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

Connie Marras, MD, PhD,[1] Anthony Lang, MD,[1] Bart P. van de Warrenburg, MD, PhD,[2] Carolyn M. Sue, MBBS, PhD,[3] Sarah J. Tabrizi, MBChB, PhD,[4] Lars Bertram, MD,[5,6] Saadet Mercimek-Mahmutoglu, MD, PhD,[7] Darius Ebrahimi-Fakhari, MD,[8,9] Thomas T. Warner, BMBCh, PhD,[10] Alexandra Durr, MD, PhD,[11] Birgit Assmann, MD,[12] Katja Lohmann, PhD,[13] Vladimir Kostic, MD, PhD,[14] and Christine Klein, MD[13]*

[1]*Toronto Western Hospital Morton, Gloria Shulman Movement Disorders Centre, and the Edmond J. Safra Program in Parkinson's Disease, University of Toronto, Toronto, Canada*
[2]*Department of Neurology, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Centre, Nijmegen, The Netherlands*
[3]*Department of Neurology, Royal North Shore Hospital and Kolling Institute of Medical Research, University of Sydney, St. Leonards, New South Wales, Australia*
[4]*Department of Neurodegenerative Disease, Institute of Neurology, University College London, London, UK*
[5]*Lübeck Interdisciplinary Platform for Genome Analytics (LIGA), Institutes of Neurogenetics and Integrative and Experimental Genomics, University of Lübeck, Lübeck, Germany*
[6]*School of Public Health, Faculty of Medicine, Imperial College, London, UK*
[7]*Division of Clinical and Metabolic Genetics, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Canada*
[8]*Division of Pediatric Neurology and Inborn Errors of Metabolism, Department of Pediatrics, Heidelberg University Hospital, Ruprecht-Karls-University Heidelberg, Heidelberg, Germany*
[9]*Department of Neurology & F. M. Kirby Neurobiology Center, Boston Children's Hospital, Boston, Massachusetts, USA*
[10]*Reta Lila Weston Institute of Neurological Studies, Department of Molecular Neurosciences, UCL Institute of Neurology, London, UK*
[11]*Sorbonne Université, UPMC, Inserm and Hôpital de la Salpêtrière, Département de Génétique et Cytogénétique, Paris, France*
[12]*Division of Pediatric Neurology, Department of Pediatrics I, Heidelberg University Hospital, Ruprecht-Karls-University Heidelberg*
[13]*Institute of Neurogenetics, University of Lübeck, Lübeck, Germany*
[14]*Institute of Neurology, School of Medicine University of Belgrade, Belgrade, Serbia*

ABSTRACT: The system of assigning locus symbols to specify chromosomal regions that are associated with a familial disorder has a number of problems when used as a reference list of genetically determined disorders,including (I) erroneously assigned loci, (II) duplicated loci, (III) missing symbols or loci, (IV) unconfirmed loci and genes, (V) a combination of causative genes and risk factor genes in the same list, and (VI) discordance between phenotype and list assignment. In this article, we report on the recommendations of the International Parkinson and Movement Disorder Society Task Force for Nomenclature of Genetic Movement Disorders and present a system for naming genetically determined movement disorders that addresses these problems. We demonstrate how the system would be applied to currently known genetically determined parkinsonism, dystonia, dominantly inherited ataxia, spastic paraparesis, chorea, paroxysmal movement disorders, neurodegeneration with brain iron accumulation, and primary familial brain calcifications. This system provides a resource for clinicians and researchers that, unlike the previous system, can be considered an accurate and criterion-based list of confirmed genetically determined movement disorders at the time it was last updated.

Key Words: genetics; movement disorders; nomenclature

*Correspondence to: Christine Klein, Institute of Neurogenetics, University of Luebeck, Ratzeburger Allee 160, 23538 Luebeck, Germany, E-mail: christine.klein@neuro.uni-luebeck.de

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Introduction

The system of locus symbols (eg, *DYT1*) was originally established to specify chromosomal regions that had been linked to a familial disorder where the gene was yet unknown.[1] This system has been adopted by clinicians and researchers to provide names for a condition as well as the chromosomal region, and the use of these names is commonplace in medical parlance, particularly in the field of movement disorders.

However, as our techniques of genetic research and our knowledge have evolved, a number of problems have developed with the system of designating locus symbols and with its use. These problems have been described elsewhere[2] but briefly they include (1) an inability to distinguish disease-causing genes from weaker genetic risk factors, (2) an inconsistent relationship between list membership and movement disorder phenotype, (3) failure of some established genetic movement disorders to be assigned a locus symbol, (4) more than one symbol being assigned for the same disorder, (5) unconfirmed associations between a gene or locus and a movement disorder, (6) erroneous labels resulting from laboratory errors or mistakes of phenotypic assignment, and (7) symbol designation in the absence of any known locus or gene. Together these problems make the locus symbols unsuitable as a reference list of genetically determined movement disorders. Unfortunately, it is currently used as such. This lack of a reference list was the justification for the International Parkinson and Movement Disorder Society (MDS) Task Force for Nomenclature of Genetic Movement Disorders to present a recommendation for a new system for naming genetically determined movement disorders.

The Task Force and Its Mandate

The MDS Task Force for the Nomenclature of Genetic Movement Disorders first convened in May 2012. The mandate of the task force was to generate recommendations for revising the naming system of genetic movement disorders, addressing the problems summarized previously. The task force included clinical neurologists and genetic experts covering the spectrum of movement disorders as well as a metabolic geneticist (S.M.-M.). Input was sought from experts in medical fields other than movement disorders, where naming systems for genetically determined disorders were in place (eg, epilepsy). Editors of general medical and neurology journals were also queried regarding their requirements from authors for assigning names for newly discovered genetic conditions or their associated genes. With this background, the task force agreed on a set of rules that should govern the naming based on a set of previously published recommendations authored by several members of the task force.[2] These previously published recommendations were developed into more concrete rules. We then proceeded to apply the rules to classes of genetically determined movement disorders. The classes are phenomenologically defined (eg, ataxias, dystonias) or defined by distinctive imaging (eg, brain calcification) or, theoretically. To date we have not found the need to classify laboratory features. The recommendations and resulting lists have been made available to the MDS membership through the society's website, and feedback was solicited. The recommendations were also shared with representatives from GeneReviews, a compendium of genetic phenotypes for commentary and suggestions. Suggestions from both sources were considered before finalizing our recommendations and tables. A summary of MDS membership feedback and the task force's responses can be found in the supplementary material and on the task force's page on the MDS website at XXX.

Recommendations

1. Include Only Genes Where Genetic Testing Is Possible

Originally, locus symbols represented chromosomal regions. However, if we know only the chromosomal region associated with a particular phenotype there are no direct implications for diagnostic testing or for (basic) research applications. Therefore, a disorder should only be listed once the causative gene is found. The exception to this is when a founder haplotype is diagnostic, as in the case of X-linked dystonia parkinsonism ("Lubag"). In this case, the disorder should be a member of the list.

2. Assign Appropriate Phenotype-Prefix Relationships

For a gene to be assigned a movement disorder prefix, the phenotype (eg, dystonia in the case of DYTs) should be a prominent feature of the disease linked to mutations in that gene in a majority of cases. When more than one movement disorder is a prominent feature and these movement disorders generally coexist in an individual, a double prefix would be assigned (eg, DYT/PARK-*ATP1A3*) and the symbol would belong to more than one list. Disorders that may less commonly present with an alternative movement disorder as the predominant manifestation would appear cross-referenced to the list of the alternative phenotype (eg, SCA17 occasionally presents as a choreic disorder, thus it is cross-referenced to the chorea list), but the prefix would reflect the phenotype that is consistent with the majority of cases. When a genetic mutation can unusually manifest with a movement disorder as the predominant manifestation but the usual phenotype is not a movement disorder (eg, *C9orf72* mutations presenting as a predominantly choreic disorder instead of the usual dementia-predominant syndrome), we have included these disorders on the lists to provide a useful resource for clinicians, but we have not conferred a movement disorder prefix on these genes. The movement disorder predominant presentation must have been reported by two independent groups to qualify for inclusion. Rarely there are gene mutations that are usually associated with a non-movement disorder phenotype but less commonly can result in a

clinically pure movement disorder. For example, *SLC2A1* (glucose transporter type 1 deficiency) mutations usually result in seizures and intellectual disability, but a minority of cases present purely with paroxysmal exercise-induced dyskinesia. We recognized the importance of drawing attention to these conditions from a movement disorder perspective and conferred a movement disorder prefix in these rare situations.

3. Replace Number Suffixes With the Gene Name

We recommend that the symbol prefix be followed by the gene name (eg, DYT-*SGCE* [currently DYT11]). This naming system conveys the responsible gene and maintains the connection between the phenotype (dystonia) and the gene. Remembering a numerical designation (eg, DYT1) is easier than remembering complex gene names. However, given the errors and confusion that have occurred in the numerical listing, we believe this new approach is justified. In addition, the exponentially growing number of identified causative genes will likely make remembering all but the most clinically important examples impossible for most. Referring to reference tables will become increasingly necessary, and with this vision, more informative names and rigorous reviews for inclusion are preferred.

4. List Disease-Causing Genes Separately From Risk Factor Genes

A locus symbol prefix (eg, PARK) would be conferred only on disease-causing genes (causing monogenic disorders) and not on risk factors, recognizing the diagnostic value of disease-causing mutations. For the latter other resources are available, e.g. the PDGene database (http://www.pdgene.org), developed by members of this group, which provides a resource for cataloging genetic risk factors for Parkinson's disease including meta-analyses of the available data.[3,4]

When disease-causing mutations and risk factors arise from the same gene (eg, *SNCA*), such genes should be represented on both lists.

We recognize that the distinction between disease-causing and risk-conferring is not clear in many instances; rather, these attributes mark two ends of a continuum of risk. Furthermore, the decision into which category a particular genetic variation falls is complicated when penetrance varies by age, sex, or ethnicity. Because there is currently no standard as to what level of penetrance of a mutation (or increase in risk) is sufficient to consider a genetic mutation as being disease causing, we have not designated a specific threshold. Rather, we have accepted the designation (disease causing or risk factor) that prevails in the field for each gene. As discussed in the following section, a criterion-based method of making such distinctions would be of value to the field.

5. Raise the Threshold of Evidence Before Assigning Locus Symbols

To avoid inaccuracies and redundancies that currently permeate the lists of locus symbols, a level of evidence for genotype–phenotype association must be met prior to conferring a place on the list. The U.S. National Human Genome Research Institute convened a working group to establish guidelines for investigating causality of sequence variants in human disease.[5] As outlined in the guidelines, the following 4 major pieces of evidence lend support to causality: (1) the presence of the variant in multiple, unrelated affected individuals; (2) evidence for segregation or statistical association of the variant with disease; (3) the variant should be conserved across different species; and (4) the variant should be predicted to alter the normal biochemical effect of a gene product as supported by functional evidence in human tissue, well-established cellular or animal models, or other biochemical or histological abnormalities, if possible. After considering these guidelines, a gene-by-gene assessment of the sum of the evidence was considered the most appropriate approach for deciding whether a gene warrants a place on the lists.

Applying the Recommendations

For each class of movement disorder, we present the new list applying the principles we listed previously. For contrast we have provided the list of existing locus symbols for each class of disorder as supplementary material, including a note in the last column indicating the problems with the entry, when applicable. In the list of existing symbols, we included those not listed by the Human Genome Nomenclature Committee (http://www.genenames.org/), reflecting the reality that many locus symbols have come into use bypassing this official channel. In our revised system, we assigned symbols to disorders known to be genetically determined but never assigned a locus symbol to provide a complete list. Wilson disease is an example. Likewise, we introduced to these lists a number of pediatric metabolic disorders, all of which manifest a predominant movement disorder phenotype in at least a subset of patients. Many of these metabolic diseases represent progressive disorders in which the movement disorder may predominate only if the metabolic defect is left untreated. Testing is commercially available for all of the listed disorders.

TABLE 1. The proposed new list of hereditary parkinsonism

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance	Locus symbol
Classical parkinsonism					
PARK-*SNCA*[9]		Missense mutations cause classical parkinsonism. Duplication or triplication of this gene cause early onset parkinsonism with prominent dementia.	168601	AD	PARK1
PARK-*LRRK2*[10]			607060	AD	PARK8
PARK-*VPS35*[11]			614203	AD	PARK17
Early onset parkinsonism					
PARK-*Parkin*		Often presents with dystonia, often in a leg	600116	AR	PARK2
PARK-*PINK1*[13]		Psychiatric features common	605909	AR	PARK6
PARK-*DJ1*[14]			606324	AR	PARK7
Atypical parkinsonism or complex phenotypes					
PARK-*ATP13A2*[15]		Kufor-Rakeb syndrome Parkinsonism, dystonia Additional clinical features: Supranuclear gaze palsy, spasticity/pyramidal signs, dementia, facial-faucial-finger mini-myoclonus, dysphagia, dysarthria, olfactory dysfunction	606693	AR	PARK9
NBIA/DYT/PARK[b]-*PLA2G6*[16]	Ataxia[17]	*PLA2G6*-associated neurodegeneration (PLAN): dystonia, parkinsonism, cognitive decline, pyramidal signs, psychiatric symptoms (adult phenotype), ataxia (childhood phenotype) Iron accumulation: GP, SN in some; adults may have striatal involvement; about half of INAD and the majority of adult-onset cases lack brain iron accumulation on MRI	612953	AR	NBIA2, PARK14
PARK-*FBXO7*[18]		Early onset parkinsonism with pyramidal signs	260300	AR	PARK15
PARK-*DNAJC6*[19]		Occasional mental retardation and seizures	615528	AR	PARK19
PARK-*SYNJ1*[20,21]		May have seizures, cognitive decline, abnormal eye movements, and dystonia	615530	AR	PARK20
DYT/PARK-*ATP1A3*[a22]		See Table 2	128235	AD	DYT12
DYT/PARK-*TAF1*[23]		Dystonia and parkinsonism	314250	X-linked	DYT3
DYT/PARK-*GCH1*[24]		See Table 2	128230	AD	*DYT5a*
			605407	AR	None
DYT/PARK-*TH*[28]		See Table 2	605407		
				AR	DYT5b
				AR	None
				AR	None
DYT/PARK-*SPR*[30]		See Table 2	612716	AR	None
DYT/PARK-*QDPR*[32]		See Table 2	612676	AR	None
DYT/PARK-*PTS*[32]		See Table 2	612719	AR	None
DYT/PARK-*SLC6A3*[33,34]		See Table 2	126455	AR	None
DYT/PARK-*SLC30A10*[36]		See Table 2	611146	AR	None
DYT/PARK-*GLB1*[38,39]		See Table 2	603921	AR	None
NBIA/PARK-*WDR45*[40]	Dystonia	See Table 8	300894	X-linked	NBIA5
NBIA/DYT/PARK-*CP*[42]	Chorea	See Table 8	604290	AR	

(Continued)

TABLE 1. *Continued*

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance	Locus symbol
Disorders that usually present with other phenotypes but can have predominant parkinsonism					
PARK-*GBA*[44]		Early onset parkinsonism.[45] Alternative or comorbid phenotype Gaucher's disease: bone lesions, hepatosplenomegaly, hematologic disorders		AR	None
SCA-*ATXN2*[46]	Parkinsonism[47]	See Table 4	183090	AD	SCA2
HSP-*KIAA1840*[48]	Parkinsonism[49]	See Table 6	640360	AR	SPG11
HSP-*ZFYVE26*[50]	Parkinsonism[49]	See Table 6	270700	AR	SPG15
POLG[52]	Parkinsonism[53]	Multiple syndromes often with progressive external ophthalmoparesis. Variable other neurological manifestations. Rare prominent parkinsonism	174763	AD or AR	None
NBIA/CHOREA-*FTL*[54]	Dystonia, Parkinsonism	See Table 8	606159	AD	NBIA3
HSP/NBIA-*FA2H*[56]	Dystonia, Parkinsonism, Ataxia[57]	See Table 6	612319	AR	SPG35
NBIA/DYT-*PANK2*[58]	Parkinsonism,[59] chorea	See Table 8	234200	AR	NBIA1
HSP/NBIA-*C19orf12*[60]	Dystonia, parkinsonism	See Table 8	614298	AR	NBIA4/SPG43

AD, autosomal dominant; AR, autosomal recessive; BG, basal ganglia; GP, globus pallidus; INAD, infantile neuroaxonal dystrophy; NBIA, neurodegeneration with brain iron accumulation; n/a, not available; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SN, substantia nigra; TCC, thinning of the corpus callosum; WML, white matter lesions.
[aa]Mutations in this gene also causes alternating hemiplegia of childhood, CAPOS (cerebellar ataxia, pes cavus, optic atrophy, and sensorineural hearing loss) syndrome as well as CAOS (episodic cerebellar ataxia, areflexia, optic atrophy, and sensorineural hearing loss) syndrome.
[bb]Mutations in this gene more commonly cause INAD: developmental delay/regression, hypotonia, spasticity/pyramidal signs, optic nerve atrophy, sensorimotor neuropathy, and seizures.

Genetically Determined Movement Disorders

Genetically Determined Parkinsonism

A total of 21 genes and loci have been assigned a PARK designation (Supplementary Table 1). For 6 of these, the relationship is unconfirmed (PARK3, 5, 11, 13, 18, 21), and 3 fall into the risk factor category (PARK10, 12, 16). PARK1 and PARK4 are identical, both referring to the *SNCA* gene.

According to the revised system, there are 23 confirmed monogenic conditions where parkinsonism is a consistent and predominant feature (Table 1). In a number of the forms of genetic parkinsonism mentioned, dystonia is a prominent feature. To guide clinicians we have divided these into 1 of the following 3 categories: (1) Those that are associated with a clinical picture closely resembling that of idiopathic Parkinson's disease, (2) those that present with parkinsonism similar to Parkinson's disease but of young onset, and (3) complex forms that have parkinsonism as a key clinical feature but also present with atypical, multisystem features or other movement disorders. We have provided references for the more complex disorders that may not have been included in previous lists of this kind; for others we refer readers to a recent review.[6,7] Of note, we have chosen not to include heterozygous mutations in *GBA* as a monogenic cause of parkinsonism in the PARK list but, rather, consider it a strong genetic risk factor for Parkinson's disease (similar to *ApoE4* in Alzheimer's disease) given its low, age-dependent penetrance.[8]

Genetically Determined Dystonia

There are currently 28 locus symbols with a numeric DYT designation (Supplementary Table 2).[62] However, a number of these currently await independent confirmation or identification of the causative gene mutation (DYT2, 3, 4, 7, 13, 15, 16, 17, 20, 21, 23, 24, 26, and 27) and several others have been shown to be erroneously designated (DYT14, 18, and 19). One of the DYT loci (DYT22) has never been linked to a locus, gene, or clinical syndrome to our knowledge, and only 9 of these disorders appear on the newly proposed list (Table 2). In addition, we have conferred a DYT prefix on Wilson disease and Lesch-Nyhan syndrome and a number of other infantile and

TABLE 2. The proposed new list of isolated, combined, and complex hereditary dystonia

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance pattern	Locus symbol
Isolated dystonias					
DYT-*TOR1A*[64]		Early-onset generalized dystonia	128100	AD	*DYT1*
DYT-*THAP1*[65]		Adolescent-onset dystonia of mixed type	602629	AD	*DYT6*
DYT-*GNAL*[66]		Adult onset cranial-cervical dystonia	615073	AD	*DYT25*
Combined dystonias (disorders where dystonia frequently coexists with other movement disorders)					
DYT-*PRKRA*[67]		Rare form of usually generalized dystonia, parkinsonism inconsistent	612067	AR	*DYT16*
DYT/PARK-*GCH1*[24]		GTP cyclohydrolase I deficiency (mild form)25: childhood-onset dopa-responsive dystonia, adult-onset dystoniaparkinsonism Additional clinical manifestations: diurnal fluctuation, pyramidal signs	128230	AD	*DYT5a*
		GTP cyclohydrolase I deficiency (severe form)[26,27]: dystonia, parkinsonism Additional clinical manifestations: developmental delay, truncal hypotonia, spasticity, oculogyric crises, seizures, with or without hyperphenylalaninemia [27]	128230	AR	None
DYT/PARK-*TH*[28]		Tyrosine hydroxylase deficiency	605407		
		Mild form: dopa-responsive infantile to early childhood onset dystonia		AR	*DYT5b*
		Severe form: infantile-onset dystonia and parkinsonism, truncal hypotonia, global developmental delay		AR	None
		Very severe form: infantile-onset dystonia and parkinsonism, oculogyric crises, severe global developmental delay, truncal hypotonia, limb spasticity, autonomic dysfunction		AR	None
DYT/PARK-*ATP1A3*[22]		Rapid-onset dystonia-parkinsonism, chorea in later life[b]	128235	AD	*DYT12*
DYT/PARK-*TAF1*[23a]		Dystonia-parkinsonism	314250	X-linked	*DYT3*
DYT-*SGCE*[69]		Myoclonus-dystonia	159900	AD	*DYT11*
CHOR/DYT-*ADCY5*[70]		See Table 5	600293	AD	None
Complex dystonias (where dystonia dominates the clinical picture but this occurs in the context of a complex phenotype including symptoms other than movement disorders)					
DYT/CHOR-*HPRT*[71,162]		Lesch-Nyhan syndrome: Dystonia, chorea, occasionally ballism Additional clinical features: hyperuricemia, crystalluria, developmental delay/intellectual disability, eye movement abnormalities, spasticity, compulsive self-injurious behavior, gouty arthritis, nephrolithiasis, renal failure behavior	300322	X-linked	None
DYT/CHOR-*ACAT1*[72]		Mitochondrial acetoacetyl-CoA thiolase deficiency: metabolic decompensation and basal ganglia injury during acute stress resulting in dystonia and chorea[73]	203750	AR	None
DYT/CHOR-*GCDH*[74]		Glutaric aciduria type I[75,76]: dystonia, chorea (usually following acute metabolic crises), parkinsonism (later) Additional clinical features: acute metabolic crises with basal ganglia injury (predominantly putamen and caudate nucleus), severe truncal hypotonia, macrocephaly, orofacial dyskinesias, spasticity, cognitive impairment (variable), enlarged subdural space, subdural hygroma/hemorrhages, headaches, seizures[77]	231670	AR	None
DYT/CHOR-*MUT*[78]		Methylmalonic aciduria[79]: dystonia, chorea, occasionally ataxia Additional clinical features: neonatal-onset vomiting, seizures, lethargy and hypotonia, ketoacidosis, hyperammonemia, developmental delay, spasticity, pancreatitis, nephritis, growth failure, acute metabolic crises with confusion/encephalopathy, basal ganglia injury (predominantly globus pallidus)		AR	None
DYT/CHOR-*PCCA/PCCB*[80]		Propionic aciduria[79]: dystonia, occasionally chorea Additional clinical features: neonatal-onset vomiting, seizures, lethargy and hypotonia, ketoacidosis, hyperammonemia, developmental delay, spasticity, cardiomyopathy, acute metabolic crises with confusion/encephalopathy, basal ganglia injury (predominantly putamen and caudate nucleus)		AR	None
NBIA/DYT- *DCAF17*[81]	Chorea[82]	See Table 8	241080	AR	None

(Continued)

TABLE 2. *Continued*

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance pattern	Locus symbol
DYT-*DDC*[84]		Aromatic l-amino acid decarboxylase deficiency[85]: dystonia, occasionally chorea, hypokinesia Additional clinical features: developmental delay, truncal hypotonia, oculogyric crises, ptosis, autonomic symptoms, sleep disorder, diurnal fluctuations with sleep benefit[34]	608643	AR	None
DYT/PARK-*SLC30A10*[36]		Hypermanganesemia with dystonia, polycythemia, and liver cirrhosis[21,37]: Dystonia, parkinsonism Additional clinical features: hypermanganesemia, polycythemia, chronic liver disease, dysarthria	611146	AR	None
DYT/PARK-*SPR*[30]		Sepiapterin reductase deficiency: Dystonia, parkinsonism Additional clinical features: motor and speech delay, truncal hypotonia, limb hypertonia and hyperreflexia, oculogyric crises, psychiatric symptoms, autonomic dysfunction, diurnal fluctuation and sleep benefit, no hyperphenylalaninemia[31]	612716	AR	None
DYT/PARK-*QDPR*[32]		Dihydropteridine reductase deficiency[32]: dystonia, parkinsonism Additional clinical features: developmental delay, truncal hypotonia, seizures, autonomic dysfunction, hyperphenylalaninemia[32]	612676	AR	None
DYT/PARK-*PTS*[32]		6-pyruvoyl-tetrahydropterin synthase deficiency[32]: dystonia, parkinsonism Additional clinical features: neonatal irritability, truncal hypotonia, developmental delay, seizures, oculogyric crises, autonomic dysfunction, hyperphenylalaninemia[32]	612719	AR	None
DYT/PARK-*SLC6A3*[33,34]		Dopamine transporter deficiency syndrome[33,34]: dystonia and parkinsonism (typically infantile-onset, atypical cases with juvenile-onset exist), occasionally chorea in infancy Additional clinical features: mild developmental delay, truncal hypotonia, ocular flutter/oculogyric crises, saccade initiation failure, bulbar dysfunction[34]	126455	AR	None
NBIA/DYT-*PANK2*[58]	Parkinsonsim, Chorea	See Table 8	234200	AR	
NBIA/DYT/PARK[d]-*PLA2G6*[86]	Ataxia[17]	See Table 8	612953	AR	NBIA2, PARK14
DYT-*ATP7B*[87]		Wilson disease: dystonia, occasionally parkinsonism, and/or chorea Additional clinical features:flapping tremor, rest, action, and intention tremor, orofacial dyskinesias, dysarthria, liver disease, Kayser Fleischer rings, psychiatric symptoms	277900	AR	None
DYT-*SLC19A3* [88]		Biotin-responsive basal ganglia disease (within the thiamine transporter–2 deficiency spectrum)[89,90]: dystonia, parkinsonism (mainly rigidity), occasionally ataxia, chorea Additional clinical features:subacute encephalopathy/coma (often triggered by febrile illness), cranial nerve palsy, pyramidal signs, cerebellar signs, dysphagia, intellectual disability, epilepsy, responsive to thiamine, and/or biotin therapy[90]	606152	AR	None
DYT-*TIMM8A*[91]		Mohr-Tranebjaerg syndrome[92]: dystonia Additional clinical features:sensorineural deafness, visual impairment, cognitive impairment, behavioral problems, pyramidal signs[92]	304700	X-linked	None
DYT-*mt-ND6*		Leber's hereditary optic neuropathy/dystonia (G14459A mutation)[93]: dystonia Additional clinical features: juvenile-onset subacute vision loss (Leber hereditary optic neuropathy), encephalopathy, spasticity, bulbar dysfunction, cognitive impairment[93]	516006	Mitochondrial	None
DYT/PARK-*GLB1*[38,39]		GM1 gangliosidosis (type III, chronic/adult form)[38,39]: dystonia, parkinsonism Additional clinical features: pyramidal signs, dysarthria, cognitive deficits (often mild initially), skeletal	230650	AR	None

(Continued)

TABLE 2. *Continued*

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance pattern	Locus symbol
		abnormalities and short statue, corneal clouding, vacuolated cells, cardiomyopathy, progressive disease			
NBIA/DYT/PARK-*CP*[42]	Chorea	See Table 8	604290	AR	
DYT-*SUCLA2*[94,95]		SUCLA2-related mitochondrial DNA (mtDNA) depletion syndrome, encephalomyopathic form, with mild methylmalonic aciduria[94,96]: dystonia Additional clinical features: severe hypotonia, developmental delay, seizures, progressive spasticity, cerebral atrophy, sensorineural hearing loss, ophthalmoplegia, feeding problems and postnatal growth retardation, ptosis	603921	AR	None
DYT[c]-*TUBB4A*[97]	HSP[98,99]	Spasmodic dysphonia is most common dystonic presentation. Alternative, phenotype: hypomyelinating leukodystrophy (see footnote)		AD	TUBB4A
Disorders that usually present with other phenotypes but can have predominant dystonia					
SCA-*ATXN3*[100]	Spastic paraphlegia, dystonia[101,102]	Marked nonataxia features; can have predominant parkinsonism, dystonia, chorea, spasticity, neuropathy, lower motor neuron involvement	109150	AD	SCA3
NBIA/PARK- *WDR45*[40]	Dystonia	Beta-propeller protein-associated neurodegeneration (BPAN, previously SENDA syndrome) [41] Iron accumulation: SN > GP Halo of hyperintensity surrounding linear hypointensity in SN on T1 scans. Additional clinical features:developmental delay/intellectual disability, progressive cognitive decline, seizures, spasticity, Rett-like stereotypies, autistic-features, neuropsychiatric symptoms, sleep disorders, bowel/bladder incontinence, infantile epileptic encephalopathy	300894	X-linked	NBIA5
NBIA/CHOREA-*FTL*[54]	Dystonia, Parkinsonism	Neuroferritinopathy[55]: dystonia, chorea, parkinsonism Iron accumulation: GP, caudate, putamen, SN, red nucleus; cystic BG changes—pallidal necrosis Additional clinical features: oromandibular dyskinesia, dysphagia, cognitive impairment, behavioral symptoms, low serum ferritin	606159	AD	NBIA3
HSP/NBIA- *FA2H*[56]	Dystonia, parkinsonism, ataxia[57]	Fatty acid hydroxylase-associated neurodegeneration (FAHN) [57]: Iron accumulation: GP (more subtle than other NBIAs) Additional clinical features:spastic tetraparesis, cognitive decline, cerebellar and brainstem atrophy, dysarthria, dysphagia, optic nerve atrophy, seizures	612319	AR	SPG35
HSP-*KIF1C*[103] Allelic with autosomal recessive spastic ataxia at the SAX2 locus	Dystonia, ataxia[103]	Pure and complicated, chorea, myoclonus, dysarthria, developmental delay, mild mental retardation, hypodontia, ptosis, short stature, sensorineural deafness, pes planus, white matter lesions	611302	AR	SPG58
HSP/NBIA-*C19orf12*[60]	Dystonia, parkinsonism	Mitochondrial membrane protein-associated neurodegeneration (MPAN)[61] Iron accumulation: GP—hyperintense streaking of medial medullary lamina between GPi and GPe; SN Additional clinical features: progressive spastic paresis, dysarthria, dysphagia, cognitive decline/dementia, motor axonal neuropathy, optic nerve atrophy, psychiatric symptoms, bowel/bladder incontinence	614298	AR	NBIA4/SPG43

AD, autosomal dominant; AR, autosomal recessive; BG, basal ganglia; GM1, monosialotetrahexosylganglioside; GP, globus pallidus; GTP, Guanosine-5′-triphosphate; INAD, infantile neuroaxonal dystrophy; NBIA, neurodegeneration with brain iron accumulation; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SN, substantia nigra.

[a]Due to a founder effect, genetic testing is possible. The pathogenicity of the *TAF1* gene is not absolutely confirmed; however, testing of selected variants in this gene is sufficient for the diagnosis.

[b]Mutations in this gene also cause alternating hemiplegia of childhood and CAPOS (cerebellar ataxia, pes cavus, optic atrophy, and sensorineural hearing loss) syndrome.

[c]Mutations in this gene more commonly cause a hypomyelinating leukodystrophy with developmental delay, dystonia,choreoathetosis, rigidity, opisthotonus, andoculogyric crises, progressive spastic tetraplegia, ataxia, and, more rarely, seizures.

[d]Mutations in this gene more commonly cause INAD: developmental delay/regression, hypotonia, spasticity/pyramidal signs, optic nerve atrophy, sensorimotor neuropathy, and seizures.

childhood onset disorders that were previously undesignated.

An international panel of dystonia experts recently developed a consensus update of the definition and classification of dystonia. The 2 main axes of dystonia classification currently considered most relevant are clinical and etiological.[63] On clinical grounds, the updated classification proposes characterization by age of onset, body distribution, temporal pattern, and association with additional features (isolated or combined with other symptoms). Formerly, isolated dystonia was referred to as primary dystonia. When additional features were primarily other movement disorders, this was referred to as dystonia plus and is now referred to as combined dystonia. When dystonia predominates the clinical picture but this occurs in the context of a complex phenotype including symptoms other than movement disorders (formerly secondary dystonia), this is now referred to as complex dystonia. The proposed new list is thus divided into isolated, combined, and complex dystonias, following the suggested scheme. Because almost all known forms of dystonia are inherited in an autosomal dominant fashion, unlike in parkinsonism, mode of transmission does not appear to be a useful feature to categorize familial dystonias.

Genetically Determined Paroxysmal Movement Disorders

There are a number of movement disorders with symptoms that occur episodically. These include the paroxysmal dyskinesias and episodic ataxias. Although these disorders could be incorporated into other lists following a phenomenologic classification system, we have suggested that they be defined according to their distinctive episodic nature. The movement disorders they display are often mixed, and overlapping phenomenology is increasingly recognized.[104] Therefore, we have proposed a new category of "Paroxysmal Movement Disorders" (PxMD). The paroxysmal dyskinesias[105,106] were previously designated "DYT" loci[62] (see Supplementary Table 2). The previous list of 7 episodic ataxias is shown in Supplementary Table 3.[107] Of these, 4 remain unconfirmed (EA3, 4, 5, 7). Table 3 shows the proposed new list of paroxysmal movement disorders. We have conferred a PxMD prefix on *SLC2A1* mutations (glucose transporter type 1 deficiency) even though mutations in this gene more frequently cause a syndrome of seizures and developmental delay that is not dominated by paroxysmal movement disorders. A minority of cases display a predominant paroxysmal ataxia, dystonia, and/or chorea. Because this is a major consideration in the differential diagnosis of paroxysmal movement disorders, we decided that omitting this would be problematic from the perspective of a clinician considering a patient with a paroxysmal exercise-induced (or more accurately exertion-induced) dyskinesia.

Genetically Determined Dominant Cerebellar Ataxia

The dominant spinocerebellar ataxias (SCAs) have previously been (and still are) referred to as autosomal dominant cerebellar ataxias. The problems with the current SCA list are numerous, including missing genes or unconfirmed associations (SCA4, 18, 20, 25, 26, 30, 32, 34, 37, 40), unidentified loci (SCA9), recessive or congenital disorders (SCA24, 29), and allelic diseases (SCA019/SCA22, and SCA15/SCA16). Supplementary Table 4 lists these locus symbols and their current status.[119] Also, some dominantly inherited ataxias have not been assigned an SCA locus, for example, Dentatorubro-pallidoluysian atrophy (DRPLA) and dominant ataxia combined with narcolepsy and deafness due to DNMT1 mutations. Although some SCAs are pure cerebellar disorders, others present with a plethora of other neurological symptoms, including other movement disorders. Occasionally, individuals with an SCA can be affected by another movement disorder as the only or clearly predominant disease feature.[120] Examples of this are parkinsonism in SCA2 and chorea in SCA17. However, unless these other movement disorders are consistently seen we have not assigned a double prefix for these disorders. For the purposes of this report we have limited our proposal to a list of dominant ataxias (Table 4), but we need similar proposals for recessive and congenital ataxias. We suggest that this should be taken up by experts from the ataxia field in close collaboration with members of this task force.

Genetically Determined Chorea

Chorea is a prominent clinical manifestation of Huntington's disease (HD), and in 4 look-alike disorders, on which the prefix HDL (Huntington disease-like) has been conferred (HDL1-4; Supplementary Table 5).[150] The gene associated with the HDL3 locus is not yet known, and HDL4 refers to the same gene as spinocerebellar ataxia 17, that is, the *TBP* gene. There are a number of other diseases in which chorea is a consistent and predominant feature, however, and these have never been unified under a single naming system such as the DYTs, PARKs, or SCAs. As a result, the proposed list for choreas is an expanded one (Table 5). Because not all genetically determined choreas have a phenotype akin to Huntington's disease, we propose a new prefix, CHOR.

Chorea can unusually be the predominant feature of several autosomal recessively inherited ataxias, in particular ataxia telangiectasia, ataxia with oculomotor apraxia types 1 and 2, and Friedreich's ataxia. As such, these ataxic disorders merit cross-referencing to the chorea list. However, given that we have not yet taken on the nomenclature of autosomal recessively

TABLE 3. The proposed new list of paroxysmal movement disorders

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance	Locus symbol
Predominant paroxysmal dyskinesias					
PxMD-*PRRT2*[108]		Paroxysmal kinesigenic dyskinesia (PKD), rarely other paroxysmal movement disorders (paroxysmal nonkinesigenic dyskinesia [PNKD], PED, episodic ataxia, writer's cramp) or hemiplegic migraine. The PRRT2-associated disease spectrum also includes benign familial infantile epilepsy (BFIE) and combined phenotypes (paroxysmal kinesigenic dyskinesia with infantile convulsions [PKD/IC])	128200	AD	*DYT10* or *DYT19*
PxMD-*PNKD* (formerly *MR1*)[109]		PNKD	118800	AD	*DYT8*
PxMD[a]-*SLC2A1*[110]		Paroxysmal exercise (exertion)-induced dyskinesia, Alternative phenotype: Glut1 deficiency syndrome (see footnote)	612126	AD	*DYT18/DYT9*
Disorders that usually present with other phenotypes but can have predominant paroxysmal dyskinesias					
GLDC	PxMD[111]	Glycine encephalopathy Intermittent chorea during febrile illness	605899		
Predominant ataxias					
PxMD-*KCNA1*[112]		Paroxysmal ataxia with interictal myokymia	160120	AD	EA1
PxMD-*CACNA1A*[113]		Paroxysmal ataxia with vertigo, nausea, headaches, weakness, and other manifestations often favorable response to acetazolamide	108500	AD	EA2
PxMD-*SLC1A3*[114]		Paroxysmal ataxia with vertigo, nausea, seizures, migraine, weakness, alternating hemiplegia and other manifestations GeneReviews n/a	612656	AD	EA6
PxMD-*PDHA1*[115]		Pyruvate dehydrogenase deficiency[116,117]: paroxysmal episodes of ataxia, dystonia, occasionally parkinsonism Additional clinical features:developmental delay/ intellectual disability, encephalopathy, truncal hypotonia, seizures, microcephaly, spasticity, facial dysmorphism, peripheral neuropathy[117]	300502	X-linked	None

n/a, not available.
[a]Mutations in this gene more commonly cause infantile-onset epileptic encephalopathy, delayed development, acquired microcephaly, ataxia, dystonia, spasticity, atypical phenotypes without epilepsy including patients with mixed movement disorders and mental retardation or adult-onset cases with minimal symptoms (Glut1 deficiency syndrome).[118]
AR, autosomal recessive.

inherited ataxias we have not included them yet. The list will be amended as we complete that work.

Chorea can be a feature in some SCAs (eg, SCA1, 2, or 7) and is also part of the phenotypic spectrum in cases with intracranial calcifications, neurodegeneration with brain iron accumulation (NBIA), pontocerebellar hypoplasia (PCH2), and several dystonias (eg, DYT-TAF1). However, chorea is not a prominent finding in these disorders, therefore they are not included in the list of genetically determined choreas. Chorea is often a prominent manifestation of paroxysmal movement disorders, but we have chosen to place these disorders on a separate list because it was decided that the paroxysmal nature of the movement disorder was a more distinctive feature.

Hereditary Spastic Paraplegia

Hereditary spastic paraplegia (HSP) is a group of inherited disorders characterized by spasticity or progressive stiffness of the limbs (usually the lower limbs more than upper limbs) associated with hyper-reflexia and gait difficulties. Symptoms may begin in early childhood through to late adulthood. Affected patients may develop signs of spasticity only and are referred to as pure forms of HSP, whereas other patients may have associated features such as muscle weakness or atrophy, ptosis and ophthalmoplegia, thin corpus callosum, ataxia, or cognitive impairment and are referred to as complicated or complex forms of HSP. A common complex phenotype includes amyotrophy of the hands and has been called Silver syndrome. Only 3 HSP genes have been reported to present with pure HSP. Distinguishing features in specific monogenic forms of HSP (eg, thinning of the corpus callosum in SPG11 and SPG15 or external ophthalmoplegia in SPG7) can provide clinical clues to the precise genetic diagnosis; however, variability of phenotypic expression even within specific genetic forms makes genetic counseling challenging.

TABLE 4. The proposed new list for the dominant spinocerebellar ataxias (SCAs)

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance	Locus symbol
Pure or relatively pure ataxia					
SCA-*SPTBN2*[121]		Pure ataxia	600224	AD	SCA5
SCA-*CACNA1A*[122]		Pure ataxia. Allelic with episodic ataxia type 2 and familial hemiplegic migraine type 1.	183086	AD	SCA6
SCA-*TTBK2*[123]		Pure ataxia	604432	AD	SCA11
SCA-*PDYN*[124]		Pure ataxia	610245	AD	SCA23
SCA-*ATXN8OS*[125]		Relatively pure; pyramidal signs, neuropsychiatric features	608768	AD	SCA8
SCA-*PPP2R2B*[126]		Relatively pure; head and hand tremor	604326	AD	SCA12
SCA-*PRKCG*[127]		Relatively pure; sometimes other movement disorders (dystonia, myoclonus)	605361	AD	SCA14
SCA-*ITPR1*[128,129]		Relatively pure; myoclonus, dystonia	606658	AD	SCA15/16
SCA-*KCND3*[130]		Relatively pure; hand tremor, peripheral neuropathy, cognitive disturbances	607346	AD	SCA19/22
SCA-*FGF14*[131]		Relatively pure; early-onset hand tremor, orofacial dyskinesia, behavioral problems	609307	AD	SCA27
SCA-*TGM6*[132]		Relatively pure; pyramidal features, cervical dystonia	613908	AD	SCA35
SCA-*ELOVL5*[133]		Relatively pure; neuropathy	615957	AD	SCA38
Complex ataxia (ataxias that can often have other neurological features)					
SCA-*ATXN1*[123]		Marked nonataxia features; can have dominant choreapyramidal features, peripheral neuropathy, ophthalmoplegia	164400	AD	SCA1
SCA-*ATXN2*[46]	Parkinsonism[47]	Marked nonataxia features, can have predominant parkinsonism or chorea; neuronopathy, dementia, myoclonus	183090	AD	SCA2
SCA-*ATXN3*[100]	HSP, dystonia[101,102]	Marked nonataxia features; can have predominant parkinsonism, dystonia, chorea, spasticity, neuropathy, lower motor neuron involvement	109150	AD	SCA3
SCA-*ATXN7*[134]		Retinitis pigmentosa with marked visual loss	164500	AD	SCA7
SCA-*ATXN10*[135]		Seizures	603516	AD	SCA10
SCA-*TBP*[136]	Chorea[137]	Marked nonataxia features, can present with predominant chorea. May be HD-like	607136	AD	SCA17, HDL4
SCA-*TMEM240*[138]		Cognitive impairment/mental retardation	607454	AD	SCA21
SCA-*AFG3L2*[139]		Ophthalmoparesis	610246	AD	SCA28
SCA-*BEAN1*[140]		Hearing loss, vertigo	117210	AD	SCA31
SCA-*NOP56*[141]		Motor neuron involvement	614153	AD	SCA36
SCA-*DNMT1*[142]		Sensorineural deafness, narcolepsy, dementia	126375	AD	None
SCA-*ATN1*[143]	Chorea[144]	Dentatorubropallidoluysian atrophy (DRPLA): myoclonus, chorea, parkinsonism, dementia, supranuclear gaze palsy, seizures (particularly in young patients)	607462	AD	None
SCA/HSP-*VAMP1*[145]		Spastic ataxia, supranuclear upgaze limitation	108600	AD	SPAX1
Disorders that usually present with other phenotypes but can have predominant ataxia					
GFAP[146]	Spastic ataxia[147]	Usually presenting with infantile onset megalencephaly, (pseudo)bulbar signs, spasticity, cognitive deficits, developmental delay, white matter changes (Alexander disease)	137780	AD	
HSP-*KIF1C*[103] Allelic with autosomal recessive spastic ataxia at the SAX2 locus.	Dystonia, ataxia[103]	See Table 6	611302	AR	SPG58
				AR	SPG35
HSP-*REEP1*[148]	Ataxia[149]	See Table 6	610250	AD	SPG31
NBIA/DYT/PARK[a]-*PLA2G6*[16]	Ataxia[17]	See Table 8	612953	AR	NBIA2, PARK14
HSP/NBIA-*FA2H*[66]	Dystonia, parkinsonism, ataxia[57]	See Table 6	612319	AR	SPG35

AD, autosomal dominant; CPEO, chronic progressive external ophthalmoplegia; GP, globus pallidus; INAD, infantile neuroaxonal dystrophy; NBIA, neurodegeneration with brain iron accumulation; SN, substantia nigra.
[a]Mutations in this gene more commonly cause INAD: developmental delay/regression, hypotonia, spasticity/pyramidal signs, optic nerve atrophy, sensorimotor neuropathy, and seizures.

TABLE 5. The proposed new list of hereditary choreas

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance	Locus symbol
CHOR-*HTT*[151]		Huntington's disease (HD): chorea and dementia, young onset may have predominant parkinsonism (Westphal variant)	143100	AD	None
CHOR-*PRNP*[152]		HD-like phenotype, seizures, dementia (variable)	603218	AD	HDL1
CHOR-*JPH3*[153]		HD-like phenotype To date only found in patients of African descent	606438	AD	HDL2
CHOR-*NKX2*-1[154]		Phenotypes 1. Brain–lung–thyroid syndrome (50%): infantile onset global developmental delay, childhood onset chorea-athetosis, hypothyroidism and pulmonary dysfunction 2. Brain and thyroid disease (30%): infantile onset global developmental delay childhood onset chorea-athetosis, hypothyroidism 3. Isolated benign hereditary chorea (13%)[155]	600635	AD	None
CHOR-*VPS13A*[156,157]		Neuroacanthocytosis[158]: chorea, occasionally parkinsonism, dystonia (feeding dystonia) Additional clinical features: orofacial dyskinesias, seizures, dementia, myopathy, psychiatric symptoms, acanthocytosis (variable), elevated CK, reduced chorein	605978	AR	none
CHOR-*XK*[160]		McLeod syndrome[161]: chorea Additional clinical features: behavioral and psychiatric symptoms, seizures, myopathy, cardiomyopathy, cardiac arrhythmias, neuropathy, acanthocytosis, elevated CK, and liver enzymes, reduced or absent Kx and Kell blood group antigens	314850	X-linked	None
NBIA/CHOREA-*FTL*[54]	Dystonia, Parkinsonism	Neuroferritinopathy[55]: dystonia, chorea, parkinsonism Iron accumulation: GP, caudate, putamen, SN, red nucleus; cystic BG changes—pallidal necrosis Additional clinical features: oromandibular dyskinesia, dysphagia, cognitive impairment, behavioral symptoms, low serum ferritin	606159	AD	NBIA3
Combined phenotypes: where chorea coexists with (an)other movement disorder(s) as a prominent and consistent feature					
CHOR/DYT-*ADCY5*[70]		Facial dyskinesias, occasional myoclonus. May have paroxysmal worsening	600293	AD	None
DYT/CHOR-*HPRT*[71]		See Table 2	300322	X-linked	None
DYT/CHOR-*ACAT1*[72]		See Table 2	607809	AR	None
DYT/CHOR-*GCDH*[74]		See Table 2	231670	AR	None
DYT/CHOR-*MUT*[78]		See Table 2	251000	AR	None
DYT/CHOR-*PCCA/PCCB*[80]		See Table 2	606054	AR	None
Disorders that usually present with other phenotypes but can have predominant chorea					
C9orf72 [163]	Chorea[164]	Chorea, dystonia myoclonus, parkinsonism, cognitive decline in small percentage. More common phenotype: frontotemporal dementia, amyotrophic lateral sclerosis.		AD	None
SCA-*TBP*[136]	Chorea[137]	See Table 4	607136	AD	SCA17, HDL4
SCA-*ATN1*[143]	Chorea[144]	See Table 4	607462	AD	None
NBIA/DYT/PARK-*CP*[42]	Chorea	See Table 8	604290	AR	
NBIA/DYT- *DCAF17*[81]	Chorea[82]	See Table 8	241080	AR	None
NBIA/DYT-*PANK2*[58]	Parkinsonsim,[59] Chorea	See Table 8	234200	AR	NBIA1

AD, autosomal dominant; AR, autosomal recessive; BG, basal ganglia; CK, Creatine Kinase; GM1, gangliosidosis; GP, globus pallidus; NBIA, neurodegeneration with brain iron accumulation; n/a, not available; SN, substantia nigra.

A total of 73 genes and loci have been reported to cause HSP and assigned an SPG (spastic paraplegia) designation to date (Supplementary Table 6).[165,166] A total of 32 HSP-causing genes have been found in only single families and remain unconfirmed (SPG5B, 14, 16, 19, 24, 25, 27, 29, 32, 34, 36, 37, 38, 40, 41, 42, 44, 52, 53, 56, 59, 60, 61, 63, 64, 66, 67, 68, 69, 70, 71, 72). For 17, no gene has been unequivocally identified, and 2 SPG designations refer to the same gene (SPG 45 and SPG65). Thus, according to the revised

TABLE 6. The proposed new list of hereditary spastic paraplegias

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance	Locus Symbol
Autosomal dominant forms					
HSP-*ATL1*[167]		Pure or complex; silver syndrome,[a] allelic with hereditary sensory neuropathy type 1, cerebral palsy (infantile onset)	182600	AD/AR	SPG3A
HSP-*SPAST*[168]		Pure or complex; dementia, epilepsy, Peripheral neuropathy, tremor, ataxia, TCC, cerebellar atrophy	182601	AD	SPG4
HSP-*NIPA1*[169]		Pure or complex; peripheral neuropathy, spinal cord atrophy, spastic dysarthria, facial dystonia, atrophy of the small hand muscles, upper limb spasticity, epilepsy	600363	AD	SPG6
HSP-*KIAA0196*[170]		Pure spastic paraplegia	603563	AD	SPG8
HSP-*KIF5A*[171]		Pure or complex; allelic to Charcot Marie Tooth neuropathy type 2, silver syndrome, mental retardation, parkinsonism, deafness, retinitis, dysautonomia, sensory spinal cord-like syndrome	604187	AD	SPG10
HSP-*RTN2*[172]		Pure spastic paraplegia	604805	AD	SPG12
HSP-*HSPD1*[173]		Pure or complex; dystonia	605280	AD	SPG13
HSP-*BSCL2*[174]		Complex; silver syndrome, these mutations may also cause distal hereditary neuropathy type 5	270685	AD	SPG17
HSP-*REEP1*[148]	Ataxia[149]	Pure or complex; distal motor neuronopathy, axonal peripheral neuropathy, silver-like syndrome, cerebellar ataxia, tremor, dementia	610250	AD	SPG31
HSP-*ZFYV327*[175]		Pure spastic paraplegia	610244	AD	SPG33
SCA/HSP-*VAMP1*[145]		See Table 4	108600	AD	SPAX1
Autosomal recessive forms					
HSP-*CYP7B1*[176]		Pure or complex; white matter lesions, optic atrophy, cerebellar ataxia, sensory ataxia	270800	AR	SPG5A
HSP-*SPG7*[177]		Pure or complex; optic atrophy, cerebellar atrophy, dysarthria, dysphagia, TCC, CPEO-like phenotype, mitochondrial abnormalities on muscle biopsy	607249	AR/AD[c]	SPG7
HSP-*KIAA1840*[48]	Parkinsonism[49]	Pure or complex; may cause Kjellin syndrome[b]; TCC, mental retardation, sensory neuropathy, amyotrophy, dysarthria, nystagmus, ataxia, maculopathy, white matter lesions. Occasional parkinsonism	640360	AR	SPG11
HSP-*ZFYVE26*[50]	Parkinsonism[49]	Complex; Kjellin syndrome. TCC, WMLs, mental retardation, dysarthria, pigmentary maculopathy, peripheral neuropathy, distal amyotrophy. Occasional parkinsonism[51]	270700	AR	SPG15
HSP-*ERLIN2*[178]		Complex; intellectual decline, speech involvement, seizures, congenital hip dislocation	611225	AR	SPG18
HSP-*SPARTIN*[179]		Complex; Troyer-syndrome. Early onset dysarthria, distal muscle wasting with contractures and cerebellar signs in some. Delayed cognition and dysmorphism	275900	AR	SPG20
HSP-*ACP33*[180]		Pure or complex; Mast syndrome, dementia, cerebellar involvement, dyskinesias, athetoid movements, TCC, white matter lesions	248900	AR	SPG21
HSP-*B4GALNT*[181]		Complex; progressive dysarthria, distal amyotrophy, nonprogressive cognitive impairment, cerebellar signs, sensory polyneuropathy, pes cavus, stereotypies, emotional lability, psychiatric illness, seizures	609195	AR	SPG26
HSP-*DDHD1*[182]		Pure and complex; cerebellar oculomotor disturbance, peripheral neuropathy	609340	AR	SPG28
HSP-*KIF1A*[183]		Pure or complex; cerebellar signs, PNP, allelic to hereditary sensory and autonomic neuropathy.	610347	AR	SPG30
HSP/NBIA-*FA2H*[56]	Dystonia, parkinsonism, ataxia[57]	Fatty acid hydroxylase-associated neurodegeneration (FAHN)[57] Iron accumulation: GP (more subtle than other NBIAs) Additional clinical features: spastic tetraparesis, cognitive decline, cerebellar and brainstem atrophy, dysarthria, dysphagia, optic nerve atrophy, seizures	612319	AR	SPG35

(Continued)

TABLE 6. *Continued*

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance	Locus Symbol
HSP-*PNPLA6/NT*[184]		Complex; axonal peripheral neuropathy, spinal cord atrophy, learning disability, speech impairment, cerebellar signs, allelic with Boucher-Neuhäuser and Gordon Holmes syndromes	612020	AR	SPG39
NBIA/HSP-*C19orf12*[60]	Dystonia, parkinsonism	See Table 8	614298	AR	NBIA4/SPG43
HSP-*NT5C2*[185]		Complex; mental retardation, ocular signs	613162	AR	SPG45
HSP-*GBA2*[186]		Complex; mental impairment, cataract, hypogonadism in males, TCC, and cerebellar atrophy on brain imaging[186]	614409	AR	SPG46
HSP-*AP4B*[187]		Complex; intellectual disability, seizures, TCC, white matter lesions	614066	AR	SPG47
HSP-*KIAA0415*[188]		Pure or complex; cervical cord hyperintensities	613647	AR	SPG48
HSP-*TECPR2*[189]		Complex; severe intellectual disability, fluctuating central hypoventilation, gastresophageal reflux disease, awake apnea, areflexia, dysmorphic features	615031	AR	SPG49
HSP-*APAM1*[190]		Complex; cerebral palsy, intellectual disability, reduction of cerebral white matter, and atrophy of the cerebellum	612936	AR	SPG50
HSP-*AP4E1*[191]		Complex; cerebral palsy, intellectual disability, and microcephaly	613744	AR	SPG51
HSP-*DDHD2*[192]		Complex; mental retardation, dysmorphism, short stature, and dysgenesis of the corpus callosum[193]	615033	AR	SPG54
HSP-*C12orf65*[194]		Complex; optic atrophy, peripheral neuropathy	615035	AR	SPG55
HSP-*KIF1C*[103] Allelic with autosomal recessive spastic ataxia at the SAX2 locus.	Dystonia, Ataxia[103]	Pure and complicated, chorea, myoclonus, dysarthria, developmental delay, mild mental retardation, hypodontia, ptosis, short stature, sensorineural deafness, pes planus, white matter lesions	611302	AR	SPG58
HSP-*ERLIN1*[185]		Pure and complex; thoracic kyphosis, borderline intelligence GeneReviews n/a	611604	AR	SPG62
HSP-*NT5C2*[185]		Complex; learning disability, optic atrophy, squint, glaucoma, congenital cataract, TCC, white matter lesions, cystic occipital leukomalacia	613162	AR	SPG65
HSP-*ALSIN*[195]		Complex, generalized dystonia, no speech GeneReviews OMIM		AR	Alsin
HSP-*SACSIN*[196]		Spastic ataxia GeneReviews OMIM		AR	SACS
HSP-*ALDH3A2*[197]		RM, ichtyosis, macular dystrophy, leukoencephalopathy GeneReviews OMIM		AR	Sjögren-Larsson syndrome
HSP-*BICD2*[198]		SMA like GeneReviews OMIM		AR	
X-linked recessive					
HSP-*L1CAM*[199]		Complex; MASA-syndrome, hydrocephalus, TCC	312920	XR	SPG1
HSP-*PLP1*[200] Allelic with Pelizaeus-Merzbacher disease.		Pure or complex; optic atrophy, ataxia, nystagmus, peripheral neuropathy, aphasia, mental retardation	312920	XR	SPG2
HSP-*SLC16A2*[201]		Complex; Allan-Herndon-Dudley syndrome	300523	XR	SPG22
Disorders that usually present with other phenotypes but can have predominant spastic paraparesis					
SCA-*ATXN1*	HSP[202]	See Table 4	164400	AD	SCA1
SCA-*ATXN3*	HSP, Dystonia[101,102]	See Table 4		AD	SCA3
DYT[d]-*TUBB4A*[97]	HSP[98,99]	See Table 2	128101	AD	TUBB4A

AD, autosomal dominant; AR, Autosomal recessive; CPEO, chronic external ophthalmoplegia; GP, globus pallidus; HSP, hereditary spastic paraplegia; MASA, Mental retardation, aphasia, shuffling gait and adductor thumbs syndrome; NBIA, neurodegeneration with brain iron accumulation; PNP, Peripheral neuropathy; SACS, spastic ataxia of Charlevoix-Saguenay; SMA, spinal muscular atrophy; SN, substantia nigra; TCC, thinning of the corpus callosum; WML, White matter lesions; XR, X-linked recessive.

[a]Silver syndrome: complex HSP involving amyotrophy of the hand muscles.

[b]Kjellin syndrome: complex HSP including thinning of the corpus callosum and central retinal degeneration.

[c]Note that some studies have suggested that some SPG7 mutations may have an autosomal dominant effect, particularly autosomal dominant optic atrophy.

[d]Mutations in this gene more commonly cause a hypomyelinating leukodystrophy with developmental delay, dystonia,choreoathetosis, rigidity, opisthotonus, andoculogyric crises, progressive spastic tetraplegia, ataxia, and, more rarely, seizures.

TABLE 7. The proposed new list of primary familial brain calcification

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance	Locus symbol
PFBC-*SLC20A2*[205]		Mixed movement disorders: dystonia, parkinsonism,[206-208] cognitive dysfunction	213600	AD	IBGC3, IBGC1
PFBC-*PDGFRB*[209]		Mixed movement disorders, parkinsonism may predominate,[210] cognitive dysfunction	615007	AD	IBGC4
PFBC-*PDGFB*[211]		Various movement disorders, dystonia may predominate,[211,212] cognitive dysfunction, migraine	615483	AD	IBGC5
PFBC-*XPR1*[213]		Heterogeneous, mixed movements disorders, often asymptomatic GeneReviews n/a	616413	AD	–

n/a, not available.

system, there are only 40 confirmed monogenic forms of hereditary spastic paraplegia. Three are transmitted following an X-linked recessive trait, 27 are autosomal recessive (AR) and 10 are autosomal dominant (AD). Given that most patients with HSP have common clinical features of spasticity and most have additional features, the spastic paraplegias are most easily classified according to mode of inheritance. We recommend the prefix HSP (and not SPG) to recognize the role of inheritance in this group of disorders. A revised classification system is outlined in Table 6.

Primary Familial Brain Calcification

Primary familial brain calcification (PFBC) refers to genetically determined calcification of various brain structures, notably but not exclusively the basal ganglia, in the absence of a known metabolic, toxic, infectious, or traumatic etiology. This condition can be associated with various neurological symptoms, frequently movement disorders, including parkinsonism, dystonia, chorea, ataxia, and tremor. Other neurological and psychiatric symptoms and signs are also common. Locus symbols for this condition use the acronym IBGC (idiopathic basal ganglia calcification), and IBGC1 through 5 have been assigned. IBGC1 and 3 refer to the same gene, and 3 other genes have since been confirmed, 1 with no previous locus symbol assigned. PFBC is a term that recognizes that the calcification can often extend well beyond the basal ganglia to involve the dentate nucleus, cerebellar gyri, brain stem, centrum semiovale, and subcortical white matter and recognizes the genetic etiology of the familial forms. Thus, we propose the prefix PFBC, consistent with the nomenclature recently used by others.[203] Table 7 shows the proposed new list of genetically determined primary familial brain calcification disorders. In this list we have not included the disorder of progressive encephalopathy and spastic tetraplegia due to mutations in the *TREX1* gene nor polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) due to mutations in the *TREM2* gene, despite the fact that they are associated with brain calcification.[204] This is because movement disorders have not been reported to predominate in any of the reported cases. We have refrained from assigning movement disorder prefixes or even from assigning less common movement disorder phenotypes to these conditions because they present in such a multifaceted way from a general neurological and movement disorder perspective.

Neurodegeneration With Brain Iron Accumulation

Neurodegeneration with brain iron accumulation (NBIA) characterizes a number of progressive neurological disorders with the hallmark of iron deposition on MRI in several brain regions, most consistently the globus pallidus.[214] Most of these are genetically determined although some patients, particularly with neurological symptoms beginning in mid to late adult life, have sporadic disorders of uncertain origin. Movement disorders, particularly dystonia and parkinsonism, dominate the clinical manifestations, but other common features include spasticity, ataxia, cognitive and psychiatric disturbances, and oculomotor abnormalities, optic nerve, retinal, and peripheral nerve involvement.

To date NBIA as a locus symbol (ie, numerical designation) has only been applied to 5 disorders. However, up to 9 distinct genetic disorders have been included under the NBIA umbrella term. Other disorders in this group have either retained the original disease name (eg, aceruloplasminenemia, neuroferritinopathy) or, for more recently described disorders, been labelled with an acronym combining the name of the causative protein with "Associated Neurodegeneration" (ie, PKAN for pantothenate kinase associated neurodegeneration). In Supplementary Table 8, we provide a listing of all disorders that have been included under the umbrella NBIA classification.[215] Table 8 provides a new designation for

TABLE 8. The proposed new list of neurodegeneration with brain iron accumulation

New designation	Less common movement phenotype	Clinical clues	OMIM	Inheritance	Locus symbol
NBIA/DYT-*PANK2*[58]	Parkinsonism,[59] Chorea	Pantothenate kinase-associated neurodegeneration (PKAN) Iron accumulation: GP—eye of the tiger sign Additional clinical features: spasticity, dysarthria, cognitive decline, gaze palsy, psychiatric symptoms, pigmentary retinopathy	234200	AR	NBIA1
NBIA/DYT/PARK[a]-*PLA2G6*[86]	Ataxia[17]	*PLA2G6*-associated neurodegeneration (PLAN): dystonia, parkinsonism, cognitive decline, pyramidal signs, psychiatric symptoms (adult phenotype), ataxia (childhood phenotype) Iron accumulation: GP, SN in some; adults may have striatal involvement; about half of INAD and the majority of adult-onset cases lack brain iron accumulation on MRI	612953	AR	NBIA2, PARK14
NBIA/DYT/PARK-*CP*[42]	Chorea[43]	Aceruloplasminemia: dystonia, ataxia, chorea, parkinsonism, tremors Iron accumulation: more homogeneous involvement of primarily, caudate, putamen, thalamus, dentate Additional clinical features: cognitive impairment, psychiatric symptoms, diabetes mellitus, retinal degeneration, anemia, liver iron storage	604290	AR	
NBIA/CHOREA-*FTL*[54]	Dystonia, parkinsonism[216]	Neuroferritinopathy[55]: dystonia, chorea, parkinsonism Iron accumulation: GP, caudate, putamen, SN, red nucleus; cystic BG changes—pallidal and putaminal necrosis Additional clinical features: oromandibular dyskinesia, dysphagia, cognitive impairment, behavioral symptoms, low serum ferritin	606159	AD	NBIA3
NBIA/PARK-*WDR45*[40]	Dystonia[41]	Beta-propeller protein-associated neurodegeneration (BPAN, previously SENDA syndrome) Iron accumulation: SN > GP Halo of hyperintensity surrounding linear hypointensity in SN on T1 scans Additional clinical features: developmental delay/intellectual disability, progressive cognitive decline, seizures, spasticity, Rett-like stereotypies, autistic-features, neuropsychiatric symptoms, sleep disorders, bowel/bladder incontinence, infantile epileptic encephalopathy	300894	X-linked	NBIA5
NBIA/DYT-*DCAF17*[81]	Chorea[82]	Woodhouse-Sakati syndrome Iron accumulation: GP, SN, other BG (variable) Additional clinical features: dysarthria, deafness, seizures, cognitive impairment, hypogonadism, alopecia, diabetes mellitus, thyroid dysfunction, acanthosis nigrans, keratoconus, camptodactyly	241080	AR	None
Members of other lists that have brain iron accumulation as a consistent feature					
HSP/NBIA-*FA2H*[56]	Dystonia, parkinsonism, ataxia[57]	See Table 6	612319	AR	SPG35
NBIA/HSP-*C19orf12*[60] (MPAN)	Dystonia, parkinsonism[217]	Mitochondrial membrane protein-associated neurodegeneration (MPAN)[61]: dystonia, parkinsonism Iron accumulation: GP—isointense streaking of medial medullary lamina between GPi and GPe; SN Additional clinical features: progressive spastic paresis, dysarthria, dysphagia, cognitive decline/dementia, motor axonal neuropathy, optic nerve atrophy, psychiatric symptoms, bowel/bladder incontinence	615043	AR	NBIA4, SPG43
Members of other lists that occasionally have brain iron accumulation on imaging as a feature					
PARK- *ATP13A2*[15]		See Table 1	606693	AR	PARK9

AD: autosomal dominant; BG, basal ganglia; GP, globus pallidus; INAD, infantile neuroaxonal dystrophy; NBIA, neurodegeneration with brain iron accumulation; n/a, not available; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SN, substantia nigra.
[a]Mutations in this gene more commonly cause INAD: developmental delay/regression, hypotonia, spasticity/pyramidal signs, optic nerve atrophy, sensorimotor neuropathy, and seizures.

each of these. Those that present consistently with one or more specific movement disorder phenotypes have been assigned a combined prefix (eg, NBIA/DYT) and are included in the list specific to that movement disorder.

Discussion

Challenges

We present a new system of nomenclature for genetically determined movement disorders that attempts to

address many of the problems that have developed with the previous system. In doing so, we have tried to develop a system that is logical, consistent, flexible to change, and comprehensive. In our desire to be comprehensive, we have included a number of childhood-onset metabolic disorders that have heretofore been left out of the locus symbol naming system. Including them will hopefully serve to increase awareness on the part of clinicians in adult medicine of disorders that can affect adults that transition from pediatric care and even occasionally present in young adulthood. We realize, however, several challenges. First, it is impossible for us to be truly comprehensive by including all genetically determined disorders that can, unusually, at some point in the course, manifest predominantly as a movement disorder. We have tried to minimize errors or nonreproducible observations by requiring that a predominant movement disorder phenotype be reported by at least 2 groups independently. This system is bound to be associated with some misclassification, however, because many valid observations may not be reported a second time. Ethnic variation in phenotype associated with a given genetic mutation can also lead to controversy regarding the most appropriate prefix to assign or even membership on a list. Second, we are conscious of the fact that knowledge of the phenotypic spectrum of these disorders will continuously evolve, and it will be necessary to change designations over time. By avoiding a sequential nomenclature (eg, numbers) we hope that this will be an easier process than it has been in the past. The need to incorporate new knowledge also implies that individuals will need to be dedicated to maintaining the lists indefinitely—we anticipate that this task will fall to the MDS's Genetic Nomenclature Task Force. Third, we are also aware of the fact that many of the disorders listed in these tables have well-known names that will continue to be used no matter how logical our new system may be. It is not our intent, for example, to advocate that Wilson disease hereafter be referred to as DYT-*ATP7B*. However, the new symbol will serve to link the *ATP7B* gene to the phenotype of dystonia; cross-referencing to other lists will acknowledge the combined movement disorders that are often a part of this disorder, and placing DYT-*ATP7B* on these lists will provide a more complete genetic differential diagnosis to clinicians faced with a particular phenotype than has been available in the past. Fourth, by attempting to avoid erroneous assignment of causative mutations we have raised the challenge of establishing criteria that will minimize false positive associations. One must be very cautious about the nature of variants found in a given gene because, with the exception of truncating or recurrent mutations or repeat expansions, the pathogenicity of a new and putatively disease-causing variant is usually difficult to establish. There are currently no error-proof criteria for establishing pathogenicity, and the system will have to be monitored for erroneous entries as new data become available.

Next Steps

Our work is not yet complete; lists need to be compiled for x-linked, recessively inherited, and congenital ataxias and for genetic causes of myoclonus. These will be taken on as the next project of the task force and involve additional experts. In addition, it would be useful to incorporate into the classification the underlying type of mutation to inform genetic counseling issues such as instability during transmission (repeat expansion disorders), heterozygous risk assessment (eg, mutations of SPG7 or Parkin) and reduced penetrance (all dominant forms of inherited movements disorders) or imprinting (eg, DYT-*SGCE*).

As mentioned previously, a formal mechanism for incorporating new knowledge into the naming system needs to be established and should include input from both clinicians and geneticists. The next project of the task force will be to establish these mechanisms.

In the process of developing these lists it became clear that there is no standard for the field as to what we consider disease causing versus risk conferring. This is important because one of the underlying principles of our naming system has been to restrict the lists to genes that are disease causing and not include genetic risk factors. Such a standard would be helpful for communication and should be a task taken on by an expert panel. Once accepted definitions are in place, there may be changes to our lists.

Finally, this system can be easily applied to other neurological disorders, and we encourage leaders in other medical fields to consider adopting a similar system and avoid many of the problems that have beset the field of genetics in movement disorders.

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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. Lill CM, Roehr JT, McQueen MB, et al. Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: The PDGene database. PLOS Genet 2012;8(3): e1002548.
4. Nalls MA, Pankratz N, Lill CM, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet 2014;46(9):989-993.
5. MacArthur DG, Manolio TA, Dimmock DP, et al. Guidelines for investigating causality of sequence variants in human disease. Nature 2014;508:469-476.
6. Bonifati V. Genetics of Parkinson's disease—state of the art, 2013. Parkinsonism Relat Disord 2014;20(suppl 1):S23-S28.
7. Trinh J, Farrer M. Advances in the genetics of Parkinson disease. Nat Rev Neurol 2013;9(8):445-454.
8. Alcalay RN, Dinur T, Quinn T, et al. Comparison of Parkinson risk in Ashkenazi Jewish patients with Gaucher disease and GBA heterozygotes. JAMA Neurol 2014;71(6):752-757.
9. Golbe LI, Di Iorio G, Bonavita V, Miller DC, Duvoisin RC. A large kindred with autosomal dominant Parkinson's disease. Ann Neurol 1990;27(3):276-282.
10. Paisan-Ruiz C, Jain S, Evans EW, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 2004;44(4):595-600.
11. Vilarino-Guell C, Wider C, Ross OA, et al. VPS35 mutations in Parkinson disease. Am J Hum Genet 2011;89(1):162-167.
12. Kitada T, Asakawa S, Hattori N, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 1998;392(6676):605-608.
13. Valente EM, Abou-Sleiman PM, Caputo V, et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science 2004;304(5674):1158-1160.
14. van Duijn CM, Dekker MC, Bonifati V, et al. Park7, a novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. Am J Hum Genet 2001;69(3):629-634.
15. Ramirez A, Heimbach A, Grundemann J, et al. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat Genet 2006; 38(10):1184-1191.
16. Paisan-Ruiz C, Bhatia KP, Li A, et al. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann Neurol 2009; 65(1):19-23.
17. Illingworth MA, Meyer E, Chong WK, et al. PLA2G6-associated neurodegeneration (PLAN): further expansion of the clinical, radiological and mutation spectrum associated with infantile and atypical childhood-onset disease. Mol Genet Metab 2014;112(2):183-189.
18. Shojaee S, Sina F, Banihosseini SS, et al. Genome-wide linkage analysis of a Parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays. Am J Hum Genet 2008;82(6):1375-1384.
19. Edvardson S, Cinnamon Y, Ta-Shma A, et al. A deleterious mutation in DNAJC6 encoding the neuronal-specific clathrin-uncoating co-chaperone auxilin, is associated with juvenile parkinsonism. PLOS ONE 2012;7(5):e36458.
20. Krebs CE, Karkheiran S, Powell JC, et al. The Sac1 domain of SYNJ1 identified mutated in a family with early-onset progressive Parkinsonism with generalized seizures. Hum Mutat 2013;34(9): 1200-1207.
21. Quadri M, Fang M, Picillo M, et al. Mutation in the SYNJ1 gene associated with autosomal recessive, early-onset parkinsonism. Hum Mutat 2013;34(9):1208-1215.
22. de Carvalho Aguiar P, Sweadner KJ, Penniston JT, et al. Mutations in the Na+/K + -ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. Neuron 2004;43(2):169-175.
23. Makino S, Kaji R, Ando S, et al. Reduced neuron-specific expression of the TAF1 gene is associated with X-linked dystonia-parkinsonism. Am J Hum Genet 2007;80(3):393-406.
24. Ichinose H, Ohye T, Takahashi E, et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nat Genet 1994;8(3):236-242.
25. Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). Ann Neurol 2003;54(suppl 6):S32-S45.
26. Horvath GA, Stockler-Ipsiroglu SG, Salvarinova-Zivkovic R, et al. Autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia: evidence of a phenotypic continuum between dominant and recessive forms. Mol Genet Metab 2008; 94(1):127-131.
27. Opladen T, Hoffmann G, Horster F, et al. Clinical and biochemical characterization of patients with early infantile onset of autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia. Mov Disord 2011;26(1):157-161.
28. Ludecke B, Dworniczak B, Bartholome K. A point mutation in the tyrosine hydroxylase gene associated with Segawa's syndrome. Hum Genet 1995;95(1):123-125.
29. Furukawa Y, Kish S. Tyrosine hydroxylase deficiency. In: Pagon RA, Adam MP, Ardinger HH et al., eds. GeneReviews. Seattle, WA: University of Washington, 1993-2015. 2008 Feb 8 [updated 2014 Jul 17].
30. Bonafe L, Thony B, Penzien JM, Czarnecki B, Blau N. Mutations in the sepiapterin reductase gene cause a novel tetrahydrobiopterin-dependent monoamine-neurotransmitter deficiency without hyperphenylalaninemia. Am J Hum Genet 2001;69(2):269-277.
31. Friedman J, Roze E, Abdenur JE, et al. Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy. Ann Neurol 2012; 71(4):520-530.
32. Opladen T, Hoffmann GF, Blau N. An international survey of patients with tetrahydrobiopterin deficiencies presenting with hyperphenylalaninaemia. J Inherit Metab Dis 2012;35(6):963-973.
33. Kurian MA, Li Y, Zhen J, et al. Clinical and molecular characterisation of hereditary dopamine transporter deficiency syndrome: an observational cohort and experimental study. Lancet Neurol 2011;10(1):54-62.
34. Ng J, Zhen J, Meyer E, et al. Dopamine transporter deficiency syndrome: phenotypic spectrum from infancy to adulthood. Brain 2014;137(Pt 4):1107-1119.
35. Sedel F, Saudubray JM, Roze E, Agid Y, Vidailhet M. Movement disorders and inborn errors of metabolism in adults: a diagnostic approach. J Inherit Metab Dis 2008;31(3):308-318.
36. Tuschl K, Clayton PT, Gospe SM Jr, et al. Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a manganese transporter in man. Am J Hum Genet 2012;90(3):457-466.
37. Tuschl K, Clayton PT, Gospe SM, Mills PB. Dystonia/parkinsonism, hypermanganesemia, polycythemia, and chronic liver disease. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews. Seattle, WA: University of Washington, 1993–2015. 2012 Aug 30 [updated 2014 Sep 11].
38. Muthane U, Chickabasaviah Y, Kaneski C, et al. Clinical features of adult GM1 gangliosidosis: report of three Indian patients and review of 40 cases. Mov Disord 2004;19(11):1334-1341.
39. Roze E, Paschke E, Lopez N, et al. Dystonia and parkinsonism in GM1 type 3 gangliosidosis. Mov Disord 2005;20(10): 1366-1369.
40. Haack TB, Hogarth P, Kruer MC, et al. Exome sequencing reveals de novo WDR45 mutations causing a phenotypically distinct, X-linked dominant form of NBIA. Am J Hum Genet 2012; 91(6):1144-1149.
41. Hayflick SJ, Kruer MC, Gregory A, et al. beta-Propeller protein-associated neurodegeneration: a new X-linked dominant disorder with brain iron accumulation. Brain 2013;136(Pt 6): 1708-1717.
42. Harris ZL, Takahashi Y, Miyajima H, Serizawa M, MacGillivray RT, Gitlin JD. Aceruloplasminemia: molecular characterization of this disorder of iron metabolism. Proc Natl Acad Sci U S A 1995; 92(7):2539-2543.
43. McNeill A, Pandolfo M, Kuhn J, Shang H, Miyajima H. The neurological presentation of ceruloplasmin gene mutations. Eur Neurol 2008;60(4):200-205.
44. Tsuji S, Choudary PV, Martin BM, et al. A mutation in the human glucocerebrosidase gene in neuronopathic Gaucher's disease. N Eng J Med 1987;316(10):570-575.
45. Tayebi N, Walker J, Stubblefield B, et al. Gaucher disease with parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? Mol Genet Metab 2003;79(2):104-109.
46. Pulst SM, Nechiporuk A, Nechiporuk T, et al. Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nat Genet 1996;14(3):269-276.

47. Shan DE, Soong BW, Sun CM, Lee SJ, Liao KK, Liu RS. Spinocerebellar ataxia type 2 presenting as familial levodopa-responsive parkinsonism. Ann Neurol 2001;50(6):812-815.
48. Stevanin G, Paternotte C, Coutinho P, et al. A new locus for autosomal recessive spastic paraplegia (SPG32) on chromosome 14q12-q21. Neurology 2007;68(21):1837-1840.
49. Renvoise B, Chang J, Singh R, et al. Lysosomal abnormalities in hereditary spastic paraplegia types SPG15 and SPG11. Ann Clin Trans Neurol 2014;1(6):379-389.
50. Hanein S, Martin E, Boukhris A, et al. Identification of the SPG15 gene, encoding spastizin, as a frequent cause of complicated autosomal-recessive spastic paraplegia, including Kjellin syndrome. Am J Hum Genet 2008;82(4):992-1002.
51. Schicks J, Synofzik M, Pétursson H, et al. Atypical juvenile parkinsonism in a consanguineous *SPG15* family. Mov Disord 2011; 26(3):564–566.
52. 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.
53. 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 Prac 2015;2(3):304-307.
54. Curtis AR, Fey C, Morris CM, et al. Mutation in the gene encoding ferritin light polypeptide causes dominant adult-onset basal ganglia disease. Nat Genet 2001;28(4):350-354.
55. Chinnery PF, Crompton DE, Birchall D, et al. Clinical features and natural history of neuroferritinopathy caused by the FTL1 460InsA mutation. Brain 2007;130(Pt 1):110-119.
56. Edvardson S, Hama H, Shaag A, et al. Mutations in the fatty acid 2-hydroxylase gene are associated with leukodystrophy with spastic paraparesis and dystonia. Am J Hum Genet 2008;83(5): 643-648.
57. Kruer MC, Paisan-Ruiz C, Boddaert N, et al. Defective FA2H leads to a novel form of neurodegeneration with brain iron accumulation (NBIA). Ann Neurol 2010;68(5):611-618.
58. Zhou B, Westaway SK, Levinson B, Johnson MA, Gitschier J, Hayflick SJ. A novel pantothenate kinase gene (PANK2) is defective in Hallervorden-Spatz syndrome. Nat Genet 2001;28(4):345-349.
59. Mak CM, Sheng B, Lee HH, et al. Young-onset parkinsonism in a Hong Kong Chinese man with adult-onset Hallervorden-Spatz syndrome. Int J Neurosci 2011;121(4):224-227.
60. Hartig MB, Iuso A, Haack T, et al. Absence of an orphan mitochondrial protein, c19orf12, causes a distinct clinical subtype of neurodegeneration with brain iron accumulation. Am J Hum Genet 2011;89(4):543-550.
61. Hogarth P, Gregory A, Kruer MC, et al. New NBIA subtype: genetic, clinical, pathologic, and radiographic features of MPAN. Neurology 2013;80(3):268-275.
62. Klein C. Genetics in dystonia. Parkinsonism Relat Disord 2014; 20(suppl 1):S137-S142.
63. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013; 28(7):863-873.
64. Ozelius LJ, Hewett JW, Page CE, et al. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet 1997;17(1):40-48.
65. Fuchs T, Gavarini S, Saunders-Pullman R, et al. Mutations in the THAP1 gene are responsible for DYT6 primary torsion dystonia. Nat Genet 2009;41(3):286-288.
66. Fuchs T, Saunders-Pullman R, Masuho I, et al. Mutations in GNAL cause primary torsion dystonia. Nat Genet 2013;45(1):88-92.
67. Camargos S, Scholz S, Simon-Sanchez J, et al. DYT16, a novel young-onset dystonia-parkinsonism disorder: identification of a segregating mutation in the stress-response protein PRKRA. Lancet Neurol 2008;7(3):207-215.
68. Tadic V, Kasten M, Bruggemann N, Stiller S, Hagenah J, Klein C. Dopa-responsive dystonia revisited: diagnostic delay, residual signs, and nonmotor signs. Arch Neurol 2012;69(12):1558-1562.
69. Zimprich A, Grabowski M, Asmus F, et al. Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. Nat Genet 2001;29(1):66-69.
70. 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.
71. Gibbs RA, Caskey CT. Identification and localization of mutations at the Lesch-Nyhan locus by ribonuclease A cleavage. Science 1987;236(4799):303-305.
72. Fukao T, Scriver CR, Kondo N. The clinical phenotype and outcome of mitochondrial acetoacetyl-CoA thiolase deficiency (beta-ketothiolase or T2 deficiency) in 26 enzymatically proved and mutation-defined patients. Mol Genet Metab 2001;72(2):109-114.
73. Mitchell GA. Inborn errors of ketone body metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill, 2001:2327–2356.
74. Biery BJ, Stein DE, Morton DH, Goodman SI. Gene structure and mutations of glutaryl-coenzyme A dehydrogenase: impaired association of enzyme subunits that is due to an A421V substitution causes glutaric acidemia type I in the Amish. Am J Hum Genet 1996;59(5):1006-1011.
75. Gitiaux C, Roze E, Kinugawa K, et al. Spectrum of movement disorders associated with glutaric aciduria type 1: a study of 16 patients. Mov Disord 2008;23(16):2392-2397.
76. Harting I, Neumaier-Probst E, Seitz A, et al. Dynamic changes of striatal and extrastriatal abnormalities in glutaric aciduria type I. Brain 2009;132(Pt 7):1764-1782.
77. Kolker S, Christensen E, Leonard JV, et al. Diagnosis and management of glutaric aciduria type I—revised recommendations. J Inherit Metab Dis 2011;34(3):677-694.
78. Jansen R, Ledley FD. Heterozygous mutations at the mut locus in fibroblasts with mut0 methylmalonic acidemia identified by polymerase-chain-reaction cDNA cloning. Am J Hum Genet 1990;47(5):808-814.
79. Kolker S, Valayannopoulos V, Burlina AB, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: the evolving clinical phenotype. J Inherit Metab Dis 2015;38(6): 1059-1074.
80. Richard E, Desviat LR, Perez B, Perez-Cerda C, Ugarte M. Three novel splice mutations in the PCCA gene causing identical exon skipping in propionic acidemia patients. Hum Genet 1997;101(1):93-96.
81. Alazami AM, Al-Saif A, Al-Semari A, et al. Mutations in C2orf37, encoding a nucleolar protein, cause hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal syndrome. Am J Hum Genet 2008;83(6):684-691.
82. Al-Semari A, Bohlega S. Autosomal-recessive syndrome with alopecia, hypogonadism, progressive extra-pyramidal disorder, white matter disease, sensory neural deafness, diabetes mellitus, and low IGF1. Am J Med Genet A 2007;143A(2):149-160.
83. Schneider SA, Bhatia KP. Dystonia in the Woodhouse Sakati syndrome: A new family and literature review. Mov Disord 2008; 23(4):592-596.
84. Chang YT, Mues G, McPherson JD, et al. Mutations in the human aromatic L-amino acid decarboxylase gene [abstract]. J Inherit Metab Dis 1998;21(Suppl 2):4.
85. Brun L, Ngu LH, Keng WT, et al. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. Neurology 2010;75(1):64-71.
86. Morgan NV, Westaway SK, Morton JE, et al. PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. Nat Genet 2006;38(7):752-754.
87. Bull PC, Thomas GR, Rommens JM, Forbes JR, Cox DW. The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. Nat Genet 1993;5(4):327-337.
88. Zeng WQ, Al-Yamani E, Acierno JS Jr, et al. Biotin-responsive basal ganglia disease maps to 2q36.3 and is due to mutations in SLC19A3. Am J Hum Genet 2005;77(1):16-26.
89. Serrano M, Rebollo M, Depienne C, et al. Reversible generalized dystonia and encephalopathy from thiamine transporter 2 deficiency. Mov Disord 2012;27(10):1295-1298.
90. Tabarki B, Al-Hashem A, Alfadhel M. Biotin-thiamine-responsive basal ganglia disease. In: Pagon RA, Adam MP, Ardinger HH,

et al., eds. GeneReviews. Seattle, WA: University of Washington, 1993–2015. 2013 Nov 21.

91. Tranebjaerg L, Hamel BC, Gabreels FJ, Renier WO, Van Ghelue M. A de novo missense mutation in a critical domain of the X-linked DDP gene causes the typical deafness-dystonia-optic atrophy syndrome. Eur J Human Genet 2000;8(6):464-467.
92. Ha AD, Parratt KL, Rendtorff ND, et al. The phenotypic spectrum of dystonia in Mohr-Tranebjaerg syndrome. Mov Disord 2012;27(8):1034-1040.
93. Kim IS, Ki CS, Park KJ. Pediatric-onset dystonia associated with bilateral striatal necrosis and G14459A mutation in a Korean family: a case report. J Korean Med Sci 2010;25(1):180-184.
94. Carrozzo R, Dionisi-Vici C, Steuerwald U, et al. SUCLA2 mutations are associated with mild methylmalonic aciduria, Leigh-like encephalomyopathy, dystonia and deafness. Brain 2007;130(Pt 3):862-874.
95. Ostergaard E, Hansen FJ, Sorensen N, et al. Mitochondrial encephalomyopathy with elevated methylmalonic acid is caused by SUCLA2 mutations. Brain 2007;130(Pt 3):853-861.
96. Morava E, Steuerwald U, Carrozzo R, et al. Dystonia and deafness due to SUCLA2 defect; Clinical course and biochemical markers in 16 children. Mitochondrion 2009;9(6):438-442.
97. Hersheson J, Mencacci NE, Davis M, et al. Mutations in the autoregulatory domain of beta-tubulin 4a cause hereditary dystonia. Ann Neurol 2013;73(4):546-553.
98. Blumkin L, Halevy A, Ben-Ami-Raichman D, et al. Expansion of the spectrum of TUBB4A-related disorders: a new phenotype associated with a novel mutation in the TUBB4A gene. Neurogenetics 2014;15(2):107-113.
99. Kancheva D, Chamova T, Guergueltcheva V, et al. Mosaic dominant TUBB4A mutation in an inbred family with complicated hereditary spastic paraplegia. Mov Disord 2015;30(6):854-858.
100. Kawaguchi Y, Okamoto T, Taniwaki M, et al. CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nat Genet 1994;8(3):221-228.
101. Munchau A, Dressler D, Bhatia KP, Vogel P, Zuhlke C. Machado-Joseph disease presenting as severe generalised dystonia in a German patient. J Neurol 1999;246(9):840-842.
102. Song Y, Liu Y, Zhang N, Long L. Spinocerebellar ataxia type 3/Machado-Joseph disease manifested as spastic paraplegia: a clinical and genetic study. Exp Ther Med 2015;9(2):417-420.
103. Dor T, Cinnamon Y, Raymond L, et al. KIF1C mutations in two families with hereditary spastic paraparesis and cerebellar dysfunction. J Med Genet 2014;51(2):137-142.
104. Gardiner AR, Bhatia KP, Stamelou M, et al. PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine. Neurology 2012;79(21):2115-2121.
105. Bhatia KP. Paroxysmal dyskinesias. Mov Disord 2011;26(6):1157-1165.
106. Fernandez-Alvarez E, Perez-Duenas B. Paroxysmal movement disorders and episodic ataxias. Handb of Clin Neurol 2013;112:847-852.
107. Jen JC. Hereditary episodic ataxias. Ann N Y Acad Sci 2008;1142:250-253.
108. Chen WJ, Lin Y, Xiong ZQ, et al. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. Nat Genet 2011;43(12):1252-1255.
109. Rainier S, Thomas D, Tokarz D, et al. Myofibrillogenesis regulator 1 gene mutations cause paroxysmal dystonic choreoathetosis. Arch Neurol 2004;61(7):1025-1029.
110. Seidner G, Alvarez MG, Yeh JI, et al. GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier. Nat Genet 1998;18(2):188-191.
111. Brunel-Guitton C, Casey B, Coulter-Mackie M, et al. Late-onset nonketotic hyperglycinemia caused by a novel homozygous missense mutation in the GLDC gene. Mol Genet Metab 2011;103(2):193-196.
112. Browne DL, Gancher ST, Nutt JG, et al. Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. Nat Genet 1994;8(2):136-140.
113. Jodice C, Mantuano E, Veneziano L, et al. Episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6) due to CAG repeat expansion in the CACNA1A gene on chromosome 19p. Hum Mol Genet 1997;6(11):1973-1978.
114. Jen JC, Wan J, Palos TP, Howard BD, Baloh RW. Mutation in the glutamate transporter EAAT1 causes episodic ataxia, hemiplegia, and seizures. Neurology 2005;65(4):529-534.
115. Endo H, Hasegawa K, Narisawa K, Tada K, Kagawa Y, Ohta S. Defective gene in lactic acidosis: abnormal pyruvate dehydrogenase E1 alpha-subunit caused by a frame shift. Am J Hum Genet 1989;44(3):358-364.
116. Castiglioni C, Verrigni D, Okuma C, et al. Pyruvate dehydrogenase deficiency presenting as isolated paroxysmal exercise induced dystonia successfully reversed with thiamine supplementation. Case report and mini-review. Eur J Paediatr Neurol 2015;19(5):497–503.
117. Patel KP, O'Brien TW, Subramony SH, Shuster J, Stacpoole PW. The spectrum of pyruvate dehydrogenase complex deficiency: clinical, biochemical and genetic features in 371 patients. [Republished from Mol Genet Metab. 2012 Jan;105(1):34-43; PMID: 22079328]. Mol Genet Metab 2012;106(3):385-394.
118. Leen WG, Klepper J, Verbeek MM, et al. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. Brain 2010;133(Pt 3):655-670.
119. Verbeek DS, van de Warrenburg BP. The autosomal dominant cerebellar ataxias. Semin Neurol 2011;31:461-469.
120. Van Gaalen J, Giunti P, van de Warrenburg BP. Movement disorders in spinocerebellar ataxias. Mov Disord 2011;26:792-800.
121. Ikeda Y, Dick KA, Weatherspoon MR, et al. Spectrin mutations cause spinocerebellar ataxia type 5. Nat Genet 2006;38(2):184-190.
122. Zhuchenko O, Bailey J, Bonnen P, et al. Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel. Nat Genet 1997;15(1):62-69.
123. Banfi S, Servadio A, Chung MY, et al. Identification and characterization of the gene causing type 1 spinocerebellar ataxia. Nat Genet 1994;7(4):513-520.
124. Bakalkin G, Watanabe H, Jezierska J, et al. Prodynorphin mutations cause the neurodegenerative disorder spinocerebellar ataxia type 23. Am J Hum Genet 2010;87(5):593-603.
125. Koob MD, Moseley ML, Schut LJ, et al. An untranslated CTG expansion causes a novel form of spinocerebellar ataxia (SCA8). Nat Genet 1999;21(4):379-384.
126. Holmes SE, O'Hearn EE, McInnis MG, et al. Expansion of a novel CAG trinucleotide repeat in the 5' region of PPP2R2B is associated with SCA12. Nat Genet 1999;23(4):391-392.
127. Chen DH, Brkanac Z, Verlinde CL, et al. Missense mutations in the regulatory domain of PKC gamma: a new mechanism for dominant nonepisodic cerebellar ataxia. Am J Hum Genet 2003;72(4):839-849.
128. Iwaki A, Kawano Y, Miura S, et al. Heterozygous deletion of ITPR1, but not SUMF1, in spinocerebellar ataxia type 16. J Med Genet 2008;45(1):32-35.
129. van de Leemput J, Chandran J, Knight MA, et al. Deletion at ITPR1 underlies ataxia in mice and spinocerebellar ataxia 15 in humans. PLOS Genet 2007;3(6):e108.
130. Lee YC, Durr A, Majczenko K, et al. Mutations in KCND3 cause spinocerebellar ataxia type 22. Ann Neurol 2012;72(6):859-869.
131. van Swieten JC, Brusse E, de Graaf BM, et al. A mutation in the fibroblast growth factor 14 gene is associated with autosomal dominant cerebellar ataxia [corrected]. Am J Hum Genet 2003;72(1):191-199.
132. Wang JL, Yang X, Xia K, et al. TGM6 identified as a novel causative gene of spinocerebellar ataxias using exome sequencing. Brain 2010;133(Pt 12):3510-3518.
133. Di Gregorio E, Borroni B, Giorgio E, et al. ELOVL5 mutations cause spinocerebellar ataxia 38. Am J Hum Genet 2014;95(2):209-217.
134. Trottier Y, Lutz Y, Stevanin G, et al. Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias. Nature 1995;378(6555):403-406.
135. Matsuura T, Yamagata T, Burgess DL, et al. Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10. Nat Genet 2000;26(2):191-194.
136. Koide R, Kobayashi S, Shimohata T, et al. A neurological disease caused by an expanded CAG trinucleotide repeat in the TATA-binding protein gene: a new polyglutamine disease? Hum Mol Genet 1999;8(11):2047-2053.

137. Schneider SA, van de Warrenburg BP, Hughes TD, et al. Phenotypic homogeneity of the Huntington disease-like presentation in a SCA17 family. Neurology 2006;67(9):1701-1703.

138. Delplanque J, Devos D, Huin V, et al. TMEM240 mutations cause spinocerebellar ataxia 21 with mental retardation and severe cognitive impairment. Brain 2014;137(Pt 10):2657-2663.

139. Di Bella D, Lazzaro F, Brusco A, et al. Mutations in the mitochondrial protease gene AFG3L2 cause dominant hereditary ataxia SCA28. Nat Genet 2010;42(4):313-321.

140. Sato N, Amino T, Kobayashi K, et al. Spinocerebellar ataxia type 31 is associated with "inserted" penta-nucleotide repeats containing (TGGAA)n. Am J Hum Genet 2009;85(5):544-557.

141. Kobayashi H, Abe K, Matsuura T, et al. Expansion of intronic GGCCTG hexanucleotide repeat in NOP56 causes SCA36, a type of spinocerebellar ataxia accompanied by motor neuron involvement. Am J Hum Genet 2011;89(1):121-130.

142. Winkelmann J, Lin L, Schormair B, et al. Mutations in DNMT1 cause autosomal dominant cerebellar ataxia, deafness and narcolepsy. Hum Mol Genet 2012;21(10):2205-2210.

143. Koide R, Ikeuchi T, Onodera O, et al. Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). Nat Genet 1994;6(1):9-13.

144. Nørremølle A, Nielsen JE, Sørensen SA, Hasholt L. Elongated CAG repeats of the B37 gene in a Danish family with dentatorubro-pallido-luysian atrophy. Hum Genet 1995;95(3):313-318.

145. Bourassa CV, Meijer IA, Merner ND, et al. VAMP1 mutation causes dominant hereditary spastic ataxia in Newfoundland families. Am J Hum Genet 2012;91(3):548-552.

146. Brenner M, Johnson AB, Boespflug-Tanguy O, Rodriguez D, Goldman JE, Messing A. Mutations in GFAP, encoding glial fibrillary acidic protein, are associated with Alexander disease. Nat Genet 2001;27(1):117-120.

147. Kaneko H, Hirose M, Katada S, et al. Novel GFAP mutation in patient with adult-onset Alexander disease presenting with spastic ataxia. Mov Disord 2009;24(9):1393-1395.

148. Zuchner S, Wang G, Tran-Viet KN, et al. Mutations in the novel mitochondrial protein REEP1 cause hereditary spastic paraplegia type 31. Am J Hum Genet 2006;79(2):365-369.

149. Goizet C, Depienne C, Benard G, et al. REEP1 mutations in SPG31: frequency, mutational spectrum, and potential association with mitochondrial morpho-functional dysfunction. Hum Mutat 2011;32(10):1118-1127.

150. Schneider SA, Walker RH, Bhatia KP. The Huntington's disease-like syndromes: what to consider in patients with a negative Huntington's disease gene test. Nat Clin Pract Neurol 2007;3(9):517-525.

151. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 1993;72(6):971-983.

152. Laplanche JL, Hachimi KH, Durieux I, et al. Prominent psychiatric features and early onset in an inherited prion disease with a new insertional mutation in the prion protein gene. Brain 1999; 122 (Pt 12):2375-2386.

153. Margolis RL, O'Hearn E, Rosenblatt A, et al. A disorder similar to Huntington's disease is associated with a novel CAG repeat expansion. Ann Neurol 2001;50(6):373-380.

154. Breedveld GJ, van Dongen JW, Danesino C, et al. Mutations in TITF-1 are associated with benign hereditary chorea. Hum Mol Genet 2002;11(8):971-979.

155. Carre A, Szinnai G, Castanet M, et al. Five new TTF1/NKX2.1 mutations in brain-lung-thyroid syndrome: rescue by PAX8 synergism in one case. Hum Mol Genet 2009;18(12):2266-2276.

156. Rampoldi L, Dobson-Stone C, Rubio JP, et al. A conserved sorting-associated protein is mutant in chorea-acanthocytosis. Nat Genet 2001;28(2):119-120.

157. Ueno S, Maruki Y, Nakamura M, et al. The gene encoding a newly discovered protein, chorein, is mutated in chorea-acanthocytosis. Nat Genet 2001;28(2):121-122.

158. Velayos Baeza A, Dobson-Stone C, Rampoldi L, et al. Chorea-Acanthocytosis. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews. Seattle, WA. 1993.

159. Baeza AV, Dobson-Stone C, Rampoldi L, et al. Chorea-Acanthocytosis. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2014.

160. Ho M, Chelly J, Carter N, Danek A, Crocker P, Monaco AP. Isolation of the gene for McLeod syndrome that encodes a novel membrane transport protein. Cell 1994;77(6):869-880.

161. Jung HH, Danek A, Walker RH. Neuroacanthocytosis syndromes. Orphanet J Rare Dis 2011;6:68.

162. Jinnah HA, Visser JE, Harris JC, et al. Delineation of the motor disorder of Lesch-Nyhan disease. Brain 2006;129(Pt 5):1201-1217.

163. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 2011;72(2):257-268.

164. Hensman Moss DJ, Poulter M, Beck J, et al. C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. Neurology 2014;82(4):292-299.

165. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. Acta Neuropathol 2013; 126(3):307-328.

166. Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. Lancet Neurol 2008;7(12):1127-1138.

167. Zhao X, Alvarado D, Rainier S, et al. Mutations in a newly identified GTPase gene cause autosomal dominant hereditary spastic paraplegia. Nat Genet 2001;29(3):326-331.

168. Nielsen JE, Koefoed P, Abell K, et al. CAG repeat expansion in autosomal dominant pure spastic paraplegia linked to chromosome 2p21-p24. Hum Mol Genet 1997;6(11):1811-1816.

169. Rainier S, Chai JH, Tokarz D, Nicholls RD, Fink JK. NIPA1 gene mutations cause autosomal dominant hereditary spastic paraplegia (SPG6). Am J Hum Genet 2003;73(4):967-971.

170. Valdmanis PN, Meijer IA, Reynolds A, et al. Mutations in the KIAA0196 gene at the SPG8 locus cause hereditary spastic paraplegia. Am J Hum Genet 2007;80(1):152-161.

171. Reid E, Kloos M, Ashley-Koch A, et al. A kinesin heavy chain (KIF5A) mutation in hereditary spastic paraplegia (SPG10). Am J Hum Genet 2002;71(5):1189-1194.

172. Montenegro G, Rebelo AP, Connell J, et al. Mutations in the ER-shaping protein reticulon 2 cause the axon-degenerative disorder hereditary spastic paraplegia type 12. J Clin Invest 2012;122(2): 538-544.

173. Hansen JJ, Durr A, Cournu-Rebeix I, et al. Hereditary spastic paraplegia SPG13 is associated with a mutation in the gene encoding the mitochondrial chaperonin Hsp60. Am J Hum Genet 2002;70(5):1328-1332.

174. Windpassinger C, Auer-Grumbach M, Irobi J, et al. Heterozygous missense mutations in BSCL2 are associated with distal hereditary motor neuropathy and Silver syndrome. Nat Genet 2004;36(3): 271-276.

175. Mannan AU, Krawen P, Sauter SM, et al. ZFYVE27 (SPG33), a novel spastin-binding protein, is mutated in hereditary spastic paraplegia. Am J Hum Genet 2006;79(2):351-357.

176. Tsaousidou MK, Ouahchi K, Warner TT, et al. Sequence alterations within CYP7B1 implicate defective cholesterol homeostasis in motor-neuron degeneration. Am J Hum Genet 2008;82(2):510-515.

177. Casari G, De Fusco M, Ciarmatori S, et al. Spastic paraplegia and OXPHOS impairment caused by mutations in paraplegin, a nuclear-encoded mitochondrial metalloprotease. Cell 1998;93(6):973-983.

178. Yildirim Y, Orhan EK, Iseri SA, et al. A frameshift mutation of ERLIN2 in recessive intellectual disability, motor dysfunction and multiple joint contractures. Hum Mol Genet 2011;20(10):1886-1892.

179. Patel H, Cross H, Proukakis C, et al. SPG20 is mutated in Troyer syndrome, an hereditary spastic paraplegia. Nat Genet 2002; 31(4):347-348.

180. Simpson MA, Cross H, Proukakis C, et al. Maspardin is mutated in mast syndrome, a complicated form of hereditary spastic paraplegia associated with dementia. Am J Hum Genet 2003;73(5): 1147-1156.

181. Boukhris A, Schule R, Loureiro JL, et al. Alteration of ganglioside biosynthesis responsible for complex hereditary spastic paraplegia. Am J Hum Genet 2013;93(1):118-123.

182. Tesson C, Nawara M, Salih MA, et al. Alteration of fatty-acid-metabolizing enzymes affects mitochondrial form and function in hereditary spastic paraplegia. Am J Hum Genet 2012;91(6):1051-1064.

183. Erlich Y, Edvardson S, Hodges E, et al. Exome sequencing and disease-network analysis of a single family implicate a mutation in KIF1A in hereditary spastic paraparesis. Genome Res 2011; 21(5):658-664.

184. Rainier S, Bui M, Mark E, et al. Neuropathy target esterase gene mutations cause motor neuron disease. Am J Hum Genet 2008; 82(3):780-785.

185. 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.

186. Martin E, Schule R, Smets K, et al. Loss of function of glucocerebrosidase GBA2 is responsible for motor neuron defects in hereditary spastic paraplegia. American Journal of Human Genetics 2013;92(2):238-244.

187. Abou Jamra R, Philippe O, Raas-Rothschild A, et al. Adaptor protein complex 4 deficiency causes severe autosomal-recessive intellectual disability, progressive spastic paraplegia, shy character, and short stature. Am J Hum Genet 2011;88(6):788-795.

188. Slabicki M, Theis M, Krastev DB, et al. A genome-scale DNA repair RNAi screen identifies SPG48 as a novel gene associated with hereditary spastic paraplegia. PLOS Biol 2010;8(6): e1000408.

189. Oz-Levi D, Ben-Zeev B, Ruzzo EK, et al. Mutation in TECPR2 reveals a role for autophagy in hereditary spastic paraparesis. Am J Hum Genet 2012;91(6):1065-1072.

190. Verkerk AJ, Schot R, Dumee B, et al. Mutation in the AP4M1 gene provides a model for neuroaxonal injury in cerebral palsy. Am J Hum Genet 2009;85(1):40-52.

191. Moreno-De-Luca A, Helmers SL, Mao H, et al. Adaptor protein complex-4 (AP-4) deficiency causes a novel autosomal recessive cerebral palsy syndrome with microcephaly and intellectual disability. J Med Genet 2011;48(2):141-144.

192. Schuurs-Hoeijmakers JH, Geraghty MT, Kamsteeg EJ, et al. Mutations in DDHD2, encoding an intracellular phospholipase A(1), cause a recessive form of complex hereditary spastic paraplegia. Am J Hum Genet 2012;91(6):1073-1081.

193. Gonzalez M, Nampoothiri S, Kornblum C, et al. Mutations in phospholipase DDHD2 cause autosomal recessive hereditary spastic paraplegia (SPG54). Eur J Hum Genet 2013;21(11):1214-1218.

194. Shimazaki H, Takiyama Y, Ishiura H, et al. A homozygous mutation of C12orf65 causes spastic paraplegia with optic atrophy and neuropathy (SPG55). J Med Genet 2012;49(12):777-784.

195. Eymard-Pierre E, Lesca G, Dollet S, et al. Infantile-onset ascending hereditary spastic paralysis is associated with mutations in the alsin gene. Am J Hum Genet 2002;71(3):518-527.

196. Bouchard JP, Barbeau A, Bouchard R, Bouchard RW. Autosomal recessive spastic ataxia of Charlevoix-Saguenay. Can J Neurol Sci 1978;5(1):61-69.

197. Sillen A, Jagell S, Wadelius C. A missense mutation in the FALDH gene identified in Sjogren-Larsson syndrome patients originating from the northern part of Sweden. Hum Genet 1997; 100(2):201-203.

198. Oates EC, Rossor AM, Hafezparast M, et al. Mutations in BICD2 cause dominant congenital spinal muscular atrophy and hereditary spastic paraplegia. Am J Hum Genet 2013;92(6):965-973.

199. Jouet M, Rosenthal A, Armstrong G, et al. X-linked spastic paraplegia (SPG1), MASA syndrome and X-linked hydrocephalus result from mutations in the L1 gene. Nat Genet 1994;7(3):402-407.

200. Saugier-Veber P, Munnich A, Bonneau D, et al. X-linked spastic paraplegia and Pelizaeus-Merzbacher disease are allelic disorders at the proteolipid protein locus. Nat Genet 1994;6(3):257-262.

201. Dumitrescu AM, Liao XH, Best TB, Brockmann K, Refetoff S. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. Am J Hum Genet 2004;74(1):168-175.

202. Pedroso JL, de Souza PV, Pinto WB, et al. SCA1 patients may present as hereditary spastic paraplegia and must be included in spastic-ataxias group. Parkinsonism Relat Disord 2015;21(10):1243-1246.

203. Sobrido MJ, Coppola G, Oliveira J, Hopfer S, Geschwind DH. Primary familial brain calcification. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, eds. GeneReviews. Seattle, WA: University of Washington; 2013.

204. Stephenson JB. Aicardi-Goutieres syndrome (AGS). Eur J Paediatr Neurol 2008;12(5):355-358.

205. 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.

206. Geschwind DH, Loginov M, Stern JM. Identification of a locus on chromosome 14q for idiopathic basal ganglia calcification (Fahr disease). Am J Hum Genet 1999;65(3):764-772.

207. Hsu SC, Sears RL, Lemos RR, et al. Mutations in SLC20A2 are a major cause of familial idiopathic basal ganglia calcification. Neurogenetics 2013;14(1):11-22.

208. Oliveira JRM, Spiteri E, Sobrido MJ, et al. Genetic heterogeneity in familial idiopathic basal ganglia calcification (Fahr disease). Neurology 2004;63(11):2165-2167.

209. 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.

210. Sanchez-Contreras M, Baker MC, Finch NA, et al. Genetic screening and functional characterization of PDGFRB mutations associated with basal ganglia calcification of unknown etiology. Hum Mut 2014;35(8):964-971.

211. 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.

212. Nicolas G, Jacquin A, Thauvin-Robinet C, et al. A de novo nonsense PDGFB mutation causing idiopathic basal ganglia calcification with laryngeal dystonia. Eur J Hum Genet 2014;22(10):1236-1238.

213. 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.

214. Doorn JM, Kruer MC. Newly characterized forms of neurodegeneration with brain iron accumulation. Curr Neurol Neurosci Rep 2013;13(12):413.

215. Schneider SA, Hardy J, Bhatia KP. Syndromes of neurodegeneration with brain iron accumulation (NBIA): an update on clinical presentations, histological and genetic underpinnings, and treatment considerations. Mov Disord 2012;27(1):42-53.

216. Nishida K, Garringer HJ, Futamura N, et al. A novel ferritin light chain mutation in neuroferritinopathy with an atypical presentation. J Neurol Sci 2014;342(1-2):173-177.

217. Kruer MC, Salih MA, Mooney C, et al. C19orf12 mutation leads to a pallido-pyramidal syndrome. Gene 2014;537(2):352-356.

218. Park JS, Blair NF, Sue CM. The role of ATP13A2 in Parkinson's disease: clinical phenotypes and molecular mechanisms. Mov Disord 2015;30(6):770-779.

Supporting Data

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