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Neuropathology of Genetic Synucleinopathies with Parkinsonism – review of the literature

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Abstract

Clinical-pathological studies remain the gold-standard for the diagnosis of Parkinson's disease (PD). However mounting data from genetic-PD autopsies challenge the diagnosis of PD based on Lewy body pathology. Most of the confirmed genetic risks for PD show heterogenous neuropathology, even within kindreds, which may or may not include Lewy body pathology.

Here we review the literature of genetic-PD autopsies from cases with molecularly-confirmed PD or parkinsonism and summarize main findings on *SNCA* (n=25), *Parkin* (n=20, 17 bi-allelic and 3 heterozygotes), *PINK1* (n=5, 1 bi-allelic and 4 heterozygotes), *DJ-1* (n=1), *LRRK2* (n=55), *GBA* (n=10 Gaucher disease patients with parkinsonism), *DNAJC13*, *GCH1*, *ATP13A2*, *PLA2G6* (n= 8 patients, two with PD), *MPAN* (n=2), *FBXO7*, *RAB39B* and *ATXN2* (SCA2), as well as on 22q deletion syndrome (n=3). Findings from autopsies of heterozygous mutation carriers of genes which are traditionally considered recessively-inherited are also discussed.

Lewy bodies may be present in syndromes clinically distinctive from PD (e.g., *MPAN*-related neurodegeneration) and absent in patients with clinical PD syndrome (e.g., *LRRK2*-PD or *Parkin*-PD). Therefore, we may conclude that the presence of Lewy bodies are not specific to the diagnosis of PD and that PD can be diagnosed even in the absence of Lewy body pathology.

Interventions that reduce alpha-synuclein load may be more justified in *SNCA*-PD or *GBA*-PD than in other genetic forms of PD. The number of reported genetic-PD autopsies remains small and there are limited genotype-clinical-pathological-phenotype studies. Therefore, larger series of autopsies from genetic-PD patients are required.

Keywords

Genetic Parkinson's disease; brain pathology; postmortem; geno-pathological correlation; Lewy body

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Parkinson's disease (PD) is the second most common neurodegenerative disease. Despite advancements in the clinical diagnosis, pathophysiological understanding and treatment of PD, the gold-standard diagnosis remains clinico-pathological, as described by Dickson and colleagues.¹ However, clinical-pathological studies report significant discordance between clinical and pathological diagnoses.² The current pathological criteria for PD require both neuronal loss in the substantia nigra pars compacta (SNpc) and Lewy body (LB) pathology.^{1, 3, 4} However, a review of mounting pathological findings from genetic syndromes which clinically do not resemble PD demonstrate that SNpc atrophy with LB pathology may be present in syndromes that are clinically very distinct from PD. Furthermore, most of the confirmed genetic risks for PD are associated with heterogenous neuropathology, which may or may not include LB pathology. Taken together, these findings challenge the current notion that LB presence is required for a pathological diagnosis of PD. Predicting which patients have LB pathology may become clinically important, since interventions targeting alpha-synuclein could be useful in rare genetic neurodegenerative syndromes with parkinsonism but may not be useful in some relatively common causes of genetic PD, such as some of the *LRRK2*-PD cases.

In this review, we update the summary⁵ of reported genetic-PD autopsies in autopsies with *SNCA*, *Parkin*, *PINK-1*, *LRRK2*, and *GBA* mutations. We further report on pathological findings in autopsies with mutations in *DNAJC13*, *GCH1*, *DJ-1*, *ATP13A2*, *PLA2G6*, *MPAN*, *Fbxo7*, *RAB39B* and *ATXN2* (SCA2), as well as with 22q deletion syndrome.

Autosomal dominant causes of alpha-synuclein associated parkinsonism

SNCA [PARK1/PARK4]

In 1997, the first gene underlying autosomal dominant PD, *SNCA*, was discovered. Both pathogenic missense mutations (A53T⁶, A30P⁷, E46K⁸ and H50Q⁹) [PARK1] and changes in gene dosage (duplications, triplications) [PARK4] occur. Interestingly, point mutation carriers and triplication carriers show nearly complete penetrance whereas penetrance in duplication carriers ranges between 30% and 50%. In keeping with the dosage effect, *SNCA* triplication carriers also tend to have even earlier onset and more severe phenotype than duplication carriers.¹⁰

Overall, the clinical phenotype has been associated with early-onset rapid motor progression and frequent dementia. Rather than presenting as typical PD, a recent review of 43 cases with *SNCA* duplications revealed clinical phenotype that overlapped with multiple system atrophy (MSA) or dementia with Lewy bodies (DLB), with symptoms including dysautonomia, rapid eye movement sleep behavior disorder, hallucinations (usually visual) and cognitive deficits leading to dementia.¹¹

Pathology is available for 25 carriers of *SNCA* gene mutations or multiplications (11 point mutations, 7 duplications and 7 triplications, Table 2 for details). Overall, the pathological features of PARK1 and PARK4 are similar. Alpha-synuclein-positive inclusions were present in all cases, with a severe degree of LB pathology in all. The majority also showed neurofibrillary tangles, corresponding to Braak stages 1–2. While neuronal loss was prominent and severe in the brainstem, particularly in the SNpc and locus coeruleus (LC), a

typical feature of autopsied *SNCA* (duplication) cases was neuronal loss in the hippocampal formation, particularly in the hippocampal cornu ammonis 2/3 regions, which is distinct from CA1 neuronal loss usually associated with TDP-43 pathology. Additional cortical involvement may explain the clinical dementia that was observed in all patients. In addition, neurofibrillary tangles (NFTs) were present in a variable distribution in a subset (affecting almost 50 percent of autopsied cases) in which tau immunohistochemistry was reported. The density of tau inclusions was too low to qualify for pathological diagnosis of AD.^{12, 13} Interestingly, some cases^{14, 15, 16, 17} showed inclusions with both tau and alpha-synuclein immunostaining, which would be atypical for classic PD. In addition, one case (A53T) showed a pattern consistent with frontotemporal lobe dementia (FTD) with TDP-43 inclusions in neurites and cell bodies in the temporal cortex,¹⁶ while another (also A53T) demonstrated MSA-like features.¹⁸

In summary, all *SNCA* associated autopsies report alpha-synuclein pathology. However, most cases were not pure synucleinopathies, as tau inclusions were frequent.

LRRK2 [PARK8]

Of all monogenic forms, mutations in *LRRK2* are the most prevalent genetic cause of PD. The International *LRRK2* Consortium study¹⁹ estimated that the most common mutation in *LRRK2*, G2019S, alone accounts for 1% of sporadic and 4% of familial PD patients. Frequencies vary between ethnic groups: North African Arabs (36% in familial, 39% in sporadic) and Ashkenazi Jews (28% in familial, 10% in sporadic) have the highest frequencies. Penetrance is age-dependent and estimations are widely variable, ranging between 30% and 74%.²⁰ Among Asian populations, the G2385R variant is a common risk factor for PD (the variant allele carrier type is associated with an increased risk for PD with an odds ratio of 2.24), particularly in Chinese populations.^{19, 21} Clinically, patients with *LRRK2* mutations cannot be distinguished on an individual basis from late-onset idiopathic PD (iPD).

A total of 55 *LRRK2* autopsies were reported on PubMed, including two reviews.^{5, 22} Table 3 summarizes findings of these 55 patients (33 G2019S carriers and 22 with other mutations). No autopsy with the G2385R Asian variant has been reported. In brief, the neuropathology of *LRRK2* is very heterogeneous²³ – even within kindreds²³ – and may be reminiscent of iPD. Kalia and colleagues²² correlated clinical and pathological findings in 37 *LRRK2*-related PD autopsy cases [33 published up to October 2013 and 4 not-previously published cases, excluding autopsies with nonpathogenic variants (n=3) and those with insufficient clinical and/or pathological data (n=17)]. They noted that cases with LBs were more likely to have a G2019S mutation. Furthermore, non-motor symptoms of PD including cognitive impairment, anxiety, and orthostatic hypotension were correlated with the presence of LB pathology, while motor symptoms of PD were present even among autopsies without LB pathology. Neuronal loss in the SNpc and LC was universal in *LRRK2* mutation carriers with parkinsonism.

Tau-inclusions were present with variable distribution and severity in approximately half of the cases (29 out of 55, including the cases of Alzheimer's disease (AD)- and progressive supranuclear palsy (PSP)-like changes with a G2019S mutation). TDP-43-positive

inclusions were identified in 3 cases. Although the overall frequency of positive TDP-43-staining is unclear because most series did not stain for it, the role of *LRRK2* in DLB is considered minor.²⁴ Overall, considering that penetrance of the *LRRK2* G2019S mutation is estimated at 30%, the autopsy reports are skewed towards autopsies of patients with clinical parkinsonism and/or neurodegeneration. Studies exploring the association between *LRRK2* mutations and tau pathology (e.g., genotyping large tau pathology brain banks for *LRRK2* mutations) are required. Additional studies including non-manifesting mutation carriers are also required to clarify whether the reduced penetrance of *LRRK2* is because the brains of non-manifesting carriers do not harbor pathological markers present in those with PD.

DNAJC13 [PARK21, role in PD susceptibility still requires confirmation²⁵]

Vilariño-Güell et al.²⁶ identified mutations in *DNAJC13* through an autosomal-dominant Canadian family, which included (across four generations) 11 individuals diagnosed with PD, one with PSP and four independent PD patients. The mean age of onset was 67 ± 9.5 years in the index family. Death occurred after an average of 13 years. PD manifested as slowly progressive, late-onset asymmetric parkinsonism with a combination of tremor, rigidity, bradykinesia and a good response to levodopa when tried. Pathological exam (from three patients, II-1, II-7 and II-9) revealed brainstem or transitional LB disease, and – in the patient with PSP – tauopathy consistent with the clinical presentation of PSP. Immunological staining against *DNAJC13* revealed finely granular cytoplasmic immunoreactivity in a subset of neurons in the dorsal motor nucleus of the vagus, raphe nuclei, oculomotor nucleus and, to a lesser extent, the SN and LC. Overall, less than 50% of LBs were labeled, but there was the suggestion of region-specificity, i.e. LB staining was absent in neurons of the LC, weak in the dorsal motor nucleus and strong in the SN.²⁶

GCHI

Mutations in *GCHI* cause dopa-responsive dystonia (DRD), also known as Segawa syndrome, typically characterized by early-onset generalized dystonia with diurnal fluctuation and a dramatic therapeutic response to L-dopa.^{27–29} Parkinsonism may be associated, and adult-onset parkinsonism in the absence of dystonia (sometimes mimicking idiopathic PD) has been reported in first-degree relatives of children with DRD. Notably, while DRD is typically considered a non-degenerative disease in most cases, recent studies showed that *GCHI* mutations are a risk factor for developing PD. These latter cases were characterized by early-onset of disease, long-term levodopa-induced motor complications and in some cases also non-motor features.³⁰ The cause of parkinsonism in these cases is likely due to nigrostriatal degeneration, rather than being simply part of the phenotypic spectrum of metabolic *GCHI*-related striatal dopamine deficiency,³⁰ in line with reports of abnormal nigrostriatal imaging in adult-onset parkinsonism in *GCHI* mutation carriers.

There is limited pathological data for *GCHI*-associated disease; most refer to cases clinically diagnosed as DRD prior to the genetic era. Some report minor morphological anomalies and/or depigmentation in the SN and striatum.^{31–33} This includes the case reported by Grötzsch et al.³³, later molecularly confirmed³⁴ as *GCHI*-associated autosomal dominant DRD, which showed neither gliosis, as assessed by glial fibrillary acidic protein immunostaining, nor intraneuronal inclusions, as assessed by ubiquitin immunostaining.

LBs, neurofibrillary tangles, and amyloid plaques were absent in the cortex. The striatum and the other brain sections studied were also unremarkable. Furukawa et al.³² reported a case with compound heterozygous *GCHI* mutations (i.e. a rare form of “autosomal recessive” *GCHI*-associated DRD). Neuropathological investigation demonstrated absence of LBs and a normal cell count in the SN, although the number of cells containing melanin was reduced.

On the other hand, positive LB pathology has been reported in *GCHI* mutation carriers. In 1991, Gibb and Lees reported a case (heterozygous for c.276delC)³⁵ who presented with juvenile-onset dopa-responsive dystonia and parkinsonism complicated by the development of early disabling levodopa-induced dyskinesias. Death occurred at 39 years. Pathological examination showed a striking combination of low melanin content in nigral neurons and devastating neuronal loss with reactive gliosis. LBs were present in surviving nigral cells and in the LC.³⁶

Thus, while *GCHI* mutations usually manifest as childhood-onset non-neurodegenerative DRD with absent LBs, a subset of patients develop late-onset parkinsonism associated with nigrostriatal degeneration and LB pathology. Further studies from independent brain banks are needed to validate this interesting finding.

Autosomal recessive causes of PD

Parkin [PARK2]

Homozygous and compound heterozygous *Parkin* mutations are an established cause of early-onset PD (EOPD) world-wide.³⁷ *Parkin* dosage mutations are more likely to be pathogenic than point mutations. Single mutations may predispose to late-onset PD, reminiscent of iPD; however, the role of heterozygous *Parkin* mutations in the pathogenesis of PD remains controversial.^{38, 39} Patients have sleep benefit, dystonia, hyperreflexia and a good response to levodopa but are prone to developing dyskinesias.⁴⁰ Older age at onset has been described.⁴¹

A summary of autopsy findings is presented in Table 4. Eighteen (17 of whom were genetically-confirmed) homozygous or compound heterozygous *Parkin* cases and three heterozygous (single mutation) carriers who went for brain autopsy were identified in the literature. In brief, the majority had SNpc neuronal loss with absent LB pathology. Presence of LBs were only reported in 6 patients (i.e. one third of reported cases): five had typical LBs^{42–45}, one^{46, 47} had basophilic LB-like inclusions in the pedunclopontine nucleus (PPN) and eosinophilic LB-like inclusions in the anterior horn cells of the lumbar spinal cord. Most cases showed more neuronal loss in the SNpc than in the LC (in contrast to iPD). Tau inclusions were present in three out of ten autopsies.

There are also three case reports of heterozygous *Parkin* mutation carriers. One case carried a heterozygous p.R275W mutation, with disease onset at age 62, that showed diffuse LBs.⁴⁸ Notably, the p.R275W mutation has been associated with later onset.⁴⁵ A more recent report⁴⁹ is of a carrier of a heterozygous exon 3–4 deletion who developed hand tremor at age 44, cognitive features at age 66 and died at age 76. Neuropathology revealed extensive

LB pathology (Braak stage 6 of 6) involving all sectors of the hippocampus, putamen, and ambient gyrus. In line with previous *Parkin* cases, the degree of neuronal loss in the SN was severe. There was a mild degree of neuronal tangles (stage 1 of 6) and no Alzheimer-type plaques.⁴⁹ A third case is an 82-year-old patient (a father of 3 children with autosomal recessive juvenile parkinsonism due to combined heterozygous mutations of the *Parkin* gene), who developed clinical features of PSP two years before death.⁵⁰ However, in addition to the mutation of one *Parkin* allele (C212Y) he was also homozygous for the A0 polymorphism and for the H1 haplotype (a risk factor for PSP), so results need to be interpreted with caution.⁵¹ Pathology showed features of PSP, involving neuronal loss, gliosis, neurofibrillary tangles, neurophilic threads, and τ -immunoreactive glial lesions in several brain areas including the cerebral cortex, basal ganglia and the brainstem. LBs were absent. Remarkably, heterozygous mutation carriers more consistently showed LBs compared to EOPD cases.

In summary, the majority of the *Parkin* autopsies are not associated with alpha-synuclein neuronal inclusions. Unlike iPD, involvement of the SN is usually more pronounced than of the LC. However, even in this presumably homogeneous genetic group there was variability, since some cases had LB pathology and tau inclusions. The role of heterozygous *Parkin* mutations and their pathological correlates remain controversial as to whether the brain pathology findings indeed relate to the *Parkin* heterozygosity.

PINK1 [PARK6]

***PINK1* mutations cause autosomal recessive early-onset PD**—Brain autopsy is available for only one patient, a compound heterozygote for an exon 7 deletion and a splicing mutation in exon 7, from a Spanish kindred with six affected members.⁵² He developed PD at age 31 and florid psychosis 6 years later. Disease duration was 8 years. Autopsy revealed LB pathology and aberrant neurites in the SNpc, the reticular nuclei of the brainstem and Meynert nucleus with sparing of the LC and amygdala. There was neuronal loss in the SNpc sparing the LC, which would be atypical for iPD. No tau- or TDP43-positive inclusions were observed.⁵² This weakens the notion that *PINK1* and *Parkin* are closely related given the different pathological correlates.

Similar to *Parkin*, the role of heterozygous *PINK1* mutations is controversial.⁵³ Extensive screening (exact number not reported) for *PINK1* mutations in PD brain bank samples revealed four heterozygotes (carrying A339T, Y431H, N451S and C575R)⁵⁴ in patients with a negative family history of PD. The clinical and pathological phenotype was compatible with a diagnosis of PD with psychiatric features. Two were cognitively impaired, one of whom had AD pathology. The PD pathology was typically distributed in all four patients, demonstrating brainstem and cortical LBs, with SNpc neuronal loss and NFT stages ranging from I to V.

In summary, data on pathological changes in *PINK1* mutation carriers remains very limited. The one *PINK1* mutation carrier who reached autopsy had LB pathology.

DJ1 [PARK7]

DJ1 mutations cause autosomal recessive early-onset PD. Only a handful of cases have been described clinically (for summary, see Bras et al. 2014⁵⁵) and brain autopsy is only available for one homozygous patient⁵⁶ (c.515T>A; p.L172Q) who developed early-onset parkinsonism at the age of 22 with tremor and falls, was poorly responsive to levodopa, and had additional features with further disease progression (had autonomic involvement and dementia; late in the course, had pyramidal signs and seizures). He died at age 49. Other causes of parkinsonism (i.e. *Parkin*, PKAN, FRAXA, and mitochondrial disorders) were molecularly excluded.

The neuropathological study showed severe SN and LC neuronal loss, with diffuse LB pathology (LBs, aberrant neurites, grain-like structures, and scattered glial pathology) resembling Braak stage 6. Similarities with iPD included the dense burden of LB pathology in the intralaminar regions of the thalamus sparing most of the other thalamic regions,⁵⁷ the alpha-synuclein pathology distribution in the hippocampus⁵⁸ and the predominance of LBs in deep cortical layers. On the other hand, there were unique features which would be unusual for iPD, such as the presence of axonal spheroids immunoreactive for alpha-synuclein. These are classically described in infantile neuroaxonal dystrophy due to mutations in the *PLA2G6* gene (see PARK14) and rarely in *SNCA*¹⁴ (as a note: details about the *PLA2G6* gene status were not published, so the question remains as to how much variants in this gene could have contributed to the pathological findings). Furthermore, there was relatively mild involvement of the dorsal motor nucleus of the vagus nerve, which is usually severely affected in late disease stages,⁵⁹ as well as neuronal loss and the presence of LB-related pathology in the basal ganglia, which are usually spared⁶⁰ in sporadic PD.

The highest alpha-synuclein pathology burden was seen in the amygdala. The midbrain, SNpc and pars reticulata, LC and raphe nuclei and the nucleus basalis of Meynert were also severely affected. In the medulla, the tegmentum was heavily affected. The dorsal vagus nucleus showed mild alpha-synuclein pathology. Cortical areas also showed alpha-synuclein pathology, with severe involvement of the CA4 and CA2/3 hippocampal regions, with much lesser degree across CA1 and subiculum. The thalamus also showed dense alpha-synuclein pathology in the intralaminar nucleus regions with the nearby nuclear masses relatively free of pathology.

There was a mild degree of tau pathology rated as Braak neurofibrillary stage 1/primary age-related tauopathy. No abnormalities were seen with anti-amyloid- β and anti-TDP-43 antibodies in any region.

In summary, *DJ1* parkinsonism showed predominant nigral neurodegenerative disease with diffuse LB (alpha-synuclein) pathology and additional spheroids. However, only one patient has come to autopsy so far.

ATP13A2/Kufor Rakeb disease [PARK9]

ATP13A2 mutations cause a young-onset pallido-pyramidal syndrome with incomplete supra-nuclear upgaze palsy, oculogyric dystonic spasms, facial-facial-finger mini-myoclonus and autonomic dysfunction.^{61–64} Psychiatric features include visual

hallucinations and dementia. There is some overlap with neuronal ceroid lipofuscinosis (NCL).^{65, 66} Histological work-up revealed membrane bound electron-dense material with resemblance to irregular primary lysosomes.

Brain pathology is not available from any patient diagnosed with Kufor-Rakeb disease. However, we identified *ATP13A2* mutations in a family diagnosed with juvenile NCL whose brain pathology is available.⁶⁵ This showed abundant neuronal and glial lipofuscinosis in cortex, basal nuclei, cerebellum, and the retina. LBs were absent.

PLA2G6 [PARK14]

Mutations in *PLA2G6* are a rare cause of autosomal recessive parkinsonism (PARK14). The typical phenotype consists of infantile neuroaxonal dystrophy characterized by progressive motor and mental retardation, marked truncal hypotonia, cerebellar ataxia, pyramidal signs, and optic atrophy.⁶⁸ Later onset (as late as in the 40s) may present with milder phenotype, for example with complicated levodopa-responsive dystonia-parkinsonism.^{69, 70, 71} Brain iron accumulation is often present. A summary of brain pathology is presented in table 5. Nine *PLA2G6* mutations carriers have been examined pathologically, including three with a diagnosis of PD (with death 5, 23 and 31 years after onset).^{67, 70, 71} Overall, presence of LBs are usually present and may be severe.⁷² In these cases, there were severe loss of neurons, replacement gliosis and rare LBs present in the SN and LC. However, pathological findings extended beyond those typically seen in iPD, with more widespread cortical and limbic involvement. Furthermore, as typically seen in infantile neuroaxonal dystrophy, there were spheroids in the SN, excessive iron deposition in the globus pallidus, SN and ventral forebrain, as well as cerebellar involvement with extensive cell loss.⁷⁰

Thus, in summary, LBs may be present in *PLA2G6*-associated parkinsonism, but other features including spheroids, brain iron accumulation and cerebellar involvement distinguish this disorder from iPD. *PLA2G6*-associated parkinsonism challenges the definition of PD: not only is the clinical phenotype complex but LBs were sparse in the SN, having more cortical and limbic involvement compared to iPD. Further clinicopathological studies will shed more light on this issue.

GBA

Homozygous mutations in the glucocerebrosidase (*GBA*) gene encoding a lysosomal enzyme lead to Gaucher disease (GD), the most common autosomal recessive lysosomal storage disease. More than 300 mutations in *GBA* have been reported.⁷³ Single (heterozygous) *GBA* mutations are also the strongest genetic risk factor for PD, with a particularly high frequency of *GBA* mutations in the Ashkenazi Jewish population, although other ethnicities are also affected.⁷⁴ Clinically, *GBA* heterozygotes may be indistinguishable from iPD. However, they may have earlier age at onset, more prevalent cognitive impairment and may not respond to levodopa as well as in iPD.^{75, 76} *GBA* mutations are also associated with other alpha-synucleinopathies, including DLB⁷⁷ (pathologically confirmed) and in some, but not all studies, with MSA.⁷⁸⁻⁸² In contrast, there was no association between *GBA* mutations and essential tremor or AD.

Numerous *GBA* cases underwent autopsy, including ten GD patients with parkinsonism with a known pre-mortem diagnosis,^{83–85} as well as numerous *GBA* heterozygotes,^{76, 86, 80–82, 85, 87–91} mostly identified in brain bank screening studies with few exceptions.⁸⁵ The frequency of *GBA* heterozygotes in PD patients ranged from 3.5% (1 of 29)⁸² and 4.5% (17 of 380)⁹⁰ to 10.5% (6 of 57).⁸⁷

In summary, Gaucher patients with parkinsonism show LB pathology and nearly all *GBA*-heterozygous PD patients had LB pathology that involved cortical areas. Less is known about the distribution of neuronal loss or additional pathology. However, co-existent AD has been reported (Table 6).

Indeed, all three larger brain bank screens – including studies from NIH/University of Pennsylvania,⁸² Columbia University⁷⁶ and the Queen Square Brain Bank⁹⁰ – reported that *GBA* mutation status was associated with widespread cortical LBs, although the latter group revised their statement after adjusting for confounding variables and re-studying the 17 PD *GBA* heterozygous carriers and 16 PD controls.⁹² An association of the E326K and T369M variants with PD has been reported,⁷⁶ even though the pathogenicity of these variants has not been clearly demonstrated in GD. The association between these variants and PD was corroborated in studies including familial and sporadic PD patients.^{93, 94} Recent studies in pathologically-proven cases also suggest an association of *GBA* mutations with MSA, especially among Ashkenazi Jews.⁹⁵

MPAN

Mutations in *C19orf12* cause mitochondrial membrane protein-associated neurodegeneration (MPAN), which belongs to the group of neurodegeneration with brain iron accumulation (NBIA) syndromes. These generally manifest as extrapyramidal syndrome with characteristic iron accumulation in the globus pallidus. The most common form is pantothenate kinase-associated neurodegeneration (PKAN). Additional features are usually present in MPAN, such as prominent cognitive decline progressing to dementia, neuropsychiatric abnormalities, a motor neuronopathy, and early upper motor neuron findings followed later by signs of lower motor neuron dysfunction and early optic atrophy. In adulthood, parkinsonism and dystonia may occur. To date, two brains of MPAN has been analyzed.^{96, 97}

The first case,⁹⁶ homozygous for c.205G>A, p.Gly69Arg, presented with clumsiness and fatigue at age 6. Other features included optic atrophy, gait spasticity ataxia, dysarthria, axonal motor neuropathy, and cognitive decline. Death occurred at age 23. Histopathological examination showed iron-containing deposits concentrated in the globus pallidus and the SN, and axonal spheroids, both typical features of neuroaxonal dystrophies. Widespread numerous alpha-synuclein-positive LBs, LB-like inclusions, and sparse Lewy neurites (LNs) were also seen, albeit less so in the hippocampus with only a small number of alpha-synuclein-containing deposits. Similar to *PLA2G6*-associated parkinsonism (see above) this finding challenges the diagnosis of PD based on LB disease. Hyperphosphorylated tau-containing neuronal inclusions were also present in various regions of the brain including numerous tau-positive pyramidal cells in the hippocampus. Loss of myelin was seen in the pyramidal tracts of the spinal cord and optic nerve, most pronounced in the optic tract.

The other case is of a compound heterozygous mutation carrier (c.294G>C and the common deletion c.204_214del11) who presented with unusually late onset at 30 years, with isolated memory impairment that progressed to frank dementia over 2 years before signs of parkinsonism developed and brain iron was noted on MRI. Death occurred 9 years after onset. Autopsy revealed neuronal loss, widespread iron deposits, and eosinophilic spheroidal structures in the basal ganglia, typical for the core NBIA syndromes with uniformly strong immunoreactivity for ubiquitin but variable staining with anti-tau antibody. However, in marked contrast to the most common type of NBIA (PKAN), LNs were also detected in the globus pallidus, and LBs and LNs were widespread in other areas of the corpus striatum and midbrain SN and neocortex structures. These were associated with almost complete neuronal loss in the SN. LNs were also present in the pons, and LBs and LNs were abundant in the hippocampus with relative sparing of the CA1 region, which contained occasional tau-positive pretangles. Minimal iron deposition was identified in the SN, and no significant iron was observed in the cortex. Notably, the burden of neocortical LB pathology was substantially greater than in typical cases of sporadic LBD.

FBXO7 [PARK15]

In 2006, Shojaei et al.⁹⁸ reported an Iranian family with a childhood-onset combined extrapyramidal pyramidal syndrome, initially characterized by dystonia which progressed to a levodopa responsive akinetic-rigid parkinsonism in some cases. Cerebellar features and dementia were absent. MRI was normal. Subsequently, cases of adolescent onset atypical parkinsonism with early development of levodopa-induced dyskinesia and prominent cognitive features, in the absence of pyramidal signs were reported.^{99, 100} Most recently, a phenotype compatible with typical idiopathic PD was described¹⁰¹ and some of the common nonmotor features often present in iPD, such as rapid eye movement sleep behavior disorder, depression, and anxiety were also present. Functionally, there are connections with other recessive forms of Parkinson's disease. Brain pathology is not available. FBXO7 participates in mitochondrial maintenance through direct interaction with *PINK1* and *Parkin* and acts in *Parkin*-mediated mitophagy.¹⁰² Studies on the expression of FBXO7 in the human brains (PD, MSA, AD and controls) (n = 5) demonstrated FBXO7 immunoreactivity and co-localization in large proportions of alpha-synuclein-positive inclusions, including LBs, Lewy neurites, and glial cytoplasmic inclusions in PD and MSA cases. By contrast, weak FBXO7 immunoreactivity was occasionally detected in tau-positive inclusions in AD and PSP, suggesting a role for FBXO7 in the pathogenesis of synucleinopathies.¹⁰³

Other causes: Non-PD syndromes with PD like pathology

22q deletion syndrome

In an observational study of a large adult cohort (n = 159) with molecularly confirmed 22q11.2 deletion syndrome, this chromosomal defect was identified as a novel genetic risk factor for early-onset PD.^{104, 105} The clinical symptom pattern, treatment response, and course were similar to idiopathic early onset PD. Neuropathological tissue is available for three of the 22q11.2DS PD cases.¹⁰⁵ There was classic loss of midbrain dopaminergic neurons in all three. Typical alpha-synuclein-positive LBs were present in the expected distribution in two cases but absent in another. While neuronal loss in the latter was observed

in the expected pattern with extensive nigral degeneration and striatal loss of TH immunoreactivity, there were no LBs or other abnormal neuronal inclusions or aggregates and immunohistochemistry was negative for alpha-synuclein, tau, TAR DNA-binding protein 43, and ubiquitin.

Overall, neuropathological presentation was variable, ranging from a classic distribution to “bland nigral degeneration” in the absence of alpha-synuclein pathology.

RAB39B

Recently, *RAB39B* mutations were identified as another cause of early-onset parkinsonism, with intellectual disability based on two unrelated families, including the Wisconsin kindred with 13 affected males.¹⁰⁶ Postmortem neuropathological studies demonstrated loss of pigmented neurons and LBs in surviving neurons. Immunoreactive staining revealed the presence of alpha-synuclein-positive LBs and LNs in >10% of the surviving neurons. Additional neuropathological features included an abundance of cortical LBs. Tau-immunoreactive NFTs were also observed in a small proportion of the surviving pigmented SN neurons. Interestingly, Perl staining revealed a modest accumulation of iron accumulation, consistent with slight T2 hypointensities in this patient, and rare axonal spheroids in the white-matter tracts, similar to the neurodegeneration with brain iron accumulation syndromes (NBIA).

Autosomal-dominant Spinocerebellar Ataxias (SCAs)

Though rare, parkinsonism may develop in patients with autosomal dominant spinal cerebellar ataxias.¹⁰⁷ Further, parkinsonism can present as the most prominent feature of the SCAs and resemble idiopathic PD.¹⁰⁸ For example, it may occur in SCA1, SCA2, SCA3, SCA6, SCA12, SCA17 or SCA21.¹⁰⁹ SCA2 causing parkinsonism seems to be more frequent among Asian patients, in whom it accounts for about 10% of familial parkinsonism.¹¹⁰

For SCA2 and SCA3, some studies point to a consistent involvement of the midbrain dopaminergic SN, both in typical (i.e., ataxic non-parkinsonian) SCA2 and SCA3,¹¹¹ while the number of reports on the pathology in patients with a parkinsonian phenotype remains scarce.¹⁰⁸ One parkinsonian SCA2 case¹¹² displayed brainstem LBs and Lewy neurites (which may be unrelated to the genotype) in addition to the neuropathologic alterations typically seen in SCA2.¹¹³ Genetic analysis revealed a CAG expansion shorter than usual for ataxic SCA patients (less than 39). In the same study two brains of SCA2 without parkinsonism were examined and showed absence of similar alpha-synuclein pathology. Autopsy of a Japanese SCA2 case¹¹⁴ with parkinsonism, dementia, autonomic disturbance and only mild cerebellar ataxia revealed atrophy of the SN and the olivo-ponto-cerebellar (OPC) in line with SCA2. The OPC atrophy, however, was less severe than that formerly reported in SCA2 cases. Anti-1C2 positive inclusions were present in the pons, inferior olive nuclei, cerebellum and SN. In addition, anti-phosphorylated alpha-synuclein-positive LBs were found in the SN, the LC, the dorsal motor nuclei of vagus, and the sympathetic nerve in the myocardium.

In a case of SCA6, alpha-synuclein-positive inclusions were absent.¹¹⁵ We are not aware of pathological data for SCA1, SCA3 or SCA17 case with a PD phenotype.¹⁰⁸

In summary, in most SCA2 patients with parkinsonism, the pathological correlate is SN atrophy; however, given two cases with LB pathology, additional studies are required to determine whether there is an association between SCA genotype and LB pathology.

Discussion

Clinical-pathological diagnosis remains the gold standard for the diagnosis of PD, with LBs and neuronal loss in the ventrolateral tier of the SNpc considered the neuropathological hallmark feature of parkinsonian motor features.^{1, 3, 4} Yet, it has become clear that even in the same genetic form, with the same molecular variants, in patients from the same family, clinical phenotype and pathological correlates may vary. These diverse findings are summarized in this paper. This diversity may reflect the many different metabolic pathways genes related to PD are involved in, including the regulation of the autophagy-lysosomal system (*alpha-synuclein*, *VPS35*, and *LRRK2*) and mitophagy (*Parkin*, *PINK1*, and *FBXO7*).

As expected, the most information is available for the common genetic types, *SNCA* and *LRRK2*, the recessive form of *Parkin* and the risk factor *GBA*. Interestingly, while the majority of autopsies across most genetic subforms displayed LBs, LBs seem neither necessary nor sufficient for the clinical expression of parkinsonism.^{22, 116} Indeed, for some genetic forms of PD (e.g. *Parkin*) most reported autopsies do *not* have LB pathology. Similarly, loss of nigral neurons is also not specific for a diagnosis of PD but is present in many other neurodegenerative disorders with prominent parkinsonism, such as PSP and multiple system atrophy, or in disorders not classified as parkinsonian (e.g. spinocerebellar ataxia).^{22, 111} This highlights the limited correlation between clinical, genetic and pathological classification systems of PD.

Among the studied PD cases are some with heterozygous mutations affecting recessively-inherited genes (e.g. *Parkin*), with variable pathological findings. The underlying disease risk and disease mechanism of this remains unsolved. Several explanations for the occurrence of LBs in the single mutation carriers with late-onset PD have been proposed by Sharp and colleagues⁴⁹: (1) LBs in these older patients may be age-related and incidental, (2) late-onset patients may lack mechanisms to clear protein accumulation, and (3) the mutations in these late-onset cases result in only partial loss of Parkin ubiquitin E3 ligase function — for instance, the R275W mutation has been associated with residual ligase activity.⁴⁹

The genes described here can be crudely divided to three groups: genes that are associated with alpha-synuclein, but not with a PD syndrome (e.g., *PLA2G6*, *C19orf12* [MPAN]), genes that are clinically associated with PD, but not always with LB pathology (e.g., *LRRK2* and *Parkin*), and genes that are associated with both a PD clinical syndrome and LB pathology (e.g., *SNCA* and *GBA*). These genes have also been associated clinically with dementia with Lewy bodies (DLB).¹¹⁷ Pathologically PD-dementia and DLB may seem similar,¹ and both have been reported with *SNCA* and *GBA* mutations. Whether the Braak

staging which was proposed for idiopathic PD¹¹⁸ applies to neuropathology in these cases remains to be investigated. Of note, genome-wide association studies identified additional genetic risk factors associated with PD and LB pathology, e.g., PARK 10.¹¹⁹

The variable pathological findings in PD have wider implications and may influence the study design and inclusion criteria of future large clinical trials exploring mechanistic treatments such as antibody-targeting agents (e.g., monoclonal antibodies that target alpha-synuclein). Indeed, experience has shown that identification of ideal candidates for PD trials poses a challenge: not only do 10–15% of patients with a clinical phenotype of PD not display PD-typical changes on functional imaging of the dopamine system¹²⁰ (i.e., people with scans without evidence of dopaminergic deficit, SWEDDs), but as highlighted in this review, amongst those with levodopa-responsive PD, not all have LB or alpha-synuclein pathology. All of these patients are unlikely to respond to synuclein-targeted agents or similar mechanistic compounds and could thereby cloud the true results of these studies. Thus, for future clinical trials, it will be crucial to enroll only those who would potentially benefit from the mechanistic therapy based on their individual pathomechanistic fingerprint.

Finally, this review once more demonstrates the need to adhere to standard operating procedures for the neuropathological diagnosis of PD,¹ since the methodological differences (e.g., areas sampled, immunostaining performed, and types of antibodies used) among the different centers may have produced variable results.²² Efforts to standardize autopsy collection, handling, and reporting in PD cases are encouraged, which will help provide better data for more detailed clinicopathological correlations in the future.

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Table 1a

Summary of conditions that present with Parkinsonism with associated 'PARK' gene locus:

| Condition | Mode of inheritance | Clinical phenotype | Pathology summary | Further reference(s) |
|----------------------------------|---------------------|---|---|---|
| <i>SNCA</i> /PARK1+4 | AD | Early-onset parkinsonism with rapid progression and dementia | Alpha-Synuclein pathology in the form of LBs or LNs in all reported cases | See Table 2 |
| <i>Parkin</i> /PARK2 | AR | Early-onset parkinsonism with slower disease course | Absent LBs in the majority of cases | See Table 4 |
| <i>PINK1</i> /PARK6 | AR | | LB present | Samaranch et al 2010 ⁵² |
| <i>DJ-1</i> /PARK7 | AR | | Nigral degeneration, diffuse LBs spheroids | Taipa et al 2016 ⁵⁶ |
| <i>LRRK2</i> /PARK8 | AD | Late-onset, often tremulous PD reminiscent of iPD | Variable pathology. LB pathology present in most, variable tau distribution | See Table 3 |
| <i>ATP13A2</i> /PARK9 | AR | Early-onset pyramidal and extrapyramidal syndromes; supranuclear gaze palsy, dementia | Absent LBs; neuronal and glial lipofuscinosis in cortex, basal nuclei, cerebellum, and the retina in a family clinically presenting with neuronal ceroid-lipofuscinosis (NCL) | Bras et al 2012 ⁶⁵ |
| <i>PLA2G6</i> /PARK14 | AR | Early-onset form: infantile neuroaxonal dystrophy; late-onset form: Early-onset pyramidal and extrapyramidal syndromes; MRI usually shows iron deposition but may be absent | LBs may be present, other features include spheroids, brain iron accumulation and cerebellar involvement | See Table 5 |
| <i>FBXO7</i> /PARK15 | AR | Early-onset extrapyramidal and pyramidal syndromes or iPD | No data | Shojaee et al. 2008 ⁹⁸ |
| <i>VPS35</i> /PARK17 | AD | Late-onset tremor-predominant dopa-responsive autosomal-dominant PD | No data | Vilariño-Güell et al. 2011 ¹²¹ ; Zimprich et al. 2011 ¹²² |
| <i>EIF4G1</i> /PARK18* | | Late-onset | LBs present in two autopsy-confirmed cases with Lewy body disease carrying EIF4G1 missense mutations | Chartier Harlin et al. 2011 ¹²³ |
| <i>DNAJC6</i> /PARK19 | AR | Juvenile PD in a consanguinous Palestinian family | No data | Edvardson et al. 2012 ¹²⁴ |
| <i>SYNJ1</i> /PARK20 | AR | Early-onset, complicated by seizures, cognitive decline, abnormal eye movements, and dystonia | No data | Picillo et al. 2014 ¹²⁵ ; Drouet and Lesage 2014 ¹²⁶ |
| <i>DNAJC13</i> /PARK21 | AD | Late-onset iPD or PSP | Brainstem or transitional LB, tauopathy | Vilariño-Güell et al. 2014 ²⁶ |
| <i>CHCHD2</i> /PARK22 (in doubt) | AD | Late-onset iPD, identified in Japanese | No data | Funayama et al. 2015 ¹²⁷ |
| <i>VPS13C</i> /PARK23 | AR | Early-onset, rapid progression, dementia | LB present | Lesage et al. 2016 ¹²⁸ |

SNCA = alpha-synuclein; LB = Lewy body; LN = Lewy neurites; AR = autosomal recessive; AD = autosomal dominant, iPD = idiopathic Parkinson's disease; PSP = progressive supranuclear palsy;

* locus needs to be confirmed

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Table 1b

(Classical) parkinsonism due to mutations in ‘other than-PARK’ genes (e.g. DYT or SCA) or yet other genes where parkinsonism may be a well-recognized concomitant or even isolated feature

| Condition | Mode of inheritance | Clinical phenotype | Pathology | References |
|--|--|--|---|---|
| <i>Glucocerebrosidase (GBA)</i> (Gaucher disease) | AR for classic Gaucher disease; AD for PD risk | iPD | Widespread LBs in Gaucher patients with parkinsonism and nearly all <i>GBA</i> -heterozygous PD patients | See Table 6 |
| <i>GTP cyclohydrolase 1</i> | AD | Dystonia, dystonia-parkinsonism, but also iPD | No LBs in classic DRD; LB in late-onset GCH-associated iPD cases | Rajput et al. 1994 ³¹ ; Furukawa et al. 1999 ³² ; Grotzsch et al. 2002 ³³ ; Gibb et al. 1991 ³⁶ |
| <i>ATP1A3/DYT12</i> | AD | Rapid-onset dystonia-parkinsonism, allelic to alternating hemiplegia of childhood | No brain pathology reported from patient with pure PD phenotype | |
| <i>TAF1/DYT3</i> Lubag | X-linked | X-linked dystonia-parkinsonism | Neuronal loss and a multifocal mosaic pattern of astrocytosis restricted to the caudate and lateral putamen | Waters et al. 1993 ¹²⁹ |
| <i>SCA2</i> | AD | Ataxia ± movement disorders | PD-like pathology with neurodegeneration of SN and pallidum, LBs. Yet, despite cell loss, only a minority exhibit parkinsonism. | Takao et al. 2011 ¹¹² ; Yomono et al. 2010 ¹¹⁴ ; Schöls et al. 2015 ¹³⁰ |
| <i>SCA3</i> Machado Joseph disease | AD | Ataxia ± movement disorders | | Schöls et al. 2015 ¹¹¹ ; Matilla et al. 1995 ¹³¹ |
| Hereditary spastic paraplegia SPG11 | AR | Spasticity, mainly of legs, parkinsonism may occur | No brain pathology reported from patient with PD phenotype | |
| Mitochondrial gene mutations | Heterogenous | Heterogenous* | Heterogenous* | Heterogenous* |
| MPAN | AR | Mixed movement disorder, optic atrophy, neuropathy | Brain iron accumulation, widespread LBs and LNs in the basal ganglia, SN and neocortex structures. | Hartig et al. 2009 ⁹⁶ ; Hogarth et al. 2013 ¹⁰⁷ |
| <i>RAB39B</i> | X-linked | Early-onset parkinsonism, delayed psychomotor development, intellectual disability | LBs inclusions cortically. Rare spheroids, modest iron accumulation | Wilson et al. 2014 ¹⁰⁶ |
| Chromosome 22q11.2 deletion syndrome | AD | Early-onset parkinsonism, delayed psychomotor development, intellectual disability | Classic loss of midbrain dopaminergic neurons with typical alpha-synuclein-positive LBs were present in 2 of 3 causes | Butcher et al. 2013 ¹⁰⁵ |

LB = Lewy body; LN = Lewy neurites; SCA = spinocerebellar ataxia; SN = substantia nigra; AR = autosomal recessive; AD = autosomal dominant; iPD = idiopathic Parkinson's disease; DRD = Dopa-responsive dystonia; SN = substantia nigra; examples include the finding of severe SN atrophy with rare (mostly absent) Lewy bodies in mitochondrial DNA polymerase gamma (*POLG*) and *C10orf2* (Twinkle) cases^{132–135}

Table 2
Summary of SNCA autopsy reports (adjusted and updated from Pouloupoulos et al.⁵)

| Report | Autopsies (n) | Genotype (n) | Phenotype (n) | Pattern of Neuronal Loss | LB, LN Pathology (n) | LB Distribution—Braak Stage (n) | Tau Pathology—NFT Stage 29, 30 (n) | Other Inclusions |
|--|---------------|-------------------|---|--|---|--|------------------------------------|---|
| Golbe et al., 1990 ¹³⁶ ; Duda et al., 2002 ¹⁵⁷ | 2 | A53T (2) | EOPD dementia (2) | SN, LC | 2 | 5 to 6 (1) incomplete data (1) | I (1) incomplete data (1) | — |
| Spira et al., 2001 ¹³⁸ | 2 | A53T (2) | EOPD, cognitive decline (2) | SN, LC, hippocampus | 2 | 5 to 6 (2) | — (2) | — |
| Zarranz et al., 2004 ⁸ | 1 | E46K (1) | PD dementia (1) | SN>LC | 1 | 6 (1) | — (1) | — |
| Markopoulou et al., 2008 ¹⁶ | 2 | A53T (2) | EOPD (1), PD (1) dementia (2) | SN, LC, hippocampus | 2 | 5 (1) 6 (1) | I (1) IV (1) | TDP-43 in TC, GCI (2) |
| Seidel et al., 2010 ¹³⁹ | 1 | A30P (1) | PD dementia (1) | SN, LC, dnV | 1 | 6 (1) | II (1) | GCI |
| Pasanen et al., 2014 ¹⁸ | 1 | A53T (1) | EOPD | SN, LC, Put, caudate, hippocampus, CA2-3, amygdala, TC, insular cortex | n.d. | n.d. | n.d. | TDP-43 positive but mostly SNCA negative perinuclear inclusions in hippocampus dentate fascia |
| Kiely et al., 2015 ⁴⁰ | 2 | G51D (3) H50Q (1) | Pallidopyramidal syndrome; PD dementia; late-onset iPD; FTD | Cortical, hippocampus, SN, LC, dnV | 6 | 6 | — | GCI, rarely coiled type II; or absent (1); TDP-43 pathology (2) |
| Wakabayashi et al., 1998 ⁴¹ | 1 | Duplication (1) | | SN, LC, nbM | 2 | 5 to 6 (2) | II (2) | — |
| Obi et al., 2008 ⁴² | 2 | Duplication (2) | PD, dementia (2) | SN, LC hippocampus | 1 | 5 to 6 (1) | I (1) | GCI |
| Ikeuchi et al., 2008 ¹⁷ | 1 | Duplication (1) | EOPD dementia autonomic (1) | SN, LC, hippocampus | 1 | 5 to 6 (1) | III (1) | — |
| Kara et al., 2014 ⁴³ | 1 | Duplication (1) | FTD with parkinsonism | DLB (diffuse neocortical) | LN, glial alpha-synuclein Inclusions | 6 | 1 | Glial alpha synuclein |
| Konno et al., 2016 ⁴⁴ | 1 | Duplication (1) | MSA | SN, LC, dnV, nbM, amygdala, hippocampus, cortex | Neuronal loss, LN, glial alpha-synuclein Inclusions | Widespread, pattern of DLB (diffuse neocortical) | 0-1 | Glial alpha synuclein |

| Report | Autopsies (n) | Genotype (n) | Phenotype (n) | Pattern of Neuronal Loss | LB, LN Pathology (n) | LB Distribution—Braak Stage (n) | Tau Pathology—NFT Stage ^{29, 30} (n) | Other Inclusions |
|--|---------------|------------------|-----------------------------|-----------------------------|----------------------|---------------------------------|---|------------------|
| Waters and Miller, 1994 ¹⁴⁵ | 1 | Triplication (1) | EOPD dementia (1) | SN, LC, hippocampus | 1 | 6 (1) | Sparse (1) | — |
| Muenter et al., 1998 ¹⁴⁶ | 4 | Triplication (4) | EOPD (4) dementia (3/4) | SN, LC, hippocampus | 4 | 5 to 6 (4) | — (4) | — |
| Gwinn-Hardy et al., 2000 ¹⁵ | 1 | Triplication (1) | EOPD dementia | SN, LC, hippocampus, cortex | 1 | 6 (1) | — (1) | GCI |
| Farrer et al., 2004 ¹⁴⁷ | 1 | Triplication (1) | EOPD dementia autonomic (1) | SN, LC, hippocampus | 1 | 6 (1) | n.d. | — |

Point mutations are listed in white cells, duplications in light grey cells and triplications in dark grey. Abbreviations: EOPD = early onset Parkinson's disease; PD = Parkinson's disease; FTD = frontotemporal dementia; MSA = multiple system atrophy; SN = substantia nigra; TC = temporal cortex; GCI = glial-cytoplasmic inclusions; dnV = dorsal nucleus of the vagus; LC = Locus coeruleus; LB = Lewy body; LN = Lewy neurites; nbM = nucleus basalis of Meynert; Put = putamen, n.d. = no data

Table 3

Summary of LRRK2 autopsy reports

| Report | Autopsies (n) | Genotype (n) | Phenotype (n) | Pattern of Neuronal Loss | LB, LN Pathology (n) | LB Distribution–Braak Stage (n) | Tau Pathology–NFT Stage (n) | Other Inclusions (n) |
|---|------------------|-----------------------|---|--------------------------------------|---|---------------------------------|---|---|
| Gilks et al., 2005 ¹⁴⁸ | 3 | G2019S (3) | PD (3) | SNpc, LC | 3 | 3 (1) 4 (2) | Sparse (1) – (2) | – |
| Gaig et al., 2008 ¹⁴⁹ , Gaig et al., 2007 ¹⁵¹ , Gomez and Ferrer, 2010 ¹⁵¹ | 3 | G2019S (3) | PD (3) | SNpc, LC | + (2) – (1) | 4 (1) 5 (1) – (1) | I (1) II (1) III (1) | – |
| Rajput et al., 2006 ¹⁵² | 1 | G2019S (1) | PD (1) | SNpc mild | – (1) | – | IV (1) | PSP-like |
| Ross et al., 2006 ¹⁵⁷ | 10 | G2019S (10) | PD (8) dementia (3/8), cognitive decline (2/8) AD (1) control (1) | SNpc, LC | + (8) – (2) | 3 (4) 4 (3) 6 (1) – (2) | – (3) I (1) III (4) AD (2) | – |
| Giasson et al., 2006 ¹⁵³ | 3 | G2019S (3) | EOPD (1), PD (2) dementia (1/3) | SNpc, LC | + (2) – (1) | 4 (1) 5 (1) – (1) | I (1) III (1) AD (1) | – |
| Dachsel et al., 2007 ¹⁵⁴ | 1 | G2019S (1) | Dementia (1) | Hippocampus | – (1) | – (1) | – (1) | FTD-U |
| Silveira-Moriyama et al., 2008 ¹⁵⁵ | 4 | G2019S (4) | PD (4) | SNpc, LC, olfactory bulb | 4 | 5 (4) | II (4) | Olfactory bulb LBs (4) |
| Poulopoulos et al., 2012 ¹⁵⁶ | 3 | G2019S (3) | EOPD (2), PD (1) dementia (2/3) | SNpc, LC | 3 | 4 (2) 6 (1) | Sparse (2) AD (1) | – |
| Kalia et al 2015 ²² | 2 <i>a. b. c</i> | G2019S | n.d. | n.d. | + (2), – (1) | n.d. | – (3); βAPs present (3) | – |
| Vilas et al. 2016 ¹⁵⁷ | 2 | G2019S (2) | PSP (1) | Severe GP, SNpc, subthalamic nucleus | Absent LBs; no alpha-synuclein | n/a | Neuronal and glial subcortical 4-repeat tau | pTau-positive tufted astrocytes; grade A3, B2, C2 AD pathology; No TDP43; coiled bodies; Globose neuronal tangles |
| Wszołek et al., 2004 ¹⁵⁸ , Zimprich et al., 2004 ²⁵ , Wider et al., 2010 ¹⁵⁹ | 6 | R1441C (4) Y1699C (2) | PD (6) | SNpc LC | LBS in cingulate and temporal cortices, amygdala, basal forebrain, SNpc, NC | 4 (1) 6 (1) – (4) | Sparse (1), AD (1) Y1699C, – (4) | coiled bodies; tufted astrocytes; Globose neuronal tangles |
| Khan et al., 2005 ¹⁶⁰ | 1 | Y1699C | PD (1) | SNpc, LC | 1 | 3 (1) | II (1) | Olfactory bulb LBs |

| Report | Autopsies (n) | Genotype (n) | Phenotype (n) | Pattern of Neuronal Loss | LB, LN Pathology (n) | LB Distribution–Braak Stage (n) | Tau Pathology–NFT Stage (n) | Other Inclusions (n) |
|---|----------------|-------------------------|--------------------------|--------------------------|----------------------|---------------------------------|-----------------------------|---|
| Giordana et al., 2007 ¹⁶¹ | 1 | I1371V (1) | PD cognitive decline (1) | SNpc>LC | 1 | 4 (1) | II (1) | – |
| Covy et al., 2009 ¹⁶² | 2 | R793M (1) L1165P (1) | PD (2) dementia (1/2) | SNpc, LC | 2 | 4 (2) | II (1) III (1) | TDP-43 in TC (2) |
| Gaig et al., 2008 ¹⁴⁹ | 1 | R1441R | PD dementia (1) | SNpc | 1 | n.d. | n.d. | – |
| Hasegawa et al., 2009 ¹⁶³ ; Hasegawa and Kowa, 1997 ¹⁶⁴ | 8 | I2020T (8) | PD (8) | SNpc, SNpr, LC spared | – (7) + (1) | – (7) 3 (1) | – (8) | GCI (1) |
| Marti-Masso et al., 2009 ¹⁶⁵ | 1 | R1441G | PD (1) | SNpc>LC | – (1) | – | I (1) | a-B crystalline in SN |
| Puschmann et al., 2011 ¹³⁰ | 1 | N1437H (1) | PD (1) | SNpc>LC | 1 | 5 (1) | Sparse (1) | Diffuse, atypical ubiquitin+ inclusions |
| Kalia et al. ²² , 2015 | 1 ^d | R1441G | n.d. | n.d. | – (1) | n.d. | – (1) | – |

G2019S mutation carriers are shaded in light gray. Abbreviations: PD = Parkinson's disease; EOPD = early onset Parkinson's disease; PSP = progressive supranuclear palsy; FTD-U = frontotemporal dementia with ubiquitin inclusions; LB = Lewy bodies; LN = Lewy neurites; β APs = β -amyloid plaques; GCI = glial-cytoplasmic inclusions; GP = globus pallidus; SNpc = substantia nigra pars compacta; SNpr = substantia nigra pars reticulata; LC = locus coeruleus; TC = temporal cortex.

^aCase provided by SM Goldman, B Schüle, J Langston (The Parkinson's Institute, Sunnyvale, CA, USA)

^bCase provided by J Aasly (University of Trondheim, Trondheim, Norway; c: Case provided by AE Lang, L Hazrati

^cMarras (University of Toronto, Toronto, Canada)

^dCase provided by J Ruiz-Martinez, J Marti-Masso, (Hospital Universitario Donostia, CIBERNED, San Sebastián, Spain)

Summary of PARKIN Autopsy reports

Table 4

| Report | Number of autopsies | Genotype | Phenotype | Pattern of Neuronal Loss | LB, LN Pathology | LB Distribution–Braak Stage | Tau Pathology–NFT Stage | Other Inclusions |
|--|---------------------|---|----------------------|--|---------------------------|-----------------------------|---|--|
| Takahashi et al., 1994 ¹⁶⁶ , Matsumine et al., 1997 ¹⁶⁷ | 2 | no details reported | JPD | LC>SNpc | – | – | n.d. | – |
| Yamamura et al., 1998 ¹⁶⁸ | 1 | Homozygous del between exon 3 and 7 | EOPD | SNpc>LC | – | – | – | – |
| Mori et al., 1998 ¹⁶⁹ | 1 | Homozygous exon 4 del | EOPD | SNpc>LC | – | – | 3 | Thorn-shaped astrocytes |
| Hayashi et al., 2000 ¹⁷⁰ | 1 | Homozygous exon 4 del | EOPD | SNpc>SNpr, LC | – | – | Sparse | – |
| van de Warrenburg et al., 2001 ¹⁷¹ | 1 | Compound heterozygous exon 3 del/exon 6 transversion | EOPD | SNpc>LC | – | – | Diffuse in the caudate nucleus, putamen, subthalamic nucleus and SN | Thorn-shaped astrocytes |
| Farrer et al., 2001 ¹⁴² | 1 | Compound heterozygous exon 7 R275W/exon 3 del | EOPD, writer's cramp | SNpc, LC | + | 4 | – | – |
| Mori et al., 2003 ⁵³ | 1 | Compound heterozygous exon 6del/exon 7 del | EOPD | SNpc>LC | – | – | – | – |
| Gouider-Khouja et al., 2003 ¹⁷² | 1 | Homozygous exon 2 del | EOPD | SNpc, SNpr>LC | – | – | – | – |
| Sasaki et al., 2004 ⁴⁷ , 2008 ⁴⁶ | 1 | Homozygous exon 3 del | EOPD | SNpc>LC | Basophilic LB-like in PPN | – | – | Eosinophilic LB in anterior horn cells |
| Pramstaller et al., 2005 ⁴³ | 1 | Compound heterozygous exon 7 del and 1072T del | PD | SNpc, LC | + | 3 | – | – |
| Orimo et al., 2005 ¹⁷³ | 3 | Homozygous exon 4 del | EOPD | n.d. [§] | n.d. | n.d. | n.d. | Numerous TH-immunoreactive nerve fibers in the epicardium |
| Miyakawa et al., 2013 ⁴⁴ | 1 | Homozygous exon 2–4 del | Late-onset PD | SNpc, LC, severe | +, fairly widespread | 4 | Yes | Eosinophilic inclusions with HE, TH and phosphorylated neurofilament in epicardium |
| Doherty et al., 2013 ⁴⁵ | 5 | R275W/del exon 6; R275W/Pro113fs; R275W/G430W; G430D/Pro113fs; R275W/del exon 6 | EOPD (2), iPD (3) | Moderate to severe in SNpc; mild to moderate in LC; SNpc>LC in all | +(in 2), –(in 3) | # | Absent (in 2) or only mild (in 3 cases) u | TDP-43–positive inclusions absent; |
| Cornejo-Olivas et al., 2015 ¹⁷⁴ | 1 | Compound heterozygous intron 5 splice site mutation (IVS5-1G>A)/exon 7 del | JPD | SNpc | – | – | n.d. | TH immunopositive fibers in striatum |
| Morales et al., 2002 ³² | 1 | Heterozygous C212Y mutation | PSP | SNpc/pr, striatum, GP, nbM, STN, thalamus | – | – | – | – |
| Ruffmann et al., 2013 ⁴⁵ | 1 | Heterozygous R275W mutation | iPD, onset 62 yrs | Severe in SN and LC | + | 6 | Pre-tangles in subiculum, transentorhinal and entorhinal cortex | Widespread cortical deposition of βAP |

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| Report | Number of autopsies | Genotype | Phenotype | Pattern of Neuronal Loss | LB, LN Pathology | LB Distribution– Braak Stage | Tau Pathology– NFT Stage | Other Inclusions |
|----------------------------------|---------------------|---------------------------|-----------|--------------------------|------------------|------------------------------|--------------------------|------------------|
| Sharp et al. 2014 ¹⁷⁵ | 1 | Heterozygous exon 3–4 del | EOPD | Severe in SN and LC | + | 6 | 1 | – |

Patients, i.e. homozygous and compound heterozygous mutation carriers, are shaded in light grey; single mutation carriers are shown in white cells. Abbreviations: del = deletion; SNpc = substantia nigra pars compacta; SNpr = substantia nigra pars reticulata; GP = globus pallidus; LB = Lewy body; LN = Lewy neurites; TH = tyrosine hydroxylase; HE = haematoxylin and eosin stain; β APs = β -amyloid plaques; EOPD = early-onset PD; JPD = juvenile-onset PD; # = the pattern of pathology did not conform well to the Braak PD staging scheme as the density of brainstem LBs did not show the expected increase when LB pathology extended beyond the brainstem; § = immunohistochemical study of heart tissues, not brain

Table 5

Summary of PLA2G6 Autopsy reports

| Report | Genotype | Age at onset (in years) | Age at death (in years) | Phenotype | LB, LN Pathology | LB Distribution—Braak Stage | Tau Pathology | Brain iron | Other |
|--|------------------------|-------------------------|-------------------------|---|------------------|---|-----------------------------|------------|---|
| Gregory et al. 2008 ⁷⁶ | G238A; 2370_2371delTG | 3 | 23 | Infantile NAD; Parkinson signs not mentioned | + | Widespread | + | + | |
| Paisan-Ruiz et al. 2012 ⁷² | p.T572I | 18 | 36 | Adult-onset ataxia, spasticity and parkinsonism | + | Stage 6 | “Mild”, tangles and threads | + | Spheroids (BG, brainstem and cord) |
| | p.R37X | 22 | n.d. * | Adult-onset dystonia-parkinsonism | + | Severe | “Moderate”, threads | – | – |
| | p.L354P/p.R654X | Infant | 8 | Infantile NAD, dystonia | + | “Mild” Braak 3 | Absent | – | Spheroids (moderate), cerebellar atrophy |
| | p.L107FsX4 | childhood | 18 | Juvenile NAD, dysphagia, dystonia | + | Stage 6 | Tangles and threads | + | Spheroids (severe) |
| Riku et al. 2013 ¹⁷⁷ | Splice site p.Y790X | 1.2 | 8 | Infantile NAD, dysphagia | + | Not formally assessed | Positive tau glia | + | Cortical and cerebellar atrophy, spheroids (BG, brainstem and cord) |
| | c.1187-2A>G; c.1612C>T | 3 | 20 | Infantile NAD, parkinsonism | + | + | + | + | Spheroids, cerebellar loss |
| Tabamo et al. 2000 ⁷¹ ; Klein et al. 2016 ⁷⁰ | n.k. | 21 | 26 | PD, dystonia | + | Common (SN, LC, nbM) | – | – | – |
| | c.610-1G>T; c.1627C>T | 21 | 52 | PD, dystonia | + | Rare to scattered | + | + | Widespread cortical and limbic atrophy; Alzheimer’s pathology |
| Miki et al. 2017 ⁶⁷ | c.1495G>A | 25 | 48 | PD | + | Dorsal vagal nucleus, LC, SN, temporal mesocortex | – | – | – |

n.d. = no data; n.k. = not known; BG = basal ganglia, LC = locus coeruleus, NAD = neuroaxonal dystrophy; nbM = nucleus basalis of Meynert; SN = substantia nigra; PD = Parkinson’s disease; LB = Lewy body; LN = Lewy neurites

Table 6

Summary of GBA Autopsy reports

| Report | Autopsies (n) | Genotype (n) | Phenotype (n) | Pattern of Neuronal Loss | LB, LN Pathology (n) | LB Distribution — Braak Stage (n) | Tau Pathology — NFT Stage (n) | Other Inclusions (n) |
|---|---|--|--|---|---------------------------------------|--|-------------------------------|--|
| Tayebi et al. 2003 ⁸³ , Wong et al. 2004 ⁸⁴ , Goker-Alpan et al. 2010 ⁸⁵ | 4 GD (type 1) | N370S/N370S (2), N370S/? (1) D409H/L444P+, duplication (1) | PD Dementia (4) | SNpc, CA2-4, calcarine layer 4b, cortical layer 5 | + (4), especially CA2-4 | 5 to 6 (2) 3 (1) 4 (1) | No details | Gaucher cells (4) GBA-reactive LB inclusions (3) Glucosylsphingosine levels as in controls |
| Lwin et al. 2004 ⁸⁷ | 2 GD 10 <i>GBA</i> heterozygotes | N370S/N370S (2), T369M (3), N370S (3), L444P (1), K198T (1), R329C (1), E326K (1) | PD (12) EOPD (2/12, 1 GD, 1 heterozygote), dementia (most) | No details | + (10) — (2) E326K and K198T carriers | 6 (2) GD, 5 <i>GBA</i> heterozygotes, 4 (3) <i>GBA</i> heterozygotes | No details | Enzyme activity: 7% to 11% in 2 GD, 43% to 100% in 10 <i>GBA</i> heterozygotes |
| Eblan et al. 2005 ⁸⁹ | 2 <i>GBA</i> heterozygotes | D140H (1) RecNcil (1) | PD (2) | No details | 2 | No details | No details | No details |
| Goker-Alpan et al. 2006 ⁸² , 2010 ⁸⁵ | 9 <i>GBA</i> heterozygotes | N370S (5) R120W (1) A359X (1) T267I (1) I161N (1) | PD dementia (9) | No details | 9 | 6 (8) 4 (1) | AD (6) — (3) | GBA-reactive LB inclusions (4) |
| Mata et al. 2008 ⁸⁸ | 2 <i>GBA</i> heterozygotes | L444P (1) N370S (1) | PD dementia (2) | No details | 2 | 6 (2) | V (1) II (1) | No details |
| Clark et al. 2009 ⁷⁶ | 1 GD (with AD) | N370S/N370S (1) | AD | | | | | |
| | 31 <i>GBA</i> heterozygotes, 2 homozygote/compound heterozygotes of mutations of unclear significance | N370S (9) T369M (4) E326K (4) 84gg (1) H255Q (1) D409H (1) L444P (1) R463C (1) R496H (1) W184R (1) E388K (1) E326K/N188R/S196P/V191G (1) T369M/T369M (1) | PD (27) EOPD (1/27) dementia (no data) | No details | 27 | 4 to 6 (26) 3 (1) | AD (5) | No details |
| | | G1444 A>G (1) P171P (1) T369M (2) G389V (1) | AD (5) | | | | | |
| | | T369M (1) | Normal (1) | | | | | |
| Farrer et al. 2009 ⁹¹ | 8 <i>GBA</i> heterozygotes | H255Q (1), IVS2 +1 G>A (1), 1263-1317del (1), E326K (5) | PD (8) dementia (6) | No details | 8 | 5 to 6 (6) 4 (2) | No details | No details |
| Neumann et al. 2009 ⁹⁰ | 17 <i>GBA</i> heterozygotes | L444P (6), N370S (3), R463C (3), D409H (1), R131C (1), C193E (1), RecNcil (1), RecA456P (1) | PD (16), EOPD (1/16), dementia (9/16), MSA (2/16), no data (1) | SNpc, LC | 17 | 5 to 6 (17) | >III (2) | No details |

| Report | Autopsies (n) | Genotype (n) | Phenotype (n) | Pattern of Neuronal Loss | LB, LN Pathology (n) | LB Distribution — Braak Stage (n) | Tau Pathology — NFT Stage (n) | Other Inclusions (n) |
|------------------------------------|--|--|---------------------|--------------------------|--|-----------------------------------|--------------------------------|--|
| Segarane et al. 2009 ⁸⁰ | 1 <i>GBA</i> heterozygote | R262H | MSA | No details | No details | No details | No details | No details |
| Nishioka et al. 2011 ⁸¹ | 3 <i>GBA</i> heterozygotes, 1 homozygote of a mutation of unclear significance | N370S (1), L444P (1), E388K (1), A292T/A292T (1) | PD (4) dementia (4) | No details | 4 | 5 to 6 (4) | No details | No details |
| Sklerov et al. 2017 ⁹⁵ | 1 <i>GBA</i> homozygote | N370S | MSA | | No LBs | | | Diffuse GCIs; Rare neurofibrillary tangles |
| | 3 <i>GBA</i> heterozygotes | T369M (1), N370S (1), R496H (1) | MSA | | Occasional neurons labeled with anti-synuclein antibodies, without LBs | | Neuropils, no neuritic plaques | Diffuse GCIs; Rare neurofibrillary tangles |

Gaucher disease (GD) patients are shaded in light gray, *GBA* heterozygotes are shaded in white. Abbreviations: AD = Alzheimer's dementia; EOPD = early-onset PD, GCI, glial-cytoplasmic inclusions; GD = Gaucher disease, LB = Lewy body; LN = Lewy neurites; MSA = multiple system atrophy; PD = Parkinson's disease