Date of Search: Dec 2016

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

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| **New designation**  | **Less common movement phenotype** | **Clinical clues** | **Inheritance pattern** | **Locus symbol** |
| **Isolated dystonias** |
| DYT-*TOR1A*[*1*](#_ENREF_1) |  | Early-onset generalized dystoniaGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1492/OMIM 128100 | AD  | *DYT1* |
| DYT-*THAP1*[*2*](#_ENREF_2) |  | Adolescent-onset dystonia of mixed typeGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1155/OMIM 602629 | AD  | *DYT6* |
| DYT-*GNAL*[*3*](#_ENREF_3) |  | Adult onset cranial-cervical dystoniaGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1155/OMIM 615073 | AD  | *DYT25* |
| DYT-ANO3[4](#_ENREF_4) | tremor | Cranial-cervical dystoniaGeneReviews <https://www.ncbi.nlm.nih.gov/books/NBK1155/>OMIM 615034 | AD | *DYT24* |
| DYT-KMT2B[5](#_ENREF_5), [6](#_ENREF_6) |  | Childhood-onset, generalized dystoniaAdditional clinical manifestations may include intellectual disability, microcephalyGeneReviews: n/aOMIM 617284 | AD | *DYT28* |
| **Combined dystonias (disorders where dystonia frequently coexists with other movement disorders)**  |
| DYT-*PRKRA*[*7*](#_ENREF_7) |  | Rare form of usually generalizeddystonia, parkinsonism inconsistent GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1155/OMIM 612067 | AR | *DYT16* |
| DYT/PARK-*GCH1*[*8*](#_ENREF_8) |  | GTP cyclohydrolase I deficiency (mild form)[9](#_ENREF_9): Childhood-onset dopa-responsive dystonia, adult-onset dystonia-parkinsonismAdditional clinical manifestations: diurnal fluctuation, pyramidal signsGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1508/OMIM 128230 | AD | *DYT5a* |
|  | GTP cyclohydrolase I deficiency (severe form)[10](#_ENREF_10): Dystonia, parkinsonismAdditional clinical manifestations: Developmental delay, truncal hypotonia, spasticity, oculogyric crises, seizures, with or without hyperphenylalaninemiaGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1508/OMIM 128230 | AR | none |
| DYT/PARK-*TH*[*11*](#_ENREF_11) |  | Tyrosine hydroxylase deficiencyGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1155/OMIM 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*[*12*](#_ENREF_12) |  | Rapid-onset dystonia-parkinsonism, chorea in later life\*\*GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1115/OMIM 128235 | AD  | *DYT12* |
| DYT/PARK-*TAF1*[*13*](#_ENREF_13)*\** |  | Dystonia-parkinsonismGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1155/OMIM 314250 | X-linked  | *DYT3* |
| DYT-*SGCE*[*14*](#_ENREF_14) |  | Myoclonus-dystoniaGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1414/OMIM 159900 | 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)** |
| CHOR/DYT-*ADCY5*[*15*](#_ENREF_15) |  | Facial dyskinesias, occasional myoclonus. May have paroxysmal worsening.GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK263441/OMIM 600293 | AD | None |
| DYT/CHOR-*HPRT*[*16*](#_ENREF_16) |  | Lesch-Nyhan syndrome: Dystonia, chorea, occasionally ballismAdditional clinical features: Hyperuricemia, crystalluria, developmental delay/intellectual disability, eye movement abnormalities, spasticity, compulsive self-injurious behavior, gouty arthritis, nephrolithiasis, renal failurebehaviorGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1149/OMIM 300322 | X-linked | None |
| DYT/CHOR-*ACAT1*[*17*](#_ENREF_17) |  | Mitochondrial acetoacetyl-CoA thiolase deficiency: metabolic decompensation and basal ganglia injury during acute stress resulting in dystonia and choreaGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1134/OMIM 203750 | AR | none |
| DYT/CHOR-*GCDH*[*18*](#_ENREF_18) |  | Glutaric aciduria type I[19](#_ENREF_19): 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, seizureshttp://www.ncbi.nlm.nih.gov/books/NBK1134/OMIM 231670 | AR | None |
| DYT/CHOR-*MUT*[*20*](#_ENREF_20) |  | Methylmalonic aciduria: Dystonia, chorea, occasionally ataxiaAdditional 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)GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1134/OMIM | AR | None |
| DYT/CHOR-*PCCA/PCCB*[*21*](#_ENREF_21) |  | Propionic aciduria[22](#_ENREF_22): Dystonia, occasionally choreaAdditional 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)GeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1134/OMIM | AR | None |
| NBIA/DYT- *DCAF17*[*23*](#_ENREF_23) | chorea[24](#_ENREF_24) | Woodhouse-Sakati syndrome[25](#_ENREF_25): Iron accumulation: GP, SN, other BG (variable)Additional clinical features: Dysarthria, deafness, seizures, cognitive impairment, hypogonadism, alopecia, diabetes mellitus, thyroid dysfunction, acanthosis nigrans, keratoconus, camptodactylyGeneReviews: n/aOMIM 241080 | AR | None |
| DYT-*DDC*[*26*](#_ENREF_26) |  | Aromatic l-amino acid decarboxylase deficiency[27](#_ENREF_27): Dystonia, occasionally chorea, hypokinesiaAdditional clinical features: Developmental delay, truncal hypotonia, oculogyric crises, ptosis, autonomic symptoms, sleep disorder, diurnal fluctuations with sleep benefitGeneReviews: n/aOMIM 608643 | AR | None |
| DYT/PARK-*SLC30A10*[*28*](#_ENREF_28)*,* [*29*](#_ENREF_29) |  | Hypermanganesemia with dystonia, polycythemia, and liver cirrhosis:Dystonia, parkinsonismAdditional clinical features: Hypermanganesemia, polycythemia, chronic liver disease, dysarthriaGeneReviews: http://www.ncbi.nlm.nih.gov/books/NBK100241/OMIM 611146 | AR | None |
| DYT/PARK-*SPR*[*30*](#_ENREF_30) |  | Sepiapterin reductase deficiency: Dystonia, parkinsonismAdditional 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](#_ENREF_31" \o "Friedman, 2012 #1503)GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK304122/OMIM 612716 | AR | None |
| DYT/PARK-*QDPR*[*32*](#_ENREF_32) |  | Dihydropteridine reductase deficiency[33](#_ENREF_33): Dystonia, parkinsonismAdditional clinical features: Developmental delay, truncal hypotonia, seizures, autonomic dysfunction, hyperphenylalaninemiaGeneReviews: n/aOMIM 612676 | AR  | None |
| DYT/PARK-*PTS*[*34*](#_ENREF_34) |  | 6-pyruvoyl-tetrahydropterin synthase deficiency[35](#_ENREF_35): Dystonia, parkinsonismAdditional clinical features: Neonatal irritability, truncal hypotonia, developmental delay, seizures, oculogyric crises, autonomic dysfunction, hyperphenylalaninemiaGeneReviews: n/aOMIM 612719 | AR | None |
| DYT/PARK-*SLC6A3*[*36*](#_ENREF_36) |  | Dopamine transporter deficiency syndrome[37](#_ENREF_37): Dystonia and parkinsonism (typically infantile-onset, atypical cases with juvenile-onset exist), occasionally chorea in infancyAdditional clinical features: Mild developmental delay, truncal hypotonia, ocular flutter / oculogyric crises, saccade initiation failure, bulbar dysfunction34GeneReviews: n/aOMIM 126455 | AR | None |
| NBIA/DYT-*PANK2*[*38*](#_ENREF_38) | parkinsonism, chorea | Pantothenate kinase-associated neurodegeneration (PKAN): Iron accumulation: GP – eye of the tiger signAdditional clinical features: Spasticity, dysarthria, cognitive decline, gaze palsy, psychiatric symptoms, pigmentary retinopathyGeneReviews: http://www.ncbi.nlm.nih.gov/books/NBK121988/OMIM 234200 | AR |  |
| NBIA/DYT/PARKǂ -*PLA2G6*[*39*](#_ENREF_39) | ataxia[40](#_ENREF_40) | *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 MRIGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1675/OMIM 612953 | AR | NBIA2, PARK14 |
| DYT-*ATP7B*[*41*](#_ENREF_41)*,* [*42*](#_ENREF_42) |  | Wilson’s disease: Dystonia, occasionally parkinsonism and/or choreaAdditional clinical features: Flapping tremor, rest-, action- and intention tremor, orofacial dyskinesias, dysarthria, liver disease, Kayser-Fleischer rings, psychiatric symptomsGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1512/OMIM 277900 | AR | None |
| DYT- *SLC19A3*[*43*](#_ENREF_43) |  | Biotin-responsive basal ganglia disease (within the thiamine transporter–2 (hTHTR2) deficiency spectrum)[44](#_ENREF_44): 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 therapyGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK169615/OMIM 606152 | AR  | None |
| DYT-*TIMM8A*[*45*](#_ENREF_45) |  | Mohr-Tranebjaerg syndrome[46](#_ENREF_46): DystoniaAdditional clinical features: Sensorineural deafness, visual impairment, cognitive impairment, behavioral problems, pyramidal signs92GeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1216/OMIM 304700 | X-linked | None |
| DYT-*mt-ND6*[*47*](#_ENREF_47) |  | Leber’s hereditary optic neuropathy/dystonia (G14459A mutation)[48](#_ENREF_48): DystoniaAdditional clinical features: Juvenile-onset subacute vision loss (Leber hereditary optic neuropathy), encephalopathy, spasticity, bulbar dysfunction, cognitive impairmentGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1174/OMIM 516006 | Mitochondrial | None |
| DYT/PARK-*GLB1*[*49*](#_ENREF_49)*,* [*50*](#_ENREF_50) |  | GM1 gangliosidosis (type III, chronic/adult form)[51](#_ENREF_51): Dystonia, parkinsonismAdditional clinical features: Pyramidal signs, dysarthria, cognitive deficits (often mild initially), skeletal abnormalities and short statue, corneal clouding, vacuolated cells, cardiomyopathy, progressive diseaseGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK164500/OMIM 230650 | AR | None  |
| NBIA/DYT/PARK-*CP*[*52*](#_ENREF_52) | chorea | Aceruloplasminemia[53](#_ENREF_53" \o "Vroegindeweij, 2017 #1564): Dystonia, ataxia, chorea, parkinsonism, tremorsIron accumulation: More homogeneous involvement of primarily, caudate, putamen, thalamus, dentateAdditional clinical features: Cognitive impairment, psychiatric symptoms, diabetes mellitus, retinal degeneration, anemia, liver iron storageGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1493/OMIM 604290 | AR |  |
| DYT-*SUCLA2*[*54*](#_ENREF_54)*,* [*55*](#_ENREF_55) |  | SUCLA2-related mitochondrial DNA (mtDNA) depletion syndrome[56](#_ENREF_56), [57](#_ENREF_57), encephalomyopathic form, with mild methylmalonic aciduria: DystoniaAdditional clinical features: Severe hypotonia, developmental delay, seizures, progressive spasticity, cerebral atrophy, sensorineural hearing loss, ophthalmoplegia, feeding problems and postnatal growth retardation, ptosisGeneReviews:http://www.ncbi.nlm.nih.gov/books/NBK6803/OMIM 603921 | AR | None |
| DYT\*\*\*-*TUBB4A*[*58*](#_ENREF_58)*,* [*59*](#_ENREF_59) | HSP[60](#_ENREF_60), [61](#_ENREF_61) | Spasmodic dysphonia is most common dystonic presentation. Alternative, phenotype: Hypomyelinating leukodystrophy[62](#_ENREF_62" \o "Simons, 2013 #1613) (see footnote)  | AD | DYT4 |
| DYT/CHOR-ADAR1[63](#_ENREF_63) | Spasticity | Aicardi-Goutières syndrome, includes dystonia and spatic paraparesis, MRI may reveal isolated bilateral striatal necrosis, adult-onset psychological difficulties[64](#_ENREF_64), linked to characteristic interferon signature (upregulation of interferon-stimulated genes)[63](#_ENREF_63)GeneReviews: <https://www.ncbi.nlm.nih.gov/books/NBK1475/>OMIM: 615010 | mostly AR, rarely AD | None |
| **Disorders that usually present with other phenotypes but can have predominant dystonia** |
| SCA-*ATXN3*[*65*](#_ENREF_65) | Spastic paraplegia[66](#_ENREF_66),Dystonia[67](#_ENREF_67) | Marked non-ataxia features; can have predominant parkinsonism, dystonia, chorea, spasticity, neuropathy, lower motor neuron involvementGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1196/OMIM 109150 | AD | SCA3 |
| NBIA/PARK- *WDR45*[*68*](#_ENREF_68) | dystonia | Beta-propeller protein-associated neurodegeneration (BPAN, previously SENDA syndrome)[69](#_ENREF_69):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 encephalopathyGeneReviews https://www.ncbi.nlm.nih.gov/books/NBK424403/OMIM 300894 | X-linked | NBIA5 |
| NBIA/CHOR-*FTL*[*70*](#_ENREF_70) | Dystonia, parkinsonism | Neuroferritinopathy:Dystonia, chorea, parkinsonism[71](#_ENREF_71)Iron accumulation: GP, caudate, putamen, SN, red nucleus; cystic BG changes – pallidal necrosisAdditional clinical features: Oromandibular dyskinesia, dysphagia, cognitive impairment, behavioral symptoms, low serum ferritinGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1141/OMIM 606159 | AD | NBIA3 |
| HSP/NBIA- *FA2H*[*72*](#_ENREF_72) | Dystonia, parkinsonism, ataxia[73](#_ENREF_73) | Fatty Acid Hydroxylase-associated Neurodegeneration (FAHN)[73](#_ENREF_73):Iron accumulation: GP (more subtle than other NBIAs)Additional clinical features: Spastic tetraparesis, cognitive decline, cerebellar and brainstem atrophy, dysarthria, dysphagia, optic nerve atrophy, seizuresGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1509/OMIM 612319 | AR | SPG35 |
| HSP-*KIF1C*[*74*](#_ENREF_74)Allelic with autosomal recessive spastic ataxia at the SAX2 locus. | Dystonia, ataxia | Pure and complicated, chorea, myoclonus, dysarthria, developmental delay, mild mental retardation, hypodontia, ptosis, short stature, sensorineural deafness, pes planus, white matter lesions.GeneReviews: http://www.ncbi.nlm.nih.gov/books/NBK1509/OMIM 611302 | AR | SPG58 |
| HSP/NBIA-*C19orf12*[*75*](#_ENREF_75) | Dystonia, parkinsonism | Mitochondrial membrane protein-associated neurodegeneration (MPAN)[76](#_ENREF_76): Iron accumulation: GP - hyperintense streaking of medial medullary lamina between GPi and GPe; SNAdditional clinical features: Progressive spastic paresis, dysarthria, dysphagia, cognitive decline/dementia, motor axonal neuropathy, optic nerve atrophy, psychiatric symptoms, bowel/bladder incontinenceGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK185329/OMIM 614298 | AR | NBIA4/SPG43 |
| GNB1[77](#_ENREF_77) | Chorea, ataxia[78](#_ENREF_78) | In combination with global development delay and seizures[79](#_ENREF_79)GeneReviews: n/aOMIM 616973 | AD | None |
| DYT/CHOR-FOXG1[80](#_ENREF_80) | Dyskinesia[81](#_ENREF_81), [82](#_ENREF_82) | Rett-like phenotype (with congenital encephalopathy), GeneReviews: <https://www.ncbi.nlm.nih.gov/books/NBK1497/>OMIM 613454 | AD | None |

INAD: infantile NeuroAxonal Dystrophy

**References**

1. Ozelius LJ, Hewett JW, Page CE, et al. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet 1997;17:40-48.

2. Fuchs T, Gavarini S, Saunders-Pullman R, et al. Mutations in the THAP1 gene are responsible for DYT6 primary torsion dystonia. Nat Genet 2009;41:286-288.

3. Fuchs T, Saunders-Pullman R, Masuho I, et al. Mutations in GNAL cause primary torsion dystonia. Nat Genet 2013;45:88-92.

4. Charlesworth G, Plagnol V, Holmstrom KM, et al. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. Am J Hum Genet 2012;91:1041-1050.

5. Meyer E, Carss KJ, Rankin J, et al. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet 2017;49:223-237.

6. Zech M, Boesch S, Maier EM, et al. Haploinsufficiency of KMT2B, Encoding the Lysine-Specific Histone Methyltransferase 2B, Results in Early-Onset Generalized Dystonia. Am J Hum Genet 2016;99:1377-1387.

7. 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;7:207-215.

8. 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;8:236-242.

9. 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;69:1558-1562.

10. 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.

11. Ludecke B, Dworniczak B, Bartholome K. A point mutation in the tyrosine hydroxylase gene associated with Segawa's syndrome. Hum Genet 1995;95:123-125.

12. 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;43:169-175.

13. Muller U, Herzfeld T, Nolte D. The TAF1/DYT3 multiple transcript system in X-linked dystonia-parkinsonism. Am J Hum Genet 2007;81:415-417; author reply 417-418.

14. Zimprich A, Grabowski M, Asmus F, et al. Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. Nat Genet 2001;29:66-69.

15. Chen YZ, Matsushita MM, Robertson P, et al. Autosomal dominant familial dyskinesia and facial myokymia: single exome sequencing identifies a mutation in adenylyl cyclase 5. Arch Neurol 2012;69:630-635.

16. Gibbs RA, Caskey CT. Identification and localization of mutations at the Lesch-Nyhan locus by ribonuclease A cleavage. Science 1987;236:303-305.

17. 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;72:109-114.

18. 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;59:1006-1011.

19. Kolker S, Christensen E, Leonard JV, et al. Diagnosis and management of glutaric aciduria type I--revised recommendations. J Inherit Metab Dis 2011;34:677-694.

20. 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;47:808-814.

21. 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;101:93-96.

22. 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;38:1059-1074.

23. 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;83:684-691.

24. 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:149-160.

25. Schneider SA, Bhatia KP. Dystonia in the Woodhouse Sakati syndrome: A new family and literature review. Mov Disord 2008;23:592-596.

26. Depienne C, Cincotta M, Billot S, et al. A novel DCC mutation and genetic heterogeneity in congenital mirror movements. Neurology 2011;76:260-264.

27. Brun L, Ngu LH, Keng WT, et al. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. Neurology 2010;75:64-71.

28. 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;90:457-466.

29. Quadri M, Federico A, Zhao T, et al. Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. Am J Hum Genet 2012;90:467-477.

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;69:269-277.

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

32. Howells DW, Forrest SM, Dahl HH, Cotton RG. Insertion of an extra codon for threonine is a cause of dihydropteridine reductase deficiency. Am J Hum Genet 1990;47:279-285.

33. Dianzani I, de Sanctis L, Smooker PM, et al. Dihydropteridine reductase deficiency: physical structure of the QDPR gene, identification of two new mutations and genotype-phenotype correlations. Hum Mutat 1998;12:267-273.

34. Thony B, Leimbacher W, Blau N, Harvie A, Heizmann CW. Hyperphenylalaninemia due to defects in tetrahydrobiopterin metabolism: molecular characterization of mutations in 6-pyruvoyl-tetrahydropterin synthase. Am J Hum Genet 1994;54:782-792.

35. Leuzzi V, Carducci CA, Carducci CL, et al. Phenotypic variability, neurological outcome and genetics background of 6-pyruvoyl-tetrahydropterin synthase deficiency. Clin Genet 2010;77:249-257.

36. Kurian MA, Zhen J, Cheng SY, et al. Homozygous loss-of-function mutations in the gene encoding the dopamine transporter are associated with infantile parkinsonism-dystonia. J Clin Invest 2009;119:1595-1603.

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

38. 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;28:345-349.

39. Paisan-Ruiz C, Bhatia KP, Li A, et al. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann Neurol 2009;65:19-23.

40. 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;112:183-189.

41. 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;5:327-337.

42. Tanzi RE, Petrukhin K, Chernov I, et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat Genet 1993;5:344-350.

43. 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;77:16-26.

44. Ortigoza-Escobar JD, Serrano M, Molero M, et al. Thiamine transporter-2 deficiency: outcome and treatment monitoring. Orphanet J Rare Dis 2014;9:92.

45. Jin H, May M, Tranebjaerg L, et al. A novel X-linked gene, DDP, shows mutations in families with deafness (DFN-1), dystonia, mental deficiency and blindness. Nat Genet 1996;14:177-180.

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

47. Kirby DM, Kahler SG, Freckmann ML, Reddihough D, Thorburn DR. Leigh disease caused by the mitochondrial DNA G14459A mutation in unrelated families. Ann Neurol 2000;48:102-104.

48. Gropman A, Chen TJ, Perng CL, et al. Variable clinical manifestation of homoplasmic G14459A mitochondrial DNA mutation. Am J Med Genet A 2004;124A:377-382.

49. Yoshida K, Oshima A, Sakuraba H, et al. GM1 gangliosidosis in adults: clinical and molecular analysis of 16 Japanese patients. Ann Neurol 1992;31:328-332.

50. Nishimoto J, Nanba E, Inui K, Okada S, Suzuki K. GM1-gangliosidosis (genetic beta-galactosidase deficiency): identification of four mutations in different clinical phenotypes among Japanese patients. Am J Hum Genet 1991;49:566-574.

51. Brunetti-Pierri N, Scaglia F. GM1 gangliosidosis: review of clinical, molecular, and therapeutic aspects. Mol Genet Metab 2008;94:391-396.

52. Yoshida K, Furihata K, Takeda S, et al. A mutation in the ceruloplasmin gene is associated with systemic hemosiderosis in humans. Nat Genet 1995;9:267-272.

53. Vroegindeweij LH, Langendonk JG, Langeveld M, et al. New insights in the neurological phenotype of aceruloplasminemia in Caucasian patients. Parkinsonism Relat Disord 2017;36:33-40.

54. Ostergaard E, Hansen FJ, Sorensen N, et al. Mitochondrial encephalomyopathy with elevated methylmalonic acid is caused by SUCLA2 mutations. Brain 2007;130:853-861.

55. 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;130:862-874.

56. 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;9:438-442.

57. Carrozzo R, Verrigni D, Rasmussen M, et al. Succinate-CoA ligase deficiency due to mutations in SUCLA2 and SUCLG1: phenotype and genotype correlations in 71 patients. J Inherit Metab Dis 2016;39:243-252.

58. Lohmann K, Wilcox RA, Winkler S, et al. Whispering dysphonia (DYT4 dystonia) is caused by a mutation in the TUBB4 gene. Ann Neurol 2013;73:537-545.

59. Hersheson J, Mencacci NE, Davis M, et al. Mutations in the autoregulatory domain of beta-tubulin 4a cause hereditary dystonia. Ann Neurol 2013;73:546-553.

60. Kancheva D, Chamova T, Guergueltcheva V, et al. Mosaic dominant TUBB4A mutation in an inbred family with complicated hereditary spastic paraplegia. Mov Disord 2015;30:854-858.

61. Sagnelli A, Magri S, Farina L, et al. Early-onset progressive spastic paraplegia caused by a novel TUBB4A mutation: brain MRI and FDG-PET findings. J Neurol 2016;263:591-593.

62. Simons C, Wolf NI, McNeil N, et al. A de novo mutation in the beta-tubulin gene TUBB4A results in the leukoencephalopathy hypomyelination with atrophy of the basal ganglia and cerebellum. Am J Hum Genet 2013;92:767-773.

63. Livingston JH, Lin JP, Dale RC, et al. A type I interferon signature identifies bilateral striatal necrosis due to mutations in ADAR1. J Med Genet 2014;51:76-82.

64. Rice GI, Kitabayashi N, Barth M, et al. Genetic, Phenotypic, and Interferon Biomarker Status in ADAR1-Related Neurological Disease. Neuropediatrics 2017;48:166-184.

65. 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;8:221-228.

66. 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;9:417-420.

67. 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;246:840-842.

68. 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;91:1144-1149.

69. Saitsu H, Nishimura T, Muramatsu K, et al. De novo mutations in the autophagy gene WDR45 cause static encephalopathy of childhood with neurodegeneration in adulthood. Nat Genet 2013;45:445-449, 449e441.

70. 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;28:350-354.

71. Devos D, Tchofo PJ, Vuillaume I, et al. Clinical features and natural history of neuroferritinopathy caused by the 458dupA FTL mutation. Brain 2009;132:e109.

72. 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;83:643-648.

73. 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;68:611-618.

74. Dor T, Cinnamon Y, Raymond L, et al. KIF1C mutations in two families with hereditary spastic paraparesis and cerebellar dysfunction. J Med Genet 2014;51:137-142.

75. 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;89:543-550.

76. Hogarth P, Gregory A, Kruer MC, et al. New NBIA subtype: genetic, clinical, pathologic, and radiographic features of MPAN. Neurology 2013;80:268-275.

77. Steinrucke S, Lohmann K, Domingo A, et al. Novel GNB1 missense mutation in a patient with generalized dystonia, hypotonia, and intellectual disability. Neurol Genet 2016;2:e106.

78. Lohmann K, Masuho I, Patil DN, et al. Novel GNB1 mutations disrupt assembly and function of G protein heterotrimers and cause global developmental delay in humans. Hum Mol Genet 2017;26:1078-1086.

79. Petrovski S, Kury S, Myers CT, et al. Germline De Novo Mutations in GNB1 Cause Severe Neurodevelopmental Disability, Hypotonia, and Seizures. Am J Hum Genet 2016;98:1001-1010.

80. Kortum F, Das S, Flindt M, et al. The core FOXG1 syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis. J Med Genet 2011;48:396-406.

81. Cellini E, Vignoli A, Pisano T, et al. The hyperkinetic movement disorder of FOXG1-related epileptic-dyskinetic encephalopathy. Dev Med Child Neurol 2016;58:93-97.

82. Papandreou A, Schneider RB, Augustine EF, et al. Delineation of the movement disorders associated with FOXG1 mutations. Neurology 2016;86:1794-1800.