Published in final edited form as:
Semin Neurol. 2014 April ; 34(2): 217–224. doi:10.1055/s-0034-1381738.

The Neurogenetics of Atypical Parkinsonian Disorders

Brent L. Fogel, MD, PhD[1], **Mary C. Clark, PhD**[1], and **Daniel H. Geschwind, MD, PhD**[1,2,3]

[1] Program in Neurogenetics, Department of Neurology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

[2] Department of Psychiatry, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

[3] Department of Human Genetics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

Abstract

Although classic Parkinson disease is the disorder most commonly associated with the clinical feature of parkinsonism, there is in fact a broader spectrum of disease represented by a collection of phenotypically similar neurodegenerative conditions which mimic many of its core features. These atypical parkinsonian disorders most commonly include progressive supranuclear palsy and corticobasal degeneration, disorders both associated with frontotemporal dementia, as well as multiple system atrophy, and dementia with Lewy bodies. While clinical distinction of these disorders still remains a challenge to physicians, recent advances in genetics are poised to tease apart the differences. Insights into the molecular etiologies underlying these conditions will improve diagnosis, yield better understanding of the underlying disease pathology, and ultimately lend stimulation to the development of potential treatments. At the same time, the wide range of phenotypes observed from mutations in a single gene warrants broad testing facilitated by advances in DNA sequencing. These expanding genomic approaches, ranging from the use of next-generation sequencing to identify causative or risk-associated gene variations to the study of epigenetic modification linking human genetics to environmental factors, are poised to lead the field into a new age of discovery.

Keywords

atypical parkinsonism; progressive supranuclear palsy; corticobasal degeneration; multiple system atrophy; dementia with Lewy bodies; frontotemporal degeneration

Introduction

The clinical evaluation of patients with hypokinetic movement disorders often involves distinguishing those patients with atypical parkinsonian disorders, specifically a group of

Address for Correspondence: Daniel H. Geschwind, MD, PhD David Geffen School of Medicine University of California at Los Angeles, Department of Neurology 695 Charles E Young Drive South, Gonda 2506 Los Angeles, CA 90095 dhg@ucla.edu Brent L. Fogel, MD PhD David Geffen School of Medicine University of California at Los Angeles, Department of Neurology 695 Charles E Young Drive South, Gonda 1206 Los Angeles, CA 90095 bfogel@ucla.edu.

heterogeneous and phenotypically overlapping neurodegenerative conditions whose clinical presentation may mimic that of classic Parkinson disease (PD). The major atypical parkinsonian disorders are comprised of progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB), although other conditions often merit consideration in various patient populations. Together these disorders represent a diagnostic challenge due to heterogeneity of presentation and phenotypic overlap not only with each other, but with other neurodegenerative disorders, especially PD.[1,2] At present, neuropathology remains the gold standard for definitive diagnosis,[1] but patient autopsies are performed less frequency at many centers and optimal clinical management demands more timely and less invasive diagnostic methods. Clinical genetics is emerging as a potential solution to this diagnostic dilemma and is becoming increasingly more valuable as a diagnostic tool. Furthermore, newer genetic technologies are poised to begin unraveling the underlying genetic basis of these conditions and may lead to new therapies and insights into pathogenesis. At a minimum, clearer understanding of the neurogenetics of atypical parkinsonism will lead to earlier and more definitive diagnosis and potentially better outcomes in the short term.

Although rare familial forms have been reported,[1,2] the atypical parkinsonisms are thought to occur sporadically and because of this, major efforts have gone into investigating the role of genetic predisposition to the development of atypical parkinsonism. Familial analysis and genome wide association studies (GWAS) have contributed to the identification of potential causal or susceptibility genes. More recently, next generation sequencing, including whole exome (WES) and genome sequencing (WGS), has been used to investigate the genetic basis of these disorders with encouraging results. As WES becomes more of a widely used clinical tool, it is likely that the spectrum of clinical conditions associated with atypical PD, and their mutational basis, will expand.[3] Here we will discuss the current state of the field and the direction of future genetic research into these atypical parkinsonian conditions.

Major Atypical Parkinsonian Disorders

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is the most common cause of parkinsonism after Parkinson disease (PD). Patients with PSP typically present after age 40 (mean onset at age 63) with parkinsonism that is non-responsive to dopamine, postural instability, supranuclear gaze palsy or slowed vertical saccades, and cognitive decline (Figure 1).[4] PSP is neuropathologically classified as a tauopathy and the brains of patients with PSP show neurofibrillary tangles composed of hyperphosphorylated tau in subcortical neurons and glia.[5] PSP shows a prevalence of 6-7 cases per 100,000, representing approximately 5% of patients with parkinsonism.[4,6] As the majority of identified cases are sporadic, initial attempts to dissect the genetics of this disease have focused on haplotype associations and GWAS to identify single nucleotide variants (SNVs) associated with a risk of developing PSP.

The strongest and most consistent association seen in PSP to date is that of the H1 haplotype of the gene *MAPT*, which encodes the protein tau (Table 1),[7-9] and is seen in over 90% of

patients.[8,10] A functional link between the H1 *MAPT* haplotype and the risk of developing PSP has further been postulated. Briefly, this model posits that presence of the H1 *MAPT* haplotype affects alternative splicing of exon 10 of *MAPT*, which may result in an increased ratio of the 4R isoform of the tau protein (4R-tau) compared to the 3R isoform (3R-tau), [11-13] but how this splicing change might occur is not known. 4R-tau and 3R-tau are found in relatively equal ratios in normal brains.[14] Interestingly, the H1 *MAPT* haplotype did not correlate to symptom severity, age of onset, or survival in a study of 63 PSP patients,[15] suggesting other modifying factors likely also exist. Recently, whole genome methylation analysis of dementia patients demonstrated that the H1 haplotype risk for neurodegenerative tauopathy is likely mediated via changes in methylation at and around the tau locus on chromosome 17.[16] Li et al. showed differential methylation at 17q21.31 correlated with the H1 haplotype in a dose-dependent manner, suggesting for the first time an epigenetic mediator of neurodegeneration that increases risk for PSP.[16]

A recent GWAS of 141 pathologically confirmed cases identified three additional genes associated with risk of PSP: *STX6* (syntaxin-6; rs1411478, odds ratio of major allele = 0.79, $p = 2.3 \times 10^{-10}$), *EIF2AK3* (eukaryotic translation initiation factor 2-alpha kinase 3; rs7571971, odds ratio of major allele = 0.75, $p = 3.2 \times 10^{-13}$), and *MOBP* (myelin-associated oligodendrocyte basic protein; rs1768208, odds ratio of major allele = 0.72, $p = 1.0 \times 10^{-16}$).[10] Ferrari et al subsequently identified point mutations in each of these genes in a subset of the PSP cases used in the original GWAS.[17] Several cellular pathways are implicated by mutations in these genes, including those involved in intracellular trafficking (*STX6*), endoplasmic reticulum-mediated clearance of misfolded proteins (*EIF2AK3*), and myelination (*MOBP*) (Table 1).[10,17] Thus far, the functional links between mutations in *STX6*, *EIF2AK3*, and *MOBP* and the development of PSP have not been established, but the identification of these risk factors opens a new area of research on disease pathophysiology.

As we learn more about PSP, interesting connections have emerged with frontotemporal degeneration (FTD), the second most common presenile dementia, clinically characterized by adult-onset, gradual decline in behavior and language resulting from frontotemporal atrophy.[18] A subset of individuals with FTD also develop motor features that are similar to the major atypical parkinsonian conditions, especially PSP and CBD,[1] and nigral depigmentation is a common neuropathological feature. Cognitive symptoms, particularly changes in behavior and language, are typically more pronounced in FTD as compared to PSP and CBD.[18] As in other tauopathies, individuals with FTD also have accumulations of tau in neurons and glia.[18] Several genes have been shown to cause FTD (Table 1). FTD has a strong familial component[19] and Mendelian mutations have been found in the genes *MAPT* (9-21% of cases),[20] *C9ORF72* (18-30% of case),[21] and *GRN* (4-23% of cases). [22,23] Clinical testing for FTD due to mutations of these genes is available commercially.

Frontotemporal dementia is also strongly associated with motor neuron disease.[24] Approximately 35% of individuals with FTD-ALS also develop atypical parkinsonism.[1] Cognitive symptoms are similar to those observed in FTD, and include changes in behavior and language. Motor symptoms include progressive muscle weakness and muscular atrophy. Unlike PSP, where the first clinical symptoms are typically motor,[4] the most common presentation of FTD-ALS involves cognitive symptoms, which typically precede motor

symptoms.[24] Most cases of FTD-ALS are caused by a hexanucleotide repeat (GGGGCC) in chromosome 9 open reading frame 72 (*C9ORF72*),[25-27] although other genes, such as *FUS* and *TARDBP*, can also cause FTD-ALS.[28] Although the mechanism by which this expansion of *C9ORF72* may cause FTD-ALS is currently unknown, recent evidence suggests that the expansion generates toxic RNA.[29,30] The identification of other nucleic acid binding proteins, such as *FUS* and *TARDBP*, in FTD-ALS, further implicates RNA-mediated toxicity in its pathophysiology.[28]

Corticobasal degeneration

Corticobasal degeneration (CBD) is the least common of the atypical parkinsonian conditions. Patients with CBD typically present after age 60 with a combination of limb apraxia and various cognitive impairments including spatial neglect, constructional or speech apraxia, and executive dysfunction (Figure 1).[31-34] Other symptoms may include dystonia, myoclonus, gait disturbances, and alien limb, which may occur in up to 60% of patients with CBD.[35] Like PSP, CBD is also a tauopathy showing accumulation of hyperphosphorylated tau on neuropathological examination.

Due to the involvement of tau pathology, several studies have investigated the role that variants in *MAPT* might play in the susceptibility to and pathogenesis of the disorder.[2] As seen in PSP, the presence of the H1 haplotype of *MAPT* was also found to be associated with the development of CBD (Table 1).[36,37] In contrast to what was observed for PSP, [15] however, presence of the H1 *MAPT* haplotype in 38 patients with CBD was found to be associated with more severe motor symptoms, although the H1 haplotype was not associated with either severity of cognitive symptoms or age of onset in these patients.[36] Based on the association of tau polymorphisms, other Mendelian genetic forms of FTD-ALS,[38,39] and the diagnosis of CBD and PSP in families with FTD, we consider PSP and CBD etiologically allied conditions within the FTD spectrum.

A recent study also examined both the coding and non-coding regions of *MAPT* in 109 pathologically confirmed patients to search for variants that might contribute to the development of CBD.[40] The authors identified a novel nonsynonymous variant in exon 13 of *MAPT* (p.N410H) that resulted in increased tau aggregation relative to wildtype, suggesting a contribution to the pathogenesis of CBD. Secondly, the authors identified novel variants in the 3' untranslated region of *MAPT* that were nominally associated with the risk of developing CBD,[40] presumably by affecting translation of tau. Again, as for PSP, WES and WGS in clinically diagnosed CBD cases over the next few years will likely open a new view of CBD etiology.

The clinical relationship of PSP, CBD and FTD represents a significant diagnostic challenge. As outlined above, a number of patients with various genetic forms of FTD may present with atypical parkinsonian syndromes, most usually PSP or CBD.[1,41,42] Since most genetic cases of FTD are caused by non-tau mutations, including *C9ORF72*, *GRN*, and *TARDBP*, the typical PSP tau pathology is absent in most of these cases on autopsy. Nevertheless, this is a common antemortem diagnostic conundrum that can be approached by genetic testing.[39] A familial form of FTD-PSP, referred to as pallido-ponto-nigral degeneration was one of the first FTD spectrum disorders found to harbor tau mutations.[43]

More recently, gene re-sequencing identified the first rare tau mutation, p.A152T, that significantly increased risk for FTD, AD and PSP,[44] and its relationship to PSP has been recently confirmed.[45] Other FTD risk factors including dominantly acting mutations in *C9ORF72*, *GRN*, and more rarely, *TARDBP* have also been associated with PSP.[39,46] A rare Sardinian founder mutation in *TARDBP*, p.A382T, has been described and associated with various forms of atypical PD, most prominently PSP and CBD.[39,45] Lastly, even risk factors for AD, such as *TREM2*, have been linked to atypical PD presenting with clinical FTD or PSP features,[47] consistent with the shared genetic risk across a variety of clinical entities whose pathology includes tau deposition. Focused genetic testing in potential familial cases of PSP or other forms of atypical parkinsonism, focusing on Mendelian forms of FTD, is warranted and clinical testing for FTD due to mutations of these genes is available commercially. Genome sequencing studies in PSP to identify rare mutations in other genes in the genome are just underway (Coppola and Geschwind, unpublished), but we expect that these studies will expand the spectrum of genes associated with PSP beyond the FTD spectrum mutations.

Multiple system atrophy

Patients with multiple system atrophy (MSA) typically present with adult-onset parkinsonism, cerebellar ataxia, and/or autonomic dysfunction (Figure 1).[48] The average age of onset is ~55 years and typically patients present initially with autonomic dysfunction and either parkinsonian features (MSA-P) or cerebellar features (MSA-C)[48,49] but often develop a mixed phenotypic picture. MSA, like PD, is considered an α-synucleinopathy.[2] The major neuropathological hallmark of MSA is glial cytoplasmic inclusions (GCIs) in oligodendrocytes.[48] GCIs are primarily composed of aggregates of abnormally folded α-synuclein, but they may also contain other protein aggregates including hyperphosphorylated tau.

α-synuclein, the major protein component of GCIs, is encoded by the gene *SNCA*. In a previous GWAS of PD, variants of *SNCA* were found to be associated with a risk of developing PD (the strongest association was for rs2736990, odds ratio = 1.23, $p = 2.24 \times 10^{-16}$).[50] As MSA also involves abnormal accumulation of α-synuclein, Scholz et al examined the 10 single nucleotide variants of *SNCA* most associated with risk of developing PD in 413 MSA cases (Table 2). The authors determined that 2/10 *SNCA* variants were significantly associated with a risk of developing MSA and confirmed their findings in an independent cohort of 108 MSA patients (rs11931074, odds ratio = 6.2, $p = 5.5 \times 10^{-12}$; rs3857059, odds ratio = 5.9, $p = 2.1 \times 10^{-10}$).[51] This finding that *SNCA* variants are associated with risk of developing MSA was further supported by subsequent studies.[52,53] Ross et al confirmed the association of the rs11931074 variant of *SNCA* in 150 MSA cases (odds ratio = 9.32, $p < 0.00001$).[52] Al-Chalabi et al examined 32 *SNCA* variants in 239 MSA cases and found 2 of the variants were associated specifically with the MSA-C subtype (rs3822086, odds ratio = 2.153, $p = 0.0024$; rs3775444, odds ratio = 4.386, $p = 0.0017$), while only rs3822086 was associated with the whole MSA cohort (odds ratio = 1.75, $p = 0.035$).[53] Thus far, however, variants of *SCNA* have only been associated with risk of developing MSA and no causal variants have been identified.[48]

The observation of rare familial cases have proved valuable for identifying potential variants that cause the development of MSA. Such genetic data has been analyzed via linkage studies, whole genome sequencing, mutational analyses, and GWAS. Recently, a combination of linkage analysis and next-generation genome sequencing was used to identify homozygous and compound heterozygous variants of the gene *COQ2* (coenzyme Q2 4-hydroxybenzoate polyprenyltransferase) as a cause of MSA (Table 2).[54] *COQ2* is crucial for the biosynthesis of coenzyme Q10, an important antioxidant and member of the respiratory chain.[1,55] In addition, this study also identified several rare variants in *COQ2* that appear to increase the risk of developing sporadic MSA. The most common of these mutations, p.V343A, was suggested to increase the risk of MSA through functional impairment of coenzyme Q10.[54] Nonfunctional coenzyme Q10 may result in increased oligodendrocyte apoptosis due to oxidative stress.[55]

A third gene with evidence for a potential causal role in MSA is *SHC2* (src homology 2 domain containing-transforming protein 2) (Table 2). Sasaki et al reported a heterozygous deletion in *SHC2* in monozygotic twins discordant for MSA.[56] They went on to explore copy number variation in unrelated MSA patients and controls of Japanese descent and observed copy number variation in *SHC2* in ~32% (10/31) MSA patients and in no controls (0/125).[56] Although this suggested that loss of *SHC2* may cause a predisposition for developing MSA, it is unclear how *SHC2* contributes to pathogenesis. A subsequent study did not find copy number variation of the *SHC2* gene to be a significant genetic factor for cohorts of MSA patients of non-Japanese descent,[57] suggesting that this copy number variation may only play a role in MSA pathogenesis in Japanese cohorts.

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is the second most common cause of dementia after Alzheimer disease (AD).[58] Patients with DLB present with a combination of dementia associated with fluctuations in alertness and concentration, parkinsonism, and visual hallucinations. In general, DLB shares many features with both AD and PD. Common symptoms of DLB include postural instability, ataxia, sleep disturbances, and impaired executive functioning (Figure 1).[58] On neuropathological examination, individuals with DLB have widespread neuronal aggregations of α-synuclein (Lewy bodies) throughout the central nervous system and occasionally in the peripheral nervous system.[58] Thus, like MSA and PD, DLB is also considered an α-synucleinopathy.[2,59]

As with other α-synucleinopathies, several studies have assessed the association of mutations in the *SNCA* gene with the development of DLB (Table 2). Ikeuchi et al observed both homozygous and heterozygous duplications of *SNCA* in pathologically confirmed cases of DLB.[60] Interestingly, a patient with homozygous duplication of *SNCA* had earlier age of onset and worse cognitive impairment compared to those with heterozygous duplications. The authors also correlated the presence of the *SNCA* gene duplication with the accumulation of phosphorylated α-synuclein in the brains of DLB patients, suggesting that *SNCA* gene duplication directly resulted in DLB pathology.[60] In addition to gene duplication, mutations in *SNCA* postulated to disturb function of α-synuclein have been

observed in a familial case of DLB.[61] The mechanism by which such mutations result in DLB pathogenesis remains to be determined.

Although not strongly associated with DLB, heterozygous variants in the *SNCB* gene, which encodes β-synuclein, have been observed in unrelated individuals with DLB.[62] Although not confirmed biochemically, it has been proposed that mutations in *SNCB* may impair the normal function of β-synuclein in inhibiting the formation of α-synuclein aggregates.

Lastly, variants in the gene *GBA*, which encodes glucocerebrosidase, have been associated with the development of DLB.[63-66] Specifically, the allele frequency of two common *GBA* variants was found to be significantly higher in individuals with DLB than in controls.[63] Glucocerebrosidase is a lysosomal enzyme, and Goker-Alpan et al postulated that mutations in *GBA* may result in decreased efficiency in lysosomal clearance of α-synuclein, thus resulting in aggregation of α-synuclein in Lewy bodies.[66]

Other Atypical Parkinsonian Disorders

In addition to the major atypical parkinsonian disorders described above, several other phenotypically related conditions warrant brief discussion as they can present similarly. In general, parkinsonism is not a typical defining feature of the disorders described below, but this can occur commonly enough to confound diagnosis.

Spinocerebellar Ataxia 3

Spinocerebellar ataxia 3 (SCA3) is an autosomal dominant disorder characterized by progressive cerebellar ataxia.[67] Additional symptoms of SCA3 may include bradykinesia, oculomotor abnormalities, peripheral neuropathy, and parkinsonism.[67,68] SCA3 is caused by a trinucleotide repeat (CAG) expansion in the *ATXN3* gene (Table 2). Specifically, normal individuals have 13-36 CAG repeats while those with SCA3 have over 60 repeats.[69,70] As for FTD-ALS, it is thought that the presence of the repeat expansion in SCA3 generates toxic RNA and the number of repeats may influence phenotypic heterogeneity of the disease.[69] The repeat expansion in *ATXN3* may also cause SCA3 by disrupting function of ataxin-3 protein, which is a deubiquitinating enzyme involved in the proteasome degradation pathway.[71] Other dominant spinocerebellar ataxias, particularly SCA1 and SCA2, can also present with a similar clinical picture (Table 2).[72,73]

Fragile X tremor ataxia syndrome

Fragile X tremor ataxia syndrome (FXTAS) is an X-linked disorder that is characterized by progressive tremor, gait ataxia, cognitive decline, and parkinsonism.[74,75] Some cases of FXTAS can mimic the clinical presentation of MSA (Table 2).[73] FXTAS affects carriers of a pre-mutation in the Fragile X syndrome gene, *FMR1*. Like Fragile X syndrome, FXTAS is also caused by a trinucleotide repeat (CGG) in the 5’ untranslated region of *FMR1*.[76] Individuals with the full *FMR1* mutation (>200 repeats) have Fragile X syndrome, while individuals with FXTAS typically have 55-200 repeats in *FMR1*.[74]

Discussion and Future Outlook

Determining the underlying genetic basis of the atypical parkinsonian disorders has been challenged in numerous ways. Diagnosis of these disorders is solely clinical and typically cannot be confirmed until post-mortem neuropathological examination.[1] Consequently, better methods of phenotyping these disorders as well as more stringent criteria for inclusion of patients in genetic studies are needed to increase the value of each study. Because the majority of the cases of these disorders are sporadic, linkage analysis, which is best performed on families with multiple affected individuals, has had limited value in determining genetic etiology of these disorders. GWAS has been used to identify variants associated with the risk of developing PSP[10] and will likely be useful in future studies of the atypical parkinsonian conditions, but these variants are expected to have small individual effect sizes, complicating functional analyses.[77] Lastly, variable expressivity, even in the case of highly penetrant mutations, is the rule, rather than the exception, reducing genotype-phenotype correlations.

Because genes predisposing to Parkinson plus syndromes may cause a wide variety of neurodegenerative conditions, it is necessary to cast a wide net when screening for mutations. Therefore, genome-wide approaches powered by advances in next-generation sequencing technology will likely have the most significant impact on future genetic studies of the atypical parkinsonian disorders.[3] These approaches produce meaningful genetic data on an individual patient basis, and have been successfully implemented to determine the genetic etiology of rare disorders as well as undiagnosed genetic conditions.[78-81] The cost and availability of such techniques makes their uses in both research and clinical settings increasingly more feasible. For the atypical parkinsonian conditions, whole exome and whole genome sequencing are likely to be useful in determining the genetic defect for an individual patient by identifying *de novo* mutations. A simultaneous widespread effort should be used to study the genomes of populations of individuals with the atypical parkinsonian conditions, as has been done for MSA,[54] to determine likely causative variants. Lastly, the identification of clear signatures of altered methylation related to neurodegenerative disease risk warrants more careful searches for epigenetic risk factors.[16] Epigenetic signatures may provide a means for integrating genetic and environmental factors so as to have a more complete etiological risk map for these conditions.

Acknowledgements

This work was supported by the National Institutes of Health (K08MH086297 and R01NS082094 to BLF).

References

1. Stamelou M, Hoeglinger GU. Atypical parkinsonism: an update. Curr Opin Neurol. 2013; 26:401–405. [PubMed: 23812308]
2. Wenning GK, Krismer F, Poewe W. New insights into atypical parkinsonism. Curr Opin Neurol. 2011; 24:331–338. [PubMed: 21577106]
3. Coppola G, Geschwind DH. Genomic medicine enters the neurology clinic. Neurology. 2012; 79:112–114. [PubMed: 22675078]
4. Lubarsky M, Juncos JL. Progressive supranuclear palsy: a current review. Neurologist. 2008; 14:79–88. [PubMed: 18332837]

5. Armstrong RA, Cairns NJ. Spatial patterns of the tau pathology in progressive supranuclear palsy. Neurol Sci. 2013; 34:337–344. [PubMed: 22411688]
6. Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. Lancet. 1999; 354:1771–1775. [PubMed: 10577638]
7. Baker M, Litvan I, Houlden H, et al. Association of an extended haplotype in the tau gene with progressive supranuclear palsy. Hum Mol Genet. 1999; 8:711–715. [PubMed: 10072441]
8. Conrad C, Andreadis A, Trojanowski JQ, et al. Genetic evidence for the involvement of tau in progressive supranuclear palsy. Ann Neurol. 1997; 41:277–281. [PubMed: 9029080]
9. Wade-Martins R. Genetics: The MAPT locus-a genetic paradigm in disease susceptibility. Nat Rev Neurol. 2012; 8:477–478. [PubMed: 22940644]
10. Höglinger GU, Melhem NM, Dickson DW, et al. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet. 2011; 43:699–705. [PubMed: 21685912]
11. Majounie E, Cross W, Newsway V, et al. Variation in tau isoform expression in different brain regions and disease states. Neurobiol Aging. 2013; 34:1922, e1927–1922, e1912. [PubMed: 23428180]
12. Ezquerra M, Gaig C, Ascaso C, et al. Tau and saitohin gene expression pattern in progressive supranuclear palsy. Brain Res. 2007; 1145:168–176. [PubMed: 17320831]
13. Takanashi M, Mori H, Arima K, et al. Expression patterns of tau mRNA isoforms correlate with susceptible lesions in progressive supranuclear palsy and corticobasal degeneration. Brain Res Mol Brain Res. 2002; 104:210–219. [PubMed: 12225876]
14. Goedert M, Spillantini MG, Jakes R, et al. Multiple isoforms of human microtubule- associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. Neuron. 1989; 3:519–526. [PubMed: 2484340]
15. Litvan I, Baker M, Hutton M. Tau genotype: no effect on onset, symptom severity, or survival in progressive supranuclear palsy. Neurology. 2001; 57:138–140. [PubMed: 11445645]
16. Li Y, Chen JA, Sears RL, et al. An epigenetic signature in peripheral blood associated with the haplotype on 17q21.31, a risk factor for neurodegenerative tauopathy. PLoS Genet. 2014; 10:e1004211. [PubMed: 24603599]
17. Ferrari R, Ryten M, Simone R, et al. Assessment of common variability and expression quantitative trait loci for genome-wide associations for progressive supranuclear palsy. Neurobiol Aging. 2014
18. Rohan Z, Matej R. Current concepts in the classification and diagnosis of frontotemporal lobar degenerations: a practical approach. Arch Pathol Lab Med. 2014; 138:132–138. [PubMed: 24377823]
19. Chow TW, Miller BL, Hayashi VN, et al. Inheritance of frontotemporal dementia. Arch Neurol. 1999; 56:817–822. [PubMed: 10404983]
20. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature. 1998; 393:702–705. [PubMed: 9641683]
21. Khan BK, Yokoyama JS, Takada LT, et al. Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. J Neurol Neurosurg Psychiatry. 2012; 83:358–364. [PubMed: 22399793]
22. Farlow JL, Foroud T. The genetics of dementia. Semin Neurol. 2013; 33:417–422. [PubMed: 24234360]
23. Cohn-Hokke PE, Elting MW, Pijnenburg YA, et al. Genetics of dementia: update and guidelines for the clinician. Am J Med Genet B Neuropsychiatr Genet. 2012; 159B:628–643. [PubMed: 22815225]
24. Achi EY, Rudnicki SA. ALS and Frontotemporal Dysfunction: A Review. Neurol Res Int. 2012; 2012:806306. [PubMed: 22919484]
25. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011; 72:245–256. [PubMed: 21944778]
26. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011; 72:257–268. [PubMed: 21944779]

27. Majounie E, Renton AE, Mok K, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012; 11:323–330. [PubMed: 22406228]
28. Harms MB, Baloh RH. Clinical neurogenetics: amyotrophic lateral sclerosis. Neurol Clin. 2013; 31:929–950. [PubMed: 24176417]
29. Donnelly CJ, Zhang PW, Pham JT, et al. RNA toxicity from the ALS/FTD C9ORF72 expansion is mitigated by antisense intervention. Neuron. 2013; 80:415–428. [PubMed: 24139042]
30. Todd PK, Paulson HL. C9orf72-associated FTD/ALS: when less is more. Neuron. 2013; 80:257–258. [PubMed: 24139028]
31. Mathew R, Bak TH, Hodges JR. Diagnostic criteria for corticobasal syndrome: a comparative study. J Neurol Neurosurg Psychiatry. 2012; 83:405–410. [PubMed: 22019546]
32. 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. [PubMed: 22550031]
33. Wadia PM, Lang AE. The many faces of corticobasal degeneration. Parkinsonism Relat Disord. 2007; 13(Suppl 3):S336–340. [PubMed: 18267261]
34. Seritan AL, Mendez MF, Silverman DH, et al. Functional imaging as a window to dementia: corticobasal degeneration. J Neuropsychiatry Clin Neurosci. 2004; 16:393–399. [PubMed: 15616165]
35. Belfor N, Amici S, Boxer AL, et al. Clinical and neuropsychological features of corticobasal degeneration. Mech Ageing Dev. 2006; 127:203–207. [PubMed: 16310834]
36. Litvan I, Chism A, Litvan J, et al. H1/H1 genotype influences symptom severity in corticobasal syndrome. Mov Disord. 2010; 25:760–763. [PubMed: 20437541]
37. Di Maria E, Tabaton M, Vigo T, et al. Corticobasal degeneration shares a common genetic background with progressive supranuclear palsy. Ann Neurol. 2000; 47:374–377. [PubMed: 10716259]
38. Kouri N, Oshima K, Takahashi M, et al. Corticobasal degeneration with olivopontocerebellar atrophy and TDP-43 pathology: an unusual clinicopathologic variant of CBD. Acta Neuropathol. 2013; 125:741–752. [PubMed: 23371366]
39. Le Ber I, Camuzat A, Guillot-Noel L, et al. C9ORF72 repeat expansions in the frontotemporal dementias spectrum of diseases: a flow-chart for genetic testing. J Alzheimers Dis. 2013; 34:485–499. [PubMed: 23254636]
40. Kouri N, Carlomagno Y, Baker M, et al. Novel mutation in MAPT exon 13 (p.N410H) causes corticobasal degeneration. Acta Neuropathol. 2014; 127(2):271–282. [PubMed: 24121548]
41. Sha S, Hou C, Viskontas IV, et al. Are frontotemporal lobar degeneration, progressive supranuclear palsy and corticobasal degeneration distinct diseases? Nat Clin Pract Neurol. 2006; 2:658–665. [PubMed: 17117169]
42. Fogel BL, Pribadi M, Pi S, et al. C9ORF72 expansion is not a significant cause of sporadic spinocerebellar ataxia. Mov Disord. 2012; 27:1832–1833. [PubMed: 23080112]
43. Clark LN, Poorkaj P, Wszolek Z, et al. Pathogenic implications of mutations in the tau gene in pallido-ponto-nigral degeneration and related neurodegenerative disorders linked to chromosome 17. Proc Natl Acad Sci U S A. 1998; 95:13103–13107. [PubMed: 9789048]
44. Coppola G, Chinnathambi S, Lee JJ, et al. Evidence for a role of the rare p.A152T variant in MAPT in increasing the risk for FTD-spectrum and Alzheimer's diseases. Hum Mol Genet. 2012; 21:3500–3512. [PubMed: 22556362]
45. Cannas A, Borghero G, Floris GL, et al. The p.A382T TARDBP gene mutation in Sardinian patients affected by Parkinson's disease and other degenerative parkinsonisms. Neurogenetics. 2013; 14:161–166. [PubMed: 23546887]
46. Kertesz A, Finger E, Murrell J, et al. Progressive Supranuclear Palsy in a family with TDP-43 pathology. Neurocase. 2014
47. Rayaprolu S, Mullen B, Baker M, et al. TREM2 in neurodegeneration: evidence for association of the p.R47H variant with frontotemporal dementia and Parkinson's disease. Mol Neurodegener. 2013; 8:19. [PubMed: 23800361]

48. Ahmed Z, Asi YT, Sailer A, et al. The neuropathology, pathophysiology and genetics of multiple system atrophy. Neuropathol Appl Neurobiol. 2012; 38:4–24. [PubMed: 22074330]
49. Roncevic D, Palma JA, Martinez J, et al. Cerebellar and parkinsonian phenotypes in multiple system atrophy: similarities, differences and survival. J Neural Transm. 2014; 121(5):507–512. [PubMed: 24337696]
50. Simón-Sánchez J, Schulte C, Bras JM, et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet. 2009; 41:1308–1312. [PubMed: 19915575]
51. Scholz SW, Houlden H, Schulte C, et al. SNCA variants are associated with increased risk for multiple system atrophy. Ann Neurol. 2009; 65(5):610–614. [PubMed: 19475667]
52. Ross OA, Vilariño-Güell C, Wszolek ZK, et al. Reply to: SNCA variants are associated with increased risk of multiple system atrophy. Ann Neurol. 2010; 67:414–415. [PubMed: 20373361]
53. Al-Chalabi A, Dürr A, Wood NW, et al. Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy. PLoS ONE. 2009; 4:e7114. [PubMed: 19771175]
54. Collaboration M-SAR. Mutations in COQ2 in familial and sporadic multiple-system atrophy. N Engl J Med. 2013; 369:233–244. [PubMed: 23758206]
55. Bleasel JM, Wong JH, Halliday GM, et al. Lipid dysfunction and pathogenesis of multiple system atrophy. Acta Neuropathol Commun. 2014; 2:15. [PubMed: 24502382]
56. Sasaki H, Emi M, Iijima H, et al. 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. [PubMed: 21658278]
57. Ferguson MC, Garland EM, Hedges L, et al. SHC2 gene copy number in multiple system atrophy (MSA). Clin Auton Res. 2014; 24:25–30. [PubMed: 24170347]
58. Morra LF, Donovick PJ. Clinical presentation and differential diagnosis of dementia with Lewy bodies: a review. Int J Geriatr Psychiatry. 2013
59. Ebersbach G, Moreau C, Gandor F, et al. Clinical syndromes: Parkinsonian gait. Mov Disord. 2013; 28:1552–1559. [PubMed: 24132843]
60. Ikeuchi T, Kakita A, Shiga A, et al. Patients homozygous and heterozygous for SNCA duplication in a family with parkinsonism and dementia. Arch Neurol. 2008; 65:514–519. [PubMed: 18413475]
61. Zarranz JJ, Alegre J, Gómez-Esteban JC, et al. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol. 2004; 55:164–173. [PubMed: 14755719]
62. Ohtake H, Limprasert P, Fan Y, et al. Beta-synuclein gene alterations in dementia with Lewy bodies. Neurology. 2004; 63:805–811. [PubMed: 15365127]
63. Mata IF, Samii A, Schneer SH, et al. Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. Arch Neurol. 2008; 65:379–382. [PubMed: 18332251]
64. Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. Lancet Neurol. 2012; 11:986–998. [PubMed: 23079555]
65. Velayati A, Yu WH, Sidransky E. The role of glucocerebrosidase mutations in Parkinson disease and Lewy body disorders. Curr Neurol Neurosci Rep. 2010; 10:190–198. [PubMed: 20425034]
66. Goker-Alpan O, Giasson BI, Eblan MJ, et al. Glucocerebrosidase mutations are an important risk factor for Lewy body disorders. Neurology. 2006; 67:908–910. [PubMed: 16790605]
67. Paulson H. Machado-Joseph disease/spinocerebellar ataxia type 3. Handb Clin Neurol. 2012; 103:437–449. [PubMed: 21827905]
68. Subramony SH, Hernandez D, Adam A, et al. Ethnic differences in the expression of neurodegenerative disease: Machado-Joseph disease in Africans and Caucasians. Mov Disord. 2002; 17:1068–1071. [PubMed: 12360561]
69. Todd PK, Paulson HL. RNA-mediated neurodegeneration in repeat expansion disorders. Ann Neurol. 2010; 67:291–300. [PubMed: 20373340]
70. Shakkottai VG, Fogel BL. Clinical neurogenetics: autosomal dominant spinocerebellar ataxia. Neurol Clin. 2013; 31:987–1007. [PubMed: 24176420]
71. Evers MM, Toonen LJ, van Roon-Mom WM. Ataxin-3 Protein and RNA Toxicity in Spinocerebellar Ataxia Type 3: Current Insights and Emerging Therapeutic Strategies. Mol Neurobiol. 2013

72. Jhunjhunwala K, Netravathi M, Purushottam M, et al. Profile of extrapyramidal manifestations in 85 patients with spinocerebellar ataxia type 1, 2 and 3. J Clin Neurosci. 2013
73. Fogel BL, Baker C, Curnow A, et al. Mutations in PDYN are not responsible for multiple system atrophy. J Neurol. 2013; 260:927–928. [PubMed: 23355175]
74. Greco CM, Berman RF, Martin RM, et al. Neuropathology of fragile X-associated tremor/ataxia syndrome (FXTAS). Brain. 2006; 129:243–255. [PubMed: 16332642]
75. Hagerman P. Fragile X-associated tremor/ataxia syndrome (FXTAS): pathology and mechanisms. Acta Neuropathol. 2013; 126:1–19. [PubMed: 23793382]
76. Todd PK, Oh SY, Krans A, et al. CGG repeat-associated translation mediates neurodegeneration in fragile X tremor ataxia syndrome. Neuron. 2013; 78:440–455. [PubMed: 23602499]
77. Fogel, BL.; Geschwind, DH. Clinical Neurogenetics.. In: Daroff, R.; Fenichel, G.; Jankovic, J., et al., editors. Neurology in Clinical Practice. 6th ed.. Elsevier; Philadelphia, PA: 2012. p. 704-734.
78. Rabbani B, Tekin M, Mahdieh N. The promise of whole-exome sequencing in medical genetics. J Hum Genet. 2014; 59:5–15. [PubMed: 24196381]
79. Wang Z, Liu X, Yang BZ, et al. The Role and Challenges of Exome Sequencing in Studies of Human Diseases. Front Genet. 2013; 4:160. [PubMed: 24032039]
80. Biesecker LG. Exome sequencing makes medical genomics a reality. Nat Genet. 2010; 42:13–14. [PubMed: 20037612]
81. Bamshad MJ, Ng SB, Bigham AW, et al. Exome sequencing as a tool for Mendelian disease gene discovery. Nat Rev Genet. 2011; 12:745–755. [PubMed: 21946919]

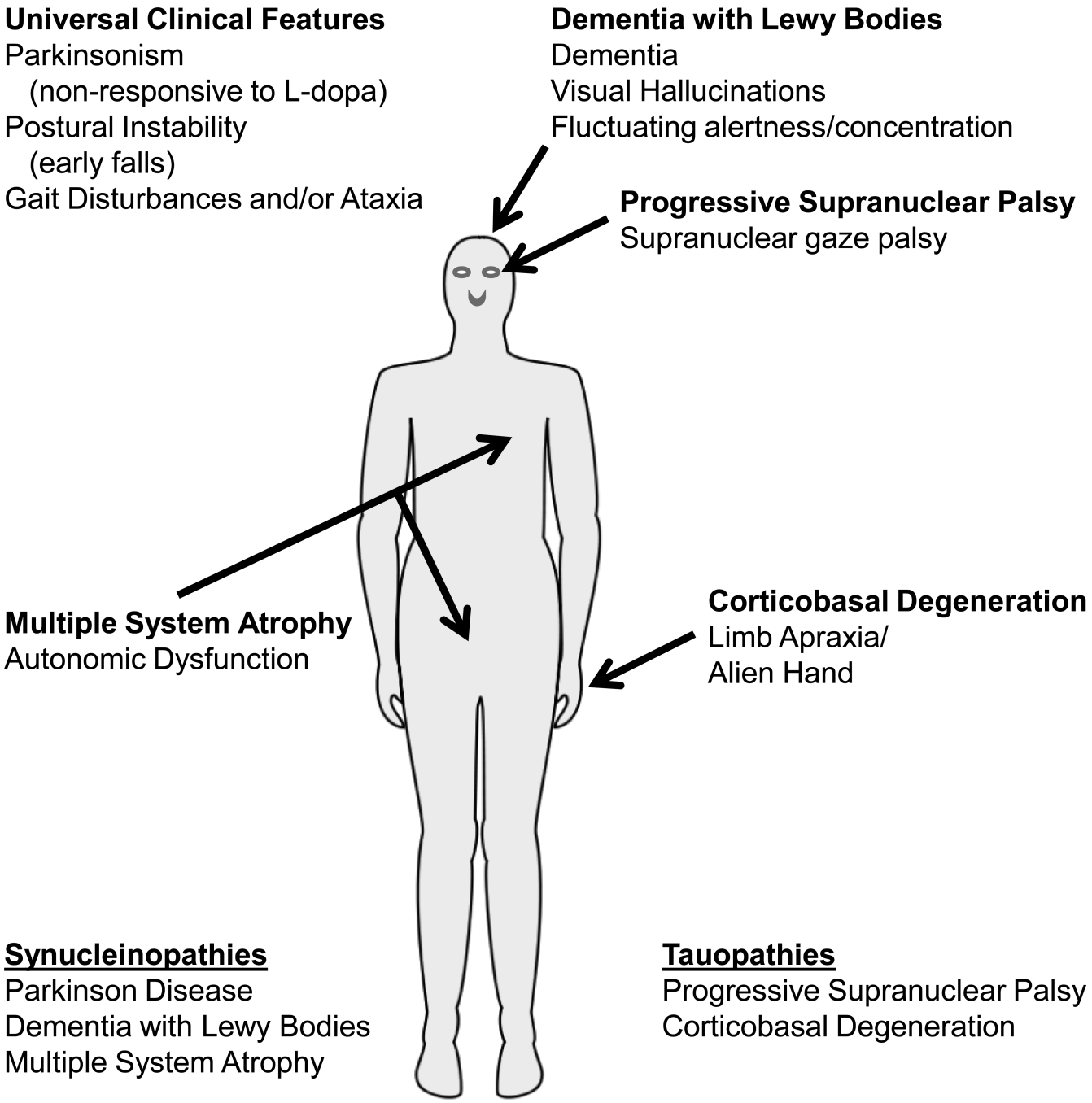

Figure 1.
Clinical features of the major atypical parkinsonian disorders.

Table 1

Genetic spectrum associated with the atypical parkinsonian tauopathies, progressive supranuclear palsy and corticobasal degeneration.

Gene	Common Genetic Phenotype	Atypical Parkinsonian Phenotype	Protein	Genetic Evidence for Atypical Parkinsonism	Potential Cellular Pathway Affected
MAPT	FTD	CBD PSP	tau	Risk-associated by haplotyping and sequencing	Protein aggregation
C9orf72	FTD FTD-ALS	CBD PSP	C9orf72 protein	Clinical overlap, Mendelian repeat expansion	Cellular trafficking
GRN	FTD	CBD PSP	granulin	Clinical overlap, Mendelian mutations	Cell growth
FUS	FTD-ALS	CBD PSP	RNA-binding protein FUS	Clinical overlap, Mendelian mutations	RNA processing
TARDBP	FTD-ALS	CBD PSP	TAR DNA binding protein	Clinical overlap, Mendelian mutations	Transcriptional regulation
STX6		PSP	syntaxin-6	Risk-associated by GWAS and sequencing	Intracellular trafficking
EIF2AK3		PSP	eukaryotic translation initiation factor 2-alpha kinase 3	Risk-associated by GWAS and sequencing	Protein quality control
MOBP		PSP	myelin-associated oligodendrocyte basic protein	Risk-associated by GWAS and sequencing	Myelination

Abbreviations: ALS, amyotrophic lateral sclerosis; CBD, corticobasal degeneration; FTD, frontotemporal degeneration; GWAS, genome-wide association study; PSP, progressive supranuclear palsy.

Table 2

Genetic spectrum associated with the atypical parkinsonian α-synucleinopathies, multiple system atrophy and dementia with Lewy bodies.

Gene	Common Genetic Phenotype	Atypical Parkinsonian Phenotype	Protein	Genetic Evidence for Atypical Parkinsonism	Potential Cellular Pathway Affected
SNCA		DLB MSA	α-synuclein	Risk-associated by copy number analysis, SNP association (MSA), and Mendelian mutations	Protein aggregation
SNCB		DLB	β-synuclein	Mendelian mutations?	Protein aggregation
GBA		DLB	glucocerebrosidase	Risk-associated by sequencing	Protein aggregation
COQ2		MSA	coenzyme Q2 4-hydroxybenzoate polyprenyltransferase	Mendelian mutations and risk-associated by linkage and sequencing	Response to oxidative stress
SHC2		MSA	src homology 2 domain containing-transforming protein 2	Risk-associated by copy number analysis	Unknown
FMR1	FXS FXTAS	MSA	fragile-X mental retardation protein	Clinical overlap, X-linked repeat expansion	RNA processing
ATXN1	SCA1	MSA	ataxin 1	Clinical overlap, Mendelian repeat expansion	Transcriptional regulation and RNA processing
ATXN2	SCA2	MSA	ataxin 2	Clinical overlap, Mendelian repeat expansion	RNA processing
ATXN3	SCA3	MSA	ataxin 3	Clinical overlap, Mendelian repeat expansion	Protein quality control
PDYN	SCA23	MSA	prodynorphin	Clinical overlap, Mendelian mutations (rare)	Cell signaling
TGM6	SCA35	MSA	transglutaminase-6	Clinical overlap, Mendelian mutations (rare)?	Protein modification

Abbreviations: DLB, dementia with Lewy bodies; FXS, fragile-X syndrome; FXTAS, fragile-X tremor/ataxia syndrome; MSA, multiple system atrophy; SCA, spinocerebellar ataxia. ? = unconfirmed.