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

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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 erroneously assigned loci, duplicated loci, missing symbols, missing loci, unconfirmed loci, combining causative genes and risk factor genes in the same list and discordance between phenotype and list assignment. In this paper we report on the recommendations of the International Parkinson and Movement Disorder Society (MDS) 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 basal ganglia 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.

Introduction

The system of locus symbols (e.g. *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 the condition, as well as the chromosomal region, and 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 with the system of designating locus symbols and with its use have arisen. 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) designating symbols 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 state of affairs was the justification for the International Parkinson and Movement Disorder Society (MDS) Task Force for Nomenclature of Genetic Movement Disorders. This report presents a recommendation for a new system for naming of genetically determined movement disorders by the Task Force.

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 system of naming of genetic movement disorders, addressing the problems summarized above. 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 (e.g. 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 upon a set of rules that should govern the naming based upon 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 (e.g. ataxias, dystonias), or defined by a distinctive imaging (e.g. basal ganglia calcification) or, theoretically, laboratory feature. To date we have not found the need to classify on any laboratory features. The recommendations and resulting lists have been made available to the membership of the MDS through the Society's website and feedback was solicited from the membership. The recommendations were also shared with representatives from GeneTests and OMIM, two compendia of genetic phenotypes for commentary and suggestions.

Commented [CR1]: CM: Their input will be sought after asking the MDS membership for their feedback.

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. Replace number suffixes by the gene name.

We recommend that the symbol prefix be followed by the gene name (e.g. 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 (e.g. DYT1) is obviously easier than remembering complex gene names. However, given the major sources of error and confusion that have arisen in the numerical listing we feel that 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 review for inclusion are preferred.

3. List disease-causing genes separately from risk factor genes.

A locus symbol prefix (e.g. PARK) would be conferred only upon disease-causing genes (causing monogenic disorders) and not upon risk factors, recognizing the diagnostic value of disease-causing mutations. The PD GENE website (http://www.pdgene.org), developed by the Max Planck Institute for Molecular Genetics, the Michael J. Fox Foundation and the Alzheimer Research Forum provides a resource for cataloguing genetic risk factors for Parkinson's disease and for continuously evaluating them in an ongoing meta-analysis. When disease-causing mutations and risk factors arise from the same gene (e.g. *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. As 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 below, a criterion-based method of making such distinctions would be of value to the field.

4. 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 in the list. The US National Human Genome Research Institute

convened a working group to establish guidelines for investigating causality of sequence variants in human disease.[3] As outlined in the guidelines, four 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 the gene product, if possible as supported by functional evidence in human tissue or well-established cellular or animal models. Considering their guidelines a gene-by-gene assessment of the sum of the evidence was considered a most appropriate approach for deciding whether or not a gene warrants a place on the lists.

5. Assign appropriate phenotype-prefix relationships.

For a gene to be a member of a particular phenotypic list, the phenotype (e.g. dystonia in the case of DYTs) should be a *consistent* and *prominent* feature of the disease linked to mutations in that gene. When more than one movement disorder is a prominent and consistent feature, a double prefix could be assigned (e.g. *DYT/PARK*-ATP1A3) and the symbol would belong to more than one list. Disorders which can *unusually* present with an alternative movement disorder as the predominant manifestation would appear cross-referenced to the list of the alternative phenotype (e.g. SCA17 occasionally presenting as a choreic disorder, thus it is cross-referenced to the chorea list) but the prefix would reflect the phenotype that is consistent with in 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 (e.g. C9orf72 mutations

presenting as a predominantly choreic disorder instead of the usual dementia-predominant syndrome), we have not included these disorders on the list. The focus of these lists is on disorders that have movement disorders as consistent and predominant features.

Applying the recommendations

For each class of movement disorder we present the new list applying the principles we have laid out above. For contrast we have provided, as supplementary material, the list of existing locus symbols for each class of disorder, including a note in the last column indicating the problems with the entry, where applicable. We have included in the list of existing symbols 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 have assigned symbols to disorders known to be genetically determined but never assigned a locus symbol, in order to provide a complete list; Wilson disease as an example. In the same spirit we have introduced to these lists a number of pediatric metabolic disorders.

Genetically determined movement disorders

Genetically determined parkinsonism

A total of 20 genes and loci have been assigned a 'PARK' designation (Supplementary Table 1). For five of these, the relationship is unconfirmed

(PARK3,5,11,13,18) and three 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 eighteen confirmed monogenic conditions where parkinsonism is a consistent and predominant feature (Table 1). In eight of the forms of genetic parkinsonism mentioned below, dystonia is a prominent feature. To guide clinicians we have divided these into three categories: 1) Those that are associated with a clinical picture closely resembling that of idiopathic Parkinson disease, 2) Those that present with parkinsonism similar to Parkinson disease but of young onset and 3) Complex forms that have parkinsonism as a key clinical feature but in addition 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.[4, 5] Of note, we have chosen not to include GBA as a monogenic cause of parkinsonism in the PARK list but rather consider it a strong genetic risk factor for Parkinson disease (similar to ApoE4 in Alzheimer disease) given its low, age-dependent prevalence.[6]

Table 1: The proposed new list of hereditary parkinsonism

New designation and Phenotypic subgroup	**Clinical clues**	**Inheri-tance**	**Locus symbol**

Classical parkinsonism			
PARK-SNCA	Missense mutations cause classical parkinsonism. Duplication or triplication mutations in this gene cause early onset parkinsonism with prominent dementia.	AD	PARK1
PARK-LRRK2		AD	PARK8
PARK-VPS35		AD	PARK17
Early onset parkinsonism			
PARK-PARKIN*	Often presents with dystonia, often in a leg	AR	PARK2
PARK-PINK1	Psychiatric features common	AR	PARK6
PARK-DJ1		AR	PARK7
Atypical parkinsonism or complex phenotypes			
PARK-ATP13A2	Kufor Rakeb syndrome; Juvenile or early onset parkinsonism, vertical gaze palsy, minifacial-faucial myoclonus, pyramidal signs.	AR	PARK9
NBIA/DYT/PARK -PLA2G6	*PLA2G6*-associated neurodegeneration (PLAN) Iron accumulation: GP, SN in some;	AR	NBIA2, PARK14

	adults may have striatal involvement; ½ INAD and majority of adult-onset lack imaging BIA on MRI. Infantile (INAD) phenotype: Developmental delay, hypotonia, ataxia, pyramidal signs, optic atrophy, sensorimotor axonal neuropathy seizures. Adult phenotype: Dystonia-parkinsonism, pyramidal signs, cognitive, psychiatric features		
PARK-FBX07	Early onset parkinsonism with pyramidal signs	AR	PARK15
PARK-DNAJC6	Occasional mental retardation and seizures	AR	PARK19
PARK-SYNJ1	May have seizures, cognitive decline, abnormal eye movements, and dystonia	AR	PARK20
DYT/PARK-ATP1A3**	Rapid onset dystonia-parkinsonism	AD	DYT12
DYT/PARK-TAF1	Dystonia and parkinsonism	X-linked	DYT3

DYT/PARK-GCH1	Guanine triphosphate cyclohydrolase deficiency:		
	Milder form: Childhood or adolescent onset dopa-responsive dystonia, adult onset parkinsonism	AD	*DYT5a*
	Severe form: generalized dystonia and parkinsonism, infantile onset global developmental delay, with or without hyperphenylalaninemia[7]	AR	none
DYT/PARK-*TH*	Tyrosine hydroxylase deficiency:[8]		
	Mild form: dopa-responsive infantile to early childhood onset dystonia	AR	DYT5b
	Severe form: infantile onset dystonia and parkinsonism with truncal hypotonia, global developmental delay and parkinsonism	AR	None
	Very severe form: infantile onset dystonia, oculogyric crises, severe global developmental delay, truncal hypotonia, parkinsonism	AR	None
DYT/PARK-*SPR*	Sepiapterin reductase deficiency, infantile to childhood onset generalized dystonia, parkinsonism, global	AR	None

	developmental delay, truncal hypotonia, spasticity[9]		
DYT/PARK-*QDPR*	Dihydropterine reductase deficiency: dystonia, parkinsonism, infantile onset global developmental delay, truncal hypotonia with hyperphenylalaninemia[10]	AR	None
DYT/PARK-*PTS*	Pyruvoyl-tetrahydropterin synthase deficiency: dystonia, parkinsonism, usually neonatal onset irritability, truncal hypotonia, infantile onset global developmental delay with hyperphenylalaninemia[10]	AR	None
DYT/PARK-SLC6A3	Dopamine transporter deficiency: classical presentation with parkinsonism-dystonia, infantile onset global developmental delay, truncal hypotonia,; atypical presentation with juvenile onset parkinsonism[11]	AR	None
DYT/PARK-SLC30A10	Childhood onset dystonia or late onset parkinsonism, hypermanganesemia, polycythemia, and chronic liver disease[12]	AR	None

INAD: Infantile NeuroAxonal Dystrophy

*PARKIN has not been assigned a gene name thus the name for the protein product is used instead.

** Mutations in this gene also causes alternating hemiplegia of childhood and CAPOS (Cerebellar ataxia, pes cavus, optic atrophy and sensorineural hearing loss) syndrome.

Genetically determined dystonia

There are currently 25 locus symbols with a numeric DYT designation (Supplementary Table 2).[13] However, a number of these currently await independent confirmation (DYT2,3,4,7,13,15,16,17,20,21,23,24) and several others have been shown to be erroneously designated (DYT14, 18 and 19). One of these (DYT22) has never been linked to a locus, gene or clinical syndrome to our knowledge. Only eight of these disorders appear on the newly proposed list (Table 2). In addition we have conferred a 'DYT' prefix upon Wilson disease and Lesch Nyhan syndrome and a number of other infantile and childhood onset disorders which were never previously designated.

An international panel of dystonia experts recently developed a consensus update of the definition and classification of dystonia. The two main axes of dystonia classification currently considered most relevant are clinical and etiological.[14] 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. As 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.

Table 2: The proposed new list of isolated and combined hereditary dystonia

New designation and phenotypic subgroup	**Clinical clues**	**Inheritance pattern**	**Locus symbol**
Isolated dystonias			
DYT-TOR1A	Early-onset generalized dystonia	AD	*DYT1*
DYT-THAP1	Adolescent-onset dystonia of mixed type	AD	*DYT6*
DYT-GNAL	Adult onset cranial-cervical dystonia	AD	*DYT25*
DYT-PRKRA	Rare form of usually generalized dystonia, parkinsonism inconsistent	AR	*DYT16*

Combined dystonias (disorders where dystonia coexists with other movement disorders and each are consistent and prominent characteristics of the disorder)			
DYT/PARK-GCH1	Guanine triphosphate cyclohydrolase deficiency		
	Milder form: Childhood or adolescent onset dopa-responsive dystonia, adult onset parkinsonism	AD	*DYT5a*
	Severe form: generalized dystonia and parkinsonism, infantile onset global developmental delay, with or without hyperphenylalaninemia[7]	AR	None
DYT/PARK-TH	Tyrosine hydroxylase deficiency:[8]		
	Mild form: dopa-responsive infantile to early childhood onset dystonia	AR	*DYT5b*
	Severe form: infantile onset dystonia and parkinsonism with truncal hypotonia, global developmental delay and parkinsonism	AR	None

	Very severe form: infantile onset dystonia, oculogyric crises, severe global developmental delay, truncal hypotonia, parkinsonism	AR	None
DYT/PARK-ATP1A3	Rapid-onset dystonia-parkinsonism, chorea in later life**	AD	*DYT12*
DYT/PARK-TAF1*	Dystonia-parkinsonism	X-linked	*DYT3*
DYT-SGCE	Myoclonus-dystonia	AD	*DYT11*
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	Lesch-Nyhan Syndrome. Infantile onset choreaathetosis, dystonia, global developmental delay, self-injuries behaviour	X-linked recessive	None
DYT/CHOR-T2	Mitochondrial acetoacetyl-CoA thiolase deficiency: metabolic decompensation and basal ganglia injury during acute stress resulting in dystonia and chorea[15]	AR	none
DYT/CHOR-GCDH	Glutaric aciduria type I, macrocephaly, metabolic decompensation and basal ganglia injury during acute stress resulting	AR	None

	in dystonia and chorea[16]		
DYT-DDC	Aromatic amino acid decarboxylase deficiency: Infantile onset generalized dystonia, may have chorea, global developmental delay, truncal hypotonia, oculogyric crises[17]	AR	None
DYT/PARK-SLC30A10	Childhood onset dystonia or late onset parkinsonism, hypermanganesemia, polycythemia, and chronic liver disease[12]	AR	None
DYT/PARK-*SPR*	Sepiapterin reductase deficiency, infantile to childhood onset generalized dystonia, parkinsonism, global developmental delay, truncal hypotonia, spasticity[9]	AR	None
DYT/PARK-QDPR	Dihydropteridine reductase deficiency: infantile onset dystonia, parkinsonism, global developmental delay, truncal hypotonia, with hyperphenylalaninemia[10]	AR	None

DYT/PARK-PTS	Pyruvoyl-tetrahydropterin synthase deficiency: premature delivery, dystonia, parkinsonism, usually neonatal onset irritability, truncal hypotonia, infantile onset global developmental delay, with hyperphenylalaninemia[10]	AR	None
DYT/PARK-SLC6A3	Dopamine transporter deficiency classical presentation with infantile onset parkinsonism-dystonia, global developmental delay, truncal hypotonia. Atypical presentation with juvenile onset parkinsonism[17]	AR	None
NBIA/DYT-PANK2	Pantothenate kinase- associated neurodegeneration (PKAN) Iron accumulation: GP - Eye of the tiger, Phenotype: Dystonia, spasticity, parkinsonism, chorea, psychiatric cognitive decline, gaze palsy, pigmentary retinopathy	AR	NBIA1
NBIA/DYT/PARK-	*PLA2G6*-associated	AR	NBIA2,

PLA2G6	neurodegeneration (PLAN) Iron accumulation: GP, SN in some; adults may have striatal involvement; ½ INAD and majority of adult-onset lack imaging BIA on MRI. Infantile (INAD) phenotype: Developmental delay, hypotonia, ataxia, pyramidal signs, optic atrophy, sensorimotor axonal neuropathy seizures. Adult phenotype: Dystonia-parkinsonism, pyramidal signs, cognitive, psychiatric features		PARK14
DYT-ATP7B	Wilson disease: dystonia with occasionally predominant chorea and/or parkinsonism. Liver disease.	AR	None
DYT- SLC19A3	Biotin-responsive basal ganglia disease, childhood onset dystonia, confusion, generalized seizures, ataxia, facial palsy, ophthalmoplegia, dysphagia[18]	AR	None

DYT-TIMM8A	Mohr-Tranebjaerg syndrome, infantile, childhood to adult onset dystonia, deafness[19]		
DYT-mtND6	Homoplasmic G14459A mutation: Childhood onset dystonia, juvenile onset subacute visual loss (Leber hereditary optic neuropathy)[20]	Mitochondrial	None

INAD: infantile NeuroAxonal Dystrophy

*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.

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

Genetically determined paroxysmal movement disorders

There are a number of movement disorders whose symptoms 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 overlap in phenomenology is increasingly recognized.[21] Therefore we have proposed a new category of “Paroxysmal Movement Disorders, or PxMD”. The paroxysmal dyskinesias[22, 23] were previously designated “DYT” loci[13] (see

Supplementary Table 2). The previous list of 7 episodic ataxias is shown in Supplementary table 3.[24] Four of these remain unconfirmed (EA3,4,5,7). Table 3 shows the proposed new list of paroxysmal movement disorders. We have conferred a PxMD prefix upon 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. It is a minority of cases that display a predominant paroxysmal ataxia, dystonia and/or chorea.[25] Because this is a major consideration in the differential diagnosis of paroxysmal movement disorders and indeed the only gene known to be responsible for the paroxysmal exertion-induced dyskinesia phenotype we felt that leaving this out to be problematic from the perspective of a clinician considering a patient with a paroxysmal exertion-induced dyskinesia. A disorder not included in the tables, known as glycine encephalopathy, deserves mention. This disorder can be caused by mutations in three different genes and can present with intermittent chorea precipitated by intercurrent illness.[26] Although intermittent chorea can be the predominant phenotype in individuals with such mutations, these variants usually present with developmental delay as the predominant symptom. Since intermittent chorea is not a consistent phenotype it has not been given a place on the list of genetically determined movement disorders.

Table 3: The proposed new list of paroxysmal movement disorders

New designation	**Clinical clues**	**Inheri-tance**	**Locus symbol**
Predominant dyskinesias			

PxMD-PRRT2	Paroxysmal kinesigenic dyskinesia, rarely paroxysmal ataxia	AD	*DYT10 or DYT19*
PxMD-MR-1	Paroxysmal non-kinesigenic dyskinesia	AD	*DYT8*
PxMD-SLC2A1	Paroxysmal exertion-induced dyskineisa*	AD	*DYT18/DYT9*
Predominant ataxias			
PxMD-KCNA1	Paroxysmal ataxia with interictal myokymia	AD	EA1
PxMD-CACNA1A	Paroxysmal ataxia with variable seizures, vertigo, headache, weakness	AD	EA2
PxMD-SLC1A3	Paroxysmal ataxia with seizures, migraine, alternating hemiplegia	AD	EA6
PxMD-PDHA1	Pyruvate dehydrogenase E1-alpha deficiency with infantile to childhood onset episodic ataxia, global developmental delay[27]	X-linked	None
PxMD-SLC6A19	Hartnup disorder with paroxysmal ataxia, cognitive dysfunction, skin rash, psychosis[28]	AR	None

*A phenotype of infantile onset dystonia, chorea, global developmental delay, epilepsy, acquired microcephaly and ataxia is the most common presentation of mutations in this gene

Genetically determined dominant cerebellar ataxia

The dominant spinocerebellar ataxias (SCAs) have previously been (and are still being) referred to as autosomal dominant cerebellar ataxias (ADCA). The problems with the current SCA list are numerous, i.e. 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 (SCA4/SCA31, SCA019/SCA22 and SCA15/SCA16). Supplementary Table 4 lists these locus symbols and their current status[29]. Also, some dominantly inherited ataxias have not been assigned a SCA locus, e.g. Dentato-rubro-pallidoluysian atrophy (DRPLA) and dominant ataxia combined with narcolepsy and deafness due to DNMT1 mutations. While 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 an 'other' movement disorder as the only or clearly predominant disease feature.[30] Examples of this are parkinsonism in SCA2 and chorea in SCA17. These disorders are cross-referenced to the lists of the alternative phenotype. We here propose a list for the dominant ataxias (Table 4), but as next steps we need similar proposals for the recessive and congenital. We suggest that this should be taken up by experts from within the ataxia field in close collaboration with members of this task force.

Table 4: The proposed new list for the dominant spinocerebellar ataxias (SCAs)

New designation	**Clinical clues**	**Inheritance**	**Locus Symbol**

and phenotypic subgroup			
Pure or relatively pure ataxia			
SCA-SPTBN2	Pure ataxia	AD	SCA5
SCA-CACNA1A	Pure ataxia	AD	SCA6
SCA-TTBK2	Pure ataxia	AD	SCA11
SCA-PDYN	Pure ataxia	AD	SCA23
SCA-ATXN8OS	Relatively pure; pyramidal signs, neuropsychiatric features	AD	SCA8
SCA-PPP2R2B	Relatively pure; head and hand tremor	AD	SCA12
SCA-PRKCG	Relatively pure; sometimes other movement disorders (dystonia, myoclonus)	AD	SCA14
SCA-ITPR1	Relatively pure; myoclonus, dystonia	AD	SCA15/16
SCA-KCND3	Relatively pure; hand tremor, peripheral neuropathy, cognitive disturbances	AD	SCA19/22

SCA-FGF14	Relatively pure; early-onset hand tremor, orofacial dyskinesia, behavioural problems	AD	SCA27
SCA-TGM6	Relatively pure; pyramidal features, cervical dystonia	AD	SCA35
SCA-ELOVL5	Relatively pure; neuropathy	AD	SCA38
Complex Ataxia (ataxias that can often have other neurological features)			
SCA-ATXN1	Marked non-ataxia features; can have dominant choreapyramidal features, peripheral neuropathy, ophthalmoplegia	AD	SCA1
SCA-ATXN2	Marked non-ataxia features, can have predominant parkinsonism or chorea; neuronopathy, dementia, myoclonus	AD	SCA2
SCA-ATXN3	Marked non-ataxia features; can have predominant parkinsonism, dystonia, chorea, spasticity, neuropathy, lower motor	AD	SCA3

	neuron involvement		
SCA-ATXN7	Marked visual loss	AD	SCA7
SCA-ATXN10	Seizures	AD	SCA10
SCA-TBP	Marked non-ataxia features, can present with predominant chorea. May be HD-like	AD	SCA17, HDL4
SCA-TMEM240	Cognitive impairment / mental retardation	AD	SCA21
SCA-AFG3L2	Ophthalmoparesis	AD	SCA28
SCA-BEAN1	Hearing loss, vertigo	AD	SCA31
SCA-NOP56	Motor neuron involvement	AD	SCA36
SCA-DNMT1	Sensorineural deafness, narcolepsy, dementia	AD	None
SCA-ATN1	Dentatorubropallidoluysian atrophy (DRPLA): Myoclonus, chorea, parkinsonism, dementia, supranuclear gaze palsy	AD	None
SCA/HSP-VAMP1	Spastic ataxia, supranuclear upgaze limitation	AD	SPAX1

SCA: spinocerebellar ataxia; AD: autosomal dominant

Genetically determined chorea

Chorea is a prominent clinical manifestation of Huntington disease (HD), and in four look-alike disorders, upon which the prefix HDL (Huntington Disease-Like) has been conferred (HDL1-4, Supplementary Table 5).[31] The gene associated with the HDL3 locus is not yet known and HDL4 refers to the same gene as spinocerebellar ataxia 17, i.e. 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 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 (e.g. SCA1, 2, or 7) and is also part of the phenotypic spectrum in cases with intracranial basal ganglia calcifications, neurodegeneration with brain iron accumulation (NBIA), pontocerebellar hypoplasia (PCH2), and several dystonias (e.g. 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 the paroxysmal nature of the movement disorder was felt to be a more distinctive feature.

Table 5: The proposed new list of hereditary choreas

New designation	**Clinical clues**	**Inheri-tance**	**Locus symbol**
CHOR-HTT	Huntington's disease (HD): Chorea and dementia, young onset may have predominant parkinsonism (Westphal variant)	AD	None
CHOR-PRNP	HD-like phenotype, seizures (variable)	AD	HDL1
CHOR-JPH3	HD-like phenotype To date only found in patients of African descent	AD	HDL2
CHOR-NKX2-1	Phenotypes 1. Brain–lung–thyroid syndrome (50%):	AD	None

	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%)[32]		
CHOR-VPS13A	Chorea-Acanthocytosis; [33] Feeding dystonia, tics, parkinsonism, seizures, cognitive and behavioral symptoms, neuropathy Laboratory: Acanthocytosis elevated creatine kinase and liver enzymes	AR	none
CHOR-XK	McLeod syndrome; Seizures, cognitive and behavioral symptoms,	X-linked recessive	none

	neuromuscular involvement, cardiomyopathy; Laboratory: Acanthocytosis, Kell antigen, elevated CK, liver enzymes		
Combined phenotypes: where chorea coexists with (an)other movement disorder(s) as a prominent and consistent feature			
DYT/CHOR-HPRT	Lesch-Nyhan Syndrome. Infantile onset global developmental delay, choreoathetosis, dystonia, self-injuries behaviour	X-linked recessive	none
DYT/CHOR-T2	Mitochondrial acetoacetyl-CoA thiolase deficiency metabolic decompensation and basal ganglia injury during acute stress resulting in dystonia and chorea[15]	AR	none
DYT/CHOR-GCDH	Glutaric aciduria type I, macrocephaly, metabolic decompensation and basal ganglia injury during acute stress resulting in dystonia and chorea[16]	AR	None

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 three HSP genes have been reported to present with *only* 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 of makes genetic counseling challenging.

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).[34, 35] Thirty-two 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 seventeen, no gene has been unequivocally identified. Two SPG designations refer to the same gene (SPG 45 and SPG65). Thus, according to the revised system, there are only 40 confirmed monogenic forms of hereditary spastic paraplegia. Three are transmitted following an X-linked recessive trait, 27 are AR and 10 are 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.

Table 6: The proposed new list of hereditary spastic paraplegias

New designation and Inheritance subgroup	**Clinical clues**	**Inheri-tance**	**Old Locus Symbol**
Autosomal dominant forms			
HSP-ATL1	Pure or complex; Silver-syndrome, allelic with hereditary sensory neuropathy type 1, cerebral palsy (infantile onset).	AD/AR	SPG3A
HSP-SPAST	Pure or complex; dementia, epilepsy, Peripheral neuropathy, tremor, ataxia, TCC, cerebellar atrophy.	AD	SPG4
HSP-NIPA1	Pure or complex; Peripheral neuropathy, spinal cord atrophy, spastic dysarthria,	AD	SPG6

	facial dystonia, atrophy of the small hand muscles, upper limb spasticity, epilepsy.		
HSP-KIAA0196	Pure spastic paraplegia	AD	SPG8
HSP-KIF5A	Pure or complex; allelic to Charcot Marie Tooth Neuropathy Type 2, Silver-syndrome, mental retardation, parkinsonism, deafness, retinitis, dysautonomia, sensory spinal cord-like syndrome.	AD	SPG10
HSP-RTN2	Pure spastic paraplegia	AD	SPG12
HSP-HSPD1	Pure or complex; dystonia.	AD	SPG13
HSP-BSCL2	Complex; Silver syndrome, these mutations may also cause distal hereditary neuropathy type 5.	AD	SPG17
HSP-REEP1	Pure or complex; distal motor neuronopathy, axonal Peripheral neuropathy, Silver-like syndrome, cerebellar	AD	SPG31

	ataxia, tremor, dementia.		
HSP-ZFYV327	Pure spastic paraplegia	AD	SPG33
Autosomal Recessive forms			
HSP-CYP7B1	Pure or complex; white matter lesions, optic atrophy, cerebellar ataxia, sensory ataxia.	AR	SPG5A
HSP-SPG7	Pure or complex; optic atrophy, cerebellar atrophy, dysarthria, dysphagia, TCC, CPEO-like phenotype, mitochondrial abnormalities on muscle biopsy.	AR/AD*	SPG7
HSP-KIAA1840	Pure or complex; May cause Kjellin syndrome; TCC, mental retardation, sensory neuropathy, amyotrophy, dysarthria, nystagmus, ataxia, parkinsonism, maculopathy, white matter lesions. Occasional parkinsonism.	AR	SPG11
HSP-ZFYVE26	Complex; Kjellin syndrome. TCC, WMLs, mental	AR	SPG15

	retardation, dysarthria, pigmentary maculopathy, peripheral neuropathy, distal amyotrophy. Occasional parkinsonism		
HSP-ERLIN2	Complex; intellectual decline, speech involvement, seizures, congenital hip dislocation.	AR	SPG18
HSP-SPARTIN	Complex; Troyer-syndrome. Early onset dysarthria, distal muscle wasting with contractures and cerebellar signs in some. Delayed cognition and dysmorphism.	AR	SPG20
HSP-ACP33	Pure or complex; Mast syndrome, Dementia, cerebellar involvement, dyskinesias, athetoid movements, TCC, white matter lesions.	AR	SPG21
HSP-B4GALNT	Complex; progressive dysarthria, distal amyotrophy, non-progressive cognitive impairment, cerebellar signs,	AR	SPG26

	sensory polyneuropathy, pes cavus, stereotypies, emotional lability, psychiatric illness, seizures.		
HSP-DDHD1	Pure and complex; cerebellar oculomotor disturbance, Peripheral neuropathy.	AR	SPG28
HSP-KIF1A	Pure or complex; cerebellar signs, PNP, allelic to hereditary sensory and autonomic neuropathy.	AR	SPG30
HSP/NBIA-FA2H (FAHN)	Pure or complex; cognitive decline, dysarthria, seizures, ataxia, dystonia, white matter lesions. Iron accumulation on imaging: GP (more subtle than other NBIAs)	AR	SPG35
HSP-PNPLA6/NT	Complex; axonal peripheral neuropathy, spinal cord atrophy, learning disability, speech impairment, cerebellar signs, allelic with Boucher-	AR	SPG39

	Neuhäuser and Gordon Holmes syndromes.		
HSP/NBIA-C19orf12	Mitochondrial membrane protein-associated neurodegeneration (MPAN) Complex; Silver-syndrome. Iron accumulation: GP – hyperintense streaking of medial medullary lamina between GPi and GPe; SN.	AR	SPG43
HSP-NT5C2	Complex; mental retardation, ocular signs	AR	SPG45
HSP-GBA2	Complex; mental impairment, cataract, hypogonadism in males, TCC and cerebellar atrophy on brain imaging.[36]	AR	SPG46
HSP-AP4B	Complex; intellectual disability, seizures, TCC, white matter lesions.	AR	SPG47
HSP-KIAA0415	Pure or complex; cervical cord hyperintensities.	AR	SPG48

HSP-TECPR2	Complex; severe intellectual disability, fluctuating central hypoventilation, gastresophageal reflux disease, awake apnea, areflexia, dysmorphic features.	AR	SPG49
HSP-APAM1	Complex; cerebral palsy, intellectual disability, reduction of cerebral white matter and atrophy of the cerebellum.	AR	SPG50
HSP-AP4E1	Complex; cerebral palsy, intellectual disability and microcephaly.	AR	SPG51
HSP-DDHD2	Complex; mental retardation, dysmorphism, short stature and dysgenesis of the corpus callosum.[37]	AR	SPG54
HSP-C12orf65	Complex; optic atrophy, peripheral neuropathy.	AR	SPG55
HSP-KIF1C. Allelic with autosomal recessive	Pure and complicated, chorea, myoclonus, dysarthria, developmental delay, mild mental retardation, hypodontia,	AR	SPG58

spastic ataxia at the SAX2 locus.	ptosis, short stature, sensorineural deafness, pes planus, white matter lesions.		
HSP-ERLIN1	Pure and complex; thoracic kyphosis, borderline intelligence.	AR	SPG62
HSP-NT5C2	Complex; learning disability, optic atrophy, squint, glaucoma, congenital cataract, TCC, white matter lesions, cystic occipital leukomalacia.	AR	SPG65
HSP-ALSIN	Complex, generalized dystonia, no speech	AR	Alsin
HSP-SACSIN	Spastic ataxia	AR	SACS
HSP- ALDH3A2	RM, ichtyosis, macular dystrophy, leukoencephalopathy	AR	Sjögren-Larsson syndrome
HSP-BICD2	SMA like	AR	
X-linked recessive			
HSP-L1CAM	Complex; MASA-syndrome, hydrocephalus, TCC.	XR	SPG1
HSP-PLP1	Pure or complex; optic	XR	SPG2

Allelic with Pelizaeus-Merzbacher disease.	atrophy, ataxia, nystagmus, peripheral neuropathy, aphasia, mental retardation.		
HSP-SLC16A2	Complex; Allan-Herndon-Dudley syndrome	XR	SPG22

TCC=thinning of the corpus callosum, SACS=Spastic Ataxia of Charlevoix-Saguenay, SMA=Spinal Muscular Atrophy

Silver syndrome: Complex HSP involving amyotrophy of the hand muscles

Kjellin syndrome: Complex HSP including thinning of the corpus callosum and central retinal degeneration

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

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, but 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 4 have been assigned, but only one has a known

and independently confirmed gene, SLC20A2 (Supplementary Table 7).[38, 39] 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.[40] No distinguishing phenotypic features of PFBC-SLC20A2 compared with the SLC20A2 mutation negative patients with familial brain calcification have yet been identified.[38] 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 despite the fact that it is associated with brain calcification.[41] This is because it does not primarily present with a movement disorder.

Table 7: The proposed new list of primary familial brain calcification

New designation	**Clinical clues**	**Inheri-tance**	**Locus symbol**
PFBC-SLC20A2	Various movement disorders, cognitive dysfunction	AD	IBGC3, IBGC1
PFBC-PDGFRB	Various movement disorders, cognitive dysfunction	AD	IBGC4
PFBC-PDGFB	Various movement disorders, cognitive dysfunction	AD	IBGC5

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 magnetic resonance imaging (MRI) in several brain regions, most consistently the globus pallidus.[42] 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, as well as oculomotor abnormalities, optic nerve,retinal and peripheral nerve involvement.

To date NBIA as a locus symbol (i.e. numerical designation) has only been applied to five disorders. However, up to nine distinct genetic disorders have been included under the NBIA umbrella term. Other disorders in this group have either retained the original disease name (e.g., aceruloplasminenemia, neuroferritinopathy) or, for more recently described disorders, been labelled with an acronym combining the name of the causative protein with "Associated Neurodegeneration" (i.e., PKAN for pantothenate kinase associated neurodegeneration). In Supplementary Table 8 we have provided a listing of all disorders that have been included under the umbrella NBIA classification.[43] Table 8 provides a new designation for each of these. Those that present consistently with one or more specific movement disorder phenotypes have been assigned a combined prefix (e.g. NBIA/DYT) and are included in the list specific to that movement disorder.

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Table 8: The proposed new list of Neurodegeneration with Brain Iron Accumulation

New designa-tion	**Clinical clues**	**Inheritance pattern**	**Locus symbol**
NBIA/DYT-PANK2	Pantothenate kinase associated neurodegeneration (PKAN) Iron accumulation: GP - Eye of the tiger, Phenotype: Dystonia, spasticity, parkinsonism, chorea, psychiatric cognitive decline, gaze palsy, pigmentary retinopathy	AR	NBIA1
NBIA/DYT/PARK-PLA2G6	*PLA2G6*-associated neurodegeneration (PLAN) Iron accumulation: GP, SN in some; adults may have striatal involvement; ½ INAD and majority of adult-onset lack imaging BIA on MRI. Infantile phenotype: Developmental delay, hypotonia, ataxia, pyramidal signs, optic atrophy, sensorimotor axonal neuropathy seizures.	AR	NBIA2, PARK14

	Adult phenotype: Dystonia-parkinsonism, pyramidal signs, cognitive, psychiatric features		
NBIA-CP	Aceruloplasminemia Iron accumulation: More homogeneous involvement of GP, caudate, putamen, thalamus, red nucleus, dentate Phenotype: Cognitive impairment, cranial dyskinesia (incl blepharospasm), ataxia, chorea, retinal degeneration, diabetes, liver disease.	AR	
NBIA-FTL	Neuroferritinopathy Iron accumulation: GP, caudate, putamen, SN, red nucleus. Cystic BG changes – pallidal necrosis. Phenotype: Chorea, stereotypies, cranial dyskinesia/dystonia, parkinsonism, ataxia, cognitive and psychiatric dysfunction.	AD	NBIA3
NBIA-WDR45	Beta-propeller protein associated neurodegeneration (BPAN – previously SENDA*) Iron accumulation: GP, SN (more than GP).	X-linked dominant	NBIA5

	Phenotype: Global developmental delay in childhood, seizures, spasticity, Rett-like features, disordered sleep; early adulthood progressive dystonia, parkinsonism seizures,dementia		
NBIA-*DCAF17*	Woodhouse-Sakati syndrome Iron accumulation: GP, SN, other BG (variable evidence for BIA). Phenotype: Generalized and focal dystonia, dysarthria, deafness, seizures, cognitive decline. Hypogonadism, alopecia, diabetes mellitus, thyroid dysfunction, keratoconus, camptodactyly, acanthosis nigrans	AR	
NBIA-*COASY*	CoA synthase protein associated neurodegeneration (CoPAN) 2 patients to date[44] Iron accumulation: GP with central hyperintensity (calcification on CT), SN; early swelling and hyperintensity in caudate, putamen and thalamus (1 patient)	AR	

	Phenotype: Dystonia, spasticity, cognitive impairment, bradykinesia, rigidity, motor axonal neuropathy, obsessive compulsive behavior, tics.		
Members of other lists that have brain iron accumulation as a consistent feature			
HSP/NBIA-FA2H (FAHN)	Fatty acid hydroxylase associated neurodegeneration (FAHN) Iron accumulation: GP (more subtle than other NBIAs) Phenotype: Pure or complex; cognitive decline, dysarthria, seizures, ataxia, dystonia, white matter lesions.	AR	SPG35
HSP/NBIA-C19orf12 (MPAN)	Mitochondrial membrane protein associated neurodegeneration (MPAN) Iron accumulation: GP – hyperintense streaking of medial medullary lamina between GPi and GPe; SN. Phenotype: Spasticity, dystonia, parkinsonism, cognitive decline, psychiatric	AR	NBIA4, SPG43

	abn, optic atrophy, motor axonopathy		
Members of other lists that occasionally have brain iron accumulation on imaging as a feature			
PARK-ATP13A2	Kufor Rakeb syndrome: Juvenile or early onset parkinsonism, vertical gaze palsy, minifacial-faucial myoclonus, pyramidal signs	AR	PARK9

BIA = Brain iron accumulation, GP – globus pallidus, GPi = GP internal segment, GPe = GP external segment, SN = substantia nigra, BG = basal ganglia, INAD = Infantile neuroaxonal dystrophy; VSNGP = vertical supranuclear gaze palsy, Bx = biopsy, ERG = electroretinogram

*SENDA: static encephalopathy of childhood with neurodegeneration in adulthood

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. However, we have tried to include all of those disorders that have a movement disorder as a *consistent* and predominant feature. At the same time, in circumstances where mutations in a specific gene can cause more than one distinct phenotype and where one of those phenotypes is a frequent cause of a particular movement disorder (e.g. SLC2A1 mutations causing infantile developmental delay and epilepsy OR paroxysmal exertion-induced dystonia) we have chosen to retain it in the lists. This system is bound to be associated with some 'misclassification' however, since for many disorders there is insufficient knowledge on the frequency of movement disorders compared with other phenotypes to render a decision on this basis. 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 (e.g. 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 conscious 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 has to be very cautious about the nature of variants found in a given gene, since except for recurrent mutations or repeat expansions, the pathogenicity of a new missense 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 becomes available.

Next steps

Our work is not yet complete - it remains to compile lists for the recessively inherited and congenital ataxias and for genetic causes of myoclonus. This will be taken on as a next project of the task force, involving 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 (for example in mutations of SPG7 or Parkin) and reduced penetrance (all dominant forms of inherited movements disorders) or imprinting (for example in DYT-SGCE).

As mentioned above, 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 task 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 vs 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 would 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. Annals of Neurology 1990;27:114-120.

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;78:1016-1024.

3. MacArthur DG, Manolio TA, Dimmock DP, et al. Guidelines for investigating causality of sequence variants in human disease. Nature 2014;508:469-476.

4. Bonifati V. Genetics of Parkinson's disease--state of the art, 2013. Parkinsonism & Related Disorders 2014;20 Suppl 1:S23-28.

5. Trinh J, Farrer M. Advances in the genetics of Parkinson disease. Nat Rev Neurol 2013;9:445-454.

6. 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;71:752-757.

7. 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;26:157-161.

8. Furukawa Y, Kish S. Tyrosine Hydroxylase Deficiency. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. Gene Reviews: University of Washingon, 2014.

9. Friedman J, Roze E, Abdenur JE, et al. Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy. Annals of Neurology 2012;71:520-530.

10. Opladen T, Hoffmann GF, Blau N. An international survey of patients with tetrahydrobiopterin deficiencies presenting with hyperphenylalaninaemia. Journal of Inherited Metabolic Disease 2012;35:963-973.

11. Sedel F, Saudubray JM, Roze E, Agid Y, Vidailhet M. Movement disorders and inborn errors of metabolism in adults: a diagnostic approach. Journal of Inherited Metabolic Disease 2008;31:308-318.

12. 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, 2012.

13. Klein C. Genetics in dystonia. Parkinsonism & Related Disorders 2014;20 Suppl 1:S137-142.

14. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;28:863-873.

15. Mitchell GA FT. 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.

16. Kolker S, Christensen E, Leonard JV, et al. Diagnosis and management of glutaric aciduria type I--revised recommendations. Journal of Inherited Metabolic Disease 2011;34:677-694.

17. Ng J, Zhen J, Meyer E, et al. Dopamine transporter deficiency syndrome: phenotypic spectrum from infancy to adulthood. Brain 2014;137:1107-1119.

18. 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, 2013.

19. Ha AD, Parratt KL, Rendtorff ND, et al. The phenotypic spectrum of dystonia in Mohr-Tranebjaerg syndrome. Mov Disord 2012;27:1034-1040.

20. 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;25:180-184.

21. Gardiner AR, Bhatia KP, Stamelou M, et al. PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine. Neurology 2012;79:2115-2121.

22. Bhatia KP. Paroxysmal dyskinesias. Mov Disord 2011;26:1157-1165.

23. Fernandez-Alvarez E, Perez-Duenas B. Paroxysmal movement disorders and episodic ataxias. Handb 2013;112:847-852.

24. Jen JC. Hereditary episodic ataxias. Annals of the New York Academy of Sciences 2008;1142:250-253.

25. Wang D, Pascual JM, De Vivo D. Glucose Transporter Type 1 Deficiency Syndrome. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews. Seattle (WA): University of Washington, 2012.

26. Van Hove J, Coughlin C, Scharer G. Glycine Encephalopathy. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews. Seattle (WA): University of Washington, 2013.

27. 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;106:385-394.

28. Seow HF, Broer S, Broer A, et al. Hartnup disorder is caused by mutations in the gene encoding the neutral amino acid transporter SLC6A19. Nature Genetics 2004;36:1003-1007.

29. Verbeek DS, van de Warrenburg BP. The autosomal dominant cerebellar ataxias. Seminars in Neurology 2011;31:461-469.

30. Van Gaalen J, Giunti P, van de Warrenburg BP. Movement disorders in spinocerebellar ataxias. Mov Disord 2011;26:792-800.

31. 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;3:517-525.

32. 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. Human Molecular Genetics 2009;18:2266-2276.

33. 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.

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

35. Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. Lancet Neurology 2008;7:1127-1138.

36. 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;92:238-244.

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

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

39. Wang C, Li Y, Shi L, et al. Mutations in SLC20A2 link familial idiopathic basal ganglia calcification with phosphate homeostasis. Nature Genetics 2012;44:254-256.

40. 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 Washington: University of Washington, Seattle, 2013.

41. Stephenson JB. Aicardi-Goutieres syndrome (AGS). Europ J Paediatr Neurol 2008;12:355-358.

42. Doorn JM, Kruer MC. Newly characterized forms of neurodegeneration with brain iron accumulation. Current Neurology & Neuroscience Reports 2013;13:413.

43. 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;27:42-53.

44. Dusi S, Valletta L, Haack TB, et al. Exome sequence reveals mutations in CoA synthase as a cause of neurodegeneration with brain iron accumulation. American Journal of Human Genetics 2014;94:11-22.