assessment of a targeted gene panel for identification of genes associated with movement disorders. JAMA Neurol 2018;75(10):1234–1245.

323. Rohani M, Lang AE, Sina F, et al. Action myoclonus and seizure in Kufor-Rakeb syndrome. Mov Disord Clin Pract 2018;5(2):195–199.

324. Yao XP, Cheng X, Wang C, et al. Biallelic mutations in MYORG cause autosomal recessive primary familial brain calcification. Neuron 2018;98(6):1116–1123 e1115.

325. Peng Y, Wang P, Chen Z, Jiang H. A novel mutation in MYORG causes primary familial brain calcification with central neuropathic pain. Clin Genet 2019;95(3):433–435.

326. Forouhideh Y, Muller K, Ruf W, et al. A biallelic mutation links MYORG to autosomal-recessive primary familial brain calcification. Brain 2019;142(2):e4.

327. Arkadir D, Lossos A, Rahat D, et al. MYORG is associated with recessive primary familial brain calcification. Ann Clin Transl Neurol 2019;6(1):106–113.

328. Anikster Y. Costeff syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews((R)). Seattle (WA); University of Washington; 1993.

329. Anikster Y, Kleta R, Shaag A, Gahl WA, Elpeleg O. Type III 3-methylglutaconic aciduria (optic atrophy plus syndrome, or Costeff optic atrophy syndrome): identification of the OPA3 gene and its founder mutation in Iraqi Jews. Am J Hum Genet 2001;69(6):1218–1224.

330. Yahalom G, Anikster Y, Huna-Baron R, et al. Costeff syndrome: clinical features and natural history. J Neurol 2014;261(12):2275–2282.

331. Ho G, Walter JH, Christodoulou J. Costeff optic atrophy syndrome: new clinical case and novel molecular findings. J Inherit Metab Dis 2008;31(Suppl 2):S419–S423.

332. Arif B, Kumar KR, Seibler P, et al. A novel OPA3 mutation revealed by exome sequencing: an example of reverse phenotyping. JAMA Neurol 2013;70(6):783–787.

333. Gaier ED, Sahai I, Wiggs JL, McGeeney B, Hoffman J, Peeler CE. Novel homozygous OPA3 mutation in an Afghani family with 3-methylglutaconic aciduria type III and optic atrophy. Ophthalmic Genet 2019;40(6):570–573.

334. Kostic VS, Lukic-Jecmenica M, Novakovic I, et al. Exclusion of linkage to chromosomes 14q, 2q37 and 8p21.1-q11.23 in a Serbian family with idiopathic basal ganglia calcification. J Neurol 2011;258(9):1637–1642.

335. Keller A, Westenberger A, Sobrido MJ, et al. Mutations in the gene encoding PDGF-B cause brain calcifications in humans and mice. Nat Genet 2013;45(9):1077–1082.

336. Van Goethem G, Dermaut B, Lofgren A, Martin JJ, Van Broeckhoven C. Mutation of POLG is associated with progressive external ophthalmoplegia characterized by mtDNA deletions. Nat Genet 2001;28(3):211–212.

337. Papandreou A, Rahman S, Fratter C, et al. Spectrum of movement disorders and neurotransmitter abnormalities in paediatric POLG disease. J Inherit Metab Dis 2018;41(6):1275–1283.

338. Batla A, Erro R, Ganos C, Stamelou M, Bhatia KP. Levodopa-responsive parkinsonism with prominent freezing and abnormal dopamine transporter scan associated with SANDO syndrome. Mov Disord Clin Pract 2015;2(3):304–307.

Supporting Data

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