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## The Neuropathology of Genetic Parkinson's Disease

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### Abstract

**Background**—Pathological data from autopsies genotyped for PD-related mutations in *alpha-synuclein*, *Parkin*, *PINK1*, *DJ1*, *LRRK2* and *glucocerebrosidase* have accumulated in recent years. The aim of this review is to systematically review all pathological reports of mutation carriers and to identify pathological patterns and gaps in the currently available data.

**Methods**—A systematic review of the English literature using the terms “Parkinson's disease”, “brain pathology”, “autopsy”, and the specific gene nomenclature, and any combination of the above.

**Results**—Most studies included reports of convenience samples, either cases that were pre-identified as mutation carriers before autopsy, or screens of Lewy body brain banks. Nineteen autopsies of *alpha-synuclein* mutation carriers, 49 of *LRRK2* mutation carriers, 9 of *Parkin* mutation carriers, one of *PINK1* mutation carrier and 90 of *glucocerebrosidase* mutation carriers were identified. Most autopsies of *alpha-synuclein*, *LRRK2* G2019S and *glucocerebrosidase* mutation carriers demonstrated Lewy body pathology as opposed to *Parkin* and *LRRK2* non-G2019S mutation carriers. However, there was a marked variability in pathological findings even among carriers of identical mutations. Pathological data from *DJ1* mutation carriers, non-manifesting mutation carriers (e.g., of *LRRK2* mutations), and carriers of a single *Parkin* mutation were lacking.

**Discussion**—In gathering together all studies of PD autopsies with an identified genetic risk, this review highlights the wealth of information generated, as well as shortcomings in the available data. In particular, there is a need for larger, unbiased pathological studies. Differential association of Lewy pathology with specific mutations may reflect heterogeneity in pathogenic mechanisms among the different PD-related genes.

### Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease.<sup>1–2</sup> PD is a complex disorder which is probably caused by interactions between genetic and environmental risk factors. However, a subset of people affected by PD carries a genetic risk factor that is associated with the disease.<sup>3</sup> Different genetic risk factors carry varying degrees of risk for PD. The penetrance of alpha-synuclein (*SNCA*) triplications and point

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mutations, and *Parkin*, *PINK-1* and *DJ-1* homozygote or compound heterozygote mutations is estimated to be very high. *SNCA* duplications and *LRRK2* mutations have incomplete penetrance. *Glucocerebrosidase* (either heterozygous or homozygous) mutations convey a risk for PD, and the role of heterozygous mutations in *Parkin*, *PINK-1* and *DJ-1* in the pathogenesis of PD is controversial. The discovery of genetic forms of PD provides insight to its pathogenesis and allows researchers to develop genetic animal models that may more closely replicate PD.<sup>4</sup>

In spite of advances in clinical and imaging diagnostic approaches, pathological confirmation is still considered the gold standard in the diagnosis of PD. The pathologic hallmark of PD is the loss of dopamine producing neurons in the substantia nigra pars compacta (SNpc) accompanied by the intraneuronal accumulation of alpha-synuclein containing Lewy bodies (LBs) and Lewy neurites (LNs) resulting in dopamine deficiency.<sup>5-6</sup>

While mutation carriers are often clinically indistinguishable from patients with idiopathic PD (iPD), neuropathological findings can be markedly different. The potential association between consistent pathological findings and specific genetic mutations may help elucidate the pathogenetic mechanisms of neurodegeneration in PD mutation carriers. In this review, we searched the literature, using the PubMed and Scopus search engines, using the terms “Parkinson’s disease”, “brain pathology”, “autopsy”, the specific gene nomenclature, and any combination of the above. Our goal was to summarize the pathological findings for each mutation and identify patterns of degeneration linked to specific gene alterations.

## **PARK1/4 (alpha-synuclein – *SNCA* gene)**

*SNCA* gene point mutations (A53T<sup>7</sup>, A30P<sup>8</sup> and E46K<sup>9</sup>), assigned as PARK1, as well as duplications<sup>10</sup> and triplications<sup>11</sup> (PARK4) cause autosomal dominant PD with variable penetrance. Penetrance in duplication carriers ranges between 30% and 50%, whereas triplication and point mutation carriers show nearly complete penetrance.<sup>12-13</sup>

Clinically, carriers may have rapid motor progression and frequent dementia. Triplications result in earlier onset of PD and dementia, whereas duplication carriers tend to develop later-onset PD with dysautonomia, although the phenotype can be variable.<sup>14</sup>

Thirteen studies reported on 19 autopsies of carriers of *SNCA* gene mutations and multiplications, all with a clinical diagnosis of PD (table 1). Six studies analyzed PARK1 carriers<sup>9, 15-19</sup> and seven studies PARK4 cases with PD.<sup>20-26</sup> Nine of the 13 studies screened only familial PD cases with known genotype. Four of the studies also analyzed participants without familial PD, including 42 controls,<sup>19, 21-22, 26</sup> eight sporadic PD,<sup>21, 26</sup> three dementia with LBs (DLB),<sup>22</sup> 12 Alzheimer’s disease (AD)<sup>21</sup> and one patient with multiple system atrophy (MSA)<sup>22</sup>; none of these were reported as mutation carriers.

In addition, two other studies screened exclusively brain tissue of 50 MSA patients and eight controls for *SNCA* gene mutations; none carried a mutation.<sup>27-28</sup>

Overall, the pathological features of PARK1 and PARK 4 mutation carriers with PD phenotype had a common pattern. All 19 autopsies showed alpha-synuclein containing neurons in the form of LBs and LNs. Five of the cases had alpha-synuclein inclusions within oligodendroglia, reminiscent of the glial cytoplasmic inclusions seen in MSA.<sup>18-19, 22, 24</sup> The neuronal loss was more severe in the brainstem, particularly in SNpc and LC. Nevertheless, it frequently involved cortical areas with a propensity for the hippocampal formation (13 out of 19 cases affected), particularly in CA2/3. Cortical neuronal loss may explain clinical dementia that was observed in all patients. In addition, neurofibrillary

tangles (NFTs) were present in a variable distribution in 9 out of 17 autopsies in which tau immunohistochemistry was reported. The density of tau inclusions was too low to qualify for pathological diagnosis of AD.<sup>29–30</sup> Interestingly, 2/17 (1 A53T,<sup>16</sup> 1 triplication<sup>22</sup>) cases showed inclusions with both tau and alpha-synuclein immunostaining, an unusual finding in PD. In addition, one case (A53T) showed TDP-43 inclusions in neurites and cell bodies in the temporal cortex, in a pattern consistent with FTLN.<sup>18</sup> In summary, all *SNCA* associated autopsies report alpha synuclein pathology. However, most cases were not pure synucleinopathies, since tau inclusions were frequent. In addition, relatively few control brains were screened for these mutations.

## PARK 8 (leucine-rich repeat kinase 2 – *LRRK2*)

*LRRK2* is a common genetic cause of PD. The G2019S mutation is the most common mutation worldwide,<sup>31</sup> and the G2385R variant is a common risk factor in Asian populations.<sup>32</sup> The International *LRRK2* Consortium study estimated that the G2019S mutation accounts for 1% of sporadic and 4% of familial PD patients. The highest frequency was found in North African Arabs (36% in familial, 39% in sporadic) and Ashkenazi Jews (28% and 10% respectively). Penetrance estimates are age-dependent and widely variable, ranging between 30 and 74%.<sup>31, 33</sup> The clinical phenotype is similar to idiopathic PD.<sup>31</sup>

The neuropathology of various *LRRK2* mutations is heterogeneous. Forty nine autopsy reports of *LRRK2* mutation carriers have been reported including 28 G2019S mutation carriers (25 with parkinsonism from ten studies,<sup>34–43</sup> one with FTLN, one with AD and one control) and 21 PD patients with other *LRRK2* mutations from ten studies.<sup>35, 44–52</sup>

Of the ten studies reporting on G2019S carriers, five studies screened a total of 891 patients with LB disorders,<sup>34–35, 37–39</sup> 363 progressive supranuclear palsy (PSP),<sup>35, 37–38</sup> 62 MSA,<sup>35, 37–38</sup> seven corticobasal degeneration (CBD),<sup>35, 37</sup> 40 essential tremor (ET),<sup>37, 53</sup> 654 AD,<sup>38</sup> 59 FTLN,<sup>35, 37, 42</sup> 102 Huntington disease (HD)<sup>34</sup> and 444 controls.<sup>37–38, 41</sup> Of these control and non-PD neurodegenerative cases, one with FTLN,<sup>42</sup> one with AD and one control were found to have the G2019S mutant.<sup>38</sup> The remaining studies analyzed PD patients with known genotype.

Most autopsy studies on 21 mutation carriers other than G2019S screened only PD patients. However, there is one study that examined brain tissue of 242 PSP patients for mutations at the R1441 residue<sup>54</sup> and another that screened for *LRRK2* mutations (G2019S, I2020T, R1441C and Y1699C) in 24 ET brains<sup>53</sup>; none was a mutation carrier.

Overall, in G2019S mutation carriers with parkinsonism neuronal loss in the SNpc and LC was universal. LB pathology was the most common finding in G2019S brains in 79% (22 of 28); the extent of cortical involvement was variable (table 2). Tau-inclusions were present in a variable distribution and severity in 22 out of the 28 reports (including the cases of AD and PSP like changes with a G2019S mutation). Clinically, dementia was infrequently reported (8 out of 28). Carriers of mutations other than G2019S (see Table 2 for specific mutations studied) were more likely to have more neuronal loss in the SNpc than the LC and less likely to have LBs, which were present only in 43% (9 out of 21). TDP-43-positive inclusions were identified in 3 cases: 1 patient each with R793M and L1156P in temporal cortex,<sup>51</sup> and 1 patient with R1441C in the substantia nigra.<sup>55</sup> The overall frequency of this finding is unclear since most series did not include TDP-43 immunostaining. Dementia was reported in only two out of 21 cases (table 2). No G2385R-related PD autopsies have been reported to date.

In summary, pathological features of different *LRRK2* mutations may vary considerably. The majority of G2019S carriers with PD had LB containing neurons as opposed to the other *LRRK2* mutations. Therefore, it may be implied from the pathological findings that the pathogenesis of PD in *LRRK2* mutation carriers is variable, depending at least partially upon the specific mutation. In addition, there are other factors involved, since patients with identical *LRRK2* mutations (even those in the same family) can have widely variable pathology.<sup>46</sup>

## **PARK2 – *Parkin***

Homozygous and compound heterozygous *Parkin* mutations are established risk factors for early-onset PD (EOPD) world-wide.<sup>56</sup> Patients were described to have sleep benefit, dystonia, hyperreflexia and good response to levodopa with high likelihood to develop dyskinesias.<sup>57</sup> Older age at onset has been described.<sup>58</sup> Mutations may be more common in Hispanics with EOPD.<sup>59–60</sup> *Parkin* dosage mutations are likely more pathogenic than point mutations. However, the role of heterozygous *Parkin* mutations in the pathogenesis of PD remains controversial.<sup>61</sup> Two brain autopsies from autosomal recessive juvenile parkinsonism cases in Japan (later linked to 6q25.2–27<sup>62</sup>) showed neuronal loss in SNpc and LC without LBs.<sup>63</sup> There are nine autopsy reports of patients with homozygous or compound heterozygous *Parkin* mutations. Six of the nine reports derived from either cases that were known *Parkin* mutation carriers before autopsy or from screening familial PD cases. Three studies screened brain banks, including 350 PD patients and 342 controls.<sup>64–66</sup> None of the control brains carried *Parkin* mutations. To our knowledge, no large brain bank screens of other neurodegenerative diseases for *Parkin* mutations have been reported.

Of the nine cases, six had SNpc neuronal loss with no LB pathology,<sup>65, 67–71</sup> two had typical LBs<sup>64, 72</sup> and one had basophilic LB-like inclusions in the pedunculopontine nucleus (PPN) and eosinophilic LB-like inclusions in the anterior horn cells of the lumbar spinal cord.<sup>66, 73</sup> All, but the two with typical LBs, showed more neuronal loss in the SNpc than the LC (in contrast to iPD). Tau inclusions were present in two out of nine autopsies (table 3).

There is only one case report of an autopsy on a heterozygous *Parkin* mutation carrier. This patient had a clinical and pathological diagnosis of PSP. Three of his six sons have clinical EOPD and are compound heterozygotes for *Parkin* mutations.<sup>74</sup>

In summary, the majority of the *Parkin* autopsies are not associated with alpha-synuclein neuronal inclusions. Unlike iPD, most reports had significantly more involvement of the SN than the LC. However, even in this presumably homogeneous genetic group there was variability, since some cases had LB pathology and tau inclusions. The small number of cases precludes any definite association between the type of *Parkin* mutation and the presence of alpha-synuclein pathology. Data on heterozygous *Parkin* carriers with PD are lacking, as no autopsy of *Parkin* heterozygotes with PD has been reported. Given the later age-at-onset among heterozygotes<sup>59</sup> and their olfactory impairment,<sup>75</sup> it is possible that heterozygous mutation carriers have different brain pathology from homozygotes or compound heterozygotes. Alternatively, *Parkin* heterozygosity may not be a risk factor for PD and thus have no bearing on pathology.

## **PARK6 – PTEN-induced putative kinase 1 (*PINK1*)**

*PINK1* is a cause of early-onset PD.<sup>76</sup> The phenotype can be similar to *Parkin* mutation carriers, although *PINK1* carriers may be prone to psychiatric co-morbidity and present with gait disturbance.<sup>77–78</sup>

Only one brain autopsy of a compound heterozygote for a deletion and a splicing mutation in exon 7 has been described. He developed PD at age 31 and florid psychosis 6 years later. Disease duration was eight years. Autopsy findings were significant for LB pathology and neuronal loss in the SNpc sparing the LC, which would be atypical for iPD. The brainstem reticular formation and the nbM were also involved. No tau- or TDP43-positive inclusions were observed.<sup>78</sup>

As in *Parkin*, the role of heterozygous *PINK1* mutations is controversial.<sup>79</sup> In a PD brain bank study, extensive screening (number not reported) for *PINK1* mutations revealed four heterozygotes with the following mutations: A339T, Y431H, N451S and C575R.<sup>80</sup> They all had clinical and pathological PD with psychiatric features and negative family history. Two had cognitive impairment, one of whom had AD pathology. On autopsy, all heterozygous *PINK1* carriers showed the typical PD distribution of brainstem and cortical LBs, with SNpc neuronal loss and NFT stage from I to V. The investigators co-studied two controls, eight PD, two DLB, two MSA, two PSP, two CBD and two AD cases.

In summary, data on pathological changes in *PINK1* mutation carriers is very limited. However, the one *PINK1* mutation carrier who reached autopsy had LB pathology. Therefore, there are no pathological correlates to the hypothesis that *PINK1* and *Parkin* are involved in similar pathways in the pathogenesis of PD.

## **PARK7 – DJ-1**

PARK 7 mutations are a rare cause of EOPD, described in Dutch, Italian and Uruguayan families.<sup>81–82</sup> It accounts for less than to 1% of early-onset parkinsonism.<sup>83</sup> The phenotype can vary from slow onset and good response to levodopa to encompass dystonic and psychiatric features,<sup>82</sup> as well as motor neuron disease with dementia.<sup>84</sup> There are no published autopsies of *DJ-1* mutation carriers. However, there are no negative reports of large brain bank screening either.

## **Glucocerebrosidase (*GBA*)**

Homozygous mutations in the gene encoding the lysosomal enzyme glucocerebrosidase (*GBA*) lead to Gaucher disease (GD), the most common autosomal recessive lysosomal storage disease. About 300 mutations in *GBA* have been reported.<sup>85</sup> Several patients with GD have been reported with parkinsonism, some with typical appearing PD.<sup>86</sup> Following on this observation, several groups have found that heterozygous *GBA* mutation carriers (i.e. without GD) are at increased risk of developing PD, especially in the Ashkenazi Jewish (AJ) population, although other ethnicities are also affected.<sup>87</sup> 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.<sup>88–89</sup>

Ten autopsies of GD patients with parkinsonism were reported from studies on cases with known pre-mortem diagnosis<sup>90–92</sup> and from one brain bank screening on PD patients blinded to the pre-mortem diagnosis.<sup>93</sup> In the latter study, two GD out of 57 PD patients (3.5%) were found and none in 44 controls. Collectively, all autopsies had LBs; five with transitional/diffuse, one with brainstem-predominant distribution and no details reported in four cases. Neuronal loss was documented in the SNpc in all cases. However, GD autopsies with no LB pathology have been reported in patients without clinical parkinsonism.<sup>89, 91</sup> Prominent gliosis and mild neuronal loss was observed in the CA2-4 layers of the hippocampal formation, calcarine layer 4b and fifth layer of the cerebral cortex.<sup>93</sup> When the characteristic Gaucher pathological features were sought in these autopsies, Gaucher cells were found in all four brains in one study,<sup>91</sup> LBs stained for *GBA* antibodies in all three in another<sup>92</sup> and enzyme activity ranged from 7–11% in both cases

studied specifically.<sup>93</sup> However, in one study, all four cases showed the same brain glucosylsphingosine (a toxic metabolite that is elevated in the brain of those with neuronopathic GD) levels as controls.<sup>90</sup> Other pathology, such as tau-inclusions, was not reported.

In addition, 80 autopsies of *GBA* heterozygotes have been described in 11 studies.<sup>53, 89, 92–100</sup> All autopsies were obtained from brain bank screens without knowledge of the genetic or clinical information, apart from one study.<sup>92</sup> Four of 11 studies examined degenerative diseases other than PD and DLB.<sup>53, 89, 97, 100</sup> Overall, a total of 843 PD/DLB,<sup>89, 92–99</sup> 24 ET,<sup>53</sup> 60 AD,<sup>89</sup> 120 MSA<sup>97, 100</sup> and 317 control<sup>89–90, 93, 95–96</sup> autopsies were analyzed. Of these, mutations and variants were found in 80 PD/DLB (9.5%), six AD (10%) two ET (8%) and one MSA (0.8%) as well as four of 317 controls (1.3%). The frequency of *GBA* heterozygotes in PD patients ranged from 3.5% (1 of 29)<sup>97</sup> and 4.5% (17 of 380)<sup>96</sup> to 10.5% (6 of 57).<sup>93</sup> Most studies did not stratify their findings by AJ ancestry. Among DLB autopsies, mutation status varied from 6% (3 of 50 DLB)<sup>95</sup> in non-AJ population to 23% (8 of 35)<sup>97</sup> and 27.5% (26 of 95)<sup>89</sup> in brain bank studies that included AJ patients. All three larger brain bank screens – including the studies from NIH/University of Pennsylvania,<sup>97</sup> Columbia University<sup>89</sup> and Queen Square Brain Bank<sup>96</sup> – reported that *GBA* mutation status was associated with widespread cortical LBs. However, the latter group retracted this statement after re-studying the 17 PD *GBA* heterozygous carriers and 16 PD controls and adjusting for confounding variables.<sup>101</sup> In addition, the Columbia group reported an association of the E326K and T369M variants with PD,<sup>89</sup> 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.<sup>102–103</sup>

On pathology, 77 of 80 *GBA* heterozygotes with parkinsonism had LB-containing neurons. The distribution involved cortical areas in 78 of 80 patients, according to the third report of the DLB consortium.<sup>104</sup> Most studies did not report in detail the neuronal loss distribution. In the five studies reporting on additional pathology, co-existent AD was present in 11 out of 55 cases (table 4).

In summary, *GBA* mutations are a common risk factor for PD, especially among Ashkenazi Jews. Nearly all PD patients who were *GBA* mutation carriers had LB pathology. However, consistent with estimated incomplete penetrance, control brains with *GBA* mutations have been reported as well. Further research is underway to test the hypothesis that *GBA* mutations are linked to cortical LBs in patients with clinical PD.

## DISCUSSION

In this review, we have compiled all of the published autopsy data on PD patients with identified genetic mutations. The data are summarized below (table 5).

There were limitations of the published studies. First of all, the majority of these studies analyzed PD or DLB populations. Only a minority screened a variety of neurodegenerative diseases and controls deriving from brain bank data. This issue was particularly relevant for *SNCA*, *Parkin* and non-G2019S *LRRK2* mutations. Second, the studies were not homogeneous with regard to the protocol followed or the ethnic background of the population studied. Third, the number of autopsies is small overall, with the exception of *GBA* mutation carriers. In particular, there are no reports on *DJ-1* mutations carriers or *Parkin* heterozygotes. Similarly, there is only one *PINK1* compound heterozygous mutation carrier who came to autopsy. Thus, the evidence from the reported autopsies may not represent the full pathological spectrum of a specific mutation. For example, while in vitro

studies implicate Parkin and PINK-1 in the same mitochondrial pathway, most *Parkin* autopsies have no LBs while the single reported *PINK-1* autopsy has LB pathology. Furthermore, most genetic risks for PD are not associated with complete penetrance. Ideally, large autopsy studies would have been able to provide a more accurate estimate of association between possible risk factors (e.g. *Parkin* heterozygosity) and PD pathology, as some mutation carriers may have subclinical pathological involvement. However, given the high cost, very few studies of control autopsies have been performed. Another complicating issue is that of phenocopies, i.e. mutation-negative family members with PD phenotype. These have been described for *SNCA*, *LRRK2*, *Parkin*, and *PINK-1* families; to date, none of these have reached autopsy.<sup>105</sup> Fourth, many of the current studies did not include a detailed description of the neuronal loss distribution. The degree of neuronal loss is important since it is more likely to correlate with clinical features than the presence and distribution of LBs, as up to 50% of cases with widespread LB pathology can be asymptomatic during life.<sup>106</sup> Fifth, additional pathologic inclusions were inconsistently reported. There is still the question of whether or not the formation of LBs and tau inclusions could share a common pathogenesis, as up to 40% of iPD may have coexistent AD pathology.<sup>107</sup> The frequent finding of tau inclusions in PD-mutation carriers, particularly those with LB pathology, supports the hypothesis of a mechanistic relation, assuming that the disease is caused by a single mutation. Other evidence also supports a link between aggregation of tau and alpha-synuclein, such as their co-localization in the brain of an A53T *SNCA* mutation carrier,<sup>16</sup> and the *LRRK2* immunostaining of LBs and tau inclusions in AD, FTLN and Pick's disease brain samples.<sup>108</sup> TDP-43 inclusions are most commonly associated with FTLN-U and ALS. One study found that 5/69 (7%) of PD and 4/21 (19%) of PDD cases were positive for TDP-43 inclusions (the genotypes of these cases is unknown).<sup>109</sup> Our review identified 4 cases (1 *SNCA*, 3 *LRRK2*) with TDP-43 inclusions. However, it should be noted that many of the studies in our review were performed prior to the identification of TDP-43. The potential interaction between alpha-synuclein and TDP-43, especially in genetic forms of PD, warrants additional work.

There is a striking difference in the association with LB pathology among the different gene mutations. LBs are seen in all mutant *SNCA* patients, nearly all *GBA* carriers, and most *LRRK2* G2019S patients. Therefore, animal models based on these mutations may more closely recapitulate the pathogenic mechanisms involved in synucleinopathies. On the other hand, the majority of the *Parkin* and *LRRK2* non-G2019S mutation carriers did not have LB pathology. This raises the issue of relying on the presence of LB for the diagnosis of PD.<sup>110</sup> Alternative criteria based on SN neuronal loss may be more inclusive.

Clearly, there is a need for comprehensive studies with a focus on brain bank screening for the PD-related mutations in patients with various neurodegenerative diseases and controls. Such an undertaking would enable us to acquire a more accurate estimate of the penetrance of these mutations and elucidate a possible correlation between specific mutations and patterns of degeneration in PD and, possibly, other neurodegenerative diseases. In order to achieve this goal, a systematic mechanism of obtaining, storing, processing and reporting autopsy findings (e.g., the common data elements proposed by the NINDS) is required.

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Table 1

Summary of *SNCA* 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 <sup>20-30</sup> (n)	Other inclusions
Golbe, 1990 <sup>15</sup> Duda, 2002 <sup>16</sup>	2	A53T (2)	EOPD Dementia (2)	SN, LC	+ (2)	5-6 (1) Incomplete data (1)	I (1) Incomplete data (1)	-
Spira, 2001 <sup>17</sup>	2	A53T (2)	EOPD, cognitive decline (2)	SN, LC, Hippocampus	+ (2)	5-6 (2)	- (2)	-
Markopoulou, 2008 <sup>18</sup>	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, 2010 <sup>19</sup>	1	A30P (1)	PD Dementia(1)	SN, LC, dnV	+ (1)	6 (1)	II (1)	GCI
Zarranz, 2004 <sup>9</sup>	1	E46K (1)	PD Dementia(1)	SN>LC	+ (1)	6 (1)	- (1)	-
Waters, 1994 <sup>20</sup>	1	Triplification (1)	EOPD Dementia(1)	SN, LC, Hippocampus	+ (1)	6 (1)	Sparse (1)	-
Muenter, 1998 <sup>21</sup>	4	Triplification (4)	EOPD (4) Dementia (3/4)	SN, LC, Hippocampus	+ (4)	5-6 (4)	- (4)	-
Gwinn-Hardy, 2000 <sup>22</sup>	1	Triplification (1)	EOPD Dementia	SN, LC, Hippo, cortex	+ (1)	6 (1)	- (1)	GCI
Farrer, 2004 <sup>26</sup>	1	Triplification (1)	EOPD Dementia Autonomic(1)	SN, LC, Hippocampus	+ (1)	6 (1)	No data	-
Wakabayashi, 1998 <sup>23</sup>	2	Duplication (2)	PD, Dementia (2)	SN, LC, nbM	+ (2)	5-6 (2)	II (2)	-
Obi, 2008 <sup>24</sup>	1	Duplication (1)	EOPD Dementia(1)	SN, LC Hippo	+ (1)	5-6 (1)	I (1)	GCI
Ikeuchi, 2008 <sup>25</sup>	1	Duplication (1)	EOPD Dementia Autonomic(1)	SN, LC, Hippocampus	+ (1)	5-6 (1)	III (1)	-

Abbreviations: LB: Lewy body, LN: Lewy neurite, NFT: Neurofibrillary tangle, EOPD, early-onset PD, SN: substantia nigra, LC: locus coeruleus, TC: temporal cortex, GCI: glial-cytoplasmic inclusions, TDP-43: TAR DNA binding protein-43, dnV: dorsal nucleus of the vagus, nbM: nucleus basalis of Meynert

**Table 2**

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, 2005 <sup>34</sup>	3	G2019S (3)	PD (3)	SNpc, LC	+ (3)	3 (1) 4 (2)	Sparse (1) - (2)	-
Gaig, 2008 <sup>35</sup> Gaig, 2007 <sup>36</sup> Gomez, 2010 <sup>40</sup>	3	G2019S (3)	PD (3)	SNpc, LC	+ (2) - (1)	4 (1) 5 (1) - (1)	I (1) II (1) III (1)	-
Rajput, 2006 <sup>37</sup>	1	G2019S (1)	PD (1)	SNpc mild	- (1)	-	IV (1)	PSP-like
Ross, 2006 <sup>38</sup>	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, 2006 <sup>39</sup>	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)	-
Silveira, 2008 <sup>41</sup>	4	G2019S (4)	PD (4)	SNpc, LC, Olfactory bulb	+ (4)	5 (4)	II (4)	Olfactory bulb LBs (4)
Daschel, 2007 <sup>42</sup>	1	G2019S (1)	Dementia (1)	Hippocampus	- (1)	- (1)	- (1)	FTLD-U
Poulopoulos <sup>43</sup>	3	G2019S (3)	EOPD (2), PD (1) Dementia (2/3)	SNpc, LC	+ (3)	4 (2) 6 (1)	Sparse (2) AD (1)	-
Hasegawa, 2009 <sup>45</sup> Hasegawa, 1997 <sup>44</sup>	8	I2020T (8)	PD (8)	SNpc, SNpr, LC spared	- (7) + (1)	- (7) 3 (1)	- (8)	GCI (1)
Wszolek 2004 <sup>47</sup> Zimprich, 2004 <sup>46</sup> Wider 2010 <sup>55</sup>	6	R1441C (4) Y1699C (2)	PD (6)	SNpc LC	+ (2/4 R1441C) - (4)	4 (1) 6 (1) - (4)	Sparse (1), AD (1 Y1699C), - (4)	PSP-like in 1 (R1441C); TDP-43 in SNpc neurites in 1 (R1441C)
Khan, 2005 <sup>48</sup>	1	Y1699C (1)	PD (1)	SNpc, LC	+ (1)	3 (1)	II (1)	Olfactory bulb LBs
Marti-Masso, 2009 <sup>49</sup>	1	R1441G (1)	PD (1)	SNpc>LC	- (1)	-	I (1)	a-B crystalline in SN
Gaig, 2008 <sup>35</sup>	1	R1441R (1)	PD Dementia (1)	SNpc	+ (1)	No details	No details	-
Giordana, 2007 <sup>50</sup>	1	I1371V (1)	PD cognitive decline (1)	SNpc>LC	+ (1)	4 (1)	II (1)	-
Covy, 2009 <sup>51</sup>	2	R793M (1) L1165P (1)	PD (2) Dementia (1/2)	SNpc, LC	+ (2)	4 (2)	II (1) III (1)	TDP-43 in TC (2)
Puschmann, 2011 <sup>52</sup>	1	N1437H (1)	PD (1)	SNpc > LC	+ (1)	5 (1)	Sparse (1)	Diffuse, atypical ubiquitin+ inclusions

Abbreviations. LB: Lewy body, LN: Lewy neurite, NFT: Neurofibrillary tangle, SNpc: substantia nigra pars compacta, SNpr: substantia nigra pars reticulata, LC: locus coeruleus, TC: temporal cortex, GCI: glial-cytoplasmic inclusions, FTLD-U: frontotemporal lobar degeneration with ubiquitin inclusions, PSP: progressive supranuclear palsy, TDP-43: TAR DNA binding protein-43.



Table 3

Summary of *Parkin* autopsy reports

Report	Autopsies	Genotype	Phenotype	Pattern of neuronal loss	LB, LN pathology	LB distribution-Braak stage	Tau pathology-NFT stage	Other inclusions
Yamamura, 1998 <sup>67</sup>	1	Homozygous del between exon 3 and 7	EOPD	SNpc>LC	-	-	-	-
Mori, 1998 <sup>65</sup>	1	Homozygous exon 4 del	EOPD	SNpc>LC	-	-	III	Thorn-shaped astrocytes
Hayashi, 2000 <sup>68</sup>	1	Homozygous exon 4 del	EOPD	SNpc>SNpr, LC	-	-	Sparse	
Van de Warrenburg, 2001 <sup>69</sup>	1	Compound heterozygous exon 3 del/exon 6 transversion	EOPD	SNpc>LC	-	-	-	Thorn-shaped astrocytes
Mori, 2003 <sup>70</sup>	1	Compound heterozygous exon 6del/exon 7 del	EOPD	SNpc>LC	-	-	-	-
Gouider-Khouja, 2003 <sup>71</sup>	1	Homozygous exon 2 del	EOPD	SNpc, SNpr>LC	-	-	-	-
Farrer, 2001 <sup>64</sup>	1	Compound heterozygous exon 7 R275W/exon 3 del	EOPD, writer's cramp	SNpc, LC	+	4	-	-
Pramstaller, 2005 <sup>72</sup>	1	Compound heterozygous exon 7 del and 1072T del	PD	SNpc, LC	+	3	-	-
Sasaki, 2004, <sup>73</sup> 2008 <sup>66, 73</sup>	1	Homozygous exon 3 del	EOPD	SNpc>LC	Basophilic LB-like in PPN	-	-	Eosinophilic LB in anterior horn cells
Morales, 2002 <sup>74</sup>	1	Heterozygous C212Y mutation	PSP	SNpc/pr, striatum, GP, nbM, STN, Thalamus	-	-	-	PSP

Abbreviations. LB: Lewy body, LN: Lewy neurite, NFT: Neurofibrillary tangle, del: deletion, EOPD: early-onset PD, SNpc: substantia nigra pars compacta, SNpr: Substantia nigra pars reticulata, LC: locus coeruleus, PSP: progressive supranuclear palsy, GP: globus pallidus, nbM: nucleus basalis Meynert, STN: subthalamic nucleus, PPN: pedunculopontine nucleus, del: deletion.

**Table 4**

Summary of *GBA*-related parkinsonism 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)
Neumann 2009 <sup>96</sup>	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),	5-6 (17)	>III (2)	No details
Tayebi 2003 <sup>90</sup>	4 GD	N370S/N370S (2), N370S/? (1), L444P/D409H + duplication (1)	EOPD Dementia (2), PD Dementia (2)	SNpc	+ (4) especially CA2-4	no details	No details	Glucosylsphingosine levels as in controls
Wong 2004 <sup>91</sup> Goker-Alpan 2010 <sup>92,*</sup>	4 GD (type I)	N370S/N370S (2), N370S/? (1), D409H/L444P + duplication (1)	PD Dementia (4)	SNpc, CA2-4, calcareine layer 4b, cortical layer 5	+ (4), especially CA2-4	5-6 (2) 3 (1) 4 (1)	No details	Gaucher cells (4) <i>GBA</i> -reactive LB inclusions (3)
Lwin 2004 <sup>93</sup>	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> ), 4 (3 <i>GBA</i> ),	No details	Enzyme activity: 7-11% in 2 GD, 43-100% in 10 <i>GBA</i> heterozygotes
Eblan 2005 <sup>98</sup>	2 <i>GBA</i> heterozygotes	D140H (1) RecNcil (1)	PD (2)	No details	+ (2)	No details	No details	No details
Goker-Alpan, 2006 <sup>97</sup> Goker-Alpan 2010 <sup>92,*</sup>	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)	<i>GBA</i> -reactive LB inclusions (4) <sup>92</sup>
Mata 2008 <sup>89</sup>	2 <i>GBA</i> heterozygotes	L444P (1) N370S (1)	PD Dementia (2)	No details	+ (2)	6 (2)	V (1) II (1)	No details
Clark 2009 <sup>89</sup>	31 <i>GBA</i> heterozygotes, 1 GD (with AD) 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)	4-6 (26) 3 (1)	AD (5)	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)
Farrer 2009 <sup>95</sup>	8 <i>GBA</i> heterozygotes	N370S/N370S (1) G1444 A>G (1) P171P (1) T369M (2) G389V (1) T369M (1)	AD (6)					
		H255Q (1), IVS2 +1 G>A (1), 1263- 1317del (1), E326K (5)	Normal (1) PD (8) Dementia (6)	No details	+ (8)	5-6 (6) 4 (2)	No details	No details
Nishioka 2011 <sup>94</sup>	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)	5-6 (4)	No details	No details
Segarane 2009 <sup>100</sup>	1 <i>GBA</i> heterozygote	R262H	MSA	No details	No details	No details	No details	No details

Abbreviations: GD: Gaucher's disease, LB: Lewy body, LN: Lewy neurite, NFT: Neurofibrillary tangle, EOPD, early-onset PD, PD: typical age at onset, AD: Alzheimer's disease, SNpc: substantia nigra pars compacta, LC: locus coeruleus, VH: visual hallucinations.

\* additional information of these autopsies was provided in the second reference

**Table 5**

Summary of all genetic autopsy reports

Gene	Locus	Mode of inheritance	Autopsies (n) <sup>1</sup>	PD phenotype (n)	Pattern of neuronal loss (n)	LB, LN pathology (n)	LB distribution-Braak stage (n)	Tau pathology-NFT stage (n)	Other inclusions (n)
<i>SNCA</i> (PARK1/4)	4q21-q22 <sup>7</sup>	AD	19	EOPD (14/19) Dementia (16/19) Autonomic (6/19)	SNpc, LC (19) Hippocampus (13/19)	+ (19)	5-6 (19)	None (11) I-IV (8)	GCI (5) TDP-43 (1)
<i>LRRK2</i> (PARK8) G2019S	12p11.2-q13.1 <sup>46</sup>	AD	28 (25 parkinsonism, 1 FTLD, 1 AD, 1 control)	EOPD (3/27) Dementia (6/27)	SNpc, LC (25)	+ (22) - (6)	3 (5) 4 (13) 5 (2) 6 (2)	None (6) I-II (16) III-IV (1) AD (4) PSP-like (1)	PSP-like (1) FTLD-U (1)
<i>LRRK2</i> non-G2019S			21	Dementia (3/21)	SNpc, LC (21)	+ (9) - (12)	3 (2) 4 (4) 5 (1) 6 (1) No data (1)	None (12) I-III (7) AD (1) No details (1)	PSP-like (1) TDP-43 (3)
<i>Parkin</i> (PARK2)	6q25.2-27	AR	9	EOPD (8/9)	SNpc>LC (7/9) SNpc equal to LC (2/9) SNpr (2/9)	+ (2) - (7)	3,4 (2)	III (1) - (8)	Thorn-shaped astrocytes (2) LB-like in anterior horn cells (1)
<i>PINK1</i> (PARK6)	1p35-p36 <sup>11</sup>	AR	1	EOPD, psychosis	SNpc, nbM (LC spared)	+	4 (1)	-	-
<i>DJ-1</i> (PARK7)	1p36 <sup>81</sup>	AR	0						
<i>GBA</i> <sup>2</sup> carriers	1q21 <sup>85</sup>		80 (79 PD, and 1 MSA)	EOPD (3/79) Dementia (25/34); data not available n=45	SNpc, LC (17) No details (62)	+ (77) - (2)	4-6 (74) 3 (1) No data (2)	- (3) II-V (4) AD (11) No data (62/80)	GBA reactive LBs (4) MSA (1)
<i>GD</i> <sup>2</sup>		AR	10	EOPD (3/10) Dementia (10)	SNpc, CA2-4, 5 <sup>th</sup> cortical layer (8) No data (2)	+ (10) <sup>2</sup>	4-6 (5) 3 (1) No data (4)	No data	Gaucher cells (4) GBA reactive LBs (3)

Abbreviations. LB: Lewy body, LN: Lewy neurite, NFT: Neurofibrillary tangle, EOPD: early-onset PD, SNpc: substantia nigra pars compacta, SNpr: substantia nigra pars reticulata, LC: locus coeruleus, nbM: nucleus basalis of Meynert, AD: Alzheimer's disease, PSP: progressive supranuclear palsy, GCI: glial-cytoplasmic inclusions, GB: glucocerebrosidase, TDP-43: TAR DNA binding protein-43.

<sup>1</sup> All autopsies are from patients with a clinical diagnosis of PD unless otherwise noted.

<sup>2</sup> GBA carriers' autopsies of patients without parkinsonism were not included