Updated complete list of hereditary parkinsonism

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| **Designation** | **Less common movement phenotype** | **Clinical features** | **OMIM** | **MOI** |
| **Classical parkinsonism** |
| PARK-*CHCHD269, 70, 297-302* |  | Typical levodopa-responsive parkinsonism | 616710 | AD |
| PARK-*LRRK2*303 |  |  Classic levodopa-responsive parkinsonism | 607060 | AD |
| PARK-*SNCA*304 |  | Missense mutations cause classical parkinsonism, duplication or triplication mutations in this gene cause early onset parkinsonism with prominent dementia | 168601 | AD |
| PARK-*VPS35*305 |  |   | 614203 | AD |
| **Early onset parkinsonism** |
| PARK-*DJ1*306 |  |   | 606324 | AR |
| PARK-*parkin*307 |  | Often presents with dystonia, often in a leg  | 600116 | AR |
| PARK-*PINK1*308 |  | Psychiatric features common  | 605909 | AR |
| **Atypical parkinsonism or complex phenotypes** |
| PARK-*DCTN1309-312* |  | Adult-onset (atypical) parkinsonism with depression or apathy, followed by weight loss and respiratory hypoventilation/failure (referred to as *Perry syndrome*); some cases reported with PSP-like phenotype  | 168605 | AD |
| PARK-*DNAJC6*313 | Dystonia | Occasional mental retardation and seizures  | 615528 | AR |
| PARK-*FBXO7*314 |  | Early onset parkinsonism with pyramidal signs  | 260300 | AR |
| PARK-*JAM2136, 137,315* |  | Atypical parkinsonism with cognitive deficits, brain imaging: calcifications in basal ganglia, cerebellum and white matter | 618824 | AR |
| PARK-*RAB39B316-318* |  | Early-onset (atypical) parkinsonism, delayed psychomotor development, impaired intellectual development (referred to as *Waisman syndrome*) | 311510 | XLR |
| PARK-*SLC20A2*-(PFBC)*315, 319* |  | Atypical parkinsonism, commonly with cognitive deficits and headaches, less commonly dystonia, chorea, and ataxia, brain imaging: calcifications in basal ganglia, thalamus, cerebellum and white matter | 213600 | AD |
| PARK-*SYNJ1*320, 321 |  | May have seizures, cognitive decline, abnormal eye movements, and dystonia  | 615530 | AR |
| PARK-*VPS13C22, 39, 65, 312, 322, 323* |  | Early-onset parkinsonism with often rapid and severe progression and loss of response to levodopa during disease course, early cognitive impairment potentially leading to dementia | 616840 | AR |
| PARK- *WDR45*-(NBIA)324 | Dystonia | Beta-propeller protein-associated neurodegeneration (BPAN, previously SENDA syndrome) 325;Iron accumulation: SN > GP Halo of hyperintensity surrounding linear hypointensity in SN on T1 scans. Additional clinical features: developmental delay/intellectual disability, progressive cognitive decline, seizures, spasticity, Rett-like stereotypies, autistic-features, neuropsychiatric symptoms, sleep disorders, bowel/bladder incontinence, infantile epileptic encephalopathy  | 300894 | XL |
| **Combined phenotypes: where parkinsonism coexists with another movement disorder as a prominent consistent feature** |
| DYT/PARK-*ATP1A3A*,326 |  | Rapid onset dystonia-parkinsonism, chorea in later life | 128235 | AD |
| DYT/PARK-*CP-*(NBIA)*327* | Chorea | Aceruloplasminemia328: 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 storage  | 604290 | AR |
| DYT/PARK-*GCH1*329 |  | GTP cyclohydrolase I deficiency (mild form)330: childhood-onset dopa-responsive dystonia, adult-onset dystonia-parkinsonismAdditional clinical manifestations: diurnal fluctuation, pyramidal signs  | 128230 | AD |
|  | GTP cyclohydrolase I deficiency (severe form)331, 332: dystonia, parkinsonismAdditional clinical manifestations: developmental delay, truncal hypotonia, spasticity, oculogyric crises, seizures, with or without hyperphenylalaninemia332 | 605407 | AR |
| DYT/PARK-*GLB1*333, 334 |  | GM1 gangliosidosis (type III, chronic/adult form): dystonia, parkinsonismAdditional clinical features: pyramidal signs, dysarthria, cognitive deficits (often mild initially), skeletal abnormalities and short statue, corneal clouding, vacuolated cells, cardiomyopathy, progressive disease  | 603921 | AR |
| DYT/PARK-*PLA2G6-*(NBIA)*B,335-337* | Ataxia | *PLA2G6*-associated neurodegeneration (PLAN): dystonia, parkinsonism, cognitive decline, pyramidal signs, psychiatric symptoms (adult phenotype), ataxia (childhood phenotype)Iron accumulation: GP, SN in some; adults may have striatal involvement; about half of INAD and the majority of adult-onset cases lack brain iron accumulation on MRI | 612953 | AR |
| DYT/PARK-*PTS338* |  | 6-pyruvoyl-tetrahydropterin synthase deficiency: dystonia, parkinsonismAdditional clinical features: neonatal irritability, truncal hypotonia, developmental delay, seizures, oculogyric crises, autonomic dysfunction, hyperphenylalaninemia338  | 612719 | AR |
| DYT/PARK-*QDPR338* |  | Dihydropteridine reductase deficiency: dystonia, parkinsonismAdditional clinical features: developmental delay, truncal hypotonia, seizures, autonomic dysfunction, hyperphenylalaninemia338  | 612676 | AR |
| DYT/PARK-*SLC6A3*339, 340 |  | Dopamine transporter deficiency syndrome: 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 dysfunction341  | 126455 | AR |
| DYT/PARK-*SLC30A10*133 |  | Hypermanganesemia with dystonia, polycythemia, and liver cirrhosis, parkinsonismAdditional clinical features: hypermanganesemia, polycythemia, chronic liver disease, dysarthria134  | 611146 | AR |
| DYT/PARK-*SPR*342 |  | 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 hyperphenylalaninemia343 | 612716 | AR |
| DYT/PARK- *TAF1\*,*135 |  | Dystonia and parkinsonism  | 314250 | XL |
| DYT/PARK-*TH344* |  |  Tyrosine hydroxylase deficiency345 | 605407 | AR |
|  | Mild form: dopa-responsive infantile to early childhood onset dystonia |  | AR |
|  | Severe form: infantile-onset dystonia and parkinsonism, truncal hypotonia, global developmental delay |  | AR |
|  | Very severe form: infantile-onset dystonia and parkinsonism, oculogyric crises, severe global developmental delay, truncal hypotonia, limb spasticity, autonomic dysfunction |  | AR |
| **Disorders that usually present with other phenotypes but can have predominant parkinsonism** |
| ***Gene*** | **Associated disease** | **OMIM** | **Clinical phenotype** | **MOI** |
| PARK*-GBA346* | Gaucher’s disease | multiple | Early onset parkinsonism347; alternative or comorbid phenotype Gaucher’s disease: bone lesions, hematologic disorders, hepatosplenomegaly  | AR |
| ATX-*ATXN2*348 | Spinocerebellar ataxia | 183090 | Marked non-ataxia features, can have predominant parkinsonism349 or chorea; neuronopathy, dementia, myoclonus | AD |
| DYT-*DNAJC12350, 351* | Hyperphenyl-alaninemia | 617384 | Increased serum phenylalanine associated with highly variable neurological defects including movement disorder phenotypes; many cases with dystonia and variable impairment of intellectual development, phenotype can also include non-progressive or mild levodopa-responsive parkinsonism | AR |
| DYT-*PANK2-*(NBIA)352 | Neuro-degeneration with Brain Iron Accumulation 1  | 234200 | Pantothenate kinase-associated neurodegeneration (PKAN); dystonia, parkinsonism353, chorea, and variable additional clinical signs: spasticity, dysarthria, cognitive decline, gaze palsy, psychiatric symptoms, pigmentary retinopathyIron accumulation: GP – eye of the tiger sign  | AR |
| CHOR-*FTL*-(NBIA)354 | Neuro-degeneration with Brain Iron Accumulation 3  | 606159 | Neuroferritinopathy355: dystonia, chorea, parkinsonism, and variable additional clinical features including oromandibular dyskinesia, dysphagia, cognitive impairment, behavioral symptoms, low serum ferritinIron accumulation: GP, caudate, putamen, SN, red nucleus; cystic BG changes – pallidal necrosis | AD |
| HSP-*C19orf12*-(NBIA)356 | Neuro-degeneration with Brain Iron Accumulation 4  | 614298 | Mitochondrial membrane protein-associated neurodegeneration (MPAN)357; progressive spastic paresis, dystonia, parkinsonism, and variable additional clinical features: dysarthria, dysphagia, cognitive decline/dementia, motor axonal neuropathy, optic nerve atrophy, psychiatric symptoms, bowel/bladder incontinenceIron accumulation: GP (hyperintense streaking of medial medullary lamina between GPi and GPe), SN | AR or AD |
| HSP-*KIAA1840*358 | Spastic paraplegia  | 604360 | Pure or complex; may cause Kjellin syndrome#; TCC, mental retardation, sensory neuropathy, amyotrophy, dysarthria, nystagmus, ataxia, maculopathy, white matter lesions, occasional parkinsonism359 | AR |
| HSP-*ZFYVE26*360 | Spastic paraplegia  | 270700 | Complex; Kjellin syndrome#; TCC, WMLs, mental retardation, dysarthria, pigmentary maculopathy, peripheral neuropathy, distal amyotrophy, occasional parkinsonism359, 361  | AR |
| HSP/ATX-*FA2H-*(NBIA)362 | Spastic paraplegia  | 612319 | Complex SPG; Fatty Acid Hydroxylase-associated Neurodegeneration (FAHN)363; variable additional clinical features: spastic tetraparesis, cognitive decline, cerebellar and brainstem atrophy, dystonia, parkinsonism, ataxia, dysarthria, dysphagia, optic nerve atrophy, seizuresIron accumulation: GP (more subtle than other NBIAs) | AR |
| MYC/ATX-*EPM2A364, 365* | Progressive myoclonus epilepsy (Lafora disease) | 254780 | Early-onset progressive neurodegeneration with myoclonus, generalized seizures, often visual hallucinations and cognitive decline, phenotype can also include ataxia or rather rarely parkinsonism | AR |
| *C9orf7241, 366* | Frontotemporal dementia (FTD) and/or Amyotrophic Lateral Sclerosis (ALS) | 105550 | Broad phenotypic spectrum including frontotemporal dementia and features of motor neuron disease, parkinsonism (mostly atypical, e.g., PSP-like, MSA or CBS), and also dystonia, cerebellar signs, or chorea | AD\*\* |
| *GRN367, 368* | Primary progressive aphasia (PPA), Frontotemporal lobar degeneration with ubiquitin-positive inclusions, and Neuronal ceroid lipofuscinosis type 11 | 607485, 607485, 614706 | Phenotypic spectrum includes atypical parkinsonism (PSP-like, CBS, and DLB)  | AD or AR |
| *MAPT41, 302, 369-374* | Frontotemporal dementia with or without parkinsonism, Pick disease, Progressive supranuclear palsy, Progressive atypical supranuclear palsy | 600274, 172700, 601104, 260540 | Broad phenotypic spectrum including mostly atypical parkinsonism (PSP-like, CBS) but also features of motor neuron disease (eg, ALS); susceptibility locus for PD (OMIM: 168600) | AD or AR |
| *PDE8B212-216* | Autosomal dominant striatal degeneration | 609161 | Neurological disorder with variable movement abnormalities due to striatal dysfunction; phenotypic spectrum includes slowly progressive parkinsonism (mainly bradykinesia and rigidity, usually no tremor) without response to levodopa, as well as dysarthria, gait disturbances, and brisk (lower limb) reflexes | AD |
| *PDGFRB375* | Idiopathic basal ganglia calcification 4 (IBGC4) | 615007 | Many asymptomatic carriers, prominent late-onset parkinsonism and cognitive impairment in a minority of patients, brain imaging: calcification most commonly in basal ganglia | AD |
| *XPR1376* | Idiopathic basal ganglia calcification 6 (IBGC6) | 616413 | Neurodegenerative disorder with adult onset neuropsychiatric and movement disorders including parkinsonism, dystonia, gait abnormalities, chorea, psychosis, and dementia, brain imaging: calcification most commonly in basal ganglia | AD |

AD = autosomal dominant, ALS = Amyotrophic lateral sclerosis, AR = autosomal recessive, BG = basal ganglia, CBS = Corticobasal syndrome, DLB = Dementia with Lewy bodies, GP = Globus pallidus, GPe = External globus pallidus, GPi = Internal globus pallidus, MOI = Mode of inheritance, MSA = Multiple system atrophy, NBIA = Neurodegeneration with brain iron accumulation, OMIM = Online Mendelian Inheritance in Man (<https://www.omim.org/about>), PD = Parkinson’s disease, PSP = Progressive supranuclear palsy, SENDA = static encephalopathy of childhood with neurodegeneration in adulthood, SN = Subthalamic nucleus, SPG = Spastic paraplegia, TCC = thinning of the corpus callosus, WML = white matter lesions, XL = x-linked, XLR = x-linked recessive

A Gene Mutations can also cause autosomal dominant alternating hemiplegia of childhood (OMIM: 614820), CAPOS syndrome (Cerebellar ataxia, pes cavus, optic atrophy and sensorineural hearing loss; OMIM: 601338), as well as CAOS syndrome (Episodic Cerebellar Ataxia, Areflexia, Optic Atrophy, and Sensorineural Hearing Loss).

B Gene mutations more commonly cause infantile neuroaxonal dystrophy (INAD) with developmental delay/regression, hypotonia, spasticity/pyramidal signs, optic nerve atrophy, sensorimotor neuropathy, and seizures.

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

\*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.

\*\* Repeat expansions

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