Chapter 3
Genetics of Atypical Parkinsonism

Maria Stamelou and Kailash P. Bhatia

Abstract In this chapter, we discuss the genetics of sporadic atypical parkinsonism, namely, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA). Major new knowledge include new susceptibility loci apart from the H1 haplotype in microtubuli-associated protein tau (*MAPT*) gene for PSP, as well as the discovery of mutations in *COQ2* gene causing familial MSA. Furthermore, we discuss atypical features of new and known PARK-related genes, such as *DNAJC6* and *SYNJ1*. Lastly, we discuss the features of atypical parkinsonism in genetic conditions presenting predominantly with other phenotypes such as dementia (*MAPT, PGRN, C9ORF72, DCTN1*), ataxia (SCAs, FXTAS), dystonia (DRD, DYT12, dopamine transporter deficiency syndrome), and others such as mitochondrial and metabolic disorders.

Keywords Progressive supranuclear palsy • Corticobasal degeneration • Multiple system atrophy • Atypical parkinsonism • PARK • Dystonia–parkinsonism • Dementia • Ataxia • Spasticity

Introduction

Atypical parkinsonian syndromes (APs) are defined as syndromes that present with parkinsonism and features atypical for Parkinson's disease. Classically, the term is used to describe sporadic neurodegenerative conditions of unknown etiology that

M. Stamelou, MD, PhD (✉)
Department of Neurology, Philipps-University Marburg, Marburg, Germany

Second Department of Neurology, National and Kapodistrian University of Athens, Attiko Hospital, Athens 12462, Greece
e-mail: mariastamelou@gmail.com

K.P. Bhatia, MD, DM, FRCP
Sobell Department, University College London/Institute of Neurology, London WC1N 3BG, UK

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constitute the major differential diagnoses from sporadic Parkinson's disease, namely, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA), which are pathological entities distinct from PD.

However, also a number of genetic conditions may cause parkinsonism with clinical features atypical for PD and diverse or yet unknown pathologies, and the term atypical parkinsonism has been used for these disorders as well. Of those, some are identified as causing predominantly parkinsonism and some as causing predominantly other phenotypes that may also include parkinsonism and in rare cases only parkinsonism. Here, we will discuss firstly the genetics of sporadic APs, secondly genes that cause predominantly APs, and thirdly genes that are linked predominantly to other phenotypes that may include atypical parkinsonism.

Genetics of Sporadic Atypical Parkinsonism: PSP, CBD, and MSA

The most common sporadic atypical parkinsonian conditions include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA). These are distinct pathological entities.

Genetics of PSP

PSP is a neurodegenerative disease characterized by symmetric parkinsonism, supranuclear palsy of vertical gaze, early postural instability with falls backwards, and subcortical dementia [111]. This typical PSP phenotype is termed Richardson's syndrome (RS), while further phenotypes have been described [161]. The prevalence of PSP is approximately 5 per 100,000, average age at onset is 63, and mean time from symptom onset to death is 7–9 years. PSP is a 4-repeat tauopathy characterized by degeneration of several subcortical structures including the substantia nigra, the subthalamic nucleus, and the midbrain. Neurofibrillary tangles are present in these areas. Tufted astrocytes (Gallyas positive) are the hallmark feature of PSP that differentiates it in pathology from other 4R tauopathies such as CBD [46]. No effective treatments are available [77, 187, 202].

PSP is almost always sporadic. A genome-wide association study has confirmed that the most common risk allele for PSP is the H1 haplotype of the microtubuli-associated tau (*MAPT*) gene, and further risk loci have been identified [78]. The H1 haplotype of the *MAPT* gene (encoding for tau) is found in over 90 % of the patients. It is suggested that the presence of the H1 *MAPT* haplotype affects alternative splicing of exon 10 of the *MAPT* gene, which may result in an increased ratio of the 4R isoform of the tau protein (4R-tau) compared with the 3R isoform (3R-tau). However, the H1 *MAPT* haplotype did not correlate with age of onset,

disease severity, or survival in a study on 63 PSP patients, implying the presence of other modifying factors [110]. Interestingly, Li et al. using genome-wide methylation analysis showed that differential methylation at 17q21.31 correlates with the H1 haplotype in a dose-dependent manner in patients with frontotemporal dementia (FTD) and PSP, pointing for the first time to an epigenetic mediator of neurodegeneration that increases risk for PSP [105].

Apart from confirming two independent variants in *MAPT* affecting risk for PSP, this study identified three significant novel signals associated with PSP risk, which may give some insight in the pathophysiology of the disease: EIF2AK3 (eukaryotic translation initiation factor 2-α kinase 3; rs7571971, OR of major allele = 0.75, $p = 3.2 \times 10^{-13}$), STX6 (syntaxin 6; rs1411478, odds ratio [OR] of major allele = 0.79, $p = 2.3 \times 10^{-10}$), and MOBP (myelin-associated oligodendrocyte basic protein; rs1768208, OR of major allele = 0.72, $p = 1.0 \times 10^{-16}$) [78]. EIF2AK3 is a gene that encodes PERK, a component of the endoplasmic reticulum (ER) unfolded protein response (UPR). When excess unfolded proteins accumulate in the ER, PERK is activated and protein synthesis is inhibited allowing the ER to clear mis-folded proteins. However, tau, which is the primary mis-folded protein in PSP, is not expected to traffic through the ER. The second PSP susceptibility gene STX6 encodes syntaxin 6 (Stx6), and genetic variation at STX6 could influence movement of mis-folded proteins from the ER to lysosomes via the endosomal system. Lastly, MOBP encodes a protein (MOBP) that is produced by oligodendrocytes and is present in the major dense line of CNS myelin. MOBP is highly expressed in the white matter of the medulla, pons, cerebellum, and midbrain, regions affected in PSP, suggesting that myelin dysfunction oligodendrocyte misfunction contributes to PSP pathogenesis [78]. Ferrari et al. subsequently identified point mutations in each of these genes in a subset of the PSP cases used in the original GWAS [57]. Although implication of EIF2AK3 and MOBP could not be fully assessed, they showed that the single nucleotide polymorphism rs1411478 (STX6) is a strong expression quantitative trait locus with significantly lower expression of STX6 in white matter in carriers of the risk allele [57]. Further research is needed to identify the functional links between these risk loci and disease pathophysiology.

Genetics of CBD

Corticobasal degeneration (CBD) is a rare neurodegenerative disorder typically characterized by progressive asymmetric levodopa-resistant parkinsonism, dystonia, myoclonus, and further cortical signs (e.g., apraxia, alien limb phenomena, cortical sensory loss) [10, 186]. This typical CBD phenotype is now called corticobasal syndrome (CBS), while further phenotypes have been described [94]. CBD is a 4R tauopathy characterized by widespread deposition of hyperphosphorylated tau protein (specifically 4-repeat tau) in the brain. There is marked neuronal degeneration in the substantia nigra and the frontoparietal cortex. The hallmark feature of

CBD pathology is the characteristic astrocytic plaques that differentiate CBD from other 4R tauopathies such as PSP (tufted astrocytes) [109].

Since CBD is also a tauopathy, several studies have investigated the possible role of *MAPT* variants in the pathogenesis of the disorder. Indeed, the H1 haplotype was also found to be associated with the development of CBD [78, 79]. In a recent study, a systematic sequence analysis of *MAPT* coding and 3′ untranslated region (3′UTR) in a large cohort of autopsy-confirmed CBD patients ($N=109$) was performed. This identified a novel *MAPT* mutation in exon 13 (p.N410H) in a case that was neuropathologically indistinguishable from sporadic CBD and represents the first case meeting neuropathologic diagnostic criteria for CBD harboring a *MAPT* mutation. On immunoblot, the p.N410H mutation carrier had the same insoluble tau profile as seen in CBD. Sequence analysis of the complete *MAPT* 3′UTR in autopsy-confirmed CBD cases further identified two rare variants with nominally significant association with CBD. An ATC nucleotide insertion ("MAPTv8") was found in 4.6 % of CBD patients compared to 1.2 % of controls ($p=0.031$, OR = 3.71) and rs186977284 in 4.6 % CBD patients, but only 0.9 % of controls ($p=0.04$, OR = 3.58). Rs186977284 was also present in 2.7 % of a large cohort of autopsy-confirmed PSP patients ($N=566$) and only 0.9 % of an additional control series ($p=0.034$, OR = 3.08), extending the association to PSP [93].

Genetics of MSA

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by autonomic failure and parkinsonism and/or cerebellar signs. MSA-parkinsonism (MSA-P) is characterized predominantly by parkinsonism and autonomic failure at presentation, whereas in MSA-cerebellar type (MSA-C), cerebellar signs occur with autonomic failure [13, 213]. The prevalence is about 4 per 100,000, typical age at onset is 53–55 [214], and mean survival time is 9 years [214]. MSA is an a-synucleinopathy characterized by abnormal a-synuclein-positive cytoplasmic inclusions in oligodendrocytes, termed glial cytoplasmic inclusions, mainly found in the basal ganglia, cerebellar structures, and motor cortex. Neuropathological examination often reveals gross abnormalities of the striatonigral and/or olivopontocerebellar systems, which upon microscopic examination are associated with severe neuronal loss, gliosis, myelin pallor, and axonal degeneration [4, 47].

SNCA (α-synuclein) gene is encoding for the a-synuclein protein. *SNCA* variants have been studied as risk factors to develop MSA. 10 single nucleotide variants of *SNCA* most associated with risk of developing PD were tested in 413 MSA cases, and 2/10 *SNCA* variants were significantly associated with a risk of developing MSA [176]. These results were confirmed in an independent cohort of 108 MSA patients (rs11931074, OR = 6.2, $p=5.5\times10^{-12}$; rs3857059, OR = 5.9, $p=2\times10^{-10}$) [5, 176]. Al-Chalabi et al. examined 32 *SNCA* variants in 239 MSA cases and found that two of the variants were associated specifically with the MSA-C subtype (rs3822086; rs3775444) [5]. A GWAS in MSA is not available as of now, but is under way.

Recently, a combination of linkage analysis and next-generation genome sequencing identified homozygous and compound heterozygous variants of the gene *COQ2* (coenzyme Q2 4-hydroxybenzoate polyprenyltransferase) as a cause of MSA in familial cases from Japan and as a risk factor to develop sporadic MSA [127]. *COQ2* is important for the biosynthesis of coenzyme Q10, which in turn is an important factor for mitochondrial respiratory chain function. The most common of these mutations, p.V343A, was suggested to increase the risk of MSA through functional impairment of coenzyme Q10, which leads to increased oligodendrocyte apoptosis due to oxidative stress [127, 138].

A heterozygous deletion in *SHC2* (src homology 2 domain containing-transforming protein 2) in monozygotic twins discordant for MSA has also been reported [173]. The authors further observed copy number variation in *SHC2* in 32 % (10 of 31 patients) of MSA patients and in no controls of Japanese descent. However, a more recent study did not find copy number variation of the *SHC2* gene to be a significant genetic factor for non-Japanese MSA patients implying that this may only play a role in MSA pathogenesis in Japanese cohorts [56].

Atypical Parkinsonism in PARK-Related Genes

Mutations in the recessive *ATP13A2*/PARK9 gene that encodes a predominantly neuronal lysosomal type 5 P-type ATPase have been detected in patients with the recessively inherited Kufor–Rakeb syndrome. Kufor–Rakeb syndrome is typically characterized by juvenile-onset (12–29 years), levodopa-responsive parkinsonism (with fluctuations and dyskinesias), vertical supranuclear gaze palsy, cognitive dysfunction (dementia and visual hallucinations), and pyramidal signs [128, 218]. Further characteristic features include oculogyric dystonic spasms and facial–faucial–finger mini-myoclonus [15, 48, 115, 160]. T2*-weighted MRI imaging may show evidence of brain iron accumulation in some patients, which can be a helpful clue to suspect this disorder [139, 140, 160, 174]. There is no pathology from a patient with Kufor–Rakeb syndrome reported, but recently exome sequencing in a family with pathologically confirmed neuronal ceroid-lipofuscinosis has identified *ATP13A2* mutations that segregated with the affected family members [29].

Mutations in *PLA2G6*/PARK14 are identified as one cause of adult-onset parkinsonism with additional dystonia and complicated by pyramidal involvement. *PLA2G6* gene mutations were previously known to cause infantile neuroaxonal dystrophy and are also one cause of neurodegeneration with brain iron accumulation. In adult-onset cases, parkinsonism is characterized by the presence of tremor including a pill-rolling rest component, rigidity, and severe bradykinesia with a good response to levodopa. However, there was early development of dyskinesias [139, 184].

Mutations in the F-box only protein 7 gene (*FBXO7*) cause PARK15, a recessive form of juvenile parkinsonism with pyramidal signs. It was identified in one Iranian kindred with predominant pyramidal signs and later demonstrated by different mutations found in further ethnicities with prominent juvenile parkinsonism with

varying degrees of levodopa response [106, 114, 139, 184, 222]. The brain pathology in patients with PARK15 remains unknown. However, FBXO7 immunoreactivity in the Lewy bodies of typical PD, and in glial cytoplasmic inclusions of multiple system atrophy, is reported, suggesting an involvement of this protein in the pathogenesis of the common forms of synucleinopathies [86, 223].

DNAJC6 and *SYNJ1* (PARK20) have been recently identified as the cause of autosomal recessive, juvenile parkinsonism, using exome sequencing combined with genome-wide homozygosity mapping [39, 53, 82, 92, 97, 136, 147, 153, 172, 194, 211]. The phenotype of *DNAJC6* mutations ranges from juvenile parkinsonism without further signs or with mental retardation, pyramidal signs, and epilepsy, while a case with obesity, epilepsy, and mental retardation but no signs of parkinsonism has been reported [53, 82, 92]. *DNAJC6* encodes the neuronal co-chaperone auxilin. In the case of *SYNJ1*, the same homozygous mutation, p.Arg258Gln, was identified independently in two consanguineous families of Iranian and Italian origins, with parkinsonism, dystonia, and cognitive deterioration. Response to levodopa was poor and limited by side effects [97, 153]. Neuroimaging revealed brain atrophy, nigrostriatal dopaminergic defects, and cerebral hypometabolism [97, 153]. *SYNJ1* encodes synaptojanin 1, which plays a role in the post-endocytic recycling of synaptic vesicles (Table 3.1).

Atypical Parkinsonism in Genetic Disorders Predominantly Presenting with Other Neurologic Features

Traditionally a gene is tied to the recognition of a characteristic phenotype, but once the genetic defect is identified, the phenotypic characterization broadens. Indeed, genes identified in cohorts of patients presenting with diverse predominant features such as dementia, ataxia, chorea, or dystonia are now well recognized to also cause atypical parkinsonism, and in fact, in some cases atypical parkinsonism may be the predominant phenotype. In some cases, the atypical parkinsonism may resemble the classical PSP, CBD, or MSA phenotypes, leading to diagnostic confusion [190]. These genetic conditions are described below and are given in Table 3.1.

Atypical parkinsonism in Genes Predominantly Causing Dementia

Microtubule-associated protein tau (*MAPT*) and progranulin (*PGRN*) gene mutations both inherited in a dominant pattern and mainly causing frontotemporal dementias (FTDs) (with 3R/4R and TDP-43 pathology, respectively) can present with atypical parkinsonism and PSP as well as CBS phenotypes [31, 32, 34–36, 64, 125, 142, 149, 164, 165, 167, 168, 192, 208]. Clues to test for *MAPT* mutations would be the earlier age at onset (between the third to fifth decade) [6, 142, 149, 166, 168, 192], a positive family history of parkinsonism or dementia [64, 125, 165], and early and prominent behavioral problems that usually precede the classical PSP or CBS signs.

Table 3.1 An incomplete list of genetic conditions that may cause atypical parkinsonism, along with their respective genes, mode of inheritance, mean age of onset, MRI, and DaTSCAN findings

	Gene	Transmission	Age of onset (years)	Major features in MRI brain	DaTSCAN
PARK-related parkinsonism					
PARK8	*LRRK2*	AD	~Mean 60–65	From normal to generalized atrophy	Abnormal
PARK9 (Kufor–Rakeb)	*ATP13A2*	AR	Juvenile	Diffuse moderate cerebral and cerebellar atrophy and in some putaminal and caudate iron accumulation	Abnormal
PARK14	*PLA2G6*	AR	Juvenile	Cortical and cerebellar atrophy, may show iron in Gpi, may show white matter changes	Abnormal
PARK15	*FBXO7*	AR	Juvenile	Brain atrophy or maybe normal	
PARK20	*SYNJ1*	AR	Juvenile to adulthood	Brain atrophy	Abnormal
Genes predominantly causing dementia					
Frontotemporal lobar degeneration	*MAPT*	AD	~Mean 40	Symmetric frontotemporal atrophy	Abnormal
	PGRN	AD	~Mean 60	Asymmetric fronto-temporo-parietal atrophy	Abnormal
	C9ORF72	AD	~Mean 52	Bilateral frontal atrophy with variable degrees of parietal +/−temporal atrophy; usually no striking asymmetry	Abnormal
Alzheimer's dementia	*PSEN1*	AD	~Mean 45	Medial temporal atrophy	May be abnormal
Perry syndrome	*DCTN1*	AD	~Mean 45–50	May show midbrain atrophy	Abnormal

(continued)

Table 3.1 (continued)

	Gene	Transmission	Age of onset (years)	Major features in MRI brain	DaTSCAN
Genes predominantly causing ataxia					
Spinocerebellar ataxias	*ATXN2*	AD	~Mean 32	Pontocerebellar atrophy 25 % have hot cross bun sign	Abnormal
	ATXN3	AD	Range 5–75	Pontocerebellar atrophy	Abnormal
Fragile X tremor-ataxia syndrome	*FMR1*	X-linked dominant	~Mean 60	Increased signal in MCP and CCS in T2-weighted images	~47 % Abnormal
Genes predominantly causing dystonia					
DYT3	*TAF1*	X-linked dominant	~Main 30	Severe atrophy of the caudate and putamen; hyperintensity with an outer rim in the putamen	Abnormal
DYT5a	*GTPCH1*	AD	~6–10	Usually normal	Normal
DTDS	*SLC6A3*	AR	Infantile to adulthood	Maybe normal, in some white matter changes	Abnormal
DYT12	*ATP1A3*	AR	4–58 years	Usually normal	Abnormal
Wilson's disease	*ATP7B*	AR	First decade (but up to adulthood)	Can show the "face of the giant panda" midbrain May show hyperintensities in basal ganglia, midbrain, thalami, and pons	Abnormal
Inborn error of manganese metabolism	*SLC30A10*	AR	First decade (but up to adulthood)	Hyperintensities in basal ganglia and cerebellum in T1-weighted images	
NBIAs	Diverse		First decade (but up to adulthood)	Eye of the tiger in PKAN, further see genetics of NBIAs	Maybe normal or abnormal
Genes causing predominantly spasticity					
HSPs	*SPG11*	AR	First decade (but up to adulthood)	Atrophy of the corpus callosum	Maybe normal or abnormal

Genes causing predominantly chorea					
Huntington's disease	*huntingtin*	AD	Wide range from early childhood to late adulthood	Caudate atrophy	Maybe normal or abnormal
Neuroacanthocytosis	*VPS13A*	AR	Wide range from early childhood to late adulthood	May show striatal atrophy in particular the head of the caudate	Maybe normal or abnormal
Others					
Cerebrotendinous xanthomatosis	*CYP27A1*	AR	~Mean 40	Cerebellar atrophy Hyperintensities in dentate in T2-weighted images	Abnormal
Gaucher's disease	*GBA*	AR	From 3rd to 7th decade	Normal	Abnormal
Niemann–Pick C	*NPC*	AR	Second to third decade	May show frontal atrophy and hyperintensities in parietal-occipital periventricular white matter	Unknown
Mitochondrial	Various	AR, AD	From juvenile to adulthood	Variable changes	Abnormal
Genetic PRION	*PRNP*	AD	Wide range from juvenile to seventh decade	Hyperintensities in putamen and caudate in T2, FLAIR, and DWI sequences	Abnormal
Leukoencephalopathy with axonal spheroids	*CSF1R*	AD	Wide range	Leukoencephalopathy	Abnormal

Abbreviations: MCP middle cerebellar peduncles, *CCS* corpus callosum splenium, *MRI* magnetic resonance imaging, *DaTSCAN* dopamine transporter imaging, *MAPT* microtubule-associated tau, *PGRN* progranulin, *C9ORF72* chromosome 9 open reading frame 72, *PSEN1* presenilin 1, *DCTN1* dynactin, *LRRK2* leucine-rich repeat kinase 2, *ATXN* ataxin, *FMR1* fragile X mental retardation 1, *GBA* glucocerebrosidase, *NPC* Niemann–Pick C, *PRNP* prion protein, *CSF1R* colony-stimulating factor 1, *SPG11* spastic paraplegia 11, *DTDS* dopamine transporter deficiency syndrome

In contrast, the mean age at onset in *PGRN* mutation carriers is 60 years (range: 35–83 years) [14, 64, 177, 221], and the penetrance reaches that of 90 % at age 70 [26], so a positive family history is not always present. Clinical clues to suspect *PGRN* in a patient with RS or CBS would be a long preceding history of frontal dysfunction [203, 221]; signs of parietal lobe involvement (e.g., dyscalculia, limb apraxia, etc.), which are unusual for sporadic PSP (but usual in CBD); and hallucinations that rarely occur in sporadic PSP and CBD. Different studies report CBS as one of the three most common phenotypes seen in *PGRN* mutation carriers (the other two being bvFTD and PNFA) [14, 17, 18, 24, 35, 36, 49, 66, 87, 141, 157, 164, 185, 209]. A careful language evaluation may help to predict *PGRN* mutations in these patients; PNFA is occasionally the initial manifestation, before the CBS phenotype emerges. MRI imaging shows asymmetric fronto-temporo-parietal atrophy [6], rarely the case in PSP, but similar to findings in CBD [91, 188]. Sequential testing for *MAPT* and *PRGN* in patients with a positive family history is recommended and available [64]. Measurement of progranulin plasma levels may also be helpful if genetic testing is not available [58].

Hexanucleotide expansions in the newly described gene, chromosome 9 open reading frame 72 (*C9ORF72)* (TDP-43 pathology), cause FTD–amyotrophic lateral sclerosis (ALS) overlap syndromes [117, 118, 156], and in 35 % of these patients, atypical parkinsonism may be present [25, 37, 38, 76, 108, 117, 118, 134, 156]. A positive family history, signs of upper or lower motor neuron disease, and the presence of hallucinations are important clues to suspect these mutations [25, 37, 38, 108, 134, 156].

Lastly, Perry syndrome, a rare autosomal dominant disorder due to mutations in the dynactin *(DCTN1)* gene (TDP-43 pathology) may present with atypical parkinsonism and an RS, CBS, as well as MSA phenotype [212, 215]. Clinical clues to suspect these mutations include central hypoventilation, weight loss, and psychiatric symptoms (e.g., apathy, hallucinations) [100, 129, 135, 145, 146, 151, 204]. Response to levodopa varies from no response to significant improvement and development of motor fluctuations and dyskinesias [22, 55, 129, 135, 145, 146, 151, 204, 212, 215, 216].

CBS has been described commonly with Alzheimer's disease (AD) pathology in sporadic AD patients [7, 23, 50, 61, 73, 83, 104], and earlier age at onset and myoclonus are thought to be more suggestive of AD rather than CBD pathology [50, 83, 99]. Increased saccadic latency has been described in AD and CBD, and thus this feature may not be helpful in the differential diagnosis [27]. Some mutations in presenilin 1 (*PSEN1*) have been described to cause parkinsonism with myoclonus, dystonia, apraxia, and frontal dementia mimicking CBD, although there is usually no striking asymmetry and there may be seizures, which rarely occur in CBD [99]. Mutations in *APP* and *PSEN2* may also present with parkinsonism but mostly mimicking dementia with Lewy bodies (DLB) [155].

Atypical parkinsonism in Genes Predominantly Causing Ataxia

Spinocerebellar ataxias (SCA) represent a clinically and genetically heterogeneous group of neurodegenerative disorders in which progressive degeneration of the cerebellum and spinocerebellar tracts of the spinal cord are associated with a variable

combination of signs of central and peripheral nervous system involvement (see also Chap. 11). Extrapyramidal features, including parkinsonism, have been described in several of these such as SCA2 and SCA3.

SCA2 (due to expansion of a glutamine tract in the ataxin-2 gene) typically presents with ataxia, slowed horizontal saccades, and peripheral neuropathy; however, phenotypes with a parkinsonism-predominant profile or purely parkinsonism, early postural instability, and vertical supranuclear gaze palsy (SGP) have been described [59, 69, 144, 167, 180, 181, 198], mostly in patients of Asian origin, with later age at onset and shorter repeat expansion [59, 69, 112, 144, 198]. SCA3 (Machado–Joseph disease) is the most frequent cause of autosomal dominantly inherited cerebellar ataxia in Europe, Japan, and the United States and is caused by an expanded polyglutamine CAG repeat size of >44 [162]. Age at onset varies from 5 to 75 years and inversely correlates with CAG repeat length. The parkinsonian variant of SCA3 is associated with lower range repeat expansions and a later age at onset, similar to SCA2 [42, 162, 175]. Cerebellar ataxia, parkinsonism, and only mild cognitive dysfunction [89, 107, 207] in addition to cardiovascular and sympathetic sweating dysautonomia (in up to 45 %) can clinically be mistaken for MSA, particularly when family history is negative [96, 197]. Further SCAs, such as SCA8, SCA17, and SCA6, more rarely present with parkinsonism [2].

Fragile X tremor-ataxia syndrome (FXTAS) is a late-onset (>50 years) neurodegenerative disorder, occurring in carriers of a premutation CGG repeat expansion (55–200 repeats) in the fragile X mental retardation 1 (*FMR1*) gene. The penetrance of FXTAS in male carriers over 50 years is ~40 %, and recently it has been postulated that female carriers develop FXTAS more often than previously suggested [199]. Autopsy reveals intranuclear inclusions in neurons and astrocytes and dystrophic white matter [12, 19, 65, 199]. The typical phenotype consists of the combination of intention tremor and ataxia, but parkinsonism, autonomic dysfunction, cognitive decline, psychiatric features, and neuropathy have been described, and tremor is not always present [12]. A family history of mental retardation or premature ovarian failure provides important clues [19]. However, in a recent series 43 % of the FXTAS patients had no family history of fragile X syndrome [9]. Additional features include autonomic dysfunction presenting, as in MSA, with impotence, orthostatic hypotension, urinary frequency, and urinary incontinence [9, 70]. However, MSA is rarely misdiagnosed as FXTAS – among 426 clinically diagnosed MSA cases, only four were found to have FXTAS in a study [84]. Dopamine transporter imaging (DaTSCAN) in few cases may be normal, and in which case, it is helpful in the differential diagnosis with MSA [116].

Atypical parkinsonism in Genes Predominantly Causing Dystonia or Dystonia–Parkinsonism

X-Linked Recessive Dystonia–Parkinsonism (DYT3; XDP; "Lubag")

DYT3 dystonia, which clusters in Filipinos, is an X-linked recessive disorder. Although this disorder typically affects males, rarely, females may also be affected, possibly due to severe X-inactivation or based on homozygosity for the mutation [103]. DYT3

reaches complete penetrance by the end of the fifth decade in males and later in females (up to 75 years) and is associated with specific sequence changes in the TAF1 gene [126, 183]. Usually symptoms start in adulthood as focal dystonia, tend to progress, and generalize. Parkinsonism is often present (up to 36 %) and in some cases may precede the onset of dystonia or can be the predominant or sole feature throughout the disease course [54, 75, 103]. Parkinsonism may improve with levodopa in the early stages but becomes less responsive or unresponsive over the course of the disease. Investigations in XPD patients show an abnormal DaTSCAN and a clearly abnormal IBZM SPECT, implying decreased dopamine D2 receptor expression. On positron emission tomography (PET), striatal glucose metabolism is selectively reduced. Fluorodopa uptake is normal, suggesting that the origin of the extrapyramidal symptoms is localized rather postsynaptically to the nigrostriatal pathway (see also Chap. 7) [196].

Dopa-Responsive Dystonias (DYT5; Segawa's Disease)

DYT5 was initially described by Segawa et al. in 1976 [178] and later by Nygaard and colleagues as dopa-responsive dystonia (DRD) because of the dramatic and sustained response to low dose of levodopa [132]. The disease is inherited as an autosomal dominant trait with reduced penetrance that appears to be gender dependent with females more frequently expressing symptoms. It is caused by mutations in the *GTPCH1* (GTP cyclohydrolase 1) gene [80]. *GTPCH1* is the rate-limiting enzyme in the synthesis of tetrahydrobiopterin, an essential cofactor for tyrosine hydroxylase (TH) which in turn is needed to synthesize dopamine, explaining the remarkable therapeutic effect of levodopa substitution. The typical phenotype includes childhood (average 6 years) limb-onset dystonia with diurnal variation (e.g., worsening of the symptoms as the day progresses), improvement after sleep, and dramatic response to levodopa [60, 193]. Later in the course of the disease, parkinsonian features occur frequently, and patients may also show typical, late-onset isolated parkinsonism, which responds well to levodopa therapy, but, unlike in idiopathic PD, patients usually do not develop motor fluctuations and dyskinesias [133], although this is not exclusive [41, 102]. Early-onset parkinsonism due to mutations in one of the recessive PARK genes (mostly Parkin) has to be considered in the differential diagnosis of a young patient presenting with prominent leg dystonia that is responsive to levodopa therapy. Early-onset DRD patients show normal DaTSCAN in contrast to patients with young-onset Parkinson's disease [28]. The latter concept has been recently challenged, by demonstrating that later-onset DRD cases presenting with PD may have abnormal DaTSCANs; thus, *GTPCH1* mutations may be risk factors to develop classic PD (see also Chap. 7) [123].

In a minority of cases, DRDs can also be inherited as an autosomal recessive disorder with mutations in the genes coding for other enzymes involved in dopamine synthesis including tyrosine hydroxylase (TH) [60, 113], sepiapterin reductase (SR), and aromatic L-amino acid decarboxylase (AADC) deficiency [3]. The clinical manifestations are often more severe and can include mental retardation, oculogyria, hypotonia, severe bradykinesia, drooling, ptosis, and seizures [189]. Recently it has been shown that TH patients may develop dyskinesias [148].

Hereditary Dopamine Transporter Deficiency Syndrome (DTDS)

Hereditary dopamine transporter deficiency syndrome (DTDS) is the first biogenic amine "transportopathy" to be described. It is an autosomal recessive condition leading to infantile parkinsonism– dystonia caused by pathogenic mutations in the *SLC6A3* gene encoding the dopamine transporter (DAT) [98], which mediates the active reuptake of dopamine and regulates the amplitude and duration of dopamine neurotransmission [98]. All children present with irritability, axial hypotonia, and feeding difficulties in infancy, with a hyperkinetic movement disorder that evolves into hypokinetic parkinsonism–dystonia. Ocular abnormalities included eye flutter, saccade initiation failure, slow saccadic eye movements, eyelid myoclonus, and oculogyric crises [98, 130, 131]. However, the phenotypic spectrum of this condition is expanding, with the first adults diagnosed with DTDS now recognized, and the condition is now considered as a differential for juvenile and early-onset parkinsonism [131]. Diagnosis can be based on CSF studies that show a raised ratio of HVA:5-HIAA >5 (normal range 1.3–4.0), a key finding in DTDS diagnosis [98]. The majority of patients are unresponsive to nearly all available therapeutic agents, including levodopa, anticholinergics, benzodiazepines, and deep brain stimulation [98, 120, 130].

Rapid-Onset Dystonia–Parkinsonism (DYT12)

Rapid-onset dystonia–parkinsonism is inherited as an autosomal dominant trait with reduced penetrance. Six heterozygous missense mutations have been identified in the Na^+, K^+-ATPase *ATP1A3* (alpha 3 subunit) gene, and all are shown to impair cell viability in cell culture experiments [30, 40, 101]. The disease phenotype designated rapid-onset dystonia–parkinsonism because of key clinical features including abrupt onset, within hours to weeks, of dystonia with signs of parkinsonism usually triggered by physical or emotional stress (fever, childbirth, running, alcohol binging). The age of onset varies from 4 to 58 years but typically presents in the teens or early twenties, and the distribution follows a rostrocaudal (face > arm > leg) gradient with prominent bulbar involvement. A presentation that could be more easily confused with PD has been recently described in a genetically proven patient with gradual onset at age 38 years of unilateral bradykinesia and rigidity, however, without improvement on levodopa therapy. This was followed by overnight onset of oromandibular dystonia 3.5 years after his first clinical presentation with parkinsonism (see also Chap. 7) [85].

Wilson's Disease

Wilson's disease (WD) is an autosomal recessive disorder with reduced biliary excretion of copper and impaired formation of ceruloplasmin, leading to copper accumulation in the liver, brain, kidney, and cornea. WD is caused by mutations in the *ATP7B* gene and usually manifests in the first decade of life, although late

presentations have also been described [72, 74, 119]. Clinical manifestations include liver damage, psychiatric symptoms, and neurologic features. Juvenile and adult-onset parkinsonism are common features, which do not respond to levodopa, but respond well to specific WD treatment [33]. Evaluation should include serum and 24-h urine copper, serum ceruloplasmin, slit lamp examination looking for Kayser-Fleischer rings, free copper estimation, and if necessary, a liver biopsy [119]. Mutational analysis is labor intensive and is thus not used for screening purposes but confirms the exact mutation in patients with suspected Wilson's disease (see also Chap. 14).

Inborn Error of Manganese Metabolism

A recessive inborn error of manganese metabolism [205] due to mutations in the *SLC30A10* (solute carrier family 30, member 10) gene, encoding a manganese transporter, results in manganese accumulation mainly in the basal ganglia and cerebellum, and the liver, and causes a syndrome of early-onset generalized dystonia, cirrhosis, polycythemia, and hypermanganesemia [152, 205, 206]. Patients with parkinsonism–dystonia have also been described [44, 45, 152]. The metabolic signature of this disorder is the extreme hypermanganesemia with polycythemia and depleted iron stores (e.g., low ferritin, increased total iron-binding capacity), while laboratory findings reflecting hepatic dysfunction vary even between members of the same family [152, 205]. Manganese induces erythropoietin gene expression, and this could be the mechanism leading to polycythemia [52]. T1-weighted MRI images show hyperintensities in the basal ganglia and cerebellum [152, 191, 205]. As in Wilson's disease, manganese chelation treatment is helpful for both neurologic and systemic features (see also Chap. 14) [191].

Neurodegeneration with Brain Iron Accumulation (NBIA) Disorders

NBIA disorders cause complex dystonia–parkinsonism phenotypes and are discussed further in Chap. 13.

Atypical parkinsonism in Genes Predominantly Causing Chorea

Huntington's Disease

Huntington's disease (HD), an autosomal dominant disorder due to a trinucleotide CAG repeat expansion in the huntingtin gene (normal: 15–30 repeats; disease associated: >40 repeats), usually begins in adulthood and is characterized by cognitive decline and psychiatric, oculomotor, and motor abnormalities, usually with chorea as the most prominent feature [51, 88, 154]. The Westphal variant of HD is a distinct

presentation characterized by a rigid-hypokinetic syndrome and is usually associated with young-onset age (<20 years) and accounts for 5–10 % of all HD cases. Juvenile HD is predominantly paternally inherited and associated with larger trinucleotide expansions in the range of 60–100 repeats, but may be as long as 250 trinucleotides [51, 170]. Clinically, juvenile HD often presents as an akinetic rigid disorder and may occur without concomitant choreic movements, and there may be supranuclear gaze palsy. Caudate volume loss on neuroimaging can be seen in both adult-onset and juvenile HD [154].

Neuroacanthocytosis

Neuroacanthocytosis may also present with parkinsonism (Table 3.1) (see also Chap. 8).

Other Genetic Disorders Causing Atypical Parkinsonism

Mitochondrial Disorders

Mitochondrial disorders may present with atypical parkinsonism and can be associated with specific point mutations, microdeletions, and also multiple mtDNA deletions due to, for example, polymerase gamma (*POLG*) mutations, which can be inherited in dominant or recessive mode [137]. PSP-like patients who presented in their sixties with parkinsonism, vertical SGP, and early cognitive dysfunction have been reported [68, 71]; associated features in these patients were deafness, ataxia, and lower motor neuron signs, which are absent in PSP [68, 71]. Of note, *POLG-related* parkinsonism can show an excellent response to levodopa, in contrast to sporadic PSP (see also Chap. 20) [137, 217].

Neurometabolic Disorders

In particular the adult-onset Niemann–Pick C (NPC1 and NPC2 gene mutations), an autosomal recessive lysosomal lipid storage disorder [81, 179], presents with vertical SGP, cerebellar ataxia, dysarthria, dysphagia, cognitive dysfunction, and psychiatric symptoms and should be thought in the differential of patients with a PSP-like phenotype [179]. Biochemical diagnosis of Niemann–Pick C is made by filipin staining of cultured skin fibroblasts, with subsequent confirmation of the diagnosis made by mutation analysis of the *NPC1* (the majority) and *NPC2* genes [1, 219]. Miglustat is the only approved treatment for the neurologic manifestations of the disease, and patients who begin treatment early respond better, highlighting the need for early diagnosis [1, 143, 219, 220].

In the adult-onset form of Gaucher's disease, patients usually have slow *horizontal* saccades and increased latency launching horizontal saccades [16], which is

usual in CBD [162], but not in PSP [11], in which the saccadic latency is normal and vertical saccades are more and earlier affected than horizontal, particularly downwards. However, some Gaucher's disease patients with prominent slowness of vertical saccades and cognitive dysfunction, mimicking PSP, have been reported [62, 63, 122, 200, 201, 210]. Other neurologic features such as head thrusting (55 %), ataxia (20 %), seizures (16 %), and spasticity (15 %), which are not seen in PSP, provide important clues [8, 43, 67, 200, 201, 210]. Systemic associated features such as splenomegaly, hepatomegaly, bone crisis, bone pain, anemia, and thrombocytopenia are helpful diagnostic clues [200, 201, 210].

Prion Disease

Genetic Creutzfeldt–Jakob disease (gCJD) has been linked to a variety of mutations within the prion protein gene (*PRNP*). Patients with disease onset between their fifth and seventh decade, vertical SGP, "worried facial appearance," postural instability, axial rigidity, and frontal dementia mimicking PSP have been described in gCJD, mostly with the E200K but rarely also with further mutations and in sporadic CJD [20, 21, 95, 121, 171, 182]. These patients often have cerebellar and pyramidal signs as well as myoclonus, and the rapidity of evolution is helpful to suspect the disorder.

Atypical Parkinsonism with White Matter Changes

The combination of parkinsonism with leukoencephalopathy should prompt to test for colony-stimulating factor 1 (*CSF1R*) mutations, causing leukoencephalopathy with axonal spheroids [90, 124, 150, 158, 195]. Also in CADASIL due to *NOTCH3* mutations, atypical parkinsonism has been described [159]. Mitochondrial disorders may also present with white matter changes in MRI.

Conclusion

The advent in genetics has changed the field of atypical parkinsonism. With regard to the sporadic conditions, PSP, CBD, and MSA, genetic susceptibility loci and rare mutations in relevant genes causing familial forms may provide important clues for the pathophysiology of these disorders. On the other hand, the list of genetic disorders causing young-onset atypical parkinsonism with various features is growing, and syndromic associations are important to suspect these. In some cases, this is quite important due to treatment implications.

References

1. Abel LA, Walterfang M, Fietz M, Bowman EA, Velakoulis D. Saccades in adult Niemann-Pick disease type C reflect frontal, brainstem, and biochemical deficits. Neurology. 2009;72:1083–6.
2. Abele M, Burk K, Schols L, Schwartz S, Besenthal I, Dichgans J, Zuhlke C, Riess O, Klockgether T. The aetiology of sporadic adult-onset ataxia. Brain. 2002;125:961–8.
3. Abeling NG, Duran M, Bakker HD, Stroomer L, Thony B, Blau N, Booij J, Poll-The BT. Sepiapterin reductase deficiency an autosomal recessive DOPA-responsive dystonia. Mol Genet Metab. 2006;89:116–20.
4. Ahmed Z, Asi YT, Sailer A, Lees AJ, Houlden H, Revesz T, Holton JL. The neuropathology, pathophysiology and genetics of multiple system atrophy. Neuropathol Appl Neurobiol. 2012;38:4–24.
5. Al-Chalabi A, Durr A, Wood NW, Parkinson MH, Camuzat A, Hulot JS, Morrison KE, Renton A, Sussmuth SD, Landwehrmeyer BG, Ludolph A, Agid Y, Brice A, Leigh PN, Bensimon G. Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy. PLoS One. 2009;4:e7114.
6. Alberici A, Cosseddu M, Padovani A, Borroni B. Chromosome 17 in FTLD: from MAPT tau to progranulin and back. Curr Alzheimer Res. 2011;8:229–36.
7. Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, Hodges JR. Focal cortical presentations of Alzheimer's disease. Brain. 2007;130:2636–45.
8. Alonso-Canovas A, Katschnig P, Tucci A, Carecchio M, Wood NW, Edwards M, Martinez Castrillo JC, Burke D, Heales S, Bhatia KP. Atypical parkinsonism with apraxia and supranuclear gaze abnormalities in type 1 Gaucher disease. Expanding the spectrum: case report and literature review. Mov Disord. 2010;25:1506–9.
9. Apartis E, Blancher A, Meissner WG, Guyant-Marechal L, Maltete D, De Broucker T, Legrand AP, Bouzenada H, Thanh HT, Sallansonnet-Froment M, Wang A, Tison F, Roue-Jagot C, Sedel F, Charles P, Whalen S, Heron D, Thobois S, Poisson A, Lesca G, Ouvrard-Hernandez AM, Fraix V, Palfi S, Habert MO, Gaymard B, Dussaule JC, Pollak P, Vidailhet M, Durr A, Barbot JC, Gourlet V, Brice A, Anheim M. FXTAS: new insights and the need for revised diagnostic criteria. Neurology. 2012;79:1898–907.
10. Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, Boxer AL, Dickson DW, Grossman M, Hallett M, Josephs KA, Kertesz A, Lee SE, Miller BL, Reich SG, Riley DE, Tolosa E, Troster AI, Vidailhet M, Weiner WJ. Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013;80:496–503.
11. Armstrong RA. Visual signs and symptoms of progressive supranuclear palsy. Clin Exp Optom. 2011;94:150–60.
12. Baba Y, Uitti RJ. Fragile X-associated tremor/ataxia syndrome and movements disorders. Curr Opin Neurol. 2005;18:393–8.
13. Batla A, Stamelou M, Mensikova K, Kaiserova M, Tuckova L, Kanovsky P, Quinn N, Bhatia KP. Markedly asymmetric presentation in multiple system atrophy. Parkinsonism Relat Disord. 2013;19:901–5.
14. Beck J, Rohrer JD, Campbell T, Isaacs A, Morrison KE, Goodall EF, Warrington EK, Stevens J, Revesz T, Holton J, Al-Sarraj S, King A, Scahill R, Warren JD, Fox NC, Rossor MN, Collinge J, Mead S. A distinct clinical, neuropsychological and radiological phenotype is associated with progranulin gene mutations in a large UK series. Brain. 2008;131:706–20.
15. Behrens MI, Bruggemann N, Chana P, Venegas P, Kagi M, Parrao T, Orellana P, Garrido C, Rojas CV, Hauke J, Hahnen E, Gonzalez R, Seleme N, Fernandez V, Schmidt A, Binkofski F, Kompf D, Kubisch C, Hagenah J, Klein C, Ramirez A. Clinical spectrum of Kufor-Rakeb syndrome in the Chilean kindred with ATP13A2 mutations. Mov Disord. 2010;25:1929–37.

16. Benko W, Ries M, Wiggs EA, Brady RO, Schiffmann R, Fitzgibbon EJ. The saccadic and neurological deficits in type 3 Gaucher disease. PLoS One. 2011;6:e22410.
17. Benussi L, Binetti G, Sina E, Gigola L, Bettecken T, Meitinger T, Ghidoni R. A novel deletion in progranulin gene is associated with FTDP-17 and CBS. Neurobiol Aging. 2008;29: 427–35.
18. Benussi L, Ghidoni R, Pegoiani E, Moretti DV, Zanetti O, Binetti G. Progranulin Leu271LeufsX10 is one of the most common FTLD and CBS associated mutations worldwide. Neurobiol Dis. 2009;33:379–85.
19. Berry-Kravis E, Abrams L, Coffey SM, Hall DA, Greco C, Gane LW, Grigsby J, Bourgeois JA, Finucane B, Jacquemont S, Brunberg JA, Zhang L, Lin J, Tassone F, Hagerman PJ, Hagerman RJ, Leehey MA. Fragile X-associated tremor/ataxia syndrome: clinical features, genetics, and testing guidelines. Mov Disord. 2007;22:2018–30, quiz 2140.
20. Bertoni JM, Brown P, Goldfarb LG, Rubenstein R, Gajdusek DC. Familial Creutzfeldt-Jakob disease (codon 200 mutation) with supranuclear palsy. JAMA. 1992;268:2413–5.
21. Bertoni JM, Label LS, Sackelleres JC, Hicks SP. Supranuclear gaze palsy in familial Creutzfeldt-Jakob disease. Arch Neurol. 1983;40:618–22.
22. Bhatia KP, Daniel SE, Marsden CD. Familial parkinsonism with depression: a clinicopathological study. Ann Neurol. 1993;34:842–7.
23. Boeve BF. Links between frontotemporal lobar degeneration, corticobasal degeneration, progressive supranuclear palsy, and amyotrophic lateral sclerosis. Alzheimer Dis Assoc Disord. 2007;21:S31–8.
24. Boeve BF, Baker M, Dickson DW, Parisi JE, Giannini C, Josephs KA, Hutton M, Pickering-Brown SM, Rademakers R, Tang-Wai D, Jack Jr CR, Kantarci K, Shiung MM, Golde T, Smith GE, Geda YE, Knopman DS, Petersen RC. Frontotemporal dementia and parkinsonism associated with the IVS1+1G->A mutation in progranulin: a clinicopathologic study. Brain. 2006;129:3103–14.
25. Boeve BF, Boylan KB, Graff-Radford NR, Dejesus-Hernandez M, Knopman DS, Pedraza O, Vemuri P, Jones D, Lowe V, Murray ME, Dickson DW, Josephs KA, Rush BK, Machulda MM, Fields JA, Ferman TJ, Baker M, Rutherford NJ, Adamson J, Wszolek ZK, Adeli A, Savica R, Boot B, Kuntz KM, Gavrilova R, Reeves A, Whitwell J, Kantarci K, Jack Jr CR, Parisi JE, Lucas JA, Petersen RC, Rademakers R. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. Brain. 2012;135:765–83.
26. Boeve BF, Hutton M. Refining frontotemporal dementia with parkinsonism linked to chromosome 17: introducing FTDP-17 (MAPT) and FTDP-17 (PGRN). Arch Neurol. 2008;65:460–4.
27. Boxer AL, Garbutt S, Seeley WW, Jafari A, Heuer HW, Mirsky J, Hellmuth J, Trojanowski JQ, Huang E, DeArmond S, Neuhaus J, Miller BL. Saccade abnormalities in autopsy-confirmed frontotemporal lobar degeneration and Alzheimer disease. Arch Neurol. 2012;69: 509–17.
28. Brajkovic LD, Svetel MV, Kostic VS, Sobic-Saranovic DP, Pavlovic SV, Artiko VM, Obradovic VB. Dopamine transporter imaging (123)I-FP-CIT (DaTSCAN) SPET in differential diagnosis of dopa-responsive dystonia and young-onset Parkinson's disease. Hell J Nucl Med. 2012;15:134–8.
29. Bras J, Verloes A, Schneider SA, Mole SE, Guerreiro RJ. Mutation of the parkinsonism gene ATP13A2 causes neuronal ceroid-lipofuscinosis. Hum Mol Genet. 2012;21:2646–50.
30. Brashear A, Dobyns WB, de Carvalho Aguiar P, Borg M, Frijns CJ, Gollamudi S, Green A, Guimaraes J, Haake BC, Klein C, Linazasoro G, Munchau A, Raymond D, Riley D, Saunders-Pullman R, Tijssen MA, Webb D, Zaremba J, Bressman SB, Ozelius LJ. The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the ATP1A3 gene. Brain. 2007;130:828–35.
31. Bugiani O, Murrell JR, Giaccone G, Hasegawa M, Ghigo G, Tabaton M, Morbin M, Primavera A, Carella F, Solaro C, Grisoli M, Savoiardo M, Spillantini MG, Tagliavini F, Goedert M, Ghetti B. Frontotemporal dementia and corticobasal degeneration in a family with a P301S mutation in tau. J Neuropathol Exp Neurol. 1999;58:667–77.

32. Casseron W, Azulay JP, Guedj E, Gastaut JL, Pouget J. Familial autosomal dominant corticobasal degeneration with the P301S mutation in the tau gene: an example of phenotype variability. J Neurol. 2005;252:1546–8.
33. Chan KH, Cheung RT, Au-Yeung KM, Mak W, Cheng TS, Ho SL. Wilson's disease with depression and parkinsonism. J Clin Neurosci. 2005;12:303–5.
34. Chen-Plotkin AS, Lee VM, Trojanowski JQ. TAR DNA-binding protein 43 in neurodegenerative disease. Nat Rev Neurol. 2010;6:211–20.
35. Chen-Plotkin AS, Martinez-Lage M, Sleiman PM, Hu W, Greene R, Wood EM, Bing S, Grossman M, Schellenberg GD, Hatanpaa KJ, Weiner MF, White 3rd CL, Brooks WS, Halliday GM, Kril JJ, Gearing M, Beach TG, Graff-Radford NR, Dickson DW, Rademakers R, Boeve BF, Pickering-Brown SM, Snowden J, van Swieten JC, Heutink P, Seelaar H, Murrell JR, Ghetti B, Spina S, Grafman J, Kaye JA, Woltjer RL, Mesulam M, Bigio E, Llado A, Miller BL, Alzualde A, Moreno F, Rohrer JD, Mackenzie IR, Feldman HH, Hamilton RL, Cruts M, Engelborghs S, De Deyn PP, Van Broeckhoven C, Bird TD, Cairns NJ, Goate A, Frosch MP, Riederer PF, Bogdanovic N, Lee VM, Trojanowski JQ, Van Deerlin VM. Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. Arch Neurol. 2011;68:488–97.
36. Chen-Plotkin AS, Xiao J, Geser F, Martinez-Lage M, Grossman M, Unger T, Wood EM, Van Deerlin VM, Trojanowski JQ, Lee VM. Brain progranulin expression in GRN-associated frontotemporal lobar degeneration. Acta Neuropathol. 2010;119:111–22.
37. Chio A, Borghero G, Restagno G, Mora G, Drepper C, Traynor BJ, Sendtner M, Brunetti M, Ossola I, Calvo A, Pugliatti M, Sotgiu MA, Murru MR, Marrosu MG, Marrosu F, Marinou K, Mandrioli J, Sola P, Caponnetto C, Mancardi G, Mandich P, La Bella V, Spataro R, Conte A, Monsurro MR, Tedeschi G, Pisano F, Bartolomei I, Salvi F, Lauria Pinter G, Simone I, Logroscino G, Gambardella A, Quattrone A, Lunetta C, Volanti P, Zollino M, Penco S, Battistini S, Renton AE, Majounie E, Abramzon Y, Conforti FL, Giannini F, Corbo M, Sabatelli M. Clinical characteristics of patients with familial amyotrophic lateral sclerosis carrying the pathogenic GGGGCC hexanucleotide repeat expansion of C9ORF72. Brain. 2012;135:784–93.
38. Cooper-Knock J, Hewitt C, Highley JR, Brockington A, Milano A, Man S, Martindale J, Hartley J, Walsh T, Gelsthorpe C, Baxter L, Forster G, Fox M, Bury J, Mok K, McDermott CJ, Traynor BJ, Kirby J, Wharton SB, Ince PG, Hardy J, Shaw PJ. Clinico-pathological features in amyotrophic lateral sclerosis with expansions in C9ORF72. Brain. 2012;135:751–64.
39. Cremona O, Nimmakayalu M, Haffner C, Bray-Ward P, Ward DC, De Camilli P. Assignment of SYNJ1 to human chromosome 21q22.2 and Synj12 to the murine homologous region on chromosome 16C3-4 by in situ hybridization. Cytogenet Cell Genet. 2000;88:89–90.
40. de Carvalho Aguiar P, Sweadner KJ, Penniston JT, Zaremba J, Liu L, Caton M, Linazasoro G, Borg M, Tijssen MA, Bressman SB, Dobyns WB, Brashear A, Ozelius LJ. Mutations in the Na+/K+ −ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. Neuron. 2004;43:169–75.
41. de la Fuente-Fernandez R. Drug-induced motor complications in dopa-responsive dystonia: implications for the pathogenesis of dyskinesias and motor fluctuations. Clin Neuropharmacol. 1999;22:216–9.
42. Degardin A, Dobbelaere D, Vuillaume I, Defoort-Dhellemmes S, Hurtevent JF, Sablonniere B, Destee A, Defebvre L, Devos D. Spinocerebellar ataxia: a rational approach to aetiological diagnosis. Cerebellum. 2012;11:289–99.
43. DePaolo J, Goker-Alpan O, Samaddar T, Lopez G, Sidransky E. The association between mutations in the lysosomal protein glucocerebrosidase and parkinsonism. Mov Disord. 2009;24:1571–8.
44. DeWitt MR, Chen P, Aschner M. Manganese efflux in Parkinsonism: insights from newly characterized SLC30A10 mutations. Biochem Biophys Res Commun. 2013;432:1–4.
45. Di Toro Mammarella L, Mignarri A, Battisti C, Monti L, Bonifati V, Rasi F, Federico A. Two-year follow-up after chelating therapy in a patient with adult-onset parkinsonism and hypermanganesaemia due to SLC30A10 mutations. J Neurol. 2014;261:227–8.

46. Dickson DW, Ahmed Z, Algom AA, Tsuboi Y, Josephs KA. Neuropathology of variants of progressive supranuclear palsy. Curr Opin Neurol. 2010;23:394–400.
47. Dickson DW, Lin W, Liu WK, Yen SH. Multiple system atrophy: a sporadic synucleinopathy. Brain Pathol. 1999;9:721–32.
48. Djarmati A, Hagenah J, Reetz K, Winkler S, Behrens MI, Pawlack H, Lohmann K, Ramirez A, Tadic V, Bruggemann N, Berg D, Siebner HR, Lang AE, Pramstaller PP, Binkofski F, Kostic VS, Volkmann J, Gasser T, Klein C. ATP13A2 variants in early-onset Parkinson's disease patients and controls. Mov Disord. 2009;24:2104–11.
49. Dopper EG, Seelaar H, Chiu WZ, de Koning I, van Minkelen R, Baker MC, Rozemuller AJ, Rademakers R, van Swieten JC. Symmetrical corticobasal syndrome caused by a novel C.314dup progranulin mutation. J Mol Neurosci. 2011;45:354–8.
50. Doran M, du Plessis DG, Enevoldson TP, Fletcher NA, Ghadiali E, Larner AJ. Pathological heterogeneity of clinically diagnosed corticobasal degeneration. J Neurol Sci. 2003;216:127–34.
51. Douglas I, Evans S, Rawlins MD, Smeeth L, Tabrizi SJ, Wexler NS. Juvenile Huntington's disease: a population-based study using the General Practice Research Database. BMJ Open. 2013;3.
52. Ebert BL, Bunn HF. Regulation of the erythropoietin gene. Blood. 1999;94:1864–77.
53. Edvardson S, Cinnamon Y, Ta-Shma A, Shaag A, Yim YI, Zenvirt S, Jalas C, Lesage S, Brice A, Taraboulos A, Kaestner KH, Greene LE, Elpeleg O. A deleterious mutation in DNAJC6 encoding the neuronal-specific clathrin-uncoating co-chaperone auxilin, is associated with juvenile parkinsonism. PLoS One. 2012;7:e36458.
54. Evidente VG, Nolte D, Niemann S, Advincula J, Mayo MC, Natividad FF, Muller U. Phenotypic and molecular analyses of X-linked dystonia-parkinsonism ("lubag") in women. Arch Neurol. 2004;61:1956–9.
55. Farrer MJ, Hulihan MM, Kachergus JM, Dachsel JC, Stoessl AJ, Grantier LL, Calne S, Calne DB, Lechevalier B, Chapon F, Tsuboi Y, Yamada T, Gutmann L, Elibol B, Bhatia KP, Wider C, Vilarino-Guell C, Ross OA, Brown LA, Castanedes-Casey M, Dickson DW, Wszolek ZK. DCTN1 mutations in Perry syndrome. Nat Genet. 2009;41:163–5.
56. Ferguson MC, Garland EM, Hedges L, Womack-Nunley B, Hamid R, Phillips 3rd JA, Shibao CA, Raj SR, Biaggioni I, Robertson D. SHC2 gene copy number in multiple system atrophy (MSA). Clin Auton Res. 2014;24:25–30.
57. Ferrari R, Ryten M, Simone R, Trabzuni D, Nicolaou N, Hondhamuni G, Ramasamy A, Vandrovcova J, Weale ME, Lees AJ, Momeni P, Hardy J, de Silva R. Assessment of common variability and expression quantitative trait loci for genome-wide associations for progressive supranuclear palsy. Neurobiol Aging. 2014;35(1514):e1511–2.
58. Finch N, Baker M, Crook R, Swanson K, Kuntz K, Surtees R, Bisceglio G, Rovelet-Lecrux A, Boeve B, Petersen RC, Dickson DW, Younkin SG, Deramecourt V, Crook J, Graff-Radford NR, Rademakers R. Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members. Brain. 2009;132:583–91.
59. Furtado S, Payami H, Lockhart PJ, Hanson M, Nutt JG, Singleton AA, Singleton A, Bower J, Utti RJ, Bird TD, de la Fuente-Fernandez R, Tsuboi Y, Klimek ML, Suchowersky O, Hardy J, Calne DB, Wszolek ZK, Farrer M, Gwinn-Hardy K, Stoessl AJ. Profile of families with parkinsonism-predominant spinocerebellar ataxia type 2 (SCA2). Mov Disord. 2004;19:622–9.
60. Furukawa Y, Graf WD, Wong H, Shimadzu M, Kish SJ. Dopa-responsive dystonia simulating spastic paraplegia due to tyrosine hydroxylase (TH) gene mutations. Neurology. 2001;56:260–3.
61. Gallo M, Marcello N, Curcio SA, Colao R, Geracitano S, Bernardi L, Anfossi M, Puccio G, Frangipane F, Clodomiro A, Mirabelli M, Vasso F, Smirne N, Muraca G, Di Lorenzo R, Maletta R, Ghidoni E, Bugiani O, Tagliavini F, Giaccone G, Bruni AC. A novel pathogenic PSEN1 mutation in a family with Alzheimer's disease: phenotypical and neuropathological features. J Alzheimers Dis. 2011;25:425–31.
62. Goker-Alpan O, Lopez G, Vithayathil J, Davis J, Hallett M, Sidransky E. The spectrum of parkinsonian manifestations associated with glucocerebrosidase mutations. Arch Neurol. 2008;65:1353–7.

63. Goker-Alpan O, Schiffmann R, LaMarca ME, Nussbaum RL, McInerney-Leo A, Sidransky E. Parkinsonism among Gaucher disease carriers. J Med Genet. 2004;41:937–40.
64. Goldman JS, Rademakers R, Huey ED, Boxer AL, Mayeux R, Miller BL, Boeve BF. An algorithm for genetic testing of frontotemporal lobar degeneration. Neurology. 2011;76:475–83.
65. Greco CM, Berman RF, Martin RM, Tassone F, Schwartz PH, Chang A, Trapp BD, Iwahashi C, Brunberg J, Grigsby J, Hessl D, Becker EJ, Papazian J, Leehey MA, Hagerman RJ, Hagerman PJ. Neuropathology of fragile X-associated tremor/ataxia syndrome (FXTAS). Brain. 2006;129:243–55.
66. Guerreiro RJ, Santana I, Bras JM, Revesz T, Rebelo O, Ribeiro MH, Santiago B, Oliveira CR, Singleton A, Hardy J. Novel progranulin mutation: screening for PGRN mutations in a Portuguese series of FTD/CBS cases. Mov Disord. 2008;23:1269–73.
67. Guimaraes J, Amaral O, Sa Miranda MC. Adult-onset neuronopathic form of Gaucher's disease: a case report. Parkinsonism Relat Disord. 2003;9:261–4.
68. Gupta SR, Brigell M, Gujrati M, Lee JM. Supranuclear eye movement dysfunction in mitochondrial myopathy with tRNA(LEU) mutation. J Neuroophthalmol. 1995;15:20–5.
69. Gwinn-Hardy K, Chen JY, Liu HC, Liu TY, Boss M, Seltzer W, Adam A, Singleton A, Koroshetz W, Waters C, Hardy J, Farrer M. Spinocerebellar ataxia type 2 with parkinsonism in ethnic Chinese. Neurology. 2000;55:800–5.
70. Hagerman RJ, Hall DA, Coffey S, Leehey M, Bourgeois J, Gould J, Zhang L, Seritan A, Berry-Kravis E, Olichney J, Miller JW, Fong AL, Carpenter R, Bodine C, Gane LW, Rainin E, Hagerman H, Hagerman PJ. Treatment of fragile X-associated tremor ataxia syndrome (FXTAS) and related neurological problems. Clin Interv Aging. 2008;3:251–62.
71. Hara K, Yamamoto M, Anegawa T, Sakuta R, Nakamura M. Mitochondrial encephalomyopathy associated with parkinsonism and a point mutation in the mitochondrial tRNA(Leu)(UUR)) gene. Rinsho Shinkeigaku. 1994;34:361–5.
72. Hassan A, Masood F. Wilson's disease: a review. JPMA J Pak Med Assoc. 2004;54:479–84.
73. Hassan A, Whitwell JL, Josephs KA. The corticobasal syndrome-Alzheimer's disease conundrum. Expert Rev Neurother. 2011;11:1569–78.
74. Heller GL. Wilson's disease (hepato-lenticular degeneration): a brief review. Psychiatry Dig. 1965;26:33–9.
75. Herzfeld T, Nolte D, Grznarova M, Hofmann A, Schultze JL, Muller U. X-linked dystonia parkinsonism syndrome (XDP, lubag): disease-specific sequence change DSC3 in TAF1/DYT3 affects genes in vesicular transport and dopamine metabolism. Hum Mol Genet. 2013;22:941–51.
76. Hodges J. Familial frontotemporal dementia and amyotrophic lateral sclerosis associated with the C9ORF72 hexanucleotide repeat. Brain. 2012;135:652–5.
77. Hoglinger GU, Huppertz HJ, Wagenpfeil S, Andres MV, Belloch V, Leon T, Del Ser T. Tideglusib reduces progression of brain atrophy in progressive supranuclear palsy in a randomized trial. Mov Disord. 2014;29:479–87.
78. Hoglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, Rademakers R, de Silva R, Litvan I, Riley DE, van Swieten JC, Heutink P, Wszolek ZK, Uitti RJ, Vandrovcova J, Hurtig HI, Gross RG, Maetzler W, Goldwurm S, Tolosa E, Borroni B, Pastor P, Cantwell LB, Han MR, Dillman A, van der Brug MP, Gibbs JR, Cookson MR, Hernandez DG, Singleton AB, Farrer MJ, Yu CE, Golbe LI, Revesz T, Hardy J, Lees AJ, Devlin B, Hakonarson H, Muller U, Schellenberg GD. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet. 2011;43:699–705.
79. Houlden H, Baker M, Morris HR, MacDonald N, Pickering-Brown S, Adamson J, Lees AJ, Rossor MN, Quinn NP, Kertesz A, Khan MN, Hardy J, Lantos PL, St George-Hyslop P, Munoz DG, Mann D, Lang AE, Bergeron C, Bigio EH, Litvan I, Bhatia KP, Dickson D, Wood NW, Hutton M. Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. Neurology. 2001;56:1702–6.
80. Ichinose H, Ohye T, Takahashi E, Seki N, Hori T, Segawa M, Nomura Y, Endo K, Tanaka H, Tsuji S, et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nat Genet. 1994;8:236–42.

81. Imrie J, Dasgupta S, Besley GT, Harris C, Heptinstall L, Knight S, Vanier MT, Fensom AH, Ward C, Jacklin E, Whitehouse C, Wraith JE. The natural history of Niemann-Pick disease type C in the UK. J Inherit Metab Dis. 2007;30:51–9.
82. Jesus S, Gomez-Garre P, Carrillo F, Caceres-Redondo MT, Huertas-Fernandez I, Bernal-Bernal I, Bonilla-Toribio M, Vargas-Gonzalez L, Carballo M, Mir P. Analysis of c.801-2A>G mutation in the DNAJC6 gene in Parkinson's disease in southern Spain. Parkinsonism Relat Disord. 2014;20:248–9.
83. Josephs KA, Whitwell JL, Boeve BF, Knopman DS, Petersen RC, Hu WT, Parisi JE, Dickson DW, Jack Jr CR. Anatomical differences between CBS-corticobasal degeneration and CBS-Alzheimer's disease. Mov Disord. 2010;25:1246–52.
84. Kamm C, Healy DG, Quinn NP, Wullner U, Moller JC, Schols L, Geser F, Burk K, Borglum AD, Pellecchia MT, Tolosa E, del Sorbo F, Nilsson C, Bandmann O, Sharma M, Mayer P, Gasteiger M, Haworth A, Ozawa T, Lees AJ, Short J, Giunti P, Holinski-Feder E, Illig T, Wichmann HE, Wenning GK, Wood NW, Gasser T, European Multiple System Atrophy Study Group. The fragile X tremor ataxia syndrome in the differential diagnosis of multiple system atrophy: data from the EMSA Study Group. Brain. 2005;128:1855–60.
85. Kamphuis DJ, Koelman H, Lees AJ, Tijssen MA. Sporadic rapid-onset dystonia-parkinsonism presenting as Parkinson's disease. Mov Disord. 2006;21:118–9.
86. Kang J, Chung KC. The F-box protein FBXO7 positively regulates bone morphogenetic protein-mediated signaling through Lys-63-specific ubiquitination of neurotrophin receptor-interacting MAGE (NRAGE). Cell Mol Life Sci. 2015;72(1):181–95.
87. Kelley BJ, Haidar W, Boeve BF, Baker M, Graff-Radford NR, Krefft T, Frank AR, Jack Jr CR, Shiung M, Knopman DS, Josephs KA, Parashos SA, Rademakers R, Hutton M, Pickering-Brown S, Adamson J, Kuntz KM, Dickson DW, Parisi JE, Smith GE, Ivnik RJ, Petersen RC. Prominent phenotypic variability associated with mutations in Progranulin. Neurobiol Aging. 2009;30:739–51.
88. Kiferle L, Mazzucchi S, Unti E, Pesaresi I, Fabbri S, Nicoletti V, Volterrani D, Cosottini M, Bonuccelli U, Ceravolo R. Nigral involvement and nigrostriatal dysfunction in Huntington's disease: evidences from an MRI and SPECT study. Parkinsonism Relat Disord. 2013;19:800–5.
89. Kim JY, Kim SY, Kim JM, Kim YK, Yoon KY, Lee BC, Kim JS, Paek SH, Park SS, Kim SE, Jeon BS. Spinocerebellar ataxia type 17 mutation as a causative and susceptibility gene in parkinsonism. Neurology. 2009;72:1385–9.
90. Kinoshita M, Yoshida K, Oyanagi K, Hashimoto T, Ikeda S. Hereditary diffuse leukoencephalopathy with axonal spheroids caused by R782H mutation in CSF1R: case report. J Neurol Sci. 2012;318:115–8.
91. Knake S, Belke M, Menzler K, Pilatus U, Eggert KM, Oertel WH, Stamelou M, Hoglinger GU. In vivo demonstration of microstructural brain pathology in progressive supranuclear palsy: a DTI study using TBSS. Mov Disord. 2010;25:1232–8.
92. Koroglu C, Baysal L, Cetinkaya M, Karasoy H, Tolun A. DNAJC6 is responsible for juvenile parkinsonism with phenotypic variability. Parkinsonism Relat Disord. 2013;19:320–4.
93. Kouri N, Carlomagno Y, Baker M, Liesinger AM, Caselli RJ, Wszolek ZK, Petrucelli L, Boeve BF, Parisi JE, Josephs KA, Uitti RJ, Ross OA, Graff-Radford NR, DeTure MA, Dickson DW, Rademakers R. Novel mutation in MAPT exon 13 (p.N410H) causes corticobasal degeneration. Acta Neuropathol. 2014;127:271–82.
94. Kouri N, Murray ME, Hassan A, Rademakers R, Uitti RJ, Boeve BF, Graff-Radford NR, Wszolek ZK, Litvan I, Josephs KA, Dickson DW. Neuropathological features of corticobasal degeneration presenting as corticobasal syndrome or Richardson syndrome. Brain. 2011; 134:3264–75.
95. Kovacs GG, Seguin J, Quadrio I, Hoftberger R, Kapas I, Streichenberger N, Biacabe AG, Meyronet D, Sciot R, Vandenberghe R, Majtenyi K, Laszlo L, Strobel T, Budka H, Perret-Liaudet A. Genetic Creutzfeldt-Jakob disease associated with the E200K mutation: characterization of a complex proteinopathy. Acta Neuropathol. 2011;121:39–57.
96. Koyama Y, Asahina M, Honma K, Arai K, Hattori T. Altered heart rate control in response to postural change in patients with Machado-Joseph disease (SCA3). Cerebellum. 2009;8:130–6.

97. Krebs CE, Karkheiran S, Powell JC, Cao M, Makarov V, Darvish H, Di Paolo G, Walker RH, Shahidi GA, Buxbaum JD, De Camilli P, Yue Z, Paisan-Ruiz C. The Sac1 domain of SYNJ1 identified mutated in a family with early-onset progressive Parkinsonism with generalized seizures. Hum Mutat. 2013;34:1200–7.
98. Kurian MA, Li Y, Zhen J, Meyer E, Hai N, Christen HJ, Hoffmann GF, Jardine P, von Moers A, Mordekar SR, O'Callaghan F, Wassmer E, Wraige E, Dietrich C, Lewis T, Hyland K, Heales Jr S, Sanger T, Gissen P, Assmann BE, Reith ME, Maher ER. Clinical and molecular characterisation of hereditary dopamine transporter deficiency syndrome: an observational cohort and experimental study. Lancet Neurol. 2011;10:54–62.
99. Larner AJ, Doran M. Clinical phenotypic heterogeneity of Alzheimer's disease associated with mutations of the presenilin-1 gene. J Neurol. 2006;253:139–58.
100. Lechevalier B, Schupp C, Fallet-Bianco C, Viader F, Eustache F, Chapon F, Morin P. Familial parkinsonian syndrome with athymhormia and hypoventilation. Rev Neurol. 1992;148:39–46.
101. Lee JY, Gollamudi S, Ozelius LJ, Kim JY, Jeon BS. ATP1A3 mutation in the first Asian case of rapid-onset dystonia-parkinsonism. Mov Disord. 2007;22:1808–9.
102. Lee JY, Yang HJ, Kim JM, Jeon BS. Novel GCH-1 mutations and unusual long-lasting dyskinesias in Korean families with dopa-responsive dystonia. Parkinsonism Relat Disord. 2013;19:1156–9.
103. Lee LV, Rivera C, Teleg RA, Dantes MB, Pasco PM, Jamora RD, Arancillo J, Villareal-Jordan RF, Rosales RL, Demaisip C, Maranon E, Peralta O, Borres R, Tolentino C, Monding MJ, Sarcia S. The unique phenomenology of sex-linked dystonia parkinsonism (XDP, DYT3, "Lubag"). Int J Neurosci. 2011;121 Suppl 1:3–11.
104. Lee SE, Rabinovici GD, Mayo MC, Wilson SM, Seeley WW, DeArmond SJ, Huang EJ, Trojanowski JQ, Growdon ME, Jang JY, Sidhu M, See TM, Karydas AM, Gorno-Tempini ML, Boxer AL, Weiner MW, Geschwind MD, Rankin KP, Miller BL. Clinicopathological correlations in corticobasal degeneration. Ann Neurol. 2011;70:327–40.
105. Li Y, Chen JA, Sears RL, Gao F, Klein ED, Karydas A, Geschwind MD, Rosen HJ, Boxer AL, Guo W, Pellegrini M, Horvath S, Miller BL, Geschwind DH, Coppola G. An epigenetic signature in peripheral blood associated with the haplotype on 17q21.31, a risk factor for neurodegenerative tauopathy. PLoS Genet. 2014;10:e1004211.
106. Lin CH, Chen ML, Lai TT, Tai CH, Wu RM. Mutational analysis of FBXO7 gene in Parkinson's disease in a Taiwanese population. Neurobiol Aging. 2013;34(1713):e1711–4.
107. Lin IS, Wu RM, Lee-Chen GJ, Shan DE, Gwinn-Hardy K. The SCA17 phenotype can include features of MSA-C, PSP and cognitive impairment. Parkinsonism Relat Disord. 2007;13:246–9.
108. Lindquist S, Duno M, Batbayli M, Puschmann A, Braendgaard H, Mardosiene S, Svenstrup K, Pinborg L, Vestergaard K, Hjermind L, Stokholm J, Andersen B, Johannsen P, Nielsen J. Corticobasal and ataxia syndromes widen the spectrum of C9ORF72 hexanucleotide expansion disease. Clin Genet. 2013;83(3):279–83.
109. Ling H, O'Sullivan SS, Holton JL, Revesz T, Massey LA, Williams DR, Paviour DC, Lees AJ. Does corticobasal degeneration exist? A clinicopathological re-evaluation. Brain. 2010;133:2045–57.
110. Litvan I, Baker M, Hutton M. Tau genotype: no effect on onset, symptom severity, or survival in progressive supranuclear palsy. Neurology. 2001;57:138–40.
111. Litvan I, Mangone CA, McKee A, Verny M, Parsa A, Jellinger K, D'Olhaberriague L, Chaudhuri KR, Pearce RK. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. J Neurol Neurosurg Psychiatry. 1996;60:615–20.
112. Lu CS, Wu Chou YH, Yen TC, Tsai CH, Chen RS, Chang HC. Dopa-responsive parkinsonism phenotype of spinocerebellar ataxia type 2. Mov Disord. 2002;17:1046–51.
113. Ludecke B, Dworniczak B, Bartholome K. A point mutation in the tyrosine hydroxylase gene associated with Segawa's syndrome. Hum Genet. 1995;95:123–5.
114. Luo LZ, Xu Q, Guo JF, Wang L, Shi CH, Wei JH, Long ZG, Pan Q, Tang BS, Xia K, Yan XX. FBXO7 gene mutations may be rare in Chinese early-onset Parkinsonism patients. Neurosci Lett. 2010;482:86–9.

115. Machner B, Sprenger A, Behrens MI, Ramirez A, Bruggemann N, Klein C, Helmchen C. Eye movement disorders in ATP13A2 mutation carriers (PARK9). Mov Disord. 2010;25:2687–9.
116. Madeo G, Alemseged F, Di Pietro B, Schillaci O, Pisani A. Early abnormalities in 123I-ioflupane (DaTSCAN) imaging in the fragile X-associated tremor ataxia syndrome (FXTAS): a case report. Neurol Sci. 2013;34(8):1475–7.
117. Mahoney CJ, Beck J, Rohrer JD, Lashley T, Mok K, Shakespeare T, Yeatman T, Warrington EK, Schott JM, Fox NC, Rossor MN, Hardy J, Collinge J, Revesz T, Mead S, Warren JD. Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. Brain. 2012;135:736–50.
118. Majounie E, Renton AE, Mok K, Dopper EG, Waite A, Rollinson S, Chio A, Restagno G, Nicolaou N, Simon-Sanchez J, van Swieten JC, Abramzon Y, Johnson JO, Sendtner M, Pamphlett R, Orrell RW, Mead S, Sidle KC, Houlden H, Rohrer JD, Morrison KE, Pall H, Talbot K, Ansorge O, Hernandez DG, Arepalli S, Sabatelli M, Mora G, Corbo M, Giannini F, Calvo A, Englund E, Borghero G, Floris GL, Remes AM, Laaksovirta H, McCluskey L, Trojanowski JQ, Van Deerlin VM, Schellenberg GD, Nalls MA, Drory VE, Lu CS, Yeh TH, Ishiura H, Takahashi Y, Tsuji S, Le Ber I, Brice A, Drepper C, Williams N, Kirby J, Shaw P, Hardy J, Tienari PJ, Heutink P, Morris HR, Pickering-Brown S, Traynor BJ. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012;11:323–30.
119. Mak CM, Lam CW. Diagnosis of Wilson's disease: a comprehensive review. Crit Rev Clin Lab Sci. 2008;45:263–90.
120. Marecos C, Ng J, Kurian MA. What is new for monoamine neurotransmitter disorders? J Inherit Metab Dis. 2014;37:619–26.
121. Matej R, Kovacs GG, Johanidesova S, Keller J, Matejckova M, Novakova J, Sigut V, Keller O, Rusina R. Genetic Creutzfeldt-Jakob disease with R208H mutation presenting as progressive supranuclear palsy. Mov Disord. 2012;27:476–9.
122. McNeill A, Duran R, Proukakis C, Bras J, Hughes D, Mehta A, Hardy J, Wood NW, Schapira AH. Hyposmia and cognitive impairment in Gaucher disease patients and carriers. Mov Disord. 2012;27(4):526–32.
123. Mencacci NE, Isaias IU, Reich MM, Ganos C, Plagnol V, Polke JM, Bras J, Hersheson J, Stamelou M, Pittman AM, Noyce AJ, Mok KY, Opladen T, Kunstmann E, Hodecker S, Munchau A, Volkmann J, Samnick S, Sidle K, Nanji T, Sweeney MG, Houlden H, Batla A, Zecchinelli AL, Pezzoli G, Marotta G, Lees A, Alegria P, Krack P, Cormier-Dequaire F, Lesage S, Brice A, Heutink P, Gasser T, Lubbe SJ, Morris HR, Taba P, Koks S, Majounie E, Raphael Gibbs J, Singleton A, Hardy J, Klebe S, Bhatia KP, Wood NW. Parkinson's disease in GTP cyclohydrolase 1 mutation carriers. Brain. 2014;137(Pt 9):2480–92.
124. Mitsui J, Matsukawa T, Ishiura H, Higasa K, Yoshimura J, Saito TL, Ahsan B, Takahashi Y, Goto J, Iwata A, Niimi Y, Riku Y, Goto Y, Mano K, Yoshida M, Morishita S, Tsuji S. CSF1R mutations identified in three families with autosomal dominantly inherited leukoencephalopathy. Am J Med Genet B Neuropsychiatr Genet. 2012;159B:951–7.
125. Morris HR, Osaki Y, Holton J, Lees AJ, Wood NW, Revesz T, Quinn N. Tau exon 10 +16 mutation FTDP-17 presenting clinically as sporadic young onset PSP. Neurology. 2003;61:102–4.
126. Muller U, Herzfeld T, Nolte D. The TAF1/DYT3 multiple transcript system in X-linked dystonia-parkinsonism. Am J Hum Genet. 2007;81:415–7; author reply 417–8.
127. Multiple-System Atrophy Research Collaboration. Mutations in COQ2 in familial and sporadic multiple-system atrophy. N Engl J Med. 2013;369:233–44.
128. Najim al-Din AS, Wriekat A, Mubaidin A, Dasouki M, Hiari M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol Scand. 1994;89:347–52.
129. Newsway V, Fish M, Rohrer JD, Majounie E, Williams N, Hack M, Warren JD, Morris HR. Perry syndrome due to the DCTN1 G71R mutation: a distinctive levodopa responsive disorder with behavioral syndrome, vertical gaze palsy, and respiratory failure. Mov Disord. 2010;25:767–70.

130. Ng J, Heales SJ, Kurian MA. Clinical features and pharmacotherapy of childhood monoamine neurotransmitter disorders. Paediatr Drugs. 2014;16:275–91.
131. Ng J, Zhen J, Meyer E, Erreger K, Li Y, Kakar N, Ahmad J, Thiele H, Kubisch C, Rider NL, Morton DH, Strauss KA, Puffenberger EG, D'Agnano D, Anikster Y, Carducci C, Hyland K, Rotstein M, Leuzzi V, Borck G, Reith ME, Kurian MA. Dopamine transporter deficiency syndrome: phenotypic spectrum from infancy to adulthood. Brain. 2014;137:1107–19.
132. Nygaard TG, Marsden CD, Duvoisin RC. Dopa-responsive dystonia. Adv Neurol. 1988;50:377–84.
133. Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia: long-term treatment response and prognosis. Neurology. 1991;41:174–81.
134. O'Dowd S, Curtin D, Waite AJ, Roberts K, Pender N, Reid V, O'Connell M, Williams NM, Morris HR, Traynor BJ, Lynch T. C9ORF72 expansion in amyotrophic lateral sclerosis/frontotemporal dementia also causes parkinsonism. Mov Disord. 2012;27:1072–4.
135. Ohshima S, Tsuboi Y, Yamamoto A, Kawakami M, Farrer MJ, Kira J, Shii H. Autonomic failures in Perry syndrome with DCTN1 mutation. Parkinsonism Relat Disord. 2010;16:612–4.
136. Olgiati S, De Rosa A, Quadri M, Criscuolo C, Breedveld GJ, Picillo M, Pappata S, Quarantelli M, Barone P, De Michele G, Bonifati V. PARK20 caused by SYNJ1 homozygous Arg258Gln mutation in a new Italian family. Neurogenetics. 2014;15:183–8.
137. Orsucci D, Caldarazzo Ienco E, Mancuso M, Siciliano G. POLG1-related and other "mitochondrial Parkinsonisms": an overview. J Mol Neurosci. 2011;44:17–24.
138. Ozawa T. The COQ2 mutations in Japanese multiple system atrophy: impact on the pathogenesis and phenotypic variation. Mov Disord. 2014;29:184.
139. Paisan-Ruiz C, Guevara R, Federoff M, Hanagasi H, Sina F, Elahi E, Schneider SA, Schwingenschuh P, Bajaj N, Emre M, Singleton AB, Hardy J, Bhatia KP, Brandner S, Lees AJ, Houlden H. Early-onset L-dopa-responsive parkinsonism with pyramidal signs due to ATP13A2, PLA2G6, FBXO7 and spatacsin mutations. Mov Disord. 2010;25:1791–800.
140. Park JS, Mehta P, Cooper AA, Veivers D, Heimbach A, Stiller B, Kubisch C, Fung VS, Krainc D, Mackay-Sim A, Sue CM. Pathogenic effects of novel mutations in the P-type ATPase ATP13A2 (PARK9) causing Kufor-Rakeb syndrome, a form of early-onset parkinsonism. Hum Mutat. 2011;32:956–64.
141. Passov V, Gavrilova RH, Strand E, Cerhan JH, Josephs KA. Sporadic corticobasal syndrome with progranulin mutation presenting as progressive apraxic agraphia. Arch Neurol. 2011;68:376–80.
142. Pastor P, Pastor E, Carnero C, Vela R, Garcia T, Amer G, Tolosa E, Oliva R. Familial atypical progressive supranuclear palsy associated with homozygosity for the delN296 mutation in the tau gene. Ann Neurol. 2001;49:263–7.
143. Patterson MC, Hendriksz CJ, Walterfang M, Sedel F, Vanier MT, Wijburg F. Recommendations for the diagnosis and management of Niemann-Pick disease type C: An update. Mol Genet Metab. 2012;106:330–44.
144. Payami H, Nutt J, Gancher S, Bird T, McNeal MG, Seltzer WK, Hussey J, Lockhart P, Gwinn-Hardy K, Singleton AA, Singleton AB, Hardy J, Farrer M. SCA2 may present as levodopa-responsive parkinsonism. Mov Disord. 2003;18:425–9.
145. Perry TL, Bratty PJ, Hansen S, Kennedy J, Urquhart N, Dolman CL. Hereditary mental depression and Parkinsonism with taurine deficiency. Arch Neurol. 1975;32:108–13.
146. Perry TL, Wright JM, Berry K, Hansen S, Perry Jr TL. Dominantly inherited apathy, central hypoventilation, and Parkinson's syndrome: clinical, biochemical, and neuropathologic studies of 2 new cases. Neurology. 1990;40:1882–7.
147. Picillo M, Ranieri A, Orefice G, Bonifati V, Barone P. Clinical progression of SYNJ1-related early onset atypical parkinsonism: 3-year follow up of the original Italian family. J Neurol. 2014;261:823–4.
148. Pons R, Syrengelas D, Youroukos S, Orfanou I, Dinopoulos A, Cormand B, Ormazabal A, Garzia-Cazorla A, Serrano M, Artuch R. Levodopa-induced dyskinesias in tyrosine hydroxylase deficiency. Mov Disord. 2013;28:1058–63.

149. Poorkaj P, Muma NA, Zhukareva V, Cochran EJ, Shannon KM, Hurtig H, Koller WC, Bird TD, Trojanowski JQ, Lee VM, Schellenberg GD. An R5L tau mutation in a subject with a progressive supranuclear palsy phenotype. Ann Neurol. 2002;52:511–6.
150. Pridans C, Sauter KA, Baer K, Kissel H, Hume DA. CSF1R mutations in hereditary diffuse leukoencephalopathy with spheroids are loss of function. Sci Rep. 2013;3:3013.
151. Purdy A, Hahn A, Barnett HJ, Bratty P, Ahmad D, Lloyd KG, McGeer EG, Perry TL. Familial fatal Parkinsonism with alveolar hypoventilation and mental depression. Ann Neurol. 1979;6:523–31.
152. Quadri M, Federico A, Zhao T, Breedveld GJ, Battisti C, Delnooz C, Severijnen LA, Di Toro Mammarella L, Mignarri A, Monti L, Sanna A, Lu P, Punzo F, Cossu G, Willemsen R, Rasi F, Oostra BA, van de Warrenburg BP, Bonifati V. Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. Am J Hum Genet. 2012;90:467–77.
153. Quadri M, Fang M, Picillo M, Olgiati S, Breedveld GJ, Graafland J, Wu B, Xu F, Erro R, Amboni M, Pappata S, Quarantelli M, Annesi G, Quattrone A, Chien HF, Barbosa ER, International Parkinsonism Genetics Network, Oostra BA, Barone P, Wang J, Bonifati V. Mutation in the SYNJ1 gene associated with autosomal recessive, early-onset Parkinsonism. Hum Mutat. 2013;34:1208–121.
154. Racette BA, Perlmutter JS. Levodopa responsive parkinsonism in an adult with Huntington's disease. J Neurol Neurosurg Psychiatry. 1998;65:577–9.
155. Raciti L, Nicoletti A, Le Pira F, Andreoli V, Contrafatto D, Lanzafame S, Maci T, Gambardella A, Quattrone A, Zappia M. Presenilin-2 gene mutation presenting as Lewy body dementia? Neurol Sci. 2011;32:533–4.
156. Rademakers R. C9orf72 repeat expansions in patients with ALS and FTD. Lancet Neurol. 2012;11:297–8.
157. Rademakers R, Baker M, Gass J, Adamson J, Huey ED, Momeni P, Spina S, Coppola G, Karydas AM, Stewart H, Johnson N, Hsiung GY, Kelley B, Kuntz K, Steinbart E, Wood EM, Yu CE, Josephs K, Sorenson E, Womack KB, Weintraub S, Pickering-Brown SM, Schofield PR, Brooks WS, Van Deerlin VM, Snowden J, Clark CM, Kertesz A, Boylan K, Ghetti B, Neary D, Schellenberg GD, Beach TG, Mesulam M, Mann D, Grafman J, Mackenzie IR, Feldman H, Bird T, Petersen R, Knopman D, Boeve B, Geschwind DH, Miller B, Wszolek Z, Lippa C, Bigio EH, Dickson D, Graff-Radford N, Hutton M. Phenotypic variability associated with progranulin haploinsufficiency in patients with the common 1477C-->T (Arg493X) mutation: an international initiative. Lancet Neurol. 2007;6:857–68.
158. Rademakers R, Baker M, Nicholson AM, Rutherford NJ, Finch N, Soto-Ortolaza A, Lash J, Wider C, Wojtas A, DeJesus-Hernandez M, Adamson J, Kouri N, Sundal C, Shuster EA, Aasly J, MacKenzie J, Roeber S, Kretzschmar HA, Boeve BF, Knopman DS, Petersen RC, Cairns NJ, Ghetti B, Spina S, Garbern J, Tselis AC, Uitti R, Das P, Van Gerpen JA, Meschia JF, Levy S, Broderick DF, Graff-Radford N, Ross OA, Miller BB, Swerdlow RH, Dickson DW, Wszolek ZK. Mutations in the colony stimulating factor 1 receptor (CSF1R) gene cause hereditary diffuse leukoencephalopathy with spheroids. Nat Genet. 2012; 44:200–5.
159. Ragno M, Berbellini A, Cacchio G, Manca A, Di Marzio F, Pianese L, De Rosa A, Silvestri S, Scarcella M, De Michele G. Parkinsonism is a late, not rare, feature of CADASIL: a study on Italian patients carrying the R1006C mutation. Stroke. 2013;44:1147–9.
160. Ramirez A, Heimbach A, Grundemann J, Stiller B, Hampshire D, Cid LP, Goebel I, Mubaidin AF, Wriekat AL, Roeper J, Al-Din A, Hillmer AM, Karsak M, Liss B, Woods CG, Behrens MI, Kubisch C. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat Genet. 2006;38:1184–91.
161. Respondek G, Stamelou M, Kurz C, Ferguson LW, Rajput A, Chiu WZ, van Swieten JC, Troakes C, Al Sarraj S, Gelpi E, Gaig C, Tolosa E, Oertel WH, Giese A, Roeber S, Arzberger T, Wagenpfeil S, Höglinger GU. Movement Disorder Society-endorsed PSP Study Group. The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. Mov Disord. 2014;29(14):1758–66.

162. Riess O, Rub U, Pastore A, Bauer P, Schols L. SCA3: neurological features, pathogenesis and animal models. Cerebellum. 2008;7:125–37.
163. Rivaud-Pechoux S, Vidailhet M, Gallouedec G, Litvan I, Gaymard B, Pierrot-Deseilligny C. Longitudinal ocular motor study in corticobasal degeneration and progressive supranuclear palsy. Neurology. 2000;54:1029–32.
164. Rohrer JD, Beck J, Warren JD, King A, Al Sarraj S, Holton J, Revesz T, Collinge J, Mead S. Corticobasal syndrome associated with a novel 1048_1049insG progranulin mutation. J Neurol Neurosurg Psychiatry. 2009;80:1297–8.
165. Rohrer JD, Warren JD. Phenotypic signatures of genetic frontotemporal dementia. Curr Opin Neurol. 2011;24:542–9.
166. Ros R, Thobois S, Streichenberger N, Kopp N, Sanchez MP, Perez M, Hoenicka J, Avila J, Honnorat J, de Yebenes JG. A new mutation of the tau gene, G303V, in early-onset familial progressive supranuclear palsy. Arch Neurol. 2005;62:1444–50.
167. Ross OA, Rutherford NJ, Baker M, Soto-Ortolaza AI, Carrasquillo MM, DeJesus-Hernandez M, Adamson J, Li M, Volkening K, Finger E, Seeley WW, Hatanpaa KJ, Lomen-Hoerth C, Kertesz A, Bigio EH, Lippa C, Woodruff BK, Knopman DS, White 3rd CL, Van Gerpen JA, Meschia JF, Mackenzie IR, Boylan K, Boeve BF, Miller BL, Strong MJ, Uitti RJ, Younkin SG, Graff-Radford NR, Petersen RC, Wszolek ZK, Dickson DW, Rademakers R. Ataxin-2 repeat-length variation and neurodegeneration. Hum Mol Genet. 2011;20:3207–12.
168. Rossi G, Gasparoli E, Pasquali C, Di Fede G, Testa D, Albanese A, Bracco F, Tagliavini F. Progressive supranuclear palsy and Parkinson's disease in a family with a new mutation in the tau gene. Ann Neurol. 2004;55:448.
169. Rossi G, Marelli C, Farina L, Laura M, Maria Basile A, Ciano C, Tagliavini F, Pareyson D. The G389R mutation in the MAPT gene presenting as sporadic corticobasal syndrome. Mov Disord. 2008;23:892–5.
170. Rossi Sebastiano D, Soliveri P, Panzica F, Moroni I, Gellera C, Gilioli I, Nardocci N, Ciano C, Albanese A, Franceschetti S, Canafoglia L. Cortical myoclonus in childhood and juvenile onset Huntington's disease. Parkinsonism Relat Disord. 2012;18:794–7.
171. Rowe DB, Lewis V, Needham M, Rodriguez M, Boyd A, McLean C, Roberts H, Masters CL, Collins SJ. Novel prion protein gene mutation presenting with subacute PSP-like syndrome. Neurology. 2007;68:868–70.
172. Saito T, Guan F, Papolos DF, Lau S, Klein M, Fann CS, Lachman HM. Mutation analysis of SYNJ1: a possible candidate gene for chromosome 21q22-linked bipolar disorder. Mol Psychiatry. 2001;6:387–95.
173. Sasaki H, Emi M, Iijima H, Ito N, Sato H, Yabe I, Kato T, Utsumi J, Matsubara K. Copy number loss of (src homology 2 domain containing)-transforming protein 2 (SHC2) gene: discordant loss in monozygotic twins and frequent loss in patients with multiple system atrophy. Mol Brain. 2011;4:24.
174. Schneider SA, Paisan-Ruiz C, Quinn NP, Lees AJ, Houlden H, Hardy J, Bhatia KP. ATP13A2 mutations (PARK9) cause neurodegeneration with brain iron accumulation. Mov Disord. 2010;25:979–84.
175. Schols L, Peters S, Szymanski S, Kruger R, Lange S, Hardt C, Riess O, Przuntek H. Extrapyramidal motor signs in degenerative ataxias. Arch Neurol. 2000;57:1495–500.
176. Scholz SW, Houlden H, Schulte C, Sharma M, Li A, Berg D, Melchers A, Paudel R, Gibbs JR, Simon-Sanchez J, Paisan-Ruiz C, Bras J, Ding J, Chen H, Traynor BJ, Arepalli S, Zonozi RR, Revesz T, Holton J, Wood N, Lees A, Oertel W, Wullner U, Goldwurm S, Pellecchia MT, Illig T, Riess O, Fernandez HH, Rodriguez RL, Okun MS, Poewe W, Wenning GK, Hardy JA, Singleton AB, Del Sorbo F, Schneider S, Bhatia KP, Gasser T. SNCA variants are associated with increased risk for multiple system atrophy. Ann Neurol. 2009;65:610–4.
177. Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. J Neurol Neurosurg Psychiatry. 2011;82:476–86.
178. Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H. Hereditary progressive dystonia with marked diurnal fluctuation. Adv Neurol. 1976;14:215–33.

179. Sevin M, Lesca G, Baumann N, Millat G, Lyon-Caen O, Vanier MT, Sedel F. The adult form of Niemann-Pick disease type C. Brain. 2007;130:120–33.
180. Shan DE, Liu RS, Sun CM, Lee SJ, Liao KK, Soong BW. Presence of spinocerebellar ataxia type 2 gene mutation in a patient with apparently sporadic Parkinson's disease: clinical implications. Mov Disord. 2004;19:1357–60.
181. Shan DE, Soong BW, Sun CM, Lee SJ, Liao KK, Liu RS. Spinocerebellar ataxia type 2 presenting as familial levodopa-responsive parkinsonism. Ann Neurol. 2001;50:812–5.
182. Shimamura M, Uyama E, Hirano T, Murakami T, Mita S, Kitamoto T, Uchino M. A unique case of sporadic Creutzfeldt-Jacob disease presenting as progressive supranuclear palsy. Intern Med. 2003;42:195–8.
183. Singleton A, Hague S, Hernandez D. X-linked recessive dystonia parkinsonism (XDP; Lubag; DYT3). Adv Neurol. 2004;94:139–42.
184. Singleton AB, Farrer MJ, Bonifati V. The genetics of Parkinson's disease: progress and therapeutic implications. Mov Disord. 2013;28:14–23.
185. Spina S, Murrell JR, Huey ED, Wassermann EM, Pietrini P, Grafman J, Ghetti B. Corticobasal syndrome associated with the A9D Progranulin mutation. J Neuropathol Exp Neurol. 2007;66:892–900.
186. Stamelou M, Alonso-Canovas A, Bhatia KP. Dystonia in corticobasal degeneration: a review of the literature on 404 pathologically proven cases. Mov Disord. 2012;27:696–702.
187. Stamelou M, de Silva R, Arias-Carrion O, Boura E, Hollerhage M, Oertel WH, Muller U, Hoglinger GU. Rational therapeutic approaches to progressive supranuclear palsy. Brain. 2010;133:1578–90.
188. Stamelou M, Knake S, Oertel WH, Hoglinger GU. Magnetic resonance imaging in progressive supranuclear palsy. J Neurol. 2011;258:549–58.
189. Stamelou M, Mencacci NE, Cordivari C, Batla A, Wood NW, Houlden H, Hardy J, Bhatia KP. Myoclonus-dystonia syndrome due to tyrosine hydroxylase deficiency. Neurology. 2012;79:435–41.
190. Stamelou M, Quinn N, Bhatia K. 'Atypical' atypical parkinsonism: new genetic disorders presenting with features of PSP, MSA or CBD. Mov Disord. 2013;28(9):1184–99.
191. Stamelou M, Tuschl K, Chong WK, Burroughs AK, Mills PB, Bhatia KP, Clayton PT. Dystonia with brain manganese accumulation resulting from SLC30A10 mutations: a new treatable disorder. Mov Disord. 2012;27:1317–22.
192. Stanford PM, Halliday GM, Brooks WS, Kwok JB, Storey CE, Creasey H, Morris JG, Fulham MJ, Schofield PR. Progressive supranuclear palsy pathology caused by a novel silent mutation in exon 10 of the tau gene: expansion of the disease phenotype caused by tau gene mutations. Brain. 2000;123(Pt 5):880–93.
193. Steinberger D, Weber Y, Korinthenberg R, Deuschl G, Benecke R, Martinius J, Muller U. High penetrance and pronounced variation in expressivity of GCH1 mutations in five families with dopa-responsive dystonia. Ann Neurol. 1998;43:634–9.
194. Stopkova P, Vevera J, Paclt I, Zukov I, Lachman HM. Analysis of SYNJ1, a candidate gene for 21q22 linked bipolar disorder: a replication study. Psychiatry Res. 2004;127:157–61.
195. Sundal C, Fujioka S, Van Gerpen JA, Wider C, Nicholson AM, Baker M, Shuster EA, Aasly J, Spina S, Ghetti B, Roeber S, Garbern J, Tselis A, Swerdlow RH, Miller BB, Borjesson-Hanson A, Uitti RJ, Ross OA, Stoessl AJ, Rademakers R, Josephs KA, Dickson DW, Broderick D, Wszolek ZK. Parkinsonian features in hereditary diffuse leukoencephalopathy with spheroids (HDLS) and CSF1R mutations. Parkinsonism Relat Disord. 2013;19:869–77.
196. Tackenberg B, Metz A, Unger M, Schimke N, Passow S, Hoeffken H, Hoffmann GF, Muller U, Nolte D, Oertel WH, Eggert K, Moller JC. Nigrostriatal dysfunction in X-linked dystonia-parkinsonism (DYT3). Mov Disord. 2007;22:900–2.
197. Takazaki KA, D'Abreu A, Nucci A, Lopes-Cendes I, Franca Jr MC. Dysautonomia is frequent in Machado-Joseph disease: clinical and neurophysiological evaluation. Cerebellum. 2013;12(4):513–9.

198. Tan EK, Tong J, Pavanni R, Wong MC, Zhao Y. Genetic analysis of SCA 2 and 3 repeat expansions in essential tremor and atypical Parkinsonism. Mov Disord. 2007;22:1971–4.
199. Tassone F, Greco CM, Hunsaker MR, Seritan AL, Berman RF, Gane LW, Jacquemont S, Basuta K, Jin LW, Hagerman PJ, Hagerman RJ. Neuropathological, clinical and molecular pathology in female fragile X premutation carriers with and without FXTAS. Genes Brain Behav. 2012;11:577–85.
200. Tayebi N, Callahan M, Madike V, Stubblefield BK, Orvisky E, Krasnewich D, Fillano JJ, Sidransky E. Gaucher disease and parkinsonism: a phenotypic and genotypic characterization. Mol Genet Metab. 2001;73:313–21.
201. Tayebi N, Walker J, Stubblefield B, Orvisky E, LaMarca ME, Wong K, Rosenbaum H, Schiffmann R, Bembi B, Sidransky E. Gaucher disease with parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? Mol Genet Metab. 2003;79:104–9.
202. Tolosa E, Litvan I, Hoglinger GU, Burn D, Lees A, Andres MV, Gomez-Carrillo B, Leon T, Del Ser T. A phase 2 trial of the GSK-3 inhibitor tideglusib in progressive supranuclear palsy. Mov Disord. 2014;29:470–8.
203. Tremolizzo L, Bertola F, Casati G, Piperno A, Ferrarese C, Appollonio I. Progressive supranuclear palsy-like phenotype caused by progranulin p.Thr272fs mutation. Mov Disord. 2011;26:1964–6.
204. Tsuboi Y, Dickson DW, Nabeshima K, Schmeichel AM, Wszolek ZK, Yamada T, Benarroch EE. Neurodegeneration involving putative respiratory neurons in Perry syndrome. Acta Neuropathol. 2008;115:263–8.
205. Tuschl K, Clayton PT, Gospe Jr SM, Gulab S, Ibrahim S, Singh P, Aulakh R, Ribeiro R, Barsottini O, Zaki M, Del Rosario ML, Dydak S, Price V, Rideout A, Gordon K, Wevers RA, Chong K, Mills PB. Syndrome of hepatic cirrhosis, dystonia, polycythemia and hypermanganesemia- caused by mutation in *SLC30A10*, a manganese transporter in man. Am J Hum Genet. 2012;90:457–66.
206. Tuschl K, Mills PB, Parsons H, Malone M, Fowler D, Bitner-Glindzicz M, Clayton PT. Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia-A new metabolic disorder. J Inherit Metab Dis. 2008;31:151–63.
207. van Gaalen J, Giunti P, van de Warrenburg BP. Movement disorders in spinocerebellar ataxias. Mov Disord. 2011;26:792–800.
208. van Swieten J, Spillantini MG. Hereditary frontotemporal dementia caused by Tau gene mutations. Brain Pathol. 2007;17:63–73.
209. van Swieten JC, Heutink P. Mutations in progranulin (GRN) within the spectrum of clinical and pathological phenotypes of frontotemporal dementia. Lancet Neurol. 2008;7:965–74.
210. Varkonyi J, Rosenbaum H, Baumann N, MacKenzie JJ, Simon Z, Aharon-Peretz J, Walker JM, Tayebi N, Sidransky E. Gaucher disease associated with parkinsonism: four further case reports. Am J Med Genet A. 2003;116A:348–51.
211. Vauthier V, Jaillard S, Journel H, Dubourg C, Jockers R, Dam J. Homozygous deletion of an 80 kb region comprising part of DNAJC6 and LEPR genes on chromosome 1P31.3 is associated with early onset obesity, mental retardation and epilepsy. Mol Genet Metab. 2012;106:345–50.
212. Vilarino-Guell C, Wider C, Soto-Ortolaza AI, Cobb SA, Kachergus JM, Keeling BH, Dachsel JC, Hulihan MM, Dickson DW, Wszolek ZK, Uitti RJ, Graff-Radford NR, Boeve BF, Josephs KA, Miller B, Boylan KB, Gwinn K, Adler CH, Aasly JO, Hentati F, Destee A, Krygowska-Wajs A, Chartier-Harlin MC, Ross OA, Rademakers R, Farrer MJ. Characterization of DCTN1 genetic variability in neurodegeneration. Neurology. 2009;72:2024–8.
213. Wenning GK, Ben Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. Brain. 1994;117(Pt 4): 835–45.
214. Wenning GK, Geser F, Krismer F, Seppi K, Duerr S, Boesch S, Kollensperger M, Goebel G, Pfeiffer KP, Barone P, Pellecchia MT, Quinn NP, Koukouni V, Fowler CJ, Schrag A, Mathias CJ, Giladi N, Gurevich T, Dupont E, Ostergaard K, Nilsson CF, Widner H, Oertel W, Eggert KM, Albanese A, Del Sorbo F, Tolosa E, Cardozo A, Deuschl G, Hellriegel H,

Klockgether T, Dodel R, Sampaio C, Coelho M, Djaldetti R, Melamed E, Gasser T, Kamm C, Meco G, Colosimo C, Rascol O, Meissner WG, Tison F, Poewe W, European Multiple System Atrophy Study Group. The natural history of multiple system atrophy: a prospective European cohort study. Lancet Neurol. 2013;12:264–74.

215. Wider C, Dachsel JC, Farrer MJ, Dickson DW, Tsuboi Y, Wszolek ZK. Elucidating the genetics and pathology of Perry syndrome. J Neurol Sci. 2010;289:149–54.
216. Wider C, Wszolek ZK. Rapidly progressive familial parkinsonism with central hypoventilation, depression and weight loss (Perry syndrome)–a literature review. Parkinsonism Relat Disord. 2008;14:1–7.
217. Wilcox RA, Churchyard A, Dahl HH, Hutchison WM, Kirby DM, Thyagarajan D. Levodopa response in Parkinsonism with multiple mitochondrial DNA deletions. Mov Disord. 2007;22:1020–3.
218. Williams DR, Hadeed A, al-Din AS, Wreikat AL, Lees AJ. Kufor Rakeb disease: autosomal recessive, levodopa-responsive parkinsonism with pyramidal degeneration, supranuclear gaze palsy, and dementia. Mov Disord. 2005;20:1264–71.
219. Wraith JE, Baumgartner MR, Bembi B, Covanis A, Levade T, Mengel E, Pineda M, Sedel F, Topcu M, Vanier MT, Widner H, Wijburg FA, Patterson MC. Recommendations on the diagnosis and management of Niemann-Pick disease type C. Mol Genet Metab. 2009;98:152–65.
220. Wraith JE, Vecchio D, Jacklin E, Abel L, Chadha-Boreham H, Luzy C, Giorgino R, Patterson MC. Miglustat in adult and juvenile patients with Niemann-Pick disease type C: long-term data from a clinical trial. Mol Genet Metab. 2010;99:351–7.
221. Yu CE, Bird TD, Bekris LM, Montine TJ, Leverenz JB, Steinbart E, Galloway NM, Feldman H, Woltjer R, Miller CA, Wood EM, Grossman M, McCluskey L, Clark CM, Neumann M, Danek A, Galasko DR, Arnold SE, Chen-Plotkin A, Karydas A, Miller BL, Trojanowski JQ, Lee VM, Schellenberg GD, Van Deerlin VM. The spectrum of mutations in progranulin: a collaborative study screening 545 cases of neurodegeneration. Arch Neurol. 2010;67:161–70.
222. Zhao T, De Graaff E, Breedveld GJ, Loda A, Severijnen LA, Wouters CH, Verheijen FW, Dekker MC, Montagna P, Willemsen R, Oostra BA, Bonifati V. Loss of nuclear activity of the FBXO7 protein in patients with parkinsonian-pyramidal syndrome (PARK15). PLoS One. 2011;6:e16983.
223. Zhao T, Severijnen LA, van der Weiden M, Zheng PP, Oostra BA, Hukema RK, Willemsen R, Kros JM, Bonifati V. FBXO7 immunoreactivity in alpha-synuclein-containing inclusions in Parkinson disease and multiple system atrophy. J Neuropathol Exp Neurol. 2013;72:482–8.